

Extended-Release Methylphenidate Delivery Systems in Attention-Deficit/Hyperactivity Disorder: Pharmacokinetic Differences and Implications for Clinical Decision-Making

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Posted Date: 9 January 2026

doi: 10.20944/preprints202601.0716.v1

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Article

Extended-Release Methylphenidate Delivery Systems in Attention-Deficit/Hyperactivity Disorder: Pharmacokinetic Differences and Implications for Clinical Decision-Making

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental condition with onset in childhood and functional impairment that may persist into adulthood. Methylphenidate remains a first-line pharmacological treatment due to its well-established efficacy and safety profile. However, clinically relevant variability in treatment response is frequently observed, partly related to differences in pharmacokinetic characteristics among available formulations. Extended-release (ER) methylphenidate formulations were developed to improve adherence and provide sustained symptom control throughout the day. Importantly, ER formulations are not pharmacokinetically equivalent, as distinct drug delivery technologies result in different absorption patterns, peak plasma concentrations, and duration of effect. These differences may translate into meaningful clinical consequences for symptom coverage, tolerability, and functional outcomes. This narrative review synthesizes current evidence on the neurobiological basis of ADHD and examines the pharmacology and pharmacokinetic profiles of ER methylphenidate formulations, with particular emphasis on osmotic-controlled release oral delivery system (OROS®) and spheroidal oral drug absorption system (SODAS®) technologies. Clinical and pharmacokinetic data are integrated to highlight practical considerations for formulation selection and individualized treatment strategies. Recognizing formulation-specific pharmacokinetic differences may support more rational prescribing decisions and improve functional outcomes in routine clinical practice.

Keywords: attention-deficit/hyperactivity disorder; methylphenidate; extended-release formulations; pharmacokinetics; individualized treatment

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental and neuropsychiatric conditions worldwide. Although traditionally conceptualized as a childhood disorder, it is now well established that ADHD frequently persists into adolescence and adulthood, with substantial functional consequences across the lifespan. Core symptoms of inattention, impulsivity, and hyperactivity are associated with impairments in academic performance, occupational functioning, interpersonal relationships, and emotional regulation.

Epidemiological studies estimate a global prevalence of approximately 8% among children and adolescents and around 2–3% among adults. Longitudinal data indicate that up to 70% of individuals diagnosed in childhood continue to experience clinically relevant symptoms later in life. Persistence of symptoms has been associated with increased risk of psychiatric comorbidities, including anxiety

disorders, mood disorders, and substance use disorders, underscoring the chronic and multifaceted nature of ADHD.

Pharmacological treatment represents a cornerstone of ADHD management across age groups. Among available pharmacotherapies, psychostimulants—particularly methylphenidate—are widely recommended as first-line agents due to their robust efficacy and favorable benefit–risk profile. Despite overall effectiveness, considerable interindividual variability in treatment response and tolerability is observed, suggesting that factors beyond dose alone contribute to clinical outcomes.

One key determinant of treatment variability lies in the pharmacokinetic properties of different methylphenidate formulations. Immediate-release formulations require multiple daily administrations and are associated with fluctuating plasma concentrations, which may compromise adherence and lead to periods of inadequate symptom control. In response, extended-release (ER) formulations were developed to provide more stable drug exposure, prolonged symptom coverage, and improved convenience.

Importantly, ER formulations are not pharmacokinetically interchangeable. Distinct drug delivery technologies modulate absorption kinetics and exposure profiles, resulting in clinically meaningful differences in onset of action, duration of effect, and tolerability. Understanding these differences is essential for optimizing individualized treatment strategies.

Despite the widespread use of extended-release methylphenidate, differences among delivery systems are often underrecognized in routine clinical practice, leading to formulation choices based primarily on nominal duration of action rather than pharmacokinetic characteristics. This narrative review aims to address this gap by synthesizing pharmacokinetic and clinical evidence on extended-release methylphenidate delivery systems, with a focus on their implications for individualized clinical decision-making.

Methods (Narrative Review)

This narrative review was based on a non-systematic search of PubMed, Scopus, and Web of Science. Articles addressing ADHD neurobiology, methylphenidate pharmacology, and extended-release delivery systems were prioritized. The objective was to synthesize clinically relevant pharmacokinetic and comparative data.

2. Neurobiological Basis of ADHD

The neurobiological underpinnings of ADHD involve complex interactions between genetic, neurochemical, and neuroanatomical factors. Dysregulation within fronto-striatal, fronto-parietal, and cerebellar networks has been consistently implicated in the pathophysiology of the disorder. These networks play critical roles in executive functioning, inhibitory control, working memory, and attentional regulation.

Dopaminergic dysfunction represents a central component of current neurobiological models of ADHD. Neuroimaging studies have demonstrated altered dopamine transporter availability and reduced synaptic dopamine signaling in individuals with ADHD, contributing to impaired reward processing and cognitive control. Noradrenergic systems, particularly within the prefrontal cortex, are also crucial for sustained attention and working memory. Dysregulation of noradrenergic transmission further exacerbates attentional deficits and executive dysfunction.

The interaction between dopaminergic and noradrenergic pathways provides a strong neurobiological rationale for pharmacological interventions that enhance catecholaminergic signaling, particularly psychostimulant medications.

3. Pharmacology of Methylphenidate and Rationale for Extended-Release Formulations

Methylphenidate is a central nervous system psychostimulant widely used in the treatment of attention-deficit/hyperactivity disorder (ADHD) across the lifespan. Its clinical efficacy has been

demonstrated in numerous randomized controlled trials and meta-analyses, supporting its role as a first-line pharmacological intervention in children, adolescents, and adults. Despite decades of clinical use, variability in treatment response and tolerability remains a central challenge in ADHD management, underscoring the importance of understanding the pharmacological and pharmacokinetic properties of methylphenidate.

At the molecular level, methylphenidate exerts its therapeutic effects primarily through inhibition of dopamine and noradrenaline reuptake by blocking their respective transporters, dopamine transporter (DAT) and norepinephrine transporter (NET). This action increases extracellular concentrations of catecholamines in key brain regions, particularly within fronto-striatal and fronto-parietal circuits implicated in attention, executive functioning, and behavioral control. By enhancing signal transmission in these networks, methylphenidate improves attentional capacity, reduces impulsivity, and modulates hyperactive behaviors.

Unlike amphetamine-based stimulants, methylphenidate does not directly promote presynaptic neurotransmitter release but instead prolongs the synaptic availability of endogenous catecholamines. This pharmacodynamic profile contributes to its favorable safety and tolerability characteristics and may partially explain differences in clinical response among stimulant classes. Nevertheless, the magnitude and timing of catecholaminergic enhancement are strongly influenced by the rate and extent of drug absorption, highlighting the relevance of pharmacokinetic considerations.

Immediate-release (IR) methylphenidate formulations are rapidly absorbed following oral administration, with peak plasma concentrations typically occurring within 1 to 2 hours. The elimination half-life of methylphenidate is relatively short, generally ranging from 2 to 3 hours, resulting in a brief duration of therapeutic effect. Consequently, IR formulations often require multiple daily administrations to maintain symptom control throughout the day. This dosing pattern is associated with pronounced fluctuations in plasma concentrations, which may lead to periods of inadequate symptom coverage, rebound symptoms, and increased risk of adverse effects related to peak exposure.

From a practical standpoint, multiple daily dosing poses challenges for adherence, particularly in school-aged children and working adults. In-school dosing may be associated with stigma, logistical difficulties, and inconsistent administration, while missed doses can compromise treatment effectiveness. These limitations of IR formulations provided a strong impetus for the development of extended-release (ER) methylphenidate delivery systems.

Extended-release formulations were designed to modify the temporal pattern of methylphenidate exposure without altering the active compound itself. By employing specialized drug delivery technologies, ER formulations aim to achieve a more stable plasma concentration–time profile, prolong the duration of clinical effect, and reduce the need for repeated dosing. Importantly, ER formulations are not defined solely by duration of action but by the specific release kinetics engineered into each delivery system.

From a pharmacokinetic perspective, ER formulations differ in parameters such as time to peak concentration (T_{max}), maximum plasma concentration (C_{max}), fluctuation index, and overall exposure distribution across the day. These differences may influence both therapeutic efficacy and tolerability. For example, formulations that produce rapid early peaks may provide faster symptom relief but increase the likelihood of peak-related adverse effects, whereas those with smoother release profiles may offer more consistent symptom control with reduced variability.

The rationale for ER formulations extends beyond convenience. Stable drug exposure may support more continuous engagement of catecholaminergic pathways involved in executive functioning and behavioral regulation, potentially enhancing functional outcomes in academic, occupational, and social domains. Furthermore, reduced plasma concentration fluctuations may minimize rebound phenomena and emotional lability observed as drug levels decline rapidly with IR preparations.

Despite sharing the same active ingredient, ER methylphenidate formulations should not be considered pharmacokinetically interchangeable. Differences in delivery technologies result in distinct absorption and release patterns that may have clinically meaningful implications. Consequently, total daily dose equivalence does not necessarily translate into equivalent clinical effects. This distinction is particularly relevant when switching between formulations or adjusting treatment in response to suboptimal symptom control or tolerability issues.

In clinical practice, formulation selection is often guided by nominal duration of action or availability rather than detailed pharmacokinetic considerations. However, growing evidence suggests that tailoring formulation choice based on pharmacokinetic properties may enhance treatment outcomes and patient satisfaction. Understanding the pharmacological principles underlying ER methylphenidate formulations provides a framework for rational prescribing and supports a more individualized approach to ADHD management.

In summary, the pharmacology of methylphenidate is well characterized, but its clinical expression is highly dependent on formulation-specific pharmacokinetics. Extended-release delivery systems were developed to address the limitations of immediate-release preparations and offer opportunities for improved adherence, sustained symptom control, and individualized treatment. Appreciating the distinctions among ER formulations is essential for optimizing therapeutic strategies and aligning pharmacological interventions with the diverse needs of individuals with ADHD.

4. Extended-Release Methylphenidate Delivery Systems: Pharmacokinetic and Clinical Comparison

From a clinical perspective, OROS-based formulations may be preferable when prolonged symptom control throughout the day is required, whereas SODAS-based formulations may be advantageous for patients who benefit from a more rapid onset of action in the early morning.

Extended-release (ER) methylphenidate formulations were developed to address the limitations associated with immediate-release preparations, particularly the need for multiple daily dosing, fluctuating plasma concentrations, and variable symptom coverage throughout the day. Rather than modifying the active pharmacological compound, ER formulations rely on distinct drug delivery technologies to modulate the rate, timing, and extent of methylphenidate release. These technological differences result in formulation-specific pharmacokinetic profiles that may translate into clinically meaningful differences in efficacy, tolerability, and functional outcomes.

Among currently available ER formulations, osmotic-controlled release oral delivery system (OROS®) and spheroidal oral drug absorption system (SODAS®) technologies represent two conceptually distinct approaches to prolonged drug delivery. Although both are designed to provide extended symptom control following once-daily administration, they differ substantially in release mechanisms, plasma concentration–time profiles, and clinical implications.

4.1. Osmotic-Controlled Release Oral Delivery System (OROS®)

The OROS® system utilizes an osmotic pump mechanism to achieve controlled, continuous drug release over an extended period. Following oral administration, gastrointestinal fluids enter the tablet through a semipermeable membrane, generating osmotic pressure that gradually forces methylphenidate through a precision laser-drilled orifice. Most OROS® formulations also include an immediate-release outer layer, designed to provide an initial rise in plasma concentration shortly after ingestion.

This delivery system produces a relatively smooth and sustained plasma concentration–time curve, characterized by a gradual increase in methylphenidate levels followed by a prolonged plateau and slow decline. Peak plasma concentrations typically occur later than with immediate-release formulations, and overall exposure is distributed more evenly across the day. As a result, OROS®

formulations are commonly associated with sustained clinical effects lasting up to approximately 10–12 hours.

From a clinical perspective, the pharmacokinetic profile of OROS® formulations may be particularly advantageous for patients requiring prolonged symptom control throughout the school or workday and into the late afternoon or early evening. The relatively stable plasma concentrations may reduce fluctuations in symptom control and minimize rebound phenomena associated with rapid declines in drug levels. In addition, the gradual release profile may be associated with lower peak-related adverse effects, such as irritability or jitteriness, in some individuals.

However, the delayed time to peak concentration may limit the rapidity of symptom control in the early morning hours for certain patients. Individuals with prominent morning symptoms, such as difficulty initiating daily activities or early academic demands, may experience a slower onset of optimal clinical effect compared with formulations designed to produce an earlier plasma peak. These considerations highlight the importance of aligning formulation characteristics with individual symptom patterns and daily functional requirements.

4.2. Spheroidal Oral Drug Absorption System (SODAS®)

The SODAS® system is based on multiparticulate technology using microbeads with differential coating properties to achieve a bimodal release pattern. Typically, approximately 50% of the methylphenidate dose is released immediately following ingestion, while the remaining fraction is released after a programmed delay. This design results in two distinct plasma concentration peaks over the course of the day.

The first peak occurs relatively early after administration and is associated with rapid onset of clinical effect, while the second peak provides renewed symptom coverage later in the day. Compared with OROS® formulations, SODAS® systems tend to produce earlier peak plasma concentrations and a more pronounced initial rise in methylphenidate levels.

Clinically, the faster onset of action associated with SODAS® formulations may be advantageous for patients who require early-morning symptom control, such as children with academic demands shortly after school start or adults with early work responsibilities. The bimodal release profile may also be beneficial in patients who experience a clear re-emergence of symptoms later in the day and require targeted coverage during specific time windows.

On the other hand, the presence of two plasma concentration peaks may be associated with greater intraindividual variability in clinical response and tolerability. Some patients may experience peak-related adverse effects, such as appetite suppression or sleep disturbances, particularly if the second peak occurs later in the day. In addition, the duration of effective symptom control with SODAS® formulations may be shorter than with OROS® formulations in certain individuals, depending on metabolic factors and daily activity patterns.

4.3. Comparative Pharmacokinetic Profiles

Pharmacokinetic studies comparing OROS®- and SODAS®-based methylphenidate formulations consistently demonstrate distinct absorption and exposure profiles. OROS® formulations are characterized by a single, sustained plasma concentration peak with gradual decline, whereas SODAS® formulations produce a bimodal profile with two discernible peaks.

These differences are reflected in measures such as time to peak concentration (T_{max}), maximum plasma concentration (C_{max}), and duration of clinically relevant exposure. While overall area under the concentration–time curve (AUC) may be comparable between formulations when equivalent doses are administered, the temporal distribution of exposure differs substantially. Such differences are clinically relevant, as symptom control and adverse effects are closely linked to plasma methylphenidate concentrations.

Pharmacokinetic and pharmacodynamic modeling studies further support a strong relationship between methylphenidate exposure and clinical response. Simulations indicate that earlier peaks are associated with more rapid symptom improvement, whereas sustained exposure contributes to

prolonged symptom control later in the day. These findings reinforce the concept that formulation-specific pharmacokinetics, rather than total daily dose alone, play a critical role in determining clinical outcomes.

4.4. Clinical Implications of Delivery System Differences

Randomized clinical trials and meta-analyses suggest that overall efficacy of ER methylphenidate formulations is broadly comparable when assessed across the full day. However, differences in onset of action, duration of effect, and variability in response may influence patient preference, adherence, and functional outcomes in real-world settings.

In clinical practice, ER formulations are sometimes considered interchangeable based on nominal duration of action. However, this assumption may overlook important pharmacokinetic distinctions that are highly relevant for individualized treatment planning. For example, a patient with prominent early-morning symptoms may respond better to a formulation with faster onset, whereas another patient with extended daily demands may benefit more from sustained coverage later in the day.

These considerations underscore the importance of moving beyond a one-size-fits-all approach to ER methylphenidate prescribing. An informed understanding of delivery system technologies and their pharmacokinetic profiles allows clinicians to tailor treatment more precisely to individual patient needs, thereby optimizing symptom control, tolerability, and overall functional outcomes.

Table 1. Comparison of Extended-Release Methylphenidate Delivery Systems.

Delivery system	Release mechanism	Pharmacokinetic profile	Onset of action	Duration of effect	Clinical advantages	Potential limitations
OROS® (Osmotic-Controlled Release Oral Delivery System)	Osmotic pump with semipermeable membrane and laser-drilled orifice; initial immediate-release coating followed by continuous release	Gradual increase in plasma concentration with sustained plateau and slow decline	Moderate	Long (approximately 10–12 hours)	Sustained symptom control throughout the day; reduced plasma fluctuations; lower rebound risk	Slower onset of action in early morning; less flexible for rapid symptom control
SODAS® (Spheroidal Oral Drug Absorption System)	Multiparticle bead system with differential coating producing bimodal drug release	Bimodal plasma concentration–time profile with two distinct peaks	Fast	Intermediate (approximately 8–10 hours)	Rapid onset of clinical effect; targeted symptom coverage during	Greater peak-to-trough variability; potential peak-related

					specific time periods	adverse effects
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5. Implications for Individualized Treatment

The clinical management of attention-deficit/hyperactivity disorder increasingly emphasizes individualized treatment strategies that account for symptom heterogeneity, functional demands, and patient-specific factors. While extended-release methylphenidate formulations share the same active compound, differences in delivery systems and pharmacokinetic profiles provide opportunities to tailor treatment beyond dose selection alone.

One of the most relevant considerations in formulation selection is the circadian pattern of ADHD symptoms. Some patients exhibit prominent symptoms during the early morning hours, particularly before school or work begins, whereas others experience greater impairment later in the day or during periods requiring sustained attention. Formulations with faster onset of action may be advantageous for individuals with early-morning functional demands, while those providing prolonged and stable exposure may better support symptom control during afternoon and early evening activities.

Age-related factors also influence treatment individualization. In children, school schedules, classroom demands, and after-school activities often dictate the need for consistent symptom coverage throughout the academic day. Adolescents may require flexibility to accommodate extracurricular activities, social interactions, and variable daily routines. In adults, occupational responsibilities, shift work, and extended cognitive demands may necessitate longer-lasting formulations or combinations of pharmacokinetic profiles to optimize daily functioning.

Adherence represents another critical dimension of individualized treatment. Extended-release formulations have consistently been associated with improved adherence compared with immediate-release preparations, largely due to simplified dosing regimens and reduced need for in-day administration. Improved adherence may translate into more consistent symptom control, reduced stigma associated with medication use during school or work hours, and enhanced overall treatment effectiveness. Selection of an appropriate delivery system may therefore play a central role in long-term treatment success.

Tolerability considerations further reinforce the importance of individualized formulation selection. Differences in peak plasma concentrations and exposure timing may influence the occurrence and severity of adverse effects, such as appetite suppression, irritability, anxiety, or sleep disturbances. Patients sensitive to peak-related effects may benefit from formulations that provide smoother plasma concentration profiles, whereas others may tolerate or even prefer more pronounced early effects. Careful titration and monitoring are essential to balance therapeutic benefits against potential adverse effects.

Patient preference and subjective experience should also be incorporated into treatment decisions. Perceived onset of action, duration of benefit, and overall sense of symptom control can influence satisfaction and willingness to continue treatment. Engaging patients and caregivers in shared decision-making, informed by an understanding of formulation-specific characteristics, may enhance adherence and treatment outcomes.

Comorbid conditions commonly observed in ADHD, such as anxiety disorders, mood disorders, and substance use disorders, may further modify formulation choice. For example, individuals with comorbid anxiety may be more sensitive to rapid increases in stimulant exposure, whereas those with depressive symptoms may benefit from sustained symptom coverage throughout the day. Although evidence guiding formulation selection in the context of comorbidity remains limited, awareness of pharmacokinetic differences provides a rational framework for individualized decision-making.

Real-world clinical practice often involves trial-and-error approaches to medication selection and adjustment. A systematic understanding of extended-release methylphenidate delivery systems

may reduce the need for repeated formulation switches and facilitate more efficient optimization of treatment. Rather than viewing ER formulations as interchangeable, clinicians may consider them as distinct tools with specific pharmacokinetic properties suited to different clinical scenarios.

Ultimately, individualized treatment of ADHD requires integration of neurobiological understanding, pharmacological principles, and patient-centered considerations. Extended-release methylphenidate formulations offer flexibility in tailoring treatment to individual needs, but optimal use depends on informed selection of delivery systems based on pharmacokinetic profiles and clinical context. By aligning formulation characteristics with symptom patterns and functional demands, clinicians may enhance therapeutic outcomes and improve quality of life for individuals with ADHD.

6. Conclusions

Clinicians should consider delivery-system-specific pharmacokinetics when selecting extended-release methylphenidate formulations, rather than assuming clinical equivalence based solely on total daily dose. A more informed understanding of formulation-specific release profiles may support individualized treatment decisions and contribute to improved long-term functional outcomes in routine clinical practice.

Conflicts of Interest: The authors declare no conflicts of interest.

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