

Review

Delivery Systems for Hydroxytyrosol Supplementation: State of the Art

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Abstract: This review aims to highlight the benefits and limitations of the main colloid-based available delivery systems for hydroxytyrosol. Hydroxytyrosol is a phenolic compound with clear biological activities for human wellness. Olive fruits, leaves and extra-virgin oil are the main food sources of hydroxytyrosol. Moreover, olive oil mill wastewaters are considered a potential source to obtain hydroxytyrosol to use in the food industry. However, recovered hydroxytyrosol needs adequate formulations and delivery systems to increase its chemical stability and bioavailability. Therefore, the application of hydroxytyrosol delivery systems in food sector is still a fascinating challenge. Principal delivery systems are based on the use of colloids, polymers able to perform gelling, thickening and stabilizing functions in various industrial sectors, including food manufacturing. Here, we review the recipes for the available hydroxytyrosol systems and their relative production methods, as well as aspects relative to system characteristics and hydroxytyrosol effectiveness.

Keywords: hydroxytyrosol; drug delivery systems; emulsions; liposomes; encapsulation; active packaging

1. Introduction

One of the aspects of the modern trends in food science is the growing demand of consumers for healthier lifestyles. In this context, hydroxytyrosol (HY) is a good candidate to satisfy this request, because it is a natural phenolic compound with proven bio-antioxidant activity and other health-promoting effects [1,2]. HY is frequently found in fruits and vegetables and is synthesized even in our body as a byproduct of dopamine oxidative metabolism [3]. However, the main sources of HY are the edible parts of olive tree (*Olea europaea*) such as olive fruits, leaves and extra virgin oil [4]. Additionally, olive by-product, especially olive mill wastewaters (OMW), a very pollutant waste [5], represent a potential source of HY [6]. Therefore, HY recovery from OMW represents a great opportunity to valorize these by-products with various environmental advantages and economic benefits [7].

Both pharmaceutical and food industries are trying to develop strategies to incorporate HY into new products, improving its solubility, stability against oxidation and bioavailability. However, suitable formulations are needed in order to increase the chemical stability and bioavailability of the HY. In this sense, one of the strategies is the application of delivery systems specific for HY [8–10]. The colloid science approach to food product preparation is centered on the supposition that the main product parameters, such as physical stability and appearance, are determined by the spatial distribution and interactions of the constituents (particles, droplets) ordered in various types of structural arrangements. Food colloids offer considerable potential for controlling several functionalities. The structure and interfacial properties of colloids are critical to manipulate food stability before and after consumption.

Examples of possible delivery systems for hydrophilic compounds can be found in molecular complexes (polyphenols can form complexes with various proteins), liposomes (vitamin C, iron and

calcium have previously been incorporated into liposome-based delivery systems), multiple emulsions (numerous applications of water-in-oil-in-water (W/O/W) emulsions for delivering water-soluble minerals, vitamins, pigments and, nutraceuticals have been reported in the literature).

The aim of this review is to present the state-of-the-art HY delivery systems, especially those based on the use of colloids already widely used in several industrial fields, including medicine and food. Specifically, emulsion-based systems, encapsulated systems, liposomes and active packaging are the HY delivery systems discussed in this review.

2. Hydroxytyrosol

2.1. General Information and Sources

Hydroxytyrosol (3,4-dihydroxyphenylethanol, 3,4-DHPEA or HY) is a natural phenolic compound with chemical formula $C_8H_{10}O_3$ and molecular mass of 154.16 g/mol. It can be found in free form or linked with other compounds, such as in the cases of the HY-4-beta-D-Glucoside, oleuropein or oleacin secoiridoid complexes, acetate form, verbascoside and others [4]. In reality, the HY free form (Figure 1) is rarely present in nature and its production requires enzymatic or chemical hydrolysis of the complex phenols wherein it is contained [11]. Natural hydrolysis mechanism is based on enzymatic processes, while acid approaches are the more ones used in laboratorial and industrial contexts.

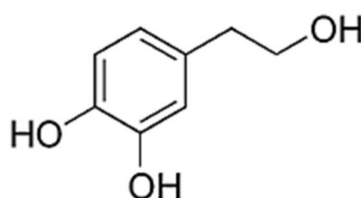


Figure 1. Molecular structure of free hydroxytyrosol.

HY is water-soluble and has a partition coefficient of $\log P_{o/w} = 1.1$ revealing also an amphiphilic character [12]. HY synthesis is based on chemical resemblance of natural compounds, as tyrosol [13] or tyrosine [14].

Regarding the extraction of HY from natural matrixes, the liquid–liquid extraction with methanol, ethanol or both [15], or solid-phase extractions [16] are commonly used. In this context, a lot of methods and technologies have been developed and patented with the aim to produce extracts rich in HY from olive oil mill by-products, such as leaves or wastewaters [2,4,17–19].

2.2. Food Application and Health Effects

It was proven that the ortho-diphenolic group of HY is responsible of its capacity to break the peroxidative chain reaction [20] and to scavenge reactive oxygen species (ROS) such as peroxy, hydroperoxy and other free radicals, reactive nitrogen species, superoxide anions and hypochlorous acid [21–24]. This group allows for the hydrogen donation process and improves radical stability by forming an intramolecular hydrogen bond between the free hydrogens of HY hydroxyl group and the phenoxyl radicals [20]. Due to these potent redox properties, HY is considered one of the strongest antioxidants in nature [25].

HY safety and HY healthiness are approved by the European Food Safety Authority (EFSA) which recommends an intake of 5 mg HY per day in order to obtain the targeted benefits [26]. The role of HY in human health has been investigated in numerous studies, and the main activities found are the following: antioxidant, cardioprotective, anti-inflammatory, antimicrobial, anti-atherogenic, anti-tumor, neuroprotective, respiratory disease prevention and metabolic syndrome prevention [27–34].

HY is absorbed in the small intestine and excreted through urine [35]. However, HY in its free form shows a good absorption but poor matrix-dependent bioavailability. After the assumption, it is

rapidly eliminated by renal and digestive systems, remaining in the plasma for about 1 min. However, HY has no known toxic effects in both cells and animal models [36].

Therefore, all the above-reported positive activities strengthen the potential of HY as nutraceutical compounds for functional foods or food supplements, especially for people that do not consume olives or olive oil on a daily basis [37]. Effectively, the interest in using HY as a nutraceutical for the prevention and treatment of different diseases is increasing. In addition, even the use of HY as a food additive is highly considered, especially as an antioxidant for extending the shelf-life of foodstuffs [38]. This last HY application should not be underestimated, especially considering the consumer's aversion to synthetic antioxidants, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) [39,40]. Unfortunately, the multiple hydroxyl groups of HY structure are very sensitive to air and light and have a very strong instability and hydrophilicity that could affect HY's biological activity, causing difficulty in mixing HY into foods or drug formulations.

3. Delivery Systems

3.1. Emulsion-Based Systems

Overall, emulsion-based systems are colloidal dispersions (CD) in which two immiscible liquids, such as water and oil, are dispersed one in the other in the form of droplets [41]. Emulsifiers (Figure 2A), also called surfactants, are amphiphilic molecules that are added to realize the colloidal dispersion. Surfactants are essential for both the formation and long-term stability of the CD against separation phenomena [42,43].

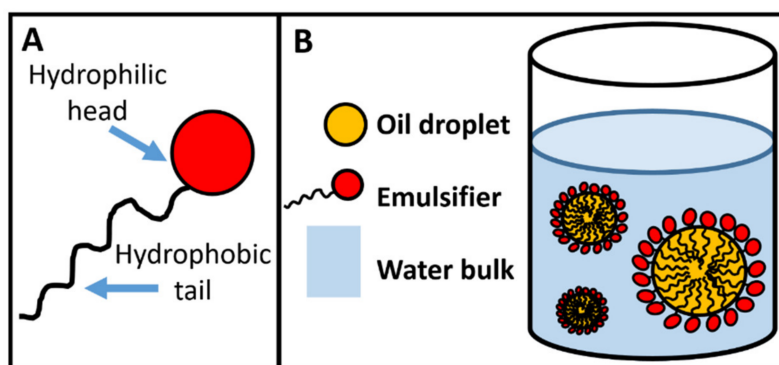


Figure 2. Schematic structure of surfactants (A) and oil-in-water emulsion-based system (B).

As functions of the ratio between these constituents, the final systems can be: (i) a continuous oil dispersion of water droplets (W/O); (ii) a confined oil domain in an aqueous environment (O/W) (Figure 2B); (iii) a bi-continuous system with an equal amount of oil and water.

Thus, oil, emulsifier and water are the main components of an emulsion-based system. Food-grade ingredients permitted by the EFSA are lecithin, monoglycerides and diglycerides such as surfactants; medium chain triglycerides (MCT) and isopropyl myristate (IPM) as oils; and ethanol and glycerol as aqueous phases. In addition, co-surfactants, such as *n*-alcohols and alkyl carboxylic acids, may be added in order to lower the interfacial tension and stabilize the dispersions [44].

3.1.1. Colloidal Dispersions

Generally, colloidal dispersions (CD) are thermodynamically stable and isotropic mixtures of two immiscible liquids, such as water and oil, stabilized by surfactants acting as an interface in the formation of isotropic self-assembled droplets.

Two different types of CD are possible: macroemulsions (MAE) and microemulsion (MIE) [45]. Both of them offer the possibility to solubilize hydrophilic and hydrophobic substances in the continuous and dispersed phases [45]. MAE are kinetically stable and almost transparent systems, but they are

thermodynamically unstable due to the interfacial tension of the large droplets that range from 100 nm to 100 μm . MIE are characterized by a smaller particle size, ranging from 5 to 50 nm with a lower interfacial tension.

Nowadays, there is an increasing interest in the formulation of food-grade microemulsions (MIE) such as reservoirs and carriers of bioactive substances, comprising phenolic antioxidants [46].

To form both MAE and MIE, HY must be dissolved at the desired concentration in distilled water in presence of a surfactant (aqueous phase (W) of the emulsion). Then, the lipidic phase (O) is gently added to the outer aqueous phase and the final system is realized, providing energy through homogenization. It was found that a large percentage of HY (> 40%) is located in the interfacial region of the emulsion, increasing antioxidant effects [47].

Both MAE and MIE obtained with medium-chain triglycerides (MCT) as the continuous phase showed to be good delivery systems for the HY, evidencing a higher releasing, long shelf life and improved solubilization and stability of the bioactive compound. However, HY losses during the preparation of MAE and MIE was observed, along with a decrease of its antioxidant effect during the storage [12].

3.1.2. Double Emulsions

Multiple or double emulsions (DE) are more complex liquid dispersions in which globules containing small fluid droplets are re-dispersed in the same fluid of the continuous phase. A typical DE is a water-in-oil-in-water (W/O/W) emulsion consisting of water droplets dispersed in oil droplets which are dispersed in a continuous aqueous phase (Figure 3).

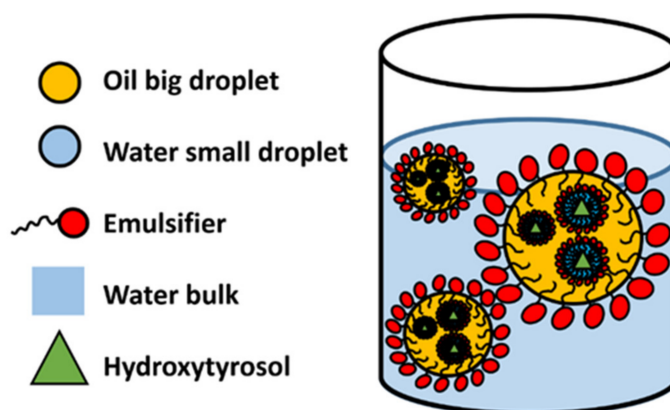


Figure 3. Schematic structure of double water-in-oil-in-water emulsion (DE) as possible system for hydroxytyrosol delivery.

DE is suitable for various food applications, for example, as ingredients in low-calorie and reduced-fat products, as systems for improving sensory characteristics, for protecting labile ingredients during storage or digestion, and finally, for the delivery of bioactive compounds [48–50]. Thus, DE offers great opportunities for the delivery of hydrophilic bioactive compounds, such as the HY.

Substantially, oily globules containing HY-enriched water droplets are dispersed in an aqueous phase [51,52]. The inner phase (W_1) is an aqueous HY solution in distilled water, while the outer aqueous phase (W_2) is prepared by dissolving the surfactants [53]. The primary coarse emulsion (W_1/O) is prepared by a gentle addition of W_1 to the lipid phase (O). Then, through energy provided by homogenization, a primary fine emulsion is realized and immediately used for the formation of the DE by its gradual addition to the W_2 . The resulting coarse $W_1/O/W_2$ is finally homogenized to obtain the HY delivery system.

Regarding the effectiveness, it was observed that the HY delivered by DE shows a good antioxidant effect in the complex matrices, but lower than that obtained by its direct addition. This aspect may be

related both to the presence of other components and to the increased surface area that causes HY losses during the preparation and storage of DE [53].

3.1.3. Gelled Double Emulsions

Gelled double emulsions (GDE) are complex structured materials in which emulsion and gel co-exist (Figure 4).

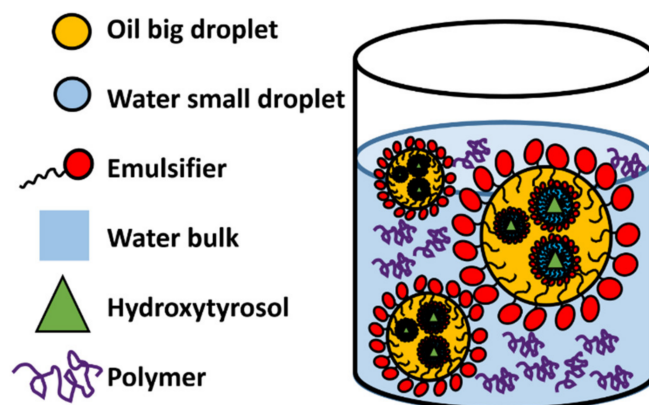


Figure 4. Schematic structure of gelled double water-in-oil-in-water emulsion (GDE) as possible system for hydroxytyrosol delivery.

In this system, emulsion droplets are enclosed within a continuous hydrogel matrix providing positive plastic properties [54]. Several biopolymers, alternatively called gums, are hydrophilic or lipophilic high-molecular weight compounds. The most commonly used in the food industry are gelatin, guar gum, carrageenan, pectin, Arabic gum, xanthan gum, carboxymethyl cellulose, alginates and agar [55]. All these are recognized as “natural”, unlike the chemically-modified biopolymers. Gums have gelling, thickening and stabilizing functions and they are added in foods with the aim to modify the rheology of aqueous suspensions, improve texture, slow down the retrogradation of starch, and increase moisture retention [56,57]. Therefore, GDE shows several physical and structural characteristics in food-based matrices, such as stability, viscoelasticity, encapsulation efficiency, phase-separation minimization. In addition, improved sensory characteristics of foods, higher control of HY release and protection of labile ingredients during storage or digestion were obtained by using GDE as an intermediate HY carrier [58].

GDE is produced through a two-step procedure [59]. At first, a liquid-like DE is produced and then transformed into a solid-like system by gelling the continuous phase and aggregating the emulsion droplets by thermal, enzymatic or chemical means. Generally, after the final homogenization of DE, the gelation is achieved under heating and, for this purpose, different polymeric ingredients such as pectin, alginate or gellan gum, can be added to the outer continuous phase to assist the gelling process and to form the emulsion gel. In addition, microbial transglutaminase allows the stabilization of the final formulation. The second step is the storage at 4 °C under dark conditions with the aim to form a structured GDE, solid at room temperature and thermally stable.

It was proven that HY, initially localized in the inner aqueous phase, is distributed in the different structural elements of the GDE, enhancing the antioxidant capacity of the system [54]. Moreover, HY losses for the GDE are lower than those occurring in the preparation of MAE or MIE and higher than those of DE's storage [60].

3.2. Encapsulated Systems

Encapsulation comprises a lot of techniques in which active compounds are coated with a polymeric shell or embedded homogeneously or heterogeneously in a polymeric matrix [61].

Encapsulated systems enclose spheres and capsules that, depending on the scale, are divided into micro-particles, with diameters of final products ranging from 1 to 1000 μm , and nano-particles, with diameter of 10–1000 nm [62]. Capsules are vesicular systems in which the target molecule is confined into a cavity, called a core (liquid or solid), surrounded by a unique polymer membrane (solid), known as a wall or shell; the spheres are polymeric matrix systems wherein the compound is uniformly dispersed [63].

The general structure of these HY-encapsulated systems are reported in Figure 5.

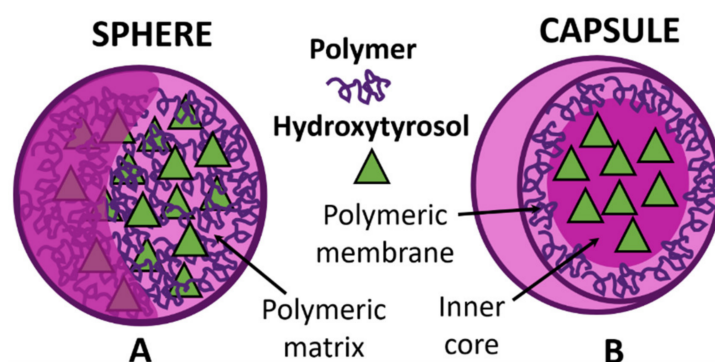


Figure 5. Schematic structure of spheres (A) and capsules (B) as possible system for hydroxytyrosol delivery.

Both capsules and spheres are made with specific materials as lipids, polymers and pure compounds [64]. In general, solid particle systems are prepared by using lipids that are solid at room or body temperature, such as triacylglycerols or waxes, while polymeric ones are made with natural polymers, such as chitosan, gelatin or albumin, or synthetic ones such as poly lactide co-glycoside acid (PLGA) and poly-lactide acid (PLA) [65,66]. In both cases, the final formulation is stabilized through the addition of surfactants. However, all the components used should be biodegradable, biocompatible, non-toxic and non-immunogenic [67].

The combination of double emulsion solvent evaporation and micro- or nano-encapsulation techniques appears to be an efficient approach for the realization of HY-encapsulated delivery systems [68,69]. Briefly, a possible procedure consists of dissolving the HY in the internal aqueous phase that in turn is mixed with the organic phase (containing the selected wall material dissolved in the organic solvent). Afterward, this primary emulsion is added to the external aqueous phase, containing the hydrophilic emulsifier, forming the DE. Then, the particles are formed and hardened by evaporation of the solvent and successively washed and recovered by filtration and freeze-dried [70–72].

3.3. Phenolipids and Liposomes

The low lipophilicity of HY affects its dissolution in apolar solvent and partition in the oil phase of oil-in-water emulsions. Several studies have proven that the HY lipophilicity may be increased through modifications of its molecular structure, for example by esterification of the primary alcohol group with various-length fatty acid groups [71–73]. In this way, the added acyl chain networks with the oil phase and the phenolic portion with the oil/water interface. HY esterification may be carried out chemically [74,75] or enzymatically [75–77]. Recently, these derivative products have been called “phenolipids”.

Change of HY lipophilicity affects its antioxidant ability according to the “antioxidant polar paradox”, stating that the hydrophilic antioxidants are more effective in bulk oils, while lipophilic antioxidants, having more affinity for the oil–water interface, inhibit lipid oxidation more efficiently in emulsions, micelles, or membranes [78]. In other words, esterified HY is more efficient in emulsion than its free polar form and this can extend its application in oil-based foods.

The length of fatty acid groups may affect lipophilicity and antioxidant ability of HY [75,79]. Generally, medium-chain fatty acid group increases significantly the HY lipophilicity without changing

the antioxidant effects. Conversely, very long acyl chains could limit the HY's antioxidant effect as result of the so-called "cut off" effect, whereby overly hydrophobic phenols show lower performance. However, HY-octanoate exhibited an antioxidant ability higher than that of HY-butyrate and HY-laurate evidencing a nonlinear tendency [78].

HY fatty acid esters, similarly to other phenolipids, show an amphiphilic behavior acting as a surfactant [76]. This could explain the better antioxidant ability in the emulsion in which the phenolipids are concentrated at the oil–water interface where they act as a shield for the oil placed into the micelles. It was proven that HY esters in the millimolar-range concentration may self-assemble in micelle, and consequently, this nanostructure could represent a possible HY delivery system without external carriers, but unfortunately, the required concentrations would be too high for food applications [80]. Alternatively, it was found that HY esters, combined with phospholipids, readily form liposome [80].

Liposomes are frequently used in pharmaceutical, cosmetic and food applications for their ability to carry both hydrophilic and lipophilic molecules, absence of cyto-toxicity, biocompatibility and biodegradability [81,82].

The liposomes containing HY are small (15–1000 nm) spherical vesicular systems comprising of one or more bilayers, usually formed by phospholipids, and surrounding aqueous cores (Figure 6).

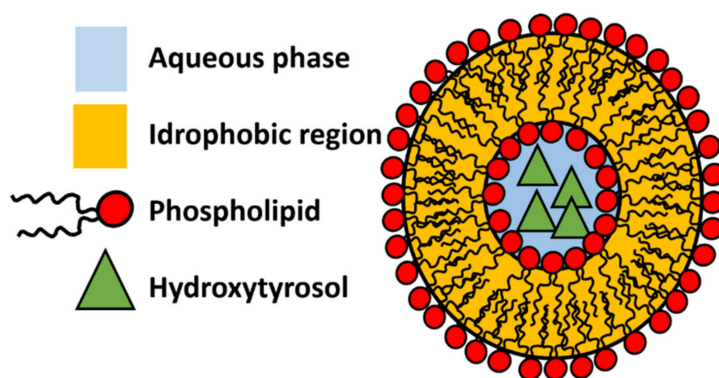


Figure 6. Schematic structure of liposome vesicles enriched with hydroxytyrosol.

Within the bilayer, the hydrophobic tails of phospholipid groups face each other, while the hydrophilic heads face the inner core and the outer boundary [82]. This peculiar structure allows for the incorporation of hydrophilic substances, like HY, directly into the core, while the hydrophobic ones could be portioned within the bilayer. Frequently, cholesterol and/or triglycerides are used with the phospholipids as an oily phase, in order to harden liposome surfaces by physical adsorption, forming a "stereo" barrier layer.

HY-carried liposomes can be prepared also using the film dispersion method (or thin film hydration method) [83,84]. Briefly, lipids (usually cholesterol and triglycerides) and phospholipids are solubilized in an organic solvent (generally ethanol) and placed into a round bottom flask with an emulsifier (the most common is Tween 80). Energy, provided by a sonicator or homogenizer, is used to dissolve the above-said ingredients and to obtain a stable solution at constant speed. Then, a vacuum rotary evaporator removes the organic solvent and a film layer is formed on the flask wall—the blank liposome film. This film is mixed with a HY aqueous solution previously prepared, and gently stirred and solubilized controlling the temperature. Finally, the obtained HY-enriched liposomes are extruded through a filter to control the size and obtain unilamellar systems that are stored at 4 °C.

Many factors can influence the formation of liposomes (temperature, phospholipids/lipids mass ratio, emulsifier's volume and HY amount). Therefore, it is necessary to study, identify and select the most important parameters that could affect the production process. Moreover, even the particle size of liposomes is an important factor because it could affect vesicle stability and HY bioavailability. Overall, HY well and fully incorporated in liposomes has shown to be more stable and active as an antioxidant than its free form in solution [84].

3.4. Active Packaging

Over the last few decades, structured composite materials for packaging applications have been intensely investigated with the aim to produce films containing bioactive compounds and improving drug delivery and film performances in industrial applications [85]. For this reason, increasing attention has been paid to designing and characterizing films, blends, coatings and micro/nanocomposite formulations with particular properties, in order to improve food safety and to prolong the shelf-life of products. Moreover, these materials, being biodegradable, are an attractive alternative to realize flexible and safe packaging solutions, also reducing environmental issues of plastic wastes [86]. In addition, these active packaging systems can easily be prepared by casting the solvent in water followed by a melt blending process [87].

Composite materials and films based on biodegradable polymers, for example, aliphatic polyesters including poly(ϵ -caprolactone) (PCL) or polyvinyl alcohol (PVA), offer an interesting alternative to conventional plastics, with high polarity, strong solubility in water, good optical, physical and thermo-mechanical properties, strength and flexibility. These polymers were studied for active packaging applications by developing films loaded with natural ingredients, comprising the HY. Specifically, HY was incorporated in polypropylene, PCL and PVA films [88–93]. For this purpose, an aqueous solution of the selected polymer, dissolved by heating, was first prepared in distilled water to obtain the polymeric matrix; then, room temperature was reached under stirring. Subsequently, a HY aqueous solution was prepared by mechanical stirring and homogenizing through a sonic bath. These two solutions were finally mixed by magnetic stirring to obtain the final film that could be compressed and molded in a hot-plate hydraulic press to liberate the trapped air bubbles. Finally, the realized composite film could be applied on the foodstuff to realize the active packaging system.

A schematic representation of a possible active packaging system for HY-delivery is showed in Figure 7.

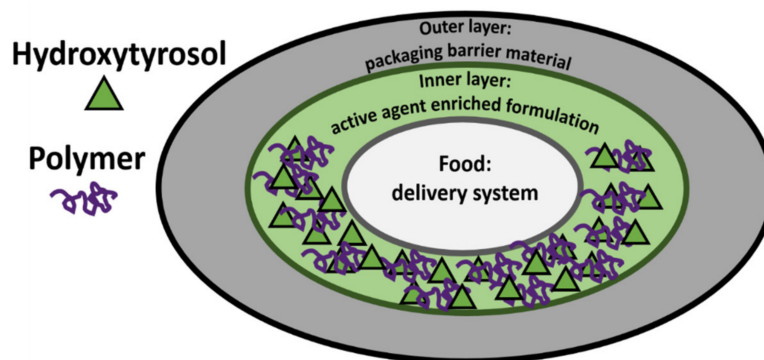


Figure 7. Schematic representation of a possible active packaging systems for hydroxytyrosol delivery.

The utilization of such systems proves that HY does not alter the morphological, optical, thermal and mechanical properties of the films [89,90]. In addition, HY-based films showed good performances by improving the shelf-life and health effects of the foodstuffs packaged. Moreover, HY improves the functional properties of packaging, preserving the homogeneity of the composite film.

Following the same method, even ternary-based composite films can be produced. For example, it has been reported that the addition of starch in the HY aqueous solution is able to tune a prolonged release of HY from the film [92]. Overall, the final systems are able to slowly release the HY added in packaging materials in substitution of common synthetic antioxidants used in foodstuffs [92].

4. Conclusions and Perspectives

The present review gives an overview of the studied delivery systems for hydroxytyrosol. Considering all the reported positive effects related to hydroxytyrosol consumption, the improvement

of its bioavailability and effectiveness *in vivo* through appropriate delivery systems represents a very interesting goal in the food and pharmaceutical fields.

Through the years, colloid science has offered a great variety of alternatives to meet the different requests for a wide spread of generic delivery systems. These molecules allow for the production of colloidal systems as emulsion-based systems (macroemulsions, microemulsions, double emulsions, gelled double emulsions), encapsulated particle systems (micro/nano spheres, micro/nano capsules), vesicular systems (liposomes) and packaging systems (active packaging) that represent suitable solutions to reach the above-mentioned target. Therefore, the reported delivery systems show promising and attractive tools for the delivery of hydroxytyrosol. However, there is still room for researchers to improve and/or design novel hydroxytyrosol delivery systems.

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