



# Recent strategies in nanodelivery systems for natural products: a review

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Received: 10 December 2020 / Accepted: 11 July 2021  
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## Abstract

Natural products are major molecules for drug discovery due to their structural diversity and their interaction with various biological targets, yet their clinical application is limited by poor water solubility or low lipophilicity, inappropriate molecular size, low dissolution rate and permeation, instability, high metabolic rate and rapid clearance. These issues can be solved by nanomedicine, by improving bioavailability and therapeutic efficacy. Here we review nanocarriers made of polymer or lipid constituents. Specifically, we describe the technological characteristics of each nanosystem, with examples of application to single natural constituents or plant extracts, and possible routes of administration. We report *in vitro* and *in vivo* studies and we conclude with the potential advantages of nanodelivery systems in terms of increased stability and solubility, improved biodistribution and efficacy, reduced adverse effects and toxicity.

**Keywords** Natural products · Nanovectors · Delivery systems · Polymeric and lipid nanosystems · Bioavailability and efficacy

## Introduction

Natural products as isolated compounds or extracts of botanical, animal and mineral origin have represented for millennia the only resource to maintain health and to cure or prevent human and animal diseases (Khan et al. 2012; Mehta et al. 2015). Currently, their role in therapy is still unquestionable and supported by numerous scientific evidences. Natural products also represent the main source of bioactive molecules and play a key role in innovative drug discovery (Newman and Cragg 2020) thanks to their enormous structural and chemical variability, which is incomparable to that of any synthetic libraries (Cameron et al. 2011; Bilia et al. 2017). The extraordinary interest for natural products is mainly due to their capacity to modulate multiple biological targets, activating various signaling or functional pathways and producing a huge therapeutic significance especially for emerging multifactorial and complex diseases, such as cancer, cardiovascular and neurological pathologies (Rodrigues

et al. 2016). Conversely, many natural products do not possess drug-like characteristics, and their efficacy and clinical use are limited because of physical and/or chemical instability, unsuitable partition coefficient ( $\log P$ ), unfavourable intrinsic dissolution rate or inappropriate molecular size. These unfavourable biopharmaceutical properties often cause low aqueous solubility, poor permeation and absorption through biological membranes and barriers, low bio-distribution or rapid metabolism and clearance, resulting in drug plasma levels below the therapeutic concentration and reduced or annulled efficacy. A low bioavailability can be also related to distribution/accumulation of drugs in non-targeted tissues and organs, leading to numerous side effects (Kesarwani et al. 2013; Jain & Chella 2020).

Diverse strategies have been used to optimise the bio-availability of natural products (Dragicevic & Maibach 2016; Jain & Chella 2020; Paroha et al. 2020; Saka et al. 2020). They are mainly chemical strategies producing semi-synthetic compounds or synthetic analogues (Fang & Leu 2006; Ita 2016), but recently there is an increasing interest in developing appropriate formulations, specifically nanodelivery systems, which present numerous advantages in comparison to conventional drug formulations, such as controlled release kinetics, targeted delivery, enhanced solubility and permeation, increased chemical and physical stability, and

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extended shelf-life, with a consequent considerable greater clinic effectiveness and less side-effects (Bilia et al. 2017, 2018, 2019b; Chamundeewari et al. 2019).

Drug delivery systems, generally between 50 and 300 nm, up to 1  $\mu\text{m}$ , have nanoscale dimensions ranging, in nature, from the size of a water molecule to the red blood cell diameter, as reported in Fig. 1. Some nanosized delivery systems have already entered in the clinic because they can offer an advanced approach to optimise the therapeutic efficacy, targeting definite tissues and organs or crossing biological barriers, in addition to improve the safety profile and the compliance of drugs (Bilia et al. 2017, 2019b).

This review reports on recent strategies in developing nanodelivery systems for natural products, according to their classification as polymeric-based and lipid-based nanovectors (Fig. 2), evidencing their characteristics, advantages and limitations. Specifically, polymeric-based nanocarriers include polymeric nanoparticles, among which nanospheres and nanocapsules, polymeric micelles and dendrimers, whereas lipid nanocarriers include solid lipid nanoparticles, nanostructured lipid carriers, vesicles, nanocochleates, nanoscale emulsions, namely nanoemulsions and microemulsions, and self-microemulsifying drug delivery systems.

This article is an abridged version of the chapter by Anna Rita Bilia, Vieri Piazzini, Maria Camilla Bergonzi (2020) Nanotechnology Applications for Natural Products Delivery. Sustainable Agriculture Reviews 44 (pp. 1-46). Springer, Cham.

## Polymeric nanocarriers

Polymeric nanocarriers include nanoparticles (nanocapsules and nanospheres), dendrimers and polymeric micelles (Fig. 2), made of natural, semi-synthetic or synthetic polymers, selected on the basis of their biodegradability, biocompatibility and surface characteristics, with the aim to produce novel and safe carriers having a controlled and targeted drug delivery. Natural polymers originate from bacteria, fungi, animals, plants, and are mainly represented by polysaccharides (principally chitosan, cellulose, alginic acid, carrageenan, arabic gum, pectin, starch, xanthan, gellan) (Divya et al. 2018; Parhi 2020) and proteins (albumin, casein, gelatin, soy protein hydrolysate) (Elzoghby et al. 2012). Synthetic polymers include poly-cyanoacrylate alkyl esters, polylactic acid, poly (N-vinyl pyrrolidone), polyvinyl alcohol, polyglycolic acid, polylactic glycolic acid (Bilia et al. 2017, 2018, 2019b; Kumar et al. 2019), whereas semi-synthetic polymers are obtained by modification of natural polymers with synthetic polymers or synthetic chemicals by different methods, such as blending, crosslinking and grafting (Sithole et al. 2017).

## Polymeric nanoparticles

Generally, polymeric nanoparticles consist of nanocapsules and nanospheres with dimensions ranging from 100 to 500 nm. In nanocapsules the drug is loaded in the central

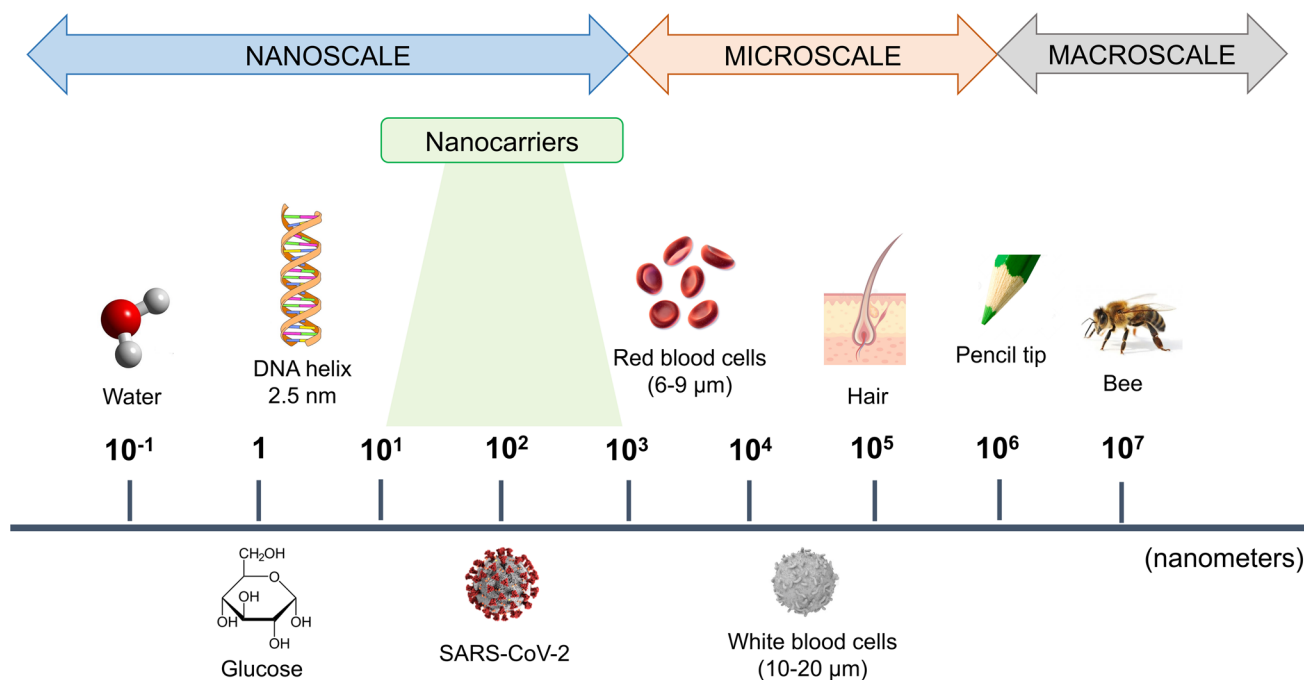
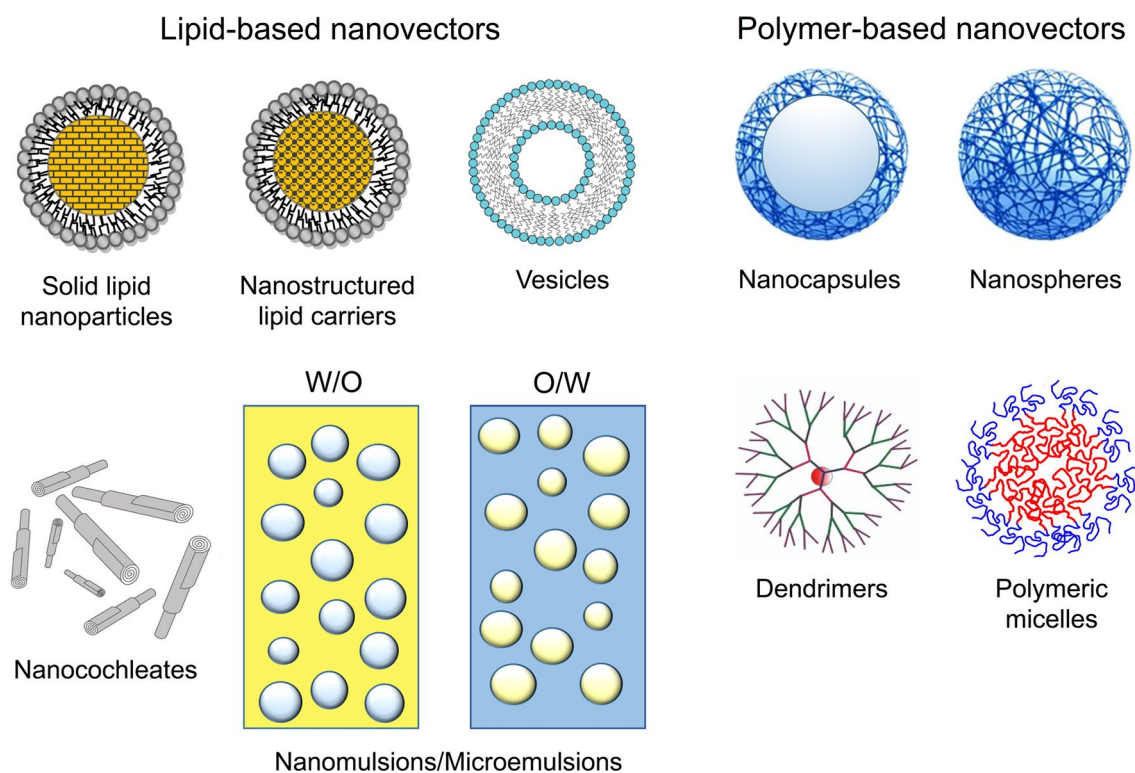


Fig. 1 Nanosized drug delivery systems in the scale of nature



**Fig. 2** Lipid-based nanovectors, including solid lipid nanoparticles, nanostructured lipid carriers, vesicles, nanocochleates and micro/nanoemulsions. Polymeric-based nanovectors, including nanospheres, nanocapsules, dendrimers and polymeric micelles. W: water, O: oil

cavity delimited by the polymeric membrane, whereas in nanospheres the drug is distributed inside the polymeric matrix. Nanoparticles can be used for different administration routes, including the oral and parenteral ones, and they can strongly increase drug bioavailability, as well as allow sustained release of the loaded drug or selectively cross barriers, such as the blood-brain barrier (Guccione et al. 2017; Ahuja et al. 2020).

Specifically, nanoparticles for parenteral administration, formulated using a mixture of polymers, namely poly lactide-co-glycolide and monomethoxy polyethylene glycol, were loaded with ginkgolides and bilobalide, the active constituents of *Ginkgo biloba* L., with an encapsulation efficiency of about 79% and a drug loading of ca. 12 mg per 150 mg of polymer. The mean diameter of developed nanoparticles was ca. 123 nm, while the zeta potential was ca. -30 mV. The half-life time of the ginkgo compounds was moreover considerably increased by loading into the polymeric nanoparticles (Han et al. 2012).

Polymeric nanoparticles are also able to modify the pharmacokinetic profile of curcumin after oral administration. Nanoparticles were prepared using polylactic polyglycolic acid, enhancing the relative oral bioavailability of curcumin by 563% compared to the unformulated curcumin. The increased bioavailability was due to the inhibition of

P-gp-mediated efflux, allowing to rise permeability and absorption of drug in the blood stream (Xie et al. 2011).

Polymeric nanoparticles have been also evaluated for their capability to cross blood-brain barrier after systemic administration in rats. Specifically, nanoparticles based on poly ethylcyanoacrylate, and coated with polysorbate 80, were loaded with salvianolic acid B and evaluated for their biodistribution (Grossi et al. 2017). Salvianolic acid B represents the main constituent of *Salvia miltiorrhiza* L. and it is able to prevent nervous degeneration in numerous animal models with different biological mechanisms (Bonaccini et al. 2015), however its poor chemical stability and low bioavailability severely limit its therapeutic use. The study included intracerebral injection of nanoparticles in healthy rats, in order to observe the distribution of nanoparticles within the injected hemisphere, where they mainly interacted with microglial cells, probably involved in their clearance by phagocytosis. Nanoparticles were furthermore found to be no toxic by chronic administration in C57/B6 mice. The encapsulation efficacy of salvianolic acid B was about 99%, whereas the loading capacity was about 53%. The mean diameter of nanoparticles resulted less than 300nm and zeta potential was about -8.4 mV. The nanoparticles moreover showed a modified release of salvianolic acid B, during 8 h (Grossi et al. 2017).

Recently, albumin nanoparticles, prepared using two different cross-linking methods, the chemical and the thermal one, were investigated as alternative approach to cross the blood-brain barrier after intravenous and intraperitoneal administration in healthy rats. Nanoparticles were found to be safe by behavioural tests on rats, including tests on locomotor and explorative activities, as well as on the cognitive function (Bergonzi et al. 2016). Also, nanoparticles did not induce any inflammatory reaction. In a further investigation, developed albumin nanoparticles were thereby loaded with the characteristic terpenoid andrographolide, the main active constituent of *Andrographis paniculate* L., whose properties in the neurodegenerative pathologies are well known (Casamonti et al. 2019a). The ability of albumin nanoparticles in crossing the blood-brain barrier was compared with that of poly ethylcyanoacrylate nanoparticles (Guccione et al. 2017). The studies were carried out using an *in vitro* model of blood–brain barrier based on human cerebral microvascular endothelial cell line (hCMEC/D3). The authors found that free andrographolide did not cross the endothelial cell line, giving consistent results with the *in silico* studies; poly ethylcyanoacrylate nanoparticles were able to cross the barrier, but they provisionally disordered the integrity of the barrier model, whereas albumin nanoparticles permeated the barrier model, preserving the integrity of the barrier (Guccione et al. 2017).

In a very recent study, andrographolide-loaded albumin nanoparticles were evaluated after parental administration for their distribution and pharmacological effects in brain using TgCRND8 mice, a mouse model of Alzheimer's disease. The nanoparticles had mean size of about 160 nm and a zeta potential of about -25 mV. Encapsulation efficiency was greater than 99%. Nanoparticles administered to TgCRND8 mice were evaluated using the step down inhibitory avoidance test and it was observed that nanoparticles significantly enhanced ( $p < 0.0001$ ) the efficacy of loaded drug in TgCRND8 mice, which reached comparable performances to those obtained in wild type mice. In the object recognition test, both animals treated and untreated with andrographolide-loaded albumin nanoparticles showed no deficiencies in locomotor activity, exploratory activity and directional movement towards objects, in addition to no cognitive impairments ( $p < 0.0001$ ). Albumin nanoparticles loaded with the fluorescent probe, fluorescein sodium salt, were traced in the brain parenchyma of TgCRND8 mice, after intravenous and intraperitoneal administration. In addition, the immunofluorescent analyses revealed the distribution of NAF-loaded nanoparticles both in the pE3-A $\beta$  plaque surroundings and inside the pE3-A $\beta$  plaque, evidencing their ability to cross the blood-brain barrier and penetrate both undamaged and damaged brain tissues (Bilia et al. 2019a).

Reviewed studies are some examples of the wide research on polymeric nanoparticles as future nanomedicines for the

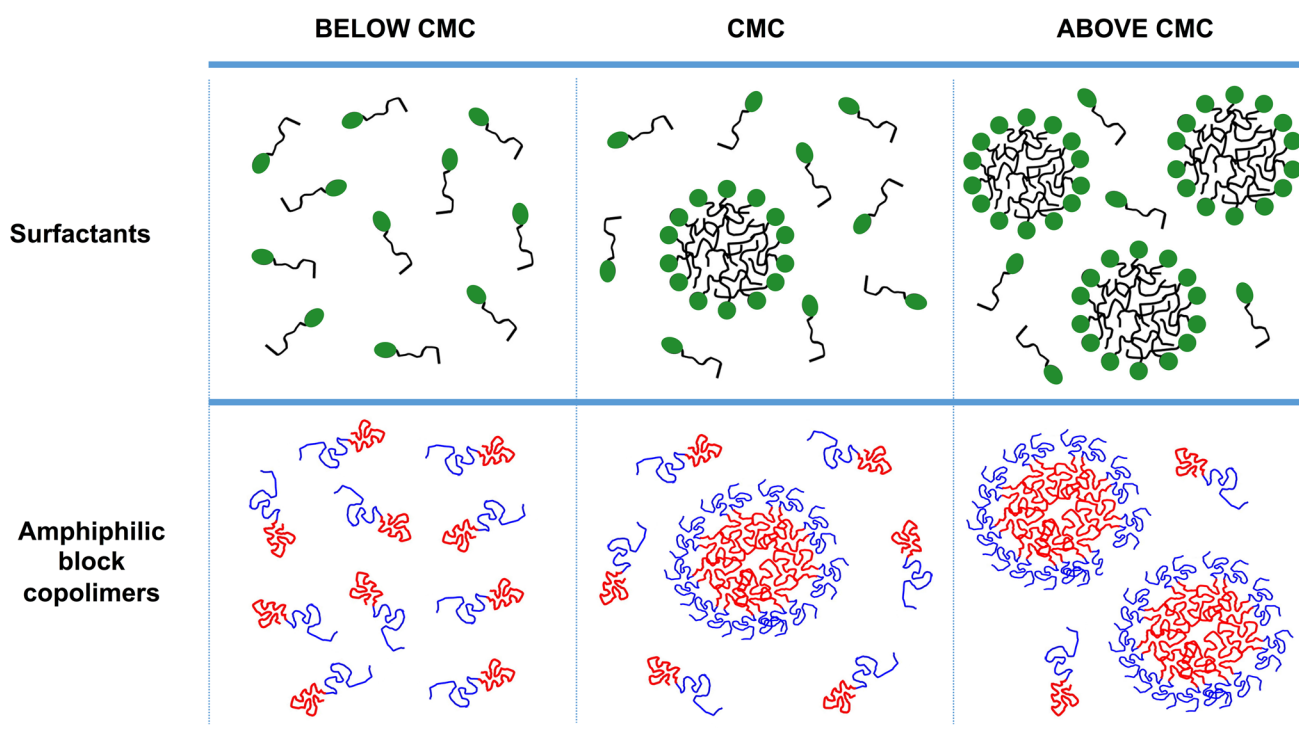
treatment of various diseases. Polymeric nanoparticles were found to be viable nano-sized delivery system in loading diverse type of natural products, such as ginkgolides, bilobalide, curcumin, salvianolic acid B and andrographolide, for oral and parenteral administration, thanks to the high biocompatibility of constituents, resulting a promising strategy for the translation in clinical therapy.

### Polymeric micelles

Polymeric micelles are nanovectors, ranging from 20 to 200 nm, formed by the aggregation of amphiphilic block copolymers made of hydrophobic and hydrophilic monomer units. Micelles spontaneously form by self-association, when the concentration of the monomer unit reaches the critical micellar concentration, similarly to the formation of surfactant-based micelles (Fig. 3). Polymeric micelles are very versatile, stable, safe and low cost nanovectors, and they can be used for almost all the administration routes (Bilia et al. 2017, 2019b).

A study on polymeric micelles loaded with curcumin was carried out to evaluate the inhibition of human brain glioblastoma proliferation. These micelles (about 142 nm) were prepared with an amphiphilic block copolymer synthesized by esterification of polyethylene glycol 400 (hydrophilic portion) and oleoyl chloride (lipophilic portion). In addition, their effects on regular human fibroblastic cells (HFSF-PI3) and adult human bone marrow stromal cells were investigated. Glioblastoma cell viability was not affected by unformulated curcumin. By contrast curcumin-loaded micelles significantly ( $p < 0.001$ ) inhibited the proliferation of glioblastoma, meanwhile the same dosages (20, 25, 30 and 35  $\mu\text{M}$ ) of micelles did not affect regular fibroblastic cells and stromal cells, demonstrating a very high selectivity (Tahmasebi Mirgani et al. 2014).

Another study focused on polymeric micelles made of soluplus (polymer of polyvinyl caprolactam, polyethylene glycol and polyvinyl acetate) and polymeric mixed micelles made of soluplus plus vitamin E polyethylene glycol 1000 succinate (TPGS) in 20:1 gravimetric ratio, for the oral administration of silymarin. Increasing amounts of the active constituent (from 0.5 to 4 mg/mL) were loaded inside micelles. Up to 3 mg/mL, silymarin-loaded micelles maintained similar sizes (about 60 nm), low polydispersity index ( $\leq 0.1$ ) and high encapsulation efficiency ( $> 92\%$ ). Apparent solubility of silymarin in the micelles was considerably increased, up 6-fold, and the nanovectors eluded silymarin degradation in the gastrointestinal tract. The *in vitro* permeation assay, by parallel artificial membranes mimicking the intestinal membrane, confirmed the enhancement of passive diffusion of silymarin when loaded in micelles, whereas the transport studies with Caco<sub>2</sub> cell lines, besides demonstrating that both types of micelles entered into Caco-2 cells



**Fig. 3** Polymeric micelles are formed by the aggregation of amphiphilic block copolymers, made of hydrophobic and hydrophilic monomer units. Micelles spontaneously form by self-association, when

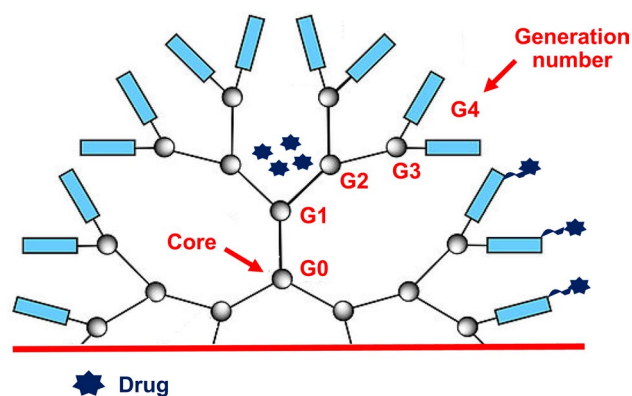
via energy-dependent mechanisms, also indicated that polymeric mixed micelles enhanced the permeability of silymarin compared to polymeric micelles and unformulated extract (Piazzini et al. 2019). In the last years, nano-sized micelles have obtained increasing interest for diagnosis and treatments of many diseases, culminated with the approval by the Food and Drug Administration of the first micelle formulation of paclitaxel for the treatment of breast, ovarian and lung cancer. The lipophilic core increases the solubility of poorly water-soluble molecules, such as curcumin and silymarin, as described in reported studies, and provides a controlled drug release, while the hydrophilic shell protects the encapsulated drug from the external medium, resulting in long circulation properties and increased drug bioavailability.

## Dendrimers

The name “dendrimer” comes from the Greek word “δένδρον” (dendron), meaning “tree”. In fact, dendrimers are self-assembling globular structures with a central core surrounded by branched polymers. Their size range (from some nanometers up to 10–20 nm) is modulated by varying dendrimer generation numbers (for instance G0, G1, G2, Fig. 4). Different surface properties can be obtained according to the linked functional groups. Drugs can be chemically

linked to the superficial moieties or encapsulated into the internal cavities. Amine derivatives (poly(amidoamine) and poly(propylene imine)) are used for the preparation of dendrimers, whereas other polymers are used to functionalise their surface, such as the poly-L-glutamic acid and the poly(ethylene glycol) (Bilia et al. 2017, 2019b).

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**Fig. 4** Dendrimers are self-assembling nanoparticles with a central core surrounded by branched polymers. Their size range is modulated by varying dendrimer generation numbers, for instance G0, G1, G2. Different surface properties can be obtained according to the different linked functional groups. Drugs can be chemically linked to the superficial moieties or encapsulated into the internal cavities

Recently, dendrimers with spherical shape and about 150 nm diameter were prepared using polyamidoamine and loaded with curcumin, in order to increase its solubility and bioavailability. The developed dendrimers had no cytotoxic effects in breast cancer MCF-7 cells and curcumin solubility was enormously increased; it was found to be up to *ca.* 415 times more soluble than unformulated curcumin (Falconieri et al. 2017).

Dendrimers are increasingly fascinating researchers and they hold a promising future not only in delivery of drugs and phytochemical bioactive compounds, but also in diagnosis and management of diseases. Multistep synthesis sometimes gives low yield which can be overcome by variation of the chemical method of preparation. A certain cytotoxicity, which depends on generation to which dendrimers belong and on nature of functional groups on their surface, was also observed, but can be managed by modifications of structure and constituents of dendrimers (Chis et al. 2020). Overall, their unique properties such as nanoscale uniform size, high degree of branching, polyvalency, water solubility, available internal cavities and convenient synthesis approaches make them promising agents for biological and drug delivery applications (Sherje et al. 2018).

## Lipid nanocarriers

Lipid-based nanovectors are prepared using natural and synthetic fatty acids, fatty alcohols, waxes, oils and fats, steroid, amphipathic steroids (Bilia et al. 2019b). These nanovectors include nano-scale emulsions (microemulsions and nanoemulsions), self-microemulsifying drug delivery systems, solid lipid nanoparticles, nanostructured lipid carriers and vesicles, which can be converted in nanocochleates (Fig. 2) (Bilia et al. 2019b).

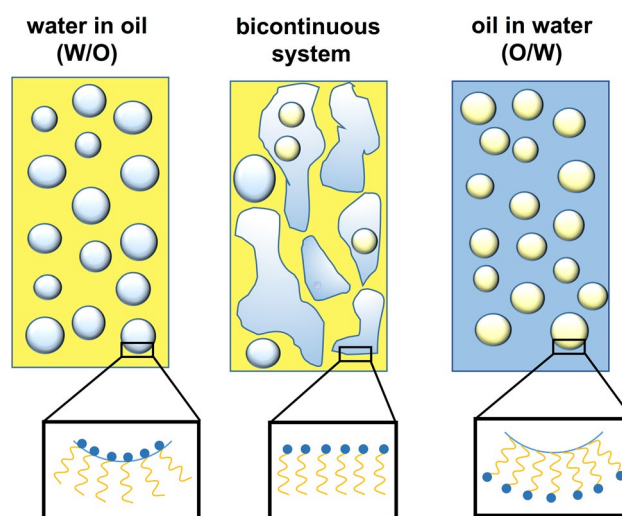
## Microemulsions and nanoemulsions

Microemulsions and nanoemulsions are prepared using an oily phase, an aqueous phase and surfactants agents (McClements et al. 2012). The resulting system is optically transparent with droplets (oil in water or water in oil) of nanosized dimensions (10–100 nm). However, the two systems are significantly different (Fig. 2). In fact, nanoemulsions have a spontaneous propensity to separate in the two initial immiscible phases and need high energy, generally by a microfluidic or ultrasonic approach, to be formed (Tayeb et al. 2018). By contrast, microemulsions can generate spontaneously when all the components are mixed together and they are optical isotropic, homogeneous and thermodynamically stable transparent systems (Tartaro et al. 2020). They can be described as oil in water emulsions, water in oil emulsion or biphasic bicontinuous systems (Fig. 5), (Bilia

et al. 2017, 2019b). In many cases, self-microemulsifying drug delivery systems can be formulated as microemulsion precursors, since the latter can form as soon as they come in contact with the external phase (Kang et al. 2004). Very interesting, microemulsions and nanoemulsion can be used for loading isolated natural compounds or complex mixtures of natural products (Kumar et al. 2018), such as extracts and essential oils (Barradas et al. 2020). In addition, all the administration routes are suitable for these versatile systems (Bilia et al. 2017, 2019b).

An oil-in-water nanoemulsion containing capsaicin was formulated with olive oil (oily phase), Tween 80, Span 80 (surfactants), ethanol (co-surfactant) and water, in order to treat pain and inflammatory disorders. The internal phase droplets had very small sizes (*ca.* 14 nm) and did not show coalescence phenomena for periods longer than 8 months, at 4°C and 45°C. The obtained nanoemulsion was formulated as gel (Carbopol®) and cream (cholesterol, liquid paraffin, soft paraffin, cetyl alcohol and beeswax) containing 0.075% capsaicin. After topical application, the capsaicin-formulation showed significant anti-inflammatory activity in rat paw oedema and high resistance to pain signals (Ghiasia et al. 2019).

Three microemulsions, made of Cremophor EL, lecithin, Tween 20 and Tween 80 as surfactants, and containing wheat germ oil, olive oil and vitamin E as oily phase, were tested *in vitro* for permeation evaluation of curcumin after oral administration, using the parallel artificial membrane permeability assay. The best performance, with a curcumin permeation of about 70%, was obtained by the formulation prepared with vitamin E (3.3 g/100 g), Tween 20 (53.8 g/100 g), ethanol (6.6 g/100 g) and water (36.3 g/100 g), (Bergonzi et al. 2014).



**Fig. 5** Microemulsions can be water (W) in oil (O), bicontinuous systems or oil in water

Recently, Piazzini and coworkers (Piazzini et al. 2017a, 2017b) successfully tested innovative oil-in-water nanoemulsions, with droplet sizes ranging from 10 to 20 nm, in order to improve the oral absorption of extracts of *Vitex agnus-castus* L. and *Silybum marianum* L. *Silybum marianum* L. extract (4% w/w) was formulated using Labrasol, Cremophor EL, Labrafil and water. *Vitex agnus-castus* L. extract (6% w/w) was instead formulated using triacetin, Labrasol, Cremophor EL and water. The studies extensively proved that nanoemulsions improved the permeation of the characteristic constituents of the extracts, when compared with the unformulated extracts.

In a further study, a microemulsion based on Labrasol, Cremophor EL, glycerol and water was formulated and loaded with green tea catechins and caffeine. The microemulsions well-preserved the antioxidant properties of the loaded constituents and the formulation was safe for mammalian cells (Gupta et al. 2019).

Another microemulsion, composed of triacetin, Tween 20, Labrasol and water, was loaded with *Salicis cortex* L. extract (40 mg/mL). Droplet sizes were about 40 nm and the solubility of the characteristic constituents of *Salicis cortex* L. was improved with respect to the unformulated extract (between 2 and 3.6 times more). *In vitro* tests, by parallel artificial membranes and Caco-2 cells, evidenced an enhanced permeation of *Salicis cortex* L. constituents when the extract was loaded in microemulsion (Piazzini et al. 2018a).

A self-microemulsifying drug delivery system, formulated with castor oil, Cremophor EL and 1,2-propanediol, was loaded in sustained-release pellets, for the oral administration of puerarin. The pharmacokinetic profile and the bioavailability of loaded drug was assessed in beagle dogs. The absolute bioavailability of puerarin loaded in the innovative formulation increased 2.6-fold, when compared with that obtained using a conventional formulation, while the relative bioavailability was found to be 259.7% (Zhang et al. 2012a).

Another study was focused on two microemulsions and two self-microemulsifying drug delivery systems for the oral administration of a complex commercial blend based on carbon dioxide extract of *Serenoa repens* L. (saw palmetto). Stability of the formulations was assessed in simulated gastric and intestinal fluids. The *in vitro* parallel artificial membrane permeation assay furthermore indicated a greater mucosal permeation for blend based on saw palmetto extract formulated in the nanosystems compared to the raw commercial blend or the single saw palmetto extract. Permeation values of developed nanoemulsions and self-microemulsifying drug delivery systems were between 30% and 70% (Guccione et al. 2018).

Recently, an olive extract from Tuscan unripe olives (*Olea europaea* L.), characterized by oleuropein (ca. 31%), ligstroside (ca. 3%) and verbascoside (ca. 2.5%) was loaded

at the concentration of 35 mg/mL in a microemulsion, for oral administration. The developed formulation, composed of Capryol 90, Cremophor EL, Transcutol and water, was stable at +4°C for three months. The permeability of phenol constituents, evaluated using the parallel artificial membrane permeation assay, was more than 2 times higher compared to that of unformulated olive extract. The transport studies carried out with Caco-2 cells moreover confirmed the increased permeation of the formulated extract ( $P_{app}$  of  $26.99 \pm 0.45 \times 10^{-6}$  cm/s versus  $16.14 \pm 0.05 \times 10^{-6}$  cm/s for the unformulated extract), (Cecchi et al. 2020).

Isolated natural products (capsaicin, curcumin, puerarin), hydroalcoholic extracts (*Vitex agnus-castus* L., *Silybium marianum* L., *Salicis cortex* L., *Olea europaea* L.) and carbon dioxide extracts (*Serenoa repens* L.) were successfully formulated in microemulsions or nanoemulsions or self-microemulsifying drug delivery systems, obtaining increased solubility or increased permeability through artificial membranes mimicking intestinal mucosa or improved bioavailability. Over the last decades, nano-sized emulsions have been areas of study for a wide range of applications, from food science to cosmetics and drug delivery. In order to facilitate the translation of nano-sized emulsion from research laboratories to the pharmaceutical market, a careful selection of constituents must be done, with regard to safety concerns including hypersensitivity. The selection of biocompatible and approved excipients is a prerequisite for any future pharmaceutical application. In addition, formulation challenges such as ease of synthesis at large scale, storage and stability must be addressed in view of the therapeutic application (Tayeb et al. 2018; Tartaro et al. 2020).

### Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles and nanostructured lipid carriers (Fig. 2) are colloidal systems with a lipid matrix stabilized by surfactants. They have dimensions ranging from 50 to 1000 nm, and they are suitable for all the administration routes (Mehnert and Mäder 2012). These nanovectors are highly biocompatible, biodegradable, safe and very stable. Typically, the lipid core of solid lipid nanoparticles consists of glycerides, fatty acids, fatty alcohols and waxes, which are solid at room temperature and generally recognized as safe ingredients. Nanostructured lipid carriers represent an evolution of solid lipid nanoparticles, obtained by modification of the lipid core structure, adding a liquid lipid at room temperature (Das and Chaudhury 2010). Due to the generation of an imperfect matrix, nanostructured lipid carriers are characterized by higher entrapment efficiency and more stable drug loading (Poonia et al. 2016; Bilia et al. 2019b). The liquid lipids are generally represented by medium chain

triglycerides and edible oils, including corn oil, soybean oil, sunflower oil, vitamin E (Tamjidi et al. 2013).

Solid lipid nanoparticles based on stearic acid, lecithin and Myrj 52 were loaded with curcumin and investigated for their efficacy in an allergic rat model of asthma by intraperitoneal injection. The nanovectors had dimensions of *ca.* 190 nm, with 75% drug entrapment efficiency. Enhanced plas-matic and tissue curcumin concentrations, especially in lung and liver, were obtained with the solid lipid nanoparticles when compared with unformulated curcumin. The nanovec-tors inhibited airway hyper-responsiveness and cell infiltra-tion, in addition to suppress the expression of interleukin-4 and interleukin-13 (Wang et al. 2012). Since curcumin has a wide spectrum of biological properties, but it is poorly soluble in water with consequent low oral bioavailability, it has been also formulated in solid lipid nanoparticles for oral administration by Righeschi and coworkers (Righeschi et al. 2016), with the aim to enhance its permeation through gastrointestinal mucous membranes. These solid lipid nano-particles, prepared with Compritol and GRAS ingredients, and loaded with curcumin, had average diameter of about 300 nm, drug loading capacity of *ca.* 1.60% and drug entrap-ment efficiency of 80%. They showed high stability over one month of storage at +4°C and significantly improved the permeation of curcumin by parallel artificial membranes.

Other interesting active molecules has been delivered by solid lipid nanoparticles, in order to improve their oral bio-availability. An example is andrographolide, formulated in nanoparticles based on compritol 888 ATO, glyceryl mon-ostearate, lecithin and Tween-80, with entrapment efficiency of about 91% and drug loading of about 3.5%. Its bioavaila-bility and antihyperlipidemic activity were improved in com-parison to the unformulated andrographolide, by increasing its solubility and stability in the intestine and by changing its transport mechanism (evaluated in Caco-2 cell line), (Yang et al. 2013). Andrographolide was also formulated in stealth solid lipid nanoparticles based on compritol 888 ATO and Brij 78, for parenteral administration and brain delivery. Developed nanoparticles remained unchanged in presence of human serum albumin and plasma, in addition to be chemi-cally and physically stable over 1 month of storage. The abil-ity of these nanovectors to cross the blood-brain barrier was assessed using parallel artificial membranes and hCMEC/ D3 cells, a well-establish *in vitro* model of human blood-brain barrier, in order to predict andrographolide absorp-tion by transcellular passive diffusion. The permeation of andrographolide loaded in nanoparticles was increased with respect to the unformulated andrographolide. Furthermore, after intravenous administration in healthy rats, fluorescent solid lipid nanoparticles were detected in brain parenchyma outside the vascular bed, confirming their ability *in vivo* to cross the blood-brain barrier (Graverini et al. 2018).

Silymarin, extracted from seeds of *Silybum marianum* L., has been used for decades as hepatoprotectant and, recently, it has been proposed for beneficial effects in type 2 diabetes patients. However, silymarin is poorly soluble in water, with limited oral bioavailability. Thus, in order to enhance its solubility and intestinal absorption, Piazzini and coworkers (Piazzini et al. 2018b) developed nanostructured lipid car-riers using stearic acid, capryol 90 and Brij S20. Obtained nanovectors were stable after incubation in simulated gastric and intestinal fluids. Evaluation of permeability of formu-lated silymarin, by parallel artificial membrane permeability assay and Caco-2 cells, evidenced an increased uptake via active transport mechanisms. Other authors also investigated nanostructured lipid carriers made of glyceryl monosteate and oleic acid, for the hepatic delivery of silymarin by oral route. *In vivo* studies in rats highlighted that silymarin loaded in the nanovectors was absorbed through the lym-phatic system after oral gavage and its relative bioavailabil-ity was 2-fold higher compared to the suspension of silyma-rin. In addition, a significant amount of silymarin reached the liver 2 h after the administration (Chaudhary et al. 2015).

However, the nanostructured lipid carriers can be for-mulated also for dermal application. Nanoparticles made of soy lecithin, glyceryl monostearate, stearic acid, and medium chain triglycerides, for instance, were loaded with quercetin and evaluated as topical delivery system. The aver-age particle sizes were *ca.* 215 nm, the drug loading was about 3% and the encapsulation efficiency was about 90%. *In vitro* permeation studies, using mouse skin, evidenced the enhanced permeation of quercetin with respect to the unformulated quercetin, whereas *in vivo* drug distribution experiments evidenced quercetin retention in epidermis and dermis (Chen-Yu et al. 2012).

Solid lipid nanocarriers were developed in the early '90s to overcome the weaknesses of traditional colloidal carri-ers, like polymeric nanoparticles and liposomes. Reviewed researches deal with the formulation of natural products, such as curcumin, andrographolide, silymarin and querce-tin, recognized as pharmacological active substances, but poorly soluble in water and with low bioavailability. The good biocompatibility of lipid excipients makes it possible to use solid lipid nanocarriers in several delivery routes, including parenteral, oral, and topical, as described. How-ever, despite the increased research interests on these drug carriers, limited pharmaceutical products containing solid lipid nanoparticles are on the market. More knowledge are required concerning the interactions between excipients and biological tissues of the target sites, as well as the fate of solid lipid nanocarriers in the systemic distribution. Addi-tionally, an easy production on large-scale may also advance the commercializing process (Mishra et al. 2018; Mu et al. 2018; Scioli Montoto et al. 2020).



## Lipid vesicles

Vesicle preparation was firstly reported in 1965 using natural phospholipids. Vesicles can be obtained using amphiphilic molecules, represented by natural or synthetic phospholipids (liposomes) or non-ionic surfactants (niosomes), (Fig. 2). Vesicles are generally spherical with sizes ranging from 50 nm to several microns and having a primary role in affecting their biodistribution and pharmacokinetics. Cholesterol is commonly added as fluidizing of the bilayer, although it does not participate in the bilayer formation (Bilia et al. 2019b; Bozzuto et al. 2015). They are characterized by high biocompatibility and biodegradability, high versatility because they are suitable for all the administration routes and can be loaded with both hydrophilic and hydrophobic drugs with resulting enhanced solubility, permeability, stability, improved bioavailability, controlled release and decreased toxicity of drugs. Vesicles also present ease surface modification to obtain passive or active targeting delivery or prolonged circulation and life time. Major limit is the possible drug leakage, due to the release from the vesicles, together with the low stability of the colloid (Bilia et al. 2014a, 2014b, 2017, 2019b).

## Conventional liposomes

Conventional liposomes are first-generation drug delivery systems but still represent extremely relevant carriers. Their usefulness is also related to their versatility and wide-ranging use because of their flexibility in being formulated in a broad range of pharmaceutical dosage forms, including (colloidal) solutions, aerosol, semi-solid or solid forms. Accordingly, many approaches of formulations have been applied both to isolated natural products, extracts and essential oils (Bilia et al. 2017, 2019b).

An *in vivo* study on verbascoside-loaded liposomes demonstrated that the liposomal formulation improved the chemical stability and the therapeutic performance of the active molecule. Liposomes, with an average diameter around 120 nm and 83% of encapsulation efficiency, were tested in two animal models of neuropathic pain and the performance of the liposomal verbascoside was compared with that of unformulated drug. Verbascoside possesses, in fact, various pharmacological activities for human health, including antioxidant, anti-inflammatory and antineoplastic properties in addition to numerous wound healing and neuroprotective properties. The paw pressure test was carried out administering verbascoside-loaded liposomes in chronic constriction injury rats by intraperitoneal injection at the dosage of 100 mg/kg, and presented a prolonged antihyperalgesic effect for loaded-verbascoside in comparison to the free drug. The effect has onset 15 min after the injection and persisted for 60 min (Isacchi et al. 2016).

Naringenin is a flavonoid with diverse pharmacological activities. However, upon ingestion it could be degraded into an active aglycone by the action of certain intestinal bacterial enzymes and the formulation in liposomes was proposed to stabilize the molecule and enhance its bioavailability, in addition to increase its water solubility. Developed liposomes had dimensions suitable for the oral route (*ca.* 70 nm), whereas *in vivo* studies in mice showed an increased area under the curve, indicating a correspondent enhanced bioavailability (about 14-fold) of naringenin after oral administration. Also, studies of tissue distribution evidenced a predominant accumulation of liposomal naringenin in the liver, with respect to the free drug (Wan et al. 2017).

As conventional liposomes are at times unstable when exposed to endogenous chemicals and enzymes in the gastrointestinal environment, an interest study reports the effect of different pluronics (F127, F87 and P85), triblock copolymers many of which approved for use as food additives and pharmaceutical ingredients, on vesicle membranes and, consequently, on their stability. Pluronic-modified liposomes were then loaded with curcumin. It was observed that particle sizes and polydispersity of vesicles were significantly decreased after adding the diverse pluronics, whereas the *in vitro* release of curcumin was slower compared to the release from conventional liposomes. Pluronics were also able to enhance thermal and pH stability of vesicles, in addition to significantly increase the absorption of curcumin in *in vitro* simulated gastrointestinal tract studies (Lia et al. 2018).

Untargeted liposomes loaded with anticancer drugs are the most successful nano-drug delivery systems translated into clinical applications, including the treatment of hematological cancers. Nanoliposomes for the simultaneous delivery of berberine chloride, antineoplastic drug, and tariquidar, P-gp efflux pump modulator, were formulated to enhance berberine chloride intracellular concentration in doxorubicin-resistant human erythroleukemia cells (K562/DOXO) due to P-gp overexpression and to contemporaneously reduce tariquidar toxicity. Developed nanoliposomes had sizes around 128 nm and good PdI (*ca.* 0.20) and  $\zeta$ -potential (*ca.* -20 mV). The stability of nanoliposomes in the cell culture medium showed only a slight variance in average sizes, PdI and encapsulation efficiency of berberine chloride and tariquidar. Analysis by transmission electron microscopy also evidenced the ability of developed nanoliposomes to enter in both cell lines by receptor-mediated endocytosis, with significant increase in berberine chloride uptake by K562/DOXO cell line. Moreover, formulated tariquidar had less toxic effects (lower cell death by necrosis) than free molecule, as nanoliposomes controlled tariquidar release, with a potential benefit in clinical therapy (Vanti et al. 2021b).

Nanoliposomes were also investigated to formulate the *Serenoa repens* L. (saw palmetto) carbon dioxide (CO<sub>2</sub>)

extract, complex mixture constituted of free fatty acids, sterols, phosphoglycerides, glycerides and carotenoids. The saw palmetto CO<sub>2</sub> extract has many biological properties, including anti-inflammation, anti-androgen and anti-proliferation activities, and it has been recently studied for the treatment of hair loss because of the inhibition of 5 $\alpha$ -reductase enzyme, responsible of the conversion of testosterone to 5 $\alpha$ -dihydrotestosterone. Nanoliposomes (ca. 145 nm) loaded with 0.1% w/v of saw palmetto CO<sub>2</sub> extract were developed and fully characterized, in terms of Size, PDI,  $\zeta$ -potential, morphology and encapsulation efficiency, for topical application (Vanti et al. 2021a).

Some studies have also evidenced the possibility to load essential oils inside liposomes. Generally, essential oils are complex mixtures of volatile, liquid, odorous, flavor and strongly active compounds. Due to their various biological properties, principally antioxidant and antimicrobial, they have been widely used since the Middle Ages and currently they also may have several applications in different fields, from medicine and cosmetics to food. However, their high volatility and low stability to direct exposure to light, oxygen, heat, and humidity can limit their efficacy and potential use. Accordingly, nanocarriers which can definitely load the essential oils, represent an innovative challenge to optimise the essential oil formulation, overcoming these main limitations (Bilia et al. 2014a; De Matos et al. 2019). The resulting nanocarriers are stable and efficient, easily and safely produced, capable of stabilizing the essential oil, modulating its release, optimising its activity and providing an innovative formulative approach to avoid irritancy in case of cutaneous administration (Bilia et al. 2019b).

The essential oil of *Artemisia annua* L. was loaded in conventional liposomes and its anti-fungal activity was evaluated against 10 different drug-resistant *Candida* strains. Formulated liposomes, containing 10 mg/mL of essential oil, had sizes around 250 nm, whereas the encapsulation efficiency of artemisia ketone, the marker constituent of the essential oil, was ca. 75%. The minimum fungicidal concentration of *Artemisia annua* essential oil loaded in liposomes, ranging 5 to 10 mg/mL, was much inferior than that of free essential oil (Risaliti et al. 2020b). Another study investigated the antioxidant, anti-inflammatory and antibacterial properties of *Salvia triloba* L. and *Rosmarinus officinalis* L. essential oils formulated in liposomes. The obtained systems, loaded with 100 mg/mL of *Salvia triloba* L. or *Rosmarinus officinalis* L. essential oil, presented encapsulation efficiency of camphor, the marker constituent, around 57% for *Salvia triloba* L. and around 65% for *Rosmarinus officinalis* L. Liposomes were physically stable over time, when stored at +4°C, and very active against *Klebsiella pneumoniae* (Risaliti et al. 2019). Specifically, liposomes enhanced the antibacterial activity of both essential oils. Their antioxidant and anti-inflammatory activities, evaluated by *in*

*vitro* tests, were also increased in comparison to those of unformulated essential oils.

### Pegylated liposomes

Surface functionalization of liposomes has played an important role in formulation of liposomes as pharmaceutical carriers, to improve their pharmacokinetics and effectiveness. For instance, conventional liposomes, when administered intravenously, are recognized by opsonin, a serum-protein, and phagocytosed in the reticuloendothelial system. In order to increase the circulation time of liposomes, the bilayer surface can be coated with a hydrophilic polymer, such as the polyethylene glycol, increasing repulsive forces between liposomes and serum-components. Such surface modified liposomes have been defined as pegylated or stealth liposomes (Riaz et al. 2018).

Therefore, in a further study, pegylated liposomes, loaded with salvianolic acid B, were developed and tested in the same animal model of neuropathic pain reported for verbasin (Isacchi et al. 2016). Salvianolic acid B was effective against mechanical hyperalgesia 15 min after administration, when injected intraperitoneally at a dose of 100 mg/kg. The antihyperalgesic activity prolonged for 30 min after administration, and the effect was still significant after 45 min (Isacchi et al. 2011b).

Some studies report instead on the performance of conventional and long circulating liposomes (pegylated) loaded with artemisinin, a sesquiterpene lactone isolated from the *Artemisia annua* L., well known as very active antimalarial drug. Conventional and long circulating liposomes, with sizes of 130–140 nm and encapsulation efficacy higher than 70%, were injected in healthy mice. Free artemisinin was quickly cleared from plasma and it was almost not more detectable 1 hour after the injection. By contrast, artemisinin was still detectable after 3 and 24 hours when formulated in conventional or pegylated liposomes, respectively. The area under the curve (0–24 h) was six times increased with respect to free artemisinin. In particular, artemisinin half-life was enhanced more than 5-fold with long circulating liposomes (Isacchi et al. 2011a). The same liposomes were tested in *Plasmodium berghei* NK-65 infected mice, a successful malaria model, at the dose of 50 mg/kg/day for artemisinin and 100 mg/kg/day for artemisinin plus curcumin. In mice treated with artemisinin-loaded liposomes or artemisinin plus curcumin-loaded liposomes (conventional and pegylated) was observed an immediate antimalarial effect. Particularly, artemisinin-loaded long circulating liposomes showed the most conspicuous and statistically significant activity (Isacchi et al. 2012). As artemisinin attracted increasing interest over years also for its antitumor properties in a variety of cancer cells, in a further study it was loaded in long circulating liposomes decorated with

transferrin, in order to increase the up-take in tumoral cells. Specifically, cell uptake and cytotoxicity of liposomes were explored using the human colon carcinoma (HCT-8) cell line, because of the overexpression of transferrin receptors. An improved delivery of artemisinin was found for transferrin decorated liposomes with respect to the long-circulating vesicles, and enhanced cytotoxicity was also observed due to iron ions, obtaining a synergic anticancer effect (Leto et al. 2016).

Conventional and pegylated liposomes were also loaded with dihydroartemisinin, the natural metabolite of artemisinin and one of the most potent anticancer compounds, able to induce cancer cell death by apoptotic pathways. Cellular uptake efficiency of liposomes was determined by flow cytometry in MCF-7 cells. Higher internalization occurred for conventional liposomes rather than for stealth liposomes, probably due to the hydrophilic steric barrier of polyethylene glycol molecules. Furthermore, cytotoxicity studies on these cancer cells evidenced an increased toxicity for the formulated dihydroartemisinin and absence of toxicity for blank formulations (Righeschi et al. 2014).

### Stabilized nanovesicles

Liposomes mostly consist of phospholipids and cholesterol. However, some solvents (ethanol, glycerol, propylene glycol) can impart stability, deformability or elasticity to the bilayer membrane of liposomes, resulting in a considerable improved drug loading and permeability through biological barriers by several orders of magnitude (Carita et al. 2018; Fernández-García et al. 2019).

Glycosomes are innovative liposomes for dermal and transdermal drug delivery, based on glycerol and characterized by high physical stability and excellent deformability (Manca et al. 2013). In a recent investigation *Melissa officinalis* L. essential oil was loaded inside glycosomes containing 10% v/v of glycerol, and it was evaluated for its anti-herpetic activity against herpes simplex virus (HSV) type 1 (herpes labialis). The encapsulation efficiency of the essential oil in terms of citral and  $\beta$ -caryophyllene, major constituents, was found to be ca. 63% and 76%, respectively. Moreover, the developed glycosomes loaded with *Melissa officinalis* L. essential oil showed extraordinary chemical and physical stability during 4 months of storage, and were very active in inhibiting HSV type 1 infection of mammalian cells *in vitro*, without producing cytotoxic effects (Vanti et al. 2020a).

Glycosomes and propylene glycol-nanovesicles loaded with essential oils of *Origanum onites* L. and *Satureja thymbra* L. were also investigated as safe and food-grade delivery systems. Essential oils represent in fact a valid alternative to synthetic preservatives in the food industry. However, in many cases their organoleptic impact in foodstuffs limits

their usage, in addition to the high volatility and chemical instability which decrease their efficacy. Techniques such as the encapsulation in nanodelivery systems can address this problem. Both pure and formulated essential oils were evaluated against different food-borne pathogens and spoilage microorganisms. Propylene glycol-nanovesicles loaded with *Origanum onites* L. essential oil were found to be the most active formulation against all tested strains. Additionally, *in vitro* studies on HaCaT cell line showed that nanovesicles loaded with the essential oils had no toxic effect. Overall, these studies unveiled that tested nanovesicles could represent potential biocontrol agents against fungal and bacterial food pathogens with promising GRAS status in mammalian systems, besides being an innovative and completely biodegradable approach for the prolonged and sustained release of the essential oils, preserving functional properties (Vanti et al. 2021c).

### Active nanovesicular carriers

Recently, innovative nanovesicular systems, escinosomes and ascosomes, were also investigated using natural bioactive molecules as vesicle bilayer components, and they were studied for the skin delivery of selected model drugs.

The first study was design to explore the conversion of the bioactive amphiphilic saponin escin, isolated from seeds of *Aesculus hippocastanum* L. and clinically used for its anti-inflammatory, anti-oedematous and venotonic properties, into vesicle bilayer forming component, because of the suited chemical structure and the fluidizing effect on phospholipid membranes. Escinosomes, the obtained nanovesicles made of phosphatidylcholine plus escin, retained escin inhibitory activity on hyaluronidase and were subsequently loaded with berberine chloride, salt of the natural quaternary isoquinoline alkaloid berberine isolated from several medicinal plants. Berberine chloride was selected as model drug of low skin absorption. Empty and berberine chloride-loaded escinosomes displayed optimal characteristics for skin delivery, with high deformability, optimal physical stability, good encapsulation efficiency of berberine chloride (about 67%) and proper release rate of drug (about 75% after 24 h), (Vanti et al. 2019). Subsequently, escinosomes were gelled using hydroxypropyl methylcellulose. Developed escinosome-hydrogels combined the benefits of a controlled release and improved transdermal permeability of both escin and berberine chloride, thanks to the escinosome components, with optimised viscosity properties thanks to the polysaccharide matrix. The escinosome-hydrogels also showed a very good safety profile with no potential skin irritation, evaluated by *in vivo* acute dermal irritation/corrosion test on Sprague-Dawley rats (Vanti et al. 2020b).

Ascosomes represent a further innovative nanocarrier for cutaneous application made of phosphatidylcholine plus

derivates of L-ascorbyl acid, ascorbyl octanoate or ascorbyl decanoate, investigated as bioactive constituents of the vesicle bilayer. L-ascorbic acid (vitamin C) plays in fact an important role in the prevention and treatment of a large number of chronic diseases, including skin disorders, but it hardly penetrate the *stratum corneum*. The synthesis of amphiphilic derivates is a promising approach to enhance its skin penetration. In addition, because of their amphiphilic nature, ascorbyl derivates form supramolecular assemblies in aqueous dispersions, and they have been investigated as potential constituents for drug delivery systems. Obtained nanovesicles, ascosomes, were thus investigated as potential nanocarriers for the skin delivery of khellin, a natural furanochromone with various applications in skin pathologies and selected as model lipophilic drug. Developed ascosomes increased the cutaneous absorption of khellin and retained the antioxidant properties of ascorbic acid (Risaliti et al. 2020a). Subsequently, a hydrogel of khellin-loaded ascosomes was developed using hydroxyethyl cellulose, in order to overcome the short residence time of the liquid formulation upon application on the skin, and to enhance the stability of the vesicles preventing their aggregation. The hydrogel of khellin-loaded ascosomes demonstrated a good safety profile in rats by the acute dermal irritation/corrosion test. Liver and dermal histological and pathological analyses also indicated that khellin formulated in the ascosome-hydrogel had no toxic effects (Risaliti et al. 2021).

### Perspectives of lipid vesicles

The development of vesicles as carriers for therapeutic molecules is an ever-growing research area. Conventional liposomes, stabilized nanovesicles (glycosomes and propylene glycol-nanovesicles), active nanovesicular carriers (escinosomes and ascosomes) have shown excellent potential in (co-)delivering natural products which belong to different chemical classes, namely phenylpropanoids (verbascoside, curcumin), flavonoids (naringenin), sesquiterpene lactones (artemisinin), saponins (escin), alkaloids (berberine chloride), furanochromones (khellin), or carbon dioxide extracts (*Serenoa repens* L.) and essential oils (*Artemisia annua* L., *Salvia triloba* L., *Rosmarinus officinalis* L., *Melissa officinalis* L., *Origanum onites* L., *Satureja thymbra* L.). All these vesicular systems, besides being biocompatible and suitable for all the administration routes, demonstrated to improve the biopharmaceutical properties of loaded natural drugs or to increase their chemical stability, with the aim of reaching an effective pharmacological activity. Lipid vesicles are still the most widely studied colloidal drug delivery systems, which also find great application in the clinical practice.

### Nanocochleates

Nanocochleates represent an alternative platform to vesicles in order to overcome their main limitations, such as possible drug leakage, due to release processes, and low stability of the colloid in biological fluids. Cochleates were firstly observed when phosphatidylserine liposomes were treated with divalent metal cations, mainly magnesium and calcium. They are characterized by an exceptional stability due to their cylindrical shape and distinctive multi-layered structure (Fig. 2) (Bozó et al. 2017; Tilawat & Bonde 2021) and they were studied to formulate different kind of natural products.

*Thymus vulgaris* L. essential oil was loaded in nanocochleates (1 mg/mL), obtaining an encapsulation efficiency of the major constituents, thymol and carvacrol, of about 46% and 51%, respectively. Developed nanocochleates, ranging from ca. 210 to 250 nm, preserved the strong antioxidant activity of the unformulated *Thymus vulgaris* essential oil and were found to be suitable to provide a practical dosage form (Asprea et al. 2017). Nanocochleates have been also investigated as delivery systems of andrographolide, extensively studied for its wide spectrum of biological activities and selected as model drug because of its low water solubility and gastrointestinal instability. The developed andrographolide-loaded nanocochleates were found to be stable after lyophilisation and resuspension in distilled water, as well as after incubation in simulated gastric and intestinal media. They also demonstrated an elevated safety profile both in macrophages and 3T3 fibroblasts even at high concentrations, in addition to extraordinary uptake properties in macrophages, evaluated by a fluorescent probe (Asprea et al. 2019).

Nanocochleate is an extremely biocompatible system with excellent stability due to the unique compact structure, gaining increasing interest in pharmaceutical research as nanocarrier.

### Conclusion

There is an increasing interest for nano-drug delivery systems for their potential application in clinic, both for local and systemic administration of drugs. Concurrently, natural products, which include a large and diverse group of substances from various natural sources, have assumed an exceptional importance for the prevention and cure of many diseases. This is due to their unique structure and their pleiotropic effects by targeting and modulating multiple pathways. For these reasons, natural products could represent the ideal drugs to a realistic approach of many diseases, especially those with emerging resistance to monofunctional agents, and they are suitable approaches against multifactorial and complex diseases, especially cancer and diabetes.

By contrast, natural products suffer of many limitations and the majority of constituents are not “drug like”. Accordingly, the various nanovectors have been attempted as potential delivery systems for natural products, increasing the stability and solubility of loaded drugs and, thus, making them suitable for the administration. These nanostructures are also able to improve the biodistribution, with a consequent increased efficacy, as well as to favour the accumulation at target sites, reducing the adverse effects. Furthermore, the selection of biocompatible nanomaterials allow to decrease the formulation toxicity.

**Acknowledgements** The author thanks MIUR-Italy (“Progetto dipartimenti di eccellenza 2018-2022” allocated to Department of Chemistry “Ugo Schiff”, University of Florence, Italy).

#### Declaration

**Funding** Open access funding provided by Università degli Studi di Firenze within the CRUI-CARE Agreement.

**Conflicts of interest** The author declares no conflict of interest

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