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Research Article

Enteric-Coated Vitamin B12 Liposomes with Chitosan–PEG Dual Coating for Enhanced Oral Delivery: A Comprehensive Review

Aniket Bhoite [1*], Jitendra Shinde [2], Ashok Bhosale [3]

[1] Student, PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Savitribai Phule Pune University, Pune, Maharashtra, India

[2] Head of Department, Pharmaceutics at PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Savitribai Phule Pune University, Pune, Maharashtra, India

[3] Principal at PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Savitribai Phule Pune University, Pune, Maharashtra, India

Corresponding Author: *Aniket Bhoite

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Abstract

Vitamin B12 (cobalamin) is an essential water-soluble vitamin involved in erythropoiesis, neurological function, and DNA synthesis. Despite the widespread preference for oral administration, the bioavailability of vitamin B12 remains significantly limited due to degradation in the acidic gastric environment, enzymatic instability, low intestinal permeability, and dependence on intrinsic factor-mediated absorption. Conventional oral formulations, therefore, often fail to achieve therapeutic efficacy, leading to poor patient outcomes and the need for parenteral supplementation[1]. In recent years, nanotechnology-based drug delivery systems have emerged as promising tools to overcome these challenges. Among them, liposomes have gained considerable attention owing to their biocompatibility, ability to encapsulate hydrophilic molecules, and potential for surface modification. However, unmodified liposomes are unstable under gastrointestinal conditions, necessitating further advancements such as enteric coating and polymeric surface functionalization. This review critically evaluates enteric-coated vitamin B12-loaded liposomes with dual coating of chitosan and polyethene glycol (PEG) as an advanced oral delivery strategy. The mechanistic roles of enteric protection, chitosan-mediated mucoadhesion, and PEG-induced steric stabilisation are discussed in detail. Additionally, formulation challenges, characterisation techniques, biological evaluation approaches, and regulatory considerations are examined. The review highlights key research gaps and future perspectives, emphasising the need for systematic experimental investigations to translate this promising delivery system into clinically viable oral vitamin B12 therapies.

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1. INTRODUCTION

Vitamin B12, also known as cobalamin, is an essential micronutrient required for normal haematological function, neurological integrity, and cellular metabolism. It plays a critical role in DNA synthesis, methylation reactions, and the maintenance of myelin sheaths in the nervous system. Deficiency of vitamin B12 is a global health concern, particularly among elderly individuals, vegetarians, pregnant women, and patients with gastrointestinal disorders such as pernicious anaemia, Crohn's disease, and gastric atrophy[2-4]. Clinical manifestations of vitamin B12 deficiency include megaloblastic anaemia, peripheral neuropathy, cognitive impairment, and irreversible neurological damage if left untreated.

Oral administration remains the most preferred route for vitamin B12 supplementation due to its convenience, safety, and patient compliance. However, the therapeutic effectiveness of conventional oral vitamin B12 formulations is often compromised by poor and variable bioavailability. This limitation arises from multiple physiological barriers, including degradation in the acidic gastric environment, enzymatic instability in the gastrointestinal tract, limited passive diffusion across the intestinal epithelium, and reliance on intrinsic factor-mediated absorption. Consequently, high oral doses or parenteral administration are frequently required to achieve adequate systemic levels, which may reduce patient adherence and increase healthcare costs.

To overcome these challenges, researchers have increasingly focused on the development of novel drug delivery systems capable of protecting vitamin B12 during gastrointestinal transit and enhancing its intestinal absorption. Nanotechnology-based delivery platforms have demonstrated significant potential in improving the oral bioavailability of poorly absorbed drugs. Among these platforms, liposomes have emerged as one of the most extensively studied carriers due to their structural similarity to biological membranes, biocompatibility, and versatility in drug encapsulation.[5-6]

Liposomes are spherical vesicles composed of phospholipid bilayers enclosing an aqueous core, making them particularly suitable for encapsulating hydrophilic molecules such as vitamin B12. Despite their advantages, conventional liposomes face several limitations when administered orally, including instability in acidic environments, aggregation, and premature drug leakage. These drawbacks have prompted the exploration of advanced formulation strategies such as enteric coating and polymeric surface modification.

Enteric coating is a well-established pharmaceutical approach designed to protect dosage forms from gastric degradation and enable site-specific drug release in the intestine. When combined with liposomal systems, enteric coating can significantly enhance stability during gastric transit. Furthermore, surface modification of liposomes with polymers such as chitosan and polyethene glycol (PEG) has been shown to improve mucoadhesion, permeability, and colloidal stability. Chitosan, a naturally derived cationic polymer, exhibits strong mucoadhesive properties and the ability to transiently open tight junctions, thereby enhancing paracellular transport. PEGylation, on the other hand, provides steric stabilisation, reduces aggregation, and facilitates mucus penetration.

The integration of enteric protection with chitosan–PEG dual coating represents a rational and multifaceted strategy to address the complex barriers associated with oral vitamin B12 delivery. This review aims to provide a comprehensive analysis of enteric-coated vitamin B12 liposomes with chitosan–PEG dual coating, focusing on their design principles, mechanisms of action, evaluation strategies, and translational challenges. By critically examining existing literature, this review identifies key research gaps and highlights future directions for the development of effective oral vitamin B12 delivery systems.

2. Vitamin B12: Physiology, Absorption Mechanism, and Oral Delivery Challenges

Vitamin B12 (cobalamin) is a complex cobalt-containing corrinoid compound that plays an indispensable role in cellular metabolism. It functions as a cofactor for methionine synthase and methylmalonyl-CoA mutase, enzymes essential for DNA synthesis, fatty acid metabolism, and neurological function. Adequate vitamin B12 levels are therefore crucial for hematopoiesis and maintenance of the nervous system.

2.1 Physiological Absorption of Vitamin B12

The absorption of vitamin B12 is a multistep and highly regulated physiological process. Dietary vitamin B12 is initially bound to proteins and is released in the stomach through the action of gastric acid and pepsin. Free vitamin B12 subsequently binds to haptocorrin (R-protein) secreted in saliva and gastric fluids. In the duodenum, pancreatic proteases degrade the vitamin B12–haptocorrin complex, allowing vitamin B12 to bind to intrinsic factor, a glycoprotein secreted by gastric parietal cells.[7-8] The intrinsic factor–vitamin B12 complex is resistant to proteolysis and travels to the terminal ileum, where it binds to specific receptors on the enterocyte surface. Following receptor-mediated endocytosis, vitamin B12 is released into systemic circulation bound to transcobalamin II. This highly specific absorption pathway limits the amount of vitamin B12 that can be absorbed through conventional oral formulations.

2.2 Factors Affecting Oral Bioavailability

Several physiological and pathological factors adversely affect oral vitamin B12 absorption. Reduced gastric acid secretion is observed in elderly patients. Impaired intrinsic factor production is also one of the reasons. Gastrointestinal disorders such as Crohn's disease and celiac disease limit the absorption of B12. Long-term use of proton pump inhibitors and metformin also affects B12 absorption. Competitive inhibition by dietary components can affect the absorption of B12. These factors contribute to low and unpredictable oral bioavailability, often necessitating high-dose oral supplementation or parenteral administration.

2.3 Limitations of Conventional Oral Formulations

Conventional oral vitamin B12 dosage forms, including tablets and capsules, rely primarily on intrinsic factor-mediated

absorption. However, this pathway becomes saturated at relatively low doses, resulting in inefficient absorption of higher doses. Passive diffusion accounts for only a small fraction of absorbed vitamin B12, further limiting therapeutic effectiveness.[9] In addition, vitamin B12 is susceptible to degradation in acidic environments, and prolonged exposure to gastric pH can significantly reduce its stability. Enzymatic degradation in the gastrointestinal tract further compromises its bioavailability.[10-12] These challenges underscore the need for alternative oral delivery strategies capable of protecting vitamin B12 during gastrointestinal transit and enhancing its absorption independently of intrinsic factor-mediated pathways.

3. Nanocarrier-Based Strategies for Oral Vitamin B12 Delivery

Nanocarrier-based drug delivery systems have gained significant attention for improving the oral bioavailability of poorly absorbed and labile drugs. These systems offer the ability to protect drugs from degradation, enhance permeability, and provide controlled release.

3.1 Polymeric Nanoparticles

Polymeric nanoparticles prepared using biodegradable polymers such as PLGA, chitosan, and alginate have been explored for oral vitamin delivery. These systems offer protection against acidic degradation and allow controlled drug release. However, polymeric nanoparticles often face challenges related to burst release, limited drug loading for hydrophilic compounds, and potential toxicity associated with residual solvents.

3.2 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) combine the advantages of lipid-based systems with enhanced physical stability. While these carriers have demonstrated improved oral bioavailability for lipophilic drugs, their application to highly hydrophilic molecules such as vitamin B12 remains limited due to low encapsulation efficiency.

3.3 Micelles and Self-Emulsifying Systems

Polymeric micelles and self-emulsifying drug delivery systems (SEDDS) have been extensively studied for enhancing oral drug absorption. These systems primarily improve solubilization and membrane permeability. However, their utility for vitamin B12 delivery is constrained by poor encapsulation stability and rapid dilution in gastrointestinal fluids.

3.4 Liposomes as Preferred Nanocarriers

Among various nanocarriers, liposomes have emerged as particularly promising systems for oral vitamin B12 delivery. Their aqueous core allows efficient encapsulation of hydrophilic molecules, while their lipid bilayer structure offers protection from harsh gastrointestinal conditions. Additionally, liposomes provide a versatile platform for surface modification and functionalization.[13] Despite these advantages, unmodified liposomes exhibit limited stability in the gastrointestinal tract, necessitating further formulation advancements such as enteric coating and polymeric surface modification.

4. Liposomes as Oral Drug Delivery Systems

Liposomes are spherical vesicular carriers composed of one or more phospholipid bilayers surrounding an aqueous core.[1] Their structural resemblance to biological membranes makes them highly biocompatible and suitable for drug delivery applications.[14]

4.1 Structural Characteristics and Classification

Liposomes can be classified based on size and lamellarity into multilamellar vesicles, small unilamellar vesicles, and large unilamellar vesicles. The choice of liposome type significantly influences drug encapsulation efficiency, release behaviour, and stability. Phospholipids such as phosphatidylcholine, phosphatidylethanolamine, and cholesterol are commonly used to formulate liposomes. Cholesterol plays a critical role in enhancing membrane rigidity and reducing permeability.

4.2 Advantages of Liposomes for Oral Delivery

Liposomes offer several advantages for oral drug delivery. It helps in the protection of encapsulated drugs from acidic and enzymatic degradation and improves drug stability. It improves the possibility of controlled and sustained release. It enhances interaction with intestinal membranes. These properties make liposomes particularly suitable for delivering labile and hydrophilic molecules such as vitamin B12.[14]

4.3 Limitations of Conventional Liposomes

Despite their advantages, conventional liposomes face several challenges when administered orally. It results in instability in acidic gastric conditions and aggregation and fusion in gastrointestinal fluids. It causes premature drug leakage and also limited mucosal adhesion. These limitations significantly reduce their effectiveness as oral delivery systems. [15-17]

4.4 Need for Advanced Liposomal Modifications

To overcome the inherent limitations of conventional liposomes, advanced strategies such as enteric coating and polymeric surface modification have been explored. Enteric coating protects against gastric degradation, while polymers such as chitosan and PEG improve mucoadhesion, permeability, and colloidal stability.

The integration of these strategies represents a rational approach to enhancing the performance of liposomal systems for oral vitamin B12 delivery. [18-20]

5. Liposomes for Oral Delivery of Vitamin B12: Design Considerations and Literature Evidence

The application of liposomes for oral drug delivery has been extensively investigated over the past few decades. However, their use for the oral delivery of hydrophilic macromolecules such as vitamin B12 requires careful consideration of formulation design, stability, and biological interactions. Vitamin B12 presents unique challenges due to its high

molecular weight, hydrophilicity, and sensitivity to gastrointestinal conditions.

5.1 Encapsulation of Hydrophilic Molecules in Liposomes

Hydrophilic drugs such as vitamin B12 are typically encapsulated within the aqueous core of liposomes. Encapsulation efficiency is influenced by several factors, including lipid composition, lamellarity, preparation technique, and hydration conditions. Literature reports suggest that increasing the internal aqueous volume of liposomes can enhance the encapsulation of hydrophilic molecules. However, higher aqueous volume may compromise membrane stability, particularly under gastrointestinal conditions.

5.2 Stability of Vitamin B12-Loaded Liposomes in Gastrointestinal Environment

The gastrointestinal tract presents a highly dynamic and hostile environment for liposomal carriers. Exposure to acidic pH, bile salts, digestive enzymes, and mechanical stress can destabilise liposomal membranes, leading to drug leakage and aggregation. Several studies have demonstrated that unmodified liposomes undergo rapid destabilisation in simulated gastric fluid, resulting in poor oral bioavailability. [15-17] For vitamin B12-loaded liposomes, this instability is particularly problematic, as premature release in the stomach not only reduces bioavailability but also exposes the vitamin to acidic degradation. These findings highlight the necessity of incorporating protective strategies such as enteric coating and polymeric surface modification.

5.3 Interaction of Liposomes with Intestinal Epithelium

The interaction of liposomes with the intestinal epithelium plays a critical role in determining their absorption and bioavailability. Conventional liposomes exhibit limited interaction with the mucus layer and epithelial surface, resulting in rapid clearance from the gastrointestinal tract. Surface modification strategies have therefore been employed to enhance liposome–mucosa interactions and promote intestinal uptake.[15-17]

5.4 Limitations of Liposomes as Standalone Oral Delivery Systems

Despite promising in-vitro results, liposomes alone are insufficient to overcome the multiple physiological barriers associated with oral vitamin B12 delivery. Their susceptibility to acidic degradation, lack of site-specific release, and limited mucoadhesion necessitate the incorporation of additional formulation strategies. This has led to growing interest in enteric-coated and polymer-modified liposomal systems. [18-20]

6. Enteric Coating Strategies for Liposomal Drug Delivery

Enteric coating is a widely established pharmaceutical approach used to protect dosage forms from the acidic gastric environment and ensure drug release in the intestine. The application of enteric coating to liposomal systems represents a critical advancement in improving their suitability for oral administration.[35-40]

6.1 Rationale for Enteric Coating of Liposomes

The primary objective of enteric coating is to prevent premature drug release in the stomach and enable site-specific release in the intestinal region. For vitamin B12-loaded liposomes, enteric coating provides dual benefits: protection of the liposomal membrane from gastric degradation and preservation of vitamin stability during gastric transit. [35-40]

6.2 Enteric Polymers Used in Liposomal Systems

Several pH-sensitive polymers have been employed for enteric coating of liposomal formulations, such as Eudragit L and S series, including methacrylic acid copolymers that dissolve at pH values above 5.5 and 6.8, respectively. Hydroxypropyl methylcellulose phthalate (HPMCP): A cellulose derivative is also widely used for enteric protection.Cellulose acetate phthalate (CAP), which is a traditional enteric polymer with proven effectiveness.

The selection of enteric polymer depends on the desired release site, polymer solubility profile, and compatibility with liposomal systems. [35-40]

6.3 Techniques for Enteric Coating of Liposomes

Various techniques have been explored for applying enteric coating to liposomal systems, including polymer layering, spray drying, and microencapsulation. Each method offers distinct advantages and challenges in terms of coating uniformity, scalability, and stability. The literature emphasises the importance of achieving uniform coating without compromising liposomal integrity. [35-40]

6.4 Impact of Enteric Coating on Drug Release Behaviour

Enteric-coated liposomal systems exhibit minimal drug release under acidic conditions, followed by rapid or controlled release upon exposure to intestinal pH. This pH-dependent release behaviour is particularly advantageous for vitamin B12 delivery, as it ensures protection during gastric transit and availability at the primary site of absorption. [35-40]

7. Chitosan-Coated Liposomes for Enhanced Oral Delivery

Chitosan, a naturally occurring cationic polysaccharide derived from chitin, has been widely investigated as a functional coating material for oral drug delivery systems. Its unique physicochemical and biological properties make it particularly suitable for modifying liposomal carriers.[21]

7.1 Physicochemical Properties of Chitosan Relevant to Drug Delivery

Chitosan possesses several characteristics that are advantageous for oral drug delivery, including biodegradability, biocompatibility, low toxicity, and mucoadhesive behaviour. Its positive charge under physiological conditions enables electrostatic interaction with negatively charged mucosal surfaces and liposomal membranes.[21]

7.2 Mechanism of Mucoadhesion and Permeability Enhancement

The mucoadhesive properties of chitosan arise from electrostatic interactions with mucin glycoproteins present in the mucus layer. This interaction prolongs the residence time of drug delivery systems at the absorption site. Additionally, chitosan has been shown to transiently open tight junctions between epithelial cells, thereby enhancing paracellular transport of hydrophilic molecules. [23-25]

7.3 Chitosan-Coated Liposomes in Oral Drug Delivery

Numerous studies have demonstrated that chitosan-coated liposomes exhibit improved stability, enhanced mucoadhesion, and increased intestinal absorption compared to uncoated liposomes. For hydrophilic drugs, chitosan coating has been shown to significantly enhance bioavailability by promoting closer contact with the intestinal epithelium. [26-28]

7.4 Limitations of Chitosan-Coated Liposomes

Despite their advantages, chitosan-coated liposomes are not without limitations. Chitosan is soluble under acidic conditions, which may compromise stability in the gastric environment. Additionally, excessive mucoadhesion may hinder diffusion through the mucus layer, limiting deeper penetration into the epithelial surface.

These limitations necessitate the integration of additional strategies, such as enteric protection and PEGylation, to achieve optimal performance. [29-30]

8. PEGylated Liposomes for Oral Drug Delivery

Polyethene glycol (PEG) is a hydrophilic, non-ionic polymer widely employed for surface modification of nanocarriers to improve their stability and biological performance. PEGylation of liposomes has been extensively investigated to overcome limitations such as aggregation, premature clearance, and poor mucus penetration. [29-30]

8.1 Role of PEGylation in Liposomal Stability

PEG chains form a hydrated steric barrier around the liposomal surface, which reduces van der Waals interactions and prevents aggregation. In the gastrointestinal environment, this steric stabilisation is particularly important due to the presence of bile salts, digestive enzymes, and fluctuating pH conditions that can destabilise conventional liposomes.[29] PEGylated liposomes demonstrate enhanced resistance to enzymatic degradation and reduced drug leakage compared to unmodified liposomes. This improved stability contributes to better preservation of encapsulated drugs during gastrointestinal transit. [31-33]

8.2 PEGylation and Mucus Penetration

The gastrointestinal mucus layer serves as a significant barrier to oral drug absorption. While mucoadhesive systems increase residence time, excessive interaction with mucus may hinder penetration toward the epithelial surface. PEGylation reduces adhesive interactions with mucus glycoproteins, thereby facilitating diffusion through the mucus layer. Several studies have reported that PEGylated nanocarriers exhibit improved mucus penetration compared to non-PEGylated counterparts. This property is particularly beneficial for hydrophilic molecules such as vitamin B12, which require proximity to the epithelial surface for absorption.[34]

8.3 Limitations of PEGylated Liposomes

Despite their advantages, PEGylated liposomes may exhibit reduced cellular interaction due to the steric barrier created by PEG chains. This phenomenon, often referred to as the “PEG dilemma,” highlights the trade-off between stability and epithelial interaction. Excessive PEGylation may reduce mucoadhesion and limit uptake across the intestinal epithelium. These limitations suggest that PEGylation alone may not be sufficient for optimal oral delivery and should be combined with other strategies, such as mucoadhesive polymers and enteric protection.[21]

9. Dual-Coated Liposomes: Chitosan–PEG Integrated Strategy with Enteric Protection

The integration of chitosan and PEG as a dual-coating strategy represents a rational approach to addressing the complex and multifactorial barriers associated with oral drug delivery. When combined with enteric protection, this strategy offers synergistic benefits that cannot be achieved by individual components alone.[46]

9.1 Rationale for Dual Coating

Chitosan and PEG exhibit complementary properties in oral drug delivery. Chitosan enhances mucoadhesion and paracellular transport, while PEG improves colloidal stability and mucus penetration. Enteric coating further ensures protection from gastric degradation and enables site-specific intestinal release.[47] The combination of these strategies aims to protect liposomes in the stomach, enhance stability during intestinal transit and optimise interaction with mucus and epithelial surfaces, thereby improving overall bioavailability.

9.2 Mechanistic Synergy of Chitosan–PEG Dual Coating

The dual-coated system is designed to balance mucoadhesion and mucopenetration. Chitosan facilitates prolonged residence at the intestinal surface, while PEG allows penetration through the mucus layer. Enteric coating ensures that these interactions occur only after gastric transit. Literature suggests that such synergistic systems can enhance intestinal absorption of hydrophilic drugs by optimising multiple transport pathways simultaneously.[47]

9.3 Advantages of Enteric-Protected Dual-Coated Liposomes

Enteric-protected chitosan–PEG dual-coated liposomes offer several potential advantages. This includes enhanced protection against acidic degradation, improved liposomal stability in gastrointestinal fluids, prolonged intestinal residence time, increased likelihood of paracellular transport, and controlled and site-specific drug release.

These features make dual-coated enteric liposomes particularly promising for oral delivery of vitamin B12. [35-40]

9.4 Challenges Associated with Dual-Coated Systems

Despite their potential, dual-coated liposomal systems present formulation and translational challenges, including optimisation of coating sequence and thickness, potential interactions between polymers, increased formulation complexityand scale-up and reproducibility concerns.

These challenges highlight the need for systematic experimental investigations and rational formulation design.

10. Characterisation and Evaluation of Enteric-Coated Dual-Coated Liposomes

Comprehensive characterisation and evaluation are essential to assess the performance and stability of advanced liposomal systems. A range of physicochemical and biological techniques is commonly employed in the literature.

10.1 Physicochemical Characterisation

Particle size and polydispersity index are assessed using dynamic light scattering to evaluate size distribution and uniformity. Zeta potential is used to confirm surface modification and coating efficiency.[50-53] Encapsulation efficiency indicates the ability of liposomes to retain vitamin B12.[54-55] Fourier-transform infrared spectroscopy (FTIR) is used to identify potential interactions between the drug and excipients.[56-57] Differential scanning calorimetry (DSC) provides information on thermal behaviour and drug encapsulation state.[56-57] Morphological analysis is conducted using scanning or transmission electron microscopy.[58-59]

10.2 In-Vitro Release Studies

In-vitro release studies are typically conducted in simulated gastric fluid followed by simulated intestinal fluid to evaluate pH-dependent release behaviour. Enteric-coated systems are expected to exhibit minimal release under acidic conditions and controlled release at intestinal pH.[60-61]

10.3 Biological Evaluation

Mucoadhesion studiesis used to assess interaction with intestinal mucus. [64-68] Ex vivo intestinal permeation is used evaluate transport across intestinal tissues. [69-70] Cellular uptake studies provide insights into absorption mechanisms. [71-72]

10.4 In-Vivo Evaluation

In-vivo studies focus on pharmacokinetic profiling and bioavailability assessment. Comparative studies with conventional formulations are essential to establish the therapeutic advantage of advanced delivery systems. [73-74]

11. Safety, Toxicity, and Regulatory Considerations

The successful translation of advanced liposomal drug delivery systems from laboratory research to clinical application depends not only on efficacy but also on safety, toxicity, and regulatory acceptability. Enteric-coated, chitosan–PEG dual-coated liposomal systems incorporate multiple functional excipients, each of which must be evaluated for biocompatibility and regulatory compliance.

11.1 Safety Profile of Liposomal Drug Delivery Systems

Liposomes are generally recognised as biocompatible and biodegradable carriers due to their structural similarity to biological membranes. Phospholipids used in liposomal formulations are commonly derived from natural or synthetic sources with established safety profiles. Several liposomal products are already approved for clinical use, supporting their translational potential. [75-77]

However, oral liposomal systems encounter prolonged exposure to gastrointestinal tissues, necessitating thorough evaluation of long-term safety and mucosal tolerance. Factors such as lipid composition, particle size, surface charge, and coating thickness influence biological interactions and toxicity profiles. [78-79]

11.2 Toxicological Considerations of Chitosan Coating

Chitosan is widely regarded as a safe polymer for pharmaceutical applications due to its biodegradability, low immunogenicity, and favourable toxicity profile. It has been approved for use in various biomedical and pharmaceutical products. However, its cationic nature may cause irritation or membrane disruption at higher concentrations.

In the context of oral delivery, chitosan-induced opening of tight junctions is generally transient and reversible. Nevertheless, prolonged or repeated exposure requires careful evaluation to ensure that intestinal barrier integrity is not compromised. [80-82]

11.3 Safety Aspects of PEGylation

PEG is considered non-toxic and non-immunogenic and has been widely used in pharmaceutical formulations. PEGylation enhances formulation stability and reduces nonspecific interactions. However, concerns related to PEG accumulation, hypersensitivity reactions, and long-term exposure have been reported in certain parenteral formulations. For oral delivery, PEGylated systems are primarily exposed to the gastrointestinal tract, reducing systemic accumulation risks. Nonetheless, optimisation of PEG molecular weight and surface density is essential to balance safety and performance. [83-85]

11.4 Regulatory Challenges and Considerations

The regulatory approval of complex nanocarrier systems remains challenging due to the lack of standardised evaluation protocols. Regulatory agencies require comprehensive characterisation, reproducibility, stability, and safety data. For dual-coated enteric liposomes, demonstrating batch-to-batch consistency and scalability is particularly critical. [89-91] Clear differentiation between excipient functionality and active pharmaceutical ingredient behaviour must be established. Regulatory frameworks are evolving, but additional guidance specific to multifunctional nanocarriers is still required. [92-93]

12. Research Gaps and Future Perspectives

Despite significant progress in liposomal drug delivery research, several critical gaps remain, particularly in the context of enteric-coated, chitosan–PEG dual-coated vitamin B12 liposomes. Addressing these gaps is essential for advancing both scientific understanding and clinical translation.

12.1 Limited Clinical Translation of Oral Liposomal Vitamin B12 Systems

Most studies on liposomal vitamin B12 delivery are limited to in-vitro and animal models. Clinical data evaluating bioavailability, safety, and therapeutic outcomes are scarce. This gap highlights the need for well-designed clinical studies to validate the translational potential of advanced liposomal systems.

12.2 Incomplete Understanding of Absorption Mechanisms

The exact mechanisms by which dual-coated liposomal systems enhance intestinal absorption of vitamin B12 remain inadequately explored. While mucoadhesion, paracellular transport, and mucus penetration have been proposed, their relative contributions under physiological conditions are not fully understood. Advanced imaging techniques and mechanistic studies are required to elucidate these pathways and optimise formulation design accordingly.

12.3 Optimisation of Dual-Coating Parameters

There is a lack of systematic studies investigating the optimal sequence, thickness, and ratio of chitosan and PEG coatings. Variations in polymer molecular weight, degree of deacetylation, and PEG chain length significantly influence system performance, yet standardised optimisation strategies are lacking. Future research should focus on establishing design-of-experiments (DoE) approaches to achieve reproducible and scalable formulations.

12.4 Stability and Shelf-Life Concerns

Long-term stability data for enteric-coated dual-coated liposomal systems are limited. Factors such as moisture sensitivity, polymer degradation, and lipid oxidation may affect shelf life. Comprehensive stability studies under various storage conditions are required to support commercialisation.

12.5 Regulatory and Manufacturing Challenges

The complexity of multifunctional liposomal systems poses challenges in large-scale manufacturing and regulatory approval. There is a need for standardised manufacturing protocols and regulatory guidelines tailored to advanced oral nanocarriers.

12.6 Future Research Directions

Future investigations should focus on clinical evaluation of oral vitamin B12 liposomal formulations, mechanistic studies of intestinal transport pathways, scalable and cost-effective manufacturing methods, integration of quality-by-design principles and regulatory harmonisation for nanomedicine products.[94-95]

13. CONCLUSION

Oral delivery of vitamin B12 remains a significant pharmaceutical challenge due to its complex absorption mechanism and poor bioavailability. Liposomal drug delivery systems offer a promising platform to overcome these limitations; however, conventional liposomes alone are insufficient to address the multifaceted barriers of the gastrointestinal tract.

Enteric-coated, chitosan–PEG dual-coated liposomal systems represent a rational and synergistic approach for enhancing oral vitamin B12 delivery. Enteric protection ensures gastric stability, chitosan enhances mucoadhesion and epithelial permeability, and PEGylation improves stability and mucus penetration. Together, these strategies address critical formulation challenges and offer substantial potential for improved therapeutic outcomes.

Despite encouraging preclinical findings, significant research gaps remain, particularly in clinical translation, mechanistic understanding, and regulatory standardisation. Addressing these gaps through systematic research and interdisciplinary collaboration will be essential for realising the full potential of advanced liposomal delivery systems.

In conclusion, enteric-coated chitosan–PEG dual-coated vitamin B12 liposomes represent a promising and innovative strategy for oral drug delivery, warranting further investigation and development for clinical application.

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About the corresponding author

Aniket Bhoite is a student at PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Savitribai Phule Pune University, Pune, Maharashtra, India. His academic interests focus on pharmaceutical sciences, research methodology, and advancing evidence-based practices in healthcare and drug development.