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REVIEW ARTICLE

A Review on Biopharmaceutical, Analytical, and Formulation Aspects of Elagolix

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Abstract: Elagolix, a first-in-class, orally active, non-peptide gonadotropin-releasing hormone (GnRH) antagonist transformed the treatment for endometriosis and uterine fibroids. Unlike traditional peptide-based GnRH agonists that require parenteral administration and induce initial hormonal flares, elagolix offers dose-dependent estrogen suppression with rapid reversibility. This review analyzes the pharmaceutical and biopharmaceutical attributes that facilitate the oral delivery of this peptide-mimetic small molecule. This work provides the physicochemical profile of elagolix sodium, highlighting its classification as a Biopharmaceutics Classification System (BCS) Class II compound and the implications of its pH-dependent solubility on formulation strategies. Furthermore, the absorption, distribution, metabolism, and excretion (ADME) characteristics are detailed, elucidating the role of hepatic transporters and metabolic enzymes in its pharmacokinetic behavior. The review emphasizes recent advancements in analytical methodologies, including high-performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS), developed for the rigorous quantification of elagolix and its degradation products in complex matrices. Additionally, the implementation of Quality by Design (QbD) principles in optimizing formulation parameters and ensuring critical quality attributes is synthesized. This review explains the pivotal role of elagolix as a model for overcoming the barriers associated with the oral delivery of therapeutics targeting the GnRH receptor by integrating data on stability, solubility enhancement techniques, and regulatory considerations.

Keywords: Elagolix; Non-peptide GnRH antagonist; Biopharmaceutics Classification System; Pharmacokinetics; Quality by Design.

1. Introduction

Endometriosis and uterine fibroids represent two of the most pervasive gynecological pathologies affecting women of reproductive age, characterized by estrogen-dependent pathophysiology that manifests as debilitating pelvic pain, dysmenorrhea, and heavy menstrual bleeding [1, 2]. The chronic nature of these conditions imposes a substantial clinical and socioeconomic burden, necessitating long-term management strategies that balance efficacy with patient quality of life. Historically, the pharmacological standard of care relied heavily on gonadotropin-releasing hormone (GnRH) agonists. While effective in suppressing ovarian steroidogenesis, these peptide analogues possess inherent limitations, including the requirement for subcutaneous or intramuscular administration, a delayed onset of action due to the initial "flare" effect, and a profound hypoestrogenic state that precludes long-term use without add-back therapy [3, 4].

The approval of elagolix (Orilissa®) by the U.S. Food and Drug Administration (FDA) marked a watershed moment in reproductive medicine, establishing the viability of oral, non-peptide small molecules capable of antagonizing the GnRH receptor [5]. Elagolix functions through a competitive blockade of pituitary GnRH receptors, resulting in a dose-dependent reduction in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. This mechanism allows for the modulation of estradiol levels rather than complete ablation, offering a tailored therapeutic approach that mitigates the severe hypoestrogenic side effects associated with complete suppression [6].

From a pharmaceutical sciences perspective, the development of elagolix illustrates the successful circumvention of the "rule of five" challenges often faced by peptidomimetics. Transforming a receptor target traditionally modulated by decapeptides into a

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druggable target for a small molecule requires sophisticated molecular engineering to ensure adequate oral bioavailability, metabolic stability, and receptor affinity. This review systematically evaluates the critical pharmaceutical and biopharmaceutical parameters of elagolix. It dissects the compound's physicochemical properties, investigates the challenges inherent in its formulation—such as solubility limitations and stability profiles—and explores the advanced analytical techniques required for its characterization. Furthermore, the application of Quality by Design (QbD) principles in the development of robust dosage forms is examined, providing a holistic overview of the scientific innovation underpinning this novel therapeutic agent.

2. Chemical and Physicochemical Characteristics

2.1. Molecular Structure and Properties

Elagolix sodium is chemically distinct from its peptide predecessors. It is a non-peptide, small molecule uracil derivative, chemically described as sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate [7]. This structure was engineered to mimic the receptor-binding pharmacophore of the native GnRH decapeptide while eliminating the peptide bonds that are susceptible to rapid enzymatic degradation in the gastrointestinal tract.

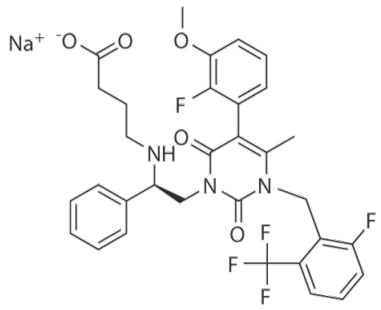

Figure 1. Structure of Elagolix Sodium

The compound exhibits moderate lipophilicity and is characterized as a zwitterion at physiological pH, possessing both acidic and basic functional groups. A critical physicochemical attribute of elagolix is its pH-dependent solubility profile. It demonstrates high solubility in acidic environments (pH < 3) but significantly reduced solubility as the pH increases towards the neutral range typical of the intestinal tract. This physicochemical behavior classifies it generally within the Biopharmaceutics Classification System (BCS) as a Class II compound, denoting low solubility and high permeability, although some literature suggests variable classification depending on the specific salt form and pH conditions [8].

Table 1. Physicochemical Properties of Elagolix Sodium

Property	Description
Chemical Name	Sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate
Molecular Formula	$C_{32}H_{30}F_2N_2NaO_5$
Molecular Weight	~610.6 g/mol
Physical State	White to off-white to light yellow powder
Solubility Profile	High solubility in acidic pH (pH < 3); low solubility in neutral/basic pH
Lipophilicity (LogP)	~2.5 (Moderate)
Hygroscopicity	Hygroscopic (requires moisture protection)
BCS Classification	Class II (Low Solubility, High Permeability)

2.2. Stability Profile

Thermal and photostability investigations serve as foundational elements in the pre-formulation characterization of elagolix. Studies indicate that while the active pharmaceutical ingredient (API) is relatively stable under controlled ambient conditions, it exhibits sensitivity to moisture and oxidative stress. Forced degradation studies have highlighted that elagolix is susceptible to hydrolytic degradation under extreme acidic or alkaline conditions and oxidative degradation when exposed to peroxides [9, 10]. These stability characteristics mandate the use of moisture-protective packaging and the inclusion of specific stabilizers or antioxidants within the drug product formulation.

3. Mechanism of Action

Elagolix operates via a direct, competitive antagonism of the GnRH receptors located on the gonadotroph cells of the anterior pituitary gland. Unlike GnRH agonists, which initially stimulate the receptor leading to a transient surge in gonadotropins (the flare effect) before causing desensitization and downregulation, elagolix induces an immediate suppression of the pituitary-ovarian axis [11].

Table 2. Comparison of Clinical Pharmacology: GnRH Agonists vs. Elagolix

Feature	GnRH Agonists (e.g., Leuprolide)	GnRH Antagonist (Elagolix)
Mechanism	Receptor stimulation followed by desensitization	Competitive receptor blockade
Initial Effect	"Flare" effect (transient increase in LH/FSH)	Immediate suppression of LH/FSH
Onset of Action	Delayed (weeks)	Rapid (hours to days)
Reversibility	Slow recovery of HPO axis	Rapidly reversible upon discontinuation
Estrogen Suppression	Complete (castrate levels)	Dose-dependent (adjustable)
Route of Administration	Parenteral (SC/IM Depot)	Oral (Tablet)

Binding of elagolix to the GnRH receptor blocks the action of endogenous GnRH, thereby inhibiting the secretion of LH and FSH. This reduction leads to a decrease in ovarian production of estradiol and progesterone. A defining pharmacological feature of elagolix is its rapid reversibility; upon discontinuation of the drug, the suppression of the hypothalamic-pituitary-ovarian (HPO) axis is quickly lifted, and hormone levels return to baseline. This rapid "on-off" kinetic profile distinguishes it from depot formulations of GnRH agonists, where the return to fertility can be prolonged and unpredictable. Furthermore, the degree of estrogen suppression is dose-dependent, allowing clinicians to titrate the dosage to achieve partial suppression—sufficient to relieve symptoms of endometriosis or fibroids while maintaining estradiol levels above the threshold that triggers severe vasomotor symptoms or rapid bone density loss [12].

4. Biopharmaceutical Properties

4.1. Absorption and Bioavailability

Following oral administration, elagolix demonstrates rapid absorption kinetics, typically reaching peak plasma concentrations (Tmax) within 0.5 to 1 hour. Despite its rapid uptake, the absolute oral bioavailability is approximately 50%, a value consistent with its classification as a peptidomimetic with moderate molecular weight and lipophilicity. The absorption process is heavily influenced by the physiological environment of the gastrointestinal tract, particularly gastric pH, due to the compound's solubility profile [13].

Food-effect studies have characterized the interaction between dietary intake and elagolix absorption. Administration with a high-fat meal has been observed to alter the pharmacokinetic profile, resulting in a decrease in the peak plasma concentration (Cmax) and area under the curve (AUC) compared to the fasted state. However, the clinical impact of this interaction is generally managed through dosing recommendations relative to meals. The rapid absorption suggests that the drug is primarily absorbed in the upper gastrointestinal tract, correlating with its higher solubility in the acidic gastric milieu [14].

Table 3. Pharmacokinetic Parameters of Elagolix

Parameter	Value/Characteristic	Clinical Significance
Tmax	0.5 – 1.0 hour	Rapid onset of action.
Bioavailability (F)	~50%	Moderate; influenced by dissolution rate.
Protein Binding	>80%	High binding limits free drug fraction but extends duration.
Metabolism	Major: CYP3A Minor: CYP2D6, CYP2C8	Potential for drug-drug interactions with CYP3A inhibitors/inducers.
Elimination Half-life (t½)	4 – 6 hours	Supports once or twice-daily dosing.
Excretion Route	Feces (~90%), Urine (<10%)	Safe for patients with mild renal impairment.
Transporter Substrate	OATP1B1, P-gp	Contraindicated with OATP1B1 inhibitors (e.g., cyclosporine).

4.2. Distribution

Elagolix exhibits a high affinity for plasma proteins, with binding exceeding 80% in human plasma. This extensive protein binding restricts the fraction of free drug available for receptor interaction but also facilitates a sustained duration of action relative to its elimination half-life. The apparent volume of distribution (Vd/F) indicates that the drug distributes extensively into tissues beyond the central vascular compartment [15]. This tissue distribution is critical for its efficacy, although the primary site of action remains the pituitary gland, which is outside the blood-brain barrier.

4.3. Metabolism and Excretion

The metabolic pathway of elagolix involves primarily hepatic clearance. It serves as a substrate for the Cytochrome P450 (CYP) enzyme system, specifically CYP3A, which plays a major role in its biotransformation. Minor metabolic contributions are attributed to CYP2D6 and CYP2C8. The metabolism yields several metabolites, the majority of which are pharmacologically inactive, thereby simplifying the pharmacodynamic profile.

In addition to Phase I metabolism, elagolix is a substrate for hepatic uptake transporters, including the Organic Anion Transporting Polypeptide 1B1 (OATP1B1). This transporter-mediated uptake is a rate-limiting step in its hepatic elimination. Excretion occurs predominantly via the fecal route, accounting for approximately 90% of the administered dose, while renal elimination plays a minor role (approximately 10%). The elimination half-life (t1/2) ranges from 4 to 6 hours, which supports a twice-daily or once-daily dosing regimen depending on the therapeutic indication and dosage strength [16, 17].

4.4. Transporter Interplay

The interplay between metabolic enzymes and transporters is a critical consideration for elagolix. As a weak inhibitor of CYP3A4 and a substrate for OATP1B1, elagolix possesses the potential for drug-drug interactions (DDIs). Co-administration with strong inhibitors of CYP3A4 or OATP1B1 (e.g., cyclosporine, gemfibrozil) can significantly increase systemic exposure to elagolix, necessitating dose adjustments or contraindications. Conversely, elagolix may induce CYP3A enzymes with chronic dosing, potentially altering the pharmacokinetics of co-administered substrates [18].

5. Pharmaceutical Formulation

The formulation development of elagolix is driven by the necessity to overcome the inherent limitations imposed by its physicochemical properties—specifically, its potential for pH-dependent precipitation and stability concerns. Achieving consistent oral bioavailability requires robust pharmaceutical strategies that enhance solubility and ensure stability across the physiological pH range.

5.1. Solubility

To address the solubility challenges, several advanced formulation techniques have been investigated. Solid dispersion technology has emerged as a primary strategy, wherein the drug is dispersed in a hydrophilic carrier matrix (typically polymers like povidone or hypromellose) at the molecular level. This approach reduces the particle size to the molecular limit and improves wettability, thereby significantly enhancing the dissolution rate [19].

Additionally, the use of pH-modifiers within the formulation is critical. Given that elagolix exhibits maximum solubility in acidic media, the incorporation of acidifying agents can create a micro-environmental pH modulation that favors dissolution, particularly in patients with elevated gastric pH (achlorhydria) or those taking acid-reducing agents. Lipid-based drug delivery systems, such as Self-Micro Emulsifying Drug Delivery Systems (SMEDDS), have also been explored to exploit the drug's lipophilic nature, facilitating absorption via the lymphatic system and bypassing first-pass hepatic metabolism [20].

5.2. Factors Affecting Manufacturing

The commercial manufacturing of elagolix tablets typically employs standard pharmaceutical unit operations such as wet granulation or dry granulation. Wet granulation is often preferred to improve the flowability and compressibility of the powder blend, ensuring content uniformity. Excipients play a vital role; microcrystalline cellulose is utilized as a diluent for its excellent compressibility, while disintegrants like croscarmellose sodium are crucial for rapid tablet disintegration. To mitigate the drug's sensitivity to moisture, a protective polymeric film coating is applied to the final dosage form. This coating not only enhances stability but also improves patient compliance by masking any potential unpalatable taste associated with the API [21, 22].

6. Analytical and Bioanalytical Method Development and Validation

The rigorous characterization of elagolix in both bulk drug substances and biological matrices is fundamental to ensuring pharmaceutical quality and understanding pharmacokinetic behavior.

6.1. Spectrophotometric and Chromatographic Analysis

UV-Visible spectrophotometry offers a cost-effective and rapid method for routine quality control. Recent studies have demonstrated the utility of UV methods using acetonitrile-water solvent systems, achieving linearity in specific concentration ranges with detection at λmax ~275 nm. These methods have shown high accuracy (recovery >98%) and precision, making them suitable for initial assay testing where high specificity is not the primary requirement [23].

For more complex separation and impurity profiling, High-Performance Liquid Chromatography (HPLC) remains the gold standard. Stability-indicating HPLC methods are critical for detecting degradation products formed under stress conditions (acidic, basic, oxidative, and photolytic). Research has established gradient elution methods capable of separating elagolix from its related organic impurities within a reasonable run time. For instance, methods utilizing C18 or phenyl-hexyl columns have proven effective in resolving degradants generated under alkaline and oxidative stress, with validation parameters meeting ICH Q2(R1) guidelines for specificity, linearity, accuracy, and robustness [24].

Table 4. Reported Analytical Methods for Elagolix Determination

Methodology	Matrix	Range / Sensitivity	Application	Reference
UV-Spectrophotometry	Bulk / Tablet	12–48 µg/mL (λmax 275 nm)	Routine QC Assay	[23]
HPLC-UV	Tablet Dosage Form	Detection at 210 nm	Impurity Profiling & Assay	[24]
LC-MS/MS	Human Plasma	LLOQ: ~1-5 ng/mL	Pharmacokinetic Studies	[25]
HPTLC	Pharmaceutical Formulation	Broad linear range	Rapid screening	[24]
HRMS / NMR	Stress samples	Structural Elucidation	Degradation Product ID	[9]

6.2. Advanced Bioanalytical Techniques

In the context of pharmacokinetic studies and therapeutic drug monitoring, Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) is the preferred analytical tool due to its superior sensitivity and selectivity. LC-MS/MS methods facilitate the quantification of elagolix in plasma at nanogram levels, essential for defining the pharmacokinetic profile in clinical trials. Recent developments have focused on establishing LC-MS compatible methods that can simultaneously identify structural analogues and metabolic byproducts. High-resolution mass spectrometry (HRMS) combined with Nuclear Magnetic Resonance (NMR) spectroscopy has been instrumental in characterizing novel degradation products, providing structural elucidation that informs the degradation pathways and stability profile of the drug [25, 26].

7. Quality by Design (QbD) Approach

The pharmaceutical industry is increasingly adopting Quality by Design (QbD) principles to move from empirical formulation development to a systematic, risk-based approach. For a complex molecule like elagolix, QbD is indispensable for defining the design space that ensures product quality.

7.1. Defining QTPP and CQAs

The first step in the QbD framework is establishing the Quality Target Product Profile (QTPP), which outlines the desired performance characteristics of the drug product, such as dosage form, route of administration, and bioavailability targets. From the QTPP, Critical Quality Attributes (CQAs) are derived. For elagolix, key CQAs include dissolution rate, assay (drug content), degradation products (impurities), and polymorphic stability.

7.2. Risk Assessment and Design of Experiments (DoE)

Risk assessment tools, such as Ishikawa diagrams or Failure Mode and Effects Analysis (FMEA), are used to identify Critical Process Parameters (CPPs) that impact CQAs. In the manufacturing of elagolix tablets, CPPs might include granulation fluid volume, mixing time, and compression force. Design of Experiments (DoE) is subsequently employed to understand the multidimensional interactions between these parameters. By systematically varying CPPs, researchers can establish a "design space"—a range of operating conditions that consistently yield a product meeting the desired quality specifications. This approach minimizes batch failures and ensures regulatory compliance [27, 28].

7.3. Regulatory Considerations

The regulatory approval of elagolix involved a comprehensive assessment of its safety and efficacy profile, with particular scrutiny on hepatic safety and bone mineral density preservation. Stability testing follows the International Council for Harmonisation (ICH) guidelines. Long-term and accelerated stability studies indicate a shelf-life of 24 months when stored at controlled room temperature (below 25°C) [29]. The packaging configuration is critical; high-density polyethylene (HDPE) bottles with desiccant or aluminum-aluminum blisters are typically required to protect the drug from moisture-induced degradation.

Table 5. Quality by Design (QbD) Risk Assessment for Elagolix Tablets

Critical Quality Attribute (CQA)	Risk Level	Critical Process Parameters (CPPs)	Control Strategy
Dissolution Rate	High	Particle size of API, Binder concentration, Granulation fluid amount	Micronization of API, optimization of disintegrant levels.
Assay (Potency)	Medium	Blending time, Mixer speed	Validation of mixing homogeneity.
Degradation Products	High	Drying temperature, Moisture content, Compression force	Control drying LOD, use moisture-protective packaging.
Content Uniformity	High	Granule size distribution, Lubrication time	Sifting and milling controls.
Hardness/Friability	Low	Compression force, Turret speed	In-process checks during compression.

8. Novel Trends

As the first oral GnRH antagonist, elagolix serves as a prototype for future drug development in reproductive health. Future research directions include:

- Nanotechnology: Investigation of nanocarriers, such as polymeric nanoparticles or liposomes, to further enhance oral bioavailability and potentially target delivery to specific tissues.
- Combination Therapies: Optimization of fixed-dose combinations with hormonal add-back therapies (estradiol/norethindrone) to improve long-term safety profiles regarding bone health.
- Modified Release: Development of extended-release formulations to reduce dosing frequency from twice daily to once daily, thereby improving patient adherence.
- *In Silico* Modeling: Enhanced utilization of physiologically based pharmacokinetic (PBPK) modeling to predict drug-drug interactions and optimize dosing regimens in special populations [30].

9. Conclusion

Elagolix is a valuable drug in pharmaceutical science, that effectively bridged the gap between peptide-based receptor targeting and oral small-molecule delivery. Its development shows the importance of a multidisciplinary approach integrating medicinal chemistry, biopharmaceutics, and advanced formulation science. Elagolix has provided a non-invasive, adjustable therapeutic option for millions of women suffering from endometriosis and uterine fibroids by overcoming significant challenges related to solubility and metabolic stability. Continued innovations in analytical characterization and QbD-driven manufacturing will further refine the quality and accessibility of this therapeutic class, paving the way for next-generation GnRH antagonists.

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