Revista Ibero-Americana de Humanidades, Ciências e Educação — REASE

OPEN ACCESS

doi.org/10.51891/rease.v12i1.23743

EXTENDED-RELEASE METHYLPHENIDATE DELIVERY SYSTEMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PHARMACOKINETIC PROFILES AND CLINICAL IMPLICATIONS FOR INDIVIDUALIZED TREATMENT

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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 (Wolraich et al., 2019). 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 (Swanson et al., 2003; Childress et al., 2019). 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, highlighting implications for individualized treatment strategies.

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 (Harpin, 2005; Faraone, Biederman & Mick, 2006).

Epidemiological studies estimate a global prevalence of approximately 8% among children and adolescents and around 2–3% among adults (Ayano, Yohannes & Abraha, 2023). Longitudinal data indicate that up to 70% of individuals diagnosed in childhood continue to experience clinically relevant symptoms later in life, with persistence associated with increased psychiatric comorbidity and functional impairment (Faraone, Biederman & Mick, 2006).

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Pharmacological treatment represents a cornerstone of ADHD management across age groups. Psychostimulants, particularly methylphenidate, are widely recommended as first-line agents due to their robust efficacy and favorable benefit–risk profile (Wolraich et al., 2019).

Immediate-release methylphenidate formulations require multiple daily administrations and are associated with fluctuating plasma concentrations, which may compromise adherence and lead to periods of suboptimal symptom control. Extended-release formulations were therefore developed to provide more stable drug exposure, prolonged symptom coverage, and improved convenience (Swanson et al., 2003).

Importantly, extended-release formulations are not pharmacokinetically interchangeable. Distinct 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.

2. NEUROBIOLOGICAL BASIS OF ADHD

The neurobiological underpinnings of attention-deficit/hyperactivity disorder 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 (Tripp & Wickens, 2012; Bayard, Thunell & Samuelsson, 2020). 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, contributing to impaired reward processing and cognitive control (Fusar-Poli et al., 2012; Nikolaus, Antke & Müller, 2021). Noradrenergic systems, particularly within the prefrontal cortex, also play a critical role in attentional regulation and executive functioning (Berridge & Spencer, 2016). 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 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 (Faraone & Buitelaar, 2010; Wolraich et al., 2019). At the molecular level, methylphenidate exerts its therapeutic effects primarily through inhibition of dopamine and noradrenaline reuptake by blocking the dopamine transporter (DAT) and norepinephrine transporter (NET), thereby increasing extracellular catecholamine concentrations in fronto-striatal and fronto-parietal circuits (Patrick et al., 2019). Immediate-release formulations are rapidly absorbed, with peak plasma concentrations occurring within 1–2 hours and an elimination half-life of approximately 2–3 hours, necessitating multiple daily administrations (Childress, Komolova & Sallee, 2019). These pharmacokinetic properties contribute to plasma concentration fluctuations and may negatively affect adherence and tolerability. Extended-release formulations were developed to provide more stable exposure, prolonged symptom control, and improved convenience. Importantly, these formulations are not pharmacokinetically interchangeable, as distinct delivery technologies result in different temporal exposure profiles with clinically meaningful implications for onset of action, duration of effect, and tolerability (Swanson et al., 2003; Jackson & Foehl, 2022).

4. EXTENDED-RELEASE METHYLPHENIDATE DELIVERY SYSTEMS: PHARMACOKINETIC AND CLINICAL COMPARISON

Extended-release (ER) methylphenidate formulations were developed to overcome the limitations associated with immediate-release preparations, particularly the need for multiple daily dosing, fluctuating plasma concentrations, and inconsistent symptom control throughout the day. Rather than modifying the active compound itself, ER formulations rely on distinct drug delivery technologies to modulate the rate, timing, and extent of methylphenidate release, resulting in formulation-specific pharmacokinetic profiles with clinically meaningful implications (Coghill et al., 2013; Childress, Komolova & Sallee, 2019).

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

The osmotic-controlled release oral delivery system (OROS®) employs an osmotic pump mechanism to achieve controlled and continuous drug release over an extended period. After oral administration, gastrointestinal fluids penetrate the semipermeable membrane of the tablet, generating osmotic pressure that gradually forces methylphenidate through a laser-drilled orifice. Most OROS® formulations also incorporate an immediate-release outer layer, which contributes to an initial rise in plasma methylphenidate concentration (Swanson et al.,

2003). According to Swanson et al. (2003, p. 1238), "the OROS methylphenidate system was designed to provide a controlled and ascending release profile that mimics multiple immediate-release doses administered throughout the day". This delivery system produces a relatively smooth plasma concentration–time profile, characterized by a gradual increase followed by a sustained plateau and slow decline. Peak plasma concentrations typically occur later than with immediate-release formulations, with clinically relevant effects lasting approximately 10–12 hours (Childress, Komolova & Sallee, 2019). Such pharmacokinetic characteristics are associated with reduced plasma fluctuations and lower risk of rebound symptoms in some patients. Clinically, OROS® formulations may be particularly advantageous for individuals requiring prolonged symptom control across the school or workday and into the late afternoon or early evening. However, the delayed time to peak concentration may limit rapid symptom control in the early morning for patients with prominent morning impairments, underscoring the importance of individualized formulation selection.

4.2 Spheroidal Oral Drug Absorption System (SODAS®)

SWANSON et al. (2003, p. 1240): The SODAS delivery system is based on multiparticulate bead technology, allowing for a bimodal release of methylphenidate. This results in an early peak associated with rapid symptom control followed by a delayed second peak designed to extend therapeutic coverage throughout the day.

The first peak occurs relatively early and is associated with rapid onset of clinical effect, whereas the second peak provides renewed symptom coverage later in the day. Compared with OROS® formulations, SODAS® systems generally exhibit earlier peak plasma concentrations (Tmax) and higher initial peak levels (Cmax), which may be advantageous for patients requiring early-morning symptom control (Lopez et al., 2003). However, the bimodal plasma concentration–time profile may be associated with greater peak-to-trough variability and, in some individuals, increased susceptibility to peak-related adverse effects such as appetite suppression or sleep disturbances, particularly if the second peak occurs later in the day.

4.3 Comparative Pharmacokinetic Profiles

Comparative pharmacokinetic studies consistently demonstrate that OROS® and SODAS® methylphenidate formulations produce distinct absorption and exposure profiles despite containing the same active compound. OROS® formulations are characterized by a

single, sustained peak with gradual decline, whereas SODAS® formulations generate a bimodal profile with two discernible peaks (Childress, Komolova & Sallee, 2019). While total daily exposure, as measured by the area under the concentration–time curve (AUC), may be comparable across formulations when equivalent doses are administered, the temporal distribution of exposure differs substantially. These differences influence clinical response, as symptom control and adverse effects are closely related to plasma methylphenidate concentrations over time (Jackson & Foehl, 2022).

4.4 Clinical Implications of Delivery System Differences

Clinical trials and meta-analyses suggest that overall efficacy of extended-release methylphenidate formulations is broadly comparable when evaluated across the full day. However, differences in onset of action, duration of effect, and intraindividual variability may influence patient preference, adherence, and functional outcomes in real-world settings (Coghill et al., 2013). Formulations with faster onset may be preferred by patients with early-morning functional demands, whereas those providing prolonged and stable exposure may better support symptom control during extended daily activities. These considerations reinforce the importance of selecting ER formulations based on individual symptom patterns rather than assuming pharmacokinetic interchangeability. The main pharmacokinetic and clinical differences between OROS® and SODAS® formulations are summarized in Table 1.

Table 1 - Comparison of Extended-Release Methylphenidate Delivery Systems

Delivery system	Release mechanism	Pharmacokinetic profile	Onset of action	Duration of effect	Clinical considerations
OROS®	Osmotic pump with semipermeable membrane and laser-drilled orifice; initial IR layer	Single sustained peak; gradual rise and slow decline	Moderate	Long (≈10–12 h)	Stable symptom control; lower rebound risk; slower early-morning onset
SODAS®	Multiparticulate beads with differential coating (bimodal release)	Two distinct plasma concentration peaks	Fast	Intermediate (≈8–10 h)	Rapid onset; flexible coverage; greater peak-related variability

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5. IMPLICATIONS FOR INDIVIDUALIZED TREATMENT

The contemporary management of attention-deficit/hyperactivity disorder increasingly emphasizes individualized treatment strategies that account for symptom heterogeneity, functional demands, and patient-specific characteristics. Although extended-release methylphenidate formulations contain the same active compound, differences in delivery systems and pharmacokinetic profiles provide clinically meaningful opportunities for treatment individualization (Coghill et al., 2013). One of the most relevant factors guiding formulation selection is the circadian pattern of ADHD symptoms. Patients with prominent early-morning impairments may benefit from formulations with faster onset of action, whereas those requiring sustained symptom control into the afternoon or evening may respond more favorably to formulations providing prolonged and stable exposure (Childress, Komolova & Sallee, 2019). Age-related and contextual factors further influence individualized treatment decisions. In children and adolescents, school schedules and extracurricular activities often dictate the need for consistent symptom coverage throughout the day. In adults, occupational demands, extended cognitive workloads, and variable daily routines may necessitate longer-lasting formulations or specific pharmacokinetic profiles tailored to functional requirements. Adherence represents a critical determinant of long-term treatment success. Extended-release formulations have been associated with improved adherence compared with immediate-release preparations, largely due to simplified dosing regimens and reduced need for in-day administration (Maldonado, 2013; Roh & Kim, 2021). Improved adherence may translate into

more consistent symptom control and better functional outcomes. Tolerability considerations also play a central role in formulation selection. Differences in peak plasma concentrations and exposure timing may influence the occurrence of adverse effects such as appetite suppression, irritability, anxiety, or sleep disturbances. Patients sensitive to peak-related effects may benefit from smoother exposure profiles, whereas others may tolerate or prefer more pronounced early effects. Patient preference and subjective experience should be incorporated into shared decision-making processes. Perceived onset of action, duration of benefit, and overall symptom control can significantly influence treatment satisfaction and persistence. By aligning formulation characteristics with symptom patterns, functional demands, and patient preferences, clinicians may optimize therapeutic outcomes and quality of life.

6. CONCLUSION

Extended-release methylphenidate formulations demonstrate comparable overall efficacy in the treatment of attention-deficit/hyperactivity disorder; however, they differ substantially in pharmacokinetic profiles and delivery mechanisms. These formulation-specific characteristics have meaningful clinical implications for onset of action, duration of symptom control, tolerability, and patient preference. A thorough understanding of extended-release delivery technologies supports rational prescribing and individualized treatment strategies, allowing clinicians to better align pharmacotherapy with symptom patterns and functional demands in real-world clinical practice.

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