

Nanotechnology-Based Antidepressant Delivery Systems and Bilayer Tablet Approaches in Depression Management: Current Advances, Challenges, and Future Perspectives

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Abstract: Depression remains one of the most prevalent neuropsychiatric disorders globally and significantly contributes to disability, reduced quality of life, and socioeconomic burden. Conventional antidepressant therapies are associated with several limitations including delayed onset of action, poor patient compliance, inadequate blood–brain barrier penetration, and systemic adverse effects. Recent pharmaceutical advancements have focused on nanotechnology-based drug delivery systems, bilayer tablets, controlled-release formulations, and chronotherapeutic approaches to improve antidepressant efficacy and safety. The present review comprehensively discusses recent progress in bilayer tablet systems, nanoformulations, intranasal antidepressant delivery, melatonin-assisted therapy, neuroinflammation-targeted treatment, and brain-targeted drug delivery technologies. The review further highlights emerging molecular pathways involved in depression and discusses future perspectives associated with personalized and translational antidepressant therapy.

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I. INTRODUCTION

Depression is a chronic multifactorial psychiatric disorder characterized by persistent sadness, cognitive dysfunction, sleep disturbances, anhedonia, and emotional instability. According to the World Health Organization, depression remains one of the leading causes of disability worldwide. The pathophysiology of depression has been associated with monoamine imbalance, oxidative stress, neuroinflammation, hypothalamic–pituitary–adrenal axis dysregulation, and impaired neuroplasticity. Although several antidepressant drugs are currently available, therapeutic outcomes remain unsatisfactory in many patients because of delayed onset of action, treatment resistance, adverse effects, and poor patient adherence.

Recent developments in advanced pharmaceutical drug delivery systems have provided new opportunities for improving antidepressant therapy. Bilayer tablet systems capable of immediate and sustained drug release have demonstrated significant potential for improving patient compliance and therapeutic efficacy. Similarly, nanotechnology-based drug delivery systems including nanoparticles, lipid carriers, nanoemulsions, nanovesicles, and intranasal systems have emerged as promising approaches for enhancing brain-targeted drug delivery and overcoming blood–brain barrier limitations.

II. ROLE OF BILAYER TABLET TECHNOLOGY

Bilayer tablets represent advanced pharmaceutical dosage forms designed to provide dual drug release profiles within a single formulation. These systems may combine immediate-release and sustained-release layers, thereby improving therapeutic efficacy and minimizing dosing frequency. Bilayer tablet systems have demonstrated considerable potential in central nervous system disorders requiring combination therapy.

In depression management, bilayer tablets containing antidepressants and sleep-regulating agents such as melatonin may provide synergistic therapeutic benefits. Controlled-release antidepressant delivery may help maintain steady plasma drug concentrations, while immediate-release melatonin may regulate circadian rhythm disturbances frequently associated with depressive disorders. Several researchers have emphasized the advantages of bilayer formulations in achieving enhanced therapeutic outcomes and improved patient compliance.

➤ *Nanotechnology-Based Antidepressant Drug Delivery*

Nanotechnology has revolutionized pharmaceutical drug delivery by improving drug stability, permeability, solubility, and targeted tissue delivery. Various nanocarriers including polymeric nanoparticles, lipid nanoparticles, solid lipid nanoparticles, nanoemulsions, dendrimers, and biomimetic nanocarriers have demonstrated promising applications in antidepressant therapy.

Nanotechnology-based antidepressant systems may improve blood–brain barrier permeability, reduce systemic toxicity, and enhance therapeutic concentration at the target site. Intranasal nanoparticle systems have attracted particular attention because they allow direct nose-to-brain delivery through olfactory pathways. Several studies have demonstrated improved antidepressant efficacy using venlafaxine nanoparticles, duloxetine-loaded lipid carriers, ketamine nanovesicles, and flavonoid-based nanoparticles.

Recent investigations involving hesperidin, quercetin, and saikosaponin-loaded nanoformulations have further demonstrated neuroprotective and anti-inflammatory antidepressant mechanisms. Nanocarriers capable of targeting oxidative stress and inflammatory pathways may therefore represent highly promising therapeutic strategies in depression management.

➤ *Melatonin and Chronotherapeutic Approaches*

Melatonin is an endogenous hormone involved in circadian rhythm regulation and sleep architecture maintenance. Disturbances in melatonin secretion and circadian rhythm have been strongly associated with depression, insomnia, anxiety, and mood disorders.

Several preclinical and clinical studies have demonstrated the therapeutic benefits of melatonin supplementation in improving sleep quality and depressive symptoms. Combination therapy involving melatonin and antidepressants may produce synergistic effects by simultaneously targeting sleep disturbances and mood dysregulation. Chronotherapeutic approaches focusing on circadian rhythm modulation may therefore significantly improve therapeutic outcomes in patients with depression-associated insomnia.

➤ *Neuroinflammation and Molecular Mechanisms*

Recent evidence has demonstrated that neuroinflammation and oxidative stress play major roles in depression pathogenesis. Elevated inflammatory cytokines including TNF- α , IL-6, and IL-1 β have been reported in depressive disorders. Molecular signaling pathways including NF- κ B, BDNF/TrkB/PI3K/AKT, Akt/mTOR, and TLR4 have also been implicated in neuroinflammatory responses associated with depression.

Natural compounds and nanoformulations targeting these molecular pathways have shown promising antidepressant activity in experimental studies. Costunolide, saikosaponin A, flavonoid nanoparticles, and antioxidant nanozymes have demonstrated neuroprotective and anti-inflammatory effects capable of improving depressive-like behavior in animal models.

➤ *Animal Models in Depression Research*

Animal models remain essential for evaluating antidepressant activity and understanding neurobehavioral mechanisms associated with depression. Reserpine-induced depression models, chronic mild stress models, forced swim tests, tail suspension tests, and sucrose preference tests are commonly employed for behavioral assessment.

Recent studies have demonstrated that nanotechnology-based antidepressant formulations significantly improve behavioral outcomes and neurochemical parameters in experimental animal models. Behavioral assessment combined with biochemical and molecular investigations may therefore provide comprehensive evaluation of antidepressant efficacy.

➤ *Research Gaps and Challenges*

Despite significant advancements in antidepressant nanomedicine research, several limitations continue to affect clinical translation. Long-term toxicity, large-scale manufacturing challenges, formulation instability, regulatory concerns, and insufficient clinical evidence remain major barriers.

Furthermore, limited studies have investigated the integration of bilayer tablet systems with nanotechnology-based brain-targeted delivery approaches. Additional translational and clinical studies will therefore be necessary

for establishing safety, efficacy, and therapeutic reliability of advanced antidepressant formulations.

III. FUTURE PERSPECTIVES

Future antidepressant research will increasingly focus on personalized medicine, biomimetic nanocarriers, artificial intelligence-assisted formulation development, and precision-targeted therapy. Brain-targeted delivery systems capable of simultaneously regulating neuroinflammation, oxidative stress, and neurotransmitter imbalance may significantly improve depression treatment outcomes.

The integration of bilayer tablet technology with nanotechnology-based delivery systems may further provide multifunctional therapeutic platforms capable of achieving controlled release, improved bioavailability, and enhanced patient compliance. Emerging translational approaches may therefore revolutionize future antidepressant therapy.

IV. CONCLUSION

Advanced bilayer tablet systems and nanotechnology-based antidepressant delivery approaches represent highly promising strategies for overcoming the limitations associated with conventional antidepressant therapy. Emerging evidence supports the use of controlled-release formulations, brain-targeted nanocarriers, intranasal delivery systems, and melatonin-assisted chronotherapy for improving therapeutic efficacy and patient compliance.

Continued translational and clinical research will be essential for successful future implementation of these innovative pharmaceutical technologies in depression management.

REFERENCES

- [1]. Brzezinski, A. (2021) 'Melatonin in sleep disorders: updated review', *Sleep Medicine Reviews*, 55, pp. 101–108.
- [2]. Ismail, A. et al. (2022) 'Development of a novel bilosomal system for improved oral bioavailability of sertraline hydrochloride', *AAPS PharmSciTech*, 23, p. 188.
- [3]. Patel, R.B. et al. (2022) 'Comprehending the potential of metallic, lipid, and polymer-based nanocarriers for treatment and management of depression', *Neurochemical International*, 153, p. 105259.
- [4]. Yuan, S. et al. (2023) 'Novel drug delivery strategies for antidepressant active ingredients from medicinal plants', *Journal of Nanobiotechnology*, 21, p. 391.
- [5]. Fu, S. et al. (2024) 'ROS-targeted depression therapy via BSA-incubated ceria nanoclusters', *Nano Letters*, 22(11), pp. 4519–4527.
- [6]. Mohammed, H.S. et al. (2025) 'Assessment of the therapeutic potential of hesperidin and quercetin nanoparticles', *Neurochemical Research*.
- [7]. Qiang, L. and Huo, Y. (2025) 'Research progress of functionalized drug delivery nanosystems in regulating depression', *Pharmaceuticals*, 18(12), p. 1858.
- [8]. Zeng, J.W. et al. (2025) 'Investigating the mechanisms of Sini San via BDNF/TrkB/PI3K/AKT pathway', *Frontiers in Psychiatry*, 16, p. 1628634.
- [9]. Zhang, S.Q. et al. (2025) 'Costunolide normalizes neuroinflammation in depression', *Acta Pharmacologica Sinica*, 46, pp. 1864–1876.
- [10]. El-Dakrouy, W.A. et al. (2026) 'Evaluation of duloxetine-loaded nanoformulations for antidepressant activity', *International Journal of Nanomedicine*.
- [11]. Zhu, T.T. et al. (2026) 'Clinical innovations and future directions of nanoparticles in psychiatric disorders', *Molecular Psychiatry*.