



Review Article

Current status and future directions of liposomal melatonin in transmucosal delivery systems: Emphasis on the active ingredient from west Bengal Chemical Industries Limited

Sunil Agarwal¹, Ranita Roy^{1*}, Argha Chakraborty¹, Turban Kar¹

¹Dept. of Research and Development, West Bengal Chemical Industries Limited, Kolkata, West Bengal, India

Abstract

Melatonin (N-acetyl-5-methoxytryptamine) plays a pivotal role in regulating circadian rhythms. It also possesses a significant therapeutic potential due to its antioxidant, anti-inflammatory, and immune-boosting activities. Despite these benefits, the clinical use of melatonin is limited due to its poor oral bioavailability. Liposomal encapsulation has emerged as a promising approach to improve the way melatonin is absorbed in the body. However, oral delivery of liposomal melatonin poses several challenges, which include enzymatic breakdown and incomplete absorption. In this review, we have explored the benefits of combining liposomal encapsulation with oral or sublingual melatonin spray formulations. Both clinical and preclinical studies demonstrate the efficacy of transmucosal sprays, including rapid onset of activity, enhanced bioavailability, and lower dosing. In this review, we have also discussed the potential of West Bengal Chemical Industries Limited (WBCIL) formulated liposomal melatonin to develop next-generation sublingual/oral spray delivery systems designed specifically for children, the elderly, and those with difficulty swallowing.

Keywords: Liposomal Melatonin, Bioavailability, Liposomal Spray, Oral absorption, WBCIL

Received: 18-12-2025; **Accepted:** 21-01-2026; **Available Online:** 02-02-2026

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

N-acetyl 5-methoxytryptamine or Melatonin, is a pineal hormone that has a remarkable effect on the nycthemeral rhythm.¹ Generally taken orally to improve sleep quality, to synchronise biological rhythms, or to enhance the quality of life of patients undergoing chemotherapeutic treatment or suffering from neurodegenerative disorders, melatonin plays a pivotal role.¹ However, due to extensive first-pass hepatic metabolism and a shorter half-life, it has an extremely low bioavailability of ~15%.¹ With significant advances in liposomal research, phospholipid-encapsulated melatonin has gained immense recognition. Though oral liposomal drugs or nutraceuticals can partially bypass the constraints of conventional oral formulations, they cannot fully overcome these constraints, which compromises the bioavailability of the active.

Therefore, ongoing research aims to develop an alternative drug-delivery route that can overcome the

shortcomings of oral liposomal formulations while retaining their significant benefits, including longer plasma retention, sustained release to reduce the number of doses, and higher bioavailability. Numerous galenic formulations have been developed to enhance bioavailability,² among which sublingual mouth-dissolving or chewable tablets have gained momentum.

Since melatonin bioavailability depends on its formulation, route of administration, and first-pass metabolism, sublingual delivery appears effective². However, sublingual/oral liposomal melatonin spray is far more effective than a conventional sublingual formulation, as it doesn't have to depend on saliva for dissolution and shows a comparatively faster absorption (**Figure 1**).

In this review article, we will delve into the importance of sublingual/oral spray and liposomal technology in enhancing the bioavailability of melatonin. We will also get an overview of the potential of WBCIL's liposomal

*Corresponding author: Ranita Roy
Email: ranita.r@eskag.in

technology for the effective delivery of melatonin in a sublingual/oral spray formulation.

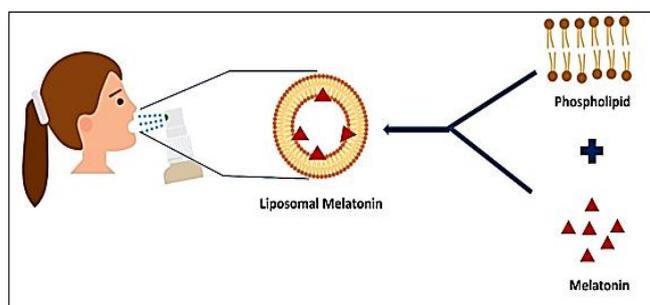


Figure 1: Liposomal melatonin mouth spray enhances bioavailability through better absorption in the buccal cavity and is helpful for people suffering from dysphagia, geriatric and paediatric patients.

2. Pharmacology and Clinical Significance of Melatonin

Melatonin is an amphiphilic molecule that possesses both hydrophilic and lipophilic characteristics.³ This amphiphilic nature of melatonin allows it to permeate the blood-brain (hemato-encephalic) barrier with ease.³ Though the importance of melatonin in regulating circadian rhythms, correcting disorders of consciousness by preserving the sleep cycle and mitigating migraine pain is well known,⁴⁻⁶ melatonin's role extends beyond this. It plays a crucial role as an antioxidant and anti-inflammatory molecule, as demonstrated by several clinical studies. In a single controlled clinical study, 41 patients suffering from chronic kidney disease (CKD) with low haemoglobin (< 11g/dl), were randomly divided into a treatment group (received 5mg melatonin + their regular treatments) and a control group (received their regular treatments only). It was observed that melatonin supplementation had a remarkable effect on increasing Hb levels, serum iron, and Transferrin Saturation Ratio (TSAT) after 12 weeks of treatment. As an anti-inflammatory molecule, melatonin treatment improved Erythropoietin Hyporesponsiveness by significantly downregulating the expression of inflammatory markers- interleukin-6 (IL-6), interleukin-1 β (IL-1 β) and tissue necrosis factor- α (TNF- α). Thus, it has a significant impact on anaemic patients with CKD.⁷ The antioxidant effects of melatonin were demonstrated in another clinical trial involving preterm infants who are at risk of oxidative stress injury during the first 7 days after birth due to melatonin deficiency. Therefore, Marseglia et al. conducted a prospective, randomised, double-blind, placebo-controlled pilot study with 36 preterm newborns. From the first day of being born, 21 infants received an oral melatonin dose of 0.5 mg/kg once a day in the morning, and 15 newborns received an equivalent dose of placebo. It was observed that early melatonin administration significantly reduced lipid peroxidation and played a pivotal role in protecting the high-risk preterm neonates.⁸ Apart from this, clinical trials have shown the profound impact of melatonin oral

supplementation in reducing the negative impact of melatonin suppression among night shift workers, who are more prone to oxidative DNA damage, which substantially increases the risk of cancer⁹ Melatonin had a significant impact in reducing follicular oxidative stress among women, thereby improving oocyte quality.¹⁰ Among thalassemia patients with low bone mineral density (BMD), melatonin significantly reduced oxidative stress, mitigated back pain and improved BMD.¹¹ Though melatonin plays a pivotal role in maintaining physiological homeostasis, its poor bioavailability significantly limits its therapeutic efficacy.

Melatonin is synthesised from tryptophan within the pinealocytes, mainly during the dark phase of the day, when there is a significant increase in the activity of the rate-limiting enzyme, serotonin-N-acetyltransferase (S-NAT) or arylalkylamine N-acetyltransferase (AA-NAT). AA-NAT transforms 5-hydroxytryptamine (5-HT) or serotonin to N-acetylserotonin (NAS). NAS is subsequently methylated into melatonin by acetylserotonin O-methyltransferase. Thus, melatonin synthesis is dependent on both AA-NAT and serotonin availability.¹² Melatonin can be synthesised in other sites of the body, such as the skin, gastrointestinal tract, retina and bone marrow beyond the pineal gland.¹² In the intestine, the level of melatonin was approximately 400 times higher than in the pineal gland.¹³ 70% of melatonin found in the blood is bound to albumin. Melatonin has a half-life of ~ 40 minutes. It undergoes extensive first-pass hepatic metabolism. ~ 90 % is converted to 6-hydroxymelatonin by cytochrome P450 enzymes (CYPs)- the 6-hydroxylating subform CYP1A2 (P450 monooxygenases) and is conjugated with sulfate or glucuronic acid to form water-soluble 6-sulfatoxymelatonin (aMT6s) or N1-acetyl-N2-formyl-5-methoxykynuramine for subsequent urinary excretion.¹²⁻¹⁴ Thus, the oral bioavailability of melatonin is reduced to 15%.¹

Melatonin regulates circadian rhythms, glucose metabolism, retinal functions, reproductive physiology and immune responses by interacting with G protein-coupled receptors (GPCRs): MT1 (found in the central nervous system, pituitary gland, retina and other peripheral tissues, such as the cardiovascular system) and MT2 receptors (peripheral tissue including the liver, kidneys, and cardiovascular system).¹³

Thus, melatonin biosynthesis, metabolism, cellular transport, and bioavailability are strongly dependent on the availability of the amino acid tryptophan and of enzymes involved in its biosynthesis, MT1 and MT2 receptors for its cellular transport, and hepatic first-pass metabolism. This leads to poor bioavailability, frequent dosing and prolonged treatment to achieve the required plasma level. Therefore, the combination of liposomal encapsulation and oral/sublingual spray formulation of melatonin to bypass these constraints is the need of the hour. Before exploring the details of liposomal spray technology, we will briefly discuss liposomal

technology, its advantages and disadvantages with respect to melatonin.

3. Oral liposomal melatonin: Advantages and Persistent Challenges

3.1. Liposomal melatonin: Its delivery and advantages

Liposomes are spherical vesicles formed by spontaneous self-assembly of phospholipid bilayers in aqueous media, encapsulating both hydrophilic and lipophilic molecules within their aqueous core or in the lipid bilayer, respectively. These lipid vesicles are made of phospholipids naturally present in our cell membranes, which enhances their ability to interact with biomembranes and deliver the encapsulated molecule efficiently within the cell.^{15,16} This feature of liposomes has made it a key player in the next-generation drug delivery system. The liposomes enhance the bioavailability of the actives not only by seamlessly interacting with the membrane, but by protecting the encapsulated molecule from physiological degradation and rapid clearance from the plasma, which makes it effective in reaching the maximum threshold required for effective functioning of the active ingredients through sustained delivery without overwhelming the system with a sudden rush of the molecule followed by a steep decline. This not only reduces the frequency of doses but also reduces the risk of side effects.¹⁷

Liposomes undergo clathrin/caveolae-mediated endocytosis on interaction with enterocytes. Once inside the cell, they have two fates. While most interact with the chylomicron and enter the systemic circulation via the lymphatic system, others undergo endosomal degradation, with the active molecule released into the cytoplasm, from which it can enter the lymphatic system or the systemic circulation, depending on its lipophilicity.^{18,19} In a study by Fang et al. on liposomal docetaxel, it was shown that blocking endocytosis and lymphatic transport reduced docetaxel's plasma concentration, underscoring the importance of endocytosis-mediated cellular drug uptake and lymphatic system-mediated drug transport to the systemic circulation.²⁰ Thus, both processes are pivotal in delivering the advantages of liposomal delivery of pharmaceuticals and nutraceuticals and in improving pharmacokinetics by protecting the majority of the actives from extensive hepatic first-pass metabolism.

The exact mechanism described above explains the processes of cellular uptake, metabolism, and systemic transport of liposomal melatonin. Liposomal encapsulation enhances melatonin bioavailability by 40.45%,²¹ effectively bypassing the transporter bottleneck and reducing CYP1A2-mediated hepatic first-pass metabolism while maintaining a sustained-release profile.

There are very few clinical studies on liposomal melatonin, of which one is a double-blind, placebo-controlled

study that used liposomal melatonin to induce sleep in paediatric patients aged 1-6 years undergoing sleep electroencephalography (EEG) to assess epilepsy.²²

3.2. Challenges of oral liposomal delivery

Despite the tremendous potential of liposomal technology to enhance the absorption and bioavailability of melatonin, the efficacy of liposomes is significantly compromised when delivered orally. A few of these limitations are as follows:

1. *Digestion:* The harsh gastric environment causes significant damage to liposomes, which could be attributed to extensive hydrolysis by digestive enzymes such as lipase, pepsin, and gastric hydrochloric acid that lowers the pH to 1-2. Under such conditions, conventional liposomes become unstable and disintegrate, releasing melatonin.²³ In the intestine, bile salts and pancreatic enzymes, such as lipase, can hydrolyse the phospholipid bilayer and disrupt its structural integrity, thereby releasing the melatonin into the lumen and reducing cellular uptake.²³
2. *Absorption:* It is the next big challenge faced by liposomes. The absorption of liposomes by intestinal cells strictly depends on their size. Studies have shown that the absorption and bioavailability of small liposomes were ~12 times higher than those of larger liposomes, which could also be due to the compact packing of intestinal epithelial cells. The mucus layer can also entrap liposomes, making it difficult for them to pass through and reach the cell.²³
3. *Incomplete bypass of first-pass metabolism:* Liposomes taken up by enterocytes interact with chylomicrons and enter the lymphatic system, bypassing the first-pass metabolism. However, a portion of melatonin enters the portal circulation and undergoes extensive hepatic metabolism, significantly reducing its bioavailability.²³
4. *Cost of production:* To protect liposomes from degradation and enhance their stability, several modifications are made, which include protective surface coating, using thermostable phospholipids or improving muco-adhesion by incorporating absorption enhancers. However, these modifications significantly increase production costs.²⁴

Thus, while oral liposomal formulations represent a technological advancement, they may not fully address the inherent bioavailability variability of the oral route.

4. Liposomal Melatonin Delivery and the Rationale for Spray Formulation

The bioavailability of any active depends on its physicochemical properties, half-life, solubility, site of administration, vascularisation of the absorption site, pH of the absorption site, delivery system and dosage.²⁵ While liposomal encapsulation of melatonin significantly enhances its bioavailability, the limitations mentioned in section 3b reduce its efficacy. Therefore, scientists aim to develop a

readily available oral/sublingual liposomal melatonin spray formulation that retains the advantages of liposomal delivery while overcoming its associated challenges. The major benefits of liposomal melatonin spray are as follows:

1. *Enhanced bioavailability:* As discussed in section 3b, the bioavailability of melatonin depends on the ability of liposomes to sustain the acidic gastric media, enzymatic disintegration in the GI tract and ability to penetrate the intestinal epithelial cells. A liposomal spray formulation can deliver melatonin directly to the buccal cavity, circumvent hepatic first-pass metabolism and deliver it to the systemic circulation. Thus, ensuring a rapid onset of activity and a 2-fold increase in bioavailability compared to a prolonged-release melatonin tablet.^{25,2}
2. *Increased absorption:* The highly vascularized buccal and throat mucosa is suitable for the absorption of liposomal melatonin. Since the activity of melatonin is mainly dependent on the amount of melatonin and the rate at which it reaches the systemic circulation.^{25,2} Liposomal spray formulations increase bioavailability substantially, thereby reducing the dosage compared to oral liposomal melatonin tablets.
3. *Ease of Use:* A fraction of the population, especially those with dysphagia, paediatric and geriatric patients, find it difficult to swallow tablets. With increased dosage, the tablet size increases, making it more challenging to swallow.²⁵ Liposomal spray formulation can easily avoid such constraints.

This underscores the importance of liposomal melatonin spray as an effective galenic form.

5. Liposomal Melatonin Spray as a Next Generation Drug Delivery System: WBCIL Perspective

West Bengal Chemical Industries Limited (WBCIL) is a pioneer in liposomal technology. Liposomes are manufactured using high-purity, stable phospholipids, with an encapsulation efficiency of not less than 80%, polydispersity index (PDI) < 0.5 and a zeta potential of < -30 mV. Liposomal melatonin synthesised according to the above-mentioned criteria exhibits enhanced stability, greater cellular uptake and mucus-binding ability, and blood compatibility, thereby ensuring greater melatonin bioavailability.^{26,27} At WBCIL, we are now focused on advancing our drug delivery technology to the next level by adopting liposomal oral/sublingual spray formulations as a next-generation drug delivery system. We aim to combine liposomal formulation with spray delivery to achieve a highly evolved delivery system that not only facilitates rapid absorption and high bioavailability but also serves the needs of paediatric, geriatric, and dysphagic patients. Scientific studies have unanimously concluded that the true potential of oral/sublingual spray lies in its rapid absorption, achieving

bioavailability comparable to that of intravenous (IV) administration.

In a recent single-centre, open-label, randomised, crossover trial, 14 healthy males received a prolonged-release melatonin tablet (1.9 mg) or two sprays of immediate-release sublingual spray (1 mg melatonin). Blood assessment showed that oral spray increased plasma melatonin levels by 2-fold (C_{max}: 2332 ± 950 pg/mL vs 1151 ± 565 pg/mL), rapidly elevating melatonin levels (T_{max}: 23.3 ± 6.5 min vs 64.2 ± 44.2 min) and prolonging the half-life. Further analysis confirms that sublingual/oral spray administration can partially bypass hepatic metabolism as evidenced by a higher melatonin-to-metabolite AUC ratio with the spray (Plasma melatonin/6-SMT AUC_{0-540/420} ratio 0.16 vs. 0.09), thus improving systemic bioavailability. Abdellah et al. concluded that fast-acting spray melatonin formulations are ideal for delayed sleep onset or transient nocturnal awakenings, and sustained-release tablets are suitable for insomnia.²

Though there is limited research on liposomal melatonin spray, clinical trials of other products have shown that liposomal encapsulation has the potential to provide better clinical outcomes by providing greater muco-adhesion, efficient transmucosal uptake, sustained release- making it suitable for both short and long-term treatment, and greater first-pass metabolism protection for melatonin that reaches the GI system.

A single study was conducted on liposomal spray, which included 98 patients with head and neck cancer who had completed cancer therapy and received liposomal sprays (LipoNasal, LipoSaliva; Optima Pharmaceutical GmbH, Germany) for both the nose and the mouth. A significant reduction in xerostomia and an increase in smell and taste sensation were observed in this study.²⁸

The potential of oral spray formulations as pharmaceutical and nutraceutical agents is reflected in several studies. Reppucia et al. conducted a retrospective study involving 100 women. They evaluated the efficacy of an oral vitamin E spray (vitamin E acetate in a medium-chain triglyceride vehicle) for treating periodontitis, a leading cause of preterm birth. They observed that vitamin E oral spray reduced the risk of periodontitis and, thus, preterm birth.²⁹ In another study, an oral spray formulation prepared using α -mangostin (α -MG) ((5 mg/ml) and lawsone methyl ether (2-methoxy-1,4-naphthoquinone) (LME) (250 μ g/ml) showed anti-inflammatory and antimicrobial properties against *Streptococcus mutans*, *Candida albicans*, and *Porphyromonas gingivalis*. Thus, it has the potential to serve as an adjunctive treatment to conventional therapy.³⁰ In a retrospective study, two galenic formulations of vitamin D were compared: oral drops and spray formulation in 136 babies. It was observed that infants treated with vitamin D oral spray had higher vitamin D serum levels than those treated with oral drops.³¹ Thus, all these studies indicate the

superior efficacy of the oral/sublingual spray formulation compared to other galenic formulations.

Research on liposomal oral/sublingual spray is ongoing, with only one study to date elucidating the efficacy of intranasal melatonin nanoniosome spray delivery. Niosomes are structurally similar to liposomes, but instead of lipids, they have a non-ionic surfactant. It was observed that nanoniosome melatonin spray took 18.3 ± 7.5 min to increase the melatonin level in the blood with AUC comparable to that of IV (1189 ± 579 vs 1601 ± 612 ng min/ml). The half-life of niosomes was 123.1 ± 81.9 min, which is significantly higher than IV, 71.5 ± 53.3 min. Bioavailability was similar to that of IV, i.e., 98.7 ± 23.6 %. From this study, we can conclude that encapsulating melatonin provides an added advantage, allowing it to remain in systemic circulation for a prolonged duration and, by bypassing enzymatic regulation and first-pass hepatic metabolism, the spray formulation significantly improves bioavailability. Thus, by expanding our knowledge, we at WBCIL have embarked on a venture to deliver advanced liposomal melatonin via oral/ sublingual spray formulation.

6. Conclusion and Future Perspective

Melatonin plays a vital role in regulating circadian rhythms. It has antioxidant and anti-inflammatory effects and shows potential for treating clinical conditions, such as sleep disorders, reproductive issues, and diseases related to oxidative stress. However, taking melatonin by mouth has limitations due to its short half-life and extensive hepatic metabolism, resulting in systemic availability of about 15%. Although liposomal encapsulation has improved melatonin's pharmacokinetic properties, oral liposomal formulations still face challenges with stomach stability, mucosal absorption, and incomplete lymphatic transport.

Sublingual or oral spray delivery of melatonin offers a promising solution. Clinical data show that transmucosal spray formulations provide a quicker onset of action, higher peak concentration, and better absorption with lower dosing needs. Liposomal encapsulation further improves this by ensuring it adheres to the mucosa, protecting it from enzyme breakdown, and allowing for a gradual release. Together, liposomal spray formulations offer greater benefits, better systemic availability, and simpler use, especially for children, the elderly, and those with swallowing difficulties.

At West Bengal Chemical Industries Limited (WBCIL), significant steps have been taken toward developing a highly effective liposomal melatonin active pharmaceutical ingredient (API) with excellent properties, including over 80% encapsulation efficiency and high stability. Integrating this platform into a sublingual or oral spray formulation could lead to new advances in melatonin therapies.

Future efforts should focus on refining the liposomal spray composition for targeted absorption, validating

pharmacokinetics in human subjects, and conducting clinical trials to compare the liposomal spray with existing oral and injectable formulations. The development of WBCIL's liposomal melatonin into a commercial spray product could change the standard for melatonin delivery and set new standards for future transmucosal therapies.

7. Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

8. Source of Funding

None.

9. Author's Contribution

All authors contributed equally in writing the draft, conceptualisation, review & editing, investigation and research. Mr Sunil Agarwal has also provided guidance and supervised the entire work.

10. Acknowledgement

We are thankful to the Honourable Director of West Bengal Chemical Industries Limited, Mr Sunil Agarwal, for granting us the opportunity to write this review article.

11. Ethical Approval

Not applicable. This article is a review and did not involve any experiments on human participants or animals.

12. Data Availability

All data analyzed during this study are included in this published article and its referenced sources.

References

1. Priprem A, Johns JR, Limsittichaikoon S, Limphirat W, Mahakunakorn P, Johns NP. Intranasal melatonin nanoniosomes: pharmacokinetic, pharmacodynamics and toxicity studies. *Therapeutic Deliv.* 2017;8(6):373–90. <https://doi.org/10.4155/tde-2017-0005>
2. Abdellah SA, Raverot V, Gal C, Guinobert I, Bardot V, Blondeau C, et al. Bioavailability of Melatonin after Administration of an Oral Prolonged-Release Tablet and an Immediate-Release Sublingual Spray in Healthy Male Volunteers. *Drugs in R & D.* 2023;23(3):257–65. <https://doi.org/10.1007/s40268-023-00431-9>
3. Dies H, Cheung B, Tang J, Rheinstädter MC. The organization of melatonin in lipid membranes. *Biochimica et Biophysica Acta (BBA) - Biomembranes.* 2015;1848(4):1032–40. <https://doi.org/10.1016/j.bbamem.2015.01.006>
4. Gandolfi JV, Di Bernardo APA, Chanes DAV, Martin DF, Joles VB, Amendola CP, et al. The Effects of Melatonin Supplementation on Sleep Quality and Assessment of the Serum Melatonin in ICU Patients: A Randomized Controlled Trial. *Crit Care Med.* 2020;48(12):e1286–93. <https://doi.org/10.1097/CCM.00000000000004690>
5. Wen X, Yu J, Zhu G, Wang J, Sun Y, Zhou J, et al. Efficacy of melatonin for prolonged disorders of consciousness: a double-blind,

- randomized clinical trial. *BMC Med.* 2024;22(1):576. <https://doi.org/10.1186/s12916-024-03793-2>.
6. Gelfand AA, Allen IE, Grimes B, Irwin S, Qubty W, Greene K, et al. Melatonin for migraine prevention in children and adolescents: A randomized, double-blind, placebo-controlled trial after single-blind placebo lead-in. *Headache.* 2023;63(9):1314–26. <https://doi.org/10.1111/head.14600>.
 7. Hameed EN, Tukmagi A, Ch H. Melatonin Improves Erythropoietin Hyporesponsiveness via Suppression of Inflammation. *Rev Recent Clin Trials.* 2019;14(3):203–8. <https://doi.org/10.2174/1574887114666190528120357>
 8. Marsiglia L, Gitto E, Laschi E, Giordano M, Romeo C, Cannavò L, et al. Antioxidant Effect of Melatonin in Preterm Newborns. Endesfelder S, editor. *Oxidative Medicine and Cellular Longevity.* 2021;2021:1–8. <https://doi.org/10.1155/2021/6308255>
 9. Zanif U, Lai AS, Parks J, Roenningen A, McLeod CB, Ayas N, et al. Melatonin supplementation and oxidative DNA damage repair capacity among night shift workers: a randomised placebo-controlled trial. *Occup Environ Med.* 2025;82(1):1–6. <https://doi.org/10.1136/oemed-2024-109824>
 10. Sadeghpour S, Ghasemnejad-Berenji M, Maleki F, Behroozi-Lak T, Bahadori R, Ghasemnejad-Berenji H. The effects of melatonin on follicular oxidative stress and art outcomes in women with diminished ovarian reserve: a randomized controlled trial. *J Ovarian Res.* 2025;18(1):5. <https://doi.org/10.1186/s13048-024-01584-0>.
 11. Piriyaikhuntorn P, Tantiworawit A, Phimphilai M, Kaewchur T, Niprapan P, Srivichit B, et al. Melatonin Supplementation Alleviates Bone Mineral Density Decline and Circulating Oxidative Stress in Iron-Overloaded Thalassemia Patients. *J Pin Res.* 2025;77(3). <https://doi.org/10.1111/jpi.70055>.
 12. Aulinas A, Arendt J. Physiology of the Pineal Gland and Melatonin. PubMed. South Dartmouth (MA): MDText.com, Inc.; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK550972/>
 13. Zimmermann P, Kurth S, Benoit Pugin, Bokulich NA. Microbial melatonin metabolism in the human intestine as a therapeutic target for dysbiosis and rhythm disorders. *NPJ Biofilms and Microbiomes.* 2024;10(1):139. <https://doi.org/10.1038/s41522-024-00605-6>.
 14. Hardeland R. Melatonin metabolism in the central nervous system. *Current Neuropharmacol.* 2010;8(3):168–81. <https://doi.org/10.2174/157015910792246244>
 15. Dymek M, Sikora E. Liposomes as biocompatible and smart delivery systems – the current state. *Advances in Colloid and Interface Science.* 2022;309:102757. <https://doi.org/10.1016/j.cis.2022.102757>.
 16. Giordani S, Marassi V, Zattoni A, Roda B, Reschiglian P. Liposomes characterization for market approval as pharmaceutical products: Analytical methods, guidelines and standardized protocols. *J Pharma Biomed Anal.* 2023;236:115751. <https://doi.org/10.1016/j.jpba.2023.115751>
 17. Guimarães D, Cavaco-Paulo A, Nogueira E. Design of liposomes as drug delivery system for therapeutic applications. *Int J Pharma.* 2021;601:120571. <https://doi.org/10.1016/j.ijpharm.2021.120571>.
 18. Ahn H, Park JH. Liposomal delivery systems for intestinal lymphatic drug transport. *Biomate Res.* 2016;20(1). <https://doi.org/10.1186/s40824-016-0083-1>
 19. Lee MK. Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs: In Vivo Evidence and Recent Approaches. *Pharm.* 2020;12(3):264. <https://doi.org/10.3390/pharmaceutics12030264>
 20. Fang G, Tang B, Chao Y, Zhang Y, Xu H, Tang X. Improved oral bioavailability of docetaxel by nanostructured lipid carriers: in vitro characteristics, in vivo evaluation and intestinal transport studies. *RSC Advances.* 2015;5(117):96437–47. <https://doi.org/10.1039/C5RA14588K>
 21. Nguyen XKT, Lee J, Shin EJ, Dang DK, Jeong JH, Nguyen TTL, et al. Liposomal melatonin rescues methamphetamine-elicited mitochondrial burdens, pro-apoptosis, and dopaminergic degeneration through the inhibition PKC δ gene. *J Pineal Res.* 2015;58(1):86–106. <https://doi.org/10.1111/jpi.12195>.
 22. Bonuccelli A, Santangelo A, Castelli F, Giulia Magherini, Volpi E, Costa E, et al. Efficacy of Liposomal Melatonin in sleep EEG in Childhood: A Double Blind Case Control Study. *Int J Environ Res Pub Health.* 2022;20(1):552–2. <https://doi.org/10.3390/ijerph20010552>
 23. Latrobdiba ZM, Fulyani F, Anjani G. Liposome optimisation for oral delivery of nutraceuticals in food: a review. *Food Res.* 2023;7(3):233–46. [https://doi.org/10.26656/fr.2017.7\(3\).022](https://doi.org/10.26656/fr.2017.7(3).022)
 24. Shade CW. Liposomes as Advanced Delivery Systems for Nutraceuticals. *Integr Med (Encinitas).* 2016;15(1):33–6.
 25. US5891465A - Delivery of biologically active material in a liposomal formulation for administration into the mouth - Google Patents. Google.com. 1996. <https://patents.google.com/patent/US5891465A/en>
 26. Banerjee PG, Paul A, Chakraborty A, Kundu S. Innovative Liposomal Vitamin C by West Bengal Chemical Industries Ltd., Kolkata, India: Enhancing nutraceutical effectiveness. *Eastern J Med Sci.* 2025;10(2):31–42. <https://doi.org/10.32677/ejms.v10i2.7302>
 27. Li LD, Crouzier T, Sarkar A, Dunphy L, Han J, Ribbeck K. Spatial Configuration and Composition of Charge Modulates Transport into a Mucin Hydrogel Barrier. *Biophysical J.* 2013;105(6):1357–65. <https://doi.org/10.1016/j.bpj.2013.07.050>
 28. Heiser C, Hofauer B, Scherer E, Schukraft J, Knopf A. Liposomal treatment of xerostomia, odor, and taste abnormalities in patients with head and neck cancer. *Head & Neck.* 2015;38(S1):E1232–7. <https://doi.org/10.1002/hed.24198>.
 29. Reppuccia S, Crocetto F, Ferrara C, Pietro D'Alessandro, M Vetrella, Saccone G, et al. Oil-based vitamin E oral spray for oral health in pregnancy. *Future Sci.* 2022;8(4):790. <https://doi.org/10.2144/foa-2021-0095>.
 30. Nittayananta W, Limsuwan S, Srichana T, Sae-Wong C, Amnuaitkit T. Oral spray containing plant-derived compounds is effective against common oral pathogens. *Arch Oral Biology.* 2018;90:80–5. <https://doi.org/10.1016/j.archoralbio.2018.03.002>.
 31. Unsur EK. Vitamin D levels of the healthy infants using oral spray or drop form of vitamin D supplement in the first year of life. *North Clin Istanb.* 2021;8(1):31–6. <https://doi.org/10.14744/nci.2020.09471>
 32. Priprem A, Johns JR, Limsitthichaikoon S, Limphirat W, Mahakunakorn P, Johns NP. Intranasal melatonin nanoniosomes: pharmacokinetic, pharmacodynamics and toxicity studies. *Therap Deliv.* 2017;8(6):373–90. <https://doi.org/10.4155/tde-2017-0005>.

Cite this article: Roy R, Agarwal S, Chakraborty A, Kar T. Current status and future directions of liposomal melatonin in trans mucosal delivery systems: Emphasis on the active ingredient from west Bengal Chemical Industries Limited. *Indian J Pharma Pharmacol.* 2025;12(4):206-211.