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Tocosome: A Cutting-Edge Drug Delivery Platform Combining Phospholipids and Tocopheryl Phosphates

Sivaram R[1], H. Gayathri[2*], N. Damodaran[3]

[1,2*,3]Department of Pharmaceutics, SRM College of Pharmacy, SRM Institute of Science & Technology, Kattankulathur, India, 603203.

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ABSTRACT

The development of novel nanocarrier systems for drug delivery is crucial for enhancing therapeutic efficacy and stability while minimizing toxicity. In this study, we explore the potential of α-tocopheryl phosphate (TP) and di-α-tocopheryl phosphate (T2P), two derivatives of vitamin E, as key components in tocosome-based drug delivery systems. Tocosomes were formulated using the Mozafari method, incorporating TP, T2P, and various lipids/phospholipids, including phosphatidylcholine, stearyl amine, Phospholipon 90H, and Phospholipon 100H, with and without cholesterol. This solvent-free preparation technique avoids the use of potentially toxic solvents, detergents, and mechanical stressors such as sonication or high-shear force homogenization. The formulated tocosomes demonstrated a narrow size distribution, high encapsulation efficiency, and excellent long-term stability, retaining their integrity for over two years. Using 5-fluorouracil as a model drug, we confirmed the feasibility of these nanocarriers for drug delivery applications. These findings highlight the potential of TP- and T2P-based tocosomes as a biocompatible, stable, and efficient drug delivery platform, offering promising applications in pharmaceutical and biomedical fields.

INTRODUCTION

Over the past few years, it is observable that drug delivery systems (DDS) have gained a lot of attention with respect to developing systems that would enhance the therapeutic effect of drugs with reduced side effects. Poor bioavailability, fast degradation, and non-specific distribution are some of the common problems associated with conventional drug delivery systems that may lessen the therapeutic potential of drugs (1). To avoid these constraints, there has been a broad examination of nanocarriers as delivery systems, capable of entrapping hydrophobic and hydrophilic drugs and liberating them in a well-regulated way. Among these, lipid-based nanocarriers tocosomes, which entrap vitamin E derivatives, have recently appeared as a promising type of nanocarriers because of their biocompatibility, antioxidant properties, and capacity to improve the delivery of numerous therapeutic agents (2).

Occurring in 2017, tocosomes have made an important improvement to drug delivery by offering a new option to both liposomes and nanoliposomes. The structure of tocosomes is made of two important phosphorylated derivatives of vitamin E—α-tocopheryl phosphate (TP) and di-α-tocopheryl phosphate (T2P)—and these phospholipids are mostly combined with phospholipids to build stable and amphiphilic bilayers. Tocosomes are different from other types of lipid-based carriers since they protect and deliver hydrophilic as well as hydrophobic medicines, and have their own antioxidant and anti-inflammatory properties (3). Tocosomes may be manufactured using conventional ways like thin-layer hydration, ethanol injection, or sonication, or green, innovative tools, such as the Mozafari method that bypasses using dangerous solvents and harsh conditions. Because tocosomes are steady, effective, and can release contents accurately, they are perfect for sending sensitive drugs, nutraceuticals, and bioactive substances into both medical and food industries (2). Delivering different nutrients in a single capsule, for example, antioxidants ascorbic acid and tocopherol, gives them additional value because it can result in better treatment and helps keep ingredients stable in various mixtures. As scientists keep working on them, tocosomes seem well-suited for targeted drug delivery with strong biocompatibility, multiple functions, and higher quality results when compared to existing nanocarrier systems (4).

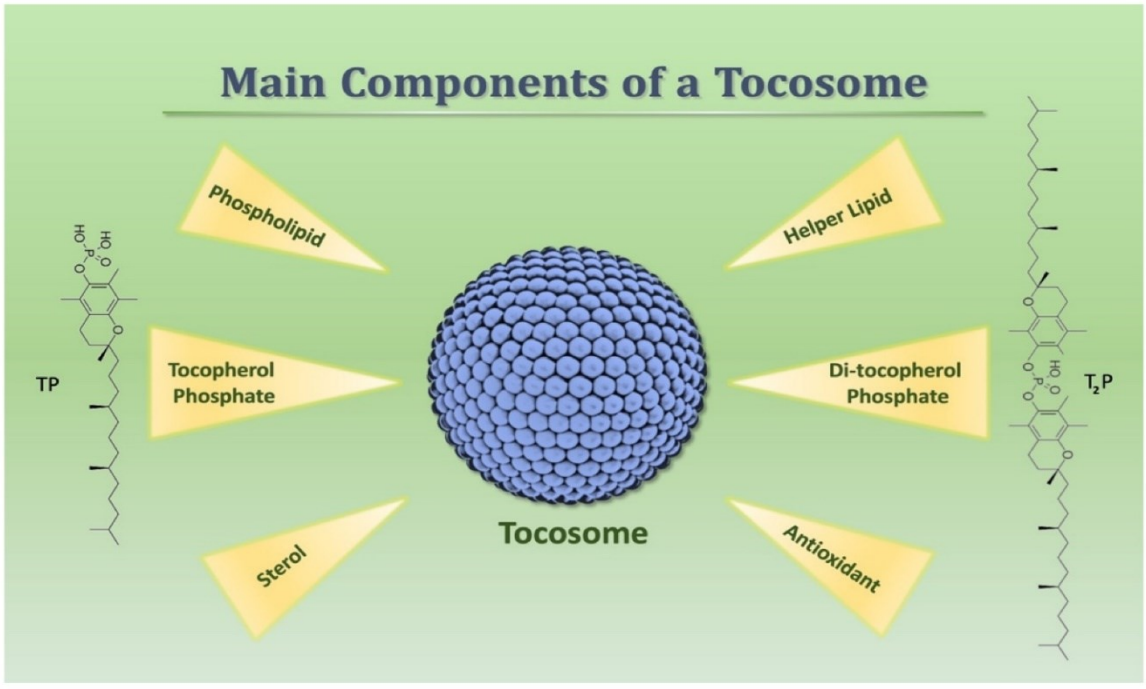


Figure 1: Main components of a Tocosome

1. Fundamentals of Tocosomes

Tocosomes are specialized vesicles (based on phospholipids) which integrate tocopheryl phosphates, a vitamin E derivative (5). These vesicles increase stability of drugs, provide a sustained release of drugs, and have greater therapeutic effect. Tocosomes are also structurally analogous to biological membranes, which ensures their effective interaction with cell components and, thus, make them suitable vehicles in targeted drug delivery (6).

2.1 Composition and Structural Features

Tocosomes are made of several constituents which enable their stability, drug loading and biologically compatibilities:

- Phospholipids
  - Be the major structuring element.
  - Make bilayer vesicles, which are able to entrap hydrophilic and hydrophobic drugs.
  - Increase biocompatibility through natural cell membrane mimicry (7).
- **Tocopheryl Phosphates (TPs)**
  - Vitamin E derivatives that have anti-oxidant and anti-inflammatory effect..
  - Oxidative degradation is prevented to enhance the stability of the medication.
  - Facilitate cellular uptake and enhance bioavailability (8).
- **Additional Excipients**
  - Cholesterol: Increases the stability and rigidity of membranes.
  - surfactants are used to recommend dispersion, to prevent the agglomeration of vesicles.
  - Cryoprotectants, e.g., sucrose, trehalose, added in the process of lyophilization to maintain the structure of the vesicles.

Tocosomes structure allows drug loading efficiency and a controlled release profile which is prolonged (6)**.**

2.2 Mechanism of Formation

Tocosomes can be synthesized using various techniques, each offering distinct advantages in controlling **size, stability, and drug loading efficiency (8)**.

2.2.1 Thin-Film Hydration Method

- **Process**:
  - Lipids and tocopheryl phosphates are dissolved in an organic solvent.
  - The solvent is evaporated, leaving behind a thin lipid film.
  - Hydration with an aqueous drug solution results in vesicle formation.
- **Advantages**:
  - Simple and scalable process.
  - Suitable for both hydrophilic and hydrophobic drugs (9).

2.2.2 Solvent Evaporation Method

- **Process**:
  - Drug and lipids are dissolved in an organic solvent.
  - The solvent is slowly evaporated, leading to vesicle self-assembly.
- **Advantages**:
  - Controlled size and encapsulation efficiency.
  - Suitable for lipophilic drugs (10).

2.2.3 Microfluidic Technology

- **Process**:
  - Lipids and drugs are mixed in controlled microfluidic channels.
  - Precise mixing enables the formation of **monodisperse** Tocosomes.
- **Advantages**:
  - Highly reproducible and scalable.
  - Produces uniform vesicle size distribution.

The choice of the preparation method depends on factors such as **drug solubility, desired vesicle size, and release kinetics** (11).

2.3 Key Advantages of Tocosomes in Drug Delivery

- **Enhanced Drug Stability**: Protection against oxidation and enzymatic degradation.
- **Sustained and Controlled Release**: Reduces dosing frequency, improving patient compliance.
- **Improved Cellular Uptake**: Facilitates interaction with biological membranes.
- **Targeted Drug Delivery**: Reduces off-target effects and enhances therapeutic outcomes.
- **Biocompatibility and Low Toxicity**: Tocopheryl phosphates provide additional protective effects (12)

2. Structure and Composition of Tocosomes

Tocosomes are nanoscale vesicular carriers that combine the principles of liposomal drug delivery with the therapeutic benefits of tocopheryl phosphate, creating a uniquely functional and

biocompatible system. Structurally, tocosomes resemble conventional liposomes, as they consist of concentric lipid bilayers enclosing an aqueous core (13). However, what distinguishes them is the strategic incorporation of tocopheryl phosphate (TP), a phosphorylated derivative of α-tocopherol (vitamin E), into the bilayer matrix. This inclusion not only stabilizes the vesicle but also imparts significant bioactivity, such as antioxidant protection, anti-inflammatory effects, and cellular signaling modulation. These intrinsic pharmacological properties of TP complement the action of the encapsulated drug, making tocosomes a dual-function platform—both a carrier and a co-therapeutic agent (14). Tocosomes mainly consist of phospholipids as the structural material that self-assembles into bilayers because of their amphiphilic property. Typical examples of phospholipids employed are natural phospholipids, typically phosphatidylcholine (soy or egg), or synthetic analogs designed to have greater stability. Such phospholipids guarantee the flexibility, biocompatibility and the ease of fusion with biological membranes. When added to this bilayer, TP does not only provide structural stability through the oxidative stress reduction in the vesicle interior, but also changes the surface property, increasing the ability to interact with cells and target tissues. Other ingredients such as cholesterol could be incorporation into some formulation to adjust the fluidity and permeability of the vesicle to assure the best kinetics of drug release and prolonged circulation of the system in the body (15).

A large variety of pharmacological agents can be encapsulated by tocosomes. Generally hydrophilic drugs are ensnared in the aqueous interior and the lipophilic drugs are incorporated in the hydrophobic bilayer area. This amphiphilic characteristic enables them to carry several therapeutic agents at the same time, leaving the prospects of combination therapy. Moreover, tocosomes could be modified to bear a surface charge or targeting ligands to improve interaction with a target cell or tissue, allowing receptor-mediated endocytosis or passive accumulation in pathological tissue by the enhanced permeability and retention (EPR) effect (16).

Physically, tocosomes appear generally spherical and range in diameter, depending on both the formulation method and purpose, between 50 nanometres to more than a micron. They may be multilamellar, i.e. have several concentric bilayers, or unilamellar, i.e. have a single lipid bilayer. These structural factors influence biodistribution and release profile of the drug and also the encapsulating efficiency (17). Moreover, at the formulation stage the physicochemical properties such as lamellarity, size distribution, and zeta potential can be optimised to ensure the maximisation of the therapeutic outcome. In all events, the cautious addition of tocopheryl phosphate to phospholipid-based vesicles has created a versatile and intriguing methodology to carry pharmaceuticals. In diseases especially characterized by oxidative stress, chronic inflammation, and unrestrained cell division such as cancer, tocosomes to treatment outcomes are relevant (18).

Figure 2: Chemical structure of Tococsome

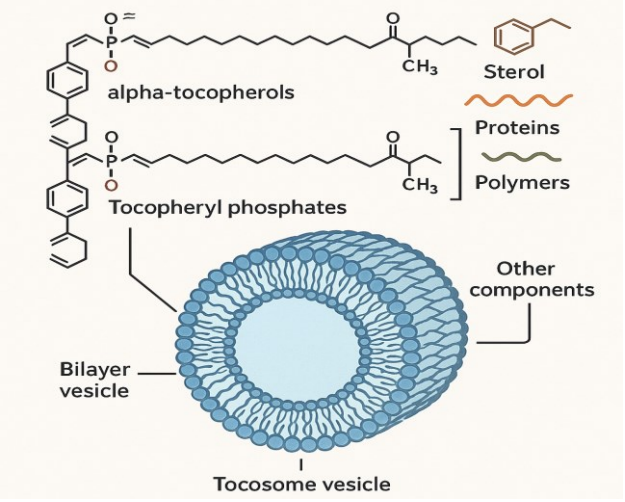
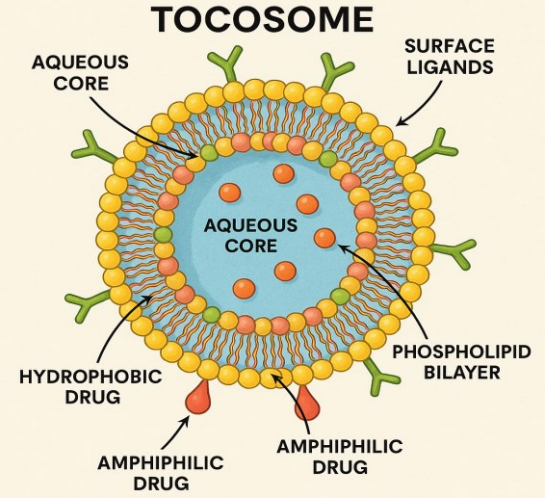


Figure 3: Structure of Tococsome



3.1 Table: Structural Components and Functional Roles of Tocosomes

Component	Nature	Function in Tocosomes
Phospholipids	Amphiphilic lipids	Form bilayer structure; enable encapsulation of both hydrophilic and lipophilic drugs
Tocopheryl Phosphate (TP)	Phosphorylated Vitamin E	Antioxidant, membrane stabilizer, enhances therapeutic effect, adds biological functionality
Cholesterol (optional)	Sterol	Modulates bilayer fluidity and permeability; improves vesicle stability
Drug/Bioactive Agent	Hydrophilic/Lipophilic	Therapeutic function; loaded in core or bilayer depending on solubility
Aqueous Core	Water-based interior	Encapsulates hydrophilic drugs
Lipid Bilayer	Hydrophobic region	Encapsulates lipophilic drugs

3. Preparation Methods of Tocosomes

The preparation of tocosomes requires a highly systematic method in order to guarantee the effective incorporation of tocopheryl phosphate into the phospholipid bilayer whilst simultaneously achieving desired vesicle properties such as uniform size, drug-loading capacity and stability (20). Tocosomes preparation uses different methods; each method presents particular advantages depending on the physicochemical drug nature, the desired release profile, and the application. The oldest method is the thin-film hydration procedure, which starts with the dissolution of a mixture of phospholipids and tocopheryl phosphate in a suitable organic solvent, e.g., chloroform or methanol. A rotary

evaporator is used to evaporate the solvent under reduced pressure forming a thin film of lipids on the walls of a round-bottom flask. This lipid coating forms multilamellar vesicles spontaneously in the presence of an aqueous buffer solution containing the medication. These are subsequently shrunk by probing sonication, high-pressure homogenisation or membrane extrusion, to small unilamellar vesicles, occasionally called nanovesicles (21).

A more scalable method is the ethanol injection method, whereby a lipid solution (of phospholipids and tocopheryl phosphate) in ethanol is injected into a rapid stirred aqueous phase. The lipids self-assemble to form nanosized tocosomes as the ethanol is diffused out. This technique is beneficial to thermolabile drugs because the process is carried out at low temperatures and under mild conditions (22). Nevertheless, it is necessary that residual ethanol after formulation is removed to make the products safe and stable. The reverse-phase evaporation method is usually preferred in order to get a higher encapsulation efficiency of hydrophilic drugs (23). Here, the water-in-oil emulsion is stable, which is achieved by sonicating the aqueous drug solution with the lipid phase in an organic solvent, such as diethyl ether. As the solvent is slowly evaporated, the vesicles are formed by collision and rearrangement of the lipid molecules as the micelles collapse (24).

The last developments in nanotechnology allow the application of microfluidics to prepare tocosomes as well. Here, organic phase lipids and aqueous drug solutions are made to flow through crossing microchannels at regulated flow rates to achieve regular and uniform vesicle formation (25). The technique offers fine control of vesicle size, lamellarity and polydispersity index, which can be of interest in translation to the clinic and largescale production. In addition, supercritical fluid technology is under investigation in solvent free preparation where supercritical CO 2 is used as a dispersion medium to circumvent the toxicity of organic solvents (26).

Every one of the techniques needs to be optimized with respect to lipid-to-drug proportion, hydration time, temperature, pH, and the ionic strength of the aqueous phase, because they affect the ultimate characteristics of the vesicles. Size reduction, purification (e.g. dialysis, centrifugation), sterilization (by filtration or gamma irradiation) and lyophilization are post-processing steps which are often used to enhance the shelf-life and efficacy of the tocosomal formulation (27). Finally, the selected approach should maintain the integrity and activity of tocopheryl phosphate and reproducibility in case of therapeutical applications (28).

4.1Table: Common Preparation Methods of Tocosomes

Method	Principle	Key Features	Advantages
Thin-Film Hydration	Lipids dissolved in organic solvent form a film; hydrated to form vesicles	Requires sonication or extrusion to reduce size	Simple and widely used; good for both hydrophilic and lipophilic drugs
Ethanol Injection	Lipids in ethanol injected into aqueous phase, forming vesicles	Rapid self-assembly; needs ethanol removal	Mild conditions; scalable; suitable for heat-sensitive drugs
Reverse-Phase Evaporation	Water-in-oil emulsion formed and evaporated to create vesicles	Forms large vesicles with high encapsulation of hydrophilic drugs	High drug loading; efficient for protein or peptide drugs
Microfluidics	Controlled mixing in microchannels allows vesicle formation	Precise control over size and uniformity	Scalable, reproducible; continuous processing
Supercritical Fluid Method	Uses supercritical CO_2 to avoid organic solvents	Experimental technique	Green, solvent-free method; promising for future industrial application

4. Development of Tocosomes Using Vitamin E Derivatives

Tocoodesmic new lipid-based nanocarriers, tocosomes are mainly composed of phospholipids and derivatives of vitamin E, with TP and T2P being the most prominent. Combined with the structural integrity provided by phospholipids, these nanocarriers offer a unique combination of the biocompatibility and antioxidant properties of vitamin E (29). typically prepared using various other lipids, such as phosphatidylcholine, stearyl amine, phospholipon 90H, phospholipon 100H and cholesterol, these components contribute to facilitate stability and activity of tocosomes (30).

5.1 Formulation Techniques

In general, the tocosome formulation is done by a solvent-free, detergent-free method similar to the Mozafari method. The method eliminates the need to use harsh mechanical disturbing rocedures, such as sonication or high shear force homogenisation, and does not utilise potentially toxic solvents or detergues. In the Mozafari method, vesicles of nanosized are obtained by mixing TP or T2P with the lipid mixture followed by hydration. Tocosomes with minimal size distribution, acceptable encapsulation efficiency, and stable over the long term are therefore ideal candidates to be used as drugs delivery vehicles (23).

5. Mechanism of Drug Encapsulation and Release

Tocosomes are lipidic vesicular systems (carriers) created out of tocopherols (vitamin E compounds) and phospholipids, which are specialized to deliver drugs efficiently (26). The physicochemical characteristics of the drugs including solubility, molecular weight, and polarity determine the ability of drugs to be encapsulated within the Tocosomes (29).

6.1 Drug Encapsulation in Tocosomes

The Tocosomes structure allows loading of various forms of drugs depending on their preferences of hydrophilic, hydrophobic or amphiphilic space :

- **Hydrophilic drugs**: These are drugs that love an aqueous environment and they are mostly trapped in the aqueous core of Tocosomes.
- **Hydrophobic drugs**: Lipophilic drugs become a part of the phospholipid bilayer which enhances the solubility and the stability of drugs.
- **Amphiphilic drugs**: These are drugs which have both hydrophilic and hydrophobic characteristics and thus straddle the boundary between the bilayer and the aqueous phase.

The degree of encapsulation is related to the lipid to drug ratio, the preparation method and the physicochemical stability of the formulation (31).

6.2 Drug Release Mechanisms

The release of drugs from Tocosomes is controlled by multiple mechanisms, ensuring a sustained or targeted drug delivery profile (32). The main release mechanisms include:

6.2.1 Passive Diffusion

- The most simple way of drugs release is the diffusion across the phospholipid bi-layer.
- The rate of diffusion is governed by Fick law and is dependent on concentration gradient, lipophilicity of the drug.
- Applicable to hydrophobic drugs, which slowly diffusion out of the bilayer, into the surrounding biological fluids (33).

6.2.2 pH-Sensitive Release

- There are certain formulations that exhibit release of drugs when there is a change in pH.
- The structural integrity of Tocosomes is destroyed in acidic conditions (e.g. in tumor tissue, or in lysosomal vesicles) and this causes the release of the drug.
- Applicable in cancer treatment in specific delivery and gastrointestinal drugs (34).

6.2.3 Enzyme-Responsive Release

- Some biological conditions have enzymes which are capable of degrading or interacting with Tocosomes resulting into the release of the drug.
- Lipases, esterases, or proteases enzymes disrupt the lipid bi-layer, thereby releasing the drug.
- Used commonly in tumor-targeted delivery and treatment of inflammatory diseases where activity of the enzyme is usually high (35).

6.2.4 Temperature-Sensitive Release

- Tocosomes also can be designed to contain thermosensitive lipids, which exhibit phase transition at certain temperatures.
- An increase in temperature leads to an increase in fluidity of lipid membranes, and increases drug diffusion.
- It is applied in localized hyperthermia therapy (e.g. cancer therapy) (36).

6.2.5 Redox-Responsive Release

- Certain formulations also involve the use redox-sensitive lipids which are responsive to oxidative or reductive environments.
- High levels of glutathione (GSH) in the tumor cell may also cause the release of drugs through the reduction of disulfide groups in the lipid structure.
- This system increases specific drug delivery to the oxidative stress-susceptible tissues (37).

6. Advantages of Tocosomes in Drug Delivery

7.1 Biocompatibility and Safety

The biocompatibility of tocosomes is one of the most important benefits it has. The derivatives of vitamin E, TP and T2P, have been known to be well-tolerated by the human body and possess low toxicity. This enables them to be applicable in the delivery of a broad therapeutic agent such as anticancer drugs, anti-inflammatory agents and other pharmaceutical agents (9)

7.2 Antioxidant Properties

The antioxidant capability of TP and T2P is crucial in preventing the degradation of the encapsulated drugs because of oxidative stress. Secondly, the vitamin E derivatives present in the tocosomes assist in reducing the oxidative damage to the tissues which makes it especially useful in treating diseases related to oxidative stress (29).

7.3 Improved Drug Encapsulation and Stability

Drugs can be assisted to enter the cells more effectively by tocosomes since they are composed of lipids, which facilitate membrane fusion and absorption. The changes of surface can also

7.4 Enhanced Cellular Uptake and Targeted Delivery

Tocosomes can be used to increase the cellular absorption of drugs because of their lipid-based composition, which enhances membrane fusion and intracellular absorption. You may also add surface modifications to enable directed administration to a particular tissue or cell and thus, increase therapeutic effect and decrease off-target effects.6. Applications of Tocosomes in Drug Delivery (36)

7. Cancer Therapy

Numerous investigations have shown tocosome potential to be used in the treatment of cancer. They have high capacity to encapsulate hydrophobic medicines (such as paclitaxel, doxorubicin and 5-fluorouracil) which enhance drug solubility and bioavailability significantly. Their antioxidant properties also serve to reduce levels of oxidative stress caused by chemotherapy and protect healthy cells against damages (35). Tocosomes can also be prepared by conjugation of ligands (folic acid and monoclonal antibodies) to achieve passive or active targeting, respectively, and therefore result in an accumulation of the drugs in neoplastic cells with no systemic side effects (32).

8.1Inflammatory and Autoimmune Diseases

Drug Delivery to Treat Inflammatory and Autoimmune Diseases: Among the inflammatory and autoimmune diseases where tocosome-based drug delivery holds promise are rheumatoid arthritis, inflammatory bowel disease (IBD) and psoriasis. Tocopherol derivative possesses anti-inflammatory effects which might complicate robust therapeutic response of NSAIDs or corticosteroids. Cosmonies can also penetrate deep into tissues because they are lipid-based and leave small quantities of the drug localised at the inflammation site, thereby minimising systemic side effects (35).

8.2 Neurological Disorders

This underlines the interest of tocosomes as new nano-carriers of neuroprotective medicines to treat Alzheimer, Parkinson and even multiple sclerosis (33). The tocosomes are ideal vehicles of neuroprotective drugs as they are able to cross the blood-brain barrier (BBB). Antioxidants, neurochemical modulators, peptides or tocosomes can encapsulate them and enhance their bioavailability in the central nervous system (CNS). Moreover, oxidative stress, which is one of the primary causes of neurodegeneration, can be alleviated with the help of the neuroprotective potential of vitamin E derivative (39).

8.3 Dermatological Applications

In dermatology, tocosomes can be rather useful due to the enhancement of the skin absorption and active components retention of pharmaceuticals (40). Their phospholipid composition permits them to relate with skin lipids, consequently permittting deeper infiltration of skin therapeutic agents, even in conditions like acne, psoriasis and eczema. Other than this, the anti-ageing effect of tocosomes is characterised by reduced oxidative damage, improved skin hydration, and wounded healing caused by vitamin E derivatives (41).

8. Recent Advances & Innovations

Recently, there have been improvements in the study of tocosomes which aimed in perfecting their formulation, targeting ability, and drug loading capacity. The outstanding innovations are:

- Targeted Therapy via Surface Engineering: Targeting of tumors and inflamed tissue is increased through functionalization with ligands, e.g. antibodies, peptides and aptamers.
- Stimuli-Responsive Tocosomes: It is investigating pH-sensitive and temperature-responsive tocosomes, which allow the release of drugs when respond to microenvironmental changes. (42)
- Combination Therapy: Tocosomes are also being formulated to co-load/encapsulate a combination of various drugs including chemotherapeutic agents and immunomodulators to achieve better therapeutic effects.
- Biodegradable and Natural Lipid-Based Tocosomes: Recent developments in formulation have resulted in biodegradable, naturally-derived lipid-based tocosomes that enhance safety and biocompatibility.
- Clinical Translation & Nanotoxicology Studies: Anyone is free to make larger quantities and at the same time, provide clinical safety by performing comprehensive toxicological tests. (43)

9. Challenges & Limitations

10.1 Stability Concerns

One of the primary challenges of medication delivery using tocosomes consists of stability. The therapeutic effect can be affected in the case where vesicle aggregation orWhere the encapsulated medication leaks out with time (44). These issues must be prevented through optimised formulations that use lyophilization processes and stabilising ingredients (45).

10.2 Scalability Issues

Tocosomes can hardly be produced on large-scale due to the complexity of both formulation methods and quality control measures (46). Addressing the issue of ensuring batch-to-batch consistency and low-cost production remains one of the greatest challenges (47).

10.3 Regulatory Hurdles

Tocosomes are subject to rigorous regulatory criteria (associated with safety, efficacy and biocompatibility) in order to be clinically approved. Their commercialization would take even more time and expense as substantial preclinical and clinical trials are necessary to verify their performance (48).

11. Future Prospects and Challenges

Researchers must address the drawbacks that are present with Tocosomes before it becomes a mainstream clinical practice. Large-scale manufacturing of Tocosomes has problems with scalability as it is difficult to achieve stability and consistency in a process of increasing their scale of production. Pharmacokinetic properties as well as safety and efficacy profiles of tocosome-

based formulations will also be ill-defined until scientists are able to subject them to stringent in vivo biologic efficacy testing coupled with clinical trials (45).

The two alternative issues relate to the maximisation of levels of therapeutic agents capacity, whilst maintaining the tocosome targeting efficacy at the same time (47). Surface modifications with ligands and functionalised coating to enhance drug therapy allow better-targeted delivery and reduce adverse effects of the drug. Clinical use approval necessitates regulatory hurdle-overcoming; authorisation necessitates pharmacodynamics testing, pharmacokinetic testing and chronic toxicity testing. In terms of its economical production methods, there lies a fundamental barrier in commercial tocosome production (49).

Commercial applications The commercial application of tocosomes requires manufacturing methods that are scalable and affordable. The microfluidics in combination with high-throughput synthesis methods can be the potential solutions to improve the fiscal efficiency and repetition quality of the tocosome manufacturing process (42).

The integration of various fields of study with innovative technologies will generate the chances that tocosome-based drug delivery systems will gain acceptance in the market and will have applications in healthcare (43).

CONCLUSION

Tocosomes are a new perspective drug delivery system, which have the advantages of phospholipids and vitamin E derivatives. Due to their biocompatibility, antioxidant capability, excellent drug loading capacity, and stability, they are promising applicants in pharmaceuticals and biomedical fields (50). Even though issues are still to be resolved in terms of their large-scal production and clinical confirmation, further research and development in this area promise to transform the manner of drug administration and enhance therapeutic efficacy in a range of disease (51).

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