"RECENT TRENDS IN NUTRACEUTICAL FORMULATION DEVELOPMENT"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

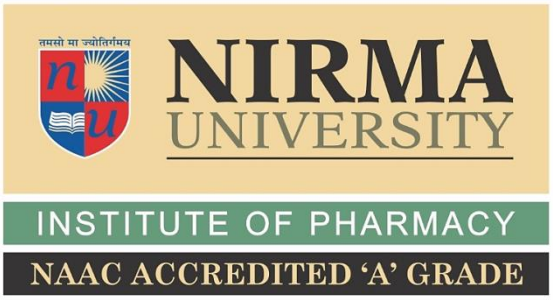
BY

VAIDEHI P. PATEL (16BPH099)

Semester VIII

UNDER THE GUIDANCE OF

DR. NIYATI S. AACHARYA (Guide)



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MAY 2020

CERTIFICATE

This is to certify that **"RECENT TRENDS IN NUTRACEUTICAL FORMULATION DEVELOPMENT"** is the bonafide work carried out by **VAIDEHI PATEL** (16BPH099),

B. Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B. Pharm Project work entitled **"RECENT TRENDS IN NUTRACEUTICAL FORMULATION DEVELOPMENT"** Submitted by **VAIDEHI PATEL (16BPH099),** B. Pharm Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of Dr. Niyati Acharya. I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by me is not reported anywhere as per best of my Knowledge.

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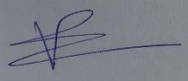
DECLARATION

I, **VAIDEHI PATEL (16BPH099),** student of VIIIth Semester of B. Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"RECENT TRENDS IN NUTRACEUTICAL FORMULATION DEVELOPMENT"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best` of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.



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1. ABSTRACT

Foundation: Aiming at the upgrade of nourishment items' wholesome and wellbeing esteem, the joining of nutraceuticals has pulled in expanding enthusiasm for the most recent years. Be that as it may, they frequently display low water solubility and solidness, constraining their immediate joining into nourishment items. Additionally, they show exceptionally low bioavailability because of constrained bio accessibility, poor assimilation as well as concoction change inside the gastrointestinal tract. This renders their wellbeing benefits very difficult to be acknowledged by the shoppers. Extension and approach: In the current survey the ongoing advancements with respect to the definition and plan of biobased micro and nano-delivery systems to encapsulate nutraceuticals is discussed; it also gives an overview of the challenges related to their turn of events; and features a few systems to improve nutraceuticals' bioavailability. An understanding about conveyance frameworks' potential poisonousness (specifically at nanoscale) is likewise given. Key findings and ends: Recent advancements in the plan of bio-based conveyance frameworks offer the chance of balancing out and upgrading nutraceuticals' usefulness inside nourishment items. Actually, different techniques can be utilized to upgrade nutraceuticals' bioavailability: I) nano-conveyance frameworks, other than indicating a colossal potential for the assurance of significant nutraceuticals during nourishment handling/assimilation, can be utilized to build their bioavailability; ii) ingestion improvement innovations have been effectively used to expand nutraceuticals' layer penetration; and iii) excipient food sources have been appeared to improve nutraceuticals' natural movement. In any case, the use of these empowering advancements to nourishment is impeded by appropriate issues that can be abridged in the effective safeguarding/expansion of the nutraceuticals' bioactivity and wellbeing, once inside the human body.

2. INTRODUCTION

In the period of constant infections (weight, Type II diabetes and cardiovascular sicknesses) and rising number of older individuals, bioactive aggravates that display wellbeing advancing effects are accepting expanding consideration. Since the solid connection between dietary propensities and wellbeing has been set up, food, moreover of being a decent wellspring of supplements with great tactile intrigue, additionally should be beneficial to the wellbeing and prosperity of the shoppers. Notwithstanding, in the advanced way of life it could be difficult to ingest the entirety of the supplements expected to keep up ordinary body works or advance great wellbeing. The consolidation of nutraceuticals in food items gives a basic method of creating novel useful nourishments. Truth be told, there is an expanding enthusiasm for the advancement of useful nourishments/refreshments enhanced with different nutraceuticals. Nutraceuticals can be defined as wholesome parts.

that give remedial or physiological benefits past the fundamental wholesome needs and incorporate a wide scope of mixes, for example, bioactive peptides, phenolic mixes, carotenoids, lipids, nutrients, and so forth. In any case, the effectiveness of nutraceuticals in giving remedial or physiologic benefits significantly depends on preserving their bioavailability, defined as the fraction of an ingested exacerbate that is assimilated and accessible for physiological capacities (for example arrives at the foundational course in a functioning structure). Different variables can bargain the bioavailability of a compound, including an insufficient gastric habitation time, low penetrability as well as solvency inside the gastrointestinal (GI) tract and shakiness during food preparing/capacity or in GI tract. Truth be told, the vast majority of nutraceuticals are probably not going to give the expected bioactive properties without the utilization of a suitable conveyance framework. This framework ought to be intended to defeat the specific factors affecting the stacked nutraceutical usefulness. Carotenoids, nutrients, unsaturated fats, polyphenols, bioactive peptides, phytosterols, fibers and basic minerals are a few instances of nutraceuticals with asserted organic movement that can benefit from fuse into conveyance frameworks. The primary difficulties of joining nutraceuticals, for example, β-carotene, curcumin, nutrients A, D, E and K in food items are their synthetic insecurity during food preparing/capacity

(for example reasonableness to light, oxygen, heat) or inside GI tract (for example effortlessly debased by catalysts as well as pH), their low water solvency and low bioavailability. Every one of these elements can affect nutraceuticals' usefulness, and thusly, their wellbeing benefits may not be perceived in any event, when ingested in high sums. Moreover, when straightforwardly fused in food items, nutraceuticals with upsetting tactile properties (for example polyunsaturated unsaturated fats) can contrarily affect nourishments' properties and timeframe of realistic usability. On the other hand, a portion of those mixes (for example nutrient C) can have unwanted co-operations with other food segments, contrarily affecting nourishments' appearance, surface, mouthfeel, steadiness, and bioavailability of significant parts. Thusly, epitome of nutraceuticals is regularly required to I) ensure them against antagonistic outside variables; ii) permit their joining into food products (for example increment the lipophilic mixes' dissolvability/unimportance in water-based conditions), iii) cover any off-flavors; iv) permit their controlled discharge; v) protect/boost their practical properties, for example to guarantee that they are kept up in their local bioactive structure until they arrive at the site of activity. Accordingly, conveyance frameworks at miniaturized scale and nanoscale have pulled in significant intrigue worldwide over the previous years. Additionally, lately, different methodologies have been utilized and significant propels have been made in the region of conveyance frameworks to upgrade the bioavailability and subsequently, nutraceuticals' efficacy. This work presents a far reaching best in class audit of the ongoing advances in the improvement of smaller scale and nano-scale conveyance frameworks to improve the bioavailability of nutraceuticals, from their detailing/structure to the assessment of their efficacy. Potential dangers that may emerge from their utilization (specifically at nanoscale) will be additionally tended to.

3. NUTRACEUTICALS

The term nutraceuticals arise from the combination of nutrition and pharmaceuticals. These are a part of food or foods which offers nutritional and pharmaceutical benefits, that is, give nutrients to the body, provide resistance against several diseases, and also help in curing of some diseases. In ancient time, the knowledgeable people working in the field of medicine thought of developing such food which could be used as medicine to prevent and cure diseases. Those brilliant ideas gave birth to the field of nutraceuticals. Nutraceuticals can be divided into three main categories—dietary supplements, functional foods, and functional beverages. Further the dietary supplements can be subdivided into vitamin and mineral supplements, herbal supplements, plant extracts and protein supplements. Functional foods include omega fatty acid foods and probiotics, whereas functional beverages can be sub segmented into energy drinks, sports drinks, and fortified juices. Some common words related to nutraceuticals or used as synonym for nutraceuticals are functional food, multifunctional food, dietary supplements, etc. Functional foods are just the same as basic foods providing nutritions, incorporated with special and specific ingredients which provide health benefits to the body. The recent advancements in the field of food technology have opened gates for the development of functional foods exclusively produced to promote good health for human being. Some basic steps taken into consideration while scrutinizing are identification, isolation, purification, and characterization of the properties of incorporated food components, that is, the nutritional value, medicinal value, etc. Primary food elements comprise of carbohydrates, proteins and lipids which are the basic necessity for proper functioning of the body and its normal energy requirements. Vitamins are secondary food elements which are commonly not synthesized within the human body, so these must be taken in food diet for proper functioning of the body. Nutraceuticals are also minor food elements which improve the body functioning by fighting against some persistent diseases. Efficacy of any nutraceutical product depends on its bioavailability. In terms of nutritional concept, bioavailability means that some nutrients in food are partially available, whereas in terms of pharmacology it refers to rate and extent to which a drug reaches to its site of action. With increasing popularity of nutraceuticals as preventive medicine, their bioavailability has become a major

issue to the regulators and manufacturers of health-related products. When administered orally, various parameters such as insufficient gastric residence time, low permeability and/or solubility within the gut and instability under conditions encountered in food processing or in the gastrointestinal (GI) tract limit the activity and hence health benefits of various nutraceuticals. Apart from their low bioavailability and poor water solubility, other challenges such as chemical instability and crystallization need to be overcome before the incorporation of these bioactive molecules into commercial food products. Patenting of new delivery systems like nanotechnology has been in trend for improving the efficacy of nutraceuticals.

4. NANOCARRIERS AS DELIVERY PLATFORMS

There has been a blast of nanotechnology in the vast majority of the segments with significant effect in wellbeing and food industry. Exemplification of dynamic food fixings in nano-based medication conveyance framework is a significant utilization of this innovation, in the field of food and sustenance. Nanoformulation of nutraceuticals additionally follow the key standards of nanotechnology. The nanotechnology stages are mainly used to get ready conveyance frameworks for nutraceuticals with poor water solvency. The innovation has an incredible potential for commercialization of the bioactives by conquering the impediments related with them and therefore a multifold increment for this innovation is famous in the coming years. Anyway, before its utilization in business food items, it is an absolute necessity to guarantee that these recently created nanoscale conveyance frameworks are protected to be joined in popularized food items. There are a few alluring qualities of nanoscale conveyance frameworks which should be mulled over. Most importantly, as decreased to nanoscale, they will carry on contrastingly inside gastrointestinal tract in contrast with regular particulate issue. In the event that the processing result of nanoscale conveyance framework is equivalent to that of regular particulate issue, at that point they cannot be relied upon to be increasingly poisonous; in any case poisonousness concern may emerge. So, it is critical to assess potential poisonousness of these food-grade nanoscale conveyance frameworks to guarantee their security. Utilization of food-grade elements for creation of these conveyance frameworks is ideal. These nanoscale frameworks

ought to be monetarily feasible, sufficiently able to stand up to capacity conditions just as strong enough for handy applications. Further, their joining into conclusive food item ought not antagonistically influence its quality viewpoints.

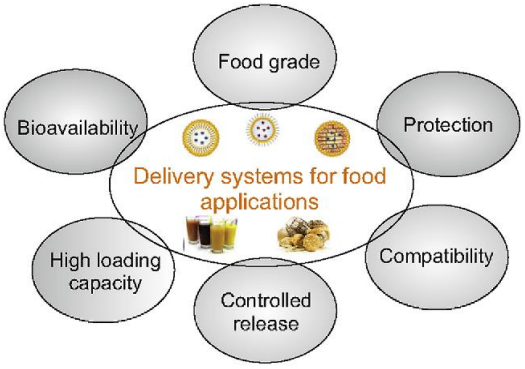
- Delivery system should be chemically and physically stable to environmental stresses while preserving its functional characteristics.
- Delivery system should be able to improve gastric stability of labile bioactive nutrients.
- Should be able to maintain constant dosage level within systemic circulation.
- In case of highly lipophilic compound, it should be capable of facilitating lymphatic transport.
- Should be able to extend gastric retention time.
- Over the past few years, several researchers have described the use of nanotechnology for nutraceutical compounds. Oral absorption and bioavailability of phenolic compounds have been reported to increase thereby promoting their nutraceutical effect. The nanoparticles have mainly been prepared using lipids, polysaccharides or proteins, loaded with different bioactive compounds. Some of the nanodelivery systems used for nutraceuticals are discussed below.

5. FORMULATION AND DESIGN OF DELIVERY SYSTEMS FOR NUTRACEUTICALS

The effective advancement of conveyance frameworks for nutraceuticals requires the information on their properties and the utilization of satisfactory materials and creation strategies. Truth be told, the decision of the sufficient exemplification strategy is a key advance once numerous nutraceuticals are touchy to warm and to high temperature during the embodiment procedure, which could cause loss of their bioactivity. The design of delivery systems for nutraceuticals that have adequate physical and substance strength just as food-grade status, cost viability and innovative plausibility can include various difficulties. Additionally, to get a palatable bioavailability for such nutraceuticals is even an all the more testing task.

5.1. Desirable characteristics of delivery systems

Being one of the conveyance frameworks' primary objectives the improvement of nutraceuticals' bioavailability, those ought to be created to advance nutraceuticals' watery dissolvability, satisfactory living arrangement time in the GI tract, assimilation over the intestinal line and solidness to changing physiological situations. During the development or choice of a conveyance framework, it is significant and valuable to think about certain parameters. The most important parameters are summed up in Fig. and briefly depicted underneath:



5.1.1. Food grade status

As opposed to pharmaceutical items, the delivery frameworks applied in food items can't be made out of engineered substance polymers because of the side effects that these can cause and because of the reality of being Integrated in foods, there is no control over the amounts that consumers may wish to allow. Consequently, administrative necessities additionally offer difficulties to the advancement of conveyance frameworks for nutraceuticals, when just food grade materials must be utilized for epitome or as center fixings. These materials can be acquired from normal sources (for example bio-based materials), which is the situation of proteins, starch, lipids, gums and cellulosic materials, or can be materials with Generally Recognized as Safe (GRAS) status, for example, cyclodextrins, low-sub-atomic weight emulsifiers (for example Tweens) and mineral salts . In addition, the preparing activities should likewise have administrative endorsement in the nation where the food will be sold. Different countries have different regulations, for model the primary legislative organizations directing sanitation are the European Food Safety Authority (EFSA) in Europe and the Food and Drug Administration (FDA) in the USA.

5.1.2. Protection of the encapsulated nutraceutical

Conveyance frameworks ought to be intended to ensure nutraceuticals during handling, stockpiling and transport from unfriendly factors, for example, unfortunate co-operations with other food fixings, pH, light, temperature or oxygen. Besides, these frameworks ought to likewise shield the nutraceuticals from the extreme GI condition (for example high action of stomach related chemicals and unforgiving acidic conditions in stomach.

5.1.3. Compatibility with the food matrix

Food framework is the first and main consideration that affects the natural destiny of the typified nutraceutical. For instance, the connections between blended micelles and mixes of the incompletely processed food framework can incite changes in the properties of the blended micelles and modify the assimilation and ingestion of the nutraceuticals epitomized inside them. Furthermore, conveyance frameworks ought to be perfect with the food lattice, not affecting the properties of the food item (for example smell, taste, appearance and surface). Conveyance frameworks can be consolidated inside different grids: I) suspended in fluid answer for be fused in refreshments and beverages, ii) caught inside a biopolymer network for joining in treats, yogurts and sauces or iii) stuck inside a strong lattice for fuse in powders and grain items. On account of clear refreshments, it is conceivable to use for instance, nanoemulsions on the grounds that the particles are little to such an extent that they do not firmly scatter the light.

5.1.4. Controlled release capacity

Another alluring trademark is the controlled discharge capacity, which comprises in discharging the typified compound with a specific fixation/time profile at the attractive site of activity. The discharge procedure may have a few profiles such as

i) Burst release – quick release of most of the encapsulated compound in a short time.
ii) Sustained release – extended release of the encapsulated compound at a constant rate.
iii) Triggered release – the encapsulated compound is released in reaction to a specific environmental stimulus such as pH, ionic strength, enzyme activity or temperature.
iv) Targeted release – the encapsulated compound is released in a specific location of the GI tract (i.e. mouth, stomach, small intestine or colon).

One of the primary test of structuring conveyance frameworks is to have the ability to discharge the nutraceutical when the framework is activated through an outer factor, for example, pH, dampness, compounds, temperature or shear and simultaneously, shield the nutraceutical from different components until it is discharged in the site of activity. Controlled release of a desirable flavor or release off od ingredient at a proper time during preparing or capacity are a few instances of utilizations of controlled arrival of epitomized mixes

5.1.5. High loading capacity

Conveyance frameworks must have the most elevated stacking limit conceivable and must hold effectively the epitomized compound until it arrives at a specific site of activity. The loading capacity (LC) is a parameter that measures the capacity of a conveyance framework to typify the bioactive compound. This parameter is resolved through the mass of exemplified material (ME) per unit mass of transporter material (MC)

$$LC = \frac{ME}{MC}$$

The loading capacity is dependent on the bioactive compound properties and on the encapsulation, material used, such as chemical nature, molecular weight, polarity and volatility of the bioactive compound and its interactions with the food matrix.

5.1.6. Bioavailability

Substance unsteadiness during processing, poor dissolvability in GI fluids, low intestinal assimilation or first-pass digestion are some basic issues that should be maintained a strategic distance from to build the nutraceuticals' bioavailability. Moreover, the bioavailability is affected by the materials used to epitomize and their physical express, the exemplification vehicle and the encompassing food framework.

5.2. Encapsulating materials

A key advance in the conveyance frameworks' improvement is the determination of the typifying materials when it will to a great extent influence the epitome efficiency and conveyance frameworks' solidness. Notwithstanding, this is additionally a key test in planning food grade conveyance frameworks for nutraceuticals because of the restricted selection of materials that can be utilized in the definition. As recently referenced, the vast majority of the conveyance frameworks created for pharmaceutical applications utilize manufactured parts that cannot be applied to food items because of its latent capacity negative effects upon incessant utilization. So, it is

imperative to structure conveyance frameworks with bio-based fixings, biocompatible with food items and non-poisonous for human utilization. Be that as it may, a few inconveniences of the usage of bio-based food fixings are the difference in their properties because of the conditions and procedures utilized for their detachment and the quality and synthesis of initial source. Moreover, embodying materials ought to have low thickness, good film framing limit, obstruction and gelling properties and unbiased smell and taste. Bio-based epitomizing materials, for example, polysaccharides, proteins, lipids and low atomic surfactants have been generally utilized as typifying materials because of their biodegradability, biocompatibility and non-harmfulness. A few instances of bio-based embodying materials, just as their specific attributes that causes them alluring contender to be utilized as exemplification materials to can be found in Table 2. Polysaccharides are the most utilized biopolymers in epitome of nutraceuticals for food applications. Polysaccharides can be applied in the development of the conveyance frameworks with different capacities, for instance as divider material in splash drying microcapsules or as structured layered oil-in-water (O/W) interfaces in emulsions. Hydrophobic connections, hydrogen bonds, van der Waals powers and ionic collaborations are the principle corporations set up among polysaccharides and nutraceuticals. Nutraceuticals' release depends mainly on the hydrolysis of the glycosidic linkages of the polysaccharides. At the point when polysaccharides are exposed to ecological changes, for example, pH, ionic quality, temperature or dissolvable creation, they may experience progress to different accumulation states and different adaptations. The fuse of nutraceuticals inside proteins has been likewise broadly examined. This can happen utilizing sub-atomic edifices (for example β-lactoglobulin), self-collected structures (for example casein micelles) or polymeric gel particles. The last can be shaped through cation-incited gelation (for example soy protein segregate), enzymatic (for example trans-glutaminase) and synthetic cross-connecting of gels (for example glutaraldehyde). The primary corporations answerable for the relationship between nutraceuticals and protein complexes and their respective compliance are hydrophobic and electrostatic communications, van der Waals powers, covalent ties and hydrogen securities. Because of their self-gathering capacities, lipids are additionally reasonable for consolidation of delicate particles, to cover up flavors and to control the arrival of the epitomized atoms. Lipid transporters can likewise improve the nutraceuticals' solubilization in the GI tract, since they can animate the emission of endogenous

biliary-inferred solubilizing segments including bile salts and phospholipids. Surfactants, particles created by a hydrophilic "head" group and a lipophilic "tail" gathering, can immediately frame micelles, turn around micelles, bilayers and vesicles, at high fixations. Other than that, they can sort out in different fluid crystalline structures, for example, lamellar, hexagonal and turned around hexagonal stages. Atomic structure qualities of surfactants and the physicochemical condition where they work decide their useful properties.

5.3. Delivery systems design

So as to structure a conveyance framework appropriate for a specific nutraceutical, for the most part, customized approach ought to be followed, contingent upon nutraceuticals' physicochemical properties (for example dissolvability, compound cooperation and dependability) and on the final application (for example measure of nutraceutical required, capacity conditions, kind of food item and its time span of usability) (Aditya, Espinosa, and Norton, 2017). Additionally, there are other significant highlights to contemplate, for example, ideal nutraceutical fixation, discharge component and final molecule size and density

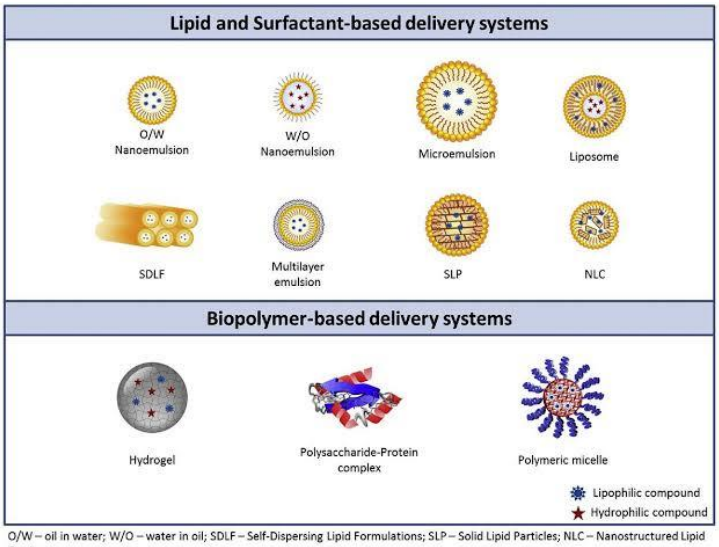
Delivery systems for food applications can be divided in two groups:

i) lipid and surfactant-based carriers, which include emulsions, liposomes, solid lipid particles, nanostructured lipid carriers and self-dispersing lipid formulations

ii) biopolymer-based carriers (i.e. polysaccharide and protein-based carriers), which include hydrogels, protein-polysaccharide complex, and polymeric micelles.

6. NEW INSIGHTS IN THE WORLD OF NUTRACEUTICALS

Formulations of nutraceuticals are hindered by numerous hindrance which adversely affect its viability. The ill effects of low dissolvability, poor penetrability, fast digestion, short half-life, and others are encountered by numerous daily dynamic fixations. Curcumin has low solvency, poor oral bioavailability, limited tissue distribution, short half-life, and fast digestion. In addition, Epigallocatechin Gallate (EGCG) is a bioactive compound in green tea which has a vasculoprotective effect due to its antioxidant and hypolipidemic activity. EGCG uses are in any case limited due to its rapid intestinal corruption and low dissolvability. These kinds of difficulties that risk the presence of nutraceuticals push researchers and formulators to use distinctive novel frameworks to increase safety and appropriateness of nutraceuticals. The process of effectively and securely entering into the body an active, pharmaceutical ingredient is called drug delivery. Owing to its dynamic design, high price and time consumption the introduction of novel delivery mechanisms to the nutraceutical market has been delayed. Traditional forms have, therefore, been used for many years, but they have many problems, as mentioned before. For several years now, permeation enhancers, surface modifiers, prodrugs, other novel carriers and colloidal lipid carriers such as traditional dosage forms have been created. Numerous forms of modern distribution systems exist. Here, it lists the most famous novel systems.



O/W – oil in water; W/O – water in oil; SDLF – Self-Dispersing Lipid Formulations; SLP – Solid Lipid Particles; NLC – Nanostructured Lipid Carriers.

6.1. Nanoparticles

Nanoparticle is a molecule that has three nanoscale measurements, which go roughly from 1 to 100 nanometer (nm). The new integrated nanoparticles have completely unique electrical, mechanical, physical and concoction properties. Nanotechnology has increased broad notoriety in the field of medication conveyance framework. These days, nanotechnology has been widely applied in the field of nutraceuticals. Subsequently, the present piece of the pie of nanotechnology in the nutraceutical business is around 1 billion dollars. It was likewise expected that the piece of the overall industry would reach more than 20 billion dollars in the following decade. incorporated epitomized curcumin nanoparticles, which comprised of N, N-dimethyl chitosan, N, N, N-trimethyl chitosan and sodium tripolyphosphate in water-in-benzyl liquor emulsion medium. This framework conquered the low solvency, high crystallinity and poor oral bioavailability of curcumin. Furthermore, the led in-vivo and in-vitro considers demonstrated the upgraded anticancer properties of this framework, as appeared in. improved the bioavailability and solvency of genistein by stacking it into enzymatically created dextran nanoparticles. Genistein is isoflavone and it has cancer prevention agent and calming properties. structured nanoparticles, which were stacked with Chinese sweet potatoes, radix astragal, rhizoma anemarrhenae, chicken's gizzard-films, radix Pueraria, crude gypsum, rhizoma alismatis as well as others to treat or forestall numerous infections, for example, diabetes, heart ailments and others.

6.2. Nanospheres and Nanocapsules

Both nanospheres and Nanocapsules are polymeric nanoparticles, which have a breadth with under 1 μm. Nanocapsules has a vesicular structure which is encircled by a polymeric film. The dynamic fixing is epitomized into Nanocapsules. Nanospheres have a scattered polymeric lattice, which dynamic fixing is scattered into. Made a polymeric nanoparticle and conjugated it with chitosan. This framework was stacked by curcumin to be utilized as cancer prevention agent. Additionally, Hu et al. portrayed this polymeric framework by means of Fourier-Transform Infrared spectroscopy (FTIR) and proton Nuclear Magnetic Resonance (1H NMR) examination. The molecule estimates and Poly Disperse Index (PDI) were estimated by means of Dynamic Light Scattering (DLS). At last, zeta potential and the morphology of nanoparticles were resolved through laser doppler microelectrophoresis and Transition Electron Microscopy (TEM), separately.

it was asserted that acylethanolamides could be stacked into nanocapsules polymeric framework, other than other novel conveyance frameworks. Acylethanolamides were utilized in avoidance or treatment of liquor reliance condition, liquor harming and obsessive inebriation. In-vivo study was directed on rodents to gauge various parameters. In the first place, neuroinflammatory, which was incited by liquor inebriation convention, was assessed by estimating blood ethanol level. Besides, the flagging course of neuroimmune (Toll-Like Receptor 4 (TLR4), myeloid separation essential reaction 88 (MyD88), Nuclear Factor Kappa-light-chain-enhancer (NF-kB)) was assessed after High Mobility Group Box 1 (HMGB1) enactment liquor. Ultimately, the withdrawal conduct was watched by means of directing raised in addition to labyrinth try

6.3. Metal Nanoparticles

Metals, for example, silver (Ag), iron (Fe), zinc oxide (ZnO), titanium oxide (TiO2), are set up in the nano size range. Metal nanoparticles have numerous favorable circumstances, including moderately huge surface region, great biocompatibility, and great synergist movement. Besides, unrivaled selectivity, metal nanoparticles are normally isolable, dispersible, and reusable impetuses. Metal nanoparticles can be applied as metal or metal-oxide, for example, nano-Ag, nano-ZnO, nano-Cu and nano-TiO2. Every ha its particular measurements, homogeneousness, and aggregative properties. These various attributes impact the compound's natural action and poisonousness.

a study to analyze silver nanoparticles (AgNPs) biological activity (antimicrobial and antioxidant activity) in three different herbal species namely, garlic, ginger, and cayenne pepper. Each active ingredient was encapsulated into AgNPs. These metallic nanoparticles had spherical shapes and average sizes of 36nm, 3-22nm and 3-18 nm for garlic, ginger, and cayenne pepper, respectively. It was concluded that AgNps exhibited more potent antibacterial activity against two gram negative and 2-gram positive bacterial strains. Additionally,1, 1diphenyl 2 picrylhydrazyl (DPPH) and 2, 2 Azinobis (3ethylbenzthiazoline6sulfonic acid) (ABTS) assays showed that AgNps had better antioxidant activity. a novel, hybrid system is designed which consisted of amyloid fibrils that were covered by iron nanoparticles on its surface. The system was loaded with amyloid fibrils and minerals, such as iron oxides, calcium phosphates and others. It was claimed that the synthesized formulation was used in treating or preventing iron deficiency anemia and diseases, which are associated with zinc deficiency. Hemoglobin

repletion bioassay was performed on rats to assess the relative bioavailability of the hybrid system. As a result of that the bioavailability of the loaded ingredients was improved.

6.4. Composite Colloidal Nanoparticles

Composite nanoparticles are half and half nanoparticles that comprise of inorganic center (metal or metal oxide) and natural shell (polymerized monomer, natural particle, chromophore, and so forth.). The primary preliminary of composite nanoparticles blend was in late-90s by means of Vollrath. Composite nanoparticles have new electronic, attractive, optical, or natural attributes. There have been numerous preliminaries to acquaint nanocomposites into nutraceutical industry with improve the adequacy of nutraceuticals. For example, covered pomegranate arils with both zinc oxide nanoparticles and carboxymethyl cellulose. This framework improved the anticancer, mitigating and cell reinforcement exercises of pomegranate. Jia and his group assessed the cell reinforcement movement through directing the DPPH radical rummaging procedure. Donsì and his group combined zein-based composite colloidal nanoparticles to typify epigallocatechin-3gallate (EGCG) inside it EGCG has hydrophobic nature and frail co-polymer collaboration with zein. Henceforth, a colloidal stabilizer, sodium caseinate (NaCas), was utilized to improve the embodiment deficiency. It was guaranteed that this framework balanced the pace of fat processing and upgraded cell reinforcement exercises. Cell reinforcement movement of polyphenols was surveyed by means of utilizing ferric decreasing cancer prevention agent power. controlled the arrival of curcumin by epitomizing it into zein-shellac nanocomposite particles. Zein is the principle stockpiling protein in corn while shellac is a tar that is delivered from lac creepy crawly. The figured zein-shellac nanocomposite demonstrated better exemplification viability, photochemical and warm strength. Additionally, this investigation indicated that zein to shellac proportion (1:1) is the best against curcumin corruption instigated by warm or ultraviolet (UV) light introduction. Zeinshellac nanocomposite would be advised to solidness in phosphate cradle saline (PBS) and recreated gastrointestinal conditions.

6.5. Self-Assembly Nanoparticles

Self-assembly strategy is an amazing and cost proficient method to control the self-association of nanoparticles. This procedure relies upon controlling the shocking and alluring powers between particles to deliver an assortment of self-collected structures of nanoparticles. Self-assembly adjusts the physical properties of the particles, for

example, optical, electronic, and attractive properties. It likewise improves the mass mechanical properties. Different strategies are utilized to upgrade self-assembly, for example, Langmuir-Blodgett strategy, templating technique and helped self-gathering strategy. A few mixes can frame self-collected nanoparticles, for example, chitosan (CS) and polyaspartic corrosive (PAA). Self-amassed nanoparticles grabbed an extraordinary eye in the field of nutraceuticals because of their latent capacity cost adequacy, basic planning, and biocompatibility. For instance, EGCG has a vasculoprotective impact through its antioxidative and hypolipidemic impact. In any case, EGCG utilizes are constrained due to their quick debasement in the gut, (as it referenced previously). exemplified EGCG into self-collected nanoparticles, which made out of chitosan and aspartic corrosive, In-vivo study was performed on male New Zealand white bunnies. The aftereffects of the in-vivo study revealed that stacked EGCG would be wise to action against atherosclerosis.

6.6. pH Responsive Formulations

A pH sensitive system is a method of distribution that regulates the release of active ingredients through a particular pH change. Multiple organs have various pH ranges in the human body, such as stomach (pH 1.5-3.5), small intestine (pH 5.5-6.8), and colon (pH 6.4-7.0). In addition, the tumor has a different pH value (around 7.4). Therefore, pH-responsive framework represents an outstanding site-specific nominee.

conceived bioresponsive nanoparticles for chitosan. These nanoparticles were filled with EGCG, which gradually released in acidic, gastric, and rapid alkaline, intestinal state. The device therefore protected EGCG from acid degradation, so that oral administration of bioresponsive nano-EGCG was successful. In addition, an in-vivo analysis was conducted on athymic xenograft nude mice to determine the efficacy of anticancer. As a result of that this system showed greater efficacy in treating prostate cancer.

a particular pH-responsive method (biodegradable food packaging). Chitosan has good mechanical resistance and permeability to air. It is edible and biodegradable, too. BSSCE is a phenolic compound derived from plants, with antioxidant activity. The best food packaging and antioxidant was the synthesized chitosan-BSSCE film that consisted of 15 wt. per cent of BSSCE. Finally, the device improved characteristics of the UV visual light barrier, antioxidant function, mechanical strength, thermal stability, and other properties.

A novel, controlled release matrix comprising casein gel to sustain caffeine release. Casein is a milk protein considered a successful candidate for distribution and targeting. As a delivery system, Casein possesses excellent criteria including high ion binding affinity, small size, water binding power, high stability, and strong emulsifying properties. Thanks to its gel swelling property, it can also be used as a managed delivery method as a response to pH Caffeine is also a natural product which is primarily used to modulate executive brain functions.

6.7. Nanohydrogel

Nanohydrogel is a water-swellable polymeric device that is cross-like and does not dissolve in water. It increases bioavailability and selectivity of the nutraceuticals. Nanohydrogel is prepared mainly through two major phases. First, they synthesize the polymeric system. Second, it cross-links the shaped biopolymers. Before synthesis of the hydrogel system, hydrophilic nutraceutical ingredients are blended with the formulated biopolymer. In comparison, lipophilic nutraceutical products, such as emulsion or nano-emulsion, are encapsulated in lipid droplets. Nanohydrogel has a tridimensional structure, large surface area and nano-sized hydrophilic networks.

Nanohydrogel has a tridimensional structure, large surface area and nano-sized hydrophilic networks. This structure therefore regulates the release of active ingredients and increases their bioavailability and stability.

Synthesized nanohydrogel coated with chitosan and consisting of lactoferrin and glycomacropeptide. The effect of chitosan on the supply of active ingredient was assessed in this analysis. Curcumin and caffeine were thus used, respectively, to represent a lipophilic model and a hydrophilic model. Efficacy of antioxidants was evaluated via DPPH assay. The framework increased the lipophilic model's bio accessibility to 72 percent. In addition, under simulated gastric and intestinal conditions, coated curcumin preserved 70 per cent of its antioxidant activity. However, under the same conditions, the free curcumin showed a loss of 68 per cent of its antioxidant activity. Under the same circumstances, with its antioxidant action. Bio accessibility and free source of coated caffeine are 63% and 59% respectively.

6.8. Lipid Based Carriers

6.8.1. Liposomes

1. Liposomes Liposome is customary lipid-based bearer. It was set up just because by Alec D. Bangham in 1965. Liposomes are round vesicles that comprise of a lipid bilayer film and a fluid cavity. The coinage of liposome was started from two Greek terms in

particular; lipid (fat) and soma (body). Liposomes have been characterized dependent on their size, arrangement and lamellarity. In the first place, as per their size, they have been ordered into little, middle, and huge. Also, as indicated by planning, they have been ordered into switch stage dissipation liposomes or vesicle expelled procedure. Finally, liposomes have been sorted into nonlamellar, oligolamellar or multilamellar vesicles dependent on their lamellarity.

In addition, liposomes can ensure dynamic fixings against enzymatic corruption. In addition, they are adaptable, biocompatible, and non-poisonous transporters. They have the benefits of double medication conveyance by stacking drugs with various physicochemical properties in their center and lipid bilayer. For hydrophobic medications, liposomes improve their solvency, solidness, and bioavailability. Be that as it may, liposomes experience the ill effects of certain downsides, for example, short half-life, poor soundness, low stacking limit and significant expense. Liposomes are expelled quickly by means of reticuloendothelial framework.

stacked characteristic fixings into liposomal framework. In addition, it was asserted that the framework could likewise be figured as continued discharged tablets, gel powder, moisturizer, and other dose structure. The characteristic fixings were crocin, crocetin, green tea separate, curcumin, resveratrol, panax ginseng extricate, α-lipoic and additionally L carnitine. The integrated detailing was utilized in treating malignant growth and improving wellbeing. In another patent, Underwood et al. arranged nanoparticles of entire organic products (dark chokeberries, fruits, plums, blueberries, pomegranates, raspberries, cranberries, and additionally dark elderberries) and typified them into emulsion as well as liposome. It was guaranteed that the readied plan was utilized in diminishing indications of joint agony, diabetes, gout, and others.

defined pegylated or cationic liposomes or niosome to typify the dynamic fixings into. It was guaranteed that the normal segments were portions of characteristic plants, for example, espresso bean, aloe vera, hazelnut oil, almond oil, and others. Moreover, Richard and his group guaranteed that their framework had numerous utilizations, for example, restoration of layer corneum and epidermis, treatment of skin break out and enemies of wrinkles. The morphology and size of vesicles were assessed by TEM. Ultimately, molecule size, PDI and zeta potential were estimated by means of DLS.

6.8.2. Solid Lipid Nanoparticles (SLNs) and Nanostructure Lipid Carriers (NLCs)

SLNs and NLCs have been brought into the delivery system since 1990 as substitutes of customary liposomes, polymeric nanoparticles, and emulsions.

6.8.2.1. Solid Lipid Nanoparticles (SLNs)

Strong Lipid Nanoparticles (SLNs) have circular structure and nano-went size (around 40 to 1000 nm). SLNs comprise of surfactant (0.1 to 30 % w/w) and strong fat (0.5 to 5%). They are strong at body and encompassing temperature. Besides, molecule size, steadiness and medication stacking rely upon kind of lipid and surfactant. SLNs are significantly reasonable for both hydrophilic and lipophilic medications. Nonetheless, the medication stacking limit relies upon sedate lipophilicity. Besides, framework precariousness during capacity and high-water content have been accounted for as detriments.

α-Lipoic corrosive is a characteristic cancer prevention agent that is used in antiaging topical arrangement. It has low disturbance impact contrasted with other antiaging operators. Also, α-lipoic is valuable for treating fragile regions (region around the eye). α-lipoic corrosive experiences concoction corruption, which prompts awful smell in topical arrangements. Souto et al. tackled such issue by consolidating α-lipoic corrosive into SLNs. Also, stacked α-lipoic corrosive indicated higher occlusive impact. Subsequently, the framework expanded skin hydration and insurance against UV light. Both pharmaceutical or regular fixings, for example, ellagic corrosive dry out, nutrients as well as minerals can be stacked into strong nanoparticles, lipid-based transporter, lipid-containing nanoparticles, tablets, fixed course, or others. It was additionally asserted that these frameworks were utilized in treating and forestalling hyperglycemia, stoutness, diabetes type I and II, gestational diabetes, dormant auto-insusceptible diabetes, metabolic condition, Alzheimer, liver illness, kidney malady, and others.

6.8.2.2. Nanostructure Lipid Carriers (NLCs)

Nanostructure Lipid Carriers (NLCs) are viewed as a change of SLNs. The fundamental alteration is that the lipids of NLCs are a blend of both strong and fluid oils. Consequently, NLCs improve strength and medication stacking. NLCs were acquainted in 1999 with defeat SLNs downsides, for example, low medication stacking limit and flimsiness (drug expulsion).

Resveratrol is a normally happening anticancer specialist. Be that as it may, resveratrol experiences photosensitivity, low dissolvability, and oral bioavailability. Neves et al. SLNs and NLCs to typify resveratrol. The two frameworks upgraded trans-resveratrol insurance against photodegradation. Besides, NLCs prevailing to improve resveratrol epitome. Furthermore, NLCs forestalled its fast crystallization and discharge in GIT.

Obviously, the two frameworks improved resveratrol oral bioavailability for malignancy treatment.

6.8.3. Nanoliposome

Nanoliposomes are lipid vesicles in nano-sized scale. The decrease of liposomal framework size prompts expanded surface region. Subsequently, the bioavailability of nanoliposomes is improved. Accordingly, nanoliposomes are utilized broadly in nutraceuticals industry to amplify the wellbeing and adequacy of these items. For instance, EGCG has low security in water and physiological liquid. stacked EGCG into nanoliposome, which made out of phosphatidylcholine and cholesterol to beat this issue. Also, nanoliposomes were covered with chitosan to upgrade the assimilation.

6.8.4. Nanoemulsion

Nanoemulsion was imagined without precedent for 1950. It is a solitary stage and stable framework. Nanoemulsion is a nanosized emulsion with nano-sized beads (20-600 nm). It by and large comprises of oil, water, surfactant and cosurfactant. Nanoemulsions were grouped into three classifications: water in oil, oil in water and bi-constant nanoemulsions. Nanoemulsions are typically translucent scatterings because of their little bead size which forestalls flocculation. They are appropriate for hydrophobic medications conveyance because of high solubilization limit. Nanoemulsion is used usefully in sedate conveyance since it builds the stacking limit, strength, and bioavailability of medications. Nanoemulsion can permit continued or controlled discharge.

planning of nutraceutical detailing containing theobromine, caffeine, amino acids, and different fixings to balance the intellectual cerebrum capacities, improve memory and upgrade vitality. Nanoemulsion was readied by means of sodium alginate as encapsulant and cocoa protein as emulsifier. Nanoemulsion with balanced out fat bead brought about controlled arrival of the dynamic fixings. In another patent, acylethanolamines were exemplified in Nanoemulsion to treat or forestall liquor reliance condition and liquor inebriation.

β-Carotene has a significant job in improving vision and treating nutrient An insufficiency since it is the antecedent of nutrient A. β-carotene is a hydrophobic nutraceutical, which requires novel framework for its conveyance because of its restricted dissolvability. epitomized β-carotene into oil in water nanoemulsions through high-pressure, double channel micro fluidization. Additionally, its dispersibility in water and steadiness were improved by utilizing quillaia saponins and whey protein

confine as emulsifiers. Luo and the remainder of the group estimated the molecule size, zeta potential and PDI by static light dissipating strategy. Moreover, the microstructure of Nanoemulsion was evaluated by optical and confocal fluorescence microscopy. formulated a Nanoemulsion to typify Eugenia barytonesis basic oil to utilize it as a food additive. The integrated Nanoemulsion demonstrated more noteworthy antimicrobial movement. Additionally, omega-3 polyunsaturated unsaturated fats have extraordinary effectiveness to lessen dangers of coronary heart maladies. defined oil-in-water Nanoemulsion by means of double channel micro fluidization strategy to exemplify omega-3 into it. It was accounted for that this definition diminished the danger of coronary illness and aggravation. It additionally improved the mind capacities.

6.9 Dendrimers

Dendrimers are profoundly spread and nanoscale polymeric macromolecules, which have a three-measurement structure. The term of dendrimer originated from the Greek expression 'dendron'. Dendrimers were first presented in 1978 by Vogtle. Dendrimers have three fundamental parts: center, rehashed units (branches) and terminal practical gathering. The center of dendrimers comprises of polymer, for example, polyamidoamine (PAMAM), ethylene diamine (EDA), diamino butyl (DAB), polypropylimine (PPI) and others. The parts of dendrimers are deposits, for example, carboxyl gathering, amino gathering and different gatherings, which are joined straightforwardly profoundly. The size of dendrimers can be constrained by quantities of these additional gatherings, which are instituted as (generation).

Dendrimers are considered attractive drug delivery systems because they can be managed in full. Size, surface load, and architectural structure can easily be altered. The active ingredient can be encapsulated in its heart or combined with its surface. Unlike typical polymers, dendrimers with a definite molecular weight are easily soluble, biocompatible, and polyvalent. Dendrimers have high efficiency of trapping, exceedingly small size up to 5 nm and low index of dispersity. In addition, the active portion may be placed on the surface or chemically reacted with the functional group.

The big downside of dendrimers, however, is their cytotoxicity, which is strongly related to their cationic properties. These nanoparticles strongly react with the cell membrane causing lysis of the cells. Diverse experiments were performed using dendrimers to deliver natural ingredients. They loaded microorganism oxidizing ammonia into new delivery systems, such as emulsions, Nanocapsules, liposomes,

dendrimers, and others. This machine was also believed to be able to treat neurological, nasal or sinus disorders, asthma, bacterial vaginosis, and dermal diseases.

6.10. Biopolymer Nanoparticles

Biopolymers are natural polymers which include proteins, polysaccharides, and nucleic acids. In addition, they were mainly graded into inclusion, hydrogels, and polyelectrolyte complexes, based on their structure. Their particle size is considered a critical factor affecting the physicochemical properties, encapsulation, GIT stability and active ingredient absorption. Biopolymer nanoparticles are ideal because they are biodegradable, non-toxic, and biocompatible for clinical use. In addition, proteins are highly stable, and they have strong binding ability. Protein-based nanoparticles, as a drug carrier, are thus highly promising model. A wide range of proteins were used for the development of nanoparticles including casein, collagen, zein, elastin, silk fibroin and others.

Preparation of colloidal zein-quercetin composite nanoparticles to solve many quercetin issues, such as poor aqueous solubility, low bioavailability, and significant bowel degradation. Quercetin is a natural flavone that has effects on anticancer, antiviral and antioxidants. This study showed that quercetin's molecular stability against pH degradation and UV irradiation and high antioxidant activity was improved with this system.

Biodegradable nanoparticles developed consisting of a hydrophobic protein (zein). In addition, naturally occurring products such as curcumin oil or pharmaceutical drugs such as chlorhexidine have been loaded into biodegradable nanoparticles. The device was believed to be used as antioxidant, anti-aging, and fungicidal agent. Ex-vivo bioadhesion study to evaluate the adherent concentration of nanoparticles in the porcine buccal mucosa via nanoparticles labeled fluorescently. Photon correlation spectroscopy measured the scale of the nanoparticles. Electrophoretic laser doppler anemometry had also determined the zeta potential. Morphology of nanoparticles was analyzed with TEM and light microscopy.

Biopolymers nanoparticles can be conjugated or connected together to enhance their physical and chemical properties and their health and effectiveness.

6.11. Conjugated Biopolymer Nanoparticles

Biopolymers may be used in their normal form Physical, chemical, or enzymatic modifications are performed to enhance their properties, however. Protein covalently bound to polysaccharide, for example, showed greater solubility and emulsifying

properties. Conjugation can be reversible (physical) or irreversible (chemical), with a greater and more lasting relationship in the chemical conjugation. Nanoparticles of the protein can be further stabilized by coating with conjugated polysaccharides. Resveratrol encapsulated into protein (zein) nanoparticles, which were coated by Maillard reaction through conjugated polysaccharides.

Conjugation efficacy was assessed through the o-Phthaldialdehyde (OPA) assay to measure the decrease in free amino groups. As a result, resveratrol's restricted water solubility, oral bioavailability, and chemical instability were reduced. Casein was additionally adsorbed onto hydrophobic particles. In addition, dextran impeded aggregation by steric repulsion. Thus, coating with caseinate-dextran prevented the aggregation of particles.

6.11.1. Cross-linked Biopolymer Nanoparticles

Cross-linking is the process of linking the chains of a polymer to form three-dimensional structures by covalent or noncovalent bonding. Cross-linking is performed to improve the mechanical properties of biopolymers and their aqueous stability.

Chemopreventive agent encapsulated EGCG into cross-linking chitosan nanoparticles (CS) and caseinophosphopeptides (CPPs). Cross-linking CS with CPPs increased oral bioavailability of the EGCG and decreased cytotoxicity of the CS. Further, crosslinking improved biocompatibility of nanoparticles.

Glucomannan polysaccharide stimulates proliferation of fibroblasts which helps with healing of wounds. Using Fluorescence Lifetime Image Microscopy (FLIM), formulated cross-linking nanoparticles composed of chitosan and glucomannan to improve wound healing and skin regeneration assessed the efficacy of nanoparticles on skin irritation. In addition, a study on rabbits was conducted in-vivo to assess certain parameters. Second, reduction in dermal discomfort was visually observed in injected rabbits. Secondly, collagen proliferation and intradermal distension within the dermis have been assessed.

6.11.1.1. Nanosuspension

Nanosuspension is one of the novel approaches to solving the low drug solubility. Nanosuspension consists of a nanosized particle that has surfactants stabilizing it. Nanosized nuclei are surrounded in this dispersion by surfactant molecules. Nanosuspension also increases drug safety and maintains a high drug load. Also enhancing the oral bioavailability as a function of solubility. Another important advantage of nanosuspension is its ability to encapsulate insoluble compounds. Many

formulators have therefore tried to employ nanosuspension as a delivery system in the nutraceutical industry.

Curcumin has beneficial effects in treating cancer and Alzheimer's disease. However, due to its low solubility and poor oral bioavailability, curcumin's pharmacological application has been limited. Made of curcumin and α-tocopherol nanosuspension Polyethylene Glycol 1000 Succinate (TPGS) using ultrasonic homogenization technique. The prepared nanosuspension improved water solubility of curcumin and the rate of dissolution. Nanocomplex system particle size, PDI, and zeta-potential were measured using DLS. In addition, nanoparticles morphology and size were assessed through field emission scanning electron microscope (FE-SEM) and TEM. Different analyzes have been carried out, such as analysis of Fourier-Transform Infrared Spectroscopy (FTIR), thermogravimetric analysis, analysis of differential calorimetry scanning (DSC), and analysis of X-ray diffraction.

6.11.1.2. Graft Copolymers

Graft copolymers are polymers composed of two or more monomers. One monomer is the principal chain (backbone) chemically bound to side chains (branches). The divisions can be distributed randomly or similarly along the backbone, depending on the synthetic techniques. In polymers such as wettability, biocompatibility, and mechanical properties, grafting is typically performed to change different properties. Grafting can be achieved using different methods, such as chemical grafting, living polymerization, photochemical grafting, enzymatic grafting, plasma radiation and nuclear grafting.

Gallic acid is a triphenolic compound of nature that has heavy antioxidant and apoptosis activities. Chitosan gallates copolymer by free reaction of the radical graft. Gallic acid was encapsulated to be used as an antioxidant in the synthesized method. The copolymer's antioxidant activity was assessed through DPPH assay. As a result, the grafted copolymer showed increased antioxidant activity due to increased degree of substitution and decreased molecular weight.

In addition, the protocatechuic acid is a natural antioxidant phenolic compound. Protocatechuic acid has been used in traditional Chinese medicines. Thus, the protocatechuic acid was grafted onto chitosan by a cross-linking reaction to improve its antioxidant function. Antioxidant activity of the grafted system was evaluated through DPPH and power assay reduction. Folin-Ciocalteu assay was used to assess the grafting ratio. Nanoparticles' morphology and size were assessed via SEM.

6.11.1.3. Nutraceuticals Toxicity

Global consumption of nutraceuticals is growing rapidly, motivated by the false belief that they are healthy since they are either a source of food or fruit. Nevertheless, side effects and toxicity have been identified on an ongoing basis not only because of ingestion of the nutraceutical itself but also because of the potential for contamination. Nutraceuticals may be tainted with pesticides, other harmful products, metals, fertilizers, or even intentional chemical adulteration. Additionally, several studies documented the occurrence of drug herbal contact after co-administration due to the complex nature of herbal products and the existence of many phytochemicals. Such interaction may result in over-exposure to drugs which increase toxicity incidence and severe side effects. It may also contribute to drug efficacy inhibition and therapeutic results reduced.

A large number of widely used nutraceuticals are associated with significant toxicity and adverse effects. Ginkgo biloba extracts are rich in flavonoids and are widely prescribed to enhance peripheral circulation for older patients. Ginkgo biloba is also indicated for the dementia, Alzheimer's, schizophrenia, and cerebral insufficiency associated with age. However, exposure to high doses of Ginkgo biloba extracts is reported to be associated with spontaneous bleeding over long periods of time. In addition, several animal studies demonstrated the Ginkgo biloba carcinogenicity.

In addition, green tea extracts contain catechins which have the properties of anticancer. Green tea extracts are also used to prevent obesity and metabolic disorders but may result in nephrotoxicity, hepatotoxicity, and reproductive toxicity over exposure. In addition, caffeine ingestion has been documented to be causing anxiety, tachycardia, osteoporosis, and reproductive disorders, particularly in early adult exposure. Many other widely consumed herbal products are associated with harmful side effects, including carcinoma, hepatotoxicity, genotoxicity, and mutagenicity, such as cinnamon, aloe vera, and St. John's wort.

6.11.1.4. Nutraceutical Contaminants

One of the most threatening issues with using nutraceuticals is the presence of nutraceutical contaminants. Thanks to the extreme toxicity resulting from their ingestion, pesticides are regarded as the most harmful nutraceutical pollutants. Toxicity can range from mild skin rash to severe breathing, neurological, and reproductive disorders. However, it is important to use pesticides to preserve the quality of the medicinal herbs. Strict residual content levels of pesticides must also be adhered to.

Organochlorines can persist in the herbal product for longer periods of time among the different classes of pesticides and have the most harmful toxic effect after chronic exposure.

Many essential nutraceutical pollutants include heavy metals such as lead, cadmium, mercury, and arsenic. The World Health Organization (WHO) has set standards and restrictions for the presence of pollutants in the environment, such as heavy metals in the final herbal product. The toxicity of heavy metals may result from acute exposure to high heavy metal concentrations or from chronic exposure to low heavy metal concentrations. The adverse effects of metal toxicity include cancer, cardiovascular toxicity, hepatic and renal dysfunction, neurological disorders.

Pyrrolizidine alkaloids are naturally occurring secondary plant metabolites in animal studies, which cause developmental toxicity, genotoxicity, carcinogenicity, and hepatotoxicity. Their acute toxicity, meanwhile, has been reported to be represented by liver damage. Because of their strong alkylating nature these forms of alkaloids exert the toxic action. They respond with cellular proteins and DNA which cause cellular dysfunction and necrosis of the tissue. Pyrrolizidine alkaloids are prevalent in almost 6000 plant species. A total of 1105 samples of food and food products obtained from online websites and supermarkets were analyzed. The study found that pyrrolizidine alkaloids polluted 60 per cent of the food supplement products.

Finally, mycotoxins are secondary fungal metabolites that may be produced during cultivation or storage of plants. Ingestion of tainted food with mycotoxins causes severe adverse effects, such as carcinogenicity, hepatotoxicity, mutagenic and teratogenic disorders. Among the mycotoxins most commonly found in food supplements are aflatoxins, ochratoxins and citrinin.

6.11.1.5. Nutraceuticals – Drug Interaction

Many studies have recently identified multiple interactions with nutraceutical-drugs. The essence of interference can be by interfering with the drug's metabolic pathway or influencing the drug carriers. It is difficult to predict the occurrence of nutraceutical-drug interactions due to the nuanced existence and lack of pharmacokinetic, pharmacodynamics, and safety studies for nutraceutics

Many of the incidents reported may be extreme and potentially life-threatening. Aspirin and other non-steroidal anti-inflammatory medications, for example, interact with herbal products that include ginkgo, turmeric, ginger, ginseng, chamomile, and garlic.

This reported interactions therefore increased the risk of bleeding due to inhibition of platelet aggregation ability.

The cytochrome P450 (CYP) enzymes are one of the metabolic enzymes mainly found in the liver and small intestine. In fact, they are active in other prescription drug metabolism pathways. Saint John's Wort herbal extract is among the most commonly identified CYP-induced nutraceuticals, including CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2E1. Induction of these enzymes has the purpose of improving the metabolism of the drugs ingested. The substance is then quickly eradicated from the body and it loses its effectiveness. It was also recorded that Saint John's Wort involved the inability of anti-depressant drugs to treat and the loss of oral contraceptive effectiveness.

When co-administered with P-glycoprotein inhibitor phytochemicals, the bioavailability of fexofenadine, which is a Glycoprotein receptor substrate, is substantially enhanced. A variety of phytochemical flavonoids, including naringenin, genistein, and quercetin, are phytochemical inhibitors to P-glycoprotein. The ingestion of nutraceuticals containing P-glycoprotein inhibitors with active substrate drugs, such as irinotecan, digoxin, or cyclosporine, could lead to life-threatening toxicity afterwards.

When co-administered with P-glycoprotein inhibitor phytochemicals, the bioavailability of fexofenadine, which is the substrate of the Glycoprotein receptor, is substantially enhanced. Several phytochemical flavonoids are phytochemical antagonists of P-glycoprotein, including naringenin, genistein, and quercetin. The ingestion of nutraceuticals containing P-glycoprotein inhibitors with active substrate drugs, such as irinotecan, digoxin, or cyclosporine, could lead to life-threatening toxicity afterwards.

Co-administration of these herbal products also has a significant effect on the absorption and bioavailability of substrate drugs, including bosentan, benzyl penicillin, aliskiren, fexofenadine, glibenclamide, nonproton, statins and other prescription medicinal products.

6.11.1.6. Nutraceuticals Advanced Delivery Systems Toxicity

The integration of nutraceuticals into nano delivery systems is emerging rapidly recently. These advanced delivery systems are used to improve nutraceuticals' absorption and bioavailability, provide a targeted and controlled release profile, and improve the stability of phytochemicals that are susceptible to degradation. Nano-sized

nutraceuticals improve the effectiveness of nutraceuticals after nanonization due to their unique, varying chemical and physical properties. Nonetheless, the same beneficial, physicochemical properties of nanoparticles are the main cause of human toxicity.

Nano delivery system security is questionable. In addition, there is insufficient knowledge and research on the absorption, metabolism, dissemination, excretion, and toxicity of nano systems. Understanding the interaction of nano particles with the biological systems at the molecular level is important for predicting their behavior and protection mechanisms. Respiratory disorders, cardiovascular diseases, carcinogenicity, and a shorter life expectancy are among the commonly reported adverse effects of nano particles. It has also been reported that most of these adverse effects are triggered at molecular level by the oxidative stress and inflammation induced by the nano particles.

Synthesized nanoparticles made of gold, silver, platinum, and palladium to load three separate dietary supplements including vitamin C, (−) epigallocatechin gallate and gallic acid. The synthesized systems were assessed for the hydroxyl radical scavenging activity. Surprisingly, they found that the prepared nanoparticles reduced the ability of the antioxidant phytochemicals to scavenge hydroxyl radical and produced a Reactive Oxygen Species (ROS). Therefore, in biological systems this system resulted in cellular damage and toxic impact.

The European Food Safety Authority (EFSA) has introduced a toxicity evaluation method resulting from the integration of nanotechnology into food products and food derivatives. A collection of physicochemical parameters to be tested for nanoparticles is recommended in the guidelines titled: "Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. The set of parameters used in EFSA

- The identity of nanoparticles and their chemical.
- Particle size
- Physical properties
- Morphology
- Mass concentration.
- Specific surface area
- Surface chemistry

- Surface charges
- Redox potential
- Partition
- Solubility properties.
- Dustiness, density, viscosity and pour density.
- Chemical reactivity
- Photocatalytic activity

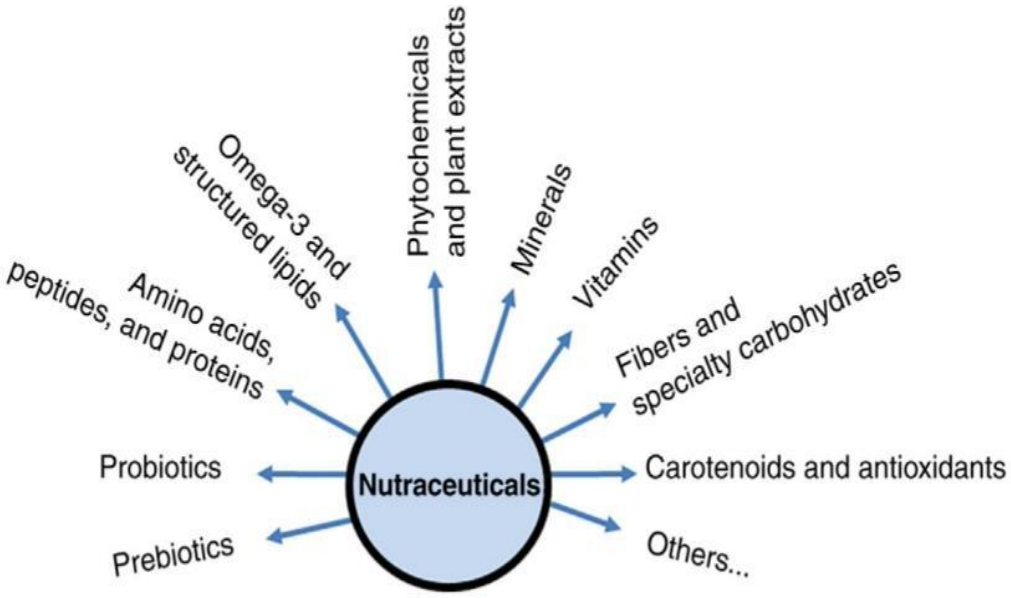
Freshly, the emphasis has been going on developing predictive types and high-quantity methods to assist the initial evaluation of toxicity in nano systems. This concept, identified as "Protection by Design," will promote the design process of nano delivery systems and allow safer systems to be manufactured. Implementing safety by design principle in product research has helped reduce the risk of drug withdrawal from the market for safety issues from 50% to just 20%.

7. MICRO- AND NANOENCAPSULATION OF NUTRACEUTICALS

Several classifications of nutraceuticals exist, several based on their availability on the market, others depending on the quality of the substance, compound, or molecule. Several nutraceutical groupings are listed in Figure.

In food, nutrition, and pharmaceutical research and industry the encapsulation of bioactive food ingredients in micro- and nanoparticles is essential. Nanoscale regulation of food molecules (and molecules or nanosystems incorporated in food) can result in modification of certain macroscale characteristics, such as color, texture, taste, processability, and shelf life. On an industrial scale, the application of nanotechnology in the food industry is faced with challenges such as (1) preserving food quality, (2) using cheap materials, (3) seeking easily scalable processes, and (4) improving the stability and bioavailability of encapsulated substances. Such technologies are being examined for bioactives experiencing problems with respect to their bioavailability or in vivo and in vitro stability. Thus, through the use of nanotechnology, the possible benefits these systems offer to bioactives through added value for human diet can be achieved. Within the next pages, some of the principal

nutraceuticals are discussed along with the efforts made to boost their bioavailability using nanoparticles.



7.1 Encapsulation of probiotics, prebiotics, and symbiotics

7.1.1 An Overview on Probiotics, Prebiotics, and Synbiotics

Probiotics are classified as foods / substances which contain micro-organisms which support the host organism. Such examples of microorganisms include: (1) the most significant probiotics of lactic acid bacteria (e.g., Bifidobacterium species, Lactococcus lactis, Enterococcus faecium); (2) nonlactic acid bacteria (e.g., Escherichia coli strain nissle); and (3) yeasts (e.g., Saccharomyces cerevisiae). The advantages to the host organism are derived by: (1) modifying the host microbial population, (2) reduction of the risk of diseases caused by pathogens, by aggregation of pathogenic bacteria or by the development of bacteriocins (antibacterial substances generated by bacteria to destroy or prevent the growth of other bacteria), (3) alteration of the structure and function of the epithelium, (4) development of many substances (e.g. organic acids, polysaccharides), improvement of host well-being, (5) modularization.

Prebiotics are characterized as non-digestible substances, i.e., resistant to gastric acid and enzymatic digestion, but are selectively fermented by the intestinal microflora, promoting the growth and/or development of beneficial bacteria that colonize the gastrointestinal tract, offering benefits for the well-being and health of the host (De Verse and Schrezenmeir, 2008; Ro The compounds currently known as prebiotics

include: (1) inulin (a soluble dietary fiber, a non-digestible heterogeneous polymer fructose mixture connected by β(2–1) fructane bonds), (2) oligofructose (OS; inulin subgroup containing 2–10 residues of monosaccharides), (3) fructooligosaccharide (FOS; products of inulin degradation or the result of transfructosylation mediated by Aspergillus Niger or Aspergillus aculeatus β-fructosidase action on sucrose), galactooligosaccharides (GOS; short chain polymers of galactose, that act as soluble fibers and have a bifidogenic effect), and some others that are still under study. And Synbiotics are the combination of a probiotic and a prebiotic that function synergistically as prebiotics, promoting the survival and operation of in vivo probiotics, and stimulating anaerobic indigenous bacteria

7.1.2 Delivery of Probiotics, Prebiotics, and Synbiotics

Probiotics are used in many food products, focusing on dairy products such as milk, cheese, and kefir and other products (e.g., puddings, fruit-based beverages, medicinal products, and dietary supplements). The therapeutic efficiency of the added bacteria depends on the dosage, preserving their viability (from growth, shelf-life to the gastrointestinal tract), which is of considerable importance in the marketability of probiotics containing foods. So one of the key reasons why probiotics are encapsulated is to improve their viability during processing, storage, and delivery. Micro- and nanoencapsulation may give major advantages, namely the protection of probiotics against environmental conditions (e.g., pH, fermentation products, temperature, oxygen, moisture) partially achieved by the physical barrier offered by the nanocarriers used, which also contributes to a better bioavailability improvement. Probiotics are usually encapsulated as cultures which are lyophilized or spray. Micro- and nanoencapsulation of probiotics depends on the choice of the encapsulating materials as they are affected by many factors such as biocompatibility, low cost , availability and also influence the viability of probiotics during storage and processing, the shape of the particles and the final appearance and texture of the drug. Biopolymers such as alginate, chitosan, gelatin, whey protein isolate, and cellulose derivatives were used to encapsulate the probiotics. The most commonly used methods include drying spray, extrusion, and emulsion.

Improvement of probiotics in vitro and in vivo gastrointestinal tract profiles, i.e., survival against the gastrointestinal tract environment, namely acidic stomach (pH around 2) and enzymatic environment (e.g., pepsin and pancreatin) has been achieved with their encapsulation in multiple matrices, namely polymeric, such as calcium

alginate, alginate-chitosan, alginate-gelatin, alginate-gelatin. The alginate is the most widely used polymer as it has the ability to resist stomach degradation, typically produces smooth surface microcapsules and also achieves a managed release. In fact, alginate provides probiotics with a metabolic stabilization. The nanocarriers' coatings may provide high mucoadhesion of the mucosal tissue in the colon 's physiological environment, leading to prolonged retention period and thus convenient release of probiotics in this region.

Overall, the micro- and nanoencapsulation of probiotics in the gastrointestinal tract appears to be important in the bioavailability, survival, and efficiency in vivo and in vitro, showing several advantages as summarized in Fig.

The natural polymers fructooligosaccharide (FOS), galactooligosaccharides (GOS), oligosaccharides (OS), inulin, and other molecules are prebiotics and Synbiotics. Some of the resulting commercial oligosaccharide products contain a significant percentage of the sugars resulting from low molecular weight, such as glucose, fructose, sucrose, galactose, and lactose, reducing end product performance and being a source of sugar assimilation. As high purity is a demand, purification and encapsulation methods have been developed to reduce the lower molecular weight contaminants and to ensure the higher molecular weight molecules are trapped. Usually, prebiotics are mainly used as matrices, or part of matrices, to encapsulate probiotics which give it the name of Synbiotics (combination of pre- and probiotics in the same system) as these types of fibers protect, transport and release probiotics and then serve as "food" for them. Synbiotics are thought to be the best way of delivering probiotics in the gastrointestinal tract, useful for treating or preventing multiple diseases.

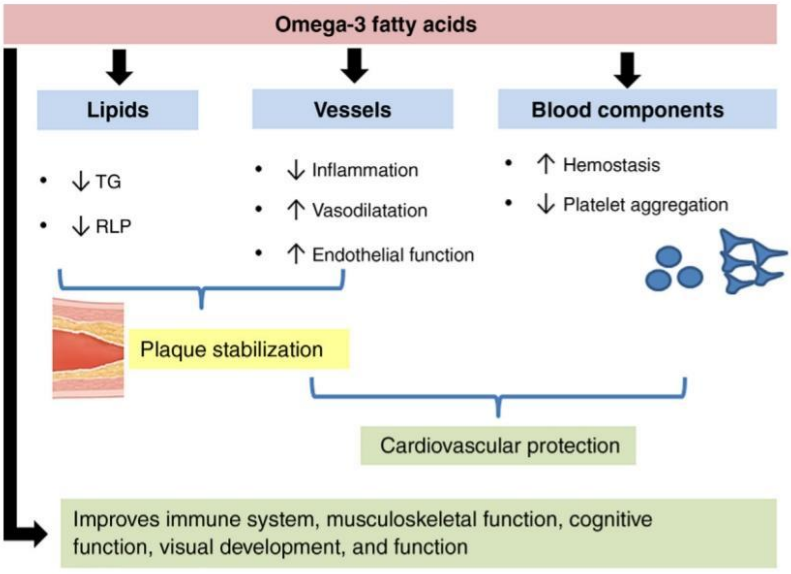
The most commonly used matrix for microencapsulation is alginate (a natural anionic polysaccharide composed of residues of d-mannuronic acid and glucuronic acid linearly connected by 1–4 glycosidic linkages), which was found to enhance probiotic survival. And alginate gel is stable at low pH due to its chemical structure, and then swell at higher pH (as in the intestinal environment) releasing the cells. The use of alginate as coating material in food matrices is also a viable option which provides the encapsulated prebiotics with stability and high viability. FOS may also serve as a carrier for probiotics, which developed suitable microcapsules in combination with whey protein isolate (WPI) or denatured whey protein isolate (DWPI) to encapsulate the probiotic bacteria Lactobacillus plantarum with reduced particle stickiness and

aggregations. These microcapsules showed high encapsulation performance, with improved storage stability providing protection of the gastric environment and a promising food industry network.

Dietary fibers contain certain prebiotics, and also use other fibers to encapsulate bioactive foods. Dietary fibers are found in foods derived from plants (e.g., fruits, vegetables, and whole grains) and play a major role in maintaining a healthy digestive system. Usually they are not fully digestible and can be separated into soluble and insoluble fibers depending on water-solubility. The first are present in bananas, peas, and beans (e.g., pectin, fructo-oligosaccharides, oligosaccharides, inulin, β-glucans), and the second are contained in whole grains and vegetables (e.g. cellulose, hemicellulose, lignin). Remember that the prebiotics are certain dietary fibers. Additionally, certain dietary fibers are used as matrices for food product nanotechnology.

7.2 Encapsulation of oils and omega-3 fatty acids

The fatty acids and the fats. Meat, nuts, and seed oils are high in omega-3 fatty acids, an essential fatty acid (not human-synthesized but dietary essential). There are three major omega-3 fatty acids found in fish oil, eicosatetraenoic acid (EPA), and docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA), contained in vegetable oils and nut. It has been shown that omega-3 fatty acids reduce cardiovascular disorders, enhance the visual and mental function and other conditions such as immunity, as outlined in Fig.



Conjugated linoleic acid (CLA), a mixture of linoleic acid isomers (omega-6 fatty acid), plays a major role in the metabolism of fats. To preserve vascular physiology a balance between omega-3 and omega-6 is necessary. Improving lipid metabolism by-circulating triglycerides (tG) and residual lipoproteins (rlp; independent cardiovascular disease predictors, including atherosclerosis). They participate in the synthesis of anti-inflammatory mediators that improve the vascular function culminating in cardiovascular protection, together with the promotion of vasodilatation and the regulation of hemostasis. Omega-3 fatty acids have other beneficial effects, as described, on healthy skin maintenance, balanced weight and others.

Since its physical and chemical properties limit its use as a nutritious food ingredient, the micro- and nanoencapsulation of this essential oil can provide a variety of benefits. With regard to its highly unsaturated nature, omega-3 fatty acids are highly unstable, susceptible to oxidation, which leads to hydroperoxide degradation and production, leading to organoleptic flavor and odor problems. Manipulation and storage are not made simpler due to these characteristics. Thus, the enhancement of their shelf life and masking capacity in their encapsulation tend to be two main goals. Coacervation (separation of colloidal systems into two liquid phases) and spray-drying and spray-chilling methodologies are the most common methods for encapsulation of omega-3 fatty acids The encapsulation of omega-3 fatty acids also needs three important steps: (1) the selection of suitable core material (source of omega-3 oils), (2) the selection of material for encapsulation, and (3) the methodology; all these properties are necessary to obtain excellent encapsulation and safety levels, resulting in a high quality and end product bioavailability. The key sources of omega-3 oils are fish, the most commonly used technique is spray-drying and others have been used for the encapsulating content (e.g., casein, gelatin, lactose, methylcellulose, gum Arabic, whey protein isolate, lecithin, chitosan, egg white, powder), as recently checked.

Performance in encapsulating omega-3 oils was obtained by means of a carbohydrate matrix consisting of k-carrageenan / polydextrose, offering a controlled release due to enhanced diffusion of the matrix oil. These oils have also been encapsulated in lipid matrices, namely SLN, whose material composition and physicochemical properties have been studied regarding their crystallization to reduce lipid peroxidation, further studies are required to use these systems in industrial processes. Compared to

nonencapsulated oil, the use of cyclodextrins also increases the oxidative stability of omega-3 oils. During digestion, a synergetic effect has been recorded between omega-3 fatty acids and probiotics, and their co-microencapsulation appears to provide greater stability.

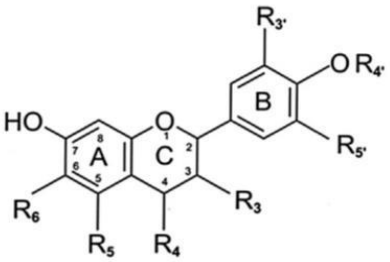
Food products are made from microencapsulated omega- 3. Microencapsulation of omega-3 oils using a spray process using whey protein concentrate with an oil / protein ratio of 0.4 has shown good results in terms of encapsulation efficiency and lipid peroxidation safety. Further incorporation of these microcapsules containing omega-3 oils in biscuits was demonstrated, following sensory evaluation and 4 months of packaging to secure the oil along with suitable physicochemical and organoleptic properties.

7.3 Encapsulation of antioxidants

In general, antioxidants are molecules / substances (natural or synthetic) which inhibit the oxidation of other molecules. Which include vitamins (e.g., vitamin A, C, and E) in the nutraceuticals group, phytochemicals (e.g., catechins, carotenoids, anthocyanidins) that neutralize oxidative organisms, decrease risk of cardiovascular diseases, and cancer, among other behavior. Most of the abovementioned nutraceuticals suffer from poor water solubility, which can lead to poor oral bioavailability and therefore reduce their effectiveness in treating and/or preventing diseases. Some antioxidants are unstable molecules that can undergo oxidation when exposed to multiple components of food.

7.3.1 Encapsulation of Polyphenols

The class of polyphenols is large, and from an antioxidant standpoint these natural molecules are interesting. Unfortunately, polyphenol concentrations that tend to be successful in vitro are not achieved in vivo, and their bioavailability is exceedingly small. In general, ingested polyphenols revealed problems due to inadequate gastrointestinal residence period, low absorption dissolution in the gut environment, structural instability due to factors such as temperature, presence of molecular oxygen, light, local pH, digestive enzymes and the presence of other compounds (e.g., fibers, nutrients) which helped to restrict their nutraceutical properties. Their bad taste is another inconvenience of certain polyphenols, such as astringency, which needs to be masked. Thus, the use of nanocarriers may be a viable solution to provide protection and preserve the active molecular shape until the time of ingestion and distribution in the gastrointestinal tract, to overcome these drawbacks.



Their bad taste is another inconvenience of certain polyphenols, such as astringency, which needs to be masked. Thus, the use of nanocarriers may be a viable solution to provide protection and preserve the active molecular shape until the time of ingestion and distribution in the gastrointestinal tract, to overcome these drawbacks and deliver such compounds.

Micro- and nanoencapsulation of polyphenols are commonly studied in the prevention and treatment of many diseases, such as cancer, cardiovascular disease, diabetes and related diseases, due to the tremendous human health benefits attributed to these molecules.

With regard to anthocyanins, these are natural pigments that occur in fruits and plants with various medicinal attributes. They have a very pH-sensitive chemical structure (color depends on the pH), oxygen, ionic strength, and temperature that affects stability and thus their bioavailability. Since they can be absorbed directly by epithelial cells in the small intestine, methodologies are required to deliver these phytochemicals directly to the small intestine. Good results have been obtained through their encapsulation in microspheres (composed of oxidized konjac glucomannan and chitosan oligosaccharides that are dietary fibers), which have been able to protect and guide the delivery of these bioactives to the intestines retaining antioxidant activity, and the regulated delivery of anthocyanins has also been encouraged. With respect to the possible involvement of anthocyanins in the modulation of intestinal microbiota, a study with cyclodextrin-encapsulated anthocyanins showed their potential colon delivery with increased bioavailability, which was accompanied by a positive effect on the population of intestinal bacteria, and that several bacteria could metabolize anthocyanins into phenolic acids (e.g., ferulic acidification). As regards the protection of anthocyanins against thermal degradation, gum Arabic nanostructures containing anthocyanins showed positive

effects on their stability at high temperatures such as 80 ° C (pasteurization temperature) and 126 ° C (autoclaving temperature) and provided stability to the effect of pH degradation (pH 5), suggesting that this form of nanostructure could be a good choice for encapsulation.

Catechins, the big green tea polyphenols with antioxidant, anti-inflammatory, Chemopreventive properties, also have beneficial effects on conditions of metabolic syndrome, such as diabetes and obesity, among others. Catechins are also susceptible to temperature, alkaline pH, free radical presence and other agents that can cause degradation of them. The encapsulation of catechins in lipid emulsions revealed excellent physicochemical properties and these systems were able to offer good stability. Our research group also showed good parameters of lipid nanoparticles that incorporate catechins, namely gallate epigallocatechin. For biopharmaceutical studies we were able to establish an HPLC method to quantify and stabilize this bioactive in physiological medium. Successfully encapsulated catechins in chitosan nanoparticles by using reduction agents to facilitate their stabilization in alkaline solutions. Thus, the use of antioxidant molecules to avoid their auto-oxidation, such as ascorbic acid, dithiothreitol or tris(2-carboxyethyl) phosphine, could be an intelligent technique to counteract catechin degradation. After their encapsulation in cyclodextrins, the antioxidant activity of catechins was evaluated, and results showed that it depends on the method of inclusion of the bioactives in cyclodextrins.

Flavonoids form a large group of polyphenolic compounds, characterized by a benzo-α-pyrone structure, their chemical composition depends on their structural type, degree of hydroxylation, substitution and conjugation, and degree of polymerization. Flavonoids can be classified into groups such as flavanones (e.g., naringenin, hesperetin), flavones (e.g., apigenin, luteolin), flavanols (e.g., quercetin, myricetin), which have variations due to oxidation rates and C ring replacement pattern. The position of the benzenoid substituent (B ring) distinguishes the relationship between flavonoids (2-position) and isoflavonoids (3-position) within a relationship in the A and B ring. Flavanols differ from flavanones because of the presence of the double bond c2–c3 and the 3-position hydroxyl group. Flavanols have a group of 3 hydroxyls that is absent in flavones. The flavanones have a heterocyclic saturated ring. Substitution pattern, Flavonoids that occur in foods and medicinal plants as aglycones, glycosides (usually connected in 3- or 7-position with d-glucose , galactose, arabinose, l-rhamnosis or glucorhamnosis) and methylated, while aglycans

are easily absorbed by the small intestine, flavonoid glycosides need to be converted into aglycans that occur in the small intestine or in the colon, depending on the degree to which they occur in the small intestine. The absorption of flavonoids in the small intestine is higher than in the colon, thus most ingested flavonoids are not absorbed as they are removed or destroyed by the colon bacteria, thus decreasing the possibility of medicinal properties, Thus, aglycan flavonoids need to be administered to the small intestine to have a nutraceutical impact.

Several nanosystems have encapsulated the flavanones. Hesperetin was encapsulated in solid lipid nanoparticles with an encapsulation efficiency of 39.90 to 63.08 percent, a fiction and dissolution process was observed after analysis of the kinetics of hesperetin release in simulated gastric fluid. Hesperetin encapsulated in SLN also showed to be stable over 30 days, at different temperatures, without detectable leakage in aqueous suspension. It was used to fortify milk and there was no bitter taste (typical from hesperetin) after sensory examination because it is poorly water-soluble. Isolated flavanones from Eysenhardtia platycarpa were encapsulated in polymeric nanoparticles and nanoemulsions, which were prepared for topical use. These systems showed sustained release, providing permeation of the skin, and substantially improved anti-inflammatory action of flavanone, suggesting that these systems can be used to encapsulate other flavanones and used for other routes of administration. Naringenin encapsulation in liposomes (multilamellar vesicles dependent on phosphatidylcholine) has been shown to be weak (< 10 percent), but it has been highly absorbed on these liposomes, raising stability and antioxidant activity. Flavones, namely apigenin, were encapsulated in distearoylphosphatidylcholine-based liposomes with an encapsulation efficiency of approximately 90 percent and were able to exercise antibacterial activity due to the intimate relationship between these nanocarriers and the bacterial membrane. Apigenin was also encapsulated in modified phospholipid micelles (phospholipids and TGPs [d-alpha tocopheryl polyethylene glycol 1000 succinate]), 87 percent of which was stable for more than 90 days following lyophilization. These micelles improved bioavailability, intestinal absorption of apigenin, and showed anticancer effects. In the case of flavanols, quercetin was encapsulated in folate-modified lipid Nanocapsules administered to H22 tumor-bearing mice, providing a longer duration of in vivo quercetin with antitumor activity. Quercetin was encapsulated with high encapsulation efficiency in nanostructured lipid carriers and the particles also showed in vitro anticancer activity,

it could be a good system for treating gastrointestinal cancers. Rutin has been encapsulated with high encapsulation efficiency (> 60 per cent) in liposomes (phosphatidylcholine-based multilamellar vesicles) and high trap performance, retaining its antimicrobial and antioxidant function, which is a strong promise for further use. High efficiency of rutin encapsulation was also observed in nanoemulsions, showing a sustained release over time.

Nowadays, isoflavones (e.g., genistein, daidzein) are of great interest due to their antioxidant activity and estrogen-like activity (phytoestrogens), which may reduce the risk of hormonal-dependent cancers as well as the incidence of hormone-related pathologies (e.g., osteoporosis), thus the dietary enrichment of isoflavones is of great interest. Food industry has developed techniques for extracting these extremely high yielding isoflavone aglycans from soybean, but this extract has poor water solubility, which is difficult to further refine into foods and other health items. Isoflavone encapsulation in sodium Producing powdered micronized polymeric microparticles in sodium carboxymethylcellulose coating / swelling matrix using spray technique that were capable of handling and storage. This technique enhanced the rate of dissolution and permeation in vitro, leading to increased bioavailability after oral administration. The encapsulated soy-isoflavones are therefore a promising ingredient in food supplements. Genistein and daidzein were successfully encapsulated by wet-kneading method into a mixture of four forms of cyclodextrins, showing improved solubility and increased membrane permeation (which was investigated in Caco-2 cells that shape a monolayer at confluence, mimicking the intestinal epithelium) along with increased bioavailability.

Hydroxybenzoic acids have been studied as gallic acids for the prevention of colon cancer. Gallic acid was encapsulated with high encapsulation efficiency in matrices of chitosan, β-cyclodextrin, and xanthan gum, retaining its antioxidant activity and improving its bioavailability and solubility. Cyclodextrins have successfully encapsulated syringic acid and vanillic acid, improving stability and bioavailability, which is a positive outcome for further food and pharmaceutical applications.

Resveratrol, a stilbene, has many biological activities (e.g., antioxidant, antimicrobial), but its effectiveness is limited due to its low bioavailability, resulting from its weak water solubility. Resveratrol encapsulated in methylated-β-cyclodextrins (in a ratio of 1:1) thus increased its water solubility (about 400-fold), thus its bioavailability, retaining its antioxidant and antibacterial activity (against

Campylobacter), which is an promising result for its application in food industry aimed at controlling both food-borne and nutraceutical pathogen.

Tannins are present in a variety of food plants, they can inhibit the activity of α-amylase and glucoamylase and are therefore modulators of postprandial hyperglycemia that decrease glucose absorption, making them good candidates for the treatment and prevention of type 2 diabetes. However, at oral administration, tannins pose some difficulties because they bind to proteins and have an astringent bitter taste, so efficient distribution mechanisms are required to ensure they enter the small intestine. Tannins were encapsulated in microparticles made of sorghum kafirin protein by co-conservation process, developed for oral delivery, showing good encapsulation capacity, and retaining anti-enzymatic action. This strategy reinforces tannin use for the treatment and prevention of type 2 diabetes and obesity.

7.3.1.1 curcumin and derivatives

Turmeric (Curcuma longa) is an Indian spice that has been used as a medicinal plant for centuries since it poses various biological activities (anti-inflammatory, anticancer, antimicrobial, anti-rheumatic, antioxidant, antidiabetic effects. Curcumin (turmeric main component) curcuminoids and curcumin oil encapsulation tend to be an approach to improving their bioavailability due to their low solubility. Curcumin was encapsulated in biodegradable nanoparticles using emulsion techniques, showing a 9-fold improvement in oral bioavailability compared to non-encapsulated bioactive with a permeation enhancer.

Curcumin's anticancer activity was also improved against human colorectal and pancreatic cancer cells, following its encapsulation in self-assembled pH-sensitive nanoparticles in sodium caseinate. Curcumin encapsulation posed benefits in managing diabetic retinopathy, as it greatly delayed the diabetic cataract progression. Curcumin-loaded into poly- (lactide-co-glycolic acid), PLGA, orally administered nanoparticles greatly enhanced its bioavailability in vivo.

Thus, curcumin encapsulation not only enhanced its solubility and permeability with increased bioavailability, but also enhanced the therapeutic effects under considerable investigation as an anticancer agent. Also examined was the co-activity of nutraceuticals, an example of two nutraceuticals, curcumin (lipophilic) and catechins (hydrophilic) were incorporated into a double emulsion (w / o / w), resulting in greater stability in gastrointestinal fluid, as well as increasing their bioavailability compared to the individual suspended curcumin and catechin solutions.

Overall, several strategies for encapsulation of polyphenols are being developed to address their physical and chemical limitations, and to enhance their bioavailability and biological activity.

7.4 vitamins

Vitamins are an important part of the human diet, and a major source of bioactive substances for many biological functions to maintain. Vitamin intake, in general human diet, is still inadequate, although we have now promoted vitamin-enriched foods, but does this enrichment boost their distribution and bioavailability in the gastrointestinal tract? This is an especially important issue, because vitamin and mineral supplementation requires the maintenance of their integrity and therefore bioavailability until the gastrointestinal tract. So, some strategies are needed and dependent on the type of vitamin to improve their bioavailability and also their stability in food products. These show poor bioavailability due to the fact that some vitamins are liposoluble (vitamins A, D, E, K) as well as their derivatives. Vitamins also have susceptibility to light, Ph, temperature, and oxygen and are relatively unstable in processing and storage environments. These are characteristics or intrinsic characteristics of vitamins that make them attractive micro- and nanoencapsulation molecules, which are essential to prevent their degradation and also to improve their bioavailability and consequent health benefits. The encapsulation strategies are partly similar to those proposed in polyphenols, as they share those characteristics. There are some recent developments in its encapsulation.

In the form of all-trans-retinol, vitamin A experiences degrading reactions that are typical of conjugated double bonds, resulting in a partial or total loss of its bioactivity. Nanoencapsulation is thus a solution for preserving their property. It was encapsulated in solid-state emulsions, developed as macroporous silica-lipid hybrid microcapsules, and demonstrated improved release, lipolysis kinetics, oral bioavailability, and shelf life, which is an improvement for further nutraceutical uses. All-trans-retinol has also been encapsulated into SLN showing improved retinol stability, photostability, and protection of its antioxidant activity.

Several B-complex vitamins were successfully encapsulated in a variety of nanocarriers, such as liposomes, polymeric nanoparticles, with increased bioavailability but maintaining the nutritional quality. Folic acid or folate is also widely used as nanomaterial for matrix or coating material development of

nanocarriers or even to conjugate with drugs because the folate receptor is over-expressed on the surface of many tumor cells.

Vitamin C is contained in microspheres, emulsions, and microcapsules. Its stabilization is a food and pharmaceutical industry challenge. Via its microencapsulation in microspheres (manufactured using microchannel emulsification) with good encapsulation performance, ascorbic acid stabilization was achieved for more than 10 days. Vitamin C (ascorbic acid) was loaded into microparticle composed of Arabic gum and rice starch using spray drying process, with high encapsulation performance, thermostability, improved chemical stability and storage.

The encapsulation of vitamin D also showed several benefits, in terms of the volatility associated with certain environmental conditions. Ergocalciferol (vitamin D2) has been successfully encapsulated in shell-core microparticles (composed primarily of guluronic alginate and mannuronic acid) manufactured by ionic gelation through ultrasonic atomization accompanied by microwave-drying particles. This shell-core microparticles allowed high encapsulation efficiency and sustained gastrointestinal pH-compatible release, being low at pH 1 (about 10 percent) and high at pH 6.8 (complete release) with minimal ergocalciferol degradation. Vitamin D3 (cholecalciferol or calcitriol) encapsulated in complex polymeric nanoparticles formed by carboxymethyl chitosan and soy protein isolate, prepared by ionic gelation process, with high encapsulation efficiency and convenient release (low at gastric pH and high at intestinal pH); This technique is ideal for encapsulating nutraceuticals for nutritional absorption and fortification. The use of nutraceuticals for beverages needs to be discreet, without altering its natural look, taste, and smell. Nanoemulsions give small droplet size, aggregation or precipitation stability, transparency while enhancing bioavailability; Vitamin D has been encapsulated in o / w nanoemulsions, increasing its bioavailability, sustaining existence (more than 1 month at room temperature) without particle aggregation except at high temperatures (> 80 ° C) where particle growth has been observed.

Before integrating vitamins E and K into functional foods and beverages, they do need the same strategies as vitamin A and D. O / W emulsions, formed by high-pressure homogenization, stabilized with a food-grade natural surfactant (Q-Natural) isolated from the Quillaia Saponaria Molina tree bark, demonstrated an edible delivery mechanism for the incorporation of vitamin E in functional foods and

beverages. A technique for its encapsulation in polymeric micelles, composed of a thermosensitive block copolymer, demonstrated in vivo (rat model) improved intestinal absorption with elevated plasma levels of vitamin K, with the goal of increasing intestinal absorption of vitamin K. Vitamin K1 was encapsulated in SLN, showing more than two stabilities in simulated gastric and intestinal fluids and improved storage stability (more than 4 months of storage at 25 ° C), becoming an effective carrier for oral vitamin K delivery.

Ultimately, vitamin micro- and nanoencapsulation is essential in overcoming some of the chemical instability of these bioactives, enhancing their stability and providing a higher bioavailability, which is crucial because of the importance of their nutritional value in human diet. In addition, promoting such approaches may improve their intake.

8. NANOENCAPSULATION PROCESSES

Nano-encapsulation includes the integration of bioactive content, including food additives, nutrients, vitamins, minerals, slimming agents and enzymes, into miniscule capsules of nanometric diameter duration. The range of applications for this technology in the food and nutraceutical industries has expanded due to the many advantages and health benefits that nano-encapsulation may confer to the encapsulated material. This includes improving stability of the encapsulated material by shielding them from heat, humidity, pH fluctuations and other severe conditions, raising the cargo bioavailability. There are several different forms of technology for encapsulation which can be used in food systems. Those include nanospheres, nanoparticles, nanoemulsions, nano-cochleates, tocosomes, liposomes, and nanoliposomes, but not limited to those.

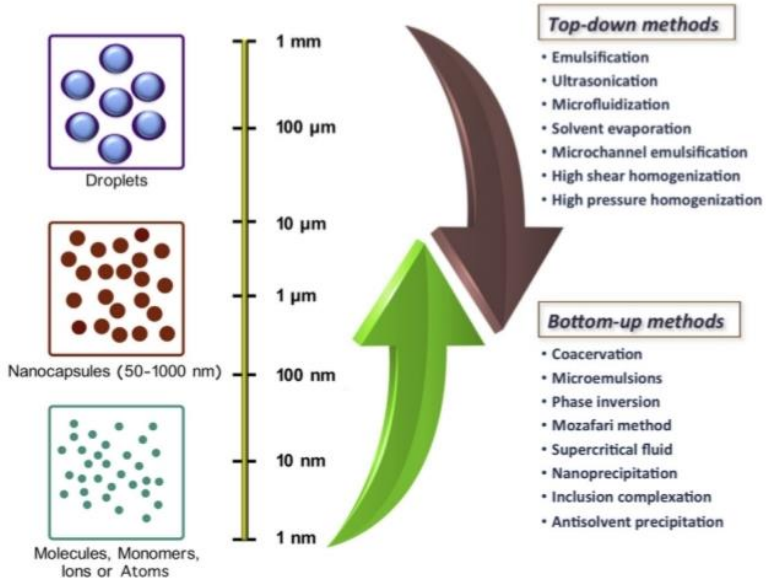
The application of nanoencapsulation systems in the food are ah as shifted toward controlled delivery in the human digestive system, for example by providing protection against the stomach environment for the encapsulated material, or by delivering nutraceuticals or probiotics to the colon during the decades. Consequently, the nanocarrier must also have sufficient protection against the destructive conditions in the human body, in addition to the protection during storage. Numerous

encapsulation systems are available in the field of nanotherapy for managed release of bioactive agents by oral administration, or to enhance the drug's bioavailability. The products and processes used to manufacture these pharmaceutical formulations, however, are also not appropriate for food applications, because they are not of food quality. In fact, they 're just too expensive to use as food ingredients.

The expertise and experience gained from nanoencapsulation applications in the medical and pharmaceutical industries offers an extraordinarily strong basis for developing food grade systems with comparable properties. The design of nanoencapsulation formulations for sustained or delayed release in the human gastrointestinal (GI) tract requires systematic understanding of the physiological conditions and the digestion processes. From a technical point of view, reversed development can be used to achieve maximum application-focused functionality, rather than to search for an application after developing the nanoencapsulation system. Due to the fact that the nanocarrier faces harsh and destructive conditions in the GI tract, a smart design is critical for success, as the digestion mechanism has developed over millions of years towards efficient food processing. The digestive factors such as bile salt composition, electrolyte balance, temperature, pH, and mechanical stress have to be counteracted to achieve controlled release of nonencapsulated compounds in the digestive tract. Alternatively, the aforementioned digestive factors may be used as triggers for bioactive release, examples of which are vesicles sensitive to temperature or liposomes sensitive to PH. "Smart carriers" (or devices that respond to stimuli) may respond to endogenous and/or exogenous stimuli. The endogenous triggers include pH, hormones, and enzymes, while the exogenous triggers at target sites, including temperature, magnetic field, and sonication, can also be used to cause or improve drug release. The future challenges of developing oral food-grade delivery systems are assumed to be: I the structure-function relationships, particularly the fate of the nanocarrier systems; (ii) the sensory properties; and (iii) the human variance and complexity of the digestive process.

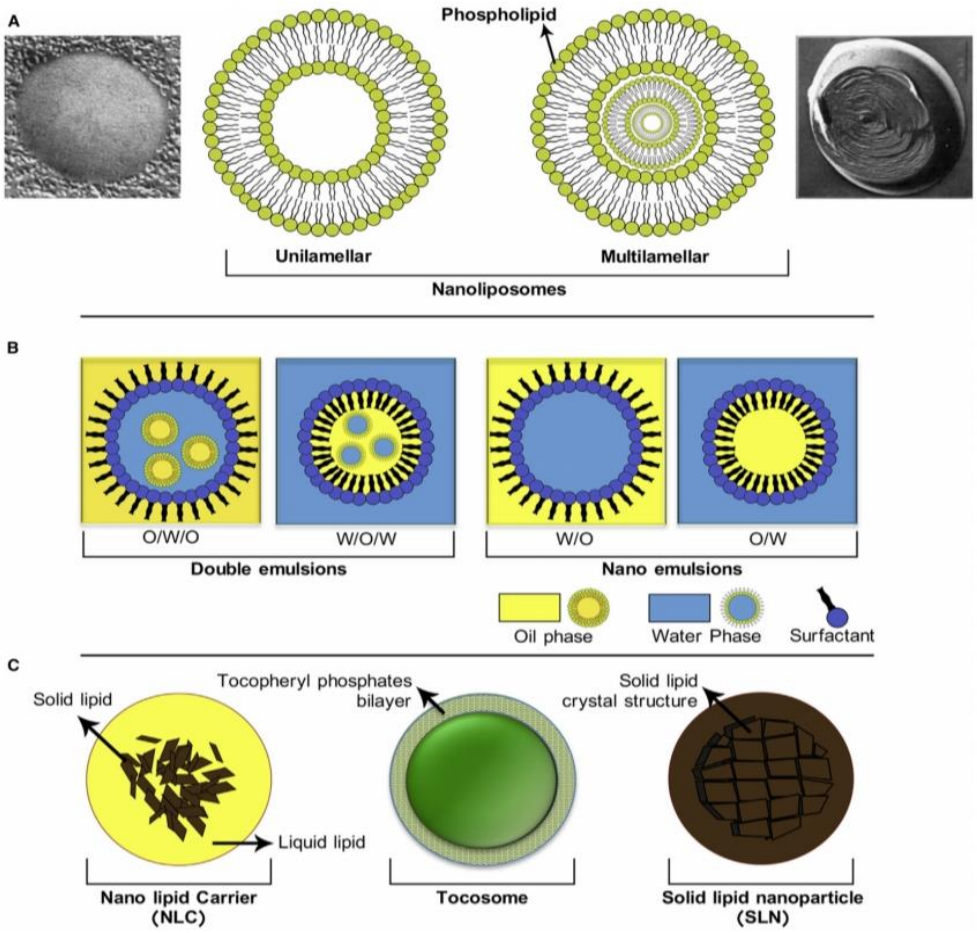
In a broad sense, both the "top-down" and the "bottom-up" techniques will accomplish the manufacture of nanocarrier systems. Downsizing to nanoscale is accomplished by energy application in the top-down method. This is while the aggregation of molecules, monomers, ions, or even atoms is regulated physico-chemically for the bottom-up fabrication to shape the nanostructures as shown in **Fig**

In the following pages, some of the key nanocarrier technologies used in the food and nutraceuticals field are clarified.



8.1 Different Types of Nanoencapsulation Techniques

Global patterns are moving from the extensive production of food materials, centered on the abundance of natural resources on the earth, to the limited production of green processes and emerging technologies for processing food products and delivering them to customers around the world. Nanotechnologies are considered to have an effect on all facets of the food chain, beginning with production e.g. agriculture, livestock farming, fish farming) and covering all intermediate processing phases, packaging, storage, distribution, sale to consumers. It is important to find strategies to improve the versatility of selected foods in order to create new food products. The common strategy for doing this is to supplement food products with natural compounds with high biological activity and established beneficial effects on human health. Various types of processes of nanoencapsulation and nanocarrier systems have been developed in that regard. Nanocarrier technologies may be divided into colloidal and non-colloidal structures in large measure. Fig Illustration Exemplifies some of the colloidal drug delivery methods used in food and nutraceutical industries. Some of the major processes of encapsulation and the bioactive delivery strategies are discussed.



8.1.1 Extrusion Techniques

Extrusion techniques include applying to the gelling solution a combination of polymer and bioactive materials through a dripping device where the collected beads were left to harden for a certain period of time. Several extrusion technologies may be implemented depending on the type of dripping tool employed. These include, I atomization of the spinning disk; (ii) piston cutting; (iii) vibrating piston / nozzle extrusion; (iv) electrostatic extrusion; and (v) coaxial extrusion of air pressure. Particles produced by extrusion processes are typically between 0.2 and 5 mm in size, although nanometric particles can also be obtained through ultrasonic-assisted extrusion. Particle diameter is primarily influenced by the dripping tool and the selected ingredients of the formulation. Moreover, the polymer used as a carrier material displays some influence on the viscosity and rheological behavior of the product.

Extrusion procedures are typically conducted under relatively mild conditions (temperature and pressure are usually lower than 118 C and 700 k Prospectively). Such procedures do not necessitate the use of any hazardous solvent, and these

methods can be used to encapsulate bioactive agents in both anaerobic and aerobic conditions. Consequently, the techniques of extrusion are applicable to the encapsulation of sensitive material, such as heat-sensitive molecules, and living cells. In addition, the carrier structures provided by the extrusion technologies have less porous structure compared to those generated by the spray-drying process for example. Nevertheless, the main disadvantages of the extrusion procedures include difficulties in achieving high industrial scale production efficiency. Another downside of the extrusion techniques is that in certain cases the size of the beads created may be too voluminous for applications in some food items. Lim and his colleagues have recently used the extrusion-dripping process to encapsulate insulin in the pH-responsive composite hydrogel beads made from natural biopolymers. Their work showed that the composite hydrogel beads successfully retained the drug at pH 1.2 by electrostatic interaction between the cationic drug (i.e., insulin as part) and the negatively charged carrageenan polymer sulfate groups. At pH 7.4, insulin as part was released slowly (sustained release), and as the concentration of k-carrageenan used in the hydrogel beads increased, the release profile reached zero-order kinetic. After incubation in an acidic artificial gastric medium of the composite hydrogel beads, about 65 percent of the insulin remained biologically active in the beads. The findings indicate a promising carrier device for the oral delivery of bioactive compounds is the alginate / k-carrageenan composite hydrogel ring, manufactured using the extrusion process.

8.1.2 Molecular Inclusion

Method of molecular inclusion encapsulation of bioactive compounds typically includes the use of cyclodextrin molecules as coating material. Cyclodextrins are a group of naturally occurring oligosaccharides containing six, seven or eight residues of glucose, interlinked by a (1/4) glycoside bonds, in a cylinder-shaped structure, and are referred to as a-, b- and gcyclodextrins. The size of the cylinder-like cavity of natural cyclodextrins, however, is around 0.8 nm, the diameter canary. Generally, all the methods used to achieve inclusion complexation rely on the simple co-precipitation theory. The encapsulation methods, as well as the required conditions for achieving the complexation, are special and differ for each and every bioactive compound that needs encapsulation. Usually, the solution containing the mixture of cyclodextrins and bioactive agents is needed to sonicise, heat or stir in order for complexation to occur. Where complex preparation involves coevaporation, heat

treatment can be applied in a vacuum oven. Alternatively, a rotary evaporator can be used to elevate the temperature of the reaction under vacuum.

Molecular inclusion using cyclodextrins provides a variety of advantages for the encapsulation of different bioactive compounds. One of the most important benefits of the molecular inclusion approach, however, is that it increases the solubility of poorly water-soluble molecules and their bioavailability is improved. The formulations would thus become more suitable for the food and nutraceutical applications. In addition, several studies have shown that carrier systems (capsules) made up of b – cyclodextrins promote controlled / sustained release of the encapsulated materials.

8.1.3 Nanoemulsion-Based Techniques

The term emulsion refers to a system consisting of two immiscible liquids, in which one component is distributed in the other component (the continuous / external phase) in the form of droplets (the distributed / internal phase). In general, the emulsions of food are in the form of water-in-oil (W / O), oil-in-water (O / W) or double emulsions. Emulsions can be classified into nano- (20 nm – submicron), micro- (1–100 mm) and macro-emulsions (0.1 mm) based on their size and diameter. Most of the emulsion properties, including stability, shape, color and shelf-life, are related to their size and distribution of droplets. Nanoemulsions can be prepared by dispersion approaches or a process known as emulsification, which can be categorized as low-energy and high-energy approaches. Emulsification is a method of combining two immiscible liquids into an emulsion and involves two primary approaches: single emulsion (i.e. water in oil, W / O and oil in water, O / W) and double emulsion (i.e. water in water, W / O / W and oil in oil, O / W / O) Emulsification technique can be used to encapsulate hydrophilic and lipophilic substances. High-energy emulsification approach includes the use of a high-shear mixer, high-speed homogenizer, microchannel homogenizer, membrane homogenizer, microfluidizer, or an ultrasound to generate micro or nanoemulsions. The characteristics of the emulsions produced vary depending on the type of high-pressure apparatus used, and thus can differ from one another.

Emulsification using a high-pressure homogenization system consists of two steps: (i) forming a coarse emulsion by a high-shear mixer, and (ii) passing the coarse emulsion through a narrow vent at high speed and pressure resulting in smaller droplets being produced. High-pressure homogenization plays an important role in regulating some of the Nanoemulsion characteristics including particle size and PDI, zeta potential, bioactive retention, and final product turbidity. Sharifa and colleagues recently

reported that high-pressure homogenization could generate small-sized nano dispersions of lycopene with a narrow PDI and good application stability for different beverages. On the other hand, the ultrasonic homogenization technique uses ultrasonic waves of high intensity (frequency > 20 kHz) in order to produce strong disrupting forces for the processing of fine emulsion droplets. High-pressure homogenization emulsification and ultrasonic emulsification techniques were applied by Freiberger and colleagues to encapsulate roasted coffee oil using poly hydroxybutyrate-co-hydroxy valerate (PHBV) and poly L-lactic acid (PLLA). The sonication technique showed maximum oil recovery for PLLA systems, while for PHBV systems, high-pressure homogenization showed maximum oil recovery.

8.1.4 Spraying Techniques

During food processing or fortification, bioactive compounds are predominantly in the liquid form. Many of the encapsulation technologies therefore involve some form of drying. To this end, a range of technologies can be applied including spray-drying, spray-cooling, spray-chilling, melt-injection, and fluidized bed coating. In this chapter we focus on spray drying, which is one of the techniques used to encapsulate bioactive compounds most extensively. This technique can be used to remove water from liquids, emulsions, and suspensions and other solvents. Compared with other techniques such as lyophilization, spray drying is a quick, easy, and convenient process. This technology is one of the most popular encapsulation methods used in the food industry due to its advantages, such as wide availability of equipment, large-scale production, easy continuous operation of units, ease of handling and relatively low process costs.

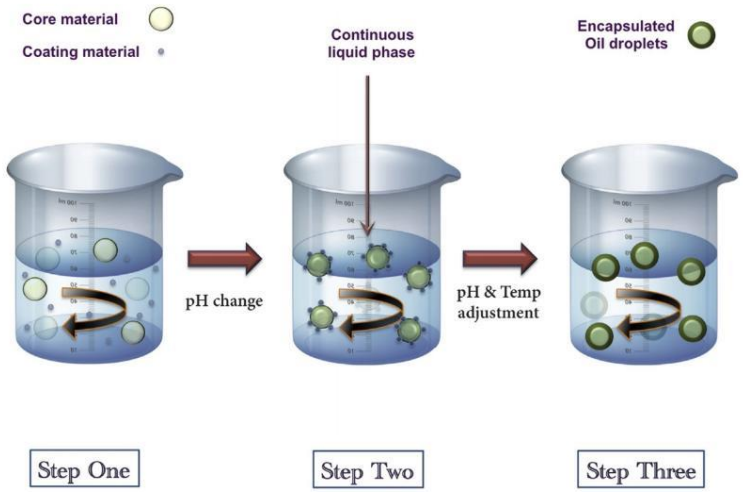
The basic principles of the spray drying technique are the atomization of the liquid sample in the drying chamber in the form of small droplets containing bioactive compounds, the supply of hot air into the drying chamber, the creation of microcapsules in the drying chamber and the separation of the microcapsules through cyclone recovery. The levels of output achieved by spray-drying technique are high. Hence it is highly relevant in the pharmaceutical, cosmetic, food and nutraceutical industries at industrial level. Using multi-nozzle spray drying equipment can help to boost output levels even higher. Spray drying is typically used to encapsulate hydrophobic compounds, but some hydrophilic compounds were successfully encapsulated as well. Desai and Park reported the manufacture of spray-dried powder-beads with an reasonable encapsulation efficiency and good stability, which were

spherical in shape. Nevertheless, the key disadvantages of the spray-drying process are: I the particle diameter is difficult to regulate and beads of desired size can be made, and (ii) heat-sensitive compounds can be harmed during the spray-drying process if the temperature of the inlet air becomes too high. There were many attempts to boost the bioactive encapsulation through the spray drying process. Microencapsulation of bioactive blueberry compounds by ultrasonically assisted spray, which demonstrated greater particle size and shape regulation compared to traditional spray and freezing techniques. Using ultrasonic technique in spray drying improved the formulation's encapsulation and retention of phenolic compounds, anthocyanins, and stabilization storage. Ultrasound-assisted atomization device produces vibrations and high frequency sound waves by piezoelectric transducers during the atomization of a liquid sample resulting in monomodal size distribution droplets being formed. The vibrational energy of the ultrasonic-assisted atomization system creates less mechanical stress and thus reduces the bioactive agents' potential for degradation. The use of vacuum chamber in spray drying instead of high drying chamber has also enhanced the keeping of heat-sensitive material such as ascorbic acid, flavonoids and phenolic compounds there. The main feature of this method is the use of low drying temperature i.e. 40–60 ° C) which reduces the risk of heat-sensitive bioactive compounds being thermally degraded. Ultrasound-assisted drying of the vacuum spray resulted in a high probiotic cell survival. In the case of nano-encapsulation, spray drying is employed to transform into nanostructured powder form as a sample of nanoparticles. A number of studies have reported successful application of nano-spray drying for nanocarrier-based product development. Nano-spray drying increased folic acid stability and enhanced the bioavailability of the capsulated curcumin in nanoscale carriers. The recent developments in spray drying techniques are thus able to give enhanced properties for formulations of micro- and nano-capsules.

8.1.5 Coacervation

Coacervation is a simple process and one of the widely used micro- and nano-encapsulation techniques of food & nutraceutical compounds. Particularly from an industrial point of view it is a promising encapsulation technology, as it can result in extremely high encapsulation efficiencies. Co-conservation cycle consists of three steps I creation of three immiscible phases (i.e. core material, coating material and continuous liquid phase), thus mixing (ii) formation of wall material (encapsulating

layer) around the bioactive compound by maintaining several parameters including molecular weight, coating material concentration, pH, ionic strength, and temp. Of phase oil, and (iii) solidifying droplets by heating, dissolving or crosslinking techniques. This technique essentially relies on the phase separation of one or more hydrocolloids from the initial solution, followed by the deposition of the coacervate layer around the active compound(s) suspended or emulsified. The coacervation technique's main steps are simplified at Fig.



Based on the number of biopolymers used in the process co-preservation approach is graded as "simple co-preservation" consisting of a single biopolymer and "complex co-preservation" consisting of two or more biopolymers. Complex co-preservation has improved functionality compared to simple co-preservation, therefore complex co-preservation is the best option in food and pharmaceutical fields. Protein polysaccharide complex is used widely for food application as a biopolymer. In addition, during the complex coacervation process, hydrophobic interactions and van der Waals intermolecular forces in proteins are also involved in phase-separation. Plant proteins and plant gums were also used to make complex coacervates. Gums experience negative ion in a wide range of pH while proteins have cationic or anionic load depending on PH. Successful complexation between protein and gum occurs at optimum pH value where polymers experience opposite loads with maximal load differences.

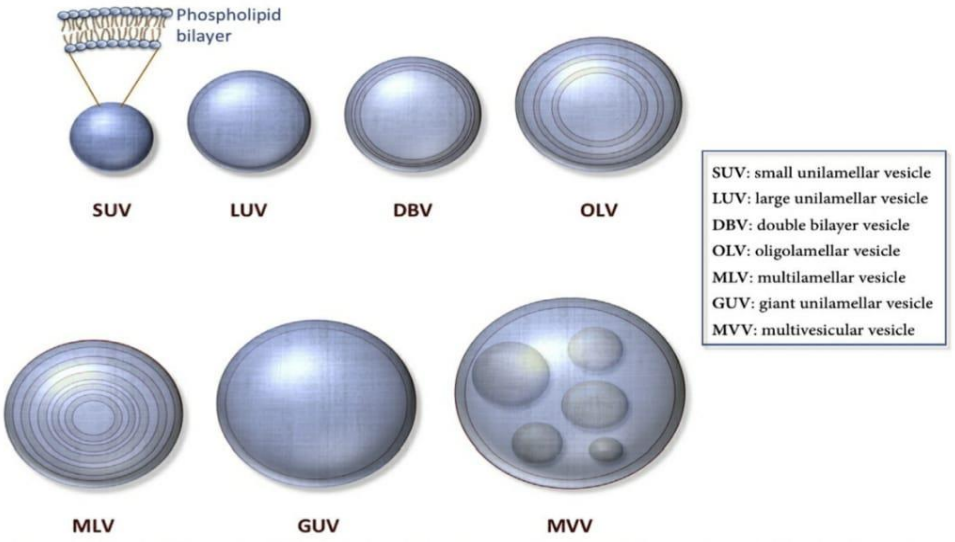
Many positive formulations of coacervate for encapsulation of various bioactive compounds have been published. For example, by using the simple coacervation

method, Stephanite and Chitprasert have produced holy basil essential oil-loaded alginate microcapsule. Optimum design using response surface methodology was found at 11.75 percent (w / v) gelatin concentration and 31 mL oil quantity, ensuring high encapsulation performance, optimum yield and high oil content. During storage at 60C for 49 days microcapsules also showed less loss of oil content. Complex co-occurrence is considered more effective than the spray process. This provides better security for the encapsulated material, as it does not require high temperature, provides high core loading power, high encapsulation performance, and greater controlled release of bioactive compounds. Using spray drying or freeze drying, the complex coacervates can be further converted to a powder form. Timilsena and coworkers recorded higher encapsulation efficiency and increased stability of chia seed protein isolate-chia seed gum complex coacervate microcapsules produced by complex coacervation followed by spray compared with simple coacervation followed by spray drying. Nonetheless, the coacervation procedures suffer from high manufacturing costs, rely on multi-factors (e.g. pH, ionic strength), exhibit limited stability in various aqueous media, and have limited control over the particle size of the droplets produced. In addition, the optimum condition of the coacervation process varies with the polymer types used, and the stability of complex coacervates within a restricted range of pH, ionic strength and temperature is reduced. Therefore, for the successful implementation of the complex co-conservation method in the food and nutraceutical industries, optimization of co-conservation conditions is necessary.

8.1.6 Nanoliposomes and Related Technologies

Nanoliposomes are contemporary technology of encapsulation derived from an older technique called "liposomes" Also known as phospholipid vesicles (or bilayer lipid vesicles) are classified as "closed, continuous structures containing one or more internal aqueous compartments separated from the external medium by one or more concentrated or non-concentrated lipid bilayers". In their aqueous space sand, they can accommodate water-soluble compounds, if necessary simultaneously, lipid-soluble moieties in their lipid phases (providing a synergistic effect) Nanoliposomes and other lipid-based nano-encapsulation systems are widely applicable in the food, nutraceutical, cosmetic, biomedical and pharmaceutical industries due to their excellent functionality, stability, biocompatibility, effectiveness in encapsulation, ability to target disease sites, controlled and sustained release profiles. Certain lipid-based nanocarrier systems include lipid nanoemulsions, archaeosomes, cochleates,

vesicular phospholipid gels, liposphere, virosomes, nanostructured lipid carriers, and solid lipid nanoparticles.



NLCs and SLNs are the two major lipidic nanoparticles that have emerged as novel, promising, and new generation lipid-based nanocarriers. Compared with the other lipid-based nanocarriers and polymeric micelles, they have differentiated encapsulation functionalities including high-load and drug stability. Two methods are commonly used to shape complex particle morphology NLCs and SLNs, which are labeled as low-energy and high energy techniques. Microemulsion, phase inversion temperature, solvent injection, solvent diffusion, mozafari process, and supercritical fluid technology are low-energy consuming methods. On the other hand, micro fluidization, high-pressure homogenization (hot and cold), and sonication methods are high-energy consuming approaches.

The liposome and nanoliposome formulation are based on the chemical interactions between the aqueous phase (water molecules) and the vesicle amphiphilic ingredients (i.e., phospholipids). When churned in an aqueous medium, the phospholipid molecules arrange themselves in the form of spherical bilayer structures via Van der Waals and hydrophilic / hydrophobic interactions under certain conditions of pH, temperature, pressure, and agitation, and form spherical lipid vesicles. In the internal and external portions of the vesicle, the polar head moieties of the phospholipid molecules are directed towards the aqueous process, and the hydrophobic tails are aligned with the lipophilic bilayer. The presence of both lipid and aqueous phases in

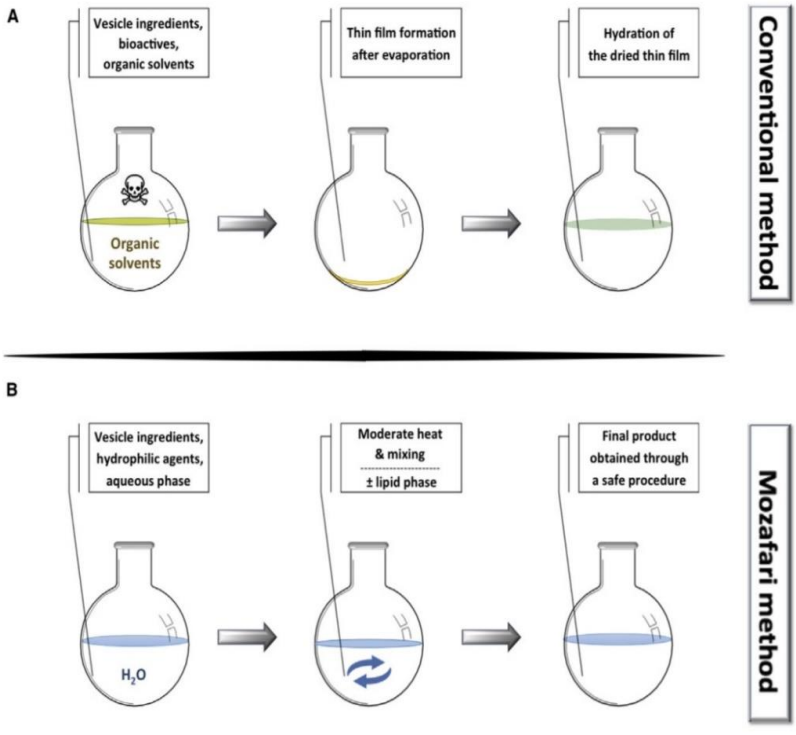
the liposome and nanoliposome structure allows for the entanglement, distribution, and regulated release of hydrophilic, hydrophobic, and amphiphilic compounds, thereby increasing bioavailability. In addition, clinical and biological studies have accepted many liposomal health benefits, including hepatic safety, improving memory, and reducing cholesterol uptake. Most notably, studies have shown that liposomes are also present in our very first natural food, that is to say the milk of mothers.

The lipid vesicles were originally primarily used as model membrane systems because their bilayer structure can be modified to closely mimic the lipid fraction of the biological membranes. The ability to simulate the characteristics of natural membranes is useful in the creation of formulations that can target membranes with a particular composition or investigate the stability and degradation of the membranes. Liposomes and proteoliposomes (i.e. liposomes that contain one or more proteins) have been shown to be highly effective carriers for encapsulation and delivery to biological, pharmacological targets of a broad range of active compounds.

8.1.7 Tocosomes

In 2017 a new encapsulation and delivery method called tocosome was launched by Mozafari and colleagues. The novel carrier consists of two vitamin E (a-tocopherol) derivatives, i.e., a-tocopheryl phosphate (αTP), and di-a-tocopheryl phosphate (αT2P). They can be made in various particle sizes, ranging from nanometer to micrometer scales, as is the case with the lipid carriers. The invention of tocosome is based on the fact that its key ingredients, i.e. αTP and αT2P, possess all the health benefits of tocopherols, particularly vitamin E, while benefiting from being hydrophilic molecules. Vitamin E's lipophilicity poses transportation and metabolic challenges to control its bioavailability and prevent its accumulation in lipid rich body parts including adipose tissue, liver, and brain. Vitamin E (a-tocopherol) hydrophilic precursors, including its acetate (αTA), succinate (αTS), or phosphate (αTP) esters, have increased water solubility and are stable against free radical reaction. However, they are easily transformed into the lipid-soluble vitamin E during their absorption. The bioavailability of these precursors is therefore inadequate, as intact molecules. However, studies have reported unusual regulatory effects, at least for αTS and αTP, on signal transduction, gene expression and regulation of cellular events ranging from proliferation, survival / apoptosis, lipid uptake and metabolism, phagocytosis, long-term potentialation, cell migration, telomer maintenance, and angiogenesis. Because

of the exquisite advantages of these ingredients, water-soluble vitamin E derivatives have been used successfully as components of a nanocarrier network i.e. tocosomes, for enhanced and targeted delivery of 5fluorouracil (5FU) anticancer agent. Tocosomal nanocarriers were produced using a safe and green process called the "Mozafari method" that does not require the use of toxic solvents, detergents, or harsh procedures such as sonication or homogenization (Fig). In addition to anticancer agents and various pharmaceutical therapies, tocosomes may also be used through various routes of administration for the safe and efficient delivery of food and nutraceutical compounds. It has been shown that Tocosomal ingredients exist naturally in animal and human tissues, as well as in food systems. TP has been reported to be present in various green vegetables, fruits, cereals, dairy products, and in some seeds and nuts. TP molecule comprises one side hydrophobic chain consisting of three units of isoprene. On the other hand, di-a-tocopheryl phosphate (αT2P) has two side chains but, unlike phospholipids, T2P's hydrophobic chains cannot interact with each other because of the presence of thick side chains of isoprene. Clinical studies have shown that TP and T2P molecules have several useful attributes, such as atherosclerotic-preventing effects, anti-inflammatory properties, and cardioprotective ability. Effects of TP as a tumor invasion inhibitor have also been reported.



9. CONCLUSION

The incorporation of nutraceuticals into food products provides a simple way of developing a variety of functional foods that could help fulfilling some of the consumers' health and wellness needs. However, the nutraceuticals' effectiveness depends on preserving their bioavailability. Delivery systems can be specifically designed to modulate bio accessibility, absorption, or transformation profile of nutraceuticals in the GI tract, boosting their bioavailability and consequently, their health benefits. Progress is being made by transferring the knowledge from pharmaceutical applications, including the use of nano delivery systems, absorption enhancers or excipient foods that have been shown to improve solubility, stability, or permeability of nutraceuticals. However, there are still some challenges that must be overcome, that include: i) the exclusive use of food-grade ingredients, ii) development of delivery systems stable in food matrices along processing and shelf life, iii) difficulty to control the release of nutraceuticals, iv) optimization of delivery systems formulations in order to increase the permeability through the intestinal walls, v) potential toxicity of absorption enhancers due to perturbation of the intestinal epithelia even for agents with GRAS status, and vi) in the case of nano-delivery systems, the risk assessment of their use of in food. This latter issue is particularly relevant, once, although the absorption of intact food grade delivery systems into the systemic circulation is unlikely due to changes after undergone gastric and intestinal digestion, reliable data regarding the risks of nano delivery systems cannot be found in the literature and also, from the existent studies, it is not possible to predict the consequences of their long-term intake. Therefore, in order to evaluate their safety, more realistic in vitro digestive models need to be designed to undoubtedly understand the fate of micro and nano-delivery systems/nutraceuticals in the GI tract; more advanced analytical methods to accurately detect and quantify nano-delivery systems must be developed; and a clear legislation and guidelines concerning their impact on human health and on environment must be assured. Also, in order to develop delivery systems with increased functionality, more efforts should be made towards understanding the interactions between the delivery systems and the food matrix. Future studies should focus on improving the physicochemical characteristics of the delivery systems, by the careful selection of the delivery systems' formulation

on a case by-case basis. The development of delivery systems that afford nutraceuticals' greatest functionality and safety may create opportunities to apply enabling technologies such as nanotechnology more broadly in the food industry.

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