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Nanotechnology-Based Bilayer Tablet Approaches for Antidepressant Drug Delivery in Depression Management

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ABSTRACT

Depression is a chronic neuropsychiatric disorder characterized by emotional instability, sadness, sleep disturbances, cognitive impairment, and loss of interest in daily activities. Conventional antidepressant therapies are associated with delayed onset of action, systemic adverse effects, poor patient compliance, low bioavailability, and inadequate blood–brain barrier penetration. Advanced pharmaceutical technologies including bilayer tablet systems and nanotechnology-based drug delivery approaches have emerged as promising strategies for improving antidepressant therapy. Bilayer tablets provide immediate and sustained drug release profiles within a single dosage form, thereby improving therapeutic efficacy and patient adherence. Nanotechnology-based systems including nanoparticles, nanoemulsions, lipid carriers, and intranasal formulations improve targeted brain delivery and reduce systemic toxicity. The present review discusses depression pathophysiology, antidepressant mechanisms, bilayer tablet technologies, tablet preparation methods, evaluation parameters, marketed antidepressant formulations, and recent advancements in nano-based antidepressant delivery systems. The review further highlights the future potential of advanced pharmaceutical approaches in depression management.

Keywords: Depression, Antidepressants, Bilayer Tablets, Nanotechnology, Brain Targeting, Controlled Release, Nano formulations

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INTRODUCTION

Depression is one of the most common psychiatric disorders worldwide and significantly contributes to disability, reduced quality of life, and socioeconomic burden. It is characterized by persistent sadness, emotional instability, insomnia, fatigue, anxiety, suicidal ideation, impaired concentration, and loss of interest in daily activities. According to the World Health Organization, depression affects millions of individuals globally and continues to increase due to stress, social isolation, chronic illnesses, and lifestyle imbalance. [4,9,22]

Depression may be classified into major depressive disorder, bipolar depression, postpartum depression, psychotic depression, and seasonal affective disorder. The exact pathophysiology of depression is highly complex and multifactorial. The monoamine hypothesis suggests that reduced levels of serotonin, dopamine, and norepinephrine contribute significantly to depressive symptoms. However, recent studies have demonstrated the involvement of neuroinflammation, oxidative stress, hypothalamic–pituitary–adrenal axis dysregulation, mitochondrial dysfunction, and impaired neuroplasticity in depression progression. [4,50]

Several inflammatory cytokines including TNF-α, IL-1β, and IL-6 are elevated in depressed patients and contribute to neuronal dysfunction. Oxidative stress damages neuronal membranes and disrupts neurotransmitter regulation. Brain regions such as the hippocampus, amygdala, and prefrontal cortex are significantly affected during depression. Reduced hippocampal neurogenesis and decreased brain-derived neurotrophic factor expression are strongly associated with cognitive dysfunction and mood disturbances. [15,24,50,77]

Despite the availability of several antidepressant therapies, treatment outcomes remain unsatisfactory in many patients because of delayed therapeutic onset, adverse effects, poor compliance, and treatment resistance. Therefore, advanced pharmaceutical approaches are required for improving antidepressant efficacy and patient compliance. [5,9,22]

Antidepressant Drugs

Antidepressant drugs are therapeutic agents used for the treatment of depression, anxiety disorders, panic disorders, obsessive-compulsive disorder, and mood-related psychiatric conditions. These drugs primarily function by modulating neurotransmitter concentrations within the central nervous system.[5,22]

Antidepressants are mainly classified into the following categories:

Table 1: Classification of antidepressants

Drug	Brand Name	Class	Dosage Form	Common Side Effects	Limitations	Drug
Fluoxetine	Prozac	SSRI	Capsule, Tablet	Insomnia, nausea, headache	Delayed onset of action	Fluoxetine
Sertraline	Zoloft	SSRI	Tablet	Diarrhea, dizziness, fatigue	Gastrointestinal side effects	Sertraline
Escitalopram	Lexapro	SSRI	Tablet	Sexual dysfunction, nausea	Withdrawal symptoms	Escitalopram
Venlafaxine	Effexor XR	SNRI	Extended-release capsule	Hypertension, insomnia	Dose-dependent toxicity	Venlafaxine
Duloxetine	Cymbalta	SNRI	Capsule	Dry mouth, constipation	Hepatic metabolism issues	Duloxetine
Amitriptyline	Elavil	TCA	Tablet	Sedation, cardiotoxicity	Poor tolerability	Amitriptyline

Selective serotonin reuptake inhibitors are among the most widely prescribed antidepressants because of improved safety profiles and reduced toxicity. However, SSRIs are still associated with insomnia, gastrointestinal disturbances, sexual dysfunction, and withdrawal symptoms. SNRIs are particularly effective in treatment-resistant depression and neuropathic pain conditions.[3,12,19]

Tricyclic antidepressants represent older therapeutic agents associated with cardiotoxicity and anticholinergic adverse effects. Monoamine oxidase inhibitors are effective but require dietary restrictions because of hypertensive crisis risk.[5,12,19]

Conventional antidepressant dosage forms exhibit several limitations including poor bioavailability, extensive first-pass metabolism, low brain-targeting efficiency, and fluctuating plasma drug concentrations. Advanced pharmaceutical technologies including bilayer tablet systems, controlled-release formulations, intranasal systems, and nanotechnology-based formulations are therefore being investigated for improving therapeutic outcomes.[5,20,40]

How Antidepressants Work

Antidepressants primarily function by increasing neurotransmitter concentrations within neuronal synapses. Serotonin, dopamine, and norepinephrine play important roles in emotional regulation, sleep, cognition, motivation, and mood stabilization.[5,50,54]

SSRIs inhibit serotonin transporter proteins, thereby increasing serotonin concentrations within synaptic clefts. SNRIs inhibit reuptake of both serotonin and norepinephrine. Tricyclic

antidepressants increase monoamine concentrations through reuptake inhibition but are associated with greater toxicity.

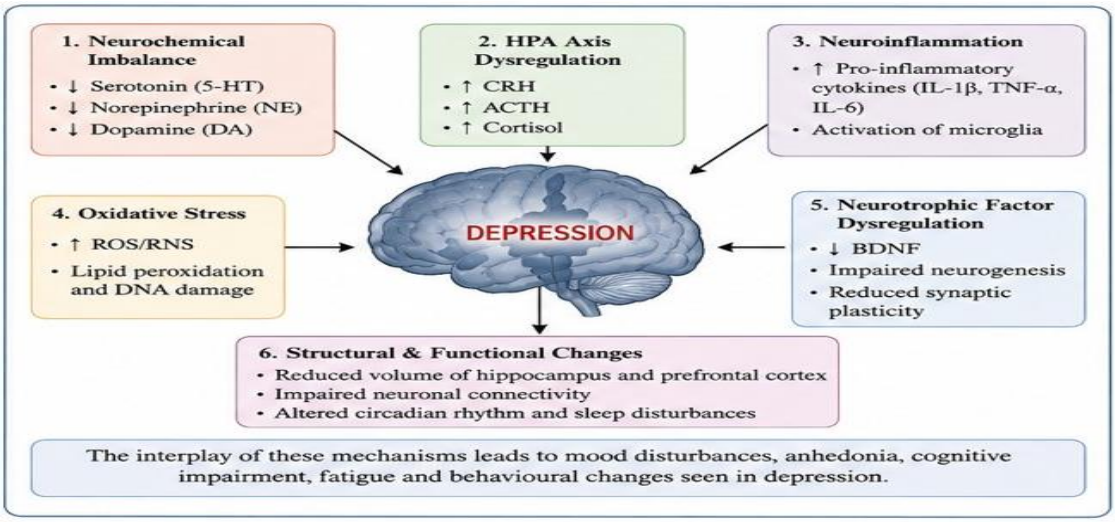

Figure 1: Pathophysiological mechanisms involved in depression

Recent studies have demonstrated that antidepressants also influence neuronal survival and neuroplasticity pathways. Brain-derived neurotrophic factor signalling plays a major role in antidepressant efficacy. Increased BDNF expression improves synaptic plasticity, neuronal regeneration, and hippocampal neurogenesis.[50,51,54]

Several molecular signalling pathways are involved in antidepressant activity:

- Akt/mTOR pathway
- BDNF/TrkB pathway
- NF-κB inflammatory pathway
- PI3K/AKT signalling
- TLR4 signalling pathway

The blood–brain barrier remains one of the major challenges associated with antidepressant delivery because many drugs exhibit limited brain penetration. Nanotechnology-based delivery systems including polymeric nanoparticles, lipid nanoparticles, nanoemulsions, and nanovesicles improve permeability and facilitate targeted brain delivery.

Intranasal nanoformulations have attracted considerable attention because they provide direct nose-to-brain delivery through olfactory pathways and bypass hepatic first-pass metabolism.[10,20,44,48]

Correlation With Research

Bilayer tablet systems are advanced pharmaceutical dosage forms capable of delivering two different release profiles within a single tablet. These systems are highly beneficial in chronic disorders requiring immediate and sustained therapeutic effects.[26,55,60]

In antidepressant therapy, bilayer tablets may combine immediate-release antidepressants with sustained-release layers for maintaining prolonged therapeutic drug concentrations. Immediate-release layers rapidly reduce depressive symptoms, whereas sustained-release layers maintain plasma drug concentrations for extended durations.[18,27,62]

Melatonin-assisted antidepressant therapy has recently gained considerable attention. Melatonin regulates circadian rhythm and improves sleep disturbances associated with depression. Combination bilayer tablets containing antidepressants and melatonin may therefore provide synergistic therapeutic effects.[1,21,30,70]

Nanotechnology integration within bilayer tablets significantly improves pharmaceutical performance including:

- Drug solubility
- Drug stability
- Controlled release
- Blood–brain barrier permeability
- Brain-targeting efficiency

Nanocarriers including lipid nanoparticles, polymeric nanoparticles, nanoemulsions, and solid lipid nanoparticles have demonstrated promising antidepressant applications. These systems reduce systemic toxicity and improve therapeutic concentration at target sites.[35,56,63]

The integration of bilayer tablet technology with nanotechnology-based drug delivery systems therefore represents a highly innovative and promising strategy for improving depression management.

TABLET PREPARATION

Bilayer tablets are generally prepared using direct compression, wet granulation, and double-compression techniques.

Direct Compression Method

This method involves blending active pharmaceutical ingredients with excipients followed by compression into tablet form. Direct compression is economical, simple, and suitable for moisture-sensitive drugs.

Wet Granulation Method

Wet granulation involves mixing powders with binding solutions to form granules. Granules are dried and compressed into tablets. This method improves powder flow properties and compressibility.

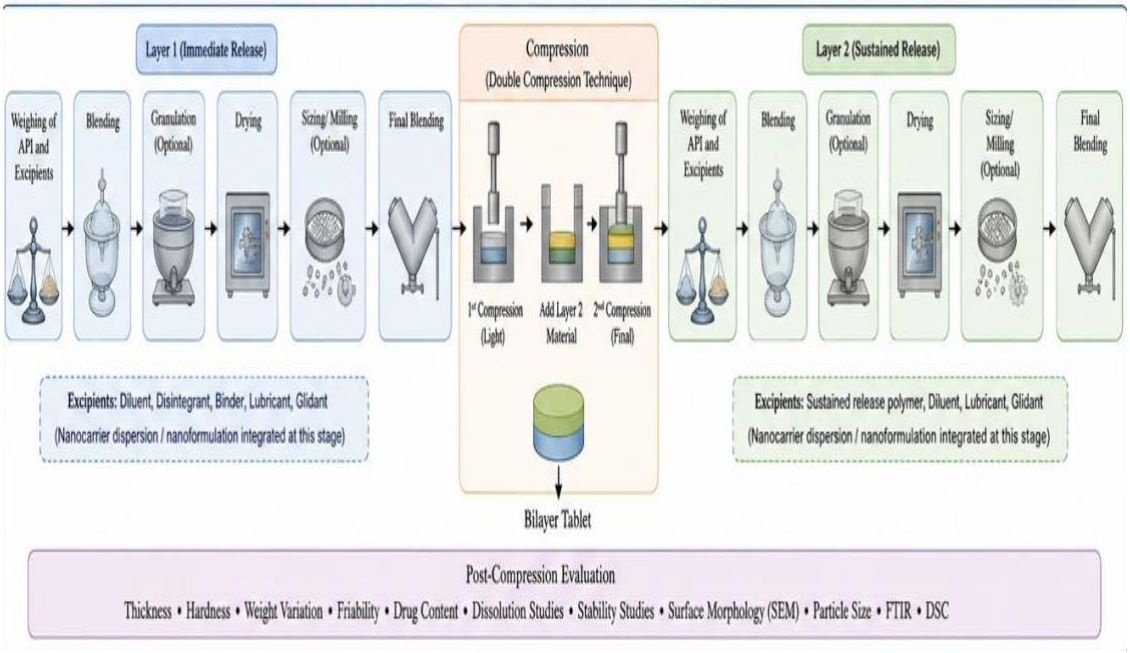

Figure 2: Bilayer tablet preparation method

Double Compression Technique

In this technique, the first layer is compressed lightly before adding the second layer. Final compression produces the bilayer tablet.

Excipients Used

Common excipients include:

- Hydroxypropyl methylcellulose
- Polyvinylpyrrolidone
- Lactose
- Magnesium stearate
- Sodium starch glycolate
- Microcrystalline cellulose

Nanoformulations Incorporation

Nanoformulations may be incorporated using:

- Nanoparticle dispersion
- Spray drying
- Solvent evaporation
- Lyophilization

- Nanoemulsions integration

Advantages of Bilayer Tablets

- Dual drug release profiles
- Improved patient compliance
- Reduced dosing frequency
- Better therapeutic efficacy
- Enhanced disease management

Evaluation of Tablet

Bilayer tablets are evaluated using several pharmaceutical parameters.

Table 2: Evaluation parameters

Parameter	Significance
Angle of repose	Flow property evaluation
Bulk density	Powder packing ability
Tapped density	Compressibility analysis
Carr's index	Flowability determination
Hausner ratio	Powder cohesion assessment

Post compression Parameters

Parameter	Purpose
Thickness	Uniformity evaluation
Hardness	Mechanical strength
Friability	Resistance to abrasion
Weight variation	Dose uniformity
Drug content	Drug distribution
Dissolution studies	Drug release analysis

Advanced Evaluation

Additional characterization techniques include:

- Scanning electron microscopy
- Particle size analysis
- Zeta potential analysis
- Fourier-transform infrared spectroscopy
- Differential scanning calorimetry
- Stability studies

Drug release kinetics are evaluated using:

- Zero-order kinetics
- First-order kinetics
- Higuchi model

- Korsmeyer–Peppas model

Currently Used Medicines.

Several antidepressant drugs are currently available for depression treatment.

Table 3: Marketed antidepressant formulations [3,5,12]

Drug	Class	Common Application
Fluoxetine	SSRI	Major depressive disorder
Sertraline	SSRI	Anxiety and depression
Escitalopram	SSRI	Mood disorders
Venlafaxine	SNRI	Resistant depression
Duloxetine	SNRI	Depression and neuropathic pain
Amitriptyline	TCA	Chronic depression
Agomelatine	Atypical antidepressant	Circadian rhythm disorders
Ketamine	NMDA antagonist	Treatment-resistant depression

Controlled-release and extended-release antidepressant formulations are increasingly being developed for improving patient compliance and therapeutic outcomes. [3,17,19]

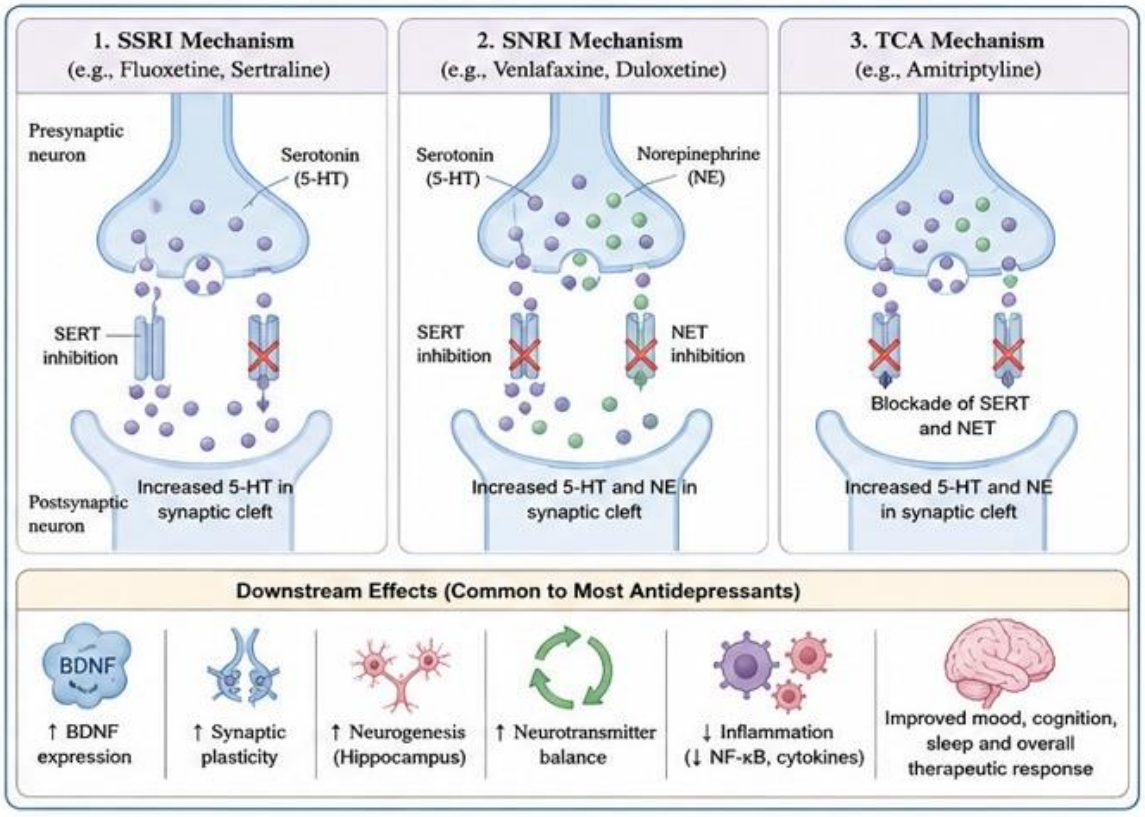

Figure 3: Mechanism of Anti-depressants conditions

Recent studies have demonstrated promising outcomes using: [53,56,57,67]

- Intranasal ketamine nanoformulations
- Duloxetine-loaded lipid nanoparticles
- Venlafaxine nanoemulsions

- Polymeric antidepressant nanoparticles
- Solid lipid nanoparticle systems

Nanotechnology-based delivery systems improve therapeutic efficacy and reduce systemic adverse effects. [44,45,68]

SUMMARY AND CONCLUSION

Depression remains one of the most challenging neuropsychiatric disorders worldwide. Conventional antidepressant therapies are associated with several limitations including delayed onset of action, systemic adverse effects, low bioavailability, poor patient compliance, and limited brain-targeting efficiency. [5,9,22]

Advanced pharmaceutical technologies including bilayer tablet systems and nanotechnology-based delivery approaches provide highly promising solutions for overcoming these limitations. Bilayer tablets improve therapeutic efficacy through immediate and sustained drug release profiles, whereas nanotechnology-based systems enhance blood–brain barrier penetration and targeted brain delivery. [26,43,55]

Recent research demonstrates that integration of nanotechnology with bilayer tablet approaches significantly improves antidepressant performance, stability, controlled release, and therapeutic reliability. Intranasal delivery systems, lipid nanoparticles, polymeric nanoparticles, and melatonin-assisted chronotherapeutic approaches may revolutionize future depression therapy. [53,56,70]

Continued translational and clinical investigations will be essential for successful future implementation of advanced antidepressant drug delivery technologies in clinical practice. [85,87,89]

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