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NANO-ENCAPSULATION OF POLYPHENOL COMPOUNDS: A REVIEW

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ABSTRACT

Natural polyphenolic compounds have several health benefits and no side effects compared to synthetic compounds. But these compounds having low water solubility, poor bioavailability, lack in long-term stability and are very sensitive to light. These compounds via nano-sized colloidal carriers such as polymeric nanoparticles offers a novel strategy to overcome these limitations. Nano-encapsulation remains to be the one of the most promising technologies having the ability to entrap polyphenolic compounds. These nano-encapsulated compounds has versatile advantages for targeted site-specific delivery and efficient absorption through cells. This review presents about main classes of polyphenolic compounds, their advantages, polymers used in the preparation of nanoparticles and the various techniques to create nanoparticles encapsulating polyphenols that will increase their solubility and bioavailability.

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INTRODUCTION

Nano-encapsulation is defined as a technology to encapsulate substances in miniature and refers to bioactive packing at the nanoscale range.[1]. Nanoencapsulation of drug molecules in nanocarriers is a very promising approach for development of nanomedicine. Nanoparticles are colloidal-sized particles with diameters ranging from 10 to 1,000 nm and are expressed both as nanocapsules and nanospheres[2]. Nanocapsules are vesicular systems in which the bioactive compound is confined to a cavity surrounded by a unique polymer membrane (Figure 1), while nanospheres are matrix systems where the bioactive compound is uniformly dispersed [3]. The delivery of any bioactive compound to various sites within the body is directly affected by the particle size[4]. Nanoencapsulation methods allow efficient loading of drug molecules inside the nano-carriers thereby reducing systemic toxicity associated with drugs. The targeting of drug can enhance the accumulation of nano-nencapsulated drug at the diseased site[5].The therapeutic agents which are nano-encapsulated will increases their efficacy, specificity and targeting ability. Nanocarriers can enhance the solubility of the drug, improving administration, taste masking, prolong presence of drug in blood and cellular uptake and protect the drug from premature degradation in the biological environment and enhance the bioavailability.

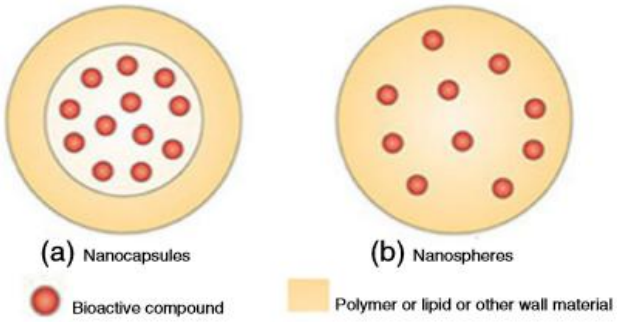

Fig. 1 Schematic structure of a) nano-capsules and b) nano-spheres.

Polyphenols are secondary metabolites produced by plants, in which they play an important role in growth and reproduction as well as resistance to pathogens, predators, and diseases. Polyphenolic compounds are recognized for their direct free-radical scavenging activity and complexing properties towards proteins. These abilities make polyphenols interesting for the treatment of various diseases like cancer, cardiovascular disease, neurological diseases, osteoporosis, diabetes, but also for anti-ageing purposes in cosmetic formulations and for nutraceutical applications. Polyphenols have a low bioavailability due to a number of intrinsic and extrinsic factors including their molecular weight and chemical structure, low hydro-solubility, binding within food matrices, low stability in the gastrointestinal (GI) environment, extensive phase II metabolism, and rapid elimination[6]. These properties will affect the shelf life of the pharmaceutical agent and they will become more sensitive to light and heat [7] .The polyphenolic compound possess a very astringent and bitter taste, which limits their use in food or in oral medications. The nano-encapsulated drug delivery systems have been developed to overcome these drawbacks and thus improves the administration and enhances bioavailability [8].

Table 1: Main classes of plant polyphenols, structures, sources, their specifications and biological properties [9,10]

	CARBON SKELETON	EXAMPLES	SOURCES	SPECIFICATIONS	SPECIFICATIONS
Phenolic acids and coumarines					
Hydroxybenzoic acids	C6-C1	Gallic acid, Vanillic acid, Protocatechuic acid, p-Hydroxy benzoic acid	Tea, Red fruit (raspberry, black currant, strawberry	Very common, in free form as well as combined,not much studied and not considered to be of great nutritional interest, sensitive to temperature, oxidation, light and pH, water soluble	Very limited therapeutic interest,antimicrobial activity and fungi toxicity,anti-inflammatory properties of salicylates
Hydroxycinnamic acids	C6-C3	Caffeic acid, p-Coumaric,Ferulic acid	Fruit (kiwis, blueberries, apples) Cereal grains (wheat, rice, oat flours)	Rarely found in free form, often esterified, sensitive to oxidation and pH, slightly soluble in water	
Coumarines		OmbelliferoneAesculetin, Scopoletin	Tonka bean, bark (chestnut), medicinal plants (Melilotus officinalis, Angelica officinalis	Free coumarines are soluble in alcohols and organic solvents, the heterosidic forms are less soluble in water	Anti-inflammatory and antiviral activities, limited pharmacological applications: hepatotoxicity
Stilbenes	C6-C2C6	Resveratrol	Medicinal plants (vine	Found only in low quantities in the human diet	Anticarcinogenic effects, anti-inflammatory activity
Flavonoids	C6-C3C6				
Flavonols		Myricetin, Quercetin, Kaempferol and their glycosylated forms	Fruit and vegetables (Onions, curly kale, leeks, broccoli, blueberries), red wine and tea	Flavonols are the most ubiquitous flavonoids in food Vitamin	Vitamin P factor protecting capillaries and veins, often anti-inflammatory, antiallergenic, antiviral, anti-spasmodic, antibacterial, antioxidant and anti-carcinogenic properties, hepatoprotector, some are powerful enzymatic inhibitors
Flavones		Aspigenin, Luteolin, Tangeretin, Nobiletin, Sinensetin	Parsley, celery, cereals (millet and wheat) Skin of citrus	Flavones are much less common than flavonols in fruit and vegetables	
Flavanones		Hesperetin, Naringenin, Eriodictyol	Citrus fruit (grapefruit, orange, lemon), tomatoes and some aromatic	Sensitive to oxidation, light and pH, bitter taste	

			plants (mint)		
Isoflavones		Genistein, Daidzein, Glycitein	Leguminous plants (soya and its processed products	Structural similarities with estrogens confers pseudohormonal properties	
Flavanols					
Monomer form		Catechin, Epicatechin	Fruit (apricot, cherry, grape, peach, apple), green and black tea, red wine and cider	Sensitive to oxidation, light and pH, astringent and bitter taste, slightly soluble in water	
Polymer form Proanthocyanidins	(C15)n	Castalin, Vescalin	Fruit (grapes, peaches, kakis, apples, berries), beverages (wine, cider, tea, beer), chocolate	Responsible for the astringent character and bitter taste, sensitive to high temperature and oxidation, water and alcohol soluble	
Anthocyanins		Cyanidin, Pelargonidin, Delphinidin, Petunidin	Red wine, some varieties of cereals, some leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), flowers and most abundant in fruit	Plant pigments, highly sensitive to temperature, oxidation, pH and light, water soluble	
Lignans	(C6-C3)2	Pinoresinol, Podophyllotoxin, Steganacin	Flax seed, sesame seed, cereals (rye, wheat, oat, barley), cruciferous vegetables (broccoli, cabbage), and fruit (apricots, strawberries)	One of the major classes of phytoestrogens, relatively stable under normal conditions, water soluble, unpleasant flavour	Hepatoprotector, antimitotic, antiviral, antihypertensive and cytostatic activities, inhibitors of enzymatic reactions

Advantages of polymeric nanoparticles [11,12]

- We can increases the stability of any volatile pharmaceutical agents.
- We can effectively improve over traditional oral and intravenous methods of administration.
- We can easily and fastly delivers the pharmaceutical agent at higher concentration to a diseased site at a desired rate.
- Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering.
- The ability to modify drug release from polymeric nanoparticles and the choice of polymer have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.

Polymers used in preparation of nanoparticles[13,14]

The polymers should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatibleThe polymers used are of two types:

Natural polymers
Synthetic polymers

NATURAL POLYMERS	SYNTHETIC POLYMERS
❖ Chitosan	❖ Polylactides(PLA)
❖ Gelatin	❖ Polyglycolides(PGA)
❖ Sodium alginate	❖ Poly(lactide co-glycolides) (PLGA)
❖ Albumin	❖ Polycyanoacrylates
	❖ Poly(N-vinyl pyrrolidone)
	❖ Poly(vinyl alcohol)
	❖ Poly(acrylic acid)
	❖ Poly(ethylene glycol)
	❖ Poly(methacrylic acid)

Techniques for the preparation of nanoparticles

The physicochemical properties such as particle size, size distribution, surface area, shape, solubility, and encapsulation efficiency, and releasing mechanisms were reported to be altered by the encapsulation technique and delivery system. Therefore, it is more essential to select the appropriate encapsulation technique based on the required size, physicochemical properties, nature of the core material, and wall material. Moreover, the techniques used for achieving nano-encapsulation are more complex than microencapsulation. It is mainly due to the difficulty in attaining a complex morphology of the capsule and core material and the demands of releasing rates of nano-encapsulates[15]. There are a very large number of encapsulation methods that can be classified as follows: Physical methods: spray-drying, fluid bed coating, extrusion-spheronization, centrifugal extrusion, processes using the supercritical fluids. Physicochemical methods: spray-cooling, hot melt coating, ionic gelation, solvent evaporation-extraction, simple or complex coacervation. Chemical methods: interfacial polycondensation, *in situ* polymerization, interfacial polymerization, interfacial cross-linking. This review mainly focuses on the most commonly used encapsulation methods applied to polyphenols.

SOLVENT EVAPORATION

Solvent evaporation was the first method developed to prepare nanoparticle (Figure 2). Polymer solutions are prepared in volatile solvents and emulsions are formulated. Dichloromethane and chloroform preformed polymer were widely used. But they are now replaced with ethyl acetate which has a better toxicological profile. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods utilize high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. Then the solidified nanoparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants. Finally, the product is lyophilized [16] .The prepared nanoparticles of PLGA with a typical particle size of 60–200nm by employing dichloromethane and acetone as the solvent system and PVA as the stabilizing agent. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultrasonication can be employed.

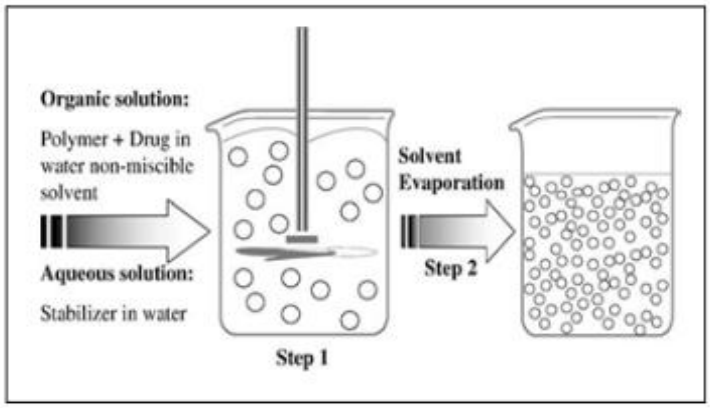

Fig. 2: Schematic representation of the solvent-evaporation technique.

NANO-PRECIPITATION

Nano-precipitation is also called solvent displacement method. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. The solvent displacement technique allows the preparation of nano-capsules when a small volume of nontoxic oil is incorporated in the organic phase. The usefulness of this simple technique is limited to water-miscible solvents, in which the diffusion rate is enough to produce spontaneous emulsification. The water-miscible solvents produce a certain instability when mixed with water, spontaneous emulsification is not observed if the coalescence rate of the formed droplets is sufficiently high. Acetone or dichloromethane are mainly used to dissolve and increase the entrapment of drugs. This method is basically applicable to lipophilic drugs because of the miscibility of the solvent with the aqueous phase. Highly loaded nanoparticulate systems based on amphiphilic hcyclodextrins to facilitate the parenteral administration of the poorly soluble antifungal drugs Bifonazole and Clotrimazole were prepared according to the solvent displacement method[17].

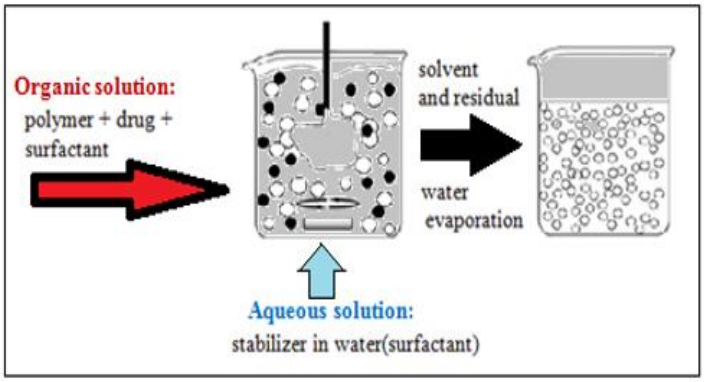

Fig. 3: Schematic representation of the nano-precipitation technique.

EMULSIFICATION/SOLVENT DIFFUSION (ESD)

Solvent diffusion is a modified version of solvent evaporation method. The encapsulating polymer is dissolved in a partially water soluble solvent such as propylene carbonate and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. In fact, , It is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partly miscible with water or with another organic solvent in the opposite case to produce the precipitation of the polymer and the consequent formation of nanoparticles. Afterwards, polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. This technique presents several advantages, such as high encapsulation efficiencies (generally >70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. This technique is suitable for encapsulating lipophilic. Several drug-loaded nanoparticles were produced by the ESD technique, including mesotetra(hydroxyphenyl) porphyrinloaded PLGA (p-THPP) nanoparticles, doxorubicin-loaded PLGA nanoparticles etc.

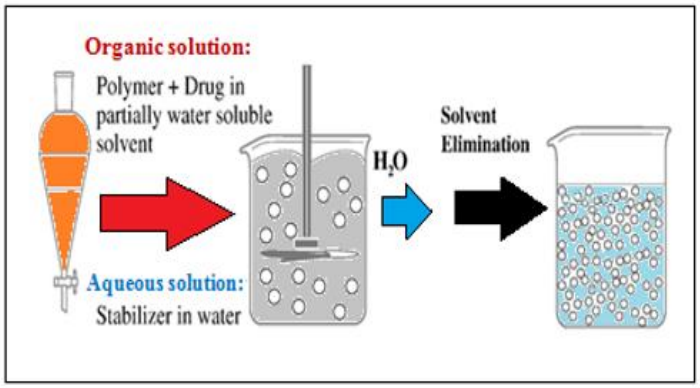

Fig. 4: Schematic representation of the emulsification/solvent diffusion technique.

SALTING OUT

The salting out method can be considered as a modification of the emulsification/solvent diffusion. Salting out is based on the separation of a water miscible solvent from aqueous solution via a salting out effect. Drug and polymer are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent (electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose) and a colloidal stabilizer such as polyvinyl pyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nano-spheres. Both the solvent and the salting out agent are then eliminated by cross-flow filtration. This technique used in the preparation of PLA, poly (methacrylic) acid, nanospheres. The main advantage of salting out is that it minimizes stress to protein. Salting out does not require an increase of temperature and therefore, may be useful when heat sensitive substances have to be used.

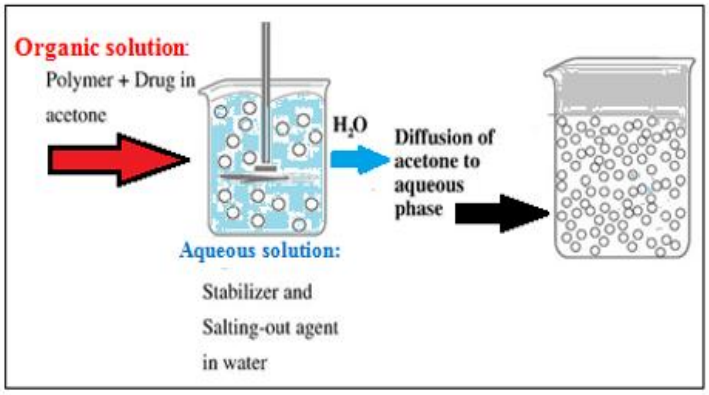

Fig. 5: Schematic representation of salting-out method.

SUPERCRITICAL FLUID TECHNOLOGY

Supercritical fluid technology (SCFT) is a new method to produce fine drug particles and is valuable for product quality, batch consistency and the reduction of manufacturing barrier in many areas of pharmaceutical applications [(18)].It is an environmentally safer methods for the production of nanoparticles with the potential to produce with high purity and without any trace of organic solvent.Supercritical fluid technology are effective technique of particle production by avoiding most of the drawbacks of the traditional methods. Two principles have been developed for the production of nanoparticles using supercritical fluids:

1. Rapid expansion of supercritical solution (RESS)
2. Rapid expansion of supercritical solution into liquid solvent

Preparation of nanoparticles by polymerization of a monomer:

Processes for the production of polymeric nanoparticles through the polymerization of monomers are discussed below:

EMULSION POLYMERIZATION

Emulsion polymerization is one of the fastest methods for nanoparticle preparation. The method is classified into two categories based on the use of an organic or aqueous continuous phase. The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse microemulsion, or into a material in which the monomer is not soluble (nonsolvent). Polyacrylamide nanospheres can be produced by this method This procedure has become less important, because it requires toxic organic solvents, surfactants, monomers and initiator, which are subsequently eliminated from the formed particles.

INTERFACIAL POLYMERIZATION

It is one of the widely used methods for the preparation of polymer nanoparticles. It involves step polymerization of two reactive monomers or agents, which are dissolved respectively in continuous and dispersed phase.The reaction takes place at the interface of the two liquids Nanometer-sized hollow polymer particles were synthesized by employing interfacial cross-linking reactions as polyaddition and polycondensation 100-102 or radical polymerization.Oil-containing nanocapsules were obtained by the polymerization of monomers at the oil/water interface of a very fine oil-in-water micro- emulsion105. The organic solvent, which are completely miscible with water, served as a monomer vehicle and the interfacial polymerization of the monomer was believed to occur at the surface of the oil droplets that formed during emulsification. To promote nanocapsule formation, the use of aprotic solvents, such as acetone and acetonitrile was recommended. Protic solvents, such as ethanol, n-butanol and isopropanol, were found to induce the formation of nanospheres in addition to nanocapsules[19]

IONIC GELATION OR COACERVATION OF HYDROPHILIC POLYMERS

Polymeric nanoparticles are prepared by using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate[20] This method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tripolyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

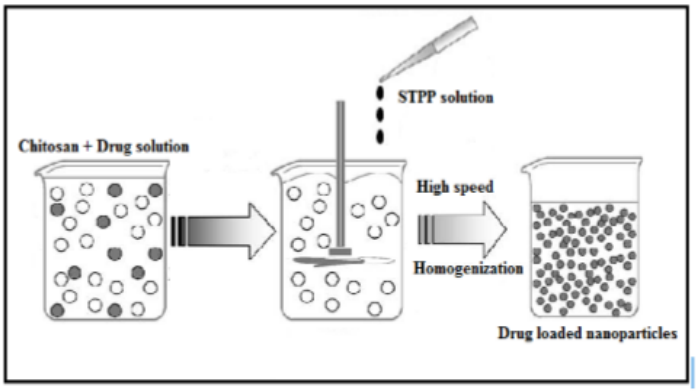

Fig.6: Schematic representation of ionic gelation method.

CONCLUSION

Polyphenols are the most powerful active compounds synthesized by plants and marine organisms. However, their limited stability, poor solubility and bioavailability, have to be resolved in order to make these compounds into a nano-encapsulated formulation. The various reported research revealed that physicochemical nano-encapsulation provided a significant protection against drastic conditions such as oxidation and thermal degradation, thereby contributing to increase the shelf life of the active ingredients. The nanoparticles are also able to control the release, change the physical properties of the initial material, and improve the bioavailability of the polyphenolic compound. Overall, the information given in this review suggests that these nanoencapsulated natural polyphenolic compound will replace the current disease therapies that using synthetic compounds in a near future.

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