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A comprehensive review on chiral insights and technological breakthroughs in fluoxetine isomer separation using capillary electrophoresis

Abstract

Fluoxetine, a widely prescribed chiral selective serotonin reuptake inhibitor, exists as two enantiomers—S-fluoxetine and R-fluoxetine—that exhibit distinct pharmacological activities. Effective separation of these enantiomers is essential to ensure therapeutic efficacy while minimizing adverse effects. This review critically examines recent advancements in fluoxetine enantioseparation using capillary electrophoresis (CE), with particular emphasis on chiral selector applications, buffer system optimization, and electrophoretic condition modifications that enhance resolution. We highlight the utilization of cyclodextrins, proteins, and ionic liquids as chiral selectors, evaluating their respective mechanisms and performance characteristics. CE offers significant advantages over conventional chromatographic techniques, including superior separation efficiency, rapid analysis times, and minimal sample volume requirements—benefits particularly valuable for analyzing fluoxetine in complex biological and pharmaceutical matrices. This comprehensive synthesis of current methodologies addresses existing knowledge gaps, provides mechanistic insights into chiral recognition, and identifies promising directions for future development, ultimately supporting safer and more effective therapeutic applications of fluoxetine.

Keywords: fluoxetine, enantiomer separation, capillary electrophoresis, chiral selectors, pharmaceutical analysis

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Introduction

Chirality fundamentally governs biological activity in pharmaceutical research, with enantiomers often exhibiting markedly different pharmacokinetic, pharmacodynamic, efficacy, and toxicological profiles. Consequently, chiral identification and separation constitute essential components of drug development and quality control. Among chiral pharmaceuticals, fluoxetine (marketed as Prozac) has garnered substantial attention due to its enantioselective pharmacological properties. As a selective serotonin reuptake inhibitor (SSRI), fluoxetine is prescribed for various anxiety and depressive disorders. Its two enantiomers demonstrate differential affinities toward serotonin transporters and off-target receptors, necessitating accurate separation for both medicinal and analytical applications.[1,2]

Capillary electrophoresis (CE) has emerged as a powerful technology for chiral separations, offering high efficiency, minimal sample requirements, and remarkable versatility in optimizing separation conditions. CE represents a green analytical chemistry approach, being faster and requiring substantially less solvent than conventional chromatographic methods.[3] The technique's inherent flexibility enables incorporation of diverse chiral selectors—including cyclodextrins, polysaccharides, and crown ethers—thereby extending its enantiomeric separation capabilities.[4]

Numerous studies have investigated fluoxetine enantiomer separation using CE, consistently identifying chiral selector choice and operating conditions as critical determinants of resolution. Recent innovations, including ionic liquids, sulfated cyclodextrins, and novel dual systems, have demonstrated considerable promise in enhancing enantioselectivity and resolution.[5,6] Nevertheless, comprehensive reviews that comparatively assess these diverse methodological advances remain scarce. This review addresses this gap through an in-depth examination of state-of-the-art CE methods for fluoxetine enantioseparation.

The distinctiveness of this review lies in its focus on synergistic effects between novel chiral selectors and advanced CE techniques that have markedly improved resolution and sensitivity. By critically evaluating and synthesizing recent work, we provide significant insights into chiral recognition mechanisms operating in CE and identify emerging trends that may guide future developments.[7,8] Furthermore, we emphasize optimization of operational parameters—buffer composition, pH, applied voltage, and temperature—that are crucial for both separation efficiency and reproducibility.

The benefits of effective fluoxetine isomer separation extend beyond analytical chemistry to pharmacology and clinical applications. Improved chiral analysis can facilitate development of enantiomerically pure formulations, potentially reducing side effects and enhancing therapeutic outcomes. Additionally, implementing CE in routine quality control can streamline regulatory compliance and accelerate drug approval processes.

This review aims to present a comprehensive overview of progress and prospects in CE-based fluoxetine enantioseparation. By integrating theoretical knowledge with practical considerations and future developments, we strive to create a valuable resource for researchers, pharmaceutical scientists, and regulatory bodies. Consolidating information in this field not only highlights current challenges but also inspires novel approaches to maximize the efficacy and relevance of chiral separations in pharmaceutical analysis.

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Fundamentals of fluoxetine chirality and pharmacology

Structure and stereochemistry of fluoxetine

Fluoxetine belongs to the SSRI class of antidepressants and contains a single chiral center at the α-carbon adjacent to the amine group, giving rise to two enantiomeric forms: (S)-fluoxetine and (R)-fluoxetine.[9,10] The (S)-enantiomer is generally considered more biologically active,[10] although the racemic mixture (1:1 combination of both enantiomers) is typically used clinically. These enantiomers are non-superimposable mirror images that interact differently with biological targets, including serotonin transporters (SERT), due to the chiral environment of receptor binding sites (Figure 1).[11]

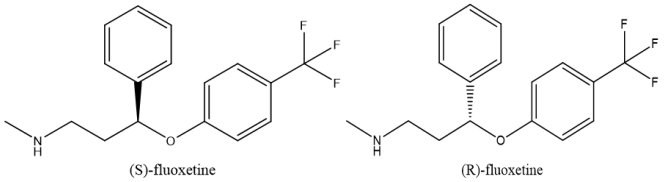

Figure 1 Chemical structures of fluoxetine enantiomers.

Because of the chiral environment of the receptor binding sites, the (S)-enantiomer and (R)-enantiomer interact differently with biological targets, including serotonin transporters (SERT), and are not superimposable mirror images.[11]

Pharmacological properties of fluoxetine enantiomers

Enantiomeric differences in fluoxetine's pharmacological activity critically influence its therapeutic efficacy and adverse effect profile. The (S)-enantiomer demonstrates significantly higher affinity for SERT, resulting in more potent serotonin reuptake inhibition and enhanced serotonergic neurotransmission. Conversely, the (R)-enantiomer exhibits weaker SERT inhibition and, while it may interact with other receptor systems, contributes minimally to overall pharmacodynamic effects.[12]

Fluoxetine enantiomers undergo differential metabolism, affecting their half-lives and systemic exposure. The primary metabolite, norfluoxetine, retains pharmacological activity, further complicating stereoselective effects. Although complete elucidation of these differences requires additional research, enantiomer-specific side effect profiles—including gastrointestinal discomfort and insomnia—have been reported.

Understanding the unique pharmacological properties of each enantiomer is indispensable for developing more targeted and effective antidepressant therapies. Single-enantiomer formulations may offer advantages when one enantiomer demonstrates superior efficacy with reduced side effects (Table 1).

Table 1 Pharmacological properties of fluoxetine

Sl. No	Pharmacological effect	Description	Research references
1	Serotonin Reuptake Inhibition	Fluoxetine selectively inhibits serotonin (5-HT) reuptake at the synapse, increasing extracellular serotonin levels and enhancing serotonergic neurotransmission.	Ampuero et al.[13]
2	Interaction with Serotonin Receptors	Fluoxetine acts as an agonist at some serotonin receptors (5-HT1A, 5-HT2A) and antagonist at others (5-HT2C), modulating diverse serotonergic signaling pathways.	Ampuero et al.[13]
3	Neuroplasticity and BDNF Modulation	Chronic fluoxetine administration promotes neurotrophic factors such as BDNF and downstream signaling proteins, facilitating neuronal growth, survival, and synaptic plasticity.	Ampuero et al.[13]
4	Cognitive Effects	Fluoxetine influences cognitive domains including memory, attention, and executive function, with effects dependent on treatment duration and brain region.	Ampuero et al.[13]
5	Immunomodulatory Effects	Fluoxetine modulates immune function via serotonin-dependent and independent pathways, including enhancing antitumor T-cell activity and reducing inflammation.	Di Rosso et al.,[14] Ampuero et al.[13]
6	Therapeutic Effects on Mental Disorders	Effective for major depressive disorder, anxiety, OCD, bulimia nervosa, and premenstrual dysphoric disorder with fewer discontinuations due to adverse effects versus TCAs.	Ampuero et al.[13]
7	Anti-inflammatory Effects	Fluoxetine exhibits anti-inflammatory properties in both central nervous system and peripheral tissues, potentially contributing to its efficacy in depression and other disorders.	Ampuero et al.[13]
8	Side Effect Profile	Common side effects include sexual dysfunction, headache, nausea, insomnia, and mild gastrointestinal symptoms; generally well tolerated with lower dropout rates.	Rossi et al.[15]

Current analytical methods for fluoxetine enantiomer separation

Various analytical methods have been employed for fluoxetine enantiomer separation and quantification, including capillary electrophoresis (CE), gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography (HPLC) with chiral stationary phases. Although HPLC remains widely used, CE offers distinct advantages for chiral separations in pharmaceutical analysis, including enhanced resolution, faster analysis times, and reduced sample volume requirements (Sweed et al., 2015). This review focuses on CE-based techniques developed and optimized for fluoxetine isomer separation.

Capillary electrophoresis method for fluoxetine enantiomer separation

Direct chiral separation using chiral selector

Cyclodextrins as chiral selectors

Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucopyranose units linked by α-1,4-glycosidic bonds, forming a toroidal structure with a hydrophilic exterior and hydrophobic cavity. Discovered by Villers in 1891 and characterized by Cramer in 1949,[17] CDs have become versatile chiral selectors applicable across numerous separation techniques, particularly CE. Native CDs—α-CD (six units), β-CD (seven units), and γ-CD (eight units)—are most commonly employed due to their differing cavity sizes, enabling inclusion complex formation with diverse analytes.[17]

CDs form transient diastereomeric species with enantiomers through stereoselective interactions, making them exceptionally useful chiral selectors in CE. This property is particularly important for enantioseparation of fluoxetine and related SSRIs such as duloxetine and atomoxetine, whose respective enantiomers exhibit different pharmacological activities.[17,18] Fluoxetine's therapeutic efficacy derives primarily from its S-enantiomer, while the R-enantiomer displays distinct pharmacokinetic properties, underscoring the clinical importance of precise enantiomeric discrimination.[19]

The adaptability and environmental compatibility of CDs further enhance their utility as chiral selectors in CE. Their near-universal applicability stems from CE's superior separation efficiency, which compensates for generally modest thermodynamic selectivity.[20] Derivatized CDs—including sulfated-β-CD and hydroxypropyl-β-CD—modify physicochemical properties to enhance binding affinities and enable resolution of structurally similar molecules.[21,22]

Mechanistic understanding of CD-analyte interactions has been advanced through spectroscopic techniques, particularly NMR combined with molecular modeling. These approaches have identified key variables influencing inclusion complexation, including analyte size, polarity, and functional groups.[23,24] Molecular modeling studies have demonstrated that fluoxetine forms complexes with β-CD derivatives stabilized by hydrogen bonds and van der Waals interactions.[24]

CE enables significant enhancements in fluoxetine enantiomer resolution through flexible optimization of operational parameters such as buffer composition, pH, and temperature. Dual systems combining CDs with other chiral selectors have also been explored to increase enantioselectivity for complex mixtures.[25,26] CDs thus constitute essential tools for fluoxetine enantioseparation and related pharmaceutical analyses, supporting advances in both pharmacological research and quality control. Future applications will benefit from continued integration of computational modeling with experimental techniques.[27,28]

Proteins as chiral selectors

Proteins serve as highly effective chiral selectors in CE due to their complex three-dimensional structures and inherent chirality. These biomacromolecules resolve numerous drug enantiomers with exceptional efficiency and selectivity through multiple interaction types, including hydrogen bonding, electrostatic interactions, hydrophobic contacts, and steric effects.[29]

CE-compatible proteins include serum albumins (human serum albumin, HSA; bovine serum albumin, BSA), glycoproteins (α1-acid glycoprotein, AGP), enzymes (pepsin, cellulase, lysozyme), and other proteins (ovotransferrin, casein).[30–32] These proteins interact with enantiomers through diverse mechanisms—hydrogen bonding, hydrophobic contacts, electrostatic interactions, and steric hindrance—enhancing their chiral discrimination capabilities.[33,34] The flexibility of protein-based selectors, whether adsorbed or immobilized in capillaries, allows customization based on drug type and desired resolution.

HSA has been successfully employed for resolving fluoxetine and structurally related SSRIs. Notably, the (R)-enantiomer exhibits approximately fourfold greater reuptake inhibition activity compared to the (S)-enantiomer. Resolution factors influencing enantiomer separation include ionic strength, presence of modifiers or displacers, and running buffer pH. Increased retention factors (k-values) generally correspond to improved resolution, as these factors directly impact chiral selector-analyte complexation. HSA effectively discriminates between tryptophan, warfarin, and various drug enantiomers, promoting resolution of fluoxetine enantiomers and providing valuable insights into protein-enantiomer dynamics.[35–37]

HSA has been documented as a robust chiral selector for SSRI enantioseparation, including fluoxetine and citalopram.[38,39] Similarly, BSA and AGP demonstrate high enantioselectivity toward fluoxetine through enantioselective complexation that modulates migration times in CE. Protein immobilization on capillary surfaces further enhances efficiency and reproducibility.[25,40,41]

Future improvements will enhance protein-based CE for chiral drug separation. Hybrid chiral selectors combining proteins with cyclodextrins, ionic liquids, or molecularly imprinted polymers represent promising approaches for enhancing enantioselectivity and expanding applicable compound ranges.[42,43] Capillary coating modifications—including nanomaterials such as graphene, gold nanoparticles, and polymer thin films—will improve immobilized protein stability and robustness, ensuring better reproducibility in CE processes. Automated and high-throughput CE systems will facilitate rapid screening of pharmacological libraries, reducing time and costs in drug development.[44,45]

Indirect chiral separation

Indirect chiral resolution involves derivatization to convert enantiomers into diastereomers, which can then be resolved using conventional achiral column techniques. Chiral derivatizing agents react with enantiomers to form diastereomeric derivatives possessing different physicochemical properties. Indirect CE methodologies for fluoxetine enantiomer resolution are less extensively documented compared to direct approaches using cyclodextrins, proteins, and other chiral selectors (discussed in preceding sections). This likely reflects the availability and efficacy of direct chiral selectors for fluoxetine.

Derivatization with reagents such as chiral anhydrides and Marfey's reagent has been employed for indirect chiral resolution of fluoxetine, enabling effective enantiomer differentiation in both HPLC and GC analyses. These techniques improve detectability by eliminating the need for chiral stationary phases and simplifying chromatographic conditions.[46,47] However, indirect methodologies introduce additional preparation steps and potential secondary reactions that may impact accuracy and reproducibility.

For fluoxetine, careful selection of chiral derivatizing agents is essential to ensure complete and stereospecific derivatization, followed by optimization of diastereomer resolution. Although comprehensive publications specifically addressing indirect CE of fluoxetine are limited, general principles of indirect chiral CE resolution can be

extrapolated when necessary. Emerging CD derivatives may provide alternative approaches when direct chiral selectors present limitations.

Enhanced separation techniques and method development

Use of ionic liquids

Ionic liquids (ILs)—designer solvents maintaining liquid state at or below 100°C—exhibit unique properties including negligible vapor pressure and high polarity.[48–50] Their non-volatile nature renders them relatively less hazardous with minimal environmental pollution, positioning them as potential "green solvents" for various applications, including CE.[51–53] Over 50% of commercially available pharmaceuticals exist as ILs, often combining pharmaceutically active cations with inactive anions.[54]

In CE, ILs serve multiple functions: additives to background electrolytes (BGEs), modifiers of inner capillary surfaces, and pseudo-stationary phases. ILs facilitate interactions between analytes and chiral selectors while modifying electroosmotic flow (EOF). Through diverse interactions—π-π interactions, hydrogen bonding, dipole-induced dipole interactions, van der Waals forces, and hydrophobic interactions—ILs significantly enhance analyte separation.[55,56] Selection criteria include IL type and concentration, BGE pH, and capillary wall composition. Chiral recognition depends on interaction degrees among ILs, CDs, and enantiomers. ILs alter running buffer ionic strength, affecting racemate efficiency and EOF. IL ion adsorption on capillary inner surfaces modifies EOF, enabling separation. Formation of inclusion complexes between ILs and CDs with racemates constitutes the key chiral recognition process. Additionally, chiral IL adsorption in BGE may reduce peak tailing for basic racemates such as fluoxetine.[57,58]

Studies on fluoxetine analogs indicate that alkyl substituents on the amine moiety minimally affect chiral recognition. However, carboxyl group addition on the amine moiety alters separation behavior depending on CD type and pH. This functional group significantly influences chiral recognition mechanisms, potentially forming hydrogen bonds and carrying negative charge at pH >5, particularly when charged CDs are employed.[59,60] Carboxyl group-containing ILs may potentially enhance fluoxetine isomer separation in CE, warranting further investigation.

Optimal conditions for simultaneous resolution of fluoxetine hydrochloride, its meta-isomer, and analogs in non-aqueous CE include 25 mM ammonium acetate with 1 M acetic acid in acetonitrile-containing buffer electrolyte, applied voltage of 30 kV, and temperature of 20°C. Acetate-to-formate ion substitution in BGE induces migration time shifts, potentially through ion-pairing processes. Online coupling with electrospray ionization-mass spectrometry (ESI-MS) has achieved successful analysis with significant improvements in selectivity and sensitivity.[61]

ILs are also being investigated with nanoparticles for enantiomer resolution. Chiral ILs such as 1-ethyl-3-methylimidazole L-tartrate (EMIML-Tar) and 1-ethyl-3-methylimidazole L-lactate (EMIML-Lac) have been utilized for gold nanoparticle (AuNP) modification in CE-based amino acid enantiomer resolution.[62] Similarly, chiral amino acid ILs supported on magnetite nanospheres have demonstrated satisfactory chiral recognition efficiency for amino acid enantiomers. Continued research combining ILs with nanotechnology holds significant potential for enhanced enantioselectivity. Given increasing IL diversity, structural variety, and favorable physicochemical properties, monitoring IL trends in CE remains essential.[63]

MS studies continue investigating intermolecular interactions between selectors and analytes in detail. Studies on fluoxetine analogs with various substituents continue elucidating chemical structure-dependent chiral recognition mechanisms. CE-MS integration with appropriate ILs can potentially deliver high-performance chiral separations.

Optimization strategies

Method development techniques have significantly improved fluoxetine enantiomer resolution, efficiency, and analysis time. Approaches including factorial design, response surface methodology (RSM), and computer-guided optimization enable systematic investigation of factors such as buffer composition, pH, voltage, and chiral selector concentration to maximize resolution while minimizing analysis time.[64,65]

Novel CE approaches

Isolation of fluoxetine has been increased even more through new trends in techniques in CE. Some of the notable breakthroughs include:

Microfluidic CE: Microfluidic CE reduces reagent consumption and analysis times immensely and maximizes efficiency in separation.[64]

Capillary electrophoresis-mass spectrometry: CE-MS, is a effective tool for use in both pharmacokinetics and in forensic analysis with its increased sensitivity and selectivity when in combination with MS.[66]

Dual-Cyclodextrin Systems: With its numerous contact points for providing fluoxetine enantiomers, dual chiral selector use in CE permits enantioseparation.

Comparison of different CE methods

Comparative analysis of CE methodologies reveals considerable variation in resolution, analysis time, sensitivity, and applicability. Table 2 summarizes performance characteristics of various CE methods for fluoxetine enantiomer resolution.

Table 2 Comparative analysis of CE methods for fluoxetine enantiomer separation

CE method	Resolution	Analysis time	Sensitivity	Applicability
Conventional CE	Moderate	Fast	Moderate	Routine Analysis
Microfluidic CE	High	Very Fast	High	Miniaturized systems
CE-MS	Very High	Moderate	Very High	Pharmacokinetics & Forensics
Dual-CD CE	Excellent	Moderate	High	Complex mixtures

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CE methodologies continue to be optimized through technological advances, providing efficient and effective analytical tools for pharmaceutical studies and quality assurance.

Advantages of removing stereoisomers from Fluoxetine

Pharmacological effects

Pharmacological advantages

Eliminating stereoisomers to use single-enantiomer fluoxetine formulations provides notable pharmacological benefits. Pure stereoisomer versions demonstrate improved receptor selectivity and stronger binding affinity, particularly at serotonin reuptake transporters and associated receptor subtypes. This enhanced targeting leads to improved drug effectiveness, enabling stronger and more precise antidepressant outcomes. Pharmacokinetic profiles of pure enantiomers are generally more predictable, featuring consistent absorption, distribution, metabolism, and elimination (ADME) patterns that minimize inter-individual variability observed with racemic mixtures. Certain stereoisomers may differentially influence secondary neurotransmitter systems, including dopamine and norepinephrine, potentially expanding antidepressant effects beyond serotonin reuptake inhibition. These improvements lead to increased efficacy and enhanced understanding of monoamine modulation mechanisms (Table 3).[37,41]

Table 3 Pharmacological advantages of single-enantiomer fluoxetine

Advantage	Description	References
Enhanced Receptor Selectivity and Efficacy	Pure enantiomers bind more selectively to serotonin transporters and receptors, increasing antidepressant potency.	Vashistha et al.,[66] Robertson et al.[37]
Predictable Pharmacokinetics	Single stereoisomers have consistent absorption, metabolism, and elimination, reducing variability.	Vashistha et al.,[67] Cârcu-Dobrin et al.,[41] Henry et al.[68]
Differential Neurotransmitter Modulation	Specific enantiomers may better modulate dopamine and norepinephrine pathways, enhancing therapeutic scope.	Koch,[16] Robertson et al.[37]

Clinical advantages

From a clinical perspective, stereoisomer removal reduces adverse side effect burden commonly associated with racemates. Certain stereoisomers contribute more to undesirable effects including sexual dysfunction, gastrointestinal symptoms, or cardiotoxicity, which are less pronounced or absent in pure enantiomer formulations. Single stereoisomers enable lower therapeutic doses due to increased potency, improving patient compliance and minimizing systemic drug exposure. Furthermore, purified enantiomers decrease drug-drug interaction potential by eliminating stereoisomers that interfere with cytochrome P450 enzymes, enhancing safety in polypharmacy contexts. These clinical benefits result in a more favorable risk-benefit ratio and widened therapeutic window for patient populations (Table 4).[41,67,68]

Table 4 Clinical advantages of single-enantiomer fluoxetine

Advantage	Description	References
Reduced Side Effects	Eliminates stereoisomers contributing to sexual dysfunction, GI symptoms, and cardiotoxicity.	Henry et al.,[68] Vashistha et al.[67]
Lower Therapeutic Dose	Increased potency allows dose reduction, improving compliance and reducing systemic exposure.	Cârcu-Dobrin et al.,[41] Vashistha et al.[67]
Decreased Drug-Drug Interactions	Less interference with cytochrome P450 enzymes reduces risk in polypharmacy.	Henry et al.[68]

Pharmaceutical manufacturing advantages

Single stereoisomer production offers significant benefits for formulation processes and quality assurance. Pure enantiomer synthesis streamlines chemical production by eliminating racemic mixture separation and handling, leading to simplified processes and improved batch-to-batch consistency. Quality control is enhanced through precise enantiomeric purity standards, simplifying analysis and facilitating regulatory compliance. Additionally, enantiomerically pure drug development enables patent extensions through chiral switches, offering financial benefits and lifecycle management opportunities. Manufacturing benefits include reduced solvent usage and waste production when enantiomer purity is achieved through advanced separation methods such as chiral chromatography or CE (Table 5).[41,69–72]

Table 5 Pharmaceutical manufacturing advantages

Advantage	Description	References
Simplified Synthesis and Quality Control	Single enantiomer production streamlines chemical synthesis and analytical testing, enhancing batch consistency and regulatory compliance.	Somogyi et al.[69]
Reduced Waste and Process Complexity	Optimized separation and purification reduce solvent use and waste production during manufacturing.	Somogyi et al.[69]
Chiral Switch Patent Opportunities	Pure stereoisomer drugs allow new patent filings and market differentiation, extending product lifecycle.	Somogyi et al.[69]

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Conclusion

The chiral separation of fluoxetine isomers using capillary electrophoresis represents a significant and actively developing research domain. This review has comprehensively examined advances in CE techniques regarding chiral selector applications, buffer composition optimization, and electrophoretic condition refinement to enhance enantioseparation efficiency. Cyclodextrins, micellar systems, and ionic liquids show considerable promise, though parameters including resolution, sensitivity, and reproducibility require continued optimization.

Enantioselectivity remains insufficiently refined, with scalability and procedural standardization in pharmaceutical and clinical contexts presenting defining challenges. Despite theoretical progress, practical translation to laboratories remains incomplete, limiting routine application in regulatory analysis and drug development.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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