

# Microencapsulation methods for plants biologically active compounds - a review

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Biologically active compounds from plants have attracted great interest due to their affordability, effectiveness and low toxicity. Herbal extracts provide an infinite resource of raw materials for pharmaceutical, cosmetic and food industry. Unfortunately, use of the valuable natural compounds can be limited by their low bioavailability, volatilization of active compounds, sensitivity to the temperature, oxidation and UV light, *in vivo* instability, as well as unpleasant taste. One of the potential strategies to overcome these issues is microencapsulation of the biologically active ingredients. In this review, preparation, applications and limitations of the most popular techniques for microencapsulation, such as spray drying, fluid bed coating, encapsulation using supercritical fluids, freeze drying, ionic gelation, emulsification-solvent removal methods and formulation of liposomes, were discussed. Also, microparticles properties produced by presented microencapsulation methods were interpreted.

**Key words:** herbal extracts; medicinal plants; microencapsulation; polyphenols; microparticles; antioxidants

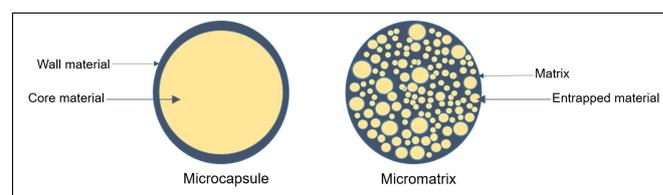
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## 1. INTRODUCTION

According to the available data, nowadays 80% of the world's population uses herbs and herbal medicaments for treatment of various ailments. The acceptability of herbal formulations is increasing due to their affordability, effectiveness and low toxicity (Atul Bhattaram et al., 2002). Unfortunately, use of the valuable natural compounds can be limited by their unpleasant taste, low bioavailability, volatilization of active compounds, sensitivity to the temperature, oxidation and UV light, as well as *in vivo* instability (Ćujić et al., 2013; Abd Manaf et al., 2015; Munin and Edwards-Levy, 2011). One of the potential strategies to overcome these issues is microencapsulation of the herbal active ingredients. Therefore, microencapsulation technology can be used for obtaining herbal products with desirable characteristics. Microencapsulation techniques of plant materials and other natural products are widely used in the food, pharmaceutical and cosmetic industries.

Microencapsulation is a process by which solids, liquids or gases are surrounded with a membrane or matrix (Desai and Jin Park, 2005; Suri et al., 2013). The entrapped material is known as the core material, actives, fill, internal phase or payload. The coating material can be called the capsule, wall material, membrane, carrier or shell (Gibbs et al., 1999). The particles with sizes ranging from 1 to 1000 µm are called microparticles or microspheres. There are two types of microparticles; microcapsules and micromatrices (Figure 1). Microcapsules

are made of one or multiple core substances, surrounded by a distinct capsule wall. Micromatrices are polymeric matrices in which the encapsulated substances are homogeneously dispersed (Park and Yeo, 2007). Terminology in this field is inconsistent, sometimes micromatrices are also called microspheres. Depending of the entrapped materials properties, core materials and methods used for preparation, particles with different structure, size and shape can be obtained (Poshadri and Aparna, 2010).



**Fig. 1.** Two major types of microparticles: microcapsules and micromatrices

Microencapsulation can be used to enhance different biologically active compounds properties (Desai and Jin Park, 2005; Singh et al., 2010):

- Improve the stability of the encapsulated bioactive compounds and to extend their shelf life
- Reduce their degradation

- Enhance physical performance and promote easier handling
- Mask the unpleasant taste of substances
- Prevent interactions
- Enable modified release
- Reduce toxicity
- Improve efficiency and/or compliance (Figure 2)

In order to obtain the products of the desired characteristics, it is necessary to consider: expected effect of the encapsulated bioactive substance(s), preferable particle size, density, stability requirements for the encapsulated ingredient(s), optimal concentration of the active principle(s) in microparticles, way of release and delivery of bioactive molecule(s), coating material properties, processing conditions that are expected to be used for preparation of the microparticle and the cost limits (Desai and Jin Park, 2005).

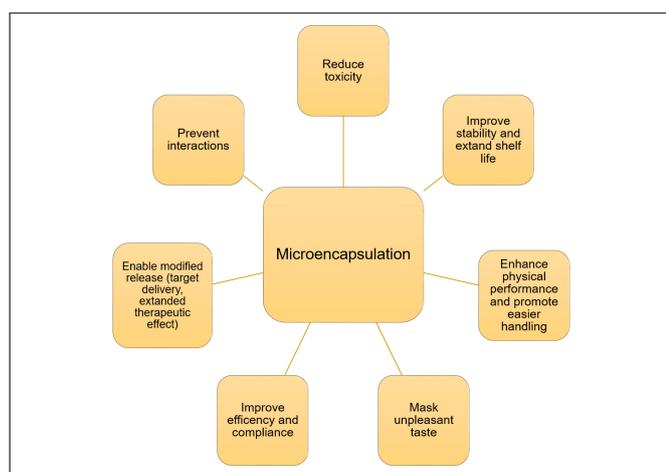


Fig. 2. Application of microencapsulation in food and pharmaceutical industry

## 2. MICROENCAPSULATION METHODS

Microencapsulated particles can be prepared by several microencapsulation techniques. The choice of the microencapsulation process is governed by the physical and chemical properties of the core and coating materials and the intended application. Various encapsulation methods have been previously used for encapsulation of plant or natural products. Some of the most popular techniques, such as spray drying, fluid bed coating, encapsulation using supercritical fluids, freeze drying, ionic gelation, emulsification-solvent removal methods and formulation of liposomes are presented in this review.

### 2.1. Spray drying

Spray drying is a widely applied method used in the food, chemical, electronics, pharmaceutical and biopharmaceutical industry (Jain et al., 2012). In the pharmaceutical industry, this technique could be applied in case of microencapsulation, granulation and complex formation. Also, spray drying is successfully used for the modification of biopharmaceutical properties of drugs and the formulation of dry powder aerosols and heat sensitive materials. This method is often used to encapsulate drugs, plant extracts, essential oils and various biologically active compounds (Belščak-Cvitanović et al., 2015; Čujić, 2017; Dias et al., 2017; Peres et al., 2011).

The principle of microencapsulation by spray drying is based on the dissolution or dispersion of the core material in the

carrier solution, dispersed in the hot air stream. The rapid evaporation of solvent causes the entrapment of the active compound into the carrier (Cocero et al., 2009). The solvent (dispersing agent) quickly evaporates, while the incorporated substance is briefly exposed to the hot air stream. The particles are collected after they fall on the bottom of the dryer (Snyder and Lechuga-Ballesteros, 2008). Numerous properties of particles can be optimized (particles shape and size, porosity, bulk density, flow rate, moisture content, etc.) by choosing the appropriate materials, equipment and process parameters. The advantages of spray drying: the ability to obtain the high quality product and to control its properties, the stability of the obtained product is improved, scale-up is simple and production costs are relatively low (Miletic, 2013). During the spray drying process of plant extracts with high sugar content, adhesion to the walls may occur as a problem, due to the low temperature of the glass transition of sugars and organic acids. This problem can be overcome using the carriers with high glass transition temperature, such as gum arabic, maltodextrins, starches, proteins, hydrocolloids and various hydrolysed starches (Tomšik, 2018).

It has been reported that the antioxidant capacity of *Quercus resinosa* leaves infusions was high. On the other hand, *Quercus resinosa* leaves are well known as adstringents. This plant material is also unstable due to polyphenolic compounds and interactions with different food ingredients. For this reason, the aim of the work by Rocha-Guzman et al. (2010) was to obtain encapsulated *Quercus resinosa* leaves infusions with appropriate stability and masked taste by the spray drying method. Sodium caseinate and lactose monohydrate were selected as carriers. Dispersion of lyophilized *Quercus resinosa* leaves infusions and wall material were homogenized at 0, 100, 200, and 300 MPa. Wall matrix was made of lactose and sodium caseinate blends in 3 ratios (110:40, 90:60, and 70:80 g/L). Homogenized dispersions were encapsulated by spray drying method. The encapsulated particles of the *Quercus resinosa* leaves infusions were in the size range from  $138.1 \pm 1.1$  to  $269.8 \pm 2.9$  nm, with significant antioxidant activity.

### 2.2. Fluid bed coating

The fluid bed encapsulation process consists spraying of the coating solution into a fluidized solid particles and several cycles of wetting and drying (Guignon et al., 2002). The coating material forms film over the particle surfaces. When the particles are fluidized, separation force is exerted to the particles, which are more or less agglomerated by the spray solution. Fluid bed processor can generate its inherent separation force, depending on the operating conditions such as the airflow pattern and the inlet airflow rate. In practice, depending on the requirement of the final particle size, the optimal processing conditions should be selected (Park and Yeo, 2007). Coating material must be thermally stable and it is important to have acceptable viscosity to enable pumping and atomizing. Suitable material for encapsulation by this process should be spherical and dense with a narrow particle size distribution and good flowability (Zuidam and Shimoni, 2010). The advantage of this procedure is that the solution of the coating agent can be applied in several layers. Also, there is a possibility of coating with several different materials during the production process. However, this method has some disadvantages and limits. It is difficult to produce particles smaller than 20  $\mu\text{m}$ . Also, this technique requires large amount of coating materials (Guignon et al., 2002).

Artificial colorants are often used to improve the sensory properties of food and pharmaceutical products. However, using has become controversial because of their toxicological potential.  $\beta$ -carotene is well-known antioxidant, which can also be used as a colorant, due to its distinct red-yellow color. On

the other hand,  $\beta$ -carotene molecules are susceptible to oxidation and thermal degradation. For this reason, the objective of the study published by [Coronel-Aguilera and San Martin-Gonzalez \(2015\)](#) was to encapsulate the spray dried emulsion of  $\beta$ -carotene by fluidized bed coating technology and to evaluate the influence of the fluidized bed coating process conditions: the inlet air temperature (60, 70 or 80 °C) and the coating solution feed rate (7 or 10 mL/min). Encapsulation was performed in a fluidizing system with a Wurster column. Coating material consisted of a 10% solution of hydroxypropyl cellulose. The particle size was in the range from 48.6 to 69.5  $\mu$ m. Smaller particle size was obtained with the higher temperature and feeding rate. The greatest encapsulation of  $\beta$ -carotene was achieved in the case of the lowest temperature and lowest feed rate. This result can be partly explained by the fact that the high temperature may contribute to  $\beta$ -carotene degradation. The stability of the obtained particles was studied at 4, 25 and 45 °C during 4 weeks. The temperature showed an effect on the stability of the tested particles. The loss in  $\beta$ -carotene content was larger at higher temperatures, in comparison to lower temperature. The major degradation in this research was observed during the first week.

### 2.3. Encapsulation using supercritical fluids

Among the numerous conventional encapsulation processes, those based on supercritical technologies have attracted the food and pharmaceutical applications because of the possibility to work with thermolabile products and the ability to engineer the particle ([Keven Silva and Angela A. Meireles, 2014](#)).

Supercritical fluids (SCFs) are fluids on the temperature and pressure above the critical pressure and temperature values for the given fluid. This state is often described as a state between the liquid and gas. SCFs have a density similar to liquid, compressibility and viscosity as a gases, whereas the diffusion capacity is higher than that of a liquid ([Medarević et al., 2013](#)). Supercritical fluids characteristics can be affected by changing the pressure and temperature of the given system. Supercritical carbon dioxide (scCO<sub>2</sub>) is the supercritical fluid, widely used since it is a non-toxic, chemically inert gas, without secondary environmental products, making it environmentally friendly and GRAS (GRAS-Generally Recognized as Safe). scCO<sub>2</sub> has other advantages, such as availability and affordability. The supercritical region of scCO<sub>2</sub> can be achieved at moderate pressures and temperatures (T<sub>c</sub> = 304.2 K, P<sub>c</sub> = 7.38 MPa) making it possible to carry out the process at near-ambient temperatures, avoiding the degradation of thermolabile substances ([Cocero et al., 2009](#)). Many different encapsulation processes are based on the use of supercritical fluids, in which SCFs performs different functions: acts as a solvent (Rapid Expansion of Supercritical Solutions, RESS), antisolvent (Supercritical Anti Solvent precipitation, SAS), co-solvent or solute (Particles from Gas Saturated Solutions, PGSS), propellant (Carbon dioxide-Assisted Nebulisation with a Bubblers Dryer CAN-BD), etc. ([Martin et al., 2010](#)). The use of scCO<sub>2</sub> as the antisolvent has been explored for different materials, such as polymers, pharmaceuticals, inorganic compounds, food and plants bioactives ([Keven Silva and Angela A. Meireles, 2014](#); [Sosa et al., 2011](#)).

Catechins present in green tea (*Camellia sinensis*) have low bioavailability (2-5%) and extensive clearance. Therefore, a group of authors ([Sosa et al., 2011](#)) encapsulated green tea polyphenols using a method based on the use of supercritical fluid, which was acting as an anti-solvent. Acetone was used to dissolve green tea extract and carrier, biodegradable polymer (poly- $\epsilon$ -caprolactone, MW: 25,000). During this study, the following process parameters influence was examined: the operating pressure (8–12 MPa) and temperature (283–307 K),

the polymer to solutes concentration (w/w) ratio (4–58), and the CO<sub>2</sub> to solution mass flow rate ratio (4–10). The particles obtained at a temperature below 290 K were small (about 5 $\pm$ 2  $\mu$ m), with high polyphenol content, which means that the efficiency of the encapsulation was high (60-100%). Polyphenols dissolution rate from microparticles shows that 30% of the antioxidants were released rapidly for the first 4 hours, which was explained by diffusion mechanism, whereas the largest amount of polyphenols were retained within the crystalline domains of the polymer matrix and was released gradually over the next 90 hours, due to the matrix degradation.

### 2.4. Freeze drying

Freeze drying or lyophilization, is a drying process in which the solvent or the suspension medium, is frozen and then sublimed from the solid state directly into the gaseous phase ([Fang and Bhandari, 2012](#)). Prior to drying, active ingredients and polymers are dissolved or dispersed in the medium. The freeze drying process is divided into three basic phases: freezing, primary drying and final (secondary) drying. This technique is simple and suitable for encapsulation of thermosensitive or unstable substances. Also, the moisture content of the final product is controllable, and the dried products generally have appropriate stability and high quality. They can be easily reconstituted in water, because they have a high specific surface area and porous structure. The long duration of the drying phase and the high cost of the process, are the limitations of this method ([Rey and May, 2004](#); [Tang and Pikal, 2004](#); [Fang and Bhandari, 2012](#)).

The properties of the freeze-dried, encapsulated products could be affected by the operating conditions and wall material properties. According to the available literature, most of these parameters were chosen based on the trial and error approach ([Fang and Bhandari, 2012](#)). Also, the freeze drying process can be used after the other encapsulation methods, in order to convert the encapsulated core materials into the powder form ([Stojanovic et al., 2012](#); [Ćujić et al., 2016](#)).

Microparticles lyophilization was used in order to improve the stability of *Rubus chamaemorus* extract ([Laine et al., 2008](#)). It has been shown that freeze drying process improved the extract stability, rich with extremely unstable ellagitannins.

### 2.5. Complex coacervation

The term complex coacervation was introduced by the Dutch chemist Bungenberg de Jong in 1949. The first patented microencapsulation process was based on the phenomenon of complex coacervation ([Lakkis, 2016](#)). This method is based on interactions between water-soluble cationic and anionic polymers, which form a polymer-rich phase called coacervate ([Munin and Edwards-Levy, 2011](#)). Polymers coacervate could be formed around the dispersed core particles. The formation of coacervate as a special phase is a main precondition for this microencapsulation process. Coacervate can be formed spontaneously by mixing the cationic and anionic polymers or by the addition of an anti-solvent, electrolyte, temperature reduction, adjustment of the medium pH, as well as in the presence of certain surfactants ([Sovilj et al., 2000](#)). The charges must be large enough to produce coacervate, but not too large in order to avoid precipitation ([Munin and Edwards-Levy, 2011](#)).

Due to anti-inflammatory, antioxidant and antimicrobial properties propolis could be applied in various products, such as toothpaste, shampoos, creams, etc. However, its using is limited due to the solubility only in alcohol, and it has specific taste and odor. The aim of the study by [Nori et al. \(2011\)](#) was to encapsulate the propolis extract by a complex coacervation with soy protein and pectin, without alcohol. The influence of different pH values (3.5; 4.0; 4.5 and 5) and the influence

of propolis concentrations (2.5 g/100 mL and 5 g/100 mL), as well as pectin (2.5 g/100 mL and 5 g/100 mL) and soy protein concentrations (2.5 g/100 mL and 5 g/100 mL) were examined. The size of the obtained microcapsules in this research was in the range from 10 to 90  $\mu\text{m}$ , which was expected for microcapsules produced by complex coacervation. According to the literature, particles size produced by complex coacervation ranged from 1 to 500  $\mu\text{m}$ . The encapsulation efficiency of formulation using 2.5 g/100 mL concentration of encapsulants and core was  $72.01 \pm 0.01\%$ ; whereas microparticles whose encapsulants and core concentration were 5 g/100 mL had slightly lower encapsulation efficiency ( $66.12 \pm 0.01\%$ ). This result was not expected since increase in the concentration of colloids and the core in solutions was supposed to promote coacervation and provide higher encapsulation efficiency. In this study, it was also shown that the application of coacervation was not deleterious for antioxidant compounds. Furthermore, the antimicrobial activity of the incorporated extract was preserved. The stability of the microcapsules during the 180 days period at 10 and 25  $^{\circ}\text{C}$  was examined. The conclusion was that these microparticles should be stored at a temperature of 10  $^{\circ}\text{C}$  in order to preserve the stability of flavonoids.

## 2.6. Ionic gelation

Ionic gelation is a physiochemical microencapsulation technique, which includes cross-linking of polyelectrolytes (or charged polymers) in the presence of multivalent counter ions (Park and Yeo, 2007). This process consists of extruding an aqueous solution of polymer through a syringe needle or a nozzle, in which the core material is dissolved or dispersed. Droplets are received in a dispersant phase and transformed into spherical gel particles, after a reaction of polyelectrolytes and multivalent counter ions (Munin and Edwards-Levy, 2011).

Catechins are a class of polyphenolic flavonoids with confirmed antioxidant activities and diverse biological properties, such as anti-inflammatory, vasodilatory, neuroprotective and chemopreventive effects. On the other hand, catechins are highly unstable. Various factors influence the stability of catechins. However, pH is the most crucial factor and the rate of oxidation increases as the pH increases. Therefore, a group of researchers encapsulated catechins with an ion-based gel process (Dube et al., 2010). Catechin and epigallocatechin are incorporated into chitosan-tripolyphosphate nanoparticles. These nanoparticles with catechin had an average size of  $163 \pm 2$  nm, with a polydispersity index of  $0.43 \pm 0.02$  and a zeta potential of  $33 \pm 1$  mV. In the case of encapsulated epigallocatechin gallate, the particle size was  $165 \pm 2$  nm, the polydispersity index was  $0.46 \pm 0.2$  nm, whereas the zeta potential was  $33 \pm 1$  mV. In general, the nanoparticles in this research had a mean size less than 200 nm and had a positive zeta potential exceeding 30 mV. These attributes are favorable for nanoparticles for oral delivery, since it has been shown that the potential way of uptake of particles having a mean size below 500 nm is translocation through the gastrointestinal mucous barrier and interactions with the absorptive epithelial cells (Florence and Hussain, 2001). It is stated that the zeta potential of these particles reflects the aspect of stability and inhibition of particle aggregation. Also, the high positive zeta potential may enhance their bioadhesive properties, which may be mediated through interactions with negatively charged cell surfaces. The study also showed that it takes 8 hours to reduce the concentration of the catechin by 50% in phosphate buffer (pH 7.4), whereas for encapsulated catechin 50% of the initial concentration degraded after 24 hours. For epigallocatechin gallate, the corresponding values were 10 and 40 minutes, respectively.

## 2.7. Emulsification-Solvent Removal Methods

Microparticles can be produced from an emulsion of two or more immiscible liquids. The most commonly used methods are solvent evaporation and the solvent extraction technique. In the solvent evaporation method, a volatile solvent has a very low miscibility with water. This technique is based on the evaporation of the hydrophobic solvent from the emulsion in which microspheres are formed and the active ingredients are trapped in the polymer matrix and encapsulated on that way. First step includes dissolving of the polymer (coating material) in the organic solvent. After that, the active principles are dissolved/dispersed in the obtained polymeric solution. The mixture is emulsified in a large amount of water containing surfactants, to obtain an oil-in-water (O/W) emulsion. Evaporation of the solvent is achieved by heating under vacuum and with gentle stirring. This method is not applicable in the case of volatile compounds encapsulation and in the case of compounds with high affinity for the continuous phase (Lu et al., 2016; Munin and Edwards-Levy, 2011).

The solvent extraction technique, also called nanoprecipitation, is a method where solvent is miscible with water in all proportions. The method involves dissolving/dispersing the bioactive compounds in a solvent in which the polymer has previously been dissolved. Then, this phase is injected under agitation into a continuous aqueous phase containing a surfactant. Nanoparticles are formed by spontaneous diffusion of solvents into the aqueous phase, while a polymer precipitates and forms particles with encapsulated active principles (Lu et al., 2016; Munin and Edwards-Levy, 2011). Following the solvent removal, the resulting particles are purified, filtered or centrifuged. Subsequently, they are dried by a conventional method or by lyophilization (Munin and Edwards-Levy, 2011). Resveratrol is a natural polyphenolic compound and it has been reported that resveratrol induces many cellular responses, including cell cycle arrest, differentiation and apoptosis, making it a novel anticancer agent. In the study reported by Shao et al. (2009), the activity of resveratrol in the free form and encapsulated resveratrol was compared, for the treatment of invasive brain tumor (malignant gliomas). mPEG-PCL (methoxy poly (ethylene glycol)-poly(caprolactone)), was used as a carrier having a hydrophilic and hydrophobic region. On this way, it is possible to incorporate the hydrophobic compound, such as resveratrol, into the core, which is surrounded by the hydrophilic chains. Resveratrol nanoparticles were prepared by nanoprecipitation method. The particles obtained in this study were spherical with smooth surface, the size of particles was not significantly changed after lyophilization ( $78.3 \pm 7.9$  nm prior to lyophilization and  $87.5 \pm 9.59$  nm afterwards). The zeta potential prior to drying was  $-6.5 \pm 1.4$ ; whereas afterwards it was  $-5.6 \pm 0.7$ . The efficiency of encapsulation was higher than 90%. The resveratrol loading content was  $19.4 \pm 2.4\%$ . *In vitro* release of resveratrol loaded in nanoparticles indicated that 50% of resveratrol was released during the first 5 hours, followed by the observed trend of prolonged release. *In vitro* study revealed that higher efficiency of encapsulated resveratrol can be explained by higher ability of encapsulated resveratrol penetration in cell membranes in comparison to the same dose of free resveratrol.

## 2.8. Liposomes

Liposomes were discovered around 1965 when British hematologist Dr Bangham described the appearance of liquid crystals of lecithin in contact with water forming structures very similar to biological membranes. Liposomes are mainly composed of phospholipids and due to their amphipathic nature they have a strong tendency to form membranes (Bozzuto and Molinari, 2015). In addition, they are biodegradable and biocompatible vesicular systems. Liposomes could be made up

of one or more lipid bilayers, which surround the core filled with water. Based on the number of double layers vesicles liposomes can be classified as: multilamellar vesicles (MLVs), oligolamellar vesicles and unilamellar vesicles (ULVs). The specific structure of these carriers makes them suitable for encapsulating compounds of various physicochemical properties. Hydrophilic active substances could be incorporated into the hydrophilic interior, while lipophilic and amphiphilic compounds could be incorporated into the liposomal lipid bilayer (Swami et al., 2015). Large aqueous core represents interior of ULVs, making them suitable for the encapsulation of hydrophilic molecules. On the other hand, MLVs preferably entrap lipid-soluble substances (Bozzuto and Molinari, 2015). Liposome preparation techniques may be divided into 1) bulk methods, whereby liposomes are obtained through transfer of phospholipids from an organic phase into an aqueous phase and 2) film methods, in which lipid films are first deposited on a substrate and then hydrated to give liposomes. Following the preparation of liposomes, various methods for particle size reduction could be used, such as: sonication, extrusion, freeze-thaw cycles or homogenization (Patil and Jadhav, 2014). Amarogentin, secoiridoid glycoside, can be potentially used as antileishmanial agent. Therefore, group of authors evaluated amarogentin efficacy in the free form and in two vesicular forms, liposomes and niosomes (Medda et al., 1999). The amarogentin in both vesicular forms was found to be a more effective antileishmanial agent compared to the free form. Experiments on hamsters were performed with the equivalent drug concentration for free, liposomal and niosomal form of this active principle. Free amarogentin reduced the parasite load by 34%. Liposomal form reduced the parasite load by 69%, whereas niosomal form reduced the parasite load by 90

## CONCLUSION

Plants contain large number of compounds of various physicochemical, biopharmaceutical, pharmacokinetic and pharmacodynamic properties. For this reason, formulation of the herbal products with appropriate properties in terms of efficiency, stability and quality is a complex task. Encapsulation methods can play a key role in achieving these goals. Review of the various research results reveals that encapsulation is a method for protection of natural compounds, increasing their shelf life. It was shown that encapsulation enables controlled release and improves bioavailability and efficiency. Moreover, in some instances encapsulation methods are being used to mask an unpleasant taste. Microencapsulation technique should be selected depending on the desirable characteristics of microparticles (size, entrapment efficacy, drug loading, bioavailability, stability). Although there are plenty possibilities how to encapsulate a biologically active compound, usually two or more encapsulation processing steps are required to get microparticles with preferable characteristics.

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