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Formulation of extended release oral dosage forms of Ashwagandha

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Abstract
Ashwagandha (*Withania somnifera*) is a well-established adaptogenic herb used in Ayurveda for stress relief, anxiety reduction, neuroprotection, and immune enhancement. Despite its therapeutic potential, clinical translation is limited by its low aqueous solubility, rapid metabolism, and short plasma half-life, leading to irregular bioavailability in conventional immediate-release (IR) preparations. The present study focuses on the formulation and evaluation of an extended-release (ER) oral tablet designed using a hydrophilic–hydrophobic polymer matrix comprising HPMC K4M and ethyl cellulose. ER tablets were developed through wet granulation and evaluated for *in vitro* dissolution, release kinetics, accelerated stability, pharmacokinetics, and anti-stress efficacy. *In vitro* dissolution indicated controlled release of 98% over 12 hours, following zero-order and Korsmeyer–Peppas kinetics, contrasting with IR tablets which released 100% in 6 hours. Stability analysis showed minimal degradation after 3 months under ICH conditions. Pharmacokinetic assessment in Wistar rats revealed lower C_max but significantly higher AUC and prolonged half-life for ER tablets. Stress-model studies demonstrated superior cortisol reduction and anxiolytic effects. Overall, the ER Ashwagandha formulation markedly enhances bioavailability, ensures steady therapeutic exposure, and improves clinical efficacy, making it a promising dosage form for chronic stress management.

Keywords: Ashwagandha, extended-release formulation, HPMC K4M, ethyl cellulose, pharmacokinetics, stress model, withanolides

Introduction

Ashwagandha (*Withania somnifera*) has been used in traditional Indian medicine for centuries as a rasayana (rejuvenator) to promote strength, vitality, and mental well-being. Modern pharmacology has confirmed its adaptogenic, anxiolytic, antioxidant, and neuroprotective actions, primarily due to bioactive compounds called withanolides. However, its widespread acceptance in modern therapeutics is hindered by poor oral bioavailability, limited solubility, extensive first-pass metabolism, and short systemic persistence. Immediate-release herbal supplements fail to maintain steady plasma concentrations, requiring multiple doses per day and showing inconsistent therapeutic responses.

Extended-release (ER) delivery systems provide a promising solution by controlling drug release rate, improving patient compliance, reducing dose frequency, and maintaining sustained plasma concentrations. Polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose create matrix systems that offer diffusion-controlled release, ensuring prolonged therapeutic effect. Yet, very few systematic studies exist on controlled-release formulations of Ashwagandha using modern pharmaceutics. The present research aims to develop a scientifically optimized ER formulation of Ashwagandha extract, characterize its release profile, verify stability under ICH conditions, and evaluate pharmacokinetic and pharmacodynamic superiority over immediate-release formulations. This systematic investigation bridges Ayurvedic therapy with advanced pharmaceutical technology by providing a standardized, effective, and stable extended-release herbal dosage form.

Materials and Methods

Ashwagandha extract standardized to 5% withanolides served as the active pharmaceutical ingredient. HPMC K4M (10–15%) functioned as the primary release-retarding polymer due to its water-induced gelling ability, while ethyl cellulose provided hydrophobic matrix support. Other excipients included PVP K30 (binder), sodium starch glycolate (disintegrant), microcrystalline cellulose (diluent), and magnesium stearate (lubricant). ER tablets of 500 mg were prepared by wet granulation. The extract and polymers were blended homogeneously, granulated with ethanol: PVP solution, dried at 50°C, milled, lubricated, and compressed at a mean hardness of 6 kg/cm².

Table 1: Composition of ER Ashwagandha Tablets

Component	Function	Quantity per Tablet (mg)
Ashwagandha extract	Active	500 (equivalent to 5% withanolides)
HPMC K4M	Release polymer	60
Ethyl cellulose	Hydrophobic polymer	40
PVP K30	Binder	20
Sodium starch glycolate	Disintegrant	15
MCC	Diluent	120
Magnesium stearate	Lubricant	5

In vitro dissolution studies used USP Type II apparatus at 50 rpm with 900 mL dissolution medium (pH 1.2 for 2 hours followed by pH 6.8 for 10 hours). Samples were withdrawn at specified intervals and analyzed at 254 nm via UV spectrophotometry. Release kinetics were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Stability studies were performed according to ICH Q1A (R2) guidelines at 40°C / 75% RH for three months. Parameters monitored included physical appearance, assay content, and 12-hour dissolution performance.

Pharmacokinetic and anti-stress efficacy studies were conducted using Wistar rats in three groups: control (stress), IR Ashwagandha, and ER Ashwagandha. Plasma samples were collected from 0 to 24 hours post-dose and analyzed by HPLC for withanolide concentration. Behavioral studies included elevated plus maze and sleep latency using actigraphic analysis. Cortisol levels were measured by ELISA.

Results

The extended-release tablets showed excellent physical characteristics, including uniform hardness, friability within limits, and consistent weight variation. *In vitro* dissolution revealed substantial differences between IR and ER behavior. The ER formulation released only 5% of its drug at 0.5 hours versus 25% in the IR, and by 12 hours, ER achieved 98% release in a controlled manner.

Table 2: *In Vitro* Dissolution Profile of IR vs. ER Tablets

Time (hours)	IR Release (%)	ER Release (%)
0.5	25	5
1	50	10
2	75	20
4	90	35
6	100	50
8	—	70
10	—	90
12	—	98

The dissolution data clearly demonstrate the contrasting release patterns of IR and ER formulations. The IR tablets showed a rapid and nearly complete release within the first 6 hours, indicating immediate availability of the drug but also suggesting the likelihood of plasma concentration spikes. In contrast, the ER tablets released only 5% of the drug at 0.5 hours and progressed gradually to 98% by 12 hours, confirming the effectiveness of the polymeric matrix in slowing and controlling drug diffusion. This sustained-release pattern highlights the ER tablet's ability to maintain prolonged therapeutic levels, reduce dosing frequency, and avoid the sharp fluctuations characteristic of IR formulations.

Table 3: Release Kinetic Model Fitting

Kinetic Model	ER R^2	IR R^2	Interpretation
Zero-order	0.961	0.758	ER follows constant release
First-order	0.845	0.932	IR dependent on concentration
Higuchi	0.974	0.808	ER diffusion-controlled
Korsmeyer–Peppas	0.987	0.801	ER anomalous diffusion (n=0.47)

The kinetic modeling results confirm that the ER formulation follows a diffusion-dominated mechanism. The strong fit with zero-order kinetics (R^2 = 0.961) indicates a nearly constant rate of drug release independent of concentration, validating the matrix design. The high Higuchi (R^2 = 0.974) and Korsmeyer–Peppas (R^2 = 0.987) values further support Fickian diffusion and polymer relaxation as the primary release mechanisms. Conversely, the IR tablets best aligned with first-order kinetics (R^2 = 0.932), which is expected for rapidly dissolving systems where the drug release rate decreases as concentration falls. These differences reflect the fundamental distinction between controlled-release and immediate-release technologies.

Table 4: Pharmacokinetic Parameters

Parameter	IR	ER
C_max (ng/mL)	110	85
T_max (hours)	1	6
$AUC_{0–12}$ (ng·hr/mL)	520	870
Half-life (hours)	3.5	7.2

The pharmacokinetic comparison reveals that the IR formulation causes a rapid surge in plasma levels, evidenced by a high C_max of 110 ng/mL at just 1 hour, followed by a quick decline. Such fluctuations may reduce therapeutic consistency and increase side-effect risk. In contrast, the ER formulation displayed a smoother absorption curve, reaching its C_max of 85 ng/mL at 6 hours and maintaining elevated levels much longer, as shown by the significantly higher AUC (870 ng·hr/mL) and extended half-life (7.2 hours). These findings confirm that the ER system enhances overall bioavailability and ensures sustained plasma concentrations, which are essential for managing chronic conditions like stress and anxiety.

Table 5: Anti-Stress Efficacy Parameters

Parameter	Stress Control	IR	ER
Cortisol (ng/mL)	103.6	74.3	62.7
Open-arm Duration (sec)	77	105	142
Sleep Latency (min)	28	21	14

The anti-stress efficacy results demonstrate the superior therapeutic performance of the ER formulation. Compared to both the stress control and IR group, ER tablets achieved the lowest cortisol levels (62.7 ng/mL), indicating stronger suppression of physiological stress responses. Behavioral improvements were also more pronounced, with the ER group showing the longest open-arm duration—reflecting enhanced anxiolytic effects—and the shortest sleep latency, indicating improved sleep initiation. These outcomes highlight the advantages of maintaining steady plasma concentrations of Ashwagandha's active constituents, reinforcing the clinical promise of the extended-release system for long-term stress management.

Discussion

The findings of this study demonstrate a significant advancement in the oral delivery of Ashwagandha by successfully developing an extended-release (ER) matrix tablet capable of maintaining therapeutic plasma levels for a prolonged duration. Traditional herbal formulations—including conventional powders, decoctions, capsules, and immediate-release tablets—suffer from intrinsic pharmacokinetic challenges such as low aqueous solubility, rapid gastrointestinal degradation, and extensive first-pass

metabolism of withanolides. These factors collectively reduce systemic bioavailability and shorten the duration of therapeutic action, necessitating multiple daily doses. By contrast, the ER formulation developed using hydroxypropyl methylcellulose (HPMC K4M) and ethyl cellulose created a robust hydrophilic–hydrophobic matrix system. Upon contact with gastrointestinal fluids, HPMC swells and forms a viscous gel layer, while ethyl cellulose modulates permeability and slows diffusion. The combination results in a highly controlled and reproducible 12-hour release pattern, which aligns well with zero-order and anomalous diffusion models, minimizing fluctuations commonly observed in IR systems.

The dissolution behaviour of the ER tablet highlights its pharmaceutical superiority. While the IR formulation released 100% of the drug within 6 hours—causing sharp peaks in plasma concentration—the ER matrix delivered the drug gradually, achieving 98% release only at 12 hours. This controlled profile reduces the likelihood of dose dumping, irritation, or peak-related adverse effects such as sedation, which is sometimes associated with high initial levels of Ashwagandha's bioactive components. The Korsmeyer–Peppas parameter (n=0.47) indicates that Fickian diffusion is the primary mechanism, supported by polymer relaxation and water penetration. Such a mechanism ensures both safety and efficacy by allowing a predictable, time-dependent release.

Pharmacokinetic results reinforce the functional advantage of the ER system. A significant increase in AUC (870 ng·hr/mL) relative to IR (520 ng·hr/mL) demonstrates improved overall drug exposure, which is critical for compounds like withanolides that naturally exhibit poor absorption and rapid clearance. Likewise, the prolonged half-life of 7.2 hours in the ER group compared to 3.5 hours in the IR group confirms sustained systemic retention and delayed elimination. These parameters directly correlate with better therapeutic maintenance and reduced dosing frequency, resulting in improved patient adherence—particularly important in chronic conditions such as stress, anxiety, insomnia, and mild cognitive dysfunction, where long-term herbal therapy is common.

The pharmacodynamic findings further strengthen the clinical relevance of the ER formulation. Animals receiving the ER tablet demonstrated greater reduction in cortisol levels (62.7 ng/mL) compared with IR (74.3 ng/mL). This outcome suggests a more stable modulation of the hypothalamic–pituitary–adrenal (HPA) axis, which is the central mechanism through which Ashwagandha exerts its adaptogenic effects. The enhanced performance in anxiolytic parameters—such as increased open-arm time in the elevated plus-maze—and improved sleep latency further support the hypothesis that steady plasma concentrations elicit stronger neuro-adaptive responses. Continuous GABAergic modulation, rather than episodic spikes, aligns with the neurobiological requirements for treating chronic stress and anxiety disorders. These findings are also consistent with previous research, such as Chandrasekhar *et al*. (2012) [1], which reported reduced stress markers with controlled supplementation of Ashwagandha, though without extended-release technology.

Stability results indicate that the ER tablets retain both chemical integrity and functional performance under accelerated conditions—showing only minor reductions in drug content and dissolution values. These findings fall well within ICH limits, confirming that the developed formulation is stable, scalable, and suitable for industrial manufacturing. The minor variations observed over three months are expected for botanical extracts and do not compromise therapeutic performance. The stability of the polymer matrix also validates the choice of HPMC and ethyl cellulose, which are known for their robustness in tropical climates.

Compared with documented literature, this formulation exhibits meaningful advantages. Gupta (2020) [2] reported ER profiles extending up to 12 hours but with inconsistent release kinetics due to polymer imbalance. Other studies using natural gums or isolated hydrophilic polymers often show initial burst release or incomplete hydration, compromising the extended-release mechanism. The present work overcomes these limitations by optimizing polymer ratios and granulation parameters, achieving superior release control, stronger diffusion characteristics, and enhanced pharmacodynamic effects. Additionally, while most earlier studies have focused on either pharmacokinetics or therapeutic efficacy, this work integrates formulation development, release kinetics, stability assessment, pharmacokinetics, and pharmacodynamics—offering a more holistic evaluation of ER feasibility for herbal drugs.

Overall, this research represents a crucial step in bridging Ayurvedic herbal therapy with modern pharmaceutical technology. By providing a controlled, consistent, and clinically advantageous release of Ashwagandha, the ER formulation expands the therapeutic potential of a widely used adaptogen and sets a model for the future development of herbal extended-release systems. The results not only validate the scientific feasibility of modifying herbal drug delivery but also indicate strong potential for translational application, subject to further human trials.

Conclusion

The extended-release Ashwagandha tablet developed in this study demonstrates a controlled and sustained 12-hour release profile, addressing the major limitations of conventional Ashwagandha formulations that typically exhibit rapid dissolution and short-lived therapeutic effects. By employing a hydrophilic–hydrophobic polymer matrix, the formulation achieves diffusion-controlled release kinetics, resulting in more consistent plasma concentrations, superior pharmacokinetic parameters—including markedly higher AUC and prolonged half-life—and improved systemic exposure of withanolides. These attributes directly translate into enhanced therapeutic outcomes, as reflected in greater reductions in cortisol levels, improved anxiolytic behavior, and smoother sleep regulation. The formulation's stability under accelerated storage conditions further confirms its robustness, manufacturability, and suitability for long-term use.

Overall, this research establishes a scientifically validated pathway for integrating Ayurvedic herbal extracts into modern pharmaceutical delivery systems. The success of this ER tablet demonstrates that controlled-release design can overcome long-standing issues of poor solubility, variable absorption, and rapid metabolism that limit the clinical potential of many natural compounds. The findings lay a solid foundation for progressing to human clinical trials to evaluate long-term safety, efficacy, and patient compliance. Importantly, this work contributes to the broader effort of standardizing traditional herbal medicines,

making them more predictable, therapeutically reliable, and compatible with evidence-based healthcare practices.

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