

Micro and nanoencapsulation: a new hope to combat the effects of chronic degenerative diseases

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In recent years, scientific evidence has demonstrated that diet and/or its bioactive components play an essential role in human health and wellness, leading to a change in the population consumption habits. The interest of the population for consuming healthier food products has motivated the food and pharmaceutical industries for the development of novel functional food products. The use of bioactive compounds for the formulation of novel functional foods has generated great expectations in the scientific community, as a new hope to improve the life quality and health disease status of the population. In this way, new technologies, which are revolutionizing the control, security and role of consuming products, have been developed as a new way to break into the field of bio-guided medicine, in order to provide to the consumers an option for the prevention and/or treatment of chronic degenerative diseases. In the last years, many studies have showed that different encapsulation systems, such as nanoemulsions, liposomes, micelles, polymeric micro or nanoparticles, have the potential to be used in many different biological and medical applications, mainly as targeted drug delivery systems to minimize and delay the negative effects of different chronic degenerative diseases. This review investigates the potential health benefits of several drug delivery systems to encapsulate bioactive compounds and its impact on the prevention and/or development of chronic degenerative diseases.

Keywords: bioactive compounds; technology; encapsulation; chronic degenerative diseases.

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INTRODUCTION

Several sources of information support the association between high intake of vegetables and fruits and low risk of chronic diseases, including cardiovascular disease, neurological disorders, cancer, and inflammatory and autoimmune diseases (Simopoulos, 2008; Vaziri, 2004). Vegetables and fruit are rich sources of a variety of nutrients, including vitamins, trace minerals, polyphenols and dietary fiber, and many other classes of biologically active compounds. These phytochemicals can have complementary and overlapping mechanisms of action, including modulation of detoxification enzymes, stimulation of the immune system, reduction of platelet aggregation, modulation of cholesterol synthesis and hormone metabolism, reduction of blood pressure, and antioxidant, antibacterial, and antiviral effects (Beecher, 1999; Vergara-Castañeda et al., 2012; Mares-Perlman et al., 2002), that leading to a delay or to prevent chronic degenerative diseases as mentioned above (Campos-Vega et al., 2010; Vergara-Castañeda et al., 2010).

Regarding all this supporting information, there is a great interest for the use of bioactive compounds within the food, cosmetic and pharmaceutical industries in order to develop functional products that help to enhance human health and wellness (Siró et al., 2008; Weiss et al., 2008). Nevertheless, there are several challenges that must be overcome before bioactive compounds can be successfully incorporated in functional products or absorbed in human organism in order to accomplish one specific biological activity: water and oil low solubility, low bioavailability, low bioaccessibility, chemical instability under conditions encountered during functional products processing and storage (e.g., temperature, oxygen, light), or in gut (pH, enzymes) (Pouton, 2006; Record y Lane, 2001). These factors impact in a negative way in the beneficial biological activities that bioactive compounds could exert in human body (Borghetti et al., 2009). Therefore, a wide variety of colloidal delivery systems, including microemulsions, nanoemulsions, solid lipid nanoparticles, multilayer emulsions, polymeric nanoparticles, inclusion complexes, and filled hydrogel particles, have been developed to encapsulate, to protect, and to target release different bioactive compounds in diverse sites of action (Matalanis et al., 2011; McClements, 2012; Pool et al., 2013).

The aim of this review is summarize the development of diverse drug delivery systems to encapsulate bioactive compounds, and its biomedical application as novel therapies against some chronic diseases, such as cancer, cardiovascular disease, neurological diseases, diabetes, among others. The information presented in this work, would have very important implications for the use of bioactive compounds-loaded delivery systems as novel approaches to treat illnesses that affect people around the world, encouraging at the same time, to enhance, and to generate important information related with.

Encapsulation technology in Cancer

Recently, nanotechnology has been assessed and implemented in different areas of cancer management and therapeutics trying to improved cancer diagnosis and treatment. It is acknowledged by the National Cancer Institute, which considers that nanotechnology offers an extraordinary, paradigm-shifting opportunity to make significant advances in cancer diagnosis and treatment (Cuenca et al, 2006). On the other hand, over several decades multiple studies have shown that there is a direct link between consumption of certain foods that reduce the risk of developing different kinds of cancer. Numerous natural products have been studied to determine the molecular pathways for cancer prevention and treatment including β -carotene, curcumin, epigallocatechin gallate, genistein, resveratrol, gingerol, capsaicin, among others (Bharali et al., 2011; Lee et al., 2011).

For these reasons, many authors have proposed ways to deliver the encapsulated compounds carry through the gastrointestinal tract of individuals, directing toward specific sites for quick and easy absorption, and thus they can provide chemoprotective or therapeutic function. Such is the case of Ha et al., (2012) which encapsulated curcumin into copolymer PLA-TPGS, 1,3-beta-glucan (Glu), O-carboxymethyl chitosan (OCMCS) and folate-conjugated OCMCs (OCMCS-Fol), prepared by nanoprecipitation technique, in order to increase the hydrophilicity and drug delivery capability, a yellow compound from rhizome of the herb *curcuma longa* was isolated. Curcumin has been receiving considerable attention because of its putative cancer prevention and anti-cancer activities which are mediated through influencing multiple signaling pathways. However its application in anti-cancer therapies is limited due to its low water solubility and poor bioavailability. The

authors found that these particles have a good solubility in water. Confocal microscopy revealed that folate enhances the uptake of curcumin into cancer cells expressing folate receptor and the anti-tumor promoting assay also shows strong positive effects of Cur-PLA-TPGS and Cur-Glu on tumor promotion of Hep-G2 cell line *in vitro*. These results open the door to new targeted therapies and hope to the patients.

Curcumin has been deeply studied because it is a prominent candidate for treating antiinflammatory, cystic fibrosis, Alzheimer's and malarial diseases in addition to cancer (Maheshwari et al., 2006). Research group of Yallapu et al., (2012) has developed a series of curcumin or nanoformulations for effective anticancer, hyperthermia and imaging applications in cancer therapy (Figure 1).

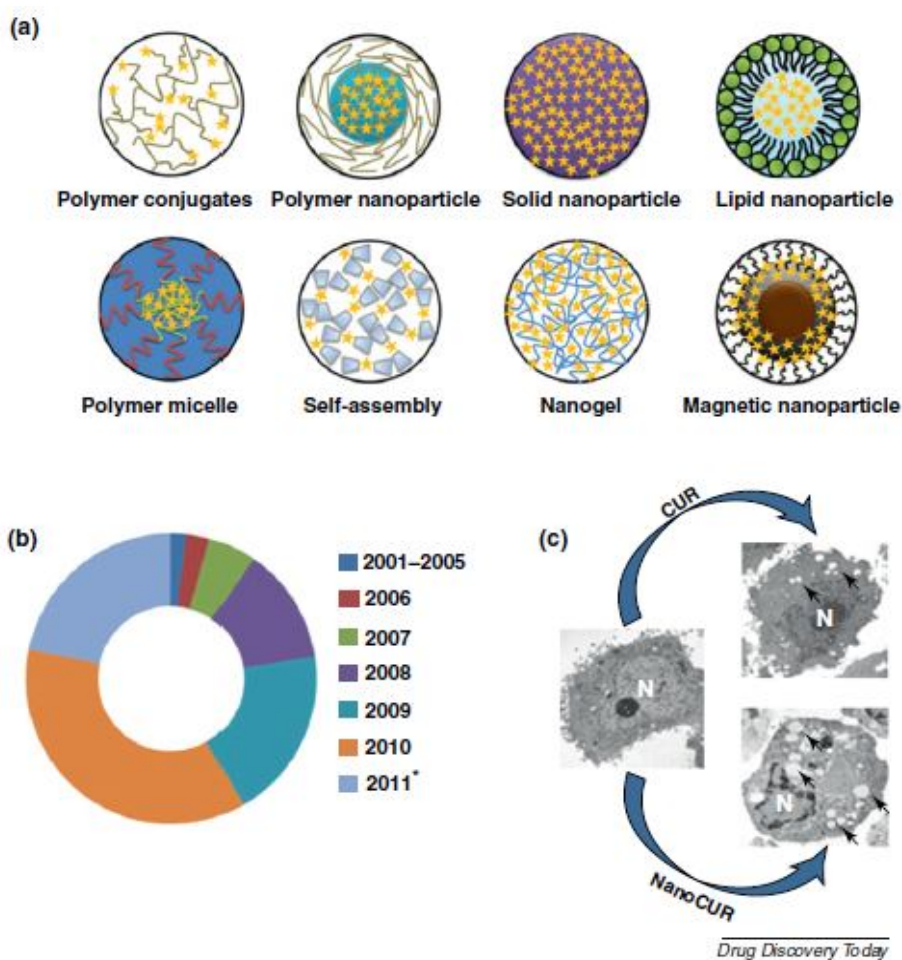


Figure 1. Types of curcumin nanoformulation used in cancer therapeutics. (a) Various types of curcumin nanoformulation developed during the past ten years. (b) Increased use of curcumin nanoformulation developed during the past ten years. (c) Increased use of curcumin nanoformulation developed during the past ten years.

curcumin nanoformulations during the past decade. Data were collected from journals published by Elsevier, Wiley Interscience, American Chemical Society, Springer, BMC Central and PubMed. *Indicates data collected from January 2011 to July 2011. (c) Improved chemotherapeutic effects in PC-3 cancer cells of poly(lactic-co-glycolic acid) (PLGA) nanoparticles (nanoCUR) over free curcumin (CUR) through the formation of vacuoles as observed under a transmission electron microscope. N, nucleus. Black arrows indicate vacuoles. Adapted from Yallapu et al., (2012).

Altunbas et al., (2011) proved a self-assembling peptide hydrogel as an effective vehicle for the localized delivery of curcumin over sustained periods of time. Hydrogels have been used to incorporate drug molecules into the gel matrix to create reservoirs that deliver bioactive agents (Slaughter et al., 2009). The authors managed to deliver sustained concentrations of curcumin locally to a delivery site. β -hairpin peptide hydrogels with encapsulated curcumin concentrations as high as 4 mM immediately display solid-like properties after shear-thinning and reheel quickly over time to stiffnesses close to pre-shear values. *In vitro* experiments with a medulloblastoma cell line showed that curcumin released from hydrogel and directly applied to the cells induce dose-dependent increase of caspase 3 and PARP cleavage inducing apoptosis by similar mechanism as non-encapsulated curcumin. The results indicated the potential effectiveness of curcumin-loaded β -hairpin hydrogels as injectable agents for local curcumin delivery (Altunbas et al., 2011). Shahani and Panyam (2011) designed a sustained and injectable microparticle formulation with higher curcumin loading capacity (i.e. 38.1 mg/100 mg of particles; 76.2% encapsulation efficiency) compared with many formulations. A cyclodextrin-curcumin self-assembly curcumin into cyclodextrin (CD) and poly(cyclodextrin) led to a self-assembly formation that promoted its anticancer potential by down-regulating pro-survival Bcl2 family genes, Bax and Bcl-xL, and induction of apoptosis (cleaved poly[ADP-ribose]polymerase, [PARP]) (Yallapu et al., 2010). Finally, Bisht et al., (2010) engineered a polymeric nanoparticle encapsulated curcumin formulation (NanoCurc), composed of N-isopropylacrylamide (NIPAAM), vinylpyrrolidone (VP), and acrylic acid (AA), that shows remarkably higher systemic bioavailability in plasma and tissues compared with free curcumin upon parenteral administration. The combination of parenteral NanoCurc with gemcitabine results in enhanced tumor growth inhibition versus single agent, reducing the activation of nuclear factor- κ B, as well as the expression of matrix metalloproteinase-9 and

cyclin D1. Furthermore, this combination completely abrogates systemic metastases in orthotopic pancreatic cancer xenograft models.

But not only curcumin has been studied for preventing cancer and others diseases. Research on the application of polyphenols, have recently attracted great interest in the functional foods, nutraceutical and pharmaceutical industries, due to their potential health benefits to humans. The utilization of encapsulated polyphenols instead of free compounds can overcome the drawbacks of their instability, alleviate unpleasant tastes or flavors, as well as improve the bioavailability and half-life of the compound *in vivo* and *in vitro* (Fang and Bhandari, 2010). Encapsulation techniques applied to extracts and/or polyphenolic compounds from plants confirmed that encapsulation is an interesting means to potentialize their activity. Among them, spray-drying is the most common technique used to encapsulate polyphenols. The challenge to convert the most powerful polyphenols into usable compounds has then been resolved through innovative formulations (Munin and Edwards-Lévy, 2011). There are several forms to encapsulate polyphenolic which has been proved to be used against diseases as cancer. Some examples of capsules involving polyphenols are showed in Figure 2.

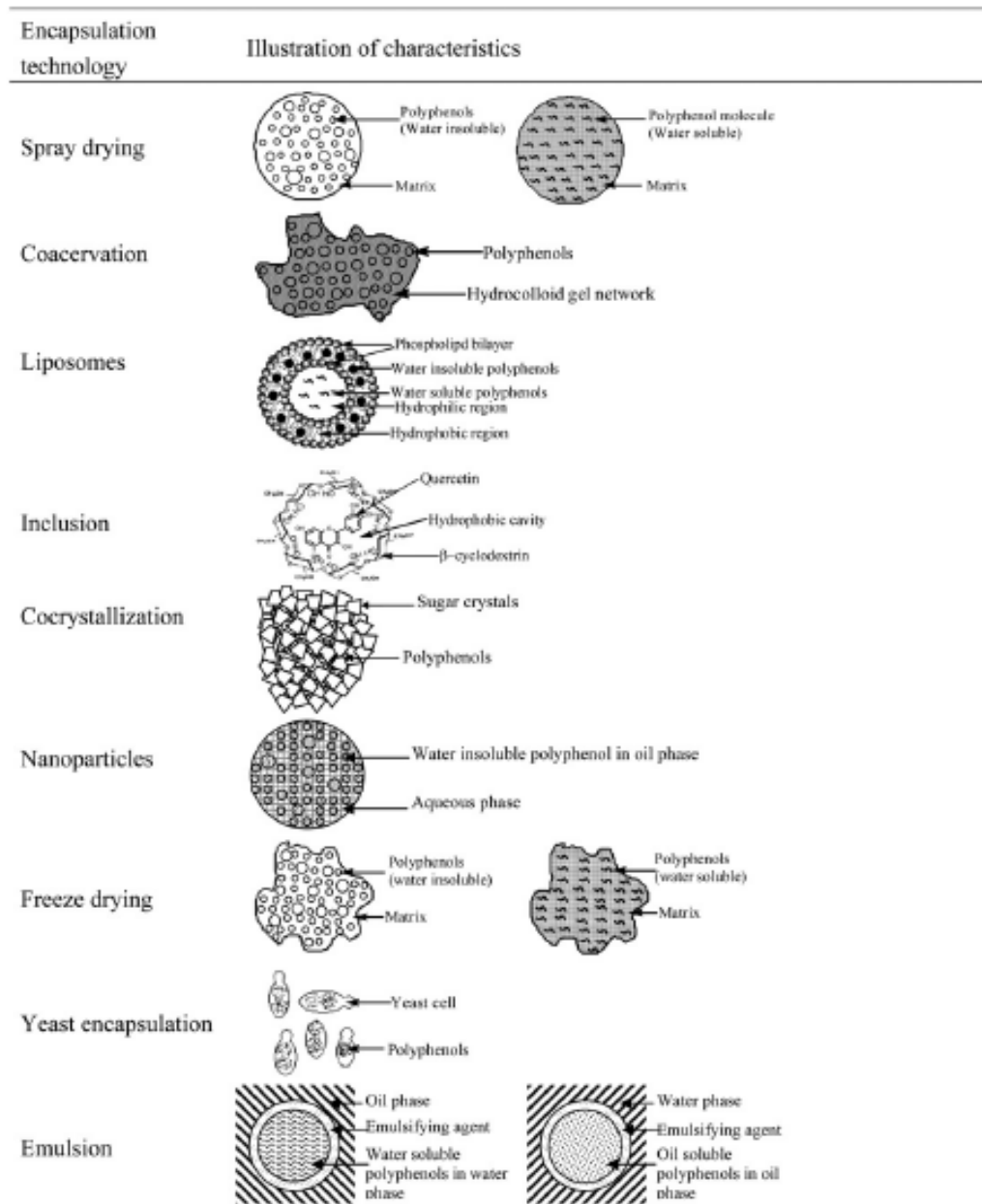


Figure 2. Illustration of the characteristics of encapsulated polyphenolic capsules produced by various encapsulation processes. Adapted from Fang and Bhandari, (2010).

Pool et al., (2012) developed a delivery system containing polymeric (Eudragit) nanoparticles having quercetin as bioactive. Quercetin is a flavonoid that has been reported to have a particularly high antioxidant activity (Calabro et al., 2004). Also, it has been reported that quercetin offers protection against a variety of chronic diseases, as cancer and others (Yao et al., 2004). Despite its potential benefits, the use of quercetin has been limited because its poor water solubility, chemical instability under conditions encountered during

food processing and storage and its low bioavailability. In addition, some studies have shown that the antioxidant capacity of flavonoid compounds (such as quercetin) decrease dramatically when they are exposed to acidic or alkaline regions of the gastrointestinal tract (GIT) (Record and Lane, 2001). Pool et al., (2012) produced small anionic polymeric (Eudragit) nanoparticles containing quercetin in a non-crystalline form. They proved that after the mouth, stomach and small intestine stages the amount of quercetin released was around 43 %, 16 % and 7 % for free quercetin dispersed in water, and around 5 %, 3 % and 22 % for quercetin encapsulated within polymeric nanoparticles (Figure 3). These results suggested that the nanoparticles protected quercetin from dissolution in the mouth and stomach but promoted its release in the small intestine. These results give a hope to the treatment of cancer patients using protected natural compounds.

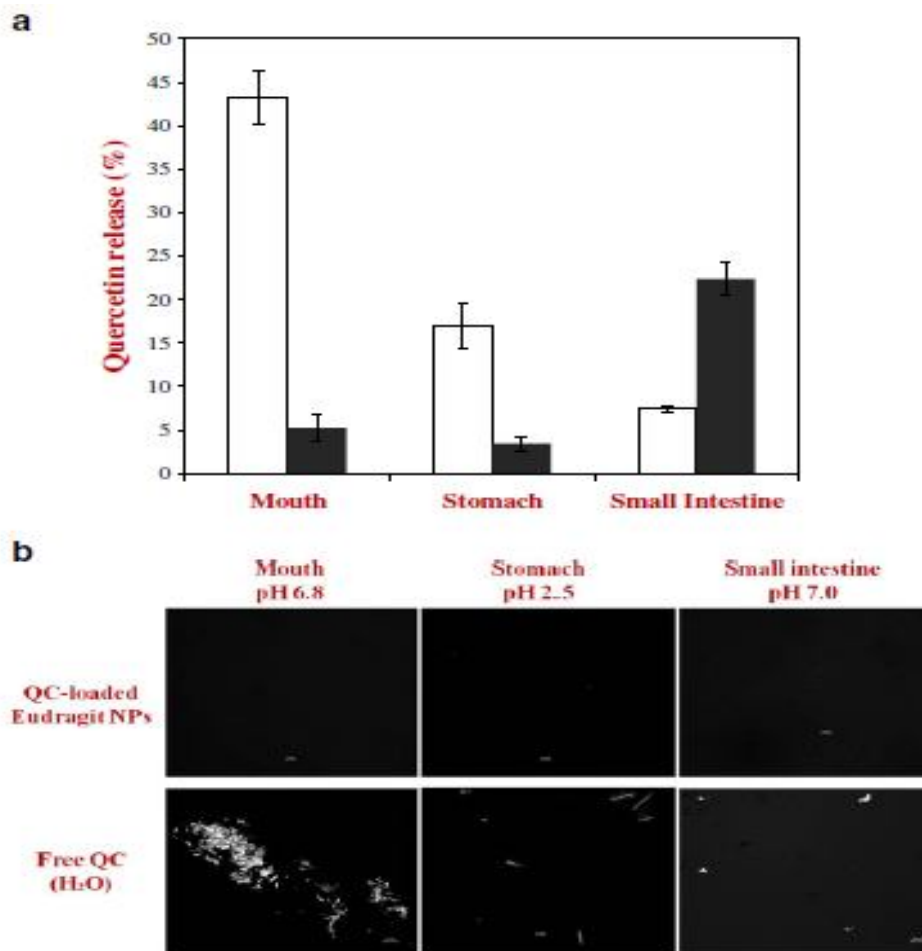


Figure 3. a. Release of quercetin from Eudragit nanoparticles (■) and from water (□) at different stages in a simulated GI model. Results are expressed as the mean±SD of three individual experiments. b Polarized light microscopy of pellets (sediments) collected by

centrifugation of samples of free or encapsulated quercetin after each stage of simulated GIT tract. Adapted from Pool et al., (2012).

Interest in resveratrol has increased due to its pharmacological cardio- and neuroprotective, chemopreventive, and antiaging effects, among others. Neves et al., (2013) developed solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) loaded with resveratrol produced by a modified hot homogenization technique. The polydispersity index for all nanoformulations indicates a satisfactory homogeneity, and the high negative zeta potential of around -30 mV suggests physical stability. Resveratrol also seems to decrease the order of the crystalline structure of the SLNs and NLCs, promoting physical stability and a more controlled release. The *in vitro* release studies on conditions of storage showed a negligible resveratrol release over several hours for both nanosystems and the *in vitro* simulation of gastrointestinal transit showed that the resveratrol remained mostly associated with the lipid nanoparticles after their incubation in digestive fluids. Sanna et al., (2012) also developed novel cationic chitosan (CS)- and anionic alginate (Alg)-coated poly(D,L-lactide-*co*-glycolide) nanoparticles (NPs) loaded with the bioactive polyphenolic *trans*-(*E*)-resveratrol by the nanoprecipitation method. The encapsulation efficiencies increased from 8% of uncoated poly(D,L-lactide-*co*-glycolide) (PLGA) to 23% and 32% of Alg- and CS-coated PLGA nanoparticles, respectively. Resveratrol was significantly protected against light-exposure degradation and the nanosystems are able to prevent the degradation of trans isoform and the leakage of resveratrol from the carrier for a period of 6 months. The encapsulation of an extract of oak (*Quercus resinosa*), very rich in polyphenols, was realized by means of a high-pressure homogenization (Rocha-Guzmán et al., 2010). The extract presents instability, bad taste and strong astringency which require its encapsulation before its incorporation in foodstuffs. Within a matrix consisting of sodium caseinate and lactose, a high antioxidant activity was measured even at very low phenolic concentrations. The anthocyanins from an extract of black currant (BCAs) (delphinidin-3-*O*-glucoside, delphinidin-3-*O*-rutinoside, cyanidin-3-*O*-glucoside and cyanidin 3-*O*-rutinoside) were encapsulated contributing on stability and antioxidant activity. The authors used β -glucan as the thermogelling polymer. In this study the release of anthocyanins was more significant with the cubic forms, and the loss of activity of the encapsulated BCAs after treatment was comparable to that of the free anthocyanins. However, the antioxidant

activity of the BCAs was stabler regarding to the free elements. Freeze-drying seemed to be less deleterious than infrared drying (Xiong et al., 2006). Capsules prepared by sonication for 20 min and with a core to coating ratio of 1:20 developed by Cilek et al., (2012) were the best conditions for encapsulation found of phenolic compounds from sour cherry pomace and the study of different maltodextrin/gum arabic ratios showed that increasing gum arabic ratio in the coating material increased encapsulation efficiency. The incorporation of EGCG in folate-mediated nanoparticles (FA-EGCG-BSA) resulted in an uptake by cultured PC-3 cells, a human prostate cancer cell line, 23.65 times more in a concentration-dependent manner. The lethality of PC-3 cells treated with FA-EGCG-BSA was 82.8%, with EGCG was 58.6%, and with EGCG-BSANP was 55.1%. Lethality of PC-3 cells was positively correlated with the nanoparticles' uptake amount (Zu et al., 2009). Since these studies, many more have been developed for the protection of the phenolic compounds through the gastrointestinal tract, not only as food additives or as nutritional supplements, but also as active cosmetics or as drugs.

Others phytochemicals has been recently recognized exhibiting anti-carcinogenesis activity by affecting a spectrum of different cellular signaling pathways. Conjugated linoleic acid (CLA) and n-3 polyunsaturated long chain fatty acids have demonstrated, both *in vivo* and *in vitro* anticancer capacity exerting a direct effect on various stages of tumor development and/or acting on the immune system of the host (Haro et al., 2006). Ip et al., (1994) suggested that consumption of 3.5 g CLA/day for a 70-kg person could provide protection from certain forms of cancer. Although CLA has many beneficial biological effects, the prevention of its oxidative deterioration must be considered when CLA is prepared, stored and used as a dietary supplement. Jimenez et al., (2004) microencapsulated CLA using whey protein concentrate (WPC) as a wall material. The authors formulated an CLA emulsion using an emulsifier formulated with a 1:4 (w/w) ratio of a 30% WPC solution and using spray-dried. The results indicated that the encapsulation efficiency was 89.60% with a surface oil concentration of 1.77 g/100 g of sample. The best stability was obtained at $a_w=0.743$ and 0.727 at 35 and 45°C, respectively, under which conditions the samples were stable to physical changes and the CLA degradation was near 30%. Pomegranate seed oil, rich in CLA, was microencapsulated by Sen Gupta et al., (2012) using sodium alginate

or trehalose as encapsulating agent and calcium caseinate was used as the emulsifier. The encapsulation efficiency for trehalose coated product was found to be 59.3%, whereas in case of alginate coated product, efficiency was observed to be 69.7%. SEM micrographs showed that the dried sodium alginate micro-capsules are very irregular in shape and have a rather rough surface with large gaps in-between. Trehalose microcapsules improved appearance; they possess uniformity in texture and are elongated in shape.

Trehalose-based microcapsules showed higher release rate. However, on subjecting the microcapsules at 110°C for specific time periods, it was observed that sodium alginate microcapsules retained their original properties. The conclusion of this study was that sodium alginate microcapsules are more heat resistant than trehalose microcapsules and they can achieve sustained-release of nutraceuticals.

Diabetes

Diabetes mellitus is a pathologic condition, resulting in severe metabolic imbalances and non-physiologic changes in many tissues, where oxidative stress plays an important role in the etiology. Diabetes is associated with the generation of reactive oxygen species (ROS), which cause oxidative damage, particularly to heart, kidney, eyes, nerves, liver, small and large blood vessels, immunological and gastrointestinal system. Diabetes mellitus is possibly the World's fastest growing metabolic disorder, and as the knowledge of the heterogeneity of this disorder increases, so does the need for more appropriate therapy (Oršolić et al., 2008; Yue et al., 2003).

It has been reported that propolis inhibits oxidative damage in various tissues of alloxan- or streptozotocin-induced diabetic animals (Khalil, 2006). Propolis, a resinous substance collected from the buds of certain trees by bees, is a traditional herb medicine in many countries. More than 300 components have been found in propolis, mainly composed of phenolic compounds (e.g., flavonoids, aromatic compounds), terpenes and essential oil (Bankova et al., 2000). Propolis has been proven to have various bioactivities that are anti-pathogenic, immunoregulatory, antioxidative, anti-tumor, hepatoprotective and anti-inflammatory (Banskota et al., 2001; Bankova et al., 2005). Zhu et al., (2011) indicated that

Chinese propolis and Brazilian propolis significantly inhibited body weight loss and blood glucose increase in diabetic rats. Chinese propolis reduced 8.4% the glycosylated hemoglobin levels in treated diabetic rats compared with untreated and propolis also decreased total cholesterol level by 16.6%. These reasons, makes to propolis a good candidate for use as a nutraceutical agent in the treatment of diabetes mellitus.

Even when propolis is considered beneficial for human health due its flavonoids and terpenoids, it cannot be utilized as foodstuffs owing to their very low aqueous solubility and bitter taste. For this reason, authors are trying to generate propolis stable forms to be used in food industry as an alternative to improved health of population. Kalogeropoulos et al., (2009) extracted nutraceutical compounds of propolis (PE) by ethanol and then they prepared inclusion complex with β -cyclodextrin (β -CD). The PE/ β -CD inclusion complexes were prepared by sonication of PE suspensions in aqueous solutions of β -CD, followed by filtration and freeze-drying. Evidently the relatively small aromatic compounds like cinnamic and benzoic acids are more effectively bound into the β -CD cavity (9.4–23.3%), compared to the more complex and bigger molecules like flavonoids, anthraquinones and terpenic acids (4.0–10.7%) (Table 1). The respective *in vitro* solubilities in simulated gastric fluid followed an opposite trend, being lower for the relatively small aromatic molecules. Thus, it is concluded that the encapsulation in β -CD may increase the solubility of PE constituents in a manner related to their structure, while the amount of substances released will depend both on their chemical properties and on their relative abundance in the matrix.

Table 1. Percentage encapsulation yield for propolis extract constituents.

Chemical class	Compound	Encapsulation yield (%)*
Cinnamic acids	Cinnamic acid	20.6
	Phloretic acid	21.7
	Ferulic acid	23.3
	Caffeic acid	19.4
Benzoic acids	<i>p</i> -Hydroxybenzoic acid	14.5
	Vanillic acid	15.4
	Syringic acid	18.8
Flavones	Chrysin	4.3

Flavonols	Kaempferol	4.7
	Quercetin	3.6
Flavanones	Naringenin	4.7
	Pinocebrin	6.6
	Pinobanksin	10.7
	Pinobanksin-3-O-acetate	4.2
Anthraquinones	1,6-Dihydroxy-3-methylanthraquinone (chrysophanol)	3.7
	1,6-Dihydroxy-8-methoxy-3-methylanthraquinone	8.4
	1,3,8-Trihydroxy-6-methylanthraquinone (emodin)	5.9
	2,7-Dihydroxy-5-methoxy-3-methylanthraquinone	3.6
	1,7-Dihydroxy-3-methoxy-6-methylanthraquinone	4.0
Terpenic acids	Oleanolic acid	5.0
	Ursolic acid	5.7
	Dehydroabietic acid	6.2
	Abietic acid	6.7

*Calculated as the amount of constituent present in the complex divided by the amount of constituent in the initial propolis extract used for complex preparation and multiplied by 100. Adapted from Kalogeropoulos et al., (2009).

Moreover, Li et al., (2012) explored the effects of encapsulated propolis on the metabolic and insulin-resistance state of type 2 diabetic rats. Encapsulation of PE was performed with β -CD using spray-drying technique. Fasting blood glucose in T2DM rats treated with encapsulated propolis was significantly depressed compared with non-treated diabetic rats as well as the insulin act index and the average rate of glucose infusion in euglycemic hyperinsulinemic clamp experiment were improved by encapsulated propolis. The results also show that encapsulated propolis inhibited the increasing of triglycerides levels in T2DM rats, and it is possibly profited by the amendment of insulin sensitivity and lipoprotein lipase activity in treated with encapsulated propolis. These findings suggest that encapsulated propolis was efficiency for T2DM blood glucose controlling and emphasize the possibility that the deterioration of blood glucose concentration over time may be prevented, with use of nanotechnology.

In the other hand, experimental studies suggest curcumin is an effective anti-diabetic agent. Data also suggest curcumin's role in glucose homeostasis is mediated through its activation

of glycolysis, inhibition of hepatic gluconeogenesis, and reduction of lipid metabolism. Oral curcumin supplementation was found to be effective for treating hyperglycemia seen in genetically diabetic KK-Ay mice and streptozotocin-induced diabetic rats. Evidence suggests curcumin may be a good antidiabetic agent. It reduces free fatty acids and cytokine release, inhibits NFκB, and reduces insulin resistance by controlling hyperglycemia (Alappat and Awad, 2010). However, oral administration of curcumin is unlikely to provide pharmacologically beneficial concentrations in the body for many disease conditions. This limitation calls for the development of appropriate carrier vehicles to increase the *in vivo* stability of the drug and bioavailability. Poly(ε-caprolactone) (PCL) is a biocompatible and biodegradable polymer that has been investigated extensively for tissue regeneration and wound healing applications. Nanofibre matrices have attracted considerable attention of late for a variety of biomedical applications because they closely mimic the diameter of collagen fibrils in the natural extracellular matrix (ECM) (Laurencin et al., 2008).

The bioactivity of encapsulated curcumin in the nanofibres with PCL was investigated by Merrell et al. (2009) in male C57/B6 mice, in order to generate a novel opportunity to treat diabetes mellitus. Curcumin was used at different concentrations. Increasing the curcumin concentration to 17% w/w did not significantly change the morphology or frequency of fibre distribution compared with fibres loaded with 3% (w/w) curcumin (Figure 6). Maximum concentration of curcumin that could be loaded in the PCL nanofibres under the optimized conditions was found to be 17% (w/w).

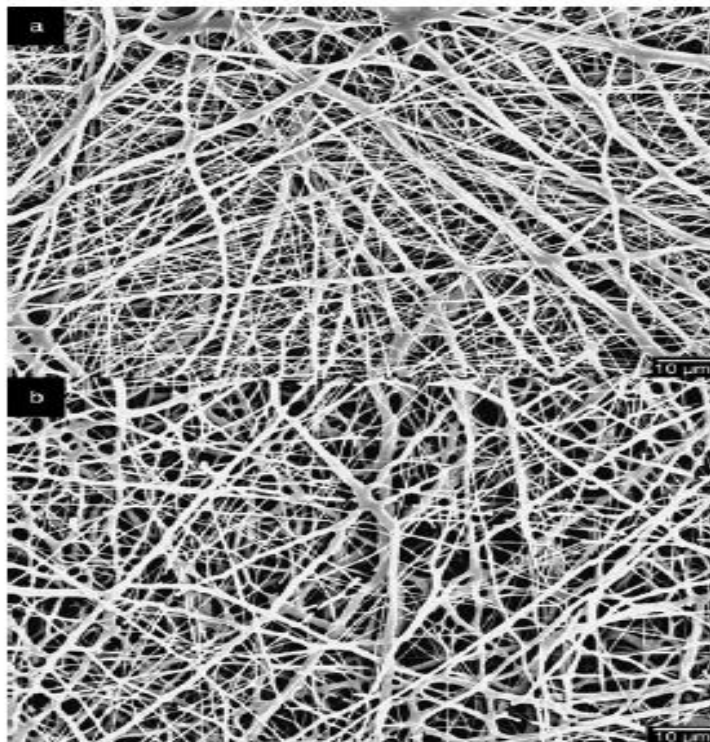


Figure 6. Morphology of poly(ϵ -caprolactone) (PCL) nanofibres loaded with (a) 3% or (b) 17% (w/w) curcumin. Adapted from Merrell et al., (2009).

The release was higher with 17% (w/w) curcumin than 3% (w/w) curcumin. Curcumin-loaded PCL nanofibres also presented a high anti-oxidant potential measured standard ORAC assay. Another biological activity of curcumin that has been investigated extensively is its ability to inhibit the induction of inflammation. In this study, IL-6 production by lipopolysaccharide stimulated macrophages was significantly decreased for cells on curcumin-loaded PCL nanofibres, indicating the potential of curcumin to reduce inflammation. This could have beneficial effects while using curcumin-loaded nanofibres the treatment of diabetic rats, which are characterized by persistent inflammation. The *in vivo* wound healing capability of the curcumin loaded PCL nanofibres was demonstrated by an increased rate of wound closure in a streptozotocin-induced diabetic mice model.

Obesity

Obesity is already recognized as a major health issue worldwide. On every continent of the globe, even in countries where malnutrition is widespread, the percent of the population that is either overweight or obese is increasing at an alarming rate. The growing problem of obesity and sedentary lifestyles also increases the risk of other major metabolic diseases

such as high blood pressure, type 2 diabetes, coronary heart disease, stroke, and some types of cancers. Plant-based diets are increasingly being recognized for their health benefits in weight management, satiety effects and glycemic control. Therefore, dietary agents that have a potential to decrease body fat or improve hyperglycemia may be used as therapeutic agents for the treatment of obesity and diabetes (Campos-Vega and Oomah, 2012).

Conjugated linoleic acid (CLA) is produced by ruminants, from linolenic (18:3) and linoleic (18:2) unsaturated fatty acids obtained in the diet, particularly dairy products and red meat; CLA or conjugated triene fatty acids are found as triglycerides in the seed oils of some plants. CLA is necessary for transporting dietary fats into cells where it can be utilized to build muscle or to produce energy. Results from animal and human studies indicate that CLA reduces body fat by several mechanisms, including a reduced energy intake, increased metabolic rate, and increased utilization of fats for energy (Gaullier, 2005; Gaullier et al., 2004; West et al., 1998). Also, CLA decreases the expression of AMPK- α 2 and satiety and consequently decreases body weight (So et al., 2009). Lalush et al., (2005) informed that amylose-CLA complexes can serve as molecular nanocapsules for protection and delivery of CLA to the intestine. The complexes formed provide stability to oxidation and thermal treatments, such as pasteurization. Control of CLA release is enabled, and the CLA release does not occur in simulated stomach conditions; rather, it is driven by amyolytic activity of pancreatin, which indicates that the location of release in the digestive tract will probably be in the intestine. Furthermore, nanoparticles containing CLA molecules have been successfully obtained in the interlayer space of zinc basic salt (ZBS) (Choy et al., 2010). According to thermogravimetric analysis, CHN analysis and inductively coupled plasma data, the chemical composition of nanoencapsulated CLA is well stabilized mainly through the charge-charge interaction between CLA and nanocapsule, demostred by the fourier-transformed infrared spectroscopic (Figure 7). The coordination bonds are formed between the carboxyl groups of the CLA molecules and the coordinatively unsaturated Zn(OH) units of the nanocapsule resulting in stabilization of CLA molecules. The CLA content in the nanocapsule was determined to be 37 wt% exhibiting high capacity of ZBS nanocapsule. The UV/VIS spectroscopic results showed that the diene structure of CLA does not change after nanoencapsulation. Nanoencapsulated

CLA improved the thermal stability of CLA, compared to pristine CLA, after frying at 180°C. Nanoencapsulation is considered to be a possible way to preserve nutrients from harsh cooking conditions.

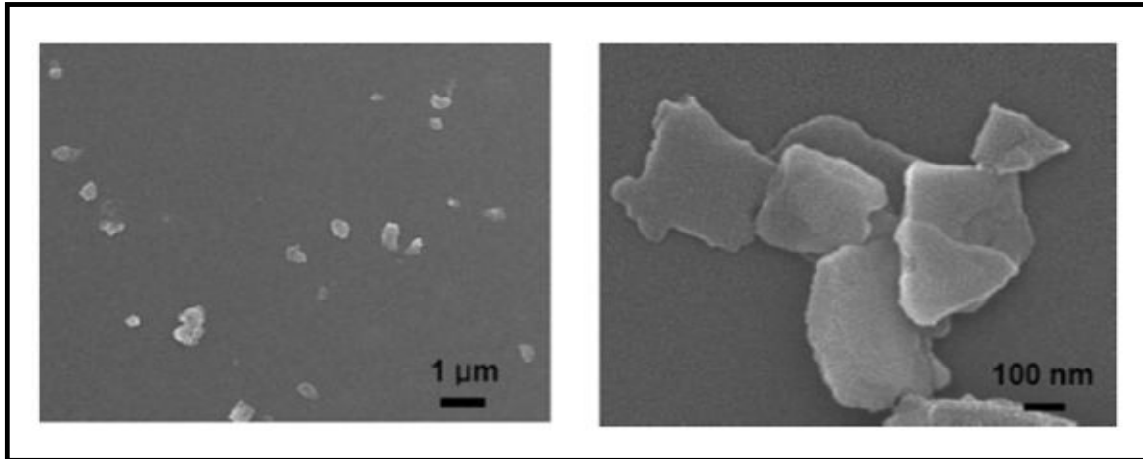


Figure 7. Fourier-transformed infrared spectroscopic images of nanoencapsulated CLA. Adapted from Choy et al., (2010).

A review showed capsaicin, the active ingredient of hot pepper, as an effective natural ingredient to increase fat oxidation, probably associated with the receptor potential vanilloid type-1 (TRPV1) (Lee et al., 2011 and references therein). In an intervention study, 34 subjects were randomized to take either placebo or supplements containing the non-burning pepper analog dihydrocapsiate (DCT) for 28 days. These results showed that energy expenditure significantly increased (almost double that of the placebo group) in the group consuming the higher amount of DCT. This suggests that eating this pepper-derived substance does not burn can have the same potential benefit as hot peppers partly by increasing food-induced heat production. DCT also significantly increased fat oxidation, pushing the body to use more fat as fuel (Sasahara et al., 2010). In this regards, a recently study addresses the effect of the degree of N-acetylation (DA ~1.4–56 %) of chitosan (CS) of low and medium molecular weight (Mw~9.5–13.2 and ~122– 266 kDa, respectively) on the biophysical properties, colloidal stability and encapsulation efficiency of capsaicin (a lipophilic drug currently used in pain therapy) of CS-based nanocapsules (NCs) (Goycoolea et al., 2012). Results informed that Mw and DA of CS have an effect on the disposition of the polysaccharide into the phospholipidic surface. Synchrotron SAXS studies revealed a

monotonic increase in Bragg interplanar distances (from ~55 up to ~67 Å) as a function of the DA, a finding that agrees with previous results that are consistent with the capacity of hydrophobic domains to disturb the crystalline state of gelled phospholipidic membranes. Colloidal stability studies carried out in cell-culture biological media revealed the determinant role of hydration forces, a short-range repulsive interaction, on the stability of the NCs. Finally, Mw and DA of CS both influenced the encapsulation efficiency of capsaicin, thus showing the effect of the harnessed NCs shell on its capacity to encapsulate lipophilic drugs. The nanoencapsulation of capsaicinoids (capsaicin and dihydrocapsaicin) is proposed as a strategy to control their release due to the reservoir characteristics of the nanocapsules. This reservoir property could prolong the topical analgesic effect and reduce the burning sensation and skin irritation caused by the capsaicinoids (Contri et al., 2011).

On the other hand, curcumin, a yellow pigment derived from the spice turmeric (an essential component of curry powder), has been investigated most extensively as a treatment for obesity and obesity-related metabolic diseases. Curcumin directly interacts with adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells (Aggarwal, 2010). A great variety of nanocapsules containing curcumin has been recently developed; this compound is one of the most evaluated compounds on biological system to show its health benefits and the biological activity enhancing by application of this new technology. Despite of that, the research has been focused on the effects of this compound on cancer (see cancer section).

Significant reductions in body weight and fat mass have been observed in a diabetic-obese mice model (KK-A^y) by administering nanocapsules containing bioactive lipids [scallop (marine bivalve mollusk)-derived phospholipids (PLs) with subsequent incorporation of Undaria lipids (ULs; Asian Kemp)] (Okada and Fukushima, 2009). The combination results in a synergistic effect as compared to administrating either lipid alone. The observed reduction in body weight may due to increases in the expression of UCP1 and UCP1 mRNA found in epididymal fat tissue (Figure 8). Up-regulation of UCP1 expressions in adipose tissues is linked to reductions in adipose tissue mass, leading to an encouraging anti-obesity effect.

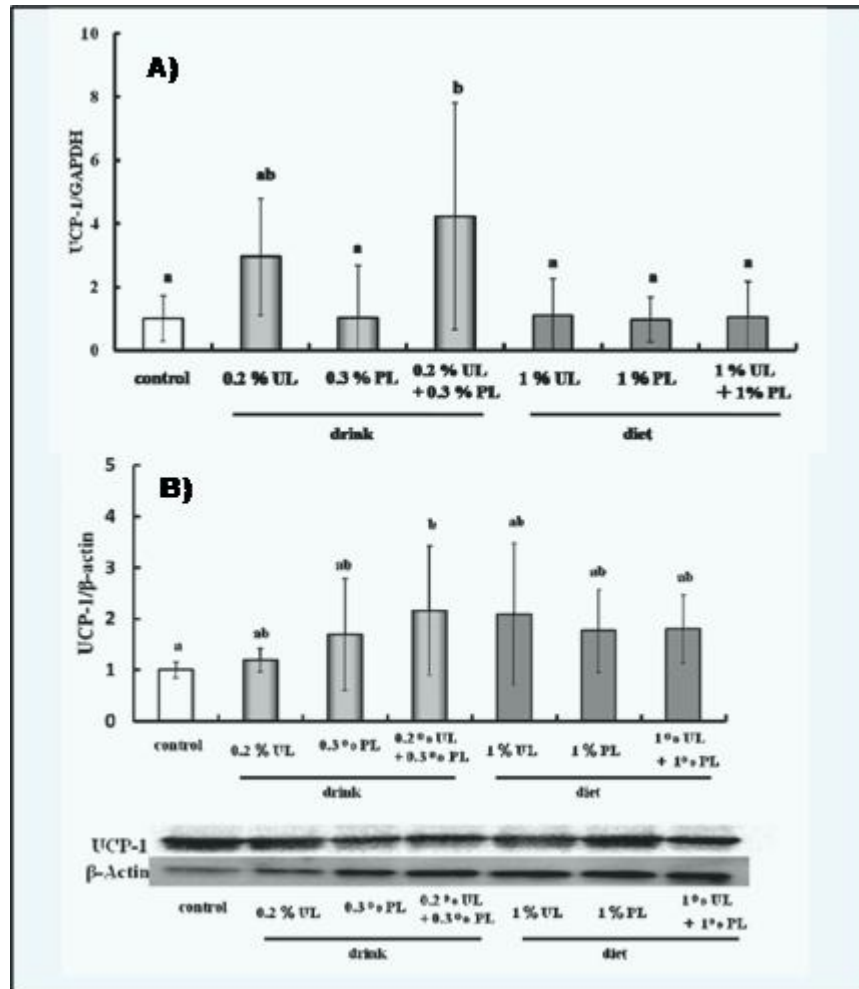


Figure 8. A) Expression of UCP-1 mRNA was estimated by quantitative real-time RT-PCR. Relative values were presented as the ratio of UCP-1 mRNA to GAPDH mRNA. Columns with different superscript letters indicate a significant difference between treatment groups ($p < 0.05$). B) Western blotting analysis of uncoupling protein 1 (UCP-1) in epididymal white adipose tissue and relative expression level of UCP-1 protein compared to β -actin. Columns with different superscript letters indicate a significant difference between treatment groups ($p < 0.05$). UCP-1 mRNA expression levels in epididymal white adipose tissue. Adapted from Okada and Fukushima, (2009).

Cardiovascular disease

Cardiovascular disease (CVD), especially coronary heart disease (CHD) and stroke, is the leading killer in Western Society and its prevalence is increasing dramatically in developing nations. Dietary interventions should be the initial step in the treatment of CVD. In particular, a group of phytochemical substances are carotenoids, which are responsible for the color of food and play an important role in the prevention of human diseases and the

maintenance of good health (Riccioni et al., 2011). However, difficulties may be encountered due to the instability of these compounds. In order to overcome the instability problem of these bioactive compounds, which results in restricted commercial applications, encapsulation has become an important tool, helping to increase shelf life and protecting the biological properties of these bioactive components (Santos and Meireles, 2010). β -Carotene nanoparticles have been developed by two different phase polymeric methods which is aqueous soluble and organic soluble polymer (Bennet and Kim, 2011), as well as proliposome with highly solubility, preserving more than 90% of the incorporated beta-carotene for 60 days of refrigerated storage under vacuum (Moraes et al., 2013). Additionally, the efficacy of the *in vitro* activities of β -carotene and α -lipoic acid in conjugation with an encapsulated lipid was assessed by Gupta and Gosh (2012). Both antioxidants were equally effective in releasing core materials; total lipid occurred within 210 min from both β -carotene and α -lipoic acid bearing nanocapsules. While β -carotene and α -lipoic acid metal-chelation activity ranged from 47.65% and 48.59% to 32.315% and 39.29% after 90 days.

On the other hand Tomé-Carneiro et al., (2012) showed, for the first time, that a dietary intervention with grape resveratrol could complement the gold standard therapy in the primary prevention of CVD. After a 1-year consumption of a resveratrol-rich grape supplement an improvement on the inflammatory and fibrinolytic status in patients who were on statins for primary prevention of CVD and at high CVD risk (i.e., with diabetes or hypercholesterolemia plus ≥ 1 other CV risk factor) was observed. Recently Cadena et al., (2013) nanoencapsulated quercetin and resveratrol into elastic liposomes, highly stable and suitable for subcutaneous injection. In this regards, an exploitation of polyphenolic extracts from grape marc as natural antioxidants by encapsulation in lipid-based nanodelivery systems (Sessa et al., 2012). The antioxidant activity of the encapsulated extracts was measured with two different chemical assays (FRAP and ORAC) showing that the antioxidant compounds, when are encapsulated, are as effective as unencapsulated polyphenols in scavenging the peroxy radicals (ORAC), but are less available in reducing the ferric tripyridyltriazine complexes (FRAP).

A review outlines a promising therapeutic opportunity by integrating a nutritional-based approach focusing on omega-3 alpha-linolenic acid as nutraceutical to prevent the devastating damage caused by brain ischemia. Western modern diets are deficient in omega-3 polyunsaturated fatty acids, which are essential for brain health. Such deficiency may constitute by itself a risk factor for stroke (Nguemini et al., 2013). Nanocapsules of alpha-linolenic acid (α -LA) have been developed by a modified emulsion diffusion technique with encapsulation efficiency of 93% by Habit et al., (2012). The bioavailability of encapsulated linseed oil (LSO), containing α -LA, as against native oil was monitored in rats by measuring the uptake *in vitro* using the intestinal reverted sac model and *in-vivo* administration of microemulsions of LSO to rats for a period of 30 days. The results indicated that ALA was taken up and metabolized to long chain omega-3 PUFA when given as microemulsion with lipoid (Sugasini et al., 2012).

Alternative treatments, berberine (bioactive compounds from *B. vulgaris*) versus ezetimibe (cholesterol absorption inhibitor drug), have shown increasing expression and stability of LDL receptors and/or suppressing proprotein convertase subtilisin/kexin type 9 (PCSK9) expression in tested in hypercholesterolemic subjects, been rather effective and safe (Pisciotta et al., 2012). Haraduga et al. (2010) informed the β -cyclodextrin nanoencapsulation of the biocompounds from *Berberis vulgaris* extracts, showing moderate yields (69.5-77%), the best being obtained in the case of leaf and root extracts, and the specific physico-chemical analyses (SEM, TG, and DSC) indicated the formation of biocompounds/ β -cyclodextrin complex (Figure 9).

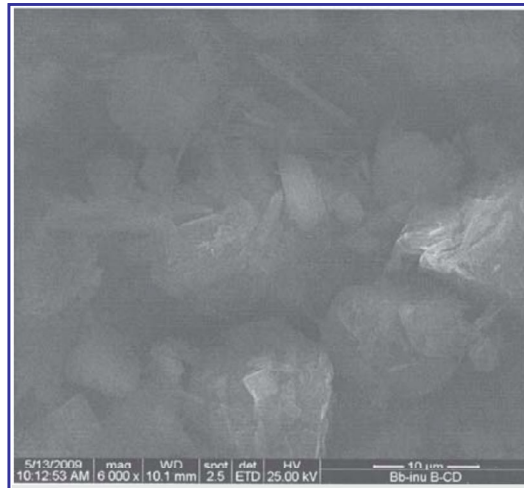


Figure 9. SEM micrograph of the *B. vulgaris* bark extract/ β -cyclodextrin micro/nanoparticles (code 32_BScM1_bCD; 6000 x magnitude). Adapted from Haraduga et al., (2010).

Delivery systems as therapeutic approaches for neurological diseases

Neurodegenerative diseases are pathologist that are characterized by a progressive and irreversible damage in the brain, which are the fourth leading cause of death in the developed world after heart diseases, cancer, and stroke (Plassman et al., 2007). The most common neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Lewy body dementia, frontotemporal dementia, amyotrophic lateral sclerosis, Huntington's disease, and prion diseases (Bertram y Tanzi, 2005). However, the most widely recognized are Alzheimer's disease and Parkinson's disease, which are among the principal debilitating conditions of the current century. Approximately 24 million people worldwide suffer from dementia, 60% of cases being due to Alzheimer's disease, which occurs in 1% of individuals aged 50 to 70 and dramatically increases to 50% for those over 70 years (Cacciatore et al., 2012; Singh et al., 2007).

Several conditions such as oxidative stress, mitochondrial dysfunction, infections, hypoxia, apoptosis, and others, play important roles in the development and prevalence of these diseases (Cacciatore et al., 2012). In this way, different pharmaceutical and bioactive compounds have been used to treat neurodegenerative diseases, however, most of these components do not reach the brain in a fully way and are, instead, metabolized totally or partially by the liver (Spuch y Navarro, 2011). Also, many of these therapeutic agents are

poorly soluble or insoluble in aqueous solutions, which difficult their use in dietary products (Pasic et al., 2011). In addition, it has been recently demonstrated that many active components are inefficient to across the blood brain barrier (BBB), which affect the beneficial effects of these components in the brain (Constantinides et al., 2008).

Therefore, there is a necessity for the development of new technologies that help to protect and maintain the integrity of the drugs until they are released at specific site of action in the brain (Cacciatore et al., 2012; Nazem y Mansoori, 2011; Spuch et al., 2011). Many delivery systems, such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, micro and nanoemulsions, among others (Figure 10), have been developed in order to provide protection, stability, to enhance the activity of different bioactive compounds and to target the release of bioactive compounds with remarkable biological properties (Acosta, 2009; Almeida et al., 2010; Allan S, 2002; Fang et al., 2011; Mcclements et al., 2007; Pool et al., 2013; Pool et al., 2012). In this section, we present some studies that have been developed by encapsulating different bioactive compounds with neuroprotective properties into different controlled delivery systems.

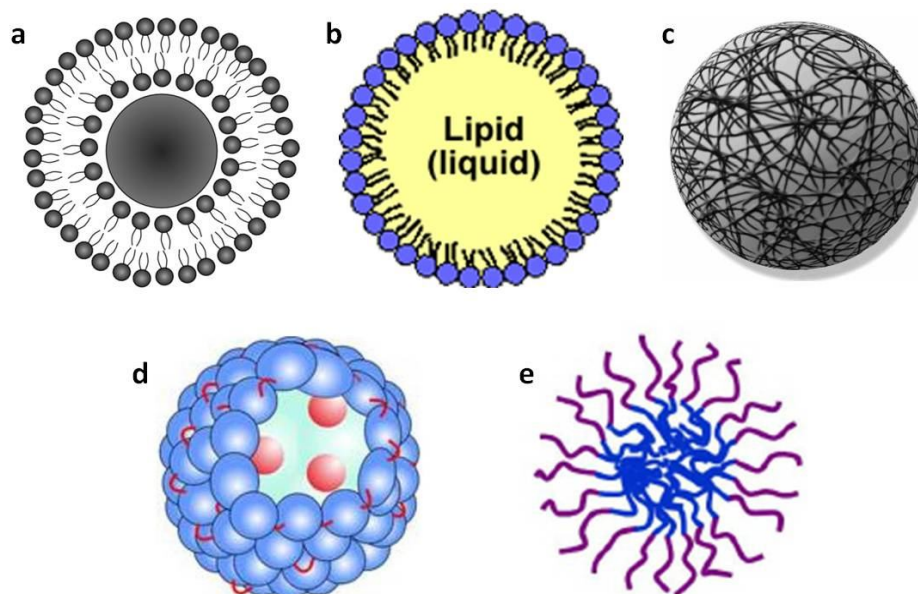


Figure 10. Schematic representation of the basic structure of unilamellar liposomes (a) O/W nanoemulsion (b), polymeric nanoparticles (c), nanogels (d) and micelles (e).

Thereby, several bioactive compounds, such as, flavonoids, vitamins, coenzyme Q10, resveratrol, monoterpenoids and others have demonstrated that can protect against neurological disorders acting by different pathways (Bahat-Stroomza et al., 2005). The mechanisms underlying these compounds have their beneficial properties are involved in their potent action as free radical scavengers, iron chelators-agents, inhibition of acetylcholinesterase activity, mainly (Mandel et al, 2008; Miyazawa et al., 1997).

It has been reported that oxidative stress (OS) is implicated in the development of neurodegenerat., mainly by the presence and attack of reactive oxygen species (ROS) that oxidize and injury neural cell components, such as lipids, proteins and DNA, leading to the appearance and prevalence of Alzheimer's or Parkinson's diseases, aging and many others neural disorders (Gilgun-Sherki et al., 2001; Rao y Balachandran, 2002; Sas et al., 2007; Uttara et al., 2009). In this way, flavonoids such as catechin, quercetin, rutin, have demonstrated that act as excellent free radical scavengers by rapid donation of a hydrogen atom to radicals (Seyoum et al., 2006). As recently reviewed by different authors, the antiradical activity of flavonoids depends on the molecular structure and the substitution pattern of hydroxyl groups, on the availability of phenolic hydrogens and on the possibility of stabilization of the resulting phenoxyl radical via hydrogen bonding or by expanded electron delocalization (Bors et al., 1990; Rice-Evans et al., 1996).

Quercetin, 3,5,7,3',4'-pentahydroxyflavone, one of the potential bioflavonoid generally found in fruits and vegetables, exert beneficial actions on the central nervous system, such as neuroprotection, antianxiety, and cognitive-enhancing effects, by acting as free radical scavenger (Cho et al., 2006). However, the poor absorption and very low distribution to the brain after oral administration, due to rapid metabolism and difficulties in the penetration thorough BBB decrease the beneficial properties in the brain of this flavonoid (Youdim et al., 2004). Due to these reasons, liposomes as nanocarriers for the delivery of quercetin into rats brain, have been developed in the last years (Priprem et al., 2008). The study was developed to investigate the anti-anxiety and cognitive effects of free quercetin and quercetin-loaded liposomes administrated by via oral and intranasal. Results showed that quercetin-loaded liposomes by intranasal administration exert better provide several

advantages including effectiveness at lower doses and a significant improvement in both anxiolytic and cognitive-enhancing effect than that of conventional quercetin and quercetin-loaded liposomes administrated via oral. Authors claimed that protective effects could be associated with the alteration of various neurotransmitters including gamma aminobutyric acid. Thus, results led to conclude that liposomes are a potential strategy to deliver bioactive compounds in to the brain for the treatment of various neuropharmacological disorders.

Also, the work of Pool et al. (2012) was based in the development of polymeric nanoparticles (NPs) using Eudragit L30-D55 (Eud) polymers for the encapsulation, protection and target release within gastrointestinal tract of quercetin. In this study, the encapsulation of quercetin into Eud enhanced the protection of multi-lamellar vesicles of soybean phosphatidylcholine against lipid peroxidation of peroxy and hydroxyl radicals. These results suggested that Eud NPs increased the lipid phase solubility of quercetin and also NPs act as protective agents against molecular oxygen, leading to a better free radical action than the free quercetin molecules used in the same experiments. Thus, these type or nanoparticulated systems might be suitable to cross the BBB and deliver antioxidants to combat the OS in brain.

Recently, one study reported the use of solid lipid NPs (SLN) as nanocarriers for ferulic acid [3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid; FA] (Picone et al., 2009), a phenolic compound that possesses anti-radical scavenging properties because its resonance-stabilized phenoxy radical, leading to strong antioxidant and anti-inflammatory activities (Ozaki, 1992). Authors showed that FA-loaded SLN were able to enhance the inhibition of neuronal oxidative stress and thus to block the cascade reactions leading to cellular death than free FA, mainly by the ability of the SLN systems to increase drug stability.

Studies have demonstrated that curcumin exerts a net protective effect against oxidative damages initiated by free radicals, divalent metals or by suppressing inflammatory damages by preventing metal induction of NF- κ B. Despite, curcumin is a highly lipophilic compound and has the ability to cross the BBB, the poor bioavailability represents a

limiting to its use in a functional product to combat neurological diseases (Kelloff et al., 2005). Accordingly, NPs decorated with appropriate ligands for curcumin brain delivery were developed lately (Mulik et al., 2010). These approaches were based in the preparation of curcumin-loaded PnBCA NPs decorated with ApoE3 ligand to exploit LDL-r- mediated transcytosis across the BBB and through SH-SY5Y cells (Figure 11). Results showed a reduction of A β 1-42 related toxicity on cells treated with the functionalized nanospheres along with a reduction of reactive oxygen species formation than the free curcumin used in this study. Another work demonstrated that curcumin-loaded PLGA nanoparticles obtained by an emulsion-diffusion evaporation method increase the neuroprotective effect on human SK-N-SH cells (neuroblastoma cell line) against the OS effect by reducing the elevation of ROS and the consumption of glutathione induced by H₂O₂. Also the uptake of the encapsulated curcumin into SK-N-SH cells was significantly improved than the free curcumin, which impact on the effects found them by researchers. Overall, this study demonstrated that the PLGA NPs have the capacity to protect human neuronal cells against oxidative damages, having a great potential to be used as bioactive compounds carriers in the application to treat several neurodegenerative disorders (Doggui et al., 2012).

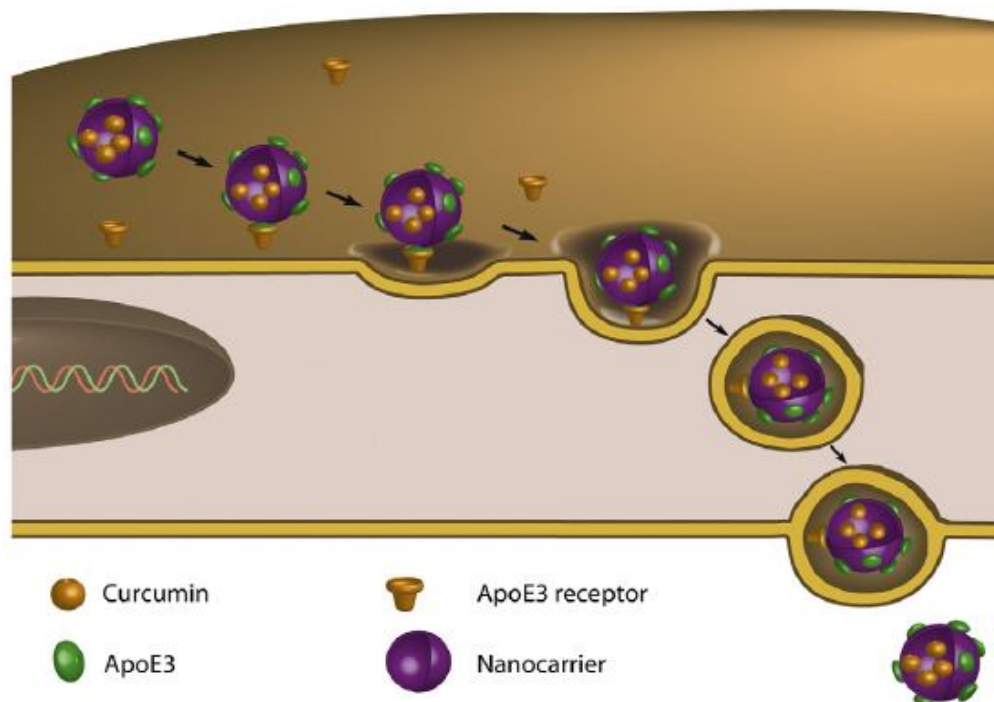


Figure 11. Schematic representation of curcumin-loaded PnBCA nanospheres decorated with ApoE3 crossing BBB via LDL-r. Adapted from Ramassamy (2006).

Brain normally contains a certain trace concentration of metal ions like Zn^{++} , Cu^{++} and Fe^{++} which possess different physiological roles. An increment of the concentration of these metals leads to several proteins and membrane lipids to toxic effects, and these concentrations of metal ions finally end in production of ROS (Bush, 2008; Castellani et al., 2007). Recently, some studies have demonstrated that green tea polyphenol, epigallocatechin-3-gallate (EGCG) have therapeutic effects for threat neurological diseases (Rezai-Zadeh et al., 2008). One of these neuroprotective effects of EGCG is by chelating Fe^{++} and Cu^{++} as shown in Figure 12. Unfortunately, the low bioavailability of EGCG alone could not be of therapeutic value if taken orally. In order to solve this problem, co-solubilized EGCG into lipid nanocarriers and EGCG:lipid complexes. Results showed that particles with diameter between 30 to 80 nm were obtained. Also, formulations showed an increase in bioavailability of EGCG than free EGCG analyzed. These results suggested a probable increase in EGCG brain uptake due to its very small size and to have great implications to delay the appearance of diverse neurological disorders.

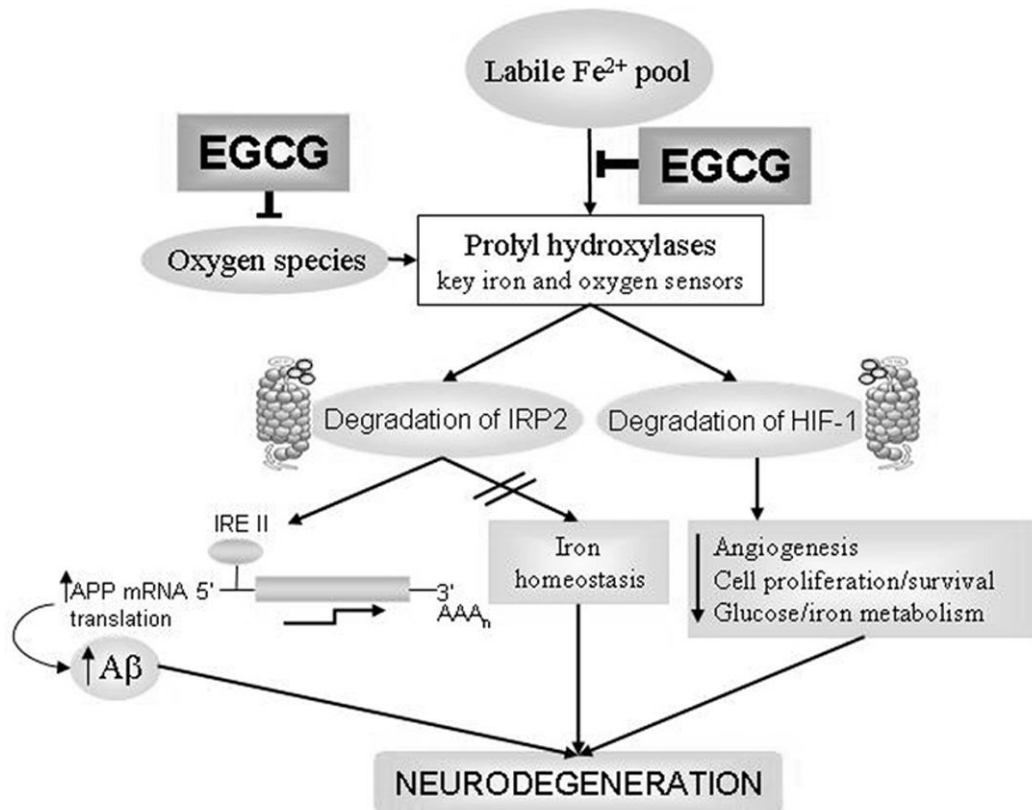


Figure 12. Iron-induced neurodegeneration in AD via transcriptional activation of APP mRNA and suppression of hypoxia-inducible genes. Increase in labile Fe²⁺ pool can elevate the production of APP via proteasomal-mediated inactivation of IRP2, thereby promoting the translation of APP mRNA from its 5'UTR-typeII). Increased iron and oxygen species may activate the prolyl hydroxylase enzymes, which are key iron and oxygen sensors, leading to proteasomal-mediated degradation of the transcription factor HIF-1 a master regulator orchestrating the coordinated induction of a wide array of survival genes. It has been suggested that IRP2, similar to HIF-1, can be enzymatically modified by a prolyl hydroxylase, routing it to proteasomal degradation. Both iron chelation and oxygen species scavenging by EGCG may prevent the degradation of IRP2 and HIF-1, resulting in the promotion of cell survival processes such as angiogenesis, glucose metabolism and maintenance of iron homeostasis. EGCG, IRP, HIF-1. Sharp arrows indicate positive inputs, whereas blunt arrows are for inhibitory inputs. Adapted from Mandel et al., (2006).

The main two sources of neurotoxicity in AD pathogenesis are A β oligomers and free radicals (Nazem y Mansoori, 2008) as shown in Figure 13.

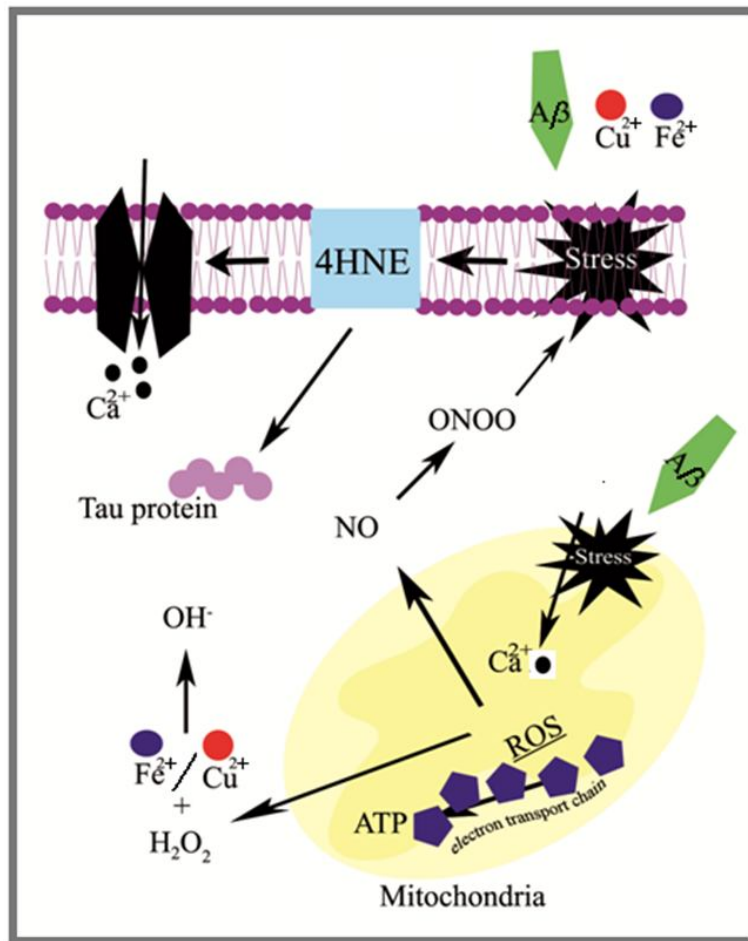


Figure 13. Schematic representation of Fe^+ and Cu^+ with $\text{A}\beta$ leading to the production of OS. Adapted from Nazem et al., (2011).

In this Figure (Figure 13) the interaction of Fe^{3+} and Cu^{2+} with $\text{A}\beta$ leading to the production of oxidative stress is shown. $\text{A}\beta$ can also oligomerize in the lipid bilayer of cell plasma membrane, leading to formation of membrane calcium channels (Quist et al., 2005). These calcium channels cause an imbalance in calcium homeostasis (Lin et al., 1999), that ends in oxidative stress. In addition, the membrane integrated $\text{A}\beta$ can chemically interact through (amino acid) Methionine 35 (not shown) with the membrane lipid molecules and the resultant lipid peroxidation produces 4-hydroxy-2-nonenal (4HNE) (Butterfield y Boyd-Kimball, 2005). Such an interaction leads to membrane disruption and production of reactive oxygen species and finally oxidative stress in the involved brain tissue. The 4HNE and other reactive oxygen species (ROS) also lead to tau phosphorylation and aggregation. Moreover, intracellular aggregates of $\text{A}\beta$ cause mitochondrial oxidative stress, and further

imbalance in Ca^{2+} hemostasis. The resultant impairment of electron transfer chain leads to overproduction of superoxide anion, which is converted either to H_2O_2 or to peroxynitrite ONOO (following interaction with nitric oxide (NO)). The interaction of H_2O_2 with Fe^{2+} or Cu^{2+} produces the hydroxyl radical (OH^*), a strong ROS that induces membrane-associated oxidative stress (Mattson, 2004).

Some of the nanotechnology-based approaches are capable of protecting neurons from $\text{A}\beta$ toxicity by preventing from amyloid oligomerization (*anti-assembly* strategy) and/or accumulation of $\text{A}\beta$ oligomeric species. The work of Ikeda et al. is an example for the $\text{A}\beta$ anti-assembly strategy (Ikeda et al., 2006). They designed an amphipathic nanogel that incorporates proteins and controls their folding and aggregation, similar to natural chaperones (proteins assisting the non-covalent folding and/or unfolding). In the case of $\text{A}\beta$, these nanogels would inhibit the amyloidogenesis process effectively through this mechanism (Figure 13). The nanogel (hydrogel nanoparticles) designed in this study was composed of cholesterol bearing pullulan (CHP). Pullulan is a natural water-soluble polysaccharide polymer consisting of maltotriose (a trisaccharide consisting of three glucose molecules linked with 1,4 glycosidic bonds) units. Inhibiting assembly at the monomer level, this technique prevents $\text{A}\beta$ oligomerization and therefore reduces the concentration of toxic $\text{A}\beta$ oligomeric species (Nazem et al., 2008). Recently, Boridy et al. (2009) demonstrated a significant reduction in $\text{A}\beta_{42}$ toxicity in the primary cortical cell culture and microglial cell culture after using CHP nanogels.

All these studies supporting the idea that different nanocarriers are suitable to improve the beneficial effect of different bioactive compounds with different neurological diseases, mainly by enhancing their poor low solubility, low bioavailability and the permeability through BBB. Also these bioactive compounds-loaded delivery systems could be in a sooner future, new therapies that replace the use of synthetic actives-loaded delivery systems.

Others uses of encapsulation technology of bioactive compounds in preventing diseases

Encapsulation constitutes a promising approach to preserve the native properties of several compounds over time. Encapsulation also represents a mean to improve biological efficiencies such as shelf life, control active components delivery and could prevent side effect apparition, such as the oxidation and degradation of the compound. In this regard, encapsulation of liposoluble vitamins has been exploited by its known benefits. Process choice, excipients physico-chemical properties and excipients/encapsulated vitamin interactions will determine particle characteristics (morphology, surface charges, permeability and encapsulation efficiency). Two major types of particles emerged: (i) lipid based formulations: in these particle vitamins are solubilized, and (ii) vitamins matricial entrapment by polymer (Gonnet et al., 2010). According to encapsulation processes various types of liposoluble vitamin carriers can be obtained as illustrated in Figure 14.

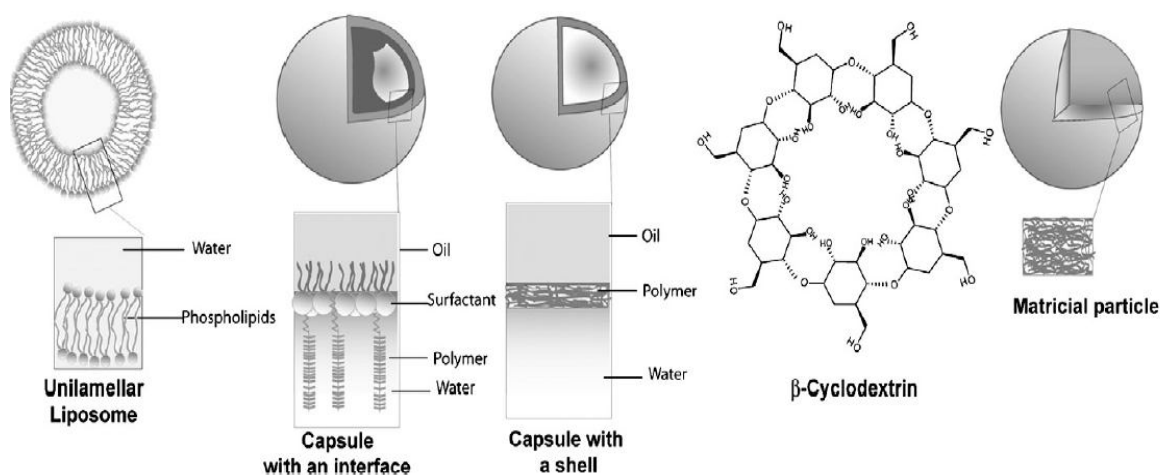


Figure 14. Type of carrier encountered in lipophilic vitamin encapsulation. Adapted from Gonnet et al., (2010).

Increasing vitamin A solubility is achieved as soon as it is incorporated into a hydrophilic structure such as protein structures, liposomes or cyclodextrins. For example, the aqueous solubility of all-trans-retinoic acid increases by more than 100 times after complexation with β -cyclodextrins (Qi and Shieh, 2002) and more than 10000 times after complexation with hydroxypropyl β -cyclodextrins (Lin et al., 2000). Vitamin A incorporation into liposome membranes is generally high. Entrapment efficiency of 95% and more is reported for retinol in liposomes (Fresno-Contreras et al., 2002). Encapsulation of retinyl-esters in self-nanoemulsified systems filled capsules and compressed tablets, have been studied

regarding absorption efficiency in rats and compared the bioavailability of the standard vitamin A oily solution filled-capsule without additive, resulting that vitamin A in self-nanoemulsified systems filled capsules and compressed tablets showed a significant increase in the rate and extent of drug absorption and bioavailability of vitamin A (a 2 fold increase in the case of capsules and a 1.4 fold increase in the case of tablets compared with oil capsules) (Taha et al., 2007). Padamwar and Pokharkar (2006) demonstrated that composition of liposome bilayers could influence tocopherol acetate release. Low concentrations of PLs and Ch might involve lower interactions between tocopherol acetate and PLs, inducing a more efficient vitamin release from liposomes. Vitamin E acetate encapsulation efficiency was about 100% and did not depend on excipient concentration. Somchue et al., (2009) reported that α -tocopherol of approx. 55% and 38% were retained and released in the simulated intestinal condition from β -lactoglobulin- and hen egg white protein-encapsulated particles, respectively. Melt extrusion has been adapted to low moisture conditions for vitamin K (dissolved in oil) and vitamin D (crystalline form) encapsulation. Encapsulation of vitamin K ranged from 66 to 99% which is high considering the temperatures employed. In the vitamin D encapsulation, granulates were formed right after the diehead by section of extruded material at high temperatures around 100 °C. Carbohydrate composition had an impact on process temperature and thus on vitamin preservation. It ranged from 66 to 99% which is high considering the temperatures employed (Petritz et al., 2006).

On the other hand, interest in the health benefits of folic acid has increased considerably over the last 15 years. It has been known for some time that optimizing blood folate levels around the time of conception and in the early weeks of pregnancy can significantly reduce the chance of neural tube defects (NTD) during pregnancy. Folates provide protection against coronary heart disease (Brouwer *et al.*, 2000), cognitive functions (Seshadri *et al.*, 2002) and prevention of certain forms of cancer (Giovannucci *et al.*, 1995). Folic acid microencapsulated into alginate-pectin capsules were incorporated into a diet with excess dietary methionine using Cheddar cheese as the food carrier and fed to mice. It was found that hyperhomocysteinemia caused by the dietary addition of 10 g/kg methionine was completely counteracted by the encapsulated folic acid compared to free folic acid.

Encapsulated folic acid caused substantial reduction in plasma homocysteine and arterial lesions in mice fed the diet supplemented with 20 g/kg methionine compared with free folic acid (Kailasapathy, 2008).

Prebiotics have been defined by Gibson and Roberfroid (1995) as: “a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve host health”. The major prebiotics which are used as human nutrition are inulin, galacto-oligosaccharides, fructo-oligosaccharides, lactulose, malto-oligosaccharides and resin starch. The prebiotics are reduces the risk of diseases such as: constipation relief that results due to the fecal bulking and intestinal motility, suppression of diarrhea associated with intestinal infections, reduction of risk of osteoporosis results in the improvement of bioavailability of calcium and minerals, reduction in the risk of cardiovascular disease associated with dyslipidemia, obesity and type 2 diabetes, as well as it shows cancer inhibitory effects, among others (Singh et al., 2012). For these reasons, the utilization of prebiotic compounds for the nano-encapsulation and delivery of bioactive material holds a promising future. The prebiotic-based nanocarrier formulations can improve the bioavailability of bioactive compounds that are prone to be degraded along the upper GI tract, giving an added value on the prevention of disease development (Heidarpour et al., 2011).

Iyer and Kailasapathy (2005) used three different complementary prebiotics (inulin, oligofructose and high amylase corn starch) separately, selected by *in vitro* fermentation, to co-encapsulated *Lactobacillus acidophilus* CSCC 2400 or CSCC 2409 and tested for their efficacy in improving the viability of bacteria under *in vitro* acidic conditions. Three different coating materials, poly-L-lysine, CS, and alginate were tested for their efficacy in protecting the viability of encapsulated bacteria at low pH (pH 2.0) and a set-type yogurt was prepared for this experiment. The results of this study showed that addition of Hi-maize (1.0% w/v) as a co-encapsulant and further coating the capsule with CS appears to improve the survival of encapsulated probiotic bacteria significantly under *in vitro* acidic condition and in yogurt compared with alginate encapsulated cells. This could be because

there is Hi-maize inside the capsular matrix blocking the pores of the capsule, thereby preventing the diffusion of acidic contents in to the capsule. Chen et al., (2005) reported an increase in the survival of probiotic bacteria when encapsulated with a prebiotic source. The authors produced capsules via extrusion containing 4.0% v/v probiotics (1.0% of each *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum* and *B. longum*), 1.0–3.0% sodium alginate, 0–3.0% prebiotics (FOS and isomaltooligosaccharides) and 0–1.0% peptides (pancreatic-digested casein). These probiotic counts remained at 10^6 to 10^7 colony-forming units (CFU)/g for microcapsules stored for 1 mo and then treated in simulated gastric fluid test and bile salt test.

Finally, curcumin possesses a wide range of biological activities including anti-bacterial properties among others mentioned above. Therefore this compound was incorporated into CS-poly(vinyl alcohol) (PVA) silver nanoparticles film by Vimala et al., (2011) to improve significantly the therapeutic antibacterial efficacy of the film. CS-PVA silver nanoparticle films demonstrated significant effects against *Escherichia coli* (*E. coli*), *Pseudomonas*, *Staphylococcus*, *Micrococcus*, *Candida albicans*, and *Pseudomonas aeruginosa* (*P. aeruginosa*). However, curcumin encapsulated CS-PVA silver nanocomposite films showed enormous growth inhibition of *E. coli* compared to curcumin and CS-PVA silver nanoparticles film alone. This bioactive compound may find potential applications in antimicrobial packaging materials and wound dressing/wound burns.

CONCLUSION

Many nutraceutical and functional food components would benefit from being encapsulated in appropriate edible delivery systems, including vitamins, bioactive peptides, antimicrobials, antioxidants, flavors, among others. Consequently, different delivery systems are usually needed to address specific molecular and physicochemical concerns associated with each nutraceutical or functional component. Simple structured delivery systems for the active ingredients can be fabricated using relatively uncomplicated processing operations, such as emulsions, colloids, suspensions, gels, and solid matrices. This review article has provided an overview of several types of structured delivery system

that are available for encapsulating bioactive compounds and it has highlighted their uses in the major diseases afflicting the world, such as diabetes, cancer, obesity, cardiovascular disease, neurogological diseases and others, offering short term use as an adjunct to treat and/or prevent their development. Overall, the information given in this review suggests that these bioactive compound-loaded delivery systems could replace the current disease therapies that using synthetic compounds in a near future. However, more studies are necessary in order to understand the pros and cons of the use of several delivery systems loaded with bioactive compounds, in order to avoid future complications in human body.

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