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Regulatory and Scientific Evaluation of Liposomal Delivery Systems: A WBCIL Perspective

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Abstract

Liposomal products have a demonstrated advantage over their non-liposomal counterparts in terms of improving their levels of bioavailability and absorption. It is established from scientific studies that nutraceuticals encapsulated in liposomes are able to reach their designated sites without losing out on their functionalities or biological activities. Unlike non-liposomal nutraceuticals wherein molecules go through significant levels of metabolic breakdown before they are even able to reach their target and start to address the ailments. This results in reduced nutritional benefits. However, for liposomal nutraceuticals, molecules can reach their target, where metabolic and enzymatic activities have little to no-effect on liposomal forms. This clear-cut advantage has brought down the dosage requirements of nutraceutical and mineral actives encapsulated in liposomes. However, when it comes to the approval of the liposomal nutraceutical products there remains a gap in the understanding for the approval of liposomal nutraceuticals. This article addresses the gap by bringing forward the understanding of the regulation of the liposomal drugs already approved by the regulatory agencies and applying this understanding for seeking approval of liposomal nutraceuticals. This article discusses the analyses required for meeting the regulatory requirements at different stages of introducing a new liposomal product into the market. An illustration describing the overall goal in improving the understanding of the scientific and regulatory perspectives is attached below.

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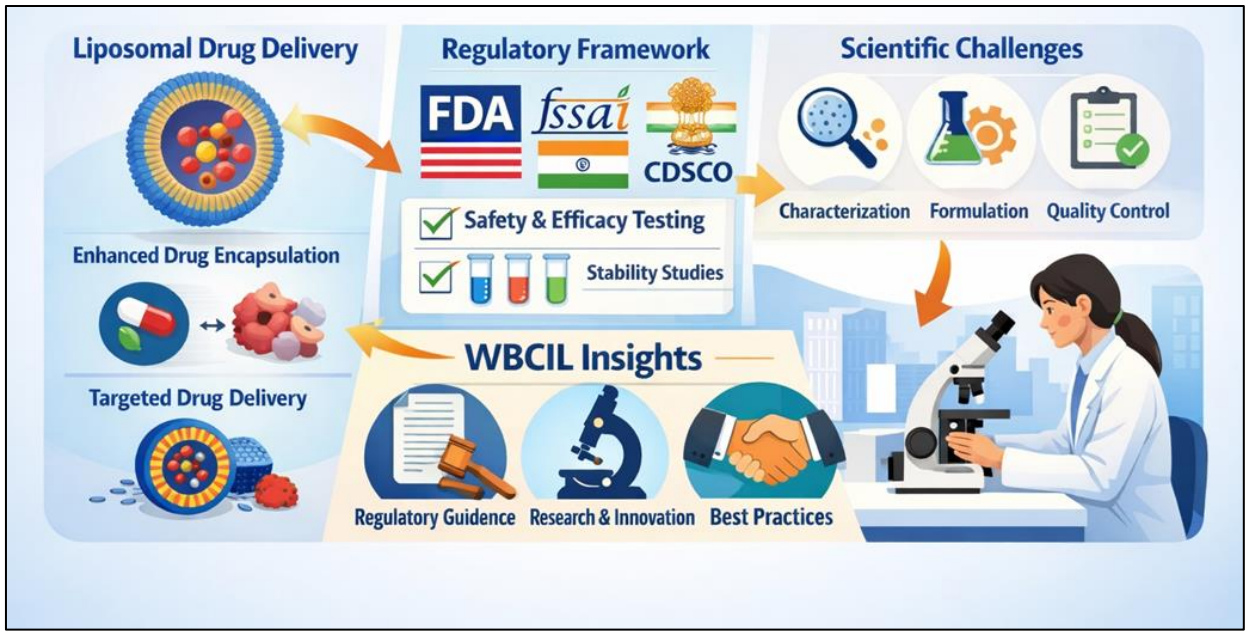
Graphical abstract

An illustration showing how the insights and regulatory perspectives from industries like WBCIL can help enhance the understanding of the approval of liposomal products for market acceptance



Keywords: Liposomal Regulation; Analytical Characterization Requirements; Market Approval; Liposomal Product Development; Lipoedge

1. Introduction

The design and development of liposomes are carried out on the basis of the type of actives that are delivered to the target cells [1]. Therefore, specific regulatory aspects to determine the safety and efficacy of liposomal products need to be considered on the basis of the functionality of the liposomes designed [2]. Till date the regulations to determine the safety and efficacy profile of liposomal products stems from the current scientific literatures on liposomes that specifically targets cancer cells [3]. However, since the early market adaptation of liposomal products from 1995, liposomal regulation is constantly evolving at a steady rate [4]. As the know-how of liposomal preparation are becoming accessible from scientific communities, new products are being developed by the industries [5,6]. Yet, translation of liposomal technologies by the industries remains to be a challenge. At-least during the early stages of adaptation as up-scaling and commercialization of pilot-scale developments in controlled laboratory environments are subjected to method development for characterizing liposomal products [7]. Nevertheless, pilot scale developments of new liposomal technologies are central to commercializing new products [8].

Regulation of liposomal products ensure that products reaching the market are safe for human consumption or usage [9]. Therefore, regulatory guidelines are updated and adapted according to industry standards for the development of new liposomal products that are able to meet consumer requirements [10]. For the development of pharmaceutical product, guidelines for the development of liposomal products are covered under the US-FDA guidance document [6]. The guideline provides a basis of the manufacturing practices that may be utilized to bring new liposomal products to the market [3]. A key aspect of the guideline suggests that the Active Pharmaceuticals Ingredients (APIs) of new liposomal products that are being developed where approval for their respective APIs are already in place may not be subjected for a separate New Drug Approval (NDAs) or Abbreviated New Drug Approval (ANDAs) [11]. As liposomes are categorized as an encapsulating or coating materials only, ingredients utilized in the process are classified as Generally Regarded As Safe (GRAS) [12]. Therefore, for all new liposomal drug products whose APIs have been approved need not go for a separate New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) filing [13]. However, in the case of nutraceuticals, currently no specific regulations exist that are specifically applicable to liposomal forms of nutraceuticals [14]. As a result, much of the guidelines related to liposomal formulations for the nutraceuticals market are adapted from Liposomal drugs [10].

Guidelines to determine the regulation of liposomal production in general are conducted with the help of organizations such as Food and Drug Administration (FDA) in the US, Ministry of Health, Labour and Welfare (MHLW) in Japan, European Food Safety Authority (EFSA) and European Medicines Agency (EMA) in Europe, Therapeutic Goods Administration (TGA) in Australia and Central Drugs Standard Control Organization (CDSCO) in India [2]. Given the diversified and widespread market for liposomal pharmaceuticals and nutraceuticals [3,15]. There is a requirement for the existence of specific regulations and guidelines to help optimize the production of liposomal nutraceuticals at an industrial scale [16]. The criticality of liposomal products, be it pharmaceuticals or nutraceuticals, are such that it requires extensive scaling-up of products manufactured and usage of analytical characterization processes to qualify the products fit for the market.

Based on the US-FDA guidelines that subjects the liposomes manufactured into separate levels of Critical Quality Attributes (CQAs), of the defined product [3]. Liposomal products manufactured goes through separate levels of quality assessments for in-vitro analyses. This is dependent on the final product that is intended to be manufactured [4]. The CQAs thus defined can be determined according to the following studies: -

- Lipid composition analysis
- Characterization of the encapsulated API
- Analytical characterization of the Liposomal product
- Stability of the product
- In-vitro release kinetics of the products

Each study ensures that liposomes manufactured are analyzed to characterize the lipids used in the encapsulation of the corresponding APIs. Followed by the characterization of the encapsulated API surrounded by the liposomal bilayer. Characterization of the encapsulated API provides insights on the interactions of the API with the liposomes. These insights are used for building an understanding of the product designed. Furthermore, physiochemical analyses of the product are utilized to confirm whether the liposomal product thus designed are able to demonstrate characteristics that may be used for positioning them in the market.

Based on the physiochemical analyses, product stability is determined using guidelines outlined in the pharmacopeias of US, India, UK or other countries for targeting a specific geography [10]. Once the stability of the product meets the prescribed requirements including leakage, encapsulation efficiency and assay, they may be considered for in-vitro analysis. In-vitro studies characterize product behavior in laboratory that is designed to reproduce physiological conditions. These studies quantify the release of the API from the liposomes. Based on the observed release profiles, liposomal products are either screened for further improvement of release profiles or finalization of Drug Metabolism and Pharmaco Kinetics (DMPK) studies for evaluation once the release profiles meet the expected criteria [17].

This article outlines the existing processes that are available for the market approval of liposomal products and tries to address the gap in the regulation of liposomal nutraceuticals. In summary, an overview of the market approval processes of liposomal products are mentioned to bridge the gap between the product guidance available for approval of liposomal nutraceuticals and pharmaceuticals. Followed by analytical characterization, pharmacokinetic and bioavailability related studies with discussions for clinical requirements for liposomal nutraceuticals products.

2. Pre-Market Approval Pathways

The pre-market approval pathways of liposomal nutraceuticals are different to that of liposomal pharmaceuticals [16,18]. Much of this difference rises from the fact that liposomal nutraceuticals are subjected to non-pharmaceutical approval pathways [19]. There is however a gap that needs to be addressed for approving liposomal nutraceuticals which is much different in its expected role and functionality in bringing about a biological effect in our body [20]. Existing regulations fundamentally guide the development of nutraceutical products that is primarily of non-liposomal in origin and is usually approved by bodies like Food Safety and Standards Authority (FSSAI) of India and European Food Safety Authority (EFSA) [21]. However, when it comes to liposomes, the approval practices are often perceived to be different to that of the existing approval pathways of un-encapsulated nutraceuticals [22]. This is primarily because of the complex composition of the liposomes that encapsulate the API [23]. The complex composition of the liposome as a nutraceutical however may need to be well-defined by the regulatory bodies including FSSAI and FDA [24]. Current practices of regulation of liposomal nutraceuticals are mostly developed in accordance to the guidelines as suggested by the guidance document issued by the US-FDA [3]. That includes in-depth analytical characterization of the product that is manufactured by industries such as West Bengal Chemical Industries Limited (WBCIL) [25]. This is majorly

because of the detailed utilization of the formulation and analytical methods for designing the products to meet market expectations in terms of improving the bioavailability of the actives [26,27].

Once the physico-chemical characterization of the product meets the intended specifications, the product is then considered for in-vitro evaluation to understand the performance of the product in standard laboratory conditions that is designed to replicate actual physiological conditions [5]. The success of product performance in-vitro qualifies the product to further pre-clinical and clinical levels of testing [11]. This however depends on the nature of the product designed [28]. For instance, if the product is defined as a pharmaceutical then it has to go through a wide level of pre-clinical testing requirements starting with immortalized and primary cell line studies [9]. If the results qualify, then the same product is subjected to in-vivo Absorption, Distribution, Metabolism, Excretion (ADME) and toxicological studies [1]. From here onwards, depending on the status of the pharmaceutical, the approval process may go through either as New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) [4]. The major difference between the two remains in the non-requirement of pre-clinical and clinical studies in case of ANDA [29]. Wherein only Chemistry Manufacturing Control (CMC) documents and bioequivalence data is utilized [8].

In case of liposomal nutraceuticals however, the regulation process is slightly undifferentiated in terms of categorizing the product in the market as a regular nutraceutical [22]. Since products coated using liposomes initially were mostly drugs, the fact that liposomes are currently utilized in the encapsulation of non-pharmacological actives, are not widely recognized by regulatory agencies that approve nutraceutical products [30]. As a result, most of the liposomal nutraceuticals produced by industries manufacturing nutraceutical actives are guided by US-FDA and Japan's Ministry of Health, Labour and Welfare (MHLW) documents available for drugs [3]. The detailed guidance suggested by the US-FDA and MHLW ensures that the nutraceuticals produced with the help of liposomal coatings are well characterized that meets product specifications [4]. This includes but not limited to API characterization, Lipid analysis, product chemical, physical and morphological stability and in-vitro release criteria [18].

Once the liposomal nutraceutical products meet the expected physio-chemical specifications defined, the chemistry, manufacturing and control (CMC) parameters are finalized for production [31]. However, a majority of the liposomal product development hurdles are met during this stage. As the behavior of the liposomal nutraceuticals in real-life scenario, i.e.: in presence of physiological conditions, largely depends on how the molecules perform in biological conditions [14]. Especially in situations involving the interaction of liposomal products with biological fluids [5]. This determines if the liposomal coatings and the chemistry of the formulation are able to stabilize the nutraceutical encapsulated inside [32]. The next sections will discuss the detailed analytical characterization processes that are considered for formulating liposomal nutraceuticals that are able to meet market approval.

3. Analytical Characterization Requirements

Liposomal products whether nutraceutical or pharmaceutical go through a detailed level of analytical characterization processes to meet product specifications as per market requirements [4]. This includes determination of physical, chemical composition, morphological, stability, leakage analysis, particle structure, loading capacity and other analytical details of the liposomal nutraceuticals [3]. Characterizations done mostly in accordance to CQAs that are suggested by the US-FDA and other regulatory guidelines available for liposomal drugs [33]. However, as nutraceuticals do not fall under this category, characterization ensures product conformity with expected specifications [30]. Specifications include but not limited to characterization of the API, analysis of the chemical make-up of the lipid used in the encapsulation process, analysis confirming encapsulation efficiency and other characteristics including particle size, poly-dispersity index and zeta potential [3].

The existing methodologies that determine regulatory guidelines for liposomal drug products are either partially available or still under development by standards such as **American Society for Testing and Materials** (ASTM), International Standard Organization (ISO) and European Nanomedicine Characterization Laboratory (EUNCL). Table 1 attached below shows the current scenario of liposomal product characterization. Wherein the techniques of Liposomal product characterization are summarized and briefly describes the parameter of characterization according to the standards established.

Table 1 A table showing the regulatory standards & protocols for liposomal characterization

Characterization Area	Technique / Method	Regulatory Standard / Protocol	Scope / Notes
Particle size, PDI & morphology	Cryo-TEM	ASTM WK54615	Liposome-specific standard
	TEM	ISO/WD 21363; ISO/TS 10797:2012	Morphology
	SEM	ISO/WD 19749	General nanomaterials
	DLS	ISO 22412:2017; ASTM E2490	Size & PDI
	NTA	ISO 19430:2016	Under development
	AF4-MALS/DLS	CEN ISO/DTS 21362:2021	Highly regulator-favored for complex liposomes
	SEC-MALS	ISO 16014:2019	Separation-based sizing
Surface charge	Zeta potential	ISO 13099-1/2/3	Electrophoretic mobility
		ASTM E2865-12 (2022)	Biomedical nanoparticles
Lipid composition & impurities	HPLC-UV / CAD / ELSD / MS	ICH Q2(R1)	Method validation
	GC-MS	ICH-validated methods	Lipid impurities
	^{1}H / ^{31}P-NMR	ICH-aligned analytical validation	Structure & quantification
	Raman spectroscopy	Supportive (non-destructive)	Structural confirmation
Drug loading / encapsulation	LC-MS / HPLC	EUNCL PCC-30 / PCC-31	Partially standardised
	UF + LC-MS	NCI-NCL	Free vs encapsulated drug
	AF4-HPLC	Emerging regulatory tool	Orthogonal separation
Physical stability	DLS	EUNCL PCC-21	Size change over time
	NTA	EUNCL PCC-23	Particle tracking stability
	AF4-MALS	EUNCL PCC-22	Stability + heterogeneity

To summarize, the gap in the analytical methods for the understanding of liposomal products remain mostly in liposomal nutraceutical loading and release [4]. This gap may be hard to address mostly due to the inherent nature of liposomes that behave specific to the chemical nature of the actives encapsulated [34]. Both loading and release of the actives from the liposomes are dependent on the modes of interaction of the nutraceuticals with the inner membrane of the liposomes [35]. The release also depends invariably on the environment to which the liposomes are subjected [36]. For instance, liposomal product behaves differently when interacting at different physiological locations in the body [17]. To elaborate on this, the liposomes present in the mouth behaves different to the liposomes present in the stomach [37]. Thus, there may be different levels of detailed analytical characterization of the products that are manufactured for both stages of release [38]. This includes development of finalized formulation of the liposomal products in lab scale. Once it qualifies the required levels of product parameters including those that meets the expected criteria, the product then maybe considered for market approval [39].

4. Bioavailability, PK, and Clinical Evidence Requirement

The requirement of clinical evidence to determine the efficacy of liposomal products remains limited to the claims made by the liposomal nutraceuticals [40]. As such there may be very little requirement to consider liposomal nutraceuticals for clinical levels of effects, as nutraceuticals by definition are not categorized as drug or pharmaceuticals and their

effects in the human body may only be limited to supplementing the nutritional uptake of the daily dietary requirement as recommended by Recommended Dietary Allowance (RDA) [40]. However, the expectations of improved levels of bioavailability of liposomal products are justified in comparison to non-liposomal systems [41]. This is due to the enhancement of cell-liposome interactions observed from in-vitro studies that shows evidences of improved nutraceutical localization in cells and tissues [42].

It is known that liposomal systems closely replicate the cellular systems due to which the encapsulated nutraceuticals are able to reach the cells to close the gap for the daily nutritional uptake required by our body [24]. However, comparative evaluation of the absorption of nutraceuticals in our body with non-encapsulated minerals helps us understand the efficiencies of the liposomal systems [26]. Therefore, comparing the pharmacokinetic (PK) profiles of liposomal and non-liposomal minerals may help address the scientific rationale to justify the advantages of liposomal nutraceutical delivery over non-liposomal nutraceutical delivery [26]. A schematic representation highlighting the process of approval for the assessment of liposomal nutraceuticals is shown in figure 2.

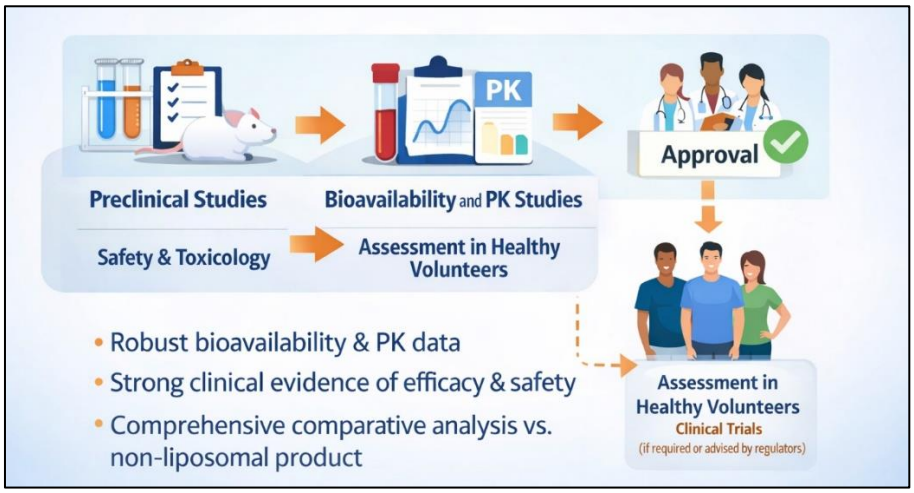


Figure 1 An illustration representing the process of approval of liposomal nutraceuticals for approval

4.1. Regulatory Oversight of Liposomal Delivery Systems

Liposomal delivery has been a forerunner in advancing the progress towards developing advanced solutions for targeted cancer cell therapeutics [30]. This understanding is now being leveraged in the advancement of delivery systems for non-cancer pharmaceutical products like anti-fungal agents including Amphotericin B and other drugs targeting a diverse range of indications starting from pain to anesthetics [18]. However, in the case for nutraceuticals, the gap in the understanding of the regulatory requirements for approving a liposomal nutraceutical is getting narrower as new products are manufactured to address the market need. This improved understanding for regulating liposomal nutraceuticals are being addressed by regulatory bodies like EFSA in the EU, Dietary Supplement Health and Education Act (DHSEA) in the US, FSSAI in India, Foods for Specified Health Use (FOSHU), Foods with Nutrient Function Claims (FNFC) and Foods with Function Claims (FFC) in Japan, NHP in Canada and TGA in Australia. However, for introducing new dietary ingredients marketed in the food and nutraceutical space much these aforementioned regulatory bodies function with the advisories from EMA in Europe, EDA in US, CDSCO in India, MHLW in Japan, Health Canada in Canada and TGA in Australia [3].

The oversight from drug agencies like Central Drugs Standard Control Organisation (CDSCO), FDA, MHLW, etc. only arises if there is a new ingredient used in foods and nutraceuticals to regulate their introduction and adaptation into the market [2]. Liposomal nutraceuticals typically require EFSA approval in the Europe [43]. EFSA may require novel food authorization before a product can be considered for marketing [26]. This is specifically for novel foods, those which have not been consumed in the EU before 15 May 1997 or the use of nano-engineered molecules in the food [44]. Use of nano-engineered molecules in the food usually recommends industries to comply with the guidance issued by EFSA [44]. For Liposomal Vitamin C however, there has been a history of consumption before 1997 [45]. Therefore, the EFSA does not consider this product to be novel as long as the ingredients utilized in the encapsulation process meets the specifications suggested. In India however, a growing sense of understanding is required for streamlining the approval of liposomal nutraceuticals in the market [43]. As nutraceuticals are designed to meet the daily Recommended Dietary Allowances (RDA), liposomal encapsulation is generally utilized to meet this requirement using a reduced dose [20]. Since liposomal nutraceuticals demonstrate improved levels of nutraceutical absorption and bioavailability [42].

Thereby surpassing the physiological bottlenecks witnessed by the non-liposomal nutraceuticals like poor bioavailability, reduced absorption and less stomach-friendly (like iron containing products) [15].

5. Key Regulatory Gaps, Risks, and Opportunities for WBCIL

The major gap lies in the process of regulating the market of liposomal nutraceuticals [40]. Current frame-works majorly depend on the approval processes outlining the introduction of liposomal products as drug [3]. Especially current CQAs of products align with the guidelines suggested for marketing liposomal drug products not nutraceuticals [4]. However, corresponding regulatory bodies overseeing the manufacturing of food and those monitoring the daily nutritional requirements including labelling of nutritional parameters on the products, need to advise methods for fast-tracking approval and application processes that might meet the specifications tailored for liposomal nutraceuticals *not drugs* [19].

The challenge for regulatory bodies, however, to issue specific guidelines for nutraceuticals lies in the determination of specific requirements for defining product safety and acceptability in the market [21]. Which can then be utilized both for safeguarding consumer perception in choosing liposomal products over other non-liposomal products and to ensure liposomal products deliver the value it promises to the consumers [16]. This challenge can be met and overcome by utilizing acceptable scientific methods already established to determining the efficacy of liposomal products by evaluating product performance in biological systems over their non-liposomal counterparts [24]. Scientific organizations such as WBCIL ensure that liposomal products meet market acceptability by ensuring that each product goes through a series of detailed scientific analyses and testing to validate the efficacy of the product to meet market requirements [26].

Given the increasing market size of liposomal nutraceutical products, organizations like WBCIL can benefit in playing a definitive role in generating scientific insights on deploying validated methods and scientific data for characterizing liposomal nutraceuticals. In essence, WBCIL using their liposomal knowledge building repository, *Lipoedge*, can support the overarching aim of establishing the enhancement of bioavailability and absorption across a range liposomal nutraceutical in addition to those which have been characterized already.

6. Conclusion

The design and development of liposomal nutraceuticals have picked-up their pace in the manufacturing of functional food. However, to ensure products reach the targeted markets, streamlining regulatory guidelines specific to the sectors catered need more careful consideration. In terms of evaluating the efficacy of liposomal products manufactured, specific guidelines must be developed and validated in accordance to the industry standards that define product specifications. Regulatory considerations must be aligned alongside such scientific considerations for determining the market readiness of the product developed. It may be suggested that regulators can involve key players like West Bengal Chemical Industries Limited and other industry partners for establishing a streamlined process for determining the efficacy of liposomal nutraceuticals for market approvals.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors confirm that there is no conflict of interest related to this manuscript.

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