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# Liposomes vs. Probiosomes: A Novel Approach for Targeted Drug Delivery

**Bruno Riccardi**
56022 Castelfranco di Sotto (Pisa), Via dei lazzeri, 33, Italy

**Sergio Resta**
53043 Chiusi (SI)-Via Monte Grappa, Italy

**Giacomo Resta**
Faculty of Pharmacy of the University of Perugia, Italy

## ABSTRACT

**Liposomal technology is a specialized branch of nanotechnology, which has allowed to improve many of the drawbacks and limitations of traditional drug therapy. By the use of this technology, in fact, you can produce very useful carriers for those drugs that have a low therapeutic index or reduced bioavailability, to make them equipped with a selective tropism for target organs. The upgrade of liposomal technology is represented by Probiosomas. Probiosomes are an innovative and promising nanocarrier system that has garnered significant attention in the field of drug delivery and therapeutics. These biocompatible lipid-based vesicles have emerged as a versatile platform for encapsulating and delivering a wide range of therapeutic agents, including drugs, genes, and diagnostic agents. This paper provides a comprehensive overview of probiosomes, including their structure, properties, fabrication methods, and applications in drug delivery and therapy. We also discuss the advantages, challenges, and future prospects of probiosomes in the context of personalized medicine and targeted therapies.**

**Keywords:** Probiosomes, drug delivery, targeted therapy, nanocarriers, personalized medicine

## INTRODUCTION

They are defined foods (from the Latin alimentum, derived from alĕre "nourish") the nutrients introduced by living organisms to support their specific energy and metabolic needs. Without food (today they are properly defined nutrients) living beings cannot survive.

Nowadays, food is produced by the food industry and processed intensively and with artificial procedures, which have consequently changed the quality standards and introduced new habits for the consumption of foods on the market which are of low nutritional value [1].

This has transformed the food we eat into substances poor in essential nutrients and rich in chemical additives, which are used to modify its organoleptic characteristics and lengthen its storage period.

The transformation of food production from artisanal to industrial level and the introduction of modern food technologies, increasingly intensive and ecologically unsustainable, have profoundly changed eating habits.

Currently, wrong eating habits are increasingly widespread, strongly influenced by the advertising pressure of the food industries, aimed at the consumption of increasing quantities of food and drinks, presented with mystified beneficial and performing properties. This epochal change in eating habits, with incongruous diets and inadequate food, has produced nutritional pathologies, become real health emergencies in recent years, such as anorexia, bulimia, obesity, metabolic syndrome, etc. with the result of serious negative consequences for public health and the social and health system [2].

Among the most advertised products available on the nutraceutical market are "natural" nutrients, such as vitamins and minerals, which absorb the share of higher consumption. They are presented as indispensable for their nutritional properties, therefore to be taken at any age without limitations.

Information is omitted that some of these substances have reduced absorption and intrinsic bioavailability and/or reduced nutritional margin with negative organoleptic properties. This is particularly evident for plant extracts, mineral salts and some essential vitamins.

The factors influencing the absorption and bioavailability of these nutrients are numerous and depend on [3]:

- chemical composition of the nutrient and its shape;
- binding to other molecules (e.g., by esterification or glycosylation)
- interaction with other components
- nature of the food matrix (e.g., solid, liquid)
- presence in food of factors that increase or counteract its absorption
- food processing (thermal, homogenisation, etc.)
- intrinsic factors of absorbing biological structures, need specific transport systems and channels, etc.
- physiological or pathological conditions

These drawbacks can be overcome by means of advanced technologies, which transform nutrients improving their absorption and organoleptic characteristics, thanks to the use of carrier and delivery systems specific to each nutrient.

## NANOTECHNOLOGY

The term Nanotechnology refers to all technologies capable of producing structures and entities of various nature and chemical-physical composition, having nanometric dimensions. The nano prefix identifies sizes between 1 nm and 100 nm for a wide range of human and industrial uses [4]. Nanotechnologies are applied in various industrial fields, from physics to electronics, engineering, chemistry, pigment industry, food industry, fertilizers, additives, etc.

Biomedical sciences benefit greatly from the use of nanoparticles or nanomaterials for both research and diagnostic or therapeutic purposes. There are many nanotechnological diagnostic/therapeutic approaches still being tested, but it is to be expected that soon we will see the large-scale application of new technologies.

## HISTORICAL BACKGROUND

The first observations and measurements of the size of nanoparticles were made during the first decade of the 20th century, by Richard Adolf Zsigmondy, 1914, with the detailed study of colloidal solutions of gold and other nanomaterials with dimensions below 10 nm and even more.

The word nanotechnology was coined in 1987 by K. Eric Drexler, a scientist at the Massachusetts Institute of Technology, in an essay titled "Engines of Creation. The age of nanotechnology" in which he presented the first hypotheses for the use of these technologies. [4]

The first mention of some of the peculiar concepts in nanotechnology (but before the use of this name) was presented in 1867 with James Clerk Maxwell.

Between the late 1990s and the beginning of the new millennium, nanotechnologies were at the center of the debate on the future of technology, with considerations on their usefulness and their dangers.

## LIPOSOMAL TECHNOLOGY

We take our cue from these brief historical notes on nanotechnology to introduce the topic that interests us more than any other: the development of liposomal technology.

The development of liposomal technology has produced profound innovations in the production method, size, specificity and overcoming of initial disadvantages and criticalities [5], [6].

In recent years have been made liposomal carriers able to overcome the immune barrier, with the use of ethylene glycol -PEG- linked to the surface of liposomes, peghilation, or other specific substances, as polypeptides able to overcome biological barriers, or polypeptides able to recognize and bind to specific receptors, functional targets, ion channels, hormonal receptors, etc. present on specific cell membranes or organs.

Currently, liposomes are in experimental therapeutic use capable of transferring portions of DNA or RNA into the cell nucleus, which have raised many ethical reservations. One example was the adoption of the spike RNA vaccine of the SARS-COV-2 virus inserted into liposomes, to counter the COVID-19 pandemic.

## NANOTECHNOLOGY

One of the biggest challenges facing the food industry is surely to produce effective nutrients that achieve their specific metabolic effect without producing adverse effects.

It is the idea of the "magic bullet" of Paul Ehrlich, a definition that the great scientist adopted for the antibodies he discovered.

Along the route, from the delivery site to the release site, nutrients may encounter numerous biological "obstacles" that must overcome [7]:

- enzyme degradation and poor stability;
- epithelial barriers /endothelial: e.g., gastroenteric barrier, immunological barriers (opsonization and reticuloendothelial system), for those nutrients that can evoke food intolerances;
- cell barriers (cell membrane), extracellular barriers (mucin and extracellular matrix).

Ensuring that a nutraceutical product reaches its "target" in its active form is the challenge that nanotechnologies face. The simplest solution is achieved by optimizing the physico-chemical properties of the nutrient (charge and size) or by changing its contact surface, while to achieve optimal nutrient absorption, specific carriers must be used.

Carriers used for nutrient transport shall demonstrate encapsulation/solubilisation characteristics, optimal release capacity, long-term stability, and low toxicity.

Ideally a carrier should be biodegradable, inexpensive, and easy to prepare, own small size, demonstrate a prolonged half-life in the bloodstream after administration and focus specifically in the areas of the body affected by the nutritional purpose (selective tropism).

The recent development of Nanotechnologies has allowed the development of very sophisticated carriers, e.g., micellar solutions, liposomes, vesicles, liquid crystals and other nanomicellar structures, which represent very promising potential solutions for this purpose.
As such, nanostructures must be observable, measurable and demonstrate a defined morphology, with the help of appropriate chemical-physical methods. We could not define them Nanostructures, that is elementary structures having exactly intrinsic nanometer dimensions if they did not respond to the peculiarities, but rather we should define them in different ways based on their chemical-physical characteristics, such as amalgams, coadeer, emulsions (usually composed of lipid substances), mixtures, etc.

This is an aspect of fundamental importance to clarify for Nanotechnologies and for those applied to Nutraceuticals that we deal with in this article.

## NANOTECHNOLOGY IN THE NUTRACEUTICAL MARKET

The nanotechnologies in use in the food market have been borrowed from the various delivery systems already widely adopted in the pharmaceutical field.

The need to improve the bioavailability and pharmacokinetics of many nutrients and reduce their adverse effects, or their reduced absorption, has led to the research and adoption of delivery systems mentioned above.

While in the pharmaceutical field such technologies are widespread and widely adopted for the indisputable advantages they offer, in the food field their use is extremely reduced and limited to a few nutrients. This depends on the high cost for their production which is not competitive and equally profitable compared to traditional technologies.

The development of nanotechnologies has produced numerous types of delivery systems, each of which has its own characteristics and specifications, so as to make them suitable for the substances they must carry and for the nutritional purposes to be achieved [8-9].

In recent years, food supplements have won the favor of a large audience of consumers, who use these products for various health purposes.

In fact, the nutraceutical market is rapidly expanding, and is one of the fastest growing markets in the world, here are the most significant data of Food Supplements Fig.1.

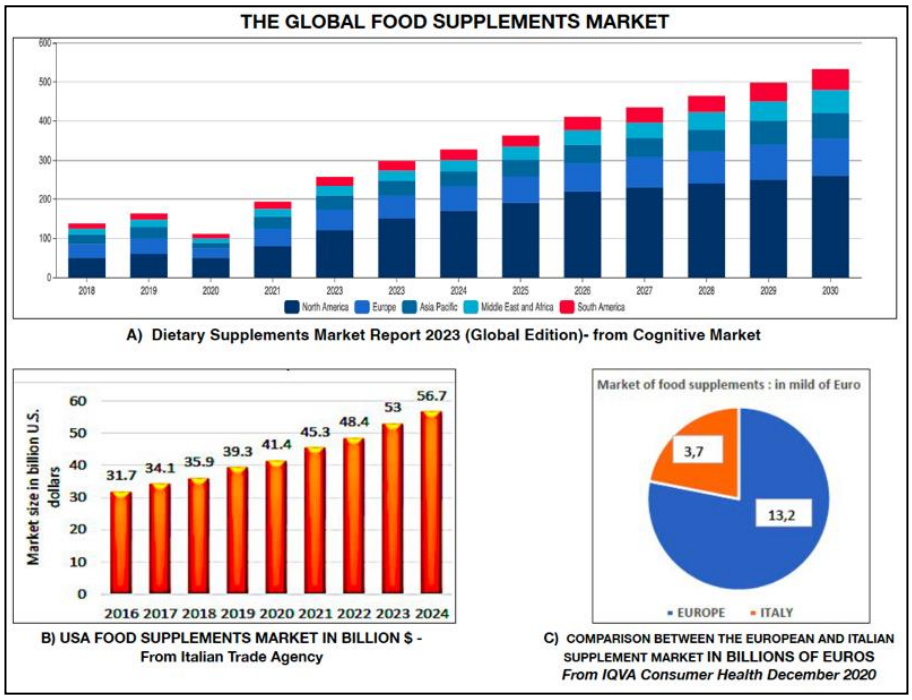


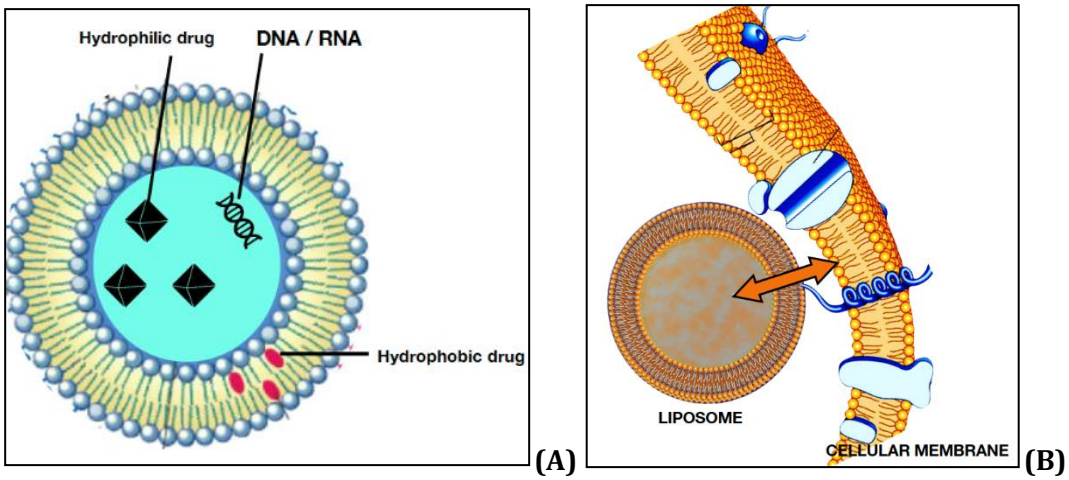

**Fig.1: The Global Food Supplements Market (references are indicated in Figure)**

The innovative thrust of nanotechnology has introduced production systems that adopt microencapsulation to preserve the organoleptic properties of food and improve its absorption. In 2018, the value of the encapsulation food market was estimated at $26,208.3 million, and is growing steadily (Source: marketsandmarkets Analysis) [10].

## LIPOSOMAL TECHNOLOGIES

Among the delivery systems, liposomes are the most successful and most widely used due to their versatility and ease of production.

Liposomes are formed by a double phospholipid wall, within which are contained substances, drugs, or nutraceuticals in solution, which must be used in therapy. If they are active substances or water-soluble ingredients, they are concentrated in the center of the liposome, if they are substances of a lipophilic nature, they are deposited inside the outer lipid layer, Fig.2A.




(A) (B)

**Figure 2: Schematic representation of a liposome (A) and analogy between liposome and cell membrane (B)**

By structure and chemical composition, the membranes of liposomes are very similar to cell membranes with which they have high affinity and easy penetration Fig.2B.

Regarding shape and size, liposomes are named according to their structural parameters. In figure Tab.1: we report the most common:

**Tab. 1: Shapes and size of liposomes -From B.Riccardi**

| Liposome Type | Size | Number of layers | Shape of liposomes |
|---|---|---|---|
| MVL, Multilamellar large vesicle | > 0,05 µm | Multiple | |
| LUV, Large unilamellar vesicle | 0,1 µm | Single | |
| SUV, Smalll Unilamellar vesicle | 0,025- 0,05 µm | Single | |
| UV, Unilamellar vesicle | All size range | Single | |
| OLV, Oligolamellar vesicle | 0,1- 1 µm | Multiple | |
| GUV, Giant unilamellar vesicle | > 1µm | Single | |
| MVV, Multivesicular vesicle | 200 nm - 3 µm | Multiple | |



Technology of production of liposomes has developed very recently. The different productive technologies mirror and answer to the purposes for which these carriers are used, every

method is specific for the employment to which it is destined and for the modalities of release of the active ingredients.

Table 2 provides a synoptic overview of the most common synthesis systems [6].

**Tab 2: Main methods of synthesis of liposomes**

| Method of synthesis | Type of liposomes |
|---|---|
| **Dehydration and rehydration (DRV)** | Used to form an oligolamellar vesicle. |
| **Extrusion technique (VET)** | multilamellar vesicles |
| **Freeze-drying** | Preserve liposomal products |
| **Sonication** | For small unilamellar vesicles |
| **Reverse phase evaporation (REV)** | for small unilamellar liposomes/vesicles, oligolamellar vesicles, and multilamellar liposomes/ vesicles |
| **Solvent dispersion method Ether and Ethanole** | Multilamellar liposomes /vesicle |
| **Solvent dispersion method** | Multilamellar vesicle whit different size |

## CHARACTERIZATION OF LIPOSOMES

### Dimensional Analysis

Laser diffraction is a technique for measuring the dimensional distribution of particles by measuring the angular variation in the intensity of light diffracted from particles of a dispersion, affected by an incident beam (Dinamic Light Scattering) [11]

In particular, the technique is based on the observation that light is diffracted from a particle with an angle inversely proportional to its size: large particles generate a high-intensity scattering signal at low angles compared to the incident laser, small particles, on the other hand, produce a signal at low intensity but at greater angles.

The angular diffraction intensity data is then analysed to calculate the particle size and obtain a dimensional distribution of the entire sample. The particle size is reported as the diameter of the sphere of equivalent volume.

### Morphological Analysis with Electron Microscope

In addition to characterizing the liposomes from the chemical-physical point of view, further investigations with electron microscopy allow to examine their morphology and structural integrity Fig.3. Several variations of electron microscopy (EM) are available, such as the TEM Electron Transmission Microscopy, which uses negative staining, and SEM scanning electron microscopy which provides valuable information on liposomes preparations since they provide a view of morphology and can solve particles of varying sizes [12]. However, sample preparation is complicated as it requires the removal of liposomes from their native environment. Reproducible and accurate results are obtained by paying particular attention to sample preparation.

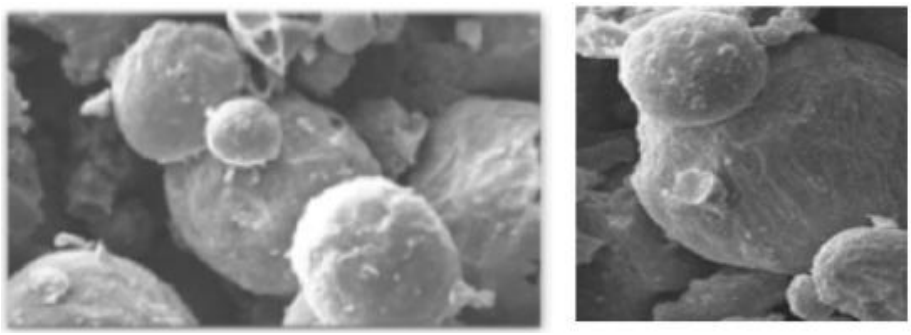


**Figure 3: Example of SEM Scanning Electron Micrograph of liposomes**

## Potential measurement z (ζ)

The surface charge of particles in a colloidal system is very important for determining their stability and behavior in vivo. The zeta potential (ζ) is a measure of the charge that a particle acquires in a particular medium and depends on the pH, ion force and concentration of a particular component [11].

## LIPOSOMAL TECHNOLOGIES IN THE NUTRACEUTICAL FIELD

We have mentioned earlier those liposomes are not very common in the nutraceutical field, with a few commendable exceptions.

Liposomal delivery systems have been used to improve the absorption and bioavailability of some nutrients particularly lacking in this respect, among these we mention some vitamins, and plant extracts [13-14], while a more widespread use has been adopted for iron integration. Some companies producing vitamins and plant extracts in liposomes are reported in Tab.3:

**Tab.3: Companies that produce liposomes with the technologies adopted**

| COMPANY | Liposomes's production method and properties | WEBSITE |
|---|---|---|
| LIPOCELLTECH | They are a dry, free-flowing granular material (powder), that immediately forms a liposomal dispersion on contact with water or a biological fluid within the body. The contents rapidly disperse to give a liposomal suspension in the aqueous solution. | https://www.lipocelltech.com |
| LIPOMIZE | Description on : Antonella Giorello, Alcides Nicastro, Claudio L. A. Berli ; Microfluidic Platforms for the Production of Nanoparticles at Flow Rates Larger Than One Liter Per Hour, Advanced Matrials Tecnologies , 3 March 2022 | http://www.lipomize.com |
| LIPOSHELL | Generic description without technological specifications : The LIPOSHELL® technology products are manufactured in compliance with the high quality standards, using innovative manufacturing processes which give them globally unique qualities. | http://www.liposhell.eu/ |
| ACTINOVO | Generic description without technological specifications | https://www.actinovo.com/ |
| LIPOTECH S.A. | Uses the freezing and defrosting method (freezing & drying process), by which liposomes in solution are obtained and subsequently separated by centrifugation. | http://www.lipotech.com.ar |

## IRON-BASED LIPOSOMES

A specific speech we must dedicate to iron-based liposomes.

Iron is an essential element for many metabolic functions, but has a limited therapeutic margin, for the adverse effects it produces and for the strong pro-oxidant activity. For this reason, several companies have enclosed it in liposomes, to improve absorption and bioavailability and reduce the negative effects [15-18].

We report in Tab.4 some liposomal iron products used in the treatment of anemia:

**TAB. 4: Comparison between various types of liposomal iron**

| AUTHOR | TECHNOLOGY | IRON SALT | PROPERTIES | REFERENCES |
|---|---|---|---|---|
| M.Gulrez Zariwala et al | Loaded solid lipid nanoparticles prepared using stearic acid by double emulsion solvent evaporation process. | Ferrous sulphate | High percentage of iron entrapment | 15 |
| Sabrina Bochicchio et al | Simil-microfluidic (SMF) apparatus. using ultrasonic energy to enhance liposomes homogenization | Ferrous sulphate | High percentage of iron entrapment | 16 |
| Sateesha S.B. et al | Liposomes of ferrous ascorbate developed by thin film hydration freeze dried | Ferrous ascorbate | 63% of Iron Intrapment | 17 |
| Shantha L. Kosaraju et al | Liposome prepared using the pro-liposome and the microfluidization technologies | Ferrous sulphate | particle size distributions around 150 to 200 nm | 18 |
| Enrique Montagud-Marrahi et al | Comparison of effectiveness between liposomes with iron sulfate and sucrose with iron pyrophosphate | Ferrous sulphate Vs Ferrous Phyrophosphate | Not mentioned | 25 |
| Bernhard Illes et al. | liposome-coated metal-organic framework (MOF) nanoparticles | Iron Fumarate | Liposomes loading with both single and multiple drugs at the same time | 26 |
| Jaideep Malhotra et al. | Not mentioned | Ferrous Phyrophosphate | Not mentioned | 27 |
| Jeannine Baumgartner et al. | scalable nanostructured FePO4 FePO4-NP) produced by flame spray pyrolysis (FSP) | Ferric Phosphate | Not mentioned | 28 |
| Flores Pacara M | Not mentioned | Not mentioned | Not mentioned | 29 |
| B. Riccardi et al. | freezing to -10 ° C -15 ° C and thawing at ambient temperature of the suspension formed in repeated cycles for at least two times , freezing fast and slow thawing | Ferrous sulphate | Iron concentration in liposomes up to 20% | 3 |

## MULTIFUNCTIONAL LIPOSOMAL TECHNOLOGY

Multiple encapsulation technology has been a recent breakthrough produced by nanotechnologies, through which it is possible to administer nanocarriers containing in addition to active nutraceutical principles, other substances that lengthen the shelf life, protect against enzyme inactivation, recognize the specific target site, etc. [19-23]. As mentioned above, nanotechnologies have not yet found a large use in the production of food supplements, yet, but recently many proposals for nutraceuticals in liposomal form have been spreading on the international market.

## PROBIOSOMAS

A revolution has been achieved with the formation of multifunctional liposomes or Probiosomi, capable of simultaneously transporting several active ingredients.

These carriers offer the advantage of simultaneously transporting more substances, generally they are substances little absorbed, that so they are better assimilated, and they also favor the synergistic effectiveness obtainable with their association.

A first fundamental result was obtained by the Argentinian Lipotech S.A. Company with the production of Lifervit, iron and vitamins association in the same liposomal carrier. [24]

An important property that characterizes liposomes of Lipotech is that they encapsulate iron sulfate, with a few other examples, all others contain iron pyrophosphate or other salts Tab.4.

The use of this iron salt has proved to be an important strategic choice, because if it is true that this substance has a reduced therapeutic margin, however, completely exceeded thanks to the use of liposomal technology, is in any case the iron salt with the highest bioavailability [25].

The second difference is that the Argentinian society was the only one to document the morphology and physico-chemical characteristics of liposomes [24] with reliable examinations, in addition to having demonstrated their absorption in cell cultures [26].

Probiosomes represent a remarkable advancement in the field of drug delivery and therapeutic interventions. These lipid-based vesicles can be characterized by liposomes, solid-lipid nanoparticles or niosomes. They offer a versatile platform for encapsulating various bioactive compounds, enabling controlled and targeted release. Probiosomes are particularly attractive for their biocompatibility, ability to improve drug solubility, and potential for personalized medicine applications.

Structure and Composition of Probiosomes are essentially composed of amphiphilic lipids, which self-assemble into vesicular structures in the presence of an aqueous phase. These lipid bilayers encase an aqueous core and can be modified to include specific ligands or surface modifications for targeted delivery. The composition of probiosomes typically includes lipids like phosphatidylcholine, cholesterol, and surfactants, which impart stability and control over membrane permeability.

A further technological upgrade has been achieved by the Company IODO srl, with the method of supercritical fluid CO2, through which liposomes with high concentration of encapsulated active ingredients can be obtained.

With this technology the efficiency of encapsulation reaches 78% concentration of active ingredients, with the advantage of lower dosage of the drug to be administered, a greater therapeutic effect and consequent reduction of adverse effects [27].

## FABRICATION OF PROBIOSOMES

Fabrication of Probiosomes Several methods are employed for the preparation of probiosomes, including film hydration, reverse phase evaporation, and microfluidic techniques. Each method offers unique advantages, such as particle size control and encapsulation efficiency. The choice of method depends on the specific application and desired characteristics of the probiosomes.

## ADVANTAGES OF PROBIOSOMES IN DRUG DELIVERY

Probiosomes offer several advantages as drug delivery vehicles, such as:

### Enhanced Bioavailability

Probiosomes can encapsulate hydrophobic drugs, improving their solubility and bioavailability.

### Biocompatibility

The lipid-based nature of probiosomes makes them biocompatible and suitable for various routes of administration.

### Simultaneous administration of several substances

They can transport multiple substances in a single carrier and produce a synergistic effectiveness of the transported substances.

### Versatile Applications

Probiosomes can be used for small molecule drugs, peptides, proteins, nucleic acids, and diagnostic agents.

## CHALLENGES AND FUTURE DIRECTIONS

While probiosomes hold immense potential, they also face certain challenges, including stability issues, scalability, and regulatory hurdles. Future research may focus on addressing these challenges and optimizing probiosome formulations for clinical applications. Additionally, the development of novel ligands and surface modifications for precise targeting will expand the scope of probiosome-based therapies.

## CONCLUSION

Probiosomes represent a promising platform for drug delivery and therapeutic interventions. Their unique structure, biocompatibility, and versatility make them a valuable tool in personalized medicine and targeted therapies. Continued research and development in this field hold the potential to revolutionize the way we deliver and administer drugs, leading to more effective and patient-specific treatments. Probiosomes are poised to play a pivotal role in the future of healthcare.

## CONCLUDING REMARKS

### The Alimentation of the Future and the Destiny of Our Planet

Nanotechnologies, if properly used, must aim to improve the well-being of people, and cannot be considered a purely technologically advanced expedient to improve productivity, and the organoleptic properties of nutrients.

Unfortunately, it happens that alongside the advanced technologies of delivery systems, very useful for improving the bioavailability of drugs and active ingredients, and reducing unwanted effects, has developed a flourishing production of food additives, which undermines and negates all the benefits of nanotechnology.

Reading the pages of magazines intended for the food industry, one is astounded by the amount of substances and additives used in the production and processing of food.

These substances such as thickeners, clarifiers, dyes, emulsifiers, sweeteners, etc. all described and encoded in special tables, enter directly into our diet, together with the food substances we consume, which are also denatured and sophisticated at the origin.

So, our dishes are transformed into a kind of containers of chemicals, which for organoleptic qualities, recall very close, hearty and tasty gourmet dishes, but with a negative nutritional effect

That said, we wonder what is the point of improving the absorption, bioavailability and reducing the undesirable effects of essential nutrients, if they then have to enter the cauldron of chemical agglomerations that we call food.

The chemical and food processing industry, it is said that it serves to address the scarcity of food resources, insufficient to feed the 8 billion people that populate our planet, a third of whom however does not have enough food or is totally lacking.

For this reason, alternative sources of food are being tested, from insects to synthetic meat, to microalgae, all to feed the planet now close to the collapse of natural food products.

In fact, we have a well-founded suspicion that behind this senseless and unnatural choice are the colossal interests of the food multinationals, which, in order to increase their profits, neglect and perhaps hinder the possible attempts to recover natural sources of food [28-29].

Reforestation, the repopulation of fish and animal fauna in their habitats, and the recovery of biodiversity seriously compromised at global level, are experiments carried out only by private non-profit organizations that have at heart the fate of the planet and humanity.

While these goals should be a priority commitment of civilization that should involve all of us, to counter the planned extinction of the human species

## Conflict of Interest

The authors declare no conflicts of interest in this research.

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