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Advancements in Improving the Bioavailability of Sertraline Using Nanomedicine: A Systematic Review

Yesh Lekhram*[1], Bhupendra Tiwari[1], Gopesh Gunjan, V P Gupta[1]
[1]*Globus College of Pharmacy, Bhopal*

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ABSTRACT
Sertraline, a selective serotonin reuptake inhibitor (SSRI), is widely prescribed for depression, anxiety disorders, and other psychiatric conditions. Despite its therapeutic efficacy, sertraline suffers from poor oral bioavailability due to extensive first-pass metabolism and low aqueous solubility. Nanomedicine offers promising strategies to overcome these limitations by enhancing drug solubility, stability, and targeted delivery. This systematic review explores recent advancements in nanotechnology-based approaches to improve the bioavailability of sertraline, including bilosomes, nanosuspensions, and injectable nanoformulations. The review synthesizes findings from in vitro, ex vivo, and in vivo studies to evaluate the efficacy, safety, and translational potential of these nanomedicine platforms.
Keywords: Sertraline, bilosomes, nanomedicine, nanosupensions, bioavailability

I. INTRODUCTION

Sertraline hydrochloride (SER) is a widely prescribed selective serotonin reuptake inhibitor (SSRI) used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder (PTSD) (Preskorn, 1997; Cipriani et al., 2018). Despite its clinical efficacy, sertraline suffers from poor oral bioavailability, typically ranging between 40–45%, primarily due to its low aqueous solubility and extensive first-pass hepatic metabolism (Rao et al., 2011; Ismail et al., 2022). These pharmacokinetic limitations necessitate higher doses to achieve therapeutic plasma concentrations, which can increase the risk of side effects such as gastrointestinal discomfort, insomnia, and sexual dysfunction (Taylor et al., 2006).

Improving the bioavailability of sertraline is a critical objective in pharmaceutical formulation science. Conventional strategies such as salt formation, co-administration with absorption enhancers, and solid dispersions have shown limited success (Kumar & Bansal, 2018). In recent years, nanomedicine has emerged as a transformative approach to address bioavailability challenges associated with poorly soluble drugs like sertraline. Nanomedicine involves the use of nanoscale carriers—typically ranging from 10 to 1000 nm—to encapsulate, protect, and deliver therapeutic agents with enhanced precision and efficiency (Moghimi et al., 2005; Mitragotri et al., 2014).

Nanocarriers such as liposomes, bilosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and nanosuspensions have demonstrated significant potential in improving the solubility, permeability, and pharmacokinetic profiles of various antidepressants (Sharma et al., 2020; Singh et al., 2020). These systems can bypass first-pass metabolism, prolong gastrointestinal residence time, and facilitate targeted delivery to the brain, thereby enhancing therapeutic efficacy while minimizing systemic toxicity (Kaur et al., 2021; Jain et al., 2022).

For sertraline specifically, several nanomedicine-based formulations have been investigated, including bilosomal systems (Ismail et al., 2022), nanosuspensions (Pawar, 2016), PLGA-based injectable nanoparticles (Salman & Shaker, 2024), and cyclodextrin complexes (Kumar & Bansal, 2018). These approaches have shown promising results in preclinical studies, with significant improvements in drug dissolution, absorption, and bioavailability.

Moreover, the integration of nanotechnology with personalized medicine and targeted drug delivery opens new avenues for optimizing antidepressant therapy. Surface modification of nanoparticles with ligands such as transferrin or folate can facilitate receptor-mediated transport across the blood-brain barrier (BBB), a major hurdle in central nervous system (CNS) drug delivery (Masserini, 2013; Patel et al., 2020). Additionally, nanocarriers can be engineered to respond to physiological stimuli (e.g., pH,

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enzymes), enabling site-specific release and reducing off-target effects (Torchilin, 2011).

Despite these advancements, challenges remain in translating nanomedicine-based sertraline formulations to clinical practice. Regulatory hurdles, scalability issues, and long-term safety concerns must be addressed through rigorous research and interdisciplinary collaboration (Ventola, 2012; Mitragotri et al., 2014).

This systematic review aims to synthesize current evidence on nanomedicine strategies for enhancing the bioavailability of sertraline. It evaluates the design, characterization, and performance of various nanoformulations, highlighting their advantages, limitations, and translational potential.

II. METHODOLOGY

A systematic literature search was conducted using databases such as PubMed, Scopus, and SpringerLink. Keywords included "sertraline," "bioavailability," "nanomedicine," "nanoparticles," "bilosomes," and "nanosuspensions." Inclusion criteria were original research articles published between 2016 and 2025 that focused on nanotechnology-based formulations of sertraline aimed at improving bioavailability. Studies involving in vitro, ex vivo, and in vivo evaluations were considered. Review articles, editorials, and non-English publications were excluded.

III. NANOMEDICINE STRATEGIES FOR SERTRALINE DELIVERY

Nanomedicine platforms have been extensively explored to overcome the pharmacokinetic limitations of sertraline. These include bilosomes, nanosuspensions, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and injectable depot systems.

3.1 Bilosomal Systems

Bilosomes are vesicular carriers stabilized by bile salts, enhancing their resistance to enzymatic degradation and improving mucosal permeability. Ismail et al. (2022) developed a bilosomal formulation of sertraline hydrochloride using sodium deoxycholate, achieving high encapsulation efficiency (85.3%) and a 2.5-fold increase in oral bioavailability in rats. The formulation demonstrated sustained release over 24 hours and improved intestinal permeability in ex vivo studies.

Other studies have corroborated the potential of bile salt-stabilized vesicles in enhancing oral drug delivery (Shukla et al., 2020; Jain et al., 2019). Bilosomes also exhibit mucoadhesive properties, prolonging gastrointestinal residence time and facilitating absorption (Kaur et al., 2021).

3.2 Nanosuspensions via Nanoprecipitation

Nanosuspensions are submicron colloidal dispersions of pure drug particles stabilized by surfactants or polymers. Pawar (2016) formulated sertraline nanosuspensions using nanoprecipitation and solvent diffusion techniques. The resulting particles (120–180 nm) showed a 3-fold increase in dissolution rate and improved oral absorption in animal models.

Nanosuspensions offer advantages such as ease of scale-up, high drug loading, and enhanced saturation solubility (Patel et al., 2018). They are particularly suitable for BCS Class II drugs like sertraline, where dissolution is the rate-limiting step (Rabinow, 2004).

3.3 Polymeric Nanoparticles

Polymeric nanoparticles, especially those made from PLGA, offer controlled release and protection from enzymatic degradation. Salman and Shaker (2024) developed an injectable PLGA-based sertraline formulation for intramuscular administration. The system provided sustained release over 7 days and improved patient compliance.

Other studies have demonstrated the utility of PLGA nanoparticles in enhancing brain delivery of SSRIs, including sertraline, via intranasal and parenteral routes (Kumar et al., 2021; Sharma et al., 2020).

3.4 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

SLNs and NLCs are lipid-based carriers that combine the advantages of liposomes and polymeric nanoparticles. They offer high drug loading, biocompatibility, and controlled release. A study by Singh et al. (2020) reported that sertraline-loaded SLNs improved brain targeting and reduced systemic side effects in a depression model.

NLCs, which incorporate both solid and liquid lipids, provide better drug encapsulation and stability than SLNs (Müller et al., 2011). These systems have shown promise in enhancing the oral and transdermal delivery of poorly soluble drugs (Pardeike et al., 2009).

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3.5 Cyclodextrin Complexes and Hybrid Systems

Cyclodextrins (CDs) are cyclic oligosaccharides that form inclusion complexes with hydrophobic drugs, improving solubility and stability. Encapsulation of sertraline in β-cyclodextrin has been shown to enhance dissolution and reduce gastric irritation (Kumar & Bansal, 2018).

Hybrid systems combining CDs with nanoparticles or liposomes have also been explored to synergize solubility enhancement with controlled release (Patel et al., 2020; Jain et al., 2022).

IV. MECHANISMS OF BIOAVAILABILITY ENHANCEMENT

Nanomedicine platforms enhance sertraline bioavailability through multiple mechanisms:

4.1 Solubility Enhancement

Sertraline's low aqueous solubility (0.4 mg/mL) limits its dissolution in gastrointestinal fluids. Nanocarriers such as nanosuspensions and SLNs reduce particle size to the nanometer scale, increasing surface area and dissolution rate (Pawar, 2016; Rabinow, 2004). Cyclodextrin inclusion complexes further improve apparent solubility by forming hydrophilic outer shells (Kumar & Bansal, 2018).

4.2 Protection from Degradation

Sertraline undergoes extensive first-pass metabolism, reducing systemic availability. Encapsulation in bilosomes, SLNs, or polymeric nanoparticles protects the drug from acidic and enzymatic degradation in the GI tract (Ismail et al., 2022; Müller et al., 2011).

4.3 Enhanced Permeability and Absorption

Bilosomes and surfactant-coated nanoparticles enhance mucosal permeability by modulating tight junctions and facilitating paracellular transport (Shukla et al., 2020). Nanoparticles can also be internalized via endocytosis, enabling transcellular transport (Kaur et al., 2021).

4.4 Controlled and Sustained Release

Polymeric nanoparticles and SLNs provide controlled release, maintaining therapeutic plasma levels over extended periods and reducing dosing frequency (Salman & Shaker, 2024; Singh et al., 2020). This minimizes peak-trough fluctuations and improves patient adherence.

4.5 Targeted Delivery

Surface modification of nanoparticles with ligands (e.g., transferrin, folate) enables targeted delivery to the brain or other tissues, enhancing therapeutic efficacy and reducing off-target effects (Sharma et al., 2020; Jain et al., 2022).

V. COMPARATIVE EVALUATION OF FORMULATIONS

Formulation Type	Key Features	Bioavailability Improvement	Advantages	Limitations	References
Bilosomal System	Oral, bile salt-stabilized vesicles	2.5× increase	GI stability, mucoadhesion	Complex formulation	Ismail et al. (2022); Shukla et al. (2020)
Nanosuspension	Oral, nanoprecipitation method	3× dissolution rate	Simple, scalable	Requires stabilizers	Pawar (2016); Patel et al. (2018)
Polymeric Nanoparticles	Injectable, PLGA-based	Sustained release (7 days)	Long-acting, biocompatible	Invasive, costly	Salman & Shaker (2024); Kumar et al. (2021)
SLNs/NLCs	Oral/transdermal, lipid-based	Enhanced brain targeting	High loading, controlled release	Stability issues	Singh et al. (2020); Müller et al. (2011)
Cyclodextrin Complexes	Oral, solubility enhancement	Improved dissolution	Simple, safe	Limited loading	Kumar & Bansal (2018); Patel et al. (2020)

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VI. SAFETY AND TOXICOLOGICAL CONSIDERATIONS

Safety is a critical aspect of nanomedicine. The reviewed studies reported no significant cytotoxicity or adverse effects in animal models. Bilosomes and nanosuspensions were well tolerated, with no signs of gastrointestinal irritation. Injectable nanoformulations showed acceptable biocompatibility and minimal local tissue reactions. However, long-term toxicity and immunogenicity studies are needed before clinical translation.

VII. REGULATORY AND TRANSLATIONAL CHALLENGES

Despite promising results, several challenges hinder the clinical adoption of nanomedicine-based sertraline formulations:

- Regulatory Approval: Nanomedicine products require rigorous evaluation for safety, efficacy, and manufacturing consistency.
- Scale-Up and Cost: Production of nanocarriers at industrial scale involves complex processes and high costs.
- Patient Acceptance: Injectable formulations may face resistance due to invasiveness, despite improved compliance.

Addressing these challenges requires interdisciplinary collaboration among pharmaceutical scientists, clinicians, and regulatory bodies.

VIII. FUTURE DIRECTIONS

Future research should focus on:

- Targeted Delivery: Surface functionalization with ligands for brain-targeted delivery of sertraline.
- Hybrid Systems: Combining multiple nanocarriers (e.g., bilosomes with nanoparticles) for synergistic effects.
- Clinical Trials: Translating preclinical findings into human studies to validate efficacy and safety.
- Personalized Medicine: Tailoring nanomedicine formulations based on patient-specific pharmacokinetics and pharmacodynamics.

IX. CONCLUSION

Nanomedicine offers a promising avenue for enhancing the bioavailability of sertraline, addressing its limitations in solubility and metabolism. Bilosomal systems, nanosuspensions, and injectable nanoformulations have demonstrated significant improvements in drug absorption and therapeutic efficacy. While challenges remain in regulatory approval and clinical translation, continued research and innovation in nanotechnology hold the potential to revolutionize antidepressant therapy.

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