Development and Use of Polymeric Nanoparticles for the Encapsulation and Administration of Plant Extracts

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1 Introduction

Plants as a natural source of different molecules possess various biological activities, which are known since long times. The treatment of diverse diseases was taken place by these molecules (WHO 2015). Nowadays, plant extracts are employing for the therapy of different health problems within approximately three quarter of people in the world (Fabricant and Farnsworth 2001). Natural products cover essential oils, plant extracts, tea, salves, and so on. Principally, natural extracts, which are the mixture of chemicals having biological activities, are obtained from the medicinal plants' leaves, stems, fruits, or roots. In fact, antifungal, antioxidants, antibiotic, antiparasitic, anticancer, hypoglycemic, and antihypertensive are from the most noticeable biological activities that are presented by the plant extracts (Clark 1996; Butler and Buss 2006; Surya et al. 2014; Memvanga et al. 2015; Chakraborty et al. 2014; Njimoh et al. 2015; Patten et al. 2016). Encapsulated plant extracts are also applied in the fields of cosmetics, food technology, and phytotherapy (Armendáriz-Barragán et al. 2016). Currently, the innovation of pharmaceutical products is being evolved thanks to the advances of scientific technologies. These advanced technologies caused conventional therapies to be gradually supplemented by further flexible and well-developed dosage forms. The undertaking of traditional drug delivery-related limitations attracted

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V. Cechinel Filho (ed.), *Natural Products as Source of Molecules with Therapeutic Potential*, https://doi.org/10.1007/978-3-030-00545-0_11

a special attention. Low bioavailability, bitter taste, poor stability, and disagreeable odor of several active ingredients are from the most commonly faced challenges. However, these obstacles toward dosage form design can be dealt with through the drug encapsulation strategy. The encapsulation approach could avoid the early degradation of active molecules such as proteins and peptides.

Moreover, controlled and targeted drug delivery systems obtaining could be supported by the encapsulation technologies. Colloidal carriers get the wide applications in the field of biomedicine and biotechnology. Dendrimers, block ionomer complexes, polymer-based biodegradable nanoparticles (NPs), polymer-based micelles, liposomes (Naseer et al. 2014; Laouini et al. 2012), nanotubes, nanorods (Wang et al. 2012), and quantum rods are the different types of colloids used in medicine (Iqbal et al. 2015). The utilization of particulate carriers creates the opportunities for more progress in the fields of biotechnology and biomedicine. These colloidal carriers were employed in both in vivo and in vitro investigations. In comparison with the simple solution of active molecules, particulate carriers have their own advantages including active ingredient protection from degradation or inactivation (by enzyme or light) and reduction of toxicity. The unpleasant taste and odor accompanying some active molecules can be masked via encapsulation of drugs. Colloidal carriers could be absorbed on the membrane and target the tissues for pharmacotherapeutic action better than drug solution.

Therefore, active ingredient reproducible and prolonged release is obtained (Cintra e Silva et al. 2012; Levchenko et al. 2012; Poletto et al. 2012; Wang et al. 2012; Cenni et al. 2008; Sahoo et al. 2007; Miladi et al. 2013). In addition, as upon encapsulation of drugs, their biodistribution no longer relates to the drugs' physicochemical characteristics but to carrier's ones; therefore, the therapeutic efficacy of active ingredients is improved (Gagliardi et al. 2012; Heneweer et al. 2012; Herrero et al. 2012; Mora-Huertas et al. 2010). The usage of carriers in biomedical application is progressively being increased (Ahmad 2013; Soares 2013; Miladi et al. 2014).

However, complex composition and toxicity to the organism are the two factors that limited therapeutic usage of plant extracts. In addition, organic solvents such as methanol, ethanol, hexane, dichloromethane, ethyl acetate, etc. are commonly used for obtaining plant extracts. Therefore, these vehicle presences by which plant extracts are obtained avoid plant extracts' direct application on the organisms. Furthermore, plant extract conservation, targeted delivery to the tissues, and protection are another obstacle that should be solved for their usage in diseases treatment (Rubió et al. 2013). Polymer-based nanoparticles are one of the most recent and modern approaches of plant extract application that decreases the already mentioned restrictions. Recently, researches are progressively concentrated on the formulation design that includes polymer-based nanoparticles and plant extracts in order to associate plant extract biological activities and polymeric nanoparticle advantages. Cosmetics, medicine, and food technology are the fields in which these formulations would be potentially applied.

Nowadays, plant extract field researchers are more focused on the issues such as encapsulation method standardization to obtain nanoparticles, drug molecule encapsulation (encapsulation efficiency), formulation stability investigation, drug release

kinetic of the carriers embedding plant extracts, free and encapsulated plant extract biological evaluations throughout in vitro and in vivo models, and nanoparticle physicochemical characterization (Armendáriz-Barragán et al. 2016).

2 History and Development of Herbal Medicine from Plant Extracts

Natural products, such as plants, have been the fundamental of human disease treatment. The main concept of the development of modern medicine can be traced to traditional medicine and therapies (Sharma et al. 2011; Patwardhan et al. 2004, 47). In several parts of the world like Africa, America, China, Egypt, and India, plants had been employed for medicinal use long before recorded history. Chemical analysis first became accessible in the early nineteenth century, which begins the extraction and modification of herbal extract (Patwardhan et al. 2004; Zuckerman and Bielory 2002). For a long duration of time, herbal medicines were not recognized for development as a novel formulation due to the lack of scientific proof, characterization, and processing, such as extraction, standardization, and identification of individual drug constituents in complex polyherbal systems.

However, modern phytopharmaceutical research dealt with the scientific requirements for herbal medicines as in modern medicine, which proffer a way for fabricating novel nanocarrier such as nanoparticles, nanoliposomes, matrix systems, microemulsions, solid dispersions, and SLNs. Nanomicellar system (Bisht et al. 2007) colloidal nanogels and nanotubes (Zheng and Song 2009) have been developed for curcumin or in combination with several other chemotherapeutic agents such as paclitaxel (Yadav et al. 2011).

3 Plant as a Source of Bioactive Compounds

Typically, bioactive compounds of plants are produced as secondary metabolites (Bernhoft 2010). The production of secondary metabolites in different species is mainly selected through the course of evaluation and the need of that species. Among secondary metabolites, some of these substances have an effect on biological systems which are considered as bioactive. Thus, a simple definition of bioactive compounds in plants is secondary plant metabolites eliciting pharmacological or toxicological effects in human and animals (Bernhoft 2010).

According to Croteau et al. (2000), bioactive compounds of plants are divided into three main categories: (a) terpenes and terpenoids (approximately 25,000 types), (b) alkaloids (approximately 12,000 types), and (c) phenolic compounds (approximately 8000 types). The plant extract's bioactivities are also related with compounds like fiber, vitamins, phytosterols, sulfur-containing compounds, carotenoids, and organic acid anions together with polyphenolics (Manach et al. 2005). Figure 1 presents some of the common bioactive compounds present in plant extracts.

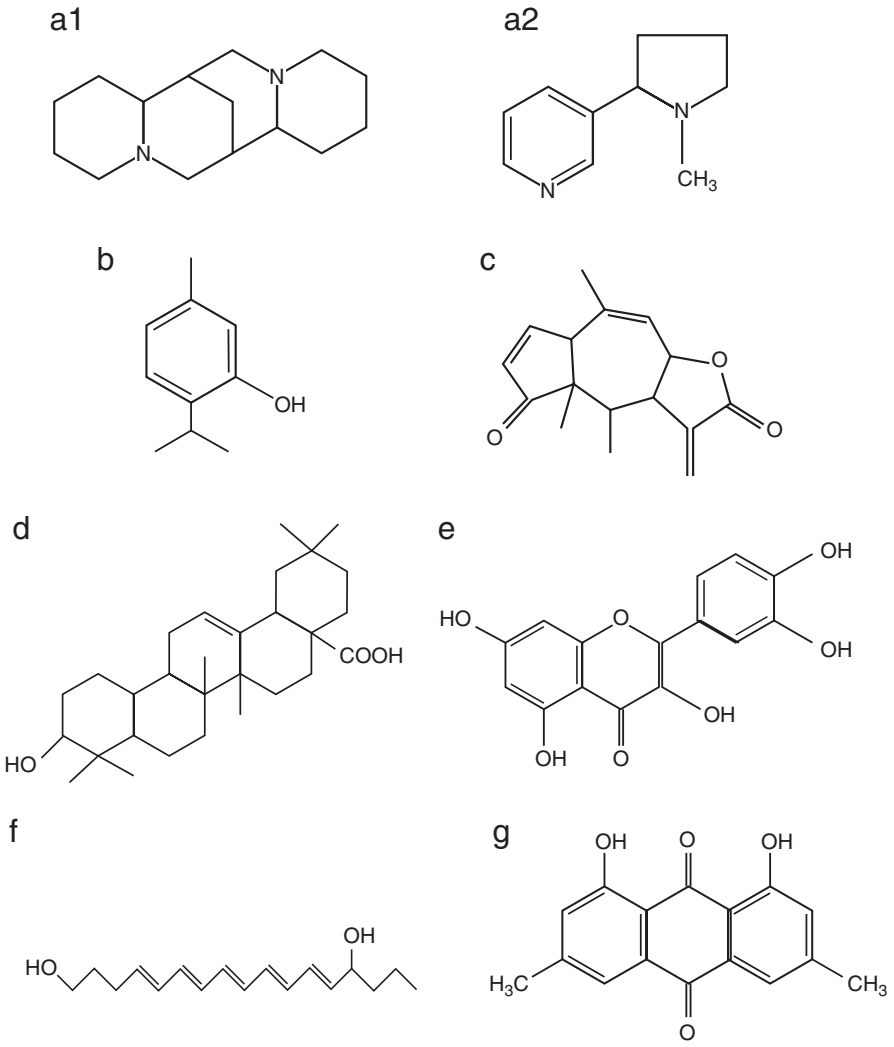

Fig. 1 General structures of different catagories of plant bioactive compounds, alkaloids (**a1, a2**), monoterpenes (**b**), sesqueterpenes (**c**), triterpenes, saponins, steroids (**d**), flavonoids (**e**), polyacetylenes (**f**), and polyketides (**g**). (Adopted from Wink 2003)

4 Different Extraction Process Employed for Nanoparticle Plant Extracts

Different techniques, many of them remaining almost the same through hundreds of years, can also be used to extract bioactive compounds. All these techniques have some common objectives:

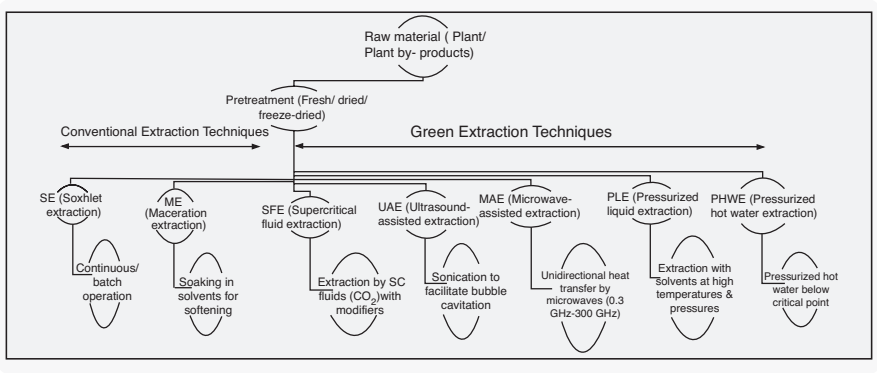

Fig. 2 Conventional and modern extraction methods for plant bioactives. (Adopted from Ameer et al. 2017)

- To extract targeted bioactive compounds from complex plant sample
- To increase selectivity of analytical methods
- To increase sensitivity of bioassay by increasing the concentration of targeted compounds
- To convert the bioactive compounds into a more suitable form for detection and separation
- To provide a strong and reproducible method that is independent of variations in the sample matrix (Smith 2003)

Some of the most promising techniques are ultrasound-assisted extraction, enzyme-assisted extraction, microwave-assisted extraction, pulsed electric field-assisted extraction, supercritical fluid extraction, and pressurized liquid extraction. These techniques are also considered as "green techniques" (Fig. 2) as they comply with standards set by the Environmental Protection Agency, USA. (http://www.epa.gov/greenchemistry/pubs/about_gc.html).

4.1 Ultrasound-Assisted Extraction (UAE)

The main benefit of UAE can be observed in solid plant sample because ultrasound energy facilitates organic and inorganic compounds leaching from plant matrix (Herrera and Luque de Castro 2005). UAE has emerged as a promising technique that fulfills the required criteria as an inexpensive green extraction technique. Rostagno et al. (2003) showed extraction efficiency of four isoflavone derivatives, namely, daidzin, genistin, glycitin, and malonyl genistin, from soybean. Herrera and Luque de Castro (2004) extracted phenolic compounds such as rutin, naringin, naringenin, quercetin, ellagic acid, and kaempferol from strawberries. Li et al. (2005) found better recovery of chlorogenic acid from fresh leaves, fresh bark, and dried

bark of *Eucommia ulmoides* Oliv. by UAE than classical extraction techniques. Yang and Zhang (2008) applied optimized sonication condition to extract bioactive compounds called rutin and quercetin from *Euonymus alatus* (Thund.) Sieb.

UAE have also been regarded as very effective for extracting three alkaloids (vindoline, catharanthine, and vinblastine) from *Catharanthus roseus* (Yang et al. 2011). Anthocyanins and phenolic compounds were also extracted from grape peel using UAE (Ghafoor et al. 2009, 2011). Phenolcarboxylic acids, carnosic acid, and rosmarinic acid were extracted from *Rosmarinus officinalis* using Ionic liquid-based UAE technique which was proved to have high efficiency and shorter extraction time than conventional extraction methods (Zu et al. 2012).

Moreover, UAE of isoflavones from *Pueraria lobata* (Willd.) stem was carried out, and extraction efficiency was compared with that of conventional solvent extraction (CSE) (Huaneng et al. 2007). Table 1 presents a comparative overview of the UAE of polyphenol from various plant matrices with benefit and use.

4.2 Microwave-Assisted Extraction (MAE)

The microwave-assisted extraction is also considered as a novel method for extracting soluble products into a fluid from a wide range of materials using microwave energy (Paré et al. 1994). MAE can extract bioactive compounds more rapidly, and a better recovery is possible than conventional extraction processes. It is a selective technique to extract organic and organometallic compounds that are more intact. MAE is also recognized as a green technology because it reduces the use of organic solvent (Alupului et al. 2012).

For polyphenols and caffeine extraction from green tea leaves, MAE achieved higher extraction yield at 4 min than any extraction methods at room temperature for 20 h (Pan et al. 2003). Ginsenosides extraction yield from ginseng root obtained by 15 min using focused MAE technique was better than conventional solvent extraction for 10 h (Shu et al. 2003). Dhobi et al. (2009) showed increased extraction efficiency of MAE by extracting a flavolignin and silybinin from *Silybum marianum* compared with the conventional extraction techniques like Soxhlet and maceration. Asghari et al. (2011) extracted some bioactive compounds (E- and Z-guggulsterone, cinnamaldehyde, and tannin) from various plants under optimum conditions. MAE was applied to release bound phenolic acids from bran and flour fractions of sorghum and maize of different hardness by Chiremba et al. (2012).

Other biomolecules such as terpenoids, alkaloids, and saponins have also been recovered utilizing MAE (Zhang et al. 2011b). Higher yields and higher antioxidant activity were obtained in peel extracts of citrus mandarin (Hayat et al. 2009), tomatoes (Li et al. 2011a), and onions (Zill-e-Huma et al. 2011) as compared to rotary extraction. MAE has been exploited for the extraction of health-promoting flavonoids from artichoke herb (*Cynara scolymus* L.) leaves (Alupului et al. 2012).

Table 1 Reported application of ultrasonic-assisted extractions (UAE) for extracting bioactive molecules (polyphenols) from plant extract and their possible therapeutic uses

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Spirulina platensis alga	Beta-carotene	Application for pharmaceuticals	Protect against cancer, diabetes, and other chronic diseases	Dey and Rathod (2013)
Forsythia suspensa plant	Phillyrin		Anti-inflammatory, antioxidant, antiviral, and vasorelaxant	Xia et al. (2011)
Penggan peel	Hesperidin	Applicable in food and pharmaceutical industries	Antioxidant, anti-inflammatory, and antiallergic	Ma et al. (2008)
Prunella vulgaris L. plant	Flavonoids		Against sore throat, reducing fever, and accelerating wound healing	Zhang et al. (2011a)
Nannochloropsis oculata alga	Lipids		Feedstock for biodiesel production	Adam et al. (2012)
Hawthorn seeds	Flavonoids		Used in coronary heart diseases	Pan et al. (2011)
Litchi seeds	Polysaccharides	Applicable in food andpharmaceutical industries	Antitumoral and antioxidant and hypoglycemic properties	Chen et al. (2011)
Chilean papaya seeds	Isothiocyanates, phenolic acids, and flavanols	Rapid and enhanced extraction process	Antioxidant and antimicrobial	Briones-Labarca et al. (2015)
Citrus peel	Flavonoids	Better yield than conventional extraction	Food supplements	Londóno-Londóno et al. (2010)
Red raspberry fruit	Anthocyanins	Better yield than conventional extraction	Antioxidant	Chen et al. (2007)
Grapes fruit	Flavonoids	Better yield than conventional extraction	Cancer, diabetes, food and cosmetic industries	Carrera et al. (2012)
Orange peel	Flavonoids	Rapid extraction and better recovery of compounds	Cancer, diabetes, food and cosmetic industries	Khan et al. (2010)
Jabuticaba skin	Anthocyanins	Rapid extraction and better recovery of compounds	Food and cosmetic industries	Santos et al. (2012)

(continued)

Table 1 (continued)

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Olive leaves	Flavonoids	Lower extraction time	Health-promoting effects	Sáhin and Sámli (2013)
Wheat bran	Flavonoids	Rapid extraction and better recovery of compounds	Health-promoting effects	Wang et al. (2008c)

Similarly, Routray and Orsat (2014) identified highbush blueberry (*Vaccinium corymbosum*) as a potent source of flavonoids, particularly chlorogenic acids and anthocyanins with the help of MAE (Table 2).

4.3 Enzyme-Assisted Extraction (EAE)

Enzymatic pre-treatment has been considered as a novel and an effective way to release bounded compounds and increase overall yield (Rosenthal et al. 1996). Some enzymes such as cellulase, β-glucosidase, xylanase, β-gluconase, and pectinase help to degrade cell wall structure and depolymerize plant cell wall polysaccharides, facilitating the release of linked compounds (Moore et al. 2006). There are two approaches for enzyme-assisted extraction: (1) enzyme-assisted aqueous extraction (EAAE) and (2) enzyme-assisted cold pressing (EACP) (Latif and Anwar 2009).

Bhattacharjee et al. (2006) described EACP as an ideal alternate for extracting bioactive components from oilseed, because of its nontoxic and noninflammable properties. The oil extracted by enzyme-assisted methods was found to contain higher amount of free fatty acids and phosphorus contents than traditional hexane extracted oil (Dominguez et al. 1995). EAE of phenolic antioxidants from grape pomace during wine production was tested by Meyer et al. (1998). Chandini et al. (2011) employed the enzymes tannase and pectinase independently to improve the quality of black tea extracts, and the maximum level of polyphenol extraction was observed when tannase was used alone.

Enzyme-assisted extraction was also used to improve the antioxidant composition of black carrot juice and, more recently, to obtain vegetable oils (Khandare et al. 2010; Szydlowska-Czerniak et al. 2010). Landbo and Meyer (2001) showed improved release of phenolic compounds from *Ribes nigrum* pomace using various enzymes. Maier et al. (2008) used mixture of pectinolytic and cellulolytic enzyme in the ratio of 2:1 to extract bioactive compounds (phenolic acids, non-anthocyanin flavonoids, and anthocyanins) from grape pomace. Extraction of phenolic antioxidant from raspberry solid wastes was increased by application of enzyme in hydroalcoholic extraction compared with nonenzymatic control (Laroze et al. 2010). Gómez-García et al. (2012) extracted phenolic compounds from grape waste using different types of enzymes. Other examples of applying EAE for extracting bioactive compounds are present in Table 3 with the therapeutic uses.

Table 2 List of some other applications of microwave-assisted extractions (MAE) in extracting bioactive molecules from plant extract and their possible therapeutic uses

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Pigeonpea leaves	Cajaninstilbene acid and pinostrobin	Rapid and enhanced extraction process	Postmenopausal osteoporosis, hypocholesterolemic and hypoglycemic effects	Kong et al. (2010)
Fucus vesiculosus alga	Sulfated polysaccharides	Rapid and enhanced extraction process	Anticoagulant, antithrombotic, antitumor, antiviral, contraceptive	Rodriguez-Jasso et al. (2011)
Peanut skins	Phenolic compounds	Applicable in food and pharmaceutical industries	Health-promoting compounds including cancer prevention	Ballard et al. (2010)
Green coffee beans	Chlorogenic acid, caffeine, and polyphenols		Used as functional foods	Upadhyay et al. (2012)
Dunaliella tertiolecta and Cylindrotheca closterium microalga	Chlorophyll a and b and β-carotene and fucoxanthin	Better yield than conventional extraction	Food, health, and biotechnological applications	Pasquet et al. (2011)
Uncaria sinensis herb	Catechin, caffeic acid, epicatechin, and rhynchophylline	Rapid and enhanced extraction process	Fears and nervous disorders	Tan et al. (2011)
Rosemary leaves	Phenolic compounds, rosmarinic and carnosic acids	Applicable in food and pharmaceutical industries	Antioxidants for the food industry	Rodríguez-Rojo et al. (2012)
Grape seeds	Polyphenols	Rapid and enhanced extraction process	Pharmaceutical, cosmetic, and food industry	Li et al. (2011b)
Huang qi (*Radix astragali*) root	Flavonoids	High yield and recovery rate		Xiao et al. (2008b)
Sea buckthorn fruit, leaves, and seeds	Flavonoids	Better yield than conventional method		Périno-Issartier et al. (2011)
Soybean beans	Isoflavone	Better yield than conventional method		Rostagno et al. (2007)
Cortex fraxini Bark	Coumarins, Flavones	96% recovery rate with high yield		Zhou et al. (2011)

(continued)

Table 2 (continued)

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Hu Zhang (*Rhizoma polygoni Cuspidati)* leaves	Resveratrol	Rapid extraction and better recovery of compounds		Wang et al. (2008b)
Red bayberry Leaves	Myricetin	Lower extraction time		Wang and Weller (2006)
Apple	Flavonoids	Rapid extraction and better recovery		Bai et al. (2010)
Rosemary leaves	Phenolic acids and flavonoids	Lower extraction time	Antioxidants for the food industry	Svarc-Gajić et al. (2013)
Dittany of crete stem	Phenolic compounds	Rapid extraction and better recovery of compounds	Pharmaceutical, cosmetic, and food industry	Proestos and Komaitis (2008)
Guava (*Psidium guajava*) leaves	Flavonoids	Lower extraction time		Du et al. (2009)

4.4 Pressurized Liquid Extraction (PLE)

This method is now known by several names, pressurized fluid extraction (PFE), accelerated fluid extraction (ASE), enhanced solvent extraction (ESE), and high-pressure solvent extraction (HSPE) (Nieto et al. 2010). Nowadays, for extraction of polar compounds, PLE is considered as a potential alternative technique to super-critical fluid extraction (Kaufmann and Christen 2002). PLE has also been used for the extraction of bioactive compounds from marine sp. (Oszmianski et al. 2011). Flavonoids extracted from spinach by PLE using a mixture of ethanol and water (70:30) solvent at 50–150°C were more effective (Howard and Pandjaitan 2008). Phenolic compounds such as gallocatechin (GCT), catechin, epicatechin gallate, caffeic acid, chlorogenic acid, and myricetin and total phenolic contents were also recovered from various parts of *Anatolia propolis* using PLE at optimum condition (Erdogan et al. 2011).

PLE has also been successfully employed for extraction of anthocyanins from freeze-dried red grape skin (Ju and Howard 2003). Other examples of applying EAE for extracting bioactive compounds are present in Table 4. Despite the advantages over conventional methods, this method is not found to be suitable for thermolabile compounds as high temperature can have deleterious effects on their structure and functional activity (Ajila et al. 2011).

Table 3 Reported some other applications of enzyme-assisted extractions (EAE) in extracting bioactive molecules from plant extract and their possible therapeutic uses

Plant source	Bioactive compounds	Enzyme used in extraction	Possible therapeutic use	References
Pigeonpea leaves	Flavones: luteolin and apigenin	Pectinase, cellulose, and beta-glucosidase	Anti-inflammatory, antiallergic, antiproliferative	Chen et al. (2010a)
Turmeric (*Curcuma longa L.*) spice	Oleoresin	Alpha-amylase and glucoamylase	Food formulations for the prevention of cancer	Fu et al. (2008)
Citrus peels: Yen Ben and Meyer lemon, grapefruit, mandarin, and orange	Total phenolics	Cellulase® MX, Cellulase® CL, and Kleerase ® AFP	Antioxidant and free radical scavenging activities. Implications in human health	Kurmudle et al. (2010)
Rapeseed	Phenolics, tocopherols, and phospholipids	ROHALASE® OS and ROHAPECT® PTE (cellulase, glucanase, and xylanase activity)	Prevention and treatment of chronic diseases: heart and neurodegenerative diseases, aging, cancer, and rheumatoid arthritis	Li et al. (2006a)
Pomace	Polyphenols	Pectinex XXL and Pectinex Ultra SPL (pectolytic enzymes)	Effectiveness against colon cancer	Munoz et al. (2004)
Grape skin from three varieties	Anthocyanins	Pectinex B3-L, Vinozym EC, and Vinozym G	Food additives providing health benefits	Oszmianski et al. (2011)
Ginkgo biloba leaves	Flavonoids: quercetin, kaempferol, and isorhamnetin	Cellulase from *Trichoderma reesei*, pectinase from *A. niger* and *P. decumbens* cellulose.	Physiological activities in therapies for inflammations, heart diseases, and cancer	Parrado et al. (2006)
Rice bran	Enzymatic extract	Endoprotease mixture	Prevention of diseases including cancer, fatty liver, hypercalciuria, kidney stones, and so on	Wang et al. (2010)

4.5 Supercritical Fluid Extraction (SFE)

Supercritical fluid technique has attracted wide scientific interest, and it was successfully used in environmental, pharmaceutical and polymer applications, and food analysis (Zougagh et al. 2004). Supercritical fluid possesses gas-like properties of diffusion, viscosity, and surface tension and liquid-like density and solvation power. These properties make it suitable for extracting compounds in a short time with higher yields (Sihvonen et al. 1999).

Table 4 Reported some other applications of pressure liquid extractions (PLE) and pressure hot water extraction (PHWE) in extracting bioactive molecules from plant extract

Plant source with parts	Bioactive compounds	Condition used	Benefit in extraction	References
Apple pulp and peel	Catechins, flavonols (quercetin), and anthocyanins	99% methanol (solvent), 313.15 K temperature, 7 MPa pressure	Comparable recovery with reduced solvent amount, handling, and time required than CSE	Alonso-Salces et al. (2001)
Jabuticaba (*Plinia cauliflora*) skin	Anthocyanins	Extractor conditions: pressure (5 MPa) and 553 K temperature	Higher recovery: 2.15-fold anthocyanins (13%) and 1.66-fold (8%) total phenolic compounds than CSE at lower temperature	Santos et al. (2012)
Parsley (*Petroselinum crispum*)	Flakes (glycone of apiin and melonyl-apiin	Temperature (313.15 K), pressure (7 MPa), particle size (<850 μm), S/F ratio (250), and 75% flush volume	Improved recovery of six phenolic compounds with wider solvent choice without any thermal degradation	Luthria (2008)
Cabbage (red) leaves (sample)	Anthocyanins 2.5 g	372.15 K at 5 MPa solvent ratios: water/ethanol/ formic acid (94:5:1, v/v/v)	Fast recovery and identification of polyphenols coupling with HPLC-DAD	Arapitsas and Turner (2008)
Bitter melon (*Momordica charantia*)	Fruit chlorogenic acid, genistic acidand catechin	Methanol as solvent at 5 MPa and 423.15–473.15 K with 2 mL/min of flow rate 120 min	Faster and high yield in short time (2 h)	Budrat and Shotipruk (2009)
Citrus (*Citrus unshiu*) peel	Flavanones (hesperidin and narirutin)	One cycle of PHWE at 433.15 K temperature and 10.13 MPa pressure	High-yield hesperidin (3.2-fold) and narirutin (3.7-fold) than CSE	Cheigh et al. (2012)

Saldaña et al. (1999) extracted purine alkaloids (caffeine, theobromine, and theophylline) from *Ilex paraguariensis* (herbal mate tea) using SFE. Supercritical CO_2 modified with ethanol (15 wt.%) gave higher extraction yields of naringin (flavonoid) from *Citrus paradise* (Giannuzzo et al. 2003). Polyphenols and procyanidins were extracted from grape seeds using SFE, where methanol was used as modifier (Khorassani and Taylor 2004). Verma et al. (2008) used optimized condition of SFE to extract indole alkaloids from *Catharanthus roseus* leaves. Zuo et al. (2008) extracted the soybean isoflavones (predominantly daidzein, genistein, and daidzin) from soybean meal. Similarly, Kong et al. (2009) reported extraction of cajaninstilbene acid (CSA) and pinostrobin (PI) are, respectively, a stilbene and flavonone from pigeonpea leaves. Hassas-Roudsari et al. (2009) studied the extraction of antioxidant compounds from canola seed meal using subcritical water and

ethanolic and hot water extraction. Other vegetable matrices that have been used to extract bioactive compounds by SFE from *Citrus pomaces* (Kim et al. 2009a) and oregano (Rodríguez-Meizoso et al. 2006), as well as some microalgae (Herrero et al. 2006). Plaza et al. (2010b, c) studied neoformation of antioxidants during SFE extraction of different natural compounds, including microalgae (*Chlorella vulgaris*), algae (*Sargassum vulgare, Sargassum muticum*, *Porphyra* spp., *Cystoseira abies-marina*, *Undaria pinnatifida*, and *Halopitys incurvus*), and plants (rosemary, *Rosmarinus officinalis* L.; thyme, *Thymus vulgaris*; and verbena, *Verbena officinalis*). Other examples of applying EAE for extracting bioactive compounds are present in Table 5 with the therapeutic uses.

5 Need for Novel Drug Delivery System (DDS) "Nanoparticles"

Before getting to the bloodstream, many phytochemicals of the plant extracts or herbal remedies will be decomposed plying through the highly acidic pH of the stomach and liver enzymatic action. Thus, the optimum amount of the plant extracts may not get to the blood. If an optimum quantity of the active molecules does not reach the infected region at "minimum effective level," then it will not be potent enough to elucidate a therapeutic effect. Nanodrug delivery for herbal remedies or plant extract can carry an optimum amount of the drug to their site of action circumventing all the barriers such as the stomach acidic pH, metabolism of the liver, and an increase in the systemic drug circulation due to their small size (Yadav et al. 2011; Bairwa et al. 2010).

Nanodrug delivery system is a novel technique to reduce the shortcomings of the traditional DDS. Nano-sized delivery system was chosen because they can deliver high concentrations of drugs to disease sites due to their unique size and high loading efficiency, they deliver the drug in an enclosed small particle size that improves the entire surface area of the drugs allowing fast distribution when they get to the bloodstream, and their concentration persists at the sites for a longer period (controlled delivery). In addition to the above-listed advantages, they show EPR (enhanced permeation and retention) effect, i.e., enhanced permeation via barriers, because of their small size and retention due to weak lymphatic drainage such in cancer. They also exhibit passive disease targeting without the attachment of any other specific ligand moiety, decrease in the side effects, and decrease in the drug formulation dose (Namdaria et al. 2017).

6 Benefits of Nanoformulation (Encapsulation)

Encapsulation of the plant extracts and/or herbal formulation into nanocarrier systems have certain added merit, such as their bulk dosing and smaller absorption which can be overcome, which poses a major problem, attracting the attention of

Table 5 Reported some other applications of supercritical fluid extraction (SFE) for extracting bioactive compounds from plant extracts and their possible therapeutic use

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Basil and oregano herbs	Terpenes: alpha-pinene, limonene, camphor, citronellol, and carvacrol	Stability of molecules increased	Anti-inflammatory and antioxidant	Yang et al. (2007)
Centella asatica herb	Asiatic acid and asiaticoside	Better yield than conventional extraction	Antibacterial and fungicidal, colon and breast cancer	Kim et al. (2009b)
Mahkota dewa fruit	Mangiferin	Better yield than conventional extraction	Antidiabetic, anti-HIV, anticancer, immunomodulatory, and antioxidant	Kim et al. (2010)
Morinda citrifolia fruit	Damnacanthal	Better yield than conventional extraction	Anticancer	Anekpankul et al. (2007)
Terminalia chebula Retz. fruit	Gallic acid, ellagic acid, and corilagin		Anticancer, antimicrobial, and anti-inflammatory	Rangsriwong et al. (2009)
Apple and peach pomaces fruit	Polyphenols		Health-promoting effects	Adil et al. (2007)
Ground red paprika fruits	Carotenoids	Better yield than conventional extraction	Protective against cancer, heart and eye diseases	Rutkowska and Stolyhwo (2009)
Olive leaves	Mannitol		Used in pharmaceutical and diabetic food products	Ghoreishi and Shahrestani (2009)
Rosemary, thyme, and verbena leaves	Phenols, protein, amino acids, and sugars		Functionals food, nutraceuticals, and antioxidant	Plaza et al. (2010a)
Quisqualis indica L. flower	Essential oil		Germicide against skin	Rout et al. (2008)
Haematococcus pluvialis	Vit. E, phenolic compounds		Antioxidant and antimicrobial	Rodríguez-Meizoso et al. (2010)
Rice bran biomass	Phenolic compounds		Cancer, diabetes, food, and cosmetic	Pourali et al. 2010
Winery grape seed	Catechins and proanthocyanidins	Lower extraction time	Pharmaceutical and food industries	García-Marino et al. (2006)

(continued)

Table 5 (continued)

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Bovine bones	Hydroxyapatite		Use as osteoconductive, osteoinductive, and bioceramics	Barakat et al. (2009)
Onion skin	Quercetin	Lower extraction time	Anticancer, antivirus, and anti-inflammatory	Ko et al. (2011)
Oregano leaves	Flavone, flavonone, and flavonols		Food ingredient	Cavero et al. (2006)
Rosemary leaves	Volatiles oil	Better yield than conventional extraction	Functional foods, antioxidant, and anticancer	Carvalho (2005)
Pfaffia paniculata and *Pfaffia glomerata* plant	Ginseng	Better yield than conventional extraction	Dermatological and cosmetic compositions	Leal et al. (2010)
Pitanga leaves	Polyphenolic compounds and flavonoids	Rapid extraction and better recovery of compounds	Antibacterial, anticarcinogenic, antiviral, and anti-inflammatory	Martinez-Correa et al. (2010)
Patrinia villosa Juss herb	Volatiles		Antiviral and antibacterial	Xie et al. (2008)
Cherry fruit	Phenols perillyl alcohol		Antioxidants, anticancer agent for the colon, skin, and lung cancer	Serra et al. (2010)
Tomato juice	Lycopene	Better yield than conventional extraction	Coloring agent	Egydio et al. (2010)
Sargassum muticum, *S. vulgare*, *Hypnea spinella*, *Porphyra* spp., *Chondrus crispus*, *Halopytis incurvus*, *Spongiochloris spongiosa*, *Scenedesmus*, and Nostoc 7 (*Cyanobacteria*)	Isoflavones	Lower extraction time	Functional foods and pharmaceuticals industries.	Klejdus et al. (2010)

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Table 5 (continued)

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Synechococcus spp. (microalga)	Carotenoids and chlorophyll	Rapid extraction and better recovery of compounds	Functional foods and in drinks and ice creams	Maćias-Śanchez et al. (2007)
Nannochloropsis gaditana, *Dunaliella salina*, and *Synechococcus* spp.	Carotenoids	Rapid extraction and better recovery of compounds	Food additives	Maćias-Śanchez et al. (2009)
Scenedesmus almeriensis (microalga)	Beta-carotene and lutein		Antioxidants and food coloring agent, preventer of cataracts, atherosclerosis and some type of cancer	Maćias-Śanchez et al. (2010)
Nannochloropsis oculata (microalga)	Carotenoids and lipids	Better yield than conventional extraction	Food supplements and functional foods	Liau et al. (2010)
Chorella pyrenoidosa (alga)	Antioxidants		Dietary supplements.	Hu et al. (2007)
Grape seed oil	Triacylglycerides		Antioxidants	Passos et al. (2010)
Tomato skins	Lycopene	Better yield than conventional extraction	Protective against cardiovascular, coronary heart diseases and cancer	Yi et al. (2009)
Roasted wheat germ	Phenolic compounds and tocopherols		Pharmaceutical, foods, cosmetic formulation, and bioinsecticide	Gelmez et al. (2009)
Coriander seeds	Antioxidant fractions	Better yield than conventional extraction	Dietary supplements	Yepez et al. (2002)
Mangosteen pericarp	Xanthones		Inhibition of lipid peroxidation, antioxidant, neuroprotective, and inhibitor of HIV-1 protease	Zarena and Udaya Sankar (2009)
Grape seed	Proanthocyanidins		Anticarcinogenic, antiviral, and anticancer	Yilmaz et al. (2010)

(continued)

Table 5 (continued)

Plant source with used parts	Bioactive compounds	Benefit in application	Possible therapeutic use	References
Hibiscus cannabinus L. seed	Edible oil	Better yield than conventional extraction	Functional foods	Chan and Ismail (2009)
Strawberry fruits	Phenolic compounds		Cancer, diabetes, food and cosmetic industries	Akay et al. (2011)
Canola	Hydroxycinnamic acid		Antibacterial, anticarcinogenic, antiviral, and anti-inflammatory	Li et al. (2010)
Wine grapes seeds	Flavonoids and phenolic acids		Antioxidant and antimicrobial	Prado et al. (2012)
Maritime pine bark	Flavonoids (catechin and epicatechin)		Health-promoting effects	Braga et al. (2008)
Grape bagasse stems, skin, and seed	Anthocyanins, catechins, and glycosides of flavonols	Rapid extraction and better recovery of compounds	Cancer, diabetes, food and cosmetic industries	Farías-Campomanes et al. (2013)
Coffee grounds and husk	Phenolic compounds	Better yield than conventional extraction	Antioxidant and antimicrobial	Andrade et al. (2012)

big pharmaceutical corporations (Chaturvedi et al. 2011). Herbal medicine activity relies on overall function of a several active components, as all the phytochemicals they presented provide synergistic action thereby enhancing the therapeutic value. Each active phytochemical plays a crucial role, and they are all connected to each other.

However, majority of the herbal origin drugs are insoluble leading to a lower bioavailability and elevated systemic clearance, which requires repeated administration or a higher dose, making the drug to be less potent for therapeutic use. In phytochemical formulation studies, developing nano-dosage forms (polymeric nanoparticles [nanospheres and nanocapsules], proliposomes, liposomes, Nanoemulsion, etc.) has a great number of merit for plant extracts that are illustrated in Fig. 3.Thus, the nanoformulation of herbal drugs or plant extracts has a probable future for improving the activity and defeating problems related to plant extracts (Table 6).

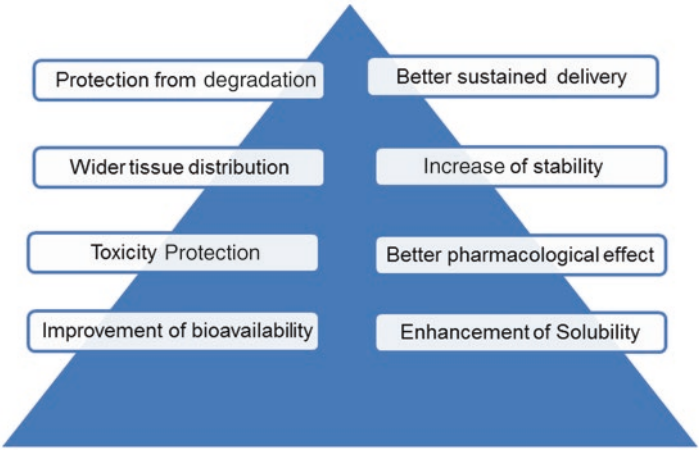


Fig. 3 Different advantages in nanoformulation with plant extract for better therapeutic use

7 General Encapsulation Processes

The process of entrapment of one substance (active agent) within another substance (wall materials) is called encapsulation, which can prepare nanospheres or nanocapsules as shown in Fig. 4 (Nedovic et al. 2011; Mora-Huertas et al. 2010). In addition, the active substance can be adsorbed on the surface of the nanoparticle (Miladi et al. 2016). Newly, the biodegradable particles are progressively prepared from the polymers that might be obtained from natural source, as gelatin, chitosan, albumin, etc. or polymers can be synthetic, like methacrylates and so on. In addition to the local therapeutic effects, drug molecule, genes, and vaccines can be delivered to the target organs by such particles (Jahanshahi 2008; Zafar et al. 2014). Polymer selection criteria are the toxicity and final application of the polymer. Indeed, polymers are used in regenerative medicines and tissue engineering as well. The used biodegradable polymers for drug encapsulation indicate excellent characteristics such as nontoxicity and stability in the blood circulation.

The physicochemical characteristics (e.g., zeta potential, hydrophobicity), drug release profile (e.g., triggered, delayed, prolonged), and biological behavior (e.g., enhanced cellular uptake, bioadhesion) modification of nanoparticles are obtained by the polymeric materials (Galindo-Rodriguez et al. 2005; Kumari et al. 2010; Rieux des et al. 2006). Poly(lactic acid), poly(glycolic acid), and poly(lactic-co-glycolic acid) (PLGA) are the common employed biodegradable polymers for the encapsulation of active ingredients. In fact, release profile of encapsulated drug within the nanoparticles is governed principally by the used polymer degradation kinetics, which consider as an advantage of biodegradable polymers. Drug molecules comprising paclitaxel, 9-nitrocamptothecin, cisplatin, insulin, dexamethasone, estradiol, progesterone, tamoxifen, tyrphostins, and haloperidol

Table 6 Examples of some very recent (2015–2017) encapsulation studies involving various plant extracts for better biological activity

Type of study	Support	Bioactive	% efficiency/loading dose	Advantages/benefit	References
Encapsulation of lycopene from plant extract	Alginate gelatin	Lycopene	79 ± 3% (in olive oil extract)	The stability against isomerization and release effect (diffusion coefficient) of lycopene was enhanced	Calvo et al. (2017)
Encapsulation of pantothenic acid	Liposome, alginate, or alginate-pectin mixture	Pantothenic acid	~80% loading in liposomes	The efficiency and stability at acidic pH (4.0) improved	Ota et al. (2018)
Synthesis and characterization of polyphenols extracted from fresh strawberry fruits	Polymer chitosan	Polyphenols	36% (loading)	Functional amino group is reported to enhance the loading of negatively charged polyphenols and improve bioavailability and sustained release	Pulicharla et al. (2016)
Microencapsulation of lutein, an extract from marigold flowers	Maltodextrin (polysaccharide base) and copovidone (polyvinyl pyrrolidone)	Lutein	95%	Improve the bioavailability, antioxidant ability, and stability	Nalawade and Gajjar (2016)
Tragacanth gum for peppermint encapsulation	Natural polysaccharide tragacanth gum	Peppermint	16.7%	The peppermint encapsulation showed better antimicrobial action over *C. albicans* than *S. aureus* and *E. coli*	Ghayempour et al. (2015)
Aloe vera extract encapsulation into natural polysaccharide tragacanth gum	Tragacanth gum	Aloe Vera	16.1%	*Aloe vera* extract reported as effective wound healer due to controlled release	Ghayempour et al. (2016)
Encapsulation of grape seed	Polylactide	Grape seed	38 wt% of proanthocyanidins extract	The proanthocyanidins are reported to enhance sustained release and dental matrix stability	Yourdkhani et al. (2017)
The encapsulation of bitter melon using spray-drying technology for antioxidant activity	Mixture of maltodextrin and arabic gum	Bitter melon	71.4 ± 1.4% (yield after spray drying powder)	The infusion of bitter melon has been reported to improve antioxidant performance of about ≥ 87.9 ± 2.6%	Tan et al. (2015)

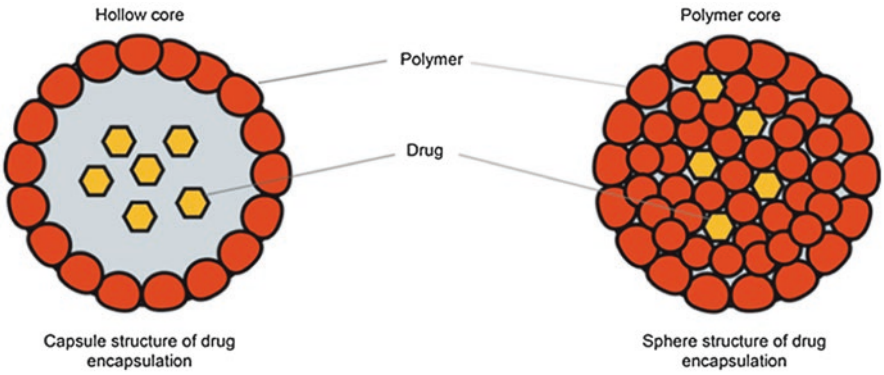


Fig. 4 Drug encapsulation structures in a depictive schema (Rivas et al. 2017)

have successfully encapsulated within different natural and synthetic polymers (Kumari et al. 2010).

Active molecule encapsulation techniques are classified into two main categories: (i) chemistry-related processes (polymerization of monomers) and (ii) physicochemical characteristic-based process (dispersion of preformed polymers). Preformed polymer methods comprise solvent evaporation, nanoprecipitation, solvent diffusion, and dialysis, while polymerization of monomers consists of processes like radical polymerization, miniemulsion, interfacial polymerization, and microemulsion (Armendáriz-Barragán et al. 2016). Such methods are used for the preparation of the various carriers such as microparticles, nanoparticles, and liposomes (Miladi et al. 2013).

The principles of encapsulation techniques or the active molecule nature that is to be encapsulated is the criterion, which differentiates these methods from each other. To design a formulation with proper characteristics for in vitro and in vivo uses, it is very crucial to select correctly the encapsulation method (Armendáriz-Barragán et al. 2016).

To obtain controlled release formulations in pharmaceutical industries, microencapsulation via solvent evaporation is frequently employed for which different methods are available to use. The choice of suitable encapsulation technique is based on the hydrophilicity and hydrophobicity characteristics of drug molecules (Mora-Huertas et al. 2010).To prepare particulate carriers, various polymers possessing different physicochemical properties are used. Generally, these polymers are biodegradable and biocompatible. Polymeric encapsulation is an approach to make drugs nontoxic, noninflammatory, and stable in blood.

Moreover, polymeric nanoparticles as a drug formulation have certain advantages as follows (Armendáriz-Barragán et al. 2016):

- Encapsulation of different chemicals having various properties within a formulation
- Drug molecule protection from environment, enzyme, etc. via encapsulation

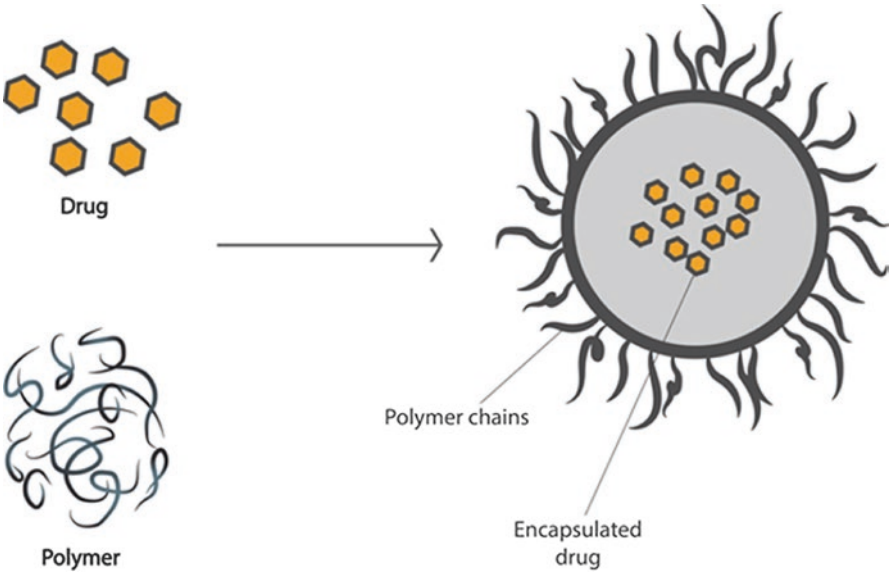


Fig. 5 Drug polymeric encapsulation schematic representation. (Adopted from Rivas et al. 2017)

- Organic solvent's easy elimination throughout the nanoparticles elaboration
- Encapsulated drug release profile control
- Particular tissue or organ targeting

As depicted in the Fig. 5, the coating of particles by substances, such as polyethylene glycol (PEG) that modulates their surface, can avoid particles uptake through macrophages (Zafar et al. 2014) (Table 7).

7.1 Nanoprecipitation

Nanoprecipitation, that is, likewise named solvent displacement or interfacial deposition, was firstly developed by Fessi et al. Nanoprecipitation is taken into account as an early developed active ingredient in encapsulation method, which was firstly employed (Fessi et al. 1989). Basically, the solvent phase can be provided by the dissolving of a film-forming substance such as a polymer, active ingredient, oil, lipophilic surfactant, and in case of need active ingredient solvent or oil solvent in a solvent or in a solvents mixture (Fig. 6). Furthermore, the non-solvent phase would be obtained from the film-forming substance non-solvent or a mixture of non-solvents, complemented with one or more naturally occurring or synthetic tensioactive (Mora-Huertas et al. 2010). In fact, nanoprecipitation method needs two miscible phases (Miladi et al. 2016). According to the study performed by Lince et al.

Table 7 List of reported polymeric nanoparticles/nanostructured (complex and precipitation) formulations using plant extract/bioactive molecules and their possible therapeutic use

Bioactive compounds/ plant extract	Particle size	Encapsulation efficiency	Possible therapeutic use	References
Euphorbia hirta L. with gold as nanocarrier	530 nm		Antibacterial and antifungal	Annamalai et al. (2013)
Silymarin from *Silybum marianum* with solid lipid formulation	22.91 μm		Antioxidant and hepatoprotectant	Pitsiree et al. (2013)
Argemone mexicana L. with iron oxide	10–30 nm		Diuretic and purgative	Arokiyaraj et al. (2013)
Indigofera aspalathoides Vahl with silver as carrier	45 and 69 nm		Hepatoprotective	Arunachalam et al. (2013)
Vincarosea from *Catharanthus roseus* Linn. G. Donn with silver as carrier	28 nm		Antimicrobial activity	Kotakadi et al. (2013)
Aloe from *Aloe* leaf extract with silver as carrier	15.2 ± 4.2 nm		Carcinogenic activity	Zhang et al. (2013a)
β-sitosterol from green tea extract with solid lipid formulation			Antioxidant activity	Lacatusu et al. (2012)
Safflower from *Carthamus tinctorius* with gold as carrier	40–200 nm			Nagaraj et al. (2012)
Ajwain and opium poppy seed from *Trachyspermum ammi and Papaver somniferum* with silver	3.2 and 7.6 μm		Antispasmodic	Vijayaraghavan et al. (2012)
English ivy from Hedera helix with nanoparticles formulation	60–85 nm		Antiaging	Burris et al. (2012)
Triptolide from *Tripterygium wilfordii* Hook F with nanoparticle formulation			Anti-inflammatory	Xue et al. (2012)
Ginger from *Zingiber officinale* rhizome with nanoparticle formulation	453.1–551.7 nm		Anti-inflammatory	Ratcharin and Indranupakorn (2012)

(continued)

Table 7 (continued)

Bioactive compounds/ plant extract	Particle size	Encapsulation efficiency	Possible therapeutic use	References
Tripterygium with nanoparticle formulation			Male reproductivetoxicity in rats	Xue et al. (2011)
Triptolide obtained from *Tripterygium wilfordii* Hook with poly(DL-lactic acid) as nanocarrier	149.7 nm	85.7%	Autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia, and antineoplastic	Liu et al. (2005)
Curcumin from the root of *Curcuma longa* with Methoxy poly(ethylene glycol)-palmitate as carrier	41.43 nm	100%	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation, and anti-inflammatory	Sahu et al. (2008)
Camptothecin from bark and stem of the oriental tree *Camptotheca acuminate* with glycol chitosan	280–330 nm	80%	Gastric, rectum, bladder, colon, lung, breast, and ovarian cancer	Min et al. (2008)
Hypericin from *Hypericum perforatum* with polylactic acid/ polylactic-co-glycolic acid as nanoparticles	200–300 nm	70%	Photosensitizer used in photochemotherapy	Labouebe et al. (2006)
Cuscuta chinensis (active constituents – flavonoids and lignans such as quercetin, kaempferol) obtained from *Cuscuta chinensis* Lam.	267 nm	90%	Used as tonic and to improve sexual function, prevent senescence, and regulate immune system. Also for anticancer, antiaging, and immunostimulatory effects	Yen et al. (2008)
Catechins (active constituents – (+)-catechin, (−)-epicatechin, (−)-epigallocatechin-3-gallate) from the *Camellia sinensis* with chitosan as nanoparticles	1.97–6.83 μm	27.9–40.12%	Chemopreventive, anticarcinogenic, antiviral, anti-oxidative, anti-obesity, anti-inflammatory, antidiabetic, antimutagenic, antiangiogenic, antibacterial, and antiaging activities	Zhang and Kosaraju (2007)

(continued)

Table 7 (continued)

Bioactive compounds/ plant extract	Particle size	Encapsulation efficiency	Possible therapeutic use	References
Plant extract of *Ziziphus mauritiana* with chitosan			Immunomodulatory activity	Bhatia et al. (2011)
Flavonoids and lignans from *Cuscuta chinensis*		90%	Hepatoprotective and antioxidant effect	Feng-Lin et al. (2008)
Triptolide			Anti-inflammatory	Zhinan et al. (2005)
Artemisinin		90–93%	Anticancer	Youfang et al. (2009)
R. salvia miltiorrhiza		96.68%	Coronary heart diseases, anginapectoris, and myocardial infarction	Su et al. (2008)
Taxel		99.44%	Anticancer	Fu et al. (2006)
Berberine		65.40 ± 0.70%	Anticancer	Lin et al. (2007)
Silibinin		95.64%	Hepatoprotective	Li et al. (2007b)
Tetrandrine		84%	Lung	Xiaoyan et al. (2008)
Glycyrrhizic acid		91.76%	Anti-inflammatory and antihypertensive	Hou and Zhou (2008)
Quercetin		over 99%	Antioxidant	Tzu-Hui et al. (2008)
Breviscapine		93.1%	Cardiovascular and cerebrovascular	Liu et al. (2008)
Zedoary turmeric oil		1.62 ± 0.15%	Hepatoprotection Anticancer and antibacterial	Lertsutthiwong et al. (2008)
Naringenin			Hepatoprotective	Feng-Lin et al. (2009)
Curcuminoids		70%	Anticancer and antioxidant	Mukerjee and Vishwanatha (2009)
Camptothecin		80%	Anticancer	Min et al. (2008)
Ginkgo biloba extract			Brain function activation	Shimada (2008)
Root extract of *Phytolacca decandra* with PLGA	25 gm/kg		Lung cancer	Das et al. (2012)
Leave extract of *Ocimum sanctum* with alginate chitosan			Antimicrobial	Rajendran et al. (2013)

(continued)

Table 7 (continued)

Bioactive compounds/ plant extract	Particle size	Encapsulation efficiency	Possible therapeutic use	References
Curcumin from *Curcuma longa*	50 nm		Pancreatic tumor cell	Bisht et al. (2007)
Curcumin-loaded polymeric nanoparticles	2–40 nm		Antibacterial activity	Basniwal et al. (2011)
Honokial from *Magnolia officinalis*			Anti-inflammatory, antithrombotic, antirheumatic, antioxidant, anxiolytic, CNS depressant, muscle relaxant, and antitumor activity	Zheng et al. (2010)
Coumarin from *Gelsemium sempervirens*			Antitumoral activity	Khuda-Bukhsh et al. (2010)
Ethanolic extract (flavonoids) of *Harungana madagascariensis* with PLG	1000 mg/ml		Antibacterial, antifungal, and antiviral	Moulari et al. (2005)
Ethyl acetate extract of *Harungana madagascariensis* with PLG	500 mg/ml		Dental caries and gingivitis due to bacteria	Moulari et al. (2006)
Quercetin with PVA		99%	Anti-inflammatory, antioxidant, and hepatoprotective	Wu et al. (2008)
Naringenin with PVA as carriers	100 mg/kg		Hepatoprotective in vivo	Yen et al. (2009)
Ethanolic extract of *Polygala senega* with PLGA			Anticancer	Paul et al. (2011)
Aq. extracts of *Plectranthus ecklonii*	1 mg/ml	About 100%	Antioxidant activity	Rijo et al. (2014)

particles within nanoprecipitation method formed throughout three steps of nucleation, growth, and aggregation (Lince et al. 2008).

Nanoprecipitation is almost restricted to the encapsulation of hydrophobic actives. However, a modified nanoprecipitation technique has been designed by Bilati et al. (2005), in order to encapsulate the hydrophilic drug molecules (Bilati et al. 2005). Biodegradable polyesters, principally poly-e-caprolactone (PCL), poly(lactide) (PLA), and poly(lactide-co-glicolide) (PLGA), are usually used as a polymer in nanoprecipitation method. In fact, greater purity and improved reproducibility can be provided by synthetic polymers in comparison with natural polymers

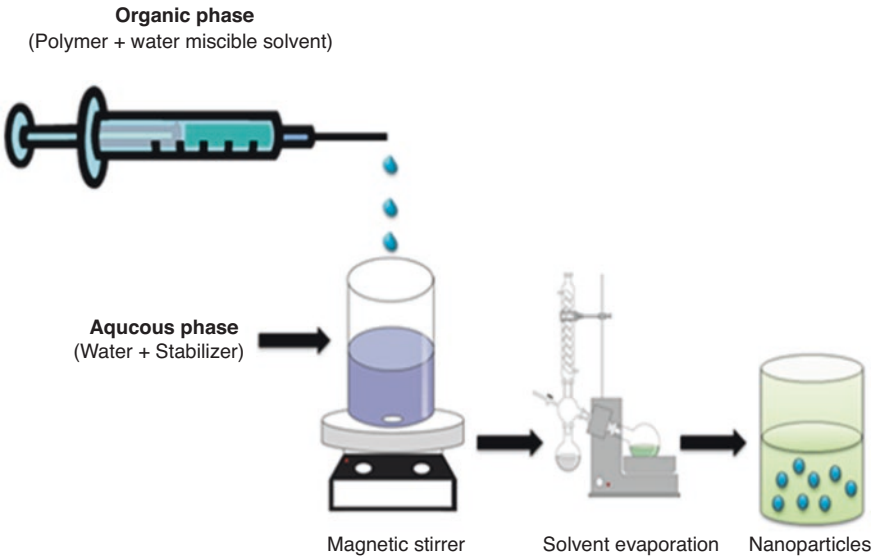


Fig. 6 Schematic representation of nanoprecipitation method. (Adopted from Badri et al. 2017)

(Khoee and Yaghoobian 2009; Mora-Huertas et al. 2010). Mostly, in this technique acetone is used as a polymer solvent. For the dissolution of active substance and oil, another solvent like ethanol is also employed. As non-solvent and stabilizer, water or buffer solutions and poloxamer 188 or polysorbate 80 are, respectively, used. Polymer's interfacial deposition after displacement of semipolar solvent miscible with water is the mechanism in which the nanoprecipitation method is based (Fessi et al. 1989). Nanoprecipitation due to its advantages that are cited in the Table 10 is a widely used method for the nanoparticle preparation (Miladi et al. 2016). The most commonly used administration route and targeted organs for obtained nanoparticles by nanoprecipitation method are shown in Fig. 7 (Table 8).

7.2 Emulsification Process

Generally, an emulsion is made up of at least two immiscible liquids where one acts as a dispersed phase and the other acts as a continuous phase, water in oil emulsion or oil in water emulsion. Emulsion can also be a multiphase water/oil/water or oil/water/oil. An emulsifier can also be used to stabilise the emulsion. The particle size of the emulsion depends on the type and amount of emulsifier used and the emulsification technique. Encapsulation efficiency depends on the particle size. During emulsification, the bioactive compound will be embedded in the continuous phase, and thus the active compound is protected from degradation and thermo-oxidation. The morphology of the encapsulated material depends on the dispersed phase, its distribution in the continuous phase, suspension viscosity, size of the droplets,

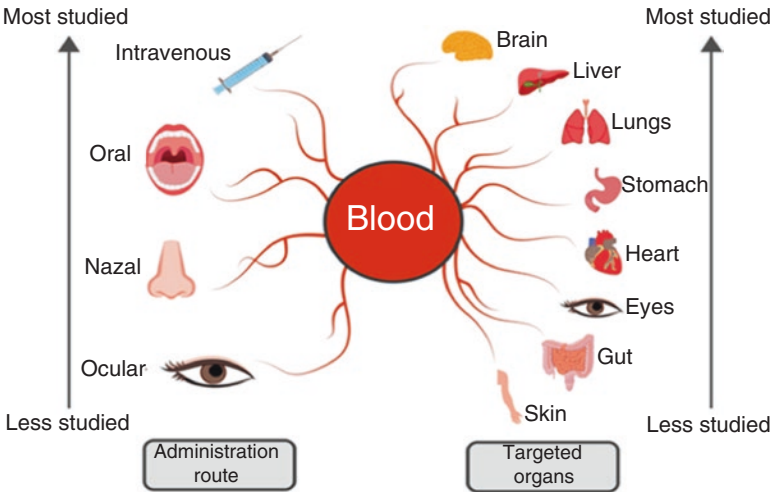


Fig. 7 The most common targeted organs and administration routes for nanoparticles designed by nanoprecipitation technique. (Adopted from Rivas et al. 2017)

processing conditions, etc. Colloidal dispersions with particle size less than 100 nm are called nanoemulsion.

For preparing nanoemulsion, small instrument like ultrasonicator, homogenizer usually used. Mohammadi et al. (2016) used nanoemulsion method to encapsulate olive leaves extract in soybean oil, and this nanoencapsulated olive oil extract exhibited better antioxidant activity. Ghayempour et al. (2016) used microemulsion technique to encapsulate *Aloe vera* extract in tragacanth gum and produced a natural wound healing product.

7.2.1 Emulsification: Solvent Evaporation

For the preparation of nanocapsules, an emulsion is first prepared by mixing the organic polymer solution with aqueous phase. An organic solution of the polymer is mixed with bioactive oil in a non-solvent to form a suspension. Then the solvent is evaporated, and nanocapsules are formed by entrapping the active component inside the polymer matrix. Solvent evaporation is an easy and commonly used method.

Yourdkhani et al. (2017) used a combination of double emulsion and solvent evaporation technique to encapsulate grape seed extract in polylactide and produced polynuclear microcapsules with an average diameter of 1.38 μm and loading efficiency of 38% weight. Microencapsulation resulted in the preservation of the bioactivity of the extract. Pink pepper is an important medicinal plant which possesses antitumor activity, anti-inflammatory property, and antioxidant property. Andrade et al. (2017) encapsulated pink pepper extract in polylactic acid by emulsification and subsequent solvent extraction (Table 9).

Table 8 List of reported microsphere-encapsulated (nanoprecipitation) formulations using plant extract/bioactive molecules and their possible therapeutic use

Bioactive compounds/ plant extract	Benefit in application	Route of admiration	Size	Possible therapeutic use	References
Jaboticaba	Applied in food	In vitro	Uniform with few wrinkles and smooth surfaces	Antioxidant activity	Silva et al. (2013)
Locust bean gum	Applied as thickening and gelling agent in food technology	Oral	734.18–293.17 μm	Hypocholesterolemic activity	Kaity et al. (2013)
Soy protein isolate	Applied as a good gelling, emulsifying, fat-absorbing, and water-binding agent	In vitro	5.5–9.3 μm	Estrogen beta-agonist (decreases serum testosterone levels inhealthy men)	Nesterenko et al. (2012)
Rosemary extract	Value addition in noninvasive drug delivery systems	In vitro	254.5 nm	Antiproliferative	Yesil-Celiktas and Cetin-Uyanikgil (2012)
Rutin	Applied for standardization of Chinese traditional medicines	In vitro	Small and uniform	Antioxidant activities	Zeng et al. (2012)
Chelerythrine	Enhance delivery of drug to a tumor organ	In vitro	12.18 μm	Antimicrobial, anti-inflammatory, antitumor, and antiplaque effect	Li et al. (2011d)
Thymol, clove, origanum, and camphor white oil	Applied for use in pest control	In vitro	5 μm to over 300 μm	Larvicidal activity	Glenn et al. (2010)
Rutin	Cerebrovascular region and cardiocascular targeting	In vitro	165–195 μm	Cerebrovascular and cardiovascular	Xiao et al. (2008a)
Zedoary oil	Sustained release and higher bioavailability	Oral	100–600 μm	Hepatoprotective	You et al. (2006)
Camptothecin	Prolonged release of camptothecin	Intraperitoneally andintravenously	10 μm	Anticancer	Machida et al. (2000)
Quercetin	Significantly decreases the dose size	In vitro	6 μm	Anticancer	Chao et al. (2010)
Cynara scolymus extract	Controlled release of neutraceuticals	Oral	6–7 μm	Nutritional supplement	Gavini et al. (2005)

Table 9 List of reported emulsion (solvent evaporation and solvent extraction method) encapsulated formulations using plant extract/bioactive molecules and their possible therapeutic use

Bioactive compounds	Benefit in application	Route of administration	Size	Possible therapeutic use	References
Triptolide	Enhance the penetration of drugs through the stratum corneum by increased hydration	Topical	Less than 100 nm	Anti-inflammatory	Zhinan et al. (2003)
Zedoary turmeric oil	Improved aqueous dispersibility, stability, and oral bioavailability	Oral	68.3 ±1.6 nm	Hepatoprotection, anticancer, and antibacterial	Zhao et al. (2010)
Docetaxel	Improve residence time	Intravenous	166 nm	Anticancer high pressure	Li et al. (2007a)
Berberine	Improve residence time and absorption	Oral	56.80 nm	Anticancer	Sun and Ouyang (2007)
Silybin	Sustained release formulation	Intramuscular	21.20 nm	Hepatoprotective	Song et al. (2005)
Quercetin	Enhance penetration into the *stratum corneum* and epidermis	Topical	10–100 nm	Antioxidant	Fabiana et al. (2008)
Triptolide from *Tripterygium wilfordii* Hook F	Reduction in toxicity of triptolide following transdermal delivery		18–20 nm	Used in treatment of autoimmune diseases, especially rheumatoid arthritis, psoriasis, leukemia, and antineoplastic activity	Chen et al. (2004)
Furocoumarin (psoralen) from seed of *Psoralea corylifolia*	Enhanced anti-inflammatory effects			Treatment of skin diseases characterized by hyperproliferation such as psoriasis	Ali et al. (2008)
Curcumin isolated from root of *Curcuma longa*	Enhanced anti-inflammatory effects		61.8–79.5 nm	Antitumor, antioxidant, anti amyloid, antiplatelet aggregation, and anti-inflammatory	Wang et al. (2008a)

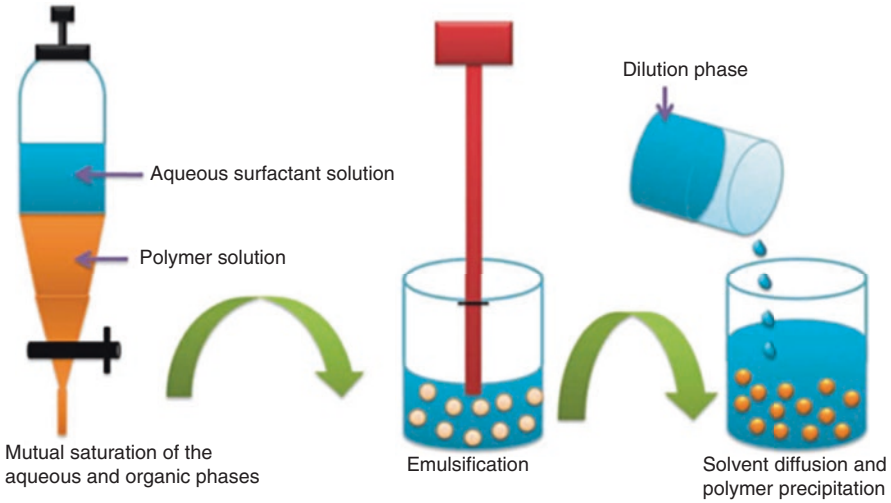


Fig. 8 Illustration of emulsion solvent diffusion method setup. (Adopted from Armendáriz-Barragán et al. 2016)

7.2.2 Emulsion-Diffusion Method

Quintanar-Guerrero and Fessi (Quintanar-Guerrero et al. 1996) for the first time developed the emulsion-diffusion method in order to prepare polylactide (PLA) nanoparticles. Both lipophilic and hydrophilic active ingredients can be nanoencapsulated by the emulsion-diffusion technique. However, emulsion-diffusion method is mainly used for the encapsulation of hydrophobic drug molecules. In emulsion-diffusion method three liquid phases, namely, organic phase, aqueous phase, and dilution phase, are required (Miladi et al. 2014). The organic, aqueous, and dilution phases might be achieved via preforming the experimental procedure. The organic phase including polymer, active ingredient, oil, and an organic solvent (partially miscible with water) has to be water-saturated, while a lipophilic active molecule is intended to be nanoencapsulated (Mora-Huertas et al. 2010). The size of the prepared particles in emulsion-diffusion method can be affected by the operating conditions such as rate of emulsification stirring, diluting water temperature and volume, concentration of polymer, and stabilizer amount and ratio of phase (Quintanar-Guerrero et al. 1996; Mora-Huertas et al. 2010). Based on the study taken place on the homogenization and sonication effect on the size of the particles, sonication is more crucial than homogenization to the particles size (Miladi et al. 2014) (Fig. 8).

For various components in this method, organic phase plays the role of solvent. In case of need, it is also possible that active ingredient solvent or oil solvent be included in the organic phase. Usually, the dilution phase is a large volume of water, while the aqueous phase forms from the stabilizing agent aqueous dispersion, which is obtained employing solvent-saturated water. Eudragit®, PCL, and PLA are the polymers, which are usually used in this technique (Mora-Huertas et al. 2010).

7.2.3 Emulsification-Ionic Gelation

Emulsification-ionic gelation can be applied in charged polymers like chitosan and alginate. In this method, charged polymer chain interacts with oppositely charged medium to form particles. The charged medium acts as a cross-linking agent. Lertsutthiwong et al. (2008) encapsulated turmeric oil by this method. Turmeric oil is emulsified in sodium alginate aqueous solution and then subjected to gelification with chitosan and calcium chloride and subsequent solvent evaporation

7.2.4 Double Emulsion Method

Double emulsion (DE) complex systems are named emulsion of emulsion as well (Garti and Bisperink 1998). Commonly double emulsions are classified into two groups of water-oil-water (w/o/w) and oil-water-oil (o/w/o). Usually double emulsions are prepared in two-step process; the size of droplets is mostly polydispersed in double emulsion. Double emulsion technique includes aqueous phase dispersion into a nonmiscible organic solvent (in the presence of short-time low-power sonication or high-shear homogenization) to obtain the first emulsion (W1/O). Once prepared emulsion is dispersed in a second aqueous phase that includes hydrophilic emulsifier, then homogenization or sonication step is conducted (Fig. 9). This step of homogenization can be repeated under the same condition. To avoid the first emulsion breaking in case if sonication is used, it should be carried out in short time and at low power. The volatile organic solvent evaporation at ambient temperature or under low pressure (via rotary evaporator) after the multiple emulsion formation permits the reparation colloidal dispersion or particulate carrier (Giri et al. 2013). In fact, small droplets of double emulsion are containing one or few droplets, while sometimes droplets are too large that each drop encompasses certain small

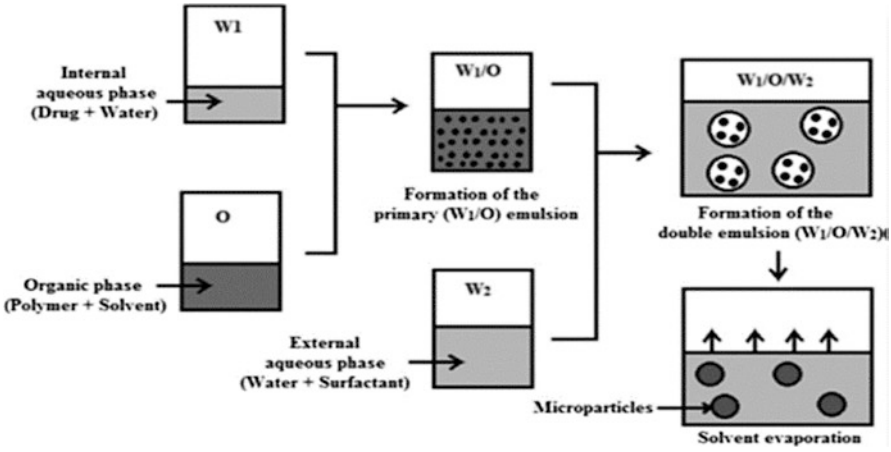


Fig. 9 Double emulsion solvent evaporation method schemes. (Adopted from Giri et al. 2013)

compartments with 50–100 droplets (Garti and Bisperink 1998; Schuch et al. 2013). Double emulsion is an appropriate method to encapsulate the hydrophilic drug molecules (Miladi et al. 2014). Prepared carrier stability and release profile are possible to be significantly enhanced via alteration of used stabilizer type and amount within the system. Cancer can be efficiently treated thanks to the targeted drug delivery and prolonged drug release, which are associated with the usage of double emulsion systems. Indeed, double emulsions possess numerous advantages such as biocompatibility, biodegradability, and versatility.

In addition, the encapsulation and protection of both hydrophobic and hydrophilic types of actives molecules can be take place by double emulsion method. Nevertheless, multiple emulsions are encountered several challenges such as vulnerability to physical and chemical degradation, formulation trouble, and bulky. To tackle the stability problems of multiple emulsions, various efforts (e.g., surfactant amount variation, polymerization gelling, steric stabilization, pro-emulsion, addition of excipients, and interfacial complexation) were made (Garti 1997; Garti and Aserin 1996; Hino et al. 2000). In order to improve the efficacy of cosmetics, through double emulsion, incompatible substances may combine within the same formulation. The disadvantages of double emulsion method are, namely, process complexity, thermodynamic instability, and production of comparatively heterogeneous and size-sensitive (sensitive to different double emulsion method-related parameter) nanoparticles. In comparison with other encapsulation methods, commonly double emulsion provides polydisperse particles. Usually, main advantages and disadvantages of drug encapsulation methods are shown (Table 10). Encapsulation of both hydrophilic and lipophilic active ingredients is the unique advantage of double emulsion method. The characteristics of nanoparticles provided by double emulsion technique can be influenced by parameters as speed of evaporation (khoee et al. 2012), external phase composition (Péan et al. 1998; Tse et al. 2009), relative ratio of phases (Khoee et al. 2012), polymer concentration, nature and molecular weight (Zambaux et al. 1998; Péan et al. 1998; Van de Ven et al. 2011), surfactants nature and amount (Zhao et al. 2007; Khoee and Yaghoobian 2009; Dhanaraju et al. 2004), and speed of homogenization (Eley and Mathew 2007; Basarkar et al. 2007).

Furthermore, encapsulation efficiency could be considerably influenced by operating condition as well (Billon et al. 2005). Nanoprecipitation, emulsion-diffusion technique, microemulsion, phase inversion temperature technique, and high-pressure homogenization are the techniques, which do not need the use of organic solvents or toxic solvents for the encapsulation of drug molecules (Iqbal et al. 2015).

7.2.5 Liposomes

Liposomes are defined as the systems made by one or several phospholipid bilayers describing one or several aqueous compartments (core) (Gulati et al. 1998; Walde and Ichikawa 2001). Cholesterol and phospholipids are the principal constituents of liposomes. Liposomes that are spherical-shaped vesicles could be categorized in

Table 10 Advantages and drawbacks of different encapsulation methods

Methods	Advantages	Disadvantages	References
Nanoprecipitation	No need for high-shear stress Monodispersed particle preparation Fast and simple Does not require highly toxic solvent High reproducibility Easy to scale-up	Prepared nanoparticle size is mainly related to the polymer concentration Commonly, restricted to the encapsulation of hydrophobicdrug molecules	Katara and Majumdar (2013), Siqueira-Moura et al. (2013), Han et al. (2013), Seremeta et al. (2013), Miladi et al. (2016)
Double emulsion method	Encapsulation of both hydrophobic and hydrophilic drug molecules	Long process (two steps) Hard to scale-up Preparation of polydispersed particles Hydrophilic drug molecule leakage into external aqueous phase	Ibraheem et al. (2013), Bitar et al. (2015), Zakeri-Milani et al. (2013)
Emulsion-diffusion method	Easy to scale-up Good reproducibility Nontoxic solvents usage Narrow particles size distribution and mean particle size reduction Thermosensitive drug incorporation Lipophilic drugs high entrapment	To prepare nanoparticles, larger volume of water is required Hydrophilic drugs poor encapsulation Final formulation ingredients concentration is needed Final formulation may contain organic solvent residues Need long emulsion agitation	Campos et al. (2013), Hao et al. (2013), Souguir et al. (2013)

multivesicular, multilamellar, oligolamellar, and unilamellar classes (Fig. 10) (Zhai and Zhai 2014).

Liposomes are broadly employed such as carrier for hydrophobic and hydrophilic drug molecules (Yoshida et al. 2010; Detoni et al. 2012). Liposomes as a nonimmunogenic, nontoxic, biocompatible, and biodegradable drug carriers have certain advantages including drug biodistribution and pharmacokinetic improvement, toxicity reduction, and specific target drug delivery design (Drulis-Kawa and Dorotkiewicz-Jach 2010; Voinea and Simionescu 2002). Thanks to the liposomes structure, they can encapsulate hydrophobic, hydrophilic, and amphiphilic active ingredients (Fig. 11) (Yoshida et al. 2010).

Usually plant extracts are susceptible to oxygen, heat, and light degradation, which have restricted their usage in medicine. Liposomes as an attractive encapsulation approach can overcome the challenges that encountered plant extracts like low water solubility-associated decreased bioavailability, problems of stability (volatility and oxygen, light, temperature sensibility), and toxicity (Detoni et al. 2012). In addition, liposomes can improve tissue targeting and enhance the biological activity

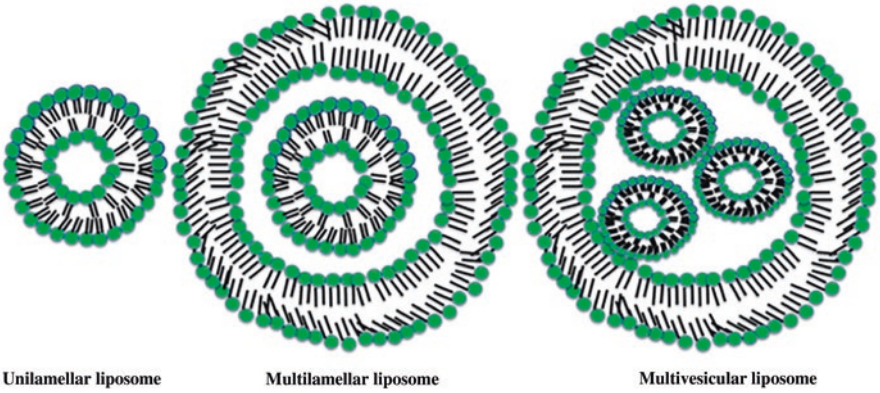


Fig. 10 Types of liposomes. (Adopted from Badri et al. 2016)

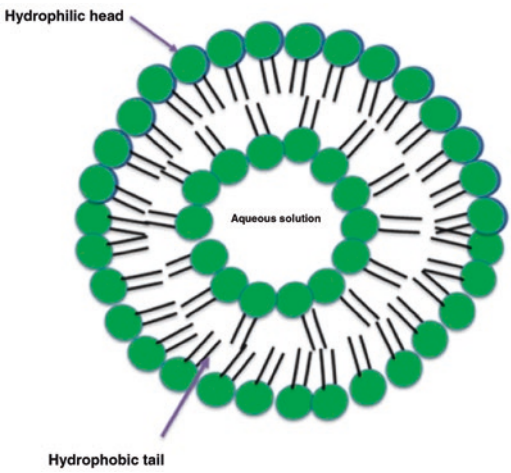


Fig. 11 The structure of liposome. (Adopted from Badri et al. 2016)

of plant extracts due to the modification of plant extract physicochemical property modification. To encapsulate plant extracts, various techniques have been employed (Detoni et al. 2012; Asbahani et al. 2015) and presented in Table 11.

7.2.6 Niosomes

Niosomes are microscopic vesicles that are composed from admixture of cholesterol and alkyl or dialkyl polyglycerol ether class of nonionic surfactants, which are successively hydrated in the aqueous media. The nonionic surfactant as Span 60 is used as vesicles forming amphiphile in noisome. For the aim of stabilization, cholesterol and small quantity of anionic surfactant like dicetyl phosphate are commonly added (Makeshwar and Wasankar 2013; Buckton 2000). Niosome's main

Table 11 List of reported liposomal formulations using plant extract/bioactive molecules with their possible therapeutic use

Bioactive compounds/plant extract	Benefit in formulations	Route of admiration	Encapsulation efficiency	Possible therapeutic use	References
Silymarin	Hepatic targeting capability for delivering silymarin to the liver	Parenteral administration	60%	Antioxidant activity	El-Mowafy et al. (2013)
Quercetin	Used to treat UVB-irradiation	Topically	80.41 ± 4.22%	Antioxidant activity	Liu et al. (2013)
Actein	To prevent and treat breast cancer	in vitro		Anticancer activity	Einbond et al. (2013)
Artemisia princeps Pampanini	Enhanced transdermal delivery	in vitro	51.96 ± 0.01	Anti-infective anti-inflammatory	Yang et al. (2013)
Persicae Semen and Carthami Flos	The bioavailability of iron, manganese, and zinc was significantly improved	in vitro	Well encapsulated	Immunosuppressive and chemotherapeutic activity	Zheng et al. (2013)
Propolis	Immunological activity of propolis flavonoids enhanced with liposome encapsulation	in vitro	Well encapsulated	Anti-inflammatory, anti-oxidative, hepatoprotective	Yuan et al. (2012)
TOH, GTE, epicatechin (EC), and catechin (C)	Protect oxidation through enhancement of the activity for endogenous antioxidants	in vitro	Well encapsulated	Antioxidant	Yin et al. (2012)
Fisetin	Suitable for in vivo administration	in vitro	73%	Antioxidant, anticarcinogenic, antiangiogenesis	Mignet et al. (2012)
Berberine and palmatine	Proton delivery to model lipid membranes as well as in isolated mitochondria	in vitro	Well encapsulated	Antioxidants rotary evaporation	Pustovidko et al. (2012)
Ginseng	Effectively suppress the depolarization of mitochondrial membrane	in vitro	234.1 ± 13.9%	Antioxidant activity	Tsai et al. (2012)
Ammonium glycyrrhizinate	Improve the drug anti-inflammatory activity in mice	Subcutaneously	28.8%	Anti-inflammatory	Marianecci et al. (2012)
Radix Salviae Miltiorrh.	Standardization of traditional Chinese medicines	Orally		Immunoreactivity	Chen et al. (2012)

(continued)

Table 11 (continued)

Bioactive compounds/plant extract	Benefit in formulations	Route of admiration	Encapsulation efficiency	Possible therapeutic use	References
Resveratrol	Protect the dopaminergic neurons in Parkinson's disease rats	Intragastrically	73.54%	Antioxidant	Wang et al. (2011)
α-Tocopherol and ascorbic acid	Orange juice-mixed liposomal formulation exhibited stable microbiological results	in vitro	99%	Antioxidant	Marsanasco et al. (2011)
Carotenoid	Successful delivery of highly lipophilic enzymatic substrate in aqueous media	in vitro	Well entrapped	Antioxidant	Nacke and Schrader (2011)
Phenolic compounds	Liposome formulation fails topical delivery of antioxidant phenolic compounds	Topical	33.03 ± 3.84%	Antioxidant	González-Paredes et al. (2011)
Quercetin	Reduced dose, enhance penetration in blood-brain barrier	Intranasal	60%	Antioxidant, anticancer	Aroonsri et al. (2008)
Silymarin	Improve bioavailability	Buccal	69.22 ± 0.6%	Hepatoprotective	El-Samaligy et al. (2006a)
Artemisia arborescens essential oil	Targeting of essential oils to cells, enhance penetration into cytoplasmatic barrier	in vitro	60–74%	Antiviral	Chiara et al. (2005)
Ampelopsin	Increase efficiency	in vitro	62.30%	Anticancer	He et al. (2008)
Paclitaxel	High entrapment efficiency and PH sensitive	in vitro	94%	Anticancer	Rane and Prabhakar (2009)
Curcumin	Long circulating with high entrapment efficiency	in vitro	88.27 ± 2.16%	Anticancer	Hong et al. (2008)
Garlicin	Increase efficiency		90.77%	Lungs	Sun et al. (2009)
Quercetin and rutin	Binding of flavonoids with Hb is enhanced	in vitro		Hemoglobin	Juqun and Rong (2007)

Usnea	Increase solubility and localization with prolonged releaseprofile	in vitro	99.5%	Antimycobacterial	Lira et al. (2009)
Wogonin	Sustained release effect	in vivo	81.20 ± 4.20%	Anticancer	Ke et al. (2007)
Colchicine	Enhance skin accumulation, prolong drug release andimprove site specificity	Topical	66.3 ± 2.2%	Antigout	Godin and Touitou (2004)
Catechins	Increased permeation through the skin	Transdermal	93.0 ± 0.1%	Antioxidant and chemopreventive	Fang et al. (2006)
Breviscapine	Sustained delivery of breviscapine	Intramuscular	87.9 ± 3.1%	Cardiovascular	Zhong et al. (2005)
Curcumin	Photoaging attenuation (demonstration in mice)	Oral		Antioxidant, Anti-inflammatory,	Agrawal and Kaur (2010)
Resveratrol	Improvement of the cellular oxidative stress via rapid and potent cellular internalization	in vitro	>70%	Antioxidant Photo-protector	Kristl et al. (2009)
Resveratrol	Nano-sized vesicles, inclusion of resveratrol retarded drug release in vitro	In vitro and in vivo Intraperitoneal injection	≈70%	Cardiovascular protector	Hung et al. (2006)
Quercetin	Reduced anxiety and cognitive functions, dose administered decrease, increase in circulation time, vectorization, increase in brain penetration efficiency	Nasal	60%	Antioxidant, anticancer	Tong-Un et al. (2010)
Quercetin	Biodisponibility increased, vectorization, hepatic membrane penetration efficiency greatly improved	Transdermic		Hepatoprotector	Mandal and Das (2005)
Myrtle (*Myrtuscommunis*) extract	Antioxidant and antimicrobial activities superior to free forms	in vitro		Antioxidant, antimicrobial	Gortzi et al. (2008)

(continued)

Table 11 (continued)

Bioactive compounds/plant extract	Benefit in formulations	Route of admiration	Encapsulation efficiency	Possible therapeutic use	References
Catechin, (-)-epicatechin and EGCG	Liposomes may influence drug deposition in tumor tissues	Topical application and intratumoral		Antioxidant, anticancer	Fang et al. (2005)
Curcumin isolated from the root of *Curcuma longa*	Improved intravenous delivery of curcumin to tissue macrophages			Antitumor, antioxidant, antiplatelet, and aggregation	Sou et al. (2008)
Silymarin (silybin, taxifolin, isosilybin, silydianin, silychristin) obtained from fruits of *Silybum marianum*	Improved permeation and stability of silymarin		70%	Hepatoprotective agent	El-Samaligy et al. (2006b)
Lectin from seeds of *Cratylia Mollis*	Production of immunoglobulins in human and causes antibacterial			Immunostimulatory action	Andrade et al. (2004)
Camptothecin isolated from *Camptotheca acuminate* Decne	Overcome insolubility and stability	IV		Antitumor	Watanabe et al. (2008)
Essential oil from *Artemisia arborescens*	Effective to treat against HSV-1 and HSV-2	tropically		Antiviral	Sinico et al. (2005)
Triptolide from *Tripterygium wilfordii* Hook	Improve permeation	in vitro		Anti-inflammatory, immunosuppressive, and antifertility	Mei et al. (2003)
Extracts from fruit of *Syagrus romanzoffiana*	Improve permeation	in vitro		Antioxidant	Mezadri (2010)

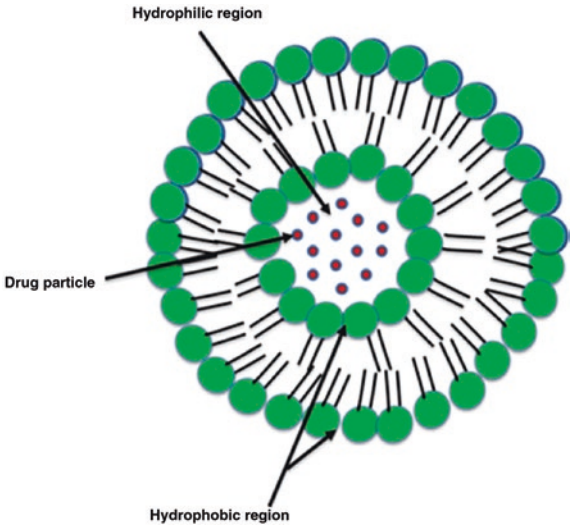


Fig. 12 Niosome structure

components are non-ionic surfactant, cholesterol, and charged molecules. Niosomes are classified based on their size into three groups of (a) small unilamellar vesicles (SUV) with a size range of 0.025–0.05 μm, (b) multilamellar vesicles (MLV) with a size of larger than 0.05 μm, and (c) large unilamellar vesicles (LUV) with a size of larger than 0.10 μm (Makeshwar and Wasankar 2013; Moghassemi and Hadjizadeh 2014).

Comparison of Liposomes with Niosomes

1. Liposome's ingredients such as phospholipids are not stable due to degradation associated with oxidative predisposition; natural phospholipids are different in terms of purity grade. Liposome's storage and handling need special care and conditions; meanwhile liposomes are expensive.
2. The properties of liposomes and niosomes are different, since double-chain phospholipids (charged or neutral) are used for the preparation of liposomes, while cholesterol and uncharged single-chain surfactants are employed for the preparation of niosomes (Moghassemi and Hadjizadeh 2014) (Fig. 12).

Niosomes Preparation

According to the wanted double-layer number, sizes, and size distribution of niosomes, vesicle membrane permeability, and aqueous phase entrapment efficiency, niosomes can be obtained through different techniques. Thus, sonication and microfluidization methods are used for the preparation of small unilamellar vesicles, while handshaking technique (thin-film hydration method) and transmembrane pH

gradient (inside acidic) drug uptake process (remote loading) are employed for the preparation of multilamellar vesicles. In addition, large unilamellar vesicles are prepared by reverse phase evaporation method (REV) and ether injection technique. Factors such as resistance to osmotic stress, structure, nature, type, and amount of surfactant, composition of membrane, hydration temperature, niosomes preparation technique, and encapsulated drug molecule nature affect the physicochemical properties of niosomes (Moghassemi and Hadjizadeh 2014).

7.2.7 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are developed in 1990, which were taken into account as the most outstanding lipid-based carriers. SLNs have certain advantages such as scale-up and sterilization feasibility, low toxicity, and good biocompatibility (Ram et al. 2012; Dolatabadi et al. 2014). Indeed, to prepare SLNs, solid lipid components (physiologically tolerated) are used. In addition to the protection of drugs within SLNs, nanoparticle's solid matrix may adjust drug release behavior as well (Pallerla and Prabhakar 2013). SLNs were the promising transdermal drug delivery system in the promptly progressive era of nanotechnology due to their structural similarity with lipids of skin epidermis layer. SLNs since several previous years are used in cosmetics (Müller et al. 2002; Wissing et al. 2004). Based on the report, SLNs as the occlusive can prevent skin water loss that consequently boosts skin moisturization. Moreover, according to the previously performed claim, UV absorbance into the skin would be enhanced through the SLNs, which is too important from the cosmetics industry point of view.

However, SLNs are not utilized within the commercialized sunscreen products until now that is most probably attributed to the SLNs pretty complex manufacturing processes, like high-pressure and high-temperature homogenization (Fang et al. 2008). The prospect is limited because of the UV sunscreen low loading in SLN final colloidal systems (Zhai and Zhai 2014). SLNs thanks to their advantages including drug release rate well control and sterilization feasibility have a constant role in the local drug delivery. SLN properties such as small size and fine size distribution make easy the penetration of drug into deeper regions of the skin (Uner and Yener 2007). Table 12 represents the different examples of different plant extracts used as solid lipid nanoparticles (Fig. 13).

7.2.8 Coacervation

There are two types of coacervation methods, simple coacervation in which one type of polymer only used and complex coacervations in which two types of polymers are used. In simple coacervation, a poor solvent is added to a colloidal solution, and two phases are formed, one rich in colloidal particles and the other colloid-free solution phase. For encapsulating the plant extract, the active

Table 12 List of reported phytosomal (solid lipid nanoparticles) formulations using plant extract/bioactive molecules and their possible therapeutic use

Bioactive compounds/plant extract	Benefit in application	Route of administration	Dose	Possible therapeutic use	References
Bacopa	Enhance the antiamnesic activity	Oral	40 mg/kg	Antiamnesic	Habbu et al. (2013)
Curcumin	Used as a sustained delivery system	Oral	100 mg/kg	Antioxidant, anti-inflammatory, antimicrobial, anti-amyloid, and antitumor activities	Zhang et al. (2013b)
Rutin	Solubility enhancement of poorly soluble rutin	in vitro		Antioxidant	Singh et al. (2012)
Trichosanthes cucumerina and *Abrus precatorius* aqueous extract	Hair growth promoters	Topical	2%	Hair growth promoter	Sandhya et al. (2012)
Catechin	Systemic absorption	in vitro		Anti-inflammatory, antioxidant, antitumour, and hepatoprotective	Semalty et al. (2012)
Gallic acid	Effective against carbon tetrachloride induced liver and kidney damage	Oral	45 mg/kg	Antibacterial, antiviral, analgesic, and anti-apoptotic activities	Shyam et al. (2012)
Quercetin, kaempferol, and isorhamnetin	Bioavailability enhancement	Oral	20.3 mg/kg	Antioxidant phospholipid complexation	Chen et al. (2010b)
Flavonoids	Flavonoids of GBP stabilize the ROS	Subcutaneous	100/200 mg/kg	Cardioprotective, antioxidant activity	Panda and Naik (2008)
Flavonoids	Inhibits lipid peroxidation (LPO), stabilize the ROS	Oral	25/50 mg/kg	Hepatoprotective, antioxidant	Naik and Panda (2008)
Flavonoids	Absorption of silybin phytosome® from silybin is approximately seven times greater	Oral	120 mg	Hepatoprotective, antioxidant	Yanyu et al. (2006)
Ginsenosides	Increase absorption nutraceutical	Oral	150 mg	Immunomodulator	Bhattacharya (2009)

(continued)

Table 12 (continued)

Bioactive compounds/plant extract	Benefit in application	Route of admiration	Dose	Possible therapeutic use	References
Epigallocatechin	Increase absorption systemic	Oral	50–100 mg	Antioxidant, anticancer	Bhattacharya (2009)
Procyanidins	A controlled elevation in the blood total radical trapping antioxidant parameter were observed	Oral	50–100 mg	Systemic antioxidant, cardioprotective	Bhattacharya (2009)
Flavonoids	To enhance the absorption rate	Oral	100 mg	Cardioprotective and antihypertensive	Bhattacharya (2009)
Quercetin	Used to get better therapeutic effect	Oral		Antioxidant, anticancer	Maiti et al. (2005)
Curcumin	Increases the bioavailability by showing antioxidant activity	Oral	360 mg/kg	Antioxidant, anticancer	Maiti et al. (2007)
Naringenin	Prolonged duration of action	Oral	100 mg/kg	Antioxidant	Maiti et al. (2006)
Flavonoids	Stabilize the ROS cardioprotective	Subcutaneous	100/200 mg/kg	Antioxidant activity	Vandana and Suresh (2008)
Flavonoids	Inhibits lipid peroxidation (LPO), stabilize the ROS	Oral	25/50 mg/kg	Hepatoprotective, antioxidant	Suresh and Vandana (2008)
Flavonoids	Absorption of silybin phytosome from silybin is approximately seven times greater	Oral	120 mg	Hepatoprotective, antioxidant for the liver and skin	Yanyu et al. (2006)
Curcuminoids	Enhanced stability of curcuminoids			Antitumor, antioxidant, antiamylodin, antiplatelet aggregation, and anti-inflammatory	Tiyaboonchai et al. (2007)
Tetrandrine	Enhanced solubility and encapsulation of tetrandrine			Anti-inflammatory, antiplatelet aggregation, and free radical scavenging activity	Li et al. (2006b)

Triptolide	Enhanced anti-inflammatory and transdermal delivery of triptolide			Used in autoimmune diseases, rheumatoid arthritis, psoriasis, leukemia and antineoplastic	Mei et al. (2003)
Podophyllotoxin (active constituent podophyllin	Reduction of adverse effects of podophyllotoxin			Antivirus in the treatment of warts through topical application and anticancer activity	Chen et al. (2006)
Cryptotanshinone	Enhancement of bioavailability of cryptotanshinone			Anti-inflammatory, cytotoxic, antibacterial, antiparasitic, anti-angiogenic, and anti-oxidative	Hu et al. (2010)
Quercetin	Enhancement of bioavailability more than five times greater	in vitro		Antioxidant, anticancer	Li et al. (2009)
Quercetin	Promote permeation in the epidermis and dermis	in vitro		Antioxidant and anti-inflammatory	Guo et al. (2012)
Curcumin	Improve bioavailability and prolonged drug release	in vitro	1, 12.5, 25, and 50 mg/kg	Antioxidant, anticancer	Kakkar et al. (2011)

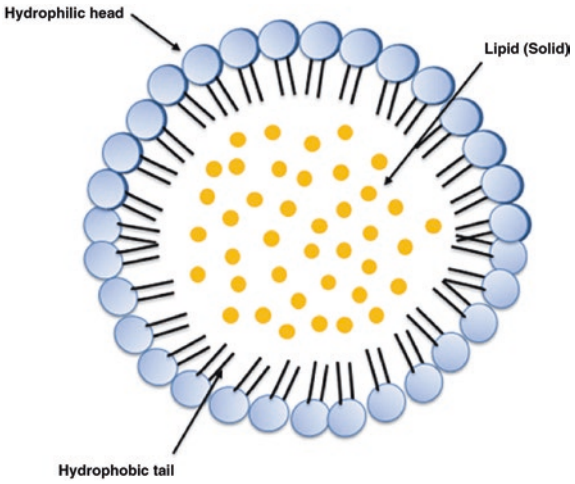


Fig. 13 Solid lipid nanoparticle schematic representation. (Adopted from Badri et al. 2016)

component is dispersed in a polymer solution, and a desolvation agent is added for phase separation. Polymer coating is deposited on the active fluidized-bed drying or component and is stabilized and hardened. The obtained microcapsules can be dried by spray drying. These microcapsules possess more than 50% encapsulation efficiency. The drawback of this technique is that they are stable only in a narrow range of pH and temperature.

In complex coacervation, complexation occurs between two oppositely charged polymers. At first, the active material (oil) is dispersed in to a polymer solution (cationic, e.g., gelatin); a second anionic polymer solution (Arabic gum) is then added to form dispersion. The two oppositely charged polymers undergo complexation and deposition of shell on the active material occurs. Prepared microcapsules can be stabilized by thermal treatment, desolvation, or chemical cross-linking. Researchers have used this method to encapsulate different oils. Patchouli oil is highly volatile, unstable oil with strong smell, which possess medicinal properties. In order to reduce the volatility and strong smell and to prevent the oxidation, Han et al. (2013) encapsulated this oil using complex coacervation technique.

7.2.9 Sol-Gel Encapsulation

Sol-gel encapsulation can be used to trap hydrophobic agents inside a spherical shell of amorphous silica. The hydrophobic material is solubilized in the silicon phases such as tetramethoxy silane or tetraethoxy silane, and oil in water emulsion is formed. Silica droplets are hydrolyzed and condensed at the oil water interface to form hard silica shell in which the hydrophobic agents are entrapped.

7.2.10 Spray Drying

Spray drying is a widely used method for encapsulation because of its low cost and simplicity. In this process, the suspension or dispersion of the active material (core) and shell material is sprayed into a hot drying chamber. During spraying, the solvent will be evaporated, and shell material gets deposited on the active component. Microparticles obtained by this method are small and spherical with homogeneous distribution. Advantages of this process are the following: it can be operated continuously, and it is a quick process. However, the use of air at high temperatures may affect the biological activity of the component. These materials are susceptible to easy oxidation; therefore, the shelf life of spray-dried products is less. Carvalho et al. (2014) used spray-drying technology to encapsulate green coffee oil. Green coffee oil has cosmetic properties like emollient, antioxidant, and UV absorption capacity. The shell material used in this method includes arabic gum, maltodextrin, and modified starch. In spray congealing method, the protective coating material is applied as melt. The core material is dispersed in the melt of the coating polymer. Solidification of the melt is achieved by passing through hot air to cold air stream.

7.2.11 Freeze-Drying

In freeze-drying, the suspension or dispersion of the active component and shell is frozen, and then solvent is evaporated via sublimation under high vacuum. Compared to spray-dried products, freeze-dried products are superior in quality and more stable to oxidation. For heat-sensitive products, freeze-drying is the best method. The drawbacks of freeze-drying process are high energy consumption and long processing time. Since the freeze-dried particles are not homogenous and possess irregular shapes, their encapsulation efficiency is less compared to spray-dried particles.

Tao et al. (2017) used freeze-drying method for encapsulating blueberry anthocyanin extract. A mixture of whey protein isolates, β-cycodextrin, maltodextrin, and gum arabic was used as the matrix material. Homogeneous mixture was prepared by magnetic stirring followed by ultrasonication. The obtained dispersion was dried using freeze dryer. In another study, tomato oleoresins, pumpkin oleoresins, and wheat bran oleoresins were encapsulated in α-cyclodextrin by freeze-drying method (Durante et al. 2016). Supercritical carbon dioxide technology was adopted to extract oleoresins.

7.2.12 Fluidized Bed Coating or Air Suspension

In this method, active agents (core material) to be coated are suspended in a stream of air, and then the coating material (polymer solution) is sprayed onto the moving particles. The solvent gets evaporated, and an outer layer is formed over the particles. Desired thickness and weight of the product can be achieved by repeating the

process. Fluid bed coater can be top spray type, bottom spray type, or tangential spray type.

7.2.13 Polymer Encapsulation by Rapid Expansion of Supercritical Fluids

Super critical fluid – highly compressed gases (CO_2, N_2O) – containing the shell material and core material maintained at high pressure is released at atmospheric pressure through a small nozzle. The sudden pressure drops cause desolvation, and the shell material gets coated over the active component (core). Coating material used in this method includes polyethylene glycol and paraffin wax. The main condition in this technique is that both the active component and the coating material should be soluble in supercritical fluid.

8 Drug Release Profiles vs Administration Route of Encapsulated Plant Extracts

The presence of different types of bioactive components (polyphenols and flavonoids) is traditionally used to treat various diseases. However, the direct oral administrations of such natural bioactive molecules degrade during the course of the administration and absorption period leading to the significant loss of bioactivity and therapeutic efficiency. The nanotherapeutics are expected to subvert the limitation of current drug therapy (conventional), which includes less target-oriented drug release, less bioavailability, and therapeutic index. In the case of drug delivery system, the biocompatible polymeric template is expected to take advantage of engineering capability to reduce burst release and improve target efficiency at the action site. Compared to conventional therapeutic approaches, the well-designed nano-based drug delivery system is expected to stabilize the phytocomponents and improve the nano delivery as shown in Fig. 14.

9 Drug Release Pattern

9.1 Effect of pH on Drug Release

The polyphenol (epigallocatechin-3-gallate) present in green tea has been encapsulated into the biocompatible polymer and used as anticancer drug. However, the bioavailability decreases, and degradation increases due to structural complication of these types of polyphenols. For instance, the presence of a number of hydroxyl and gallolyl groups has the difficulty to diffuse through the intestinal epithelium (Li et al. 2011c). The presence of acidic pH environment in human gastrointestinal

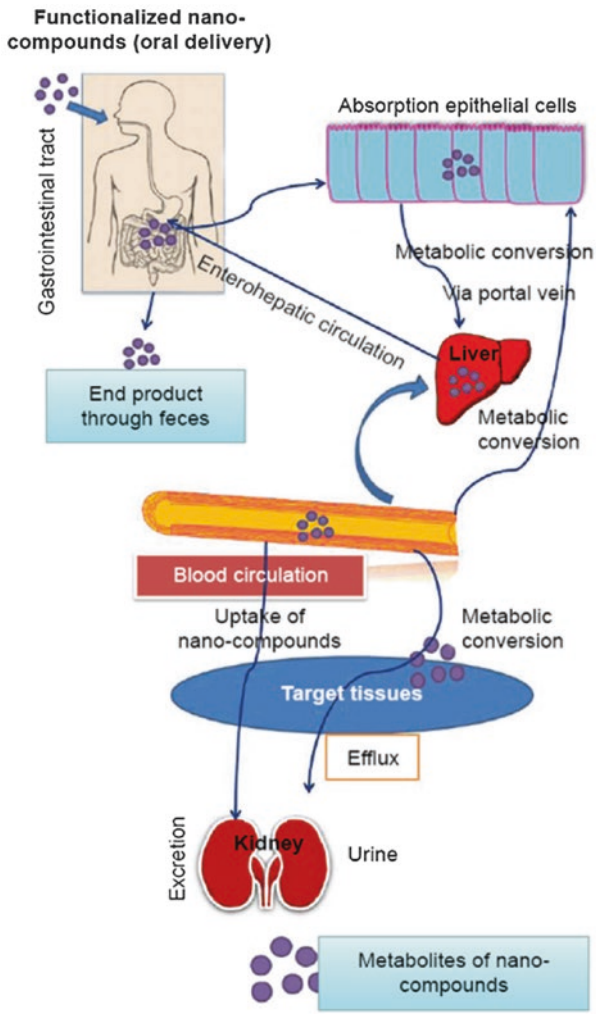


Fig. 14 Nano-based phytobioactive molecule bioavailability route through oral delivery in humans. (Adopted from Ganesan et al. 2017)

tract also reported to degrade the content through formation of dimerization process (Lun Su et al. 2003). Therefore, encapsulation into nanomaterials are gaining importance, which is reported to favor the detainment of the plant extract property through stabilization and therefore enhancing their medicinal property availability (biocompatibility) for a longer time.

The effect of pH was observed when the synthesis and characterization of polyphenols extracted from fresh strawberry fruits were assessed through chitosan encapsulation. The presence of positively charged functional amino group is reported to enhance the loading of negatively charged polyphenols and improve bioavailability and sustained release. The trapping of polyphenols was reported to

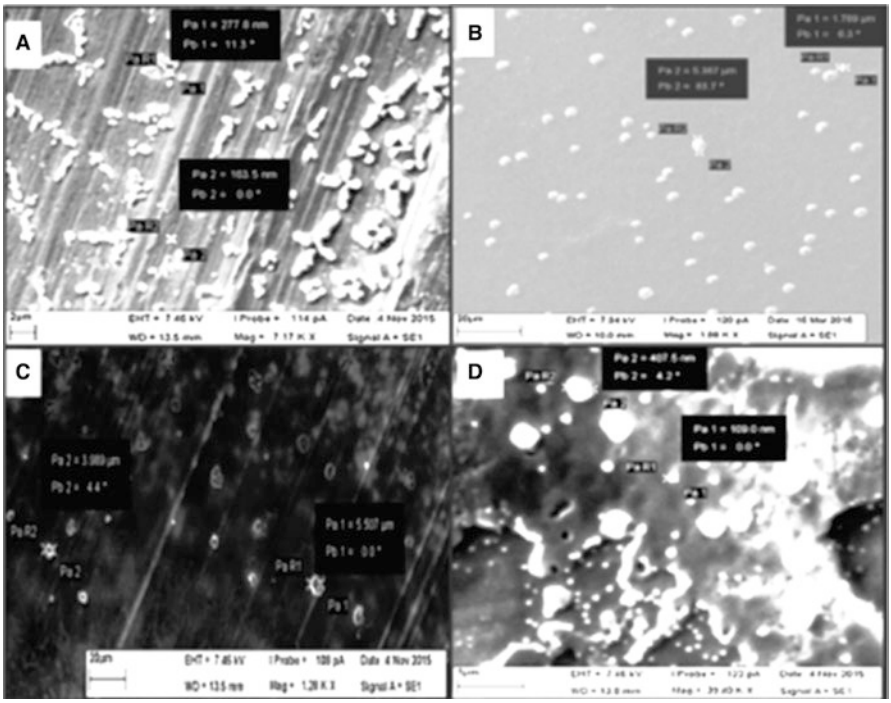


Fig. 15 Scanning electron microscopy images of chitosan-TPP NPs before and after release, (**a**) before release, (**b**) after release at pH 1.4, (**c**) after release at pH 7.4, and (**d**) after release at pH 10.4. (Adopted from Pulicharla et al. 2016)

be 58%, while optimum-loading capability was found to be 36%. The release profile was found to be pH dependent by studying the drug release at pH 1.4, pH 7.4, and 10.4, respectively. An initial burst release profile for polyphenols was observed at pH 7.4, while sustained release was observed at pH 1.4 (Pulicharla et al. 2016) (Fig. 15).

The release profiles of polyphenols are corroborated with particle size distributions using SEM images (Fig. 14). The polyphenol's sustained release at pH 1.4 shows the presence of small-sized particle in sustained manner, while increased release of polyphenols with large particle sizes are observed at high pH condition (Pulicharla et al. 2016).

9.2 Food Intake and Body Weight Influence the Drug Release

Microencapsulation of shrub-based *Catha edulis* termed as Khat using gelation was reported to be effective against obesity. The slow release rate of Khat through subcutaneous injection route in controlled fashion is studied on food intake (FI),

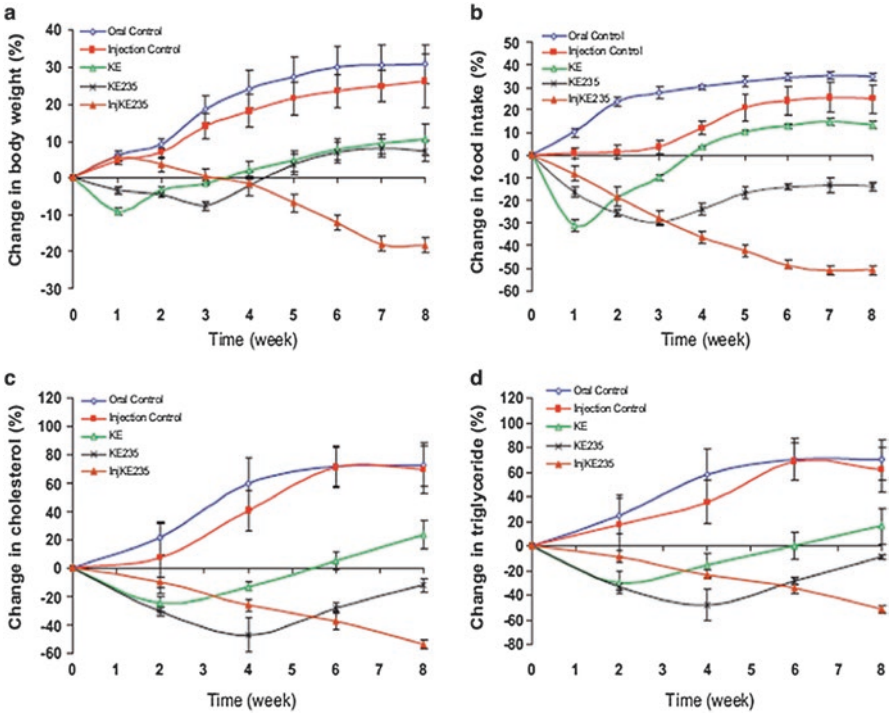


Fig. 16 The change in (**a**) body weight, (**b**) food intake, (**c**) cholesterol, and (**d**) triglyceride levels (%). Mean ± SEM, N = 12. (Adopted from Aziz et al. 2011)

body weight (BW), cholesterol (CS), and triglyceride (TG) levels. The study showed correlation between $T_{50\%}$ and reduction of BW, CS, and TG (Aziz et al. 2011) (Fig. 16).

9.3 Route of Administration Influence the Drug Release

The solubility of plant extract camptothecin derived from *Camptotheca acuminate* Decne was reported to improve and shown to exert anticancer effect through intravenous injection route. The hydrophobically designed glycol-based chitosan with about 80% camptothecin loading through dialysis technique has shown to target intracellular topoisomerase. The injection amount of 10 mg per kg and 30 mg per kg is reported to be an effective dose compared to free camptothecin with 30 mg per kg. Primarily the activity was attributed due to enhanced solubility and longer blood circulation at the targeted tumor region (Min et al. 2008).

Moreover, intravenous injection route of natural polyphenol resveratrol-loaded lipid was reported to be effective for Alzheimer disease. The low solubility of

flavonoid subdues the biological advantage of resveratrol that further tends to isomerize and degrade during environmental exposures (pH, temperature, and light). However, the encapsulation of resveratrol into lipid core hydrophobic structure is reported to bypass the filtration by the liver and spleen and also helps to cross endothelial cells of the blood-brain barrier. The lipid functionalization with antibody, in particular anti-transferrin receptor monoclonal antibody, was reported to help the transfer of natural component to the targeted brain (Loureiro et al. 2017). In addition, solid-based lipids like glyceryl dilaurate, stearic acid, hydrine, cetyl alcohol, and glyceryl monostearate and liquid-based lipids (glyceryl monodicaprylate, oleic acid, and capric acid) are found to be effective for dermal administration route. The lipids tend to enhance the encapsulation efficiency of drugs by about 70%, and the nanoform increases the dermal penetration by improving contact with stratum corneum (Santos et al. 2013). Quercetin-lipid nanoformulations with particle size in the range of 215.2 nm and entrapment ability of 89.95% are reported to be effective for dermal delivery route. The flavonoid-rich quercetin was reported to improve the traverse through stratum corneum and exert anti-inflammatory action (Guo et al. 2012). Some other recent developments of route of administration in case of encapsulation drug efficiency can be summarized in Table 13**.**

10 Commercially Available Plant Extract/Herbal Formulations

Nano-phytomedicines are prepared from plant extracts or with their therapeutically active constituents. Nano-drug delivery systems help in better bioavailability that decreases side effects and toxicity. Nowadays, there are many companies involved to market nano-herbal formulation. Among them, two companies dominate the market, viz., Cosmetochem and Indena. For herbal drug delivery, Cosmetochem launches Herbasec® technology in the market which is actually a liposomal preparation of various herbal constituents like extracts of white tea, green tea, white hibiscus, guarana, and aloe vera. These extracts are used in cosmetics because of their antioxidant effects for prevention of aging. Indena patented the technology of Phytosomes® and launched many products in the market under this having diverse therapeutic benefits. Indena commercializes the plant constituents/extracts of liquorice (18ß-glycyrrhetinic acid), *Ammi visnaga* (visnadin), *Centella asiatica* (triterpenes), *Ginkgo biloba* (ginkgo flavone glucosides, ginkgolides, bilobalide), hawthorn flower (vitexin-2″-O-rhamnoside), milk thistle (silymarin and silybin), horse chestnut (escin ß-sitosterol), *Terminalia sericea* (sericoside), *Panax* ginseng (ginsenosides), grape seed (polyphenols), green tea (polyphenols), etc. (Devi et al. 2010; Pinto 2010). Table 14 presents some of the marketed nano-plant extract or herbal medicines.

Table 13 Summary of recent encapsulation studies involving various plant extracts and administration routes

Study type	Nanocarrier	Bioactives	% efficiency	Finding/benefits	References
Anthocyanin encapsulation using liposomes in supercritical CO_2	Liposomes	Anthocyanin	50.6% (EE)	The flavonoid release from liposome carrier was found to be a sustained release (≤3509%) in simulated intestinal fluid condition	Zhao et al. (2017)
In vitro and in vivo study of curcumin-mixed micelles (mPEG-PLA/TPGS) for oral route	Mixed micelles Poly(ethylene glycol)-poly (lactide)	Curcumin	16.1% (curcumin loading)	The in vitro study in simulated gastrointestinal solution showed the controlled curcumin release and improved bioavailability	Duan et al. (2016)
Oral administration of Soluplus-*Angelica gigas* Nakai nanocombination extract fabricated through electrohydro dynamic technique	Soluplus (polyethylene glycol 6000)	*Angelica gigas* Nakai	Mean entrapment efficiency (EE) of decursin and decursinol angelate to be 100% and 85.4%	The study showed that herb loaded over nanocomposite (AGN/SP2 NC) can be efficiently used for oral delivery that showed high exposure effect and high concentration in plasma	Lee et al. (2016)
Antioxidant derived from red grapes in combination with micelle chitosan for oral route study	Quaternary ammonium (thiolated or non-thiolated) and chitosan	Grape seed extract (antioxidant)	15–20% loading (80% EE)	The technique improved the loading of antioxidant (15–20%) and internalization by endothelial progenitor cells	Fabiano et al. (2016)
Curcumin/microparticles for ulcerative colitis through oral route administration	Eudragit, polymer poly(lactide-co-glycolide) (PLGA)	Curcumin	80% (curcumin loading)	Curcumin in the micron-sized particles ranging 1.52–1.91 μm was shown to be effective for ulcerative colitis	Xiao et al. (2015)
Oral administration of quercetin on a mouse model of Alzheimer's disease	Zein	Quercetin	70 ± 1.3 μg/mg payload (EE of 81.2 ± 1.3%)	Quercetin flavonoid has been loaded over zein (a natural type of polymer) and treated for Alzheimer's disease through oral absorption	Moreno et al. (2017)

(continued)

Table 13 (continued)

Study type	Nanocarrier	Bioactives	% efficiency	Finding/benefits	References
Enhancing the bioavailability of *Silybum marianum* dry extract	Coground (Gelucire)	*Silybum marianum*	Production yield of 94–95 by wt and EE of 92–98%	Mechanochemical and spray drying of dry extract of *Silybum marianum* along with activated coground (Gelucire) improve bioavailability	Passerini et al. (2012)
Self-assembly of green tea catechin derivatives in nanoparticles for oral lycopene delivery	Green tea catechin derivatives	Lycopene	9% (lycopene loading), EE (89%)	The in vivo study in mice showed an improved pharmacokinetics and can be potential oral drug delivery system	Li et al. (2017)
Self-assembly of green tea catechin derivatives in nanoparticles for oral lycopene delivery	Green tea-derived oligomerized (-)-epigallocatechin-3-O-gallate	Lycopene	9% (lycopene loading), 89% (EE)	Green tea-based nanoparticle-chitosan polymer was used to load lycopene (natural antioxidant). The composite showed an improved pharmacokinetics and can be potential oral drug delivery system	Li et al. (2017)
Oridonin-mixed micelles (Soluplus-Pluronic P105) for oral administration study	Soluplus and Pluronic P105	Oridonin, a diterpenoid compound ($C_{20}H_{28}O_6$)	15.08 ± 0.38% (loading), 90.48 ± 1.85% (EE)	The optimized drug formulation showed improved bioavailability (210.55%) and can be a potential drug therapy for cancer treatment	Ke et al. (2017)
Proliposomes containing a bile salt for oral delivery of *Ginkgo biloba* extract: formulation optimization, characterization, oral bioavailability, and tissue distribution in rats	Proliposomes	*Ginkgo biloba*	Up to 88% (encapsulation efficiency)	The nanoformulation enhanced the absorption in gastrointestinal tract and subsequently reduced elimination	Zheng et al. (2015)

Table 14 Commercially available herbal formulations with plant extract in pharmaceutical and cosmetic industry

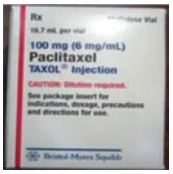
Product name with photo	Plant extract with active ingredients	Formulation	Route of administration	Therapeutic use	References
	*Cuscuta chinensis* A/I: flavonoids and lignans	Nano-suspension method	Oral	Hepatoprotective and antioxidants effect	Yen et al. (2008)
	*Artemisinin* A/I: artemisinin	Self-assembly procedure	IV	Anticancer	Youfang et al. (2009)
	*Radix salvia miltiorrhiza A/C: R. salvia miltiorrhiza extracts*	Spray-drying technique	IV	Coronary heart diseases, angina pectoris, and myocardial infarction	Su et al. (2008)
	Taxel-loaded nanoparticles A/I: taxel	Emulsion solvent evaporation method	IV	Anticancer	Fu et al. (2006)
	Berberine-loaded nanoparticles A/I: berberine	Ionic gelation method	IV	Anticancer	Lin et al. (2007)
	Sunscreens A/I: ultraviolet filters	Nano-form	Topical	UV protection	Online data

Table 14 (continued)

Product name with photo	Plant extract with active ingredients	Formulation	Route of administration	Therapeutic use	References
	Breast cream *Pueraria mirifica* A/I: St. herb	Niosomes	Topical	Increased size	Online data
	Hair care Nettle leaf extract, black elderberry extract, hamomile combined with citrus and mint oils	Nanoceutical-shampoo	Topical	Diminish dandruff and increase hair volume and shine	Online data

11 Future Prospective

Throughout the whole world, research is ongoing on plant extract remedies and natural products. Herbal formulation development is being carried out in a number of institutes at the basic and clinical trial levels (Namdaria et al. 2017). The only concern is to develop the best systems for the suitable delivery of such drugs at the sites and in the whole body, with a dose that won't compromise with the basic treatment (Yadav et al. 2011). In the future, herbal nanoparticle concepts for infectious disease and cancer drug delivery may also entice some potential research groups and create attention-grabbing results. Therefore, using "herbal/plant extract" enclosed in nanocarriers will elevate its potential for the treatment of several chronic diseases and health benefits. Plant extracts are also potent antioxidants and constituents that can be made useful in the food industry (Sethiya et al. 2010). This type of integrative research between the traditional "herbal/plant extract" and modern drug delivery system, i.e., "nanotechnology," has established attraction to the pharmaceutical industry which may be taken advantage of in the near future that will promote peoples' health.

12 Conclusions

Research in this area is still at the exploratory stage. Many problems in the research, production, and application need to be solved. In addition, more attention should be paid to the research on the carrier materials in order to develop more suitable

carriers which can reduce the toxicity of drugs, enhance their activity, and improve the overall quality of the agents. Herbal drugs have enormous therapeutic potential, which should be explored through some value-added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be and phytomolecules, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting to poor absorption and poor bioavailability. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, and xanthones when administered through novel drug delivery system show much better absorption profile which enables them to cross the biological membrane, resulting in enhanced bioavailability. Hence more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney, etc.) at similar or less dose as compared to the conventional plant extract or phytomolecule. Hence, pharmaceutical nanotechnology is the most ideal and suitable carrier systems for the improvement of pharmacokinetics and bioavailability of plant actives and extracts.

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