Advanced Drug Delivery Reviews 234 (2026) 115882

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

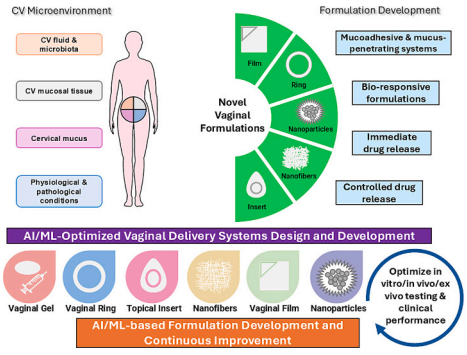
journal homepage: www.elsevier.com/locate/adr

Artificial intelligence and machine learning in smart vaginal formulation development☆

Deborah A. Ogundemuren [a,c,1], Vivek Agrahari [b,1], Andrew P. Wong [b], Carolina Herrera [b], Margaret O. Ilomuanya [a,c], Gustavo F. Doncel [b,*]

[a] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Lagos, Lagos, Nigeria
[b] CONRAD, Macon & Joan Brock Virginia Health Sciences, Old Dominion University, Norfolk, VA 23507, USA
[c] MEDAFRICA GMP Laboratory, Faculty of Pharmacy, University of Lagos, Lagos, Nigeria

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Artificial intelligence
Machine learning
Intravaginal administration
Women's health
Drug delivery systems
Vaginal microenvironment

ABSTRACT

Vaginal drug delivery in women's health remains underutilized and insufficiently studied, largely due to the complexity and dynamic nature of the vaginal microenvironment. Variations in vaginal pH, hormonal levels, and microbiota composition introduce significant biological variability, complicating formulation design and contributing to inconsistent therapeutic outcomes and poor patient adherence. Conventional vaginal formulations often fail to account for these individual differences, highlighting the need for more adaptive and predictive approaches. Emerging advances in artificial intelligence (AI) and machine learning (ML) offer promising strategies to address these challenges by enabling multi-parameter, data-driven formulation development that explicitly considers biological variability. Despite their transformative potential, the application of AI and ML in vaginal drug delivery remains limited. This review addresses this gap by examining the emerging role of AI/ML in the design, optimization, and development of next-generation vaginal formulations, including mucoadhesive, mucus-penetrating, bio-responsive, and controlled-release systems. Key factors influencing formulation performance, such as vaginal microbiota composition, are discussed, and ethical, regulatory, and technical challenges

☆ This article is part of a Special issue entitled: 'AI/ML in Drug Delivery' published in Advanced Drug Delivery Reviews.

* Corresponding author.
E-mail address: doncelgf@odu.edu (G.F. Doncel).

[1] These authors contributed equally.

https://doi.org/10.1016/j.addr.2026.115882
Received 23 January 2026; Received in revised form 22 April 2026; Accepted 24 April 2026
Available online 27 April 2026

relevant to integrating AI/ML into vaginal drug delivery are also considered. Although research is in its early stages, existing studies indicate that AI and ML integration can enhance predictability, efficiency, and reproducibility in vaginal formulation development. Finally, we highlight the potential of developing personalized medicines through the integration of AI/ML and digital health monitoring devices to create patient-centered vaginal drug delivery systems, thereby advancing therapeutic outcomes and transforming women's health.

1. Introduction

Reproductive health lies at the heart of women's well-being, shaping both health outcomes and quality of life [1]. Women account for nearly half of the global population, and equitable access to high-quality sexual and reproductive healthcare is recognized as a global priority [2]. However, the biological and contextual diversity that characterizes women's health is not adequately reflected in currently marketed drug delivery technologies, which largely remain standardized and poorly suited to inter-individual variability. Intravaginal drug delivery has gained increasing attention as a platform for both local and systemic treatment of women's health conditions [3], offering several pharmacological advantages, including high tissue vascularization and avoidance of hepatic first-pass metabolism, which support enhanced local bioavailability and reduced systemic dose-related side effects. However, drug delivery within this highly specialized biological microenvironment is also associated with significant practical and formulation-related challenges, such as risk of local irritation and disturbance of the vaginal microenvironment, poor retention, leakage, and messiness, which lead to low patient adherence, making conventional formulations such as hydrogels and creams perform sub-optimally [4]. The vaginal environment undergoes continuous remodeling across the female lifespan from the neonatal period through reproductive and menopausal stages [5,6], driven by fluctuations in estrogen levels, glycogen availability, epithelial thickness, and microbial colonization patterns [5,7,8]. This remodeling contributes to marked inter-individual and temporal variability in vaginal pH, microbiota, enzymatic activity, mucus composition, hormonal status, and cervicovaginal (CV) fluid volume. Here, CV fluid refers to the total fluid present within the vaginal lumen, including CV mucus (CVM), other vaginal secretions, and serum transudate. In contrast, CVM specifically denotes the mucus component secreted by the endocervix. The physiological dynamics found in the CV compartment directly influence drug solubility, diffusion, stability, absorption, and tissue retention, thereby limiting the development of fixed-dose, one-size-fits-all vaginal formulations that satisfy the necessary duration of action and patient comfort, safety, or adherence [4,9,10].

These challenges highlight the need for more adaptive and responsive vaginal formulation development strategies. Advanced formulations, such as nanocarriers, lipid-based formulations, bioadhesive systems, and controlled-release devices, such as intravaginal rings (IVR), are being developed to enhance mucoadhesion, mucus-penetration, fine-tune drug release profiles, and facilitate epithelial penetration [4,7,11]. Though the preclinical results are promising, developing such novel but complex vaginal formulations typically relies on trial-and-error methods that are time- and resource-intensive, involve numerous experiments with limited predictive insights, and result in higher costs and longer development timelines [12–14]. In this regard, Artificial Intelligence (AI) and Machine Learning (ML) could offer powerful tools to reduce reliance on traditional empirical approaches in formulation development and accelerate the development timeline [15,16].

Several recent reviews have examined the application of AI and ML in pharmaceutical product development for different indications [17–21]; however, their specific role in vaginal product development has not been comprehensively explored. This review addresses this gap by exploring how the transformative potential of AI and ML in the design, development, and optimization of next-generation vaginal drug delivery systems has been utilized thus far. Data-driven decision-making and precise formulation design that can efficiently account for inter-individual variability using AI/ML technologies could significantly improve therapeutic effectiveness across various clinical indications within the highly specialized vaginal microenvironment, including sexually transmitted infections, pregnancy-related complications, and menopausal conditions. Additionally, integrating AI and ML with advanced vaginal delivery systems may accelerate the development of complex multipurpose prevention and treatment strategies for women's health conditions.

2. Complexity and variability in the vaginal microenvironment affecting formulation development and drug delivery

The performance of vaginal drug delivery systems is governed by a complex interplay of physiological, microbiological, and formulation-related factors that influence drug absorption, retention, and therapeutic efficacy. A clear understanding of these determinants is essential for the rational design and optimization of vaginal formulations. While these factors have been discussed in the literature [6,22], a focused summary of the key variables influencing formulation performance is presented here. The complex, dynamic nature of the vaginal microenvironment is continuously influenced by hormonal fluctuations, alterations in the microbiota, sexual activity, and hygiene practices that influence pH, fluid volume, epithelial structure, mucus, and enzymatic activity, factors that can substantially affect local drug delivery and product performance [6,23–27].

Vaginal microbiota is a key determinant of vaginal health and directly influences drug release, absorption, and therapeutic efficacy. Vaginal eubiosis is defined by dominance of *Lactobacillus* species (e.g., *L. crispatus, L. gasseri, L. iners,* and L. *jensenii*), which maintain an acidic environment and support epithelial and immune homeostasis [22,28,29]. In contrast, dysbiosis, characterized by increased microbial diversity and loss of *Lactobacillus* dominance, is associated with enhanced enzymatic activity and pathogenic biofilm formation, thereby limiting drug penetration and reducing therapeutic outcomes [30–32]. According to Gustin et al., women harboring highly diverse vaginal microbiota prior to treatment had a reduced response to standard metronidazole therapy for bacterial vaginosis (BV) [32].

BV significantly impairs the barrier properties of CVM [33,34]. BV-associated degradation of the mucus barrier reduces viscosity and structural integrity, making it less effective at retaining vaginal formulations. As a result, drugs may diffuse more rapidly but are also cleared more quickly due to reduced mucoadhesion and increased fluidity [35,36]. Evidence shows that CVM associated with BV permits greater viral and nanoparticle mobility, largely due to reduced adhesive interactions within the mucus network [33]. This mucus dysfunction, resulting from the loss of lactobacilli, overgrowth of pathogenic bacteria, and associated inflammation, has significant implications for vaginal drug delivery [34]. Additionally, the altered pH and elevated enzymatic activity can compromise drug stability and modulate release profiles, particularly for formulations engineered to be bio-responsive to the higher pH of semen during intercourse. Consequently, formulations optimized for a healthy, low-pH, *Lactobacillus*-dominant normal vaginal environment may perform unpredictably in the setting of BV [37–40]. For example, clinical data from a 90-day tenofovir (TFV) vaginal ring showed that vaginal microbiota composition influenced drug release and mucosal pharmacokinetics [38]. A secondary analysis of TFV gel clinical efficacy has shown that TFV displays lower efficacy in

preventing HIV-1 acquisition in the presence of vaginal inflammatory conditions and prevalence of anaerobic microbiota [40]. A pH-sensitive release of TFV from a vaginal ring may be used as a smart property to increase drug release when needed in the presence of anaerobic bacteria and BV, which are typically associated with higher vaginal pH.

In healthy reproductive-age women, vaginal pH is typically acidic (pH 3.5–4.5) due to lactic acid production by *Lactobacillus* spp. [6]. These bacteria metabolize glycogen-derived substrates from desquamated vaginal epithelial cells, a process enhanced by estrogen-mediated increases in intracellular glycogen [41,42]. In addition to microbial metabolism, luminal pH is also regulated by host mechanisms, including estrogen-dependent activity of V-type H^+-ATPases in vaginal epithelial cells [43]. This acidic environment provides protection against pathogens but can also influence drug stability, ionization, and dissolution [44–46]. For example, TFV and its prodrugs show pH-dependent stability and undergo degradation under strongly acidic hydrolytic conditions. At the typical vaginal pH, however, TFV remains stable [45]. It is worth noting that the vaginal pH is dynamic and influenced by both physiological and behavioral factors. Hormonal fluctuations across the menstrual cycle play a central role, as estrogen regulates epithelial maturation, glycogen availability, and vaginal secretions, thereby modulating lactic acid production [42,43]. During the proliferative and peri-ovulatory phases, elevated estrogen levels promote glycogen accumulation and increased lactic acid production, resulting in a more acidic environment. In contrast, the secretory phase is associated with reduced glycogen content and epithelial thickness, leading to decreased lactic acid production and a corresponding increase in pH [42,43].

Transient elevations in vaginal pH also occur under specific conditions. During menstruation, menstrual blood (pH ~7.2–7.4) temporarily neutralizes the acidic milieu, increasing pH toward near-neutral values before it returns to baseline following menses. This shift is accompanied by alterations in the vaginal microbiota, including reduced *Lactobacillus* dominance and a relative increase in non-*Lactobacillus* spp., with recovery observed post-menses. Similarly, unprotected intercourse elevates vaginal pH (pH 7–8) due to the alkaline nature of semen [47]. Additional factors, such as coital frequency, the volume and distribution of CV secretions, vaginal transudate, and spatial variation along the vaginal canal, further contribute to pH variability [41]. These fluctuations are closely linked to shifts in microbial composition, particularly the balance between *Lactobacillus* and non-*Lactobacillus* spp., which collectively regulate vaginal acidity. In pregnancy, the vaginal microbiota is generally more stable and predominantly *Lactobacillus*-dominated compared to the non-pregnant state, where greater temporal variability is observed. This increased *Lactobacillus* dominance is associated with lower microbial diversity and likely contributes to the maintenance of an acidic vaginal environment [48,49]. Such pH variations can alter drug ionization and bioavailability, underscoring the importance of considering vaginal pH during formulation design. Szymańska et al. demonstrated the effect of changes in vaginal pH on polymer behavior, drug release kinetics, and tissue permeation by showing that vaginal pH contributes to variability in tenofovir disoproxil fumarate (TDF) bioavailability from chitosan (CS) and poly (ethylene oxide) (PEO)-based nanofibrous delivery systems [44].

CV fluid volume changes with the phases of the menstrual cycle, reproductive life stages, and pathologies. An average follicular and luteal phase volume, at a given time, typically ranges from 0.5 to 1.5 mL, with a transient increase near ovulation (up to 3–5 mL) [50,51]. Daily CV fluid production is estimated to be 1–3 mL on average in women of reproductive age, with significant increases possible during infections (e.g., trichomonas) and decreases during post-menopause [52–54]. This fluid serves as the medium for drug dissolution and transport [55–57]. Limited fluid volumes may restrict drug solubility, whereas increased volumes can accelerate drug clearance, thereby reducing the residence time [6]. The vaginal epithelium, local enzymatic activity, and mucus turnover further influence drug delivery [11]. Vaginal epithelial structure and integrity can regulate drug permeation, while local enzymatic activity may degrade susceptible compounds, particularly peptide- and protein-based therapeutics [22,41]. Together, these factors (summarized in Fig. 1 and Table 1) vary substantially across individuals, which creates significant challenges in the design and development of robust vaginal formulations and delivery devices .

Conventional delivery systems are often not designed to accommodate the substantial variability of the vaginal environment. As a result, formulations such as liquid and hydrogel-based systems are rapidly cleared, leading to leakage, reduced residence time, and inconsistent performance across users [65]. While innovative strategies such as mucoadhesive and mucus-penetrating systems can improve performance [66–68], this biological variability highlights the limitations of trial-and-error methods in formulation development. In parallel, drug physicochemical properties, including molecular weight, lipophilicity, ionization state, particle size, and solubility, play a central role in determining vaginal drug disposition and bioavailability [4]. In this context, AI- and ML-based approaches emerge as powerful tools for integrating physiological, drug-related, and formulation variables that govern vaginal drug delivery, thereby enhancing therapeutic efficacy.

3. Role of artificial intelligence and machine learning in formulation development

AI is broadly defined as the ability of computational systems to learn from data and adapt to new information in ways that resemble human intelligence. Advances in big data availability, algorithm development, and computing power have driven rapid progress in AI, enabling its successful application across a wide range of scientific domains, including drug delivery [69]. ML, a key subset of AI, uses data-driven algorithms to learn patterns and relationships from experimental or clinical data without explicit programming and is particularly well-suited for modeling complex, high-dimensional, and nonlinear relationships [13]. Deep learning, a subset of ML, employs multi-layer neural networks to capture subtle nonlinear interactions and automatically extract higher-level features from complex datasets [70,71]. At a basic level, ML tasks fall into two categories: regression, which predicts continuous outcomes, and classification, which assigns samples to predefined categories [72]. Common ML paradigms include supervised learning, which predicts outputs from labeled data; unsupervised learning, which identifies patterns in unlabeled data; and reinforcement learning, which iteratively optimizes decisions, for example, in adaptive dosing strategies [16,73,74]. While a wide range of algorithms exists, from decision trees and support vector machines to neural networks, the key consideration is matching the method to the dataset, problem type, and desired interpretability [75–79].

In pharmaceutical research, ML has enabled a deeper understanding of how subtle variations in formulation variables influence product performance, while also facilitating key tasks such as drug-release prediction, encapsulation efficiency estimation, and formulation optimization in advanced delivery systems [13,80–83]. Supervised learning models, a subset of ML, such as random forest and gradient-boosting algorithms, have been successfully applied to predict drug release profiles and kinetic parameters directly from formulation composition, highlighting their ability to capture complex dissolution behavior that is difficult to describe using traditional mechanistic models [72,84].

ML approaches have shown promise in enhancing the design and performance of controlled-release systems. For example, neural networks and genetic programming have been applied to model macromolecule release from poly(lactic-*co*-glycolic acid) (PLGA) microspheres, while ensemble ML models have accurately predicted small-molecule drug release and simultaneously identified critical formulation drivers [85,86]. In parallel, natural language processing (NLP) has emerged as a valuable tool to support formulation development by extracting relevant insights from unstructured data sources, such as scientific literature and clinical records [87–89]. Shetty et al., for instance, employed a domain-specific NLP model to extract polymer-

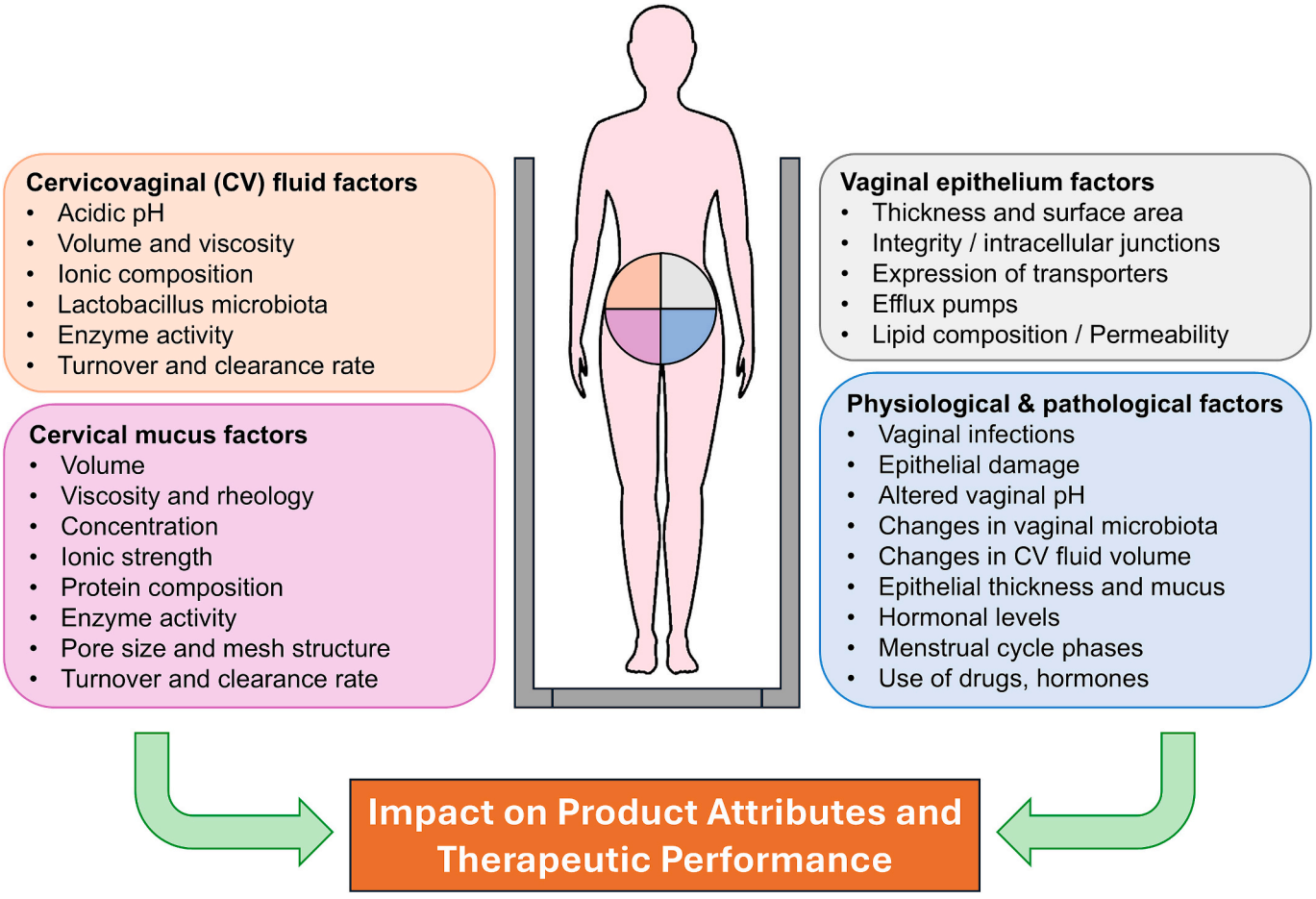


Fig. 1. Cervicovaginal (CV) microenvironment-related factors affecting formulation development and drug delivery.

related information from thousands of published abstracts, demonstrating how unstructured literature can be transformed into structured datasets for data-driven materials and formulation research [89]. Beyond data extraction, AI-driven experimental workflows are increasingly being used to guide formulation design and optimization. Cao et al. reported an integrated formulation platform combining ML and robotic experimentation, guided by Bayesian decision-making, to optimize a complex commercial liquid formulation in the absence of established physical models [90]. The commercial formulation used by Cao et al. consisted of three different surfactants (Texapon SB3, Dehyton AB30, and Plantacare 818), a polymer (Dehyquart CC7), and a thickener (Arlyon TT). Targeting specific properties, including stability and turbidity, viscosity, and low ingredient cost in iterations of a formulated liquid product without physical models, semi-automated, ML-driven robotic experiments identified formulations that met customer-defined performance criteria within 15 working days. This approach outperformed the best solutions from a previous dataset created by expert formulation scientists using factorial design to accelerate development and achieve target formulation performance.

These studies demonstrate that AI- and ML-based frameworks enable multivariate analysis of complex, nonlinear interactions between formulation composition and drug-release kinetics, which are often difficult to capture with conventional statistical methods [84,91]. Several recent review articles have also comprehensively discussed the application and impact of AI and ML in formulation development, highlighting their potential to enhance formulation design, optimization, and performance prediction [15,19,73,75,92]. As a result, AI/ML-based data-driven methodologies can accelerate development timelines, reduce costs, and improve the robustness and reproducibility of pharmaceutical formulations, including the rational design of advanced vaginal delivery systems [12,93].

3.1. *Integration of AI and ML tools in vaginal formulation design and development*

Empirical mathematical models and molecular dynamics simulations have advanced our understanding of the behavior of vaginal drug delivery systems [94]. However, empirical models are typically applied after experimental data have been generated and therefore provide limited predictive ability, while molecular dynamics simulations are computationally intensive and cannot yet replace in vitro testing. These constraints have driven growing interest in ML-based approaches, which can integrate information across multiple variables and offer more efficient, adaptable predictive tools for formulation development [92]. Such data-driven methods enable the prediction of key product performance parameters, even under complex and variable use conditions. For instance, an artificial neural network (ANN)-based optimization framework was used to relate ethylene–vinyl acetate (EVA) polymer membrane composition and thickness to drug (estradiol) permeation behavior, with constrained optimization applied to identify formulation parameters capable of achieving predefined target doses [95]. Such approaches could be used to develop polymer-based vaginal devices for hormones or small-molecule drug delivery.

Currently, Design of Experiments (DoE) remains a valuable methodology for systematic experimental investigation; however, it is inherently constrained by prespecified parameter ranges and limited scalability [96,97]. In contrast, ML models can assimilate heterogeneous data sources and capture complex, multifactorial relationships between

Table 1
A summary of key vaginal microenvironmental, physiological, and socio-behavioral factors that may influence product performance and serve as inputs for AI/ML-enabled drug delivery design.

Variability factor	Primary drivers	Implications for vaginal drug delivery	Ref
Vaginal pH	Microbiome composition (e.g., *Lactobacillus* spp.), hormonal activity, menstrual cycle, age	Alters drug ionization and solubility, modifies absorption profiles, and may lead to drug precipitation or unfavorable changes in formulation matrices	[11,58,59]
Vaginal microbiota	Pathological conditions (e.g., vaginitis, BV), hormonal changes, age, ethnicity, hygiene practices, sexual activity	Influences local drug metabolism and inflammatory state, potentially altering drug release behavior and overall therapeutic efficacy of the product	[6,28,60,61]
Cervicovaginal fluid	Hormonal state, microbiome composition, immune mediators, sexual arousal, epithelial turnover, age	Affects drug bioavailability and residence time, as reduced mucoadhesion may limit prolonged vaginal retention of dosage forms; variability in fluid volume and composition can influence drug solubility and absorption, where increased fluid levels may enhance dissolution but also accelerate formulation clearance	[59,62]
Vaginal enzymatic activity	Hormonal variation	Enzymatic activity, including proteolytic processes, may degrade susceptible drugs (e.g., peptides), affecting drug stability and delivery profiles	[6,22,59]
Hormonal activity	Menstrual cycle phase, pregnancy status, hormonal contraception, age	Modulates epithelial permeability, mucus properties, microbiome composition, and fluid secretion, contributing to variability in drug absorption and performance	[11,23,25]
Epithelial and Immune cell structure and function	Hormonal regulation (e.g., estradiol, progesterone) and environmental factors (e.g., pH, oxygen levels)	Changes in epithelial barrier integrity and immune signaling may alter drug transport and flux across the vaginal epithelium	[24,25,60]
Socio-behavioral factors	Sexual activity, hygiene practices, and cultural norms	May reduce drug levels, formulation retention, and bioavailability by perturbing vaginal pH and microbiome stability	[62–64]

formulation attributes and vaginal physiology. For example, Pałkowski et al. applied a dominance-based rough set approach, a rule-based AI technique, to analyze the relationships between formulation composition, processing parameters, and post-application vaginal pH in tablets and pessaries [98]. They assessed how excipients (methylcellulose, glycerol, lactic acid, chitosan, Eudragit E-100) influenced vaginal acidic pH to optimize formulations that rapidly disintegrate or deform while maintaining physiological pH. Sustained release of lactic acid was achieved using its complexes with chitosan or E-100 in different ratios. Formulations were characterized for post-swelling viscosity, with vaginal pH following administration as the primary outcome measure. The decision rules generated by the study identified lactic acid content and lactic acid-to-polymer ratios as the primary determinants in maintaining physiological pH after administration of the dosage form, while indicating that formulation type (pessary versus tablet) had minimal influence on quality classification. More advanced ML architectures have also been applied to model drug transport behavior in vaginal delivery systems. An ML cascade model was previously developed to relate drug diffusivity from a mucoadhesive delivery system to formulation and local physiological conditions [99]. When evaluated in simulated vaginal fluid (SVF), this hybrid model demonstrated superior predictive accuracy compared with conventional regression-based approaches, further illustrating the advantages of ML in capturing complex interactions between formulation variables and physiological conditions.

Below, we highlight representative studies demonstrating the application of AI and ML in the development of vaginal drug delivery systems, including mucoadhesive, mucus-penetrating, bio-responsive, controlled-release, and immediate-release formulations. Schematics illustrating both conventional and innovative vaginal delivery platforms are presented in Fig. 2. A summary of studies applying AI and ML methodologies to vaginal formulation development is provided in Table 2. In addition, the use of AI- and ML-based approaches in other routes of administration with relevance to vaginal formulation design and development is discussed.

3.2. *Mucoadhesive and mucus-penetrating vaginal delivery systems*

Mucoadhesive formulations are designed to prolong residence time at the site of action, enabling drug delivery over extended periods [106]. By adhering to the vaginal mucosa, mucoadhesive systems resist natural clearance mechanisms and maintain contact with the epithelium, which improves local drug absorption [106,107]. Many factors, including polymer chemistry, drug physicochemical properties, formulation rheology, vaginal pH, fluid volume, and mucus turnover, affect the interactions between the formulation and the CV mucus layer [6,36,107]. While studies on AI/ML applied exclusively to vaginal mucoadhesive formulation design are still emerging, some relevant examples illustrate the potential of these technologies.

Ndesendo et al. combined ANN with molecular modeling to optimize bioadhesion and erosion behavior in intravaginal polymeric devices [101]. They formulated caplet-shaped devices containing zidovudine and polystyrene sulfonate, and an ANN-driven analysis enabled the rational selection of the polymer to maximize bioadhesion while maintaining matrix integrity under simulated vaginal conditions. This study demonstrated the integration of molecular mechanic simulations with ANN to optimize polymer composition, advancing rational design strategies for improved formulation performance. New deep generative models, such as Variationally Encoded Conditional Tabular Generative Adversarial Network (VECT-GAN), have been developed to support the discovery of polymers with desirable mucoadhesive properties, demonstrating proof-of-concept for data-driven polymer design [108]. By improving model performance across multiple datasets and enabling the design and experimental validation of novel mucoadhesive polymers, this work highlights the potential of synthetic data generation to accelerate and enhance pharmaceutical research. An earlier work

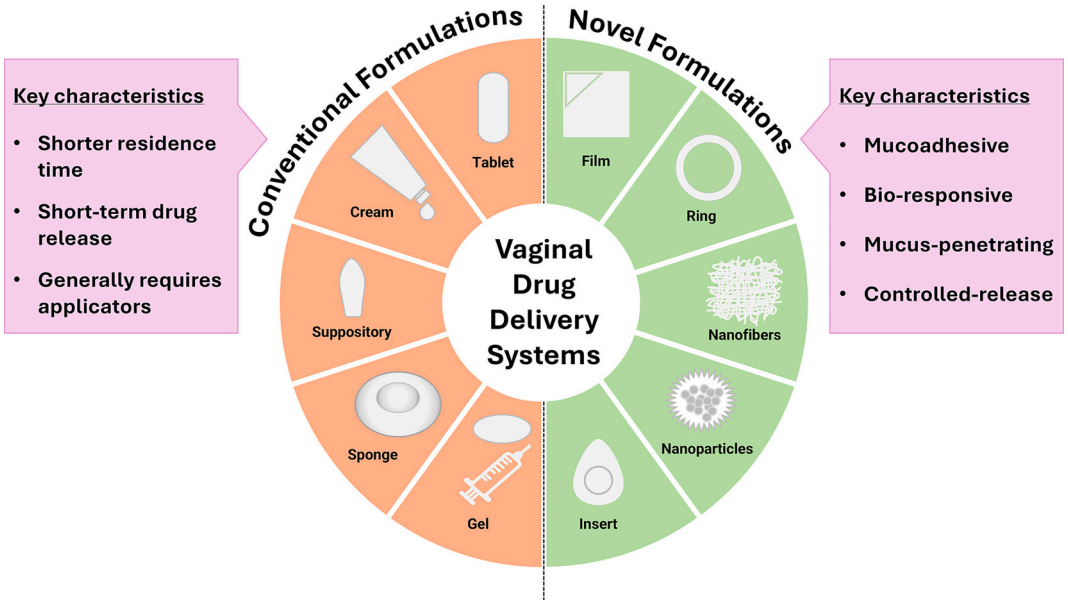


Fig. 2. Schematics for conventional and novel vaginal drug delivery formulations.

described the development of mucoadhesive gels and freeze-dried tablets for the HIV microbicide dapivirine [93]. Here, an ANN model was used to investigate the effects of polymer ratio, mucoadhesion, and delivery system (gel or tablet) on drug release, mucoadhesive force, and formulation viscosity. As predicted and confirmed by experimental data, freeze-dried systems with a lower HPMC:PVP ratio and a higher carbopol concentration showed optimal results [93]. Another study applied an ANN model integrated with response surface methodology to optimize a vaginal hydrogel formulation combining TFV and cyanovirin-N [104]. Researchers employed a Box-Behnken design to systematically evaluate how varying concentrations of excipients (PEG, sodium carboxylmethylcellulose, and calcium chloride) influenced drug release, permeation flux, and mucoadhesion. ANN models enabled efficient exploration of the formulation space, improved optimization through increased accuracy, and fewer experimental runs [104]. These studies demonstrated how ML-augmented design can support the optimization of complex vaginal formulations.

Research on mucoadhesive systems from other routes of administration uses ML optimization frameworks that can also be adapted to vaginal formulations. In predictive modeling, AI models trained on in vitro datasets can anticipate the performance of new formulations by simulating mucoadhesive behavior under varying physiological conditions, thereby guiding formulation development. Similarly, these tools can assist in testing vaginal formulations, which traditionally require multiple in vitro assays, such as rheology, mucoadhesion, and drug release [109,110]. For instance, ML models have been used to optimize the properties of oral chitosan-coated mucoadhesive nanostructured lipid carriers (NLCs) loaded with fluconazole [111], highlighting their potential to inform the design of vaginal mucoadhesive systems. In this study, a Box-Behnken design, ANN, and variable-weight desirability were employed to optimize the effects of drug, surfactant, and solid lipid concentrations on size and drug entrapment efficiency. The resulting optimized NLCs exhibited a particle size of 335 ± 13.5 nm and an entrapment efficiency of 73.1 ± 4.9%, closely matching predicted values of 330 nm and 75%, respectively. The low prediction errors (1.5% for particle size and 2.6% for entrapment efficiency) supported the model's reliability and predictive capability. This demonstrated the use of AL/ML models trained on in vitro data to inform mucoadhesive performance characteristics of an oral formulation, and a similar framework could be implemented in vaginal mucoadhesive formulation development.

Vaginal mucus-penetrating systems are important because they facilitate efficient and uniform transport of therapeutic agents through the mucus barrier to the underlying epithelium, ensuring effective delivery to the target cells [66,112,113]. Traditional mucoadhesive systems, such as hydrogels, often become trapped in the outer mucus layer and are rapidly cleared by natural mucus turnover, limiting drug distribution and residence time. In contrast, mucus-penetrating particles are engineered to avoid adhesive interactions with mucin and are small enough to diffuse deeply into the mucus, leading to more uniform epithelial coverage and prolonged retention. This enhanced penetration and retention of vaginal nanoparticles have been shown to provide greater protection against viral challenges than conventional formulations [66]. Since vaginal mucus is a viscoelastic, heterogeneous gel that acts as a protective barrier to effective drug delivery, AI and ML can specifically help parse this complex interplay by analyzing large, multidimensional datasets on mucus rheology, nanoparticle size, surface chemistry, and diffusion behavior, enabling predictive models of mucus diffusivity.

While studies on AI/ML applied exclusively to vaginal mucus-penetrating formulations are still emerging, and no published work has yet appeared, research from other routes of administration using ML optimization frameworks shows that this approach can be adapted to vaginal formulations. For example, ML models have been used to classify polyethylene glycolylated nanoparticle diffusion modes and predict mobility patterns by combining particle-tracking data with mathematical diffusion models, thereby providing insights into which design factors most strongly influence transport across human airway mucus barriers [114]. The authors identified diffusion mode and mucus microstructure (e.g., solids concentration and pore size) as key factors governing nanoparticle mobility and penetration. Since airway and CVM share fundamental similarities as viscoelastic gels with comparable mucin polymer networks and compositions, findings from airway mucus studies can offer valuable insights for understanding nanoparticle diffusion in CVM, despite differences in mucin types and local physiological conditions [115,116]. Another notable example applies supervised ML to distinguish patterns of diffusion of nano- and micro-particles within complex colonic mucus models by incorporating microrheological features extracted from particle trajectories [117]. The authors showed that ML-driven diffusional fingerprinting characterizes particle motion across sizes and charges and identifies key factors such as particle size, surface charge, mucus viscoelasticity, and microscale

Table 2
Applications of AI/ML technologies in vaginal drug delivery systems.

Vaginal drug delivery system	Input data and AI models used	Optimized outputs	ML performance and key findings	Translational relevance
Segmented combination-type (anastrazole / levonogestrel) vaginal ring for endometriosis [12]	XGBoost: Core material, membrane material, membrane thickness, cross-sectional diameter, drug concentration, and drug segment length	Daily drug release profiles and optimized segmented ring designs	Good agreement was observed between predicted and experimental day 4 release values, with high accuracy for LNG and acceptable performance for ATZ, while formulation parameters were predicted with errors within acceptable limits.	Model developed from in vitro data; no reported IVIVC or in vivo validation
Dapivirine polymeric vaginal film for HIV prevention [100]	ANN (single hidden layer, 7 neurons, feed-forward) combined with an evolutionary algorithm: HME process parameters (barrel temperature, screw speed, feed rate) and experimental film performance data	Film dissolution at 30 min, puncture strength, and drug content; optimized HME processing conditions	The model demonstrated strong predictive performance, with training and validation RMSE values of 0.043 and 0.098, respectively. Validation R^2 values ranged from 0.822 to 0.997 across the outputs, and blind test evaluation further confirmed the model's robustness, with $R^2 = 0.987$ and $r = 0.999$. Prediction errors ranged from 5.32% to 15.46%, with the highest deviation observed for drug content.	Model developed from in vitro data; no reported IVIVC or in vivo validation
Freeze-dried mucoadhesive vaginal tablets and gels for HIV prevention [93]	ANN; (multilayer perceptron, feed forward backpropagation) Formulation variables: Polymer composition (HPMC:PVP ratio), formulation type (gel vs freeze-dried tablet)	Dapivirine cumulative release at 24 h, mucoadhesive force (Fmax), zero-rate viscosity; optimized formulation composition	ANN accurately modeled formulation-performance relationships, with no significant difference between predicted and experimental values ($p > 0.05$). Statistical significance was used for reporting, and no regression-based error metrics were reported. Optimal formulations achieved balanced release, adhesion, and viscosity.	In vitro modeling performed under sink conditions using release testing and rheological characterization; no in vivo validation or IVIVC analysis was conducted
Intravaginal bioadhesive polymeric device (IBPD) for HIV prevention [101]	ANN, Multi-Layered Perceptron (MLP) feedback Neural Network, Polymer type and composition, matrix erosion experimental data	Optimized polymer composite for molecular bioadhesivity and controlled matrix erosion	The ANN demonstrated high predictive performance for matrix erosion behavior, showing strong agreement between predicted and experimental outputs ($R^2 = 0.99$; MSE = 0.001). The model effectively identified the key polymer components that influence matrix erosion. Hydrophobic polymers (EC, PLGA) were associated with reduced erosion, whereas hydrophilic polymers (PVA, PAA) increased erosion rates.	Study based on in vitro matrix erosion modeling and computational optimization; no in vivo validation or IVIVC assessment
Trigger-sensitive hyaluronic acid/palm oil-based organogel for HIV prevention [102]	ANN-multilayer full feed-forward and multilayer normal feed-forward networks: Hyaluronic acid (HA) concentration, Volume of surfactant and Reaction time.	Mucin adsorption (%) and drug flux ($\mu g/cm^2/min^{1/2}$); optimized trigger-responsive release performance	The model showed good performance, with R^2 values of 0.81 for mucin adsorption and 0.97 for flux, and adjusted R^2 values of 0.78 and 0.96, respectively. Prediction errors were within acceptable limits (RMSE: 6.39 and 0.12; AAD: 7.56 and 1.18; MAD: 11.75 and 0.56), with better predictive accuracy for flux than for mucin adsorption.	Model developed from in vitro data; no reported IVIVC or in vivo validation
Layered vaginal suppositories containing metronidazole and *Lactobacillus* spp. for BV [103]	ANN integrated with central composite design, Ovucire/PEG ratio and surfactant concentration	Optimized drug release, *Lactobacillus* spp. viability	The ANN models showed excellent predictive performance, with R^2 values of 0.9995 for drug release and 0.9999 for Lactobacilli viability, and similarly high adjusted R^2 values (0.9995 and 0.9999, respectively). Error metrics were very low (RMSE: 0.2161 and 0.0225; MAE: 0.0985 and 0.0052; AAD: 0.1140 and 0.0169), indicating highly accurate predictions, with slightly better performance for Lactobacilli viability.	Study based on in vitro modeling and validation; no in vivo or IVIVC data
Multipurpose preventive vaginal hydrogel containing tenofovir and cyanovirin-N for HIV prevention [104]	ANN integrated with Box–Behnken design: The concentrations of CaCl2, NaCMC, and PEG2000	Optimized hydrogel composition balancing drug release, mucoadhesion and flux	The ANN model demonstrated strong predictive performance across all responses. The R^2 values were 0.9495 for mucoadhesion, 0.9801 for flux, and 0.9981 for drug release, indicating strong agreement between predicted and experimental	Study based on in vitro modeling and validation; no in vivo or IVIVC data

(*continued on next page*)

Table 2 (*continued*)

Vaginal drug delivery system	Input data and AI models used	Optimized outputs	ML performance and key findings	Translational relevance
			data. Error metrics were generally low, confirming acceptable prediction accuracy, although flux and drug release showed higher absolute error values due to scale effects.	
Mucoadhesive barrier-based female-controlled drug delivery system (FcDDS) [105]	Cascade computer model integrating statistical regression, KNN, and back-propagation ANN in a sequential ensemble framework, Intrinsic (vaginal fluid pH, secretion rate, rotation, and vibration speed of physical movement), formulation (loading weight, dose), and extrinsic variables (insertion position)	Drug diffusivity identification of dominant variables influencing diffusivity	The cascade model demonstrated superior predictive performance (R^2 = 0.993), with reduced prediction error and faster training than individual models (regression, KNN, ANN), indicating improved accuracy and efficiency in predicting drug diffusivity.	Primarily based on in vitro simulations and computational modeling; no direct in vivo validation

heterogeneity that most influence mobility, capturing variations beyond bulk rheology [117]. These observations could help in the rational design of future vaginal mucus-penetrating delivery systems.

Collectively, the above examples illustrate how AI- and ML-based strategies can be applied to the development of vaginal mucoadhesive and mucus-penetrating formulations, enabling virtual screening and systematic optimization of formulation parameters prior to in vitro and in vivo evaluation. Several earlier studies [66,118–122] explored the development of vaginal mucoadhesive or mucus-penetrating formulations, with or without pH-responsive drug release, but did not utilize AI/ML despite generating useful in vitro and in vivo data that could be integrated into ML models to accelerate future formulation designs. As the field continues to evolve, more targeted AI/ML applications focused explicitly on vaginal mucoadhesion and mucus penetration are anticipated, particularly for advanced nanocarrier and microcarrier systems designed to enhance drug delivery efficiency.

3.3. Bio-responsive vaginal formulations

Bio-responsive systems are designed to respond dynamically to local physiological or pathological changes, such as variations in pH, enzymes, or microbial activity within the vaginal environment [7]. By responding to disease-specific signals, bio-responsive formulations hold promises for on-demand therapy, minimizing off-target exposure, enhancing efficacy, and supporting personalized approaches to vaginal health management.

Enzyme-responsive formulations are engineered to release the drug when they encounter enzymes (e.g., hyaluronidases, acid phosphatases) that are specifically present in the vaginal environment during infection or sexual activity [123,124]. AI and ML can accelerate the optimization of these formulations by learning from multidimensional formulations and biological datasets to predict how variations in polymer chemistry, enzyme kinetics, and local physiology affect drug release profiles and responsiveness [72]. In this regard, supervised learning models (e.g., random forests, Gaussian process regression, gradient boosting machines, neural networks) are well suited to handling nonlinear and high-dimensional data, making them ideal for modeling enzyme-material interactions and predicting enzyme-triggered drug release behavior [72,125,126]. AI/ML tools can also analyze outputs from enzyme assays and SVF dissolution tests to identify patterns and predict in vivo behavior under physiological conditions. For example, predictive models can be calibrated using enzyme concentration gradients to forecast how different formulations respond across individual variations in vaginal enzyme expression [127]. Moreover, methods such as explainable AI (XAI) can help elucidate which features (e.g., polymer hydrophobicity, enzyme affinity) most strongly influence product performance, thereby providing further scientific insights [128,129].

Vaginal pH-responsive formulations respond intelligently to the unique vaginal pH, which typically ranges from about 3.8 to 4.5 but can vary significantly during infection, sexual activity, or physiological changes, making pH-responsive drug release particularly valuable for targeted local therapies [9,130]. pH-responsive polymers can undergo phase changes or structural transformations in response to pH shifts, enabling controlled, on-demand drug release [131]. However, designing such systems has historically relied on empirical screening of multiple variables, and AI/ML can enrich this process by learning complex relationships among formulation and biological variables, enabling more predictive and efficient product development [132].

Based on our search to date, no studies have reported the direct integration of AI or ML methodologies into the design and optimization of enzyme- or pH-responsive vaginal drug delivery formulations, but beyond vaginal systems, AI/ML is increasingly applied to model drug release profiles from stimuli-responsive platforms (e.g., polymeric nanoparticles) to capture complex release kinetics [133]. Several studies have developed enzyme-responsive or pH-responsive vaginal formulations [118,123,124,134–136], and although these studies did not apply AI/ML to formulation development, they highlighted the data (bio-responsive drug release) that could be integrated into ML models to accelerate future vaginal formulation designs. Recent studies from other indications are also laying a foundation for bio-responsive vaginal formulation design and development. For example, researchers used ML models to predict pH-dependent oxaliplatin release from nanomicelles in acidic breast cancer environments, achieving high accuracy and mechanistic insight into pH-triggered release kinetics [137]. Another study used ML algorithms, including principal component analysis, Gaussian process regression, and ANN, to analyze the influence of environmental pH, drug properties, and particle characteristics on drug release from PLGA nanoparticles, guiding the design of in vitro experiments [133]. The ML predictions were used to guide in vitro experiments, and the observed release profiles closely matched the algorithmic predictions.

3.4. Immediate and controlled drug-release vaginal systems

Immediate-release vaginal formulations, such as gels, films, or inserts, enable rapid drug action at the site of administration. By rapidly releasing the drug, these formulations help achieve high local concentrations while minimizing systemic exposure and associated side effects [138,139]. Vaginal controlled-release systems, such as IVR, intrauterine devices, and long-acting films, aim to maintain therapeutic drug levels at the site of action over extended periods [7,140,141]. Controlled-release profiles help reduce dosing frequency, minimize fluctuations in drug

concentration, and improve patient compliance. Furthermore, vaginally administered formulations are typically amenable to self-administration, providing ease of use, greater user control, and supporting patient autonomy [142,143]. Self-administration has been associated with improved adherence, as patients can manage their treatment discreetly and on their own schedule. Clinical studies have consistently reported high adherence and user acceptability, likely reflecting the convenience and reduced burden across a range of vaginal formulations, including rings [144,145], fibers [146], tablets [147,148], and films [149]. However, achieving precise, predictable drug release profiles is inherently complex, as it depends on numerous interrelated factors. ML models can be trained on datasets that include formulation parameters and in vitro release profiles to identify which features most strongly influence drug release kinetics. For example, a recent study reported the development of an ML-based intelligent formulation design tool for segmented combination vaginal rings [12]. They successfully fabricated and tested a segmented combination IVR containing anastrozole (ATZ) and levonorgestrel (LNG) using an XGBoost model to optimize polymer and drug load combinations and validate their release characteristics. This work confirms the feasibility of AI in designing complex vaginal delivery systems to guide formulation composition and processing decisions early in development. Another study used an ANN combined with an evolutionary algorithm to model how hot-melt extrusion (HME) process parameters affect the performance of a dapivirine-loaded vaginal film formulation [100]. The authors assessed dissolution, puncture strength, and drug content of the film formulation. This quantitative framework can aid in formulation development and optimization and was used to understand the relationship between HME parameters and vaginal film performance, specifically correlating the dissolution profile with drug release.

Although the application of AI- and ML-based approaches in controlled- or immediate-release vaginal drug delivery systems remains limited, insights from studies on other routes of administration can inform the design and development of vaginal formulations. For example, foundational work in AI-assisted formulation design tools and predictive modeling in oral fast-dissolving solid dosage forms illustrates how these methods could be adapted to the specific application of AI/ML to immediate-release systems [150–153]. For instance, research on neural networks for predicting oral tablet disintegration time and mechanical properties demonstrated that AI can accelerate and optimize formulation decisions [153]. The authors compiled a comprehensive dataset of 1983 formulations, including excipient types and quantities, drugs, and various physicochemical properties, to predict two essential control test parameters: tablet disintegration time and hardness. A 12-layer deep neural network achieved 73% accuracy for disintegration time and 99% accuracy for tablet hardness. Similar ML models could be trained using vaginal dissolution datasets to forecast drug release performance.

AI and ML approaches also have the potential to transform the correlation between in vitro release data and in vivo behavior. Novel algorithms have been applied to predict drug release profiles and kinetic parameters, demonstrating that ML can capture complex release behavior with reasonable accuracy [84]. In this study, 377 formulations were prepared in-house, and their release profiles were analyzed for up to 8 h. Six ML techniques were employed to predict drug release profiles, and the results indicated that ML can reliably forecast drug release during dynamic dissolution studies while also providing insights into kinetic parameters. Jiménez et al. utilized simulations to analyze drug diffusion kinetics in controlled-release systems [154]. By modeling parameters such as polymer swelling and erosion, they identified optimal conditions for elucidating the dynamics of drug release. These studies highlight the versatility of AI/ML tools for modeling both immediate- and sustained-release phenomena in vaginal formulation development.

Vaginal nanofibers also represent a promising delivery system that can be engineered to provide mucoadhesive, bio-responsive, or controlled/immediate drug release profiles [155]. Recent studies have applied supervised ML models to predict time-dependent drug release from acetalated dextran electrospun nanofibers, identifying critical material features that govern drug release kinetics [80]. The developed Gaussian process regression model was validated and optimized using release profiles from thirty nanofibers. This work presents a drug-agnostic ML model that can streamline early-stage formulation development and improve the characterization of drug release over time. However, formulation and process variables during electrospinning, such as polymer composition, solution properties, and processing parameters, must be carefully controlled to achieve the desired mechanical strength, porosity, and fiber diameter [156]. Another study developed an ML framework to model the electrospinning process and predict key characteristics of poly(vinyl alcohol) nanofibers [157]. By linking process conditions (voltage, the tip-to-collector distance, and polymer concentration) to fiber outcomes (aligned nanofiber production and nanofiber diameter), the approach helped optimize manufacturing parameters, enhancing control over fiber alignment and properties for advanced material applications. Such predictions and control are particularly advantageous for designing vaginal nanofibers, where uniformity, mechanical integrity, and consistent drug release are critical. Efforts are also underway to integrate ML algorithms into electrospinning machines to automate the manufacturing process, enabling precise control over fiber properties while ensuring reproducibility and scalability [158]. Such ML-driven strategies can enhance process understanding, improve reproducibility, and optimize fiber properties, providing a roadmap that could be readily adapted for the development of vaginal nanofibers.

3.5. *Integrating AI/ML into vaginal formulation design*

In summary, integrating AI and ML has the potential to transform vaginal formulation development into a more predictive, efficient, and reproducible process, thereby accelerating translation from laboratory design to clinically effective drug-delivery systems. AI-driven tools have also transformed biomaterials design and screening, enabling dynamic interactions among materials, drugs, and biological systems that could be applied to vaginal formulations [159]. Fig. 3 presents schematics of vaginal drug delivery development and optimization integrated with AI/ML platforms. Despite growing interest in using AI and ML to develop vaginal drug delivery systems, progress remains limited due to several challenges such as restricted access to high-quality datasets and limited mechanistic understanding of complex models in predicting formulation attributes. These challenges are briefly discussed below.

4. Challenges in incorporating AI and ML in the development of vaginal drug delivery systems

The application of AI and ML to the development of vaginal drug delivery systems is primarily constrained by the limited availability and heterogeneity of high-quality, standardized experimental data [160,161]. Preclinical datasets are often limited, inconsistent, and generated using methodologies that are not validated for scale-up product development [41,162]. This disconnect between lab-scale and commercial developments hampers data integration, reduces model robustness, and limits the generalizability of ML-based predictions. These limitations are further exacerbated by the intrinsic complexity and physiological variability of the vaginal environment, which introduces significant variability that is difficult to capture in current models.

In addition to biological variability, formulation-specific challenges further complicate AI/ML integration. Controlled-release vaginal systems, for instance, must balance drug-release kinetics with sufficient mucosal adhesion while preserving mechanical integrity and user acceptability. These requirements are governed by complex, often nonlinear interactions among formulation excipients (e.g., polymers, lipids, surfactants), active pharmaceutical ingredients, and the dynamic

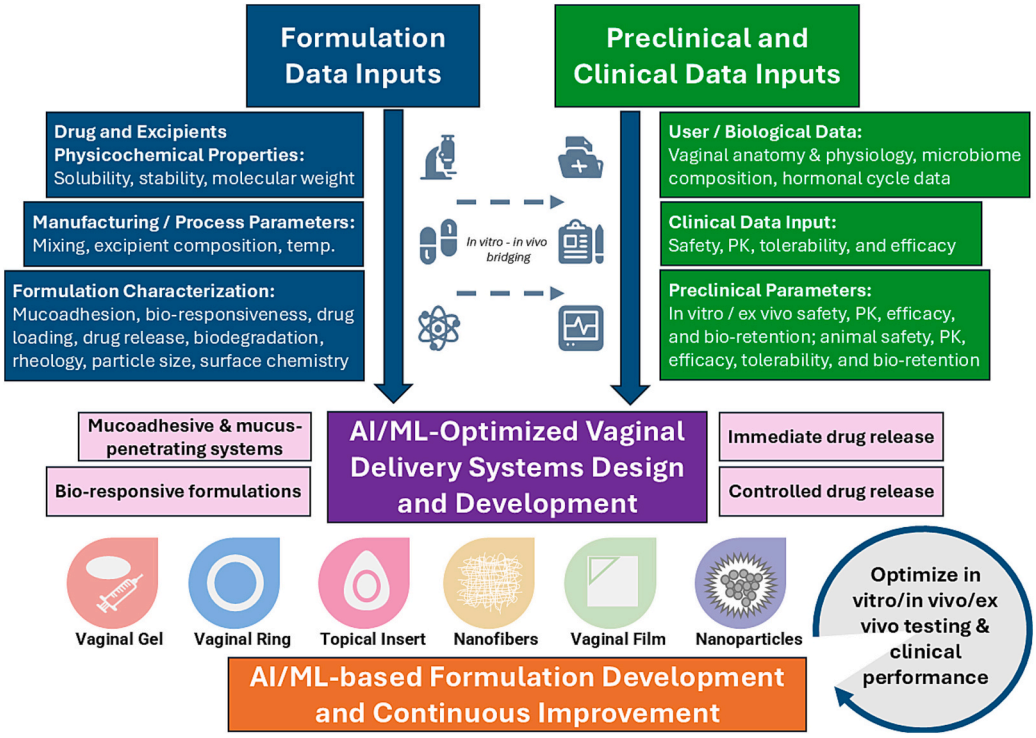


Fig. 3. Schematics for vaginal drug delivery development integrated with AI and ML platforms.

vaginal environment. Accurately capturing and optimizing such multi-scale physicochemical and biological interactions within AI/ML frameworks remains challenging, given limited mechanistic understanding, a lack of standardized formulation datasets, and the difficulty of establishing reliable correlations across in vitro, ex vivo, and in vivo model systems. These models include in vitro Franz diffusion and CV epithelial cell-based models to assess drug permeation, release, and biocompatibility; ex vivo porcine or bovine vaginal tissues to assess permeation and mucoadhesion; and in vivo animal models (e.g., rats, rabbits, sheep) for safety, PK, and efficacy [162–164]. ML models trained predominantly on in vitro data may poorly predict in vivo performance and not extrapolate reliably across diverse patient populations. This challenge arises from the difficulty of translating in vitro results to in vivo performance. For example, while human epithelial cell-based models enable evaluation of formulation behavior, drug release, and biocompatibility [162,165–169], they fail to fully capture systemic bioavailability or dynamic physiological processes such as tissue permeability influenced by blood perfusion [170,171]. Ex vivo models, such as excised human or animal CV mucosal tissue explants, better preserve native tissue structure and mucus barriers, making them beneficial for studying permeability and mucoadhesion [162,171–173]. However, differences in anatomy, mucus composition, hormonal status, and microbiota, as well as limited duration in culture, constrain extrapolation to humans. Similarly, in vivo models in rodents or larger animals provide insight into drug distribution and clearance, but interspecies differences in CV fluid, pH, microbiota, and hormonal cycles must be carefully considered when translating findings to humans [162,163,170].

From a technical perspective, issues related to model interpretability, reproducibility, and validation pose additional barriers to the effective implementation of AI/ML in vaginal formulation development [161]. Many advanced ML algorithms function as “black-box” models, offering limited insight into the relationships between formulation variables, material attributes, and biological responses [125,174]. Additionally, vaginal drug delivery research remains relatively underexplored, frequently yielding small, fragmented datasets that restrict robust model training and compromise predictive performance. The lack of rigorous external validation using in vivo or clinical data further undermines confidence in the model's reliability, particularly when applied across different formulation platforms. Although AI/ML methodologies have been successfully deployed for drug delivery systems administered via other routes, their translation to vaginal delivery remains comparatively underdeveloped, despite clear opportunities to adapt existing approaches. In this context, concerns regarding mechanistic relevance and safety are especially critical, given the importance of mucosal compatibility and local tolerability for vaginal products. Integrating AI-driven insights into vaginal formulation workflows also requires interdisciplinary expertise and organizational infrastructure that are not widely available.

Beyond formulation design, scaling up the manufacturing of AI/ML-assisted, complex vaginal formulations introduce additional challenges, particularly in maintaining batch-to-batch consistency and controlling critical quality attributes (CQAs). In this regard, AI-enabled process analytical technologies (PAT), which leverage real-time sensor data such as spectroscopy and rheological measurements, offer promising solutions for continuous monitoring and control of key process parameters [18,175,176]. When combined with ML models, PAT systems can be used to predict process outcomes and recommend corrective actions, thereby enhancing manufacturing robustness and product consistency [177,178].

Ethical and regulatory considerations also represent barriers to broader adoption, since regulatory agencies currently lack clearly defined frameworks for the evaluation, validation, and approval of AI-assisted tools in pharmaceutical development, creating uncertainty regarding their qualification for vaginal product development [179,180]. Regulatory authorities require transparent evidence of safety, efficacy, and reproducibility; however, many ML models are proprietary, complicating risk assessment and regulatory review. Importantly, biases in training datasets, often arising from the underrepresentation of specific age groups, ethnicities, or physiological conditions, may lead to inequitable model predictions that affect material selection, dosing strategies, and therapeutic outcomes. Addressing these

risks requires systematic bias assessment and continuous model validation across diverse populations, establishing standardized validation frameworks, and implementing robust documentation practices to align AI/ML technologies with regulatory expectations and ensure patient safety [181]. Achieving these goals requires coordinated, multidisciplinary collaboration across formulation science, clinical research, ethics, and regulatory affairs to fully realize the potential of AI-driven vaginal drug delivery development [161,182].

5. Future directions

Integrating principles of personalized medicine into vaginal drug delivery, with AI and ML as key enabling technologies, represents a critical research and clinical priority for advancing therapeutics for women's health. Personalized medicine seeks to tailor interventions to individual biological and clinical characteristics, accounting for patient-specific variability [183–186]. This need is particularly pronounced in vaginal drug delivery, where the highly dynamic vaginal microenvironment, including fluctuations in pH, microbiota composition, and fluid volume, can substantially influence drug release, distribution, and product performance [6,23]. For example, formulations optimized for a low-pH, *Lactobacillus*-dominant environment may perform unpredictably in the presence of dysbiosis or elevated pH, potentially compromising dosing consistency, user comfort, and adherence.

AI-assisted formulation development, combined with microenvironment-responsive materials and user-centered design, holds significant promise for the rational development of intravaginal products that accommodate interindividual variability. Such approaches enable formulations to better accommodate differences and align with each woman's distinct physiological, pathological, and behavioral profile. More broadly, AI and ML are reshaping women's health research through high-throughput data integration, advanced predictive modeling, and the generation of individualized insights, supported by emerging concepts such as digital twins and interconnected digital health ecosystems [64]. Digital health technologies further strengthen AI-enabled personalization by generating real-world, longitudinal datasets relevant to vaginal drug delivery. Platforms designed for menstrual cycle tracking, fertility monitoring, pregnancy, and menopause management offer increasingly precise assessments of reproductive health parameters, which can be leveraged to inform formulation design and optimize drug release kinetics [187]. In parallel, wearable and AI-enabled medical devices continuously capture physiological, behavioral, and contextual data, establishing a robust foundation for precision medicine approaches in women's health [185]. Representative examples include ML-driven fertility and cycle-prediction wearables such as the Ava fertility tracker bracelet and the Oura ring [188,189], hormone biosensors integrated into platforms such as OvuSense [190], pH-sensing intravaginal rings [191], and sensors embedded in tampons [192] that transmit real-time pH data. Collectively, these technologies have the potential to close the gap between real-world physiological dynamics and formulation design and development, ultimately enabling adaptive, patient-centric intravaginal therapeutics.

Patient-specific vaginal microbiota profiles generated using stratification and sequencing-based tools can be integrated into AI/ML models to support personalized therapeutic strategies. Such approaches have already demonstrated utility in clinical prediction tasks, including pregnancy outcome assessment and BV diagnosis [193–197]. Similar frameworks could be extended to connect clinical outcomes to novel vaginal formulation development research in future studies. Given the critical role of the vaginal microbiome in modulating local drug metabolism and microenvironmental conditions, incorporating microbiome data into formulation design frameworks represents another promising direction for the future.

Smart polymer-based vaginal formulations that respond to physiological triggers such as pH or enzymatic activity, or that enable enhanced mucus penetration, are also being actively explored to support on-demand and precision drug release [4,7]. These strategies closely align with the principles of personalized medicine and are further supported by advanced manufacturing technologies, including three-dimensional (3D) printing, which allows the fabrication of anatomy-matched devices with customizable dosing, geometry, and release kinetics [11]. To fully realize the potential of these innovations, future efforts should prioritize generating and curating high-quality in vitro, ex vivo, and in vivo datasets that encompass vaginal formulation performance and women's health parameters. Such datasets are essential for improving the robustness of AI/ML models and accelerating the clinical translation of personalized vaginal drug delivery systems.

In summary, AI and ML provide powerful tools to address the biological complexity and interindividual variability inherent to vaginal drug delivery. Their integration with personalized medicine frameworks has the potential to transform vaginal delivery platforms into more predictive, efficient, and patient-focused processes within women's health. By enabling data-driven formulation design, predictive performance modeling, and microenvironment-responsive customization, AI- and ML-driven strategies may substantially accelerate development while improving therapeutic precision and clinical relevance.

6. Conclusion

The transformative potential of AI and ML in the development of vaginal drug delivery systems continues to be explored, along with the characterization of key vaginal microenvironment variables that influence formulation performance, including vaginal biology, pathological conditions, and behavioral practices. This complexity necessitates the integration of biological, clinical, behavioral, and formulation datasets with predictive ML algorithms that can rapidly screen and suggest vaginal formulation ingredients for predefined formulation characteristics such as mucoadhesiveness, mucus-penetration, bio-responsiveness, controlled drug-release rates, drug permeation, stability, and, ultimately, in vivo performance, thereby reducing experimental time and development costs. Despite a handful of formulation development studies demonstrating the application of AI and ML to vaginal delivery platforms, the overall application of AI/ML in vaginal drug delivery remains limited compared with more established areas of drug delivery, such as oral or injectable formulations. Accumulating evidence indicates that AI/ML approaches can streamline development by capturing complex interactions between formulation components and the vaginal microenvironment. Moreover, studies employing AI/ML across diverse drug delivery modalities and routes of administration are establishing a valuable foundation that can be leveraged to accelerate vaginal formulation design and development. One specific case is mucus-penetrating formulations. While AI/ML applications specifically for vaginal mucus-penetrating formulations have not yet been reported, studies in other administration routes, such as human airway and colonic mucus, highlight their potential [114]. These ML-driven approaches characterize particle motion across sizes and charges, identifying key factors that govern mobility. Applying such strategies could guide the rational design of next-generation vaginal delivery systems.

Despite these promising advances, significant challenges persist, including limited availability of high-quality datasets, scarcity of clinical data specific to vaginal formulations, and pronounced biological variability, all of which constrain the robustness and generalizability of AL/ML models. Addressing these barriers will require coordinated, multidisciplinary efforts focused on improved data generation, transparent and responsible modeling practices, and supportive regulatory frameworks. Priorities include increasing the inclusion of women in clinical and formulation research, implementing privacy-conscious data collection strategies, strengthening collaboration among academic, industrial, and clinical stakeholders, and rigorously validating AI/ML models using specific datasets. Collectively, these efforts are essential to ensuring the reliability, equity, and regulatory acceptance of AI/ML-driven technologies in vaginal drug delivery and women's health. Ultimately, the

integration of AI and ML has the potential to transform vaginal formulation into a more predictive, efficient, and reproducible process, accelerating the translation of innovative delivery systems from laboratory design to clinically approved products.

Funding

The research involved in preparing this review has been supported by a Science for Africa Foundation grant to CONRAD through the Old Dominion University Research Foundation (PSA-25-623A) and CONRAD/VHS/ODU institutional funds. DAO had her PhD studentship partially supported by the MEDAFRICA Foundation Inc., Scotch Plains, NJ, USA (award number 01/2021/22).

Declaration of competing interest

GFD and VA are named inventors on intellectual property related to the topical insert, including US Patent No. 12,370,203 B2 and Australian Patent No. 2019365204, as well as related pending applications and foreign counterparts. MOI is named inventor on intellectual property related to multipurpose electrospun fiber inserts, including Nigerian Patent Pending Application No. NG/PT/NC/O/2026/22147. The authors declare no additional financial interests that may represent conflicts of interest.

Data availability

No data was used for the research described in the article.

References

[1] World Health Organization, Sexual and Reproductive Health Rights, 2025.
[2] World Health Organization, 6 Priorities for Women and Health, Accessed on 8th Dec 2025, 2021.
[3] B. Silva, E.F. Marques, A.C. Gomes, Recent advances in *in vitro* models simulating the female genital tract toward more effective intravaginal therapeutic delivery, Expert Opin. Drug Deliv. 21 (2024) 1007–1027, https://doi.org/10.1080/17425247.2024.2380338.
[4] E. Sanchez Armengol, F. Veider, G. Millotti, G. Kali, A. Bernkop-Schnürch, F. Laffleur, Exploring the potential of vaginal drug delivery: innovations, efficacy, and therapeutic prospects, J. Pharm. Pharmacol. (2025), https://doi.org/10.1093/jpp/rgaf045.
[5] S. Das, M.J. Bhattacharjee, A.K. Mukherjee, M.R. Khan, Recent advances in understanding of multifaceted changes in the vaginal microenvironment: implications in vaginal health and therapeutics, Crit. Rev. Microbiol. 49 (2023) 256–282, https://doi.org/10.1080/1040841X.2022.2049696.
[6] G. Leyva-g, L. Del, S. Ortega-peña, Modifications in Vaginal Microbiota and Their Influence on Drug Release: Challenges and Opportunities, 2019.
[7] T. Osmałek, A. Froelich, B. Jadach, A. Tatarek, P. Gadzinski, A. Falana, et al., Recent advances in polymer-based vaginal drug delivery systems, Pharmaceutics 13 (2021), https://doi.org/10.3390/pharmaceutics13060884.
[8] C.A. Stennett, M. France, M. Shardell, S.J. Robbins, S.E. Brown, E.D. Johnston, et al., Longitudinal profiles of the vaginal microbiota of pre-, peri-, and postmenopausal women: preliminary insights from a secondary data analysis, Menopause 31 (2024) 537–545, https://doi.org/10.1097/GME.0000000000002358.
[9] Z. Yang, X. Wu, H. Wang, J. Zhou, X. Lin, P. Yang, Vagina, a promising route for drug delivery, J. Drug Delivery Sci. Technol. 93 (2024), https://doi.org/10.1016/j.jddst.2024.105397.
[10] J. Gu, E.A. Ho, Encyclopedia of Biomedical Polymers and Polymeric Biomaterials 1st ed, 11, CRC Press, 2015.
[11] S. Kokare, S. Khot, O. Daware, A. Gavali, C. Kokare, Exploring novel approaches for vaginal delivery, Next Nanotechnol. 8 (2025) 100279, https://doi.org/10.1016/j.nxnano.2025.100279.
[12] Z. Shu, Y. Huang, S. Wu, J. Guo, M. Ning, Machine Learning-Based Intelligent Formulation Design Tool for Segmented Combination Vaginal Rings: Construction and Validation, 2025.
[13] W. Wang, Z. Ye, H. Gao, D. Ouyang, Computational pharmaceutics - a new paradigm of drug delivery, J. Control. Release 338 (2021) 119–136, https://doi.org/10.1016/j.jconrel.2021.08.030.
[14] B. Fotouh, A.J. Kyser, H.B. Frieboes, Drug and therapeutic intravaginal delivery targeting diseases in the female reproductive tract: a mathematical modeling perspective, J. Control. Release 384 (2025) 113924, https://doi.org/10.1016/j.jconrel.2025.113924.
[15] D.R. Serrano, F.C. Luciano, B.J. Anaya, B. Ongoren, A. Kara, G. Molina, et al., Artificial intelligence (AI) applications in drug discovery and drug delivery: revolutionizing personalized medicine, Pharmaceutics 16 (2024) 1328, https://doi.org/10.3390/pharmaceutics16101328.
[16] L.K. Vora, A.D. Gholap, K. Jetha, R.R.S. Thakur, H.K. Solanki, V.P. Chavda, Artificial intelligence in pharmaceutical technology and drug delivery design, Pharmaceutics 15 (2023), https://doi.org/10.3390/pharmaceutics15071916.
[17] K.P. Das, J. C, Nanoparticles and convergence of artificial intelligence for targeted drug delivery for cancer therapy: current progress and challenges, Front. Med. Technol. 4 (2023), https://doi.org/10.3389/fmedt.2022.1067144.
[18] D. Nithyanantham, A. Nair, U.Y. Nayak, Leveraging artificial intelligence for advancements in liquid dosage formulations in the pharmaceutical industry, Ther. Innov. Regul. Sci. 59 (2025) 1004–1031, https://doi.org/10.1007/s43441-025-00823-w.
[19] V. Agrahari, Y.E. Choonara, M. Mosharraf, S.K. Patel, F. Zhang, The role of artificial intelligence and machine learning in accelerating the discovery and development of nanomedicine, Pharm. Res. 41 (2024) 2289–2297, https://doi.org/10.1007/s11095-024-03798-9.
[20] S. Singh, A. De, The paradigm shift in therapeutics: a comprehensive review of artificial intelligence in drug delivery systems, RSC Pharmaceut. (2026), https://doi.org/10.1039/D5PM00235D.
[21] P. Bhatt, S. Singh, V. Kumar, K. Nagarajan, S.K. Mishra, P. Kumar Dixit, et al., Artificial intelligence in pharmaceutical industry: revolutionizing drug development and delivery, Curr. Artif. Intell. 02 (2024), https://doi.org/10.2174/0129503752250813231124092946.
[22] A. Dedeloudi, A. Siamidi, P. Pavlou, M. Vlachou, Recent advances in the excipients used in modified release vaginal formulations, Materials 15 (2022), https://doi.org/10.3390/ma15010327.
[23] Q. Zhai, Y. Gao, M. Wang, L. Li, L. Li, J. Li, et al., Characterization of vaginal microbiota across female reproductive phases, Front. Microbiol. 16 (2025), https://doi.org/10.3389/fmicb.2025.1599965.
[24] B.J. Moncla, C.A. Chappell, L.K. Mahal, B.M. Debo, L.A. Meyn, S.L. Hillier, Impact of bacterial vaginosis, as assessed by Nugent criteria and hormonal status on glycosidases and lectin binding in cervicovaginal lavage samples, PLoS One 10 (2015) e0127091, https://doi.org/10.1371/journal.pone.0127091.
[25] S.D. Song, K.D. Acharya, J.E. Zhu, C.M. Deveney, M.R.S. Walther-Antonio, M. J. Tetel, et al., Daily vaginal microbiota fluctuations associated with natural hormonal cycle, contraceptives, diet, and exercise, mSphere 5 (2020), https://doi.org/10.1128/msphere.00593-20.
[26] S. Ayehunie, A. Islam, C. Cannon, T. Landry, J. Pudney, M. Klausner, et al., Characterization of a hormone-responsive organotypic human vaginal tissue model: morphologic and immunologic effects, Reprod. Sci. 22 (2015) 980–990, https://doi.org/10.1177/1933719115570906.
[27] I.K. Gipson, R. Moccia, S. Spurr-Michaud, P. Argüeso, A.R. Gargiulo, J.A. Hill, et al., The amount of MUC5B mucin in cervical mucus peaks at midcycle 1, J. Clin. Endocrinol. Metab. 86 (2001) 594–600, https://doi.org/10.1210/jcem.86.2.7174.
[28] J. Ravel, P. Gajer, Z. Abdo, G.M. Schneider, S.S.K. Koenig, S.L. McCulle, et al., Vaginal microbiome of reproductive-age women, Proc. Natl. Acad. Sci. USA 108 (2011) 4680–4687, https://doi.org/10.1073/pnas.1002611107.
[29] X. Zhou, M.A. Hansmann, C.C. Davis, H. Suzuki, C.J. Brown, U. Schütte, et al., The vaginal bacterial communities of japanese women resemble those of women in other racial groups, FEMS Immunol. Med. Microbiol. 58 (2010) 169–181, https://doi.org/10.1111/j.1574-695X.2009.00618.x.
[30] S. Swidsinski, W.M. Moll, A. Swidsinski, Bacterial vaginosis—vaginal polymicrobial biofilms and dysbiosis, Dtsch. Arztebl. Int. (2023), https://doi.org/10.3238/arztebl.m2023.0090.
[31] E. Amabebe, M. Tatiparthy, A.K. Kammala, L.S. Richardson, B.D. Taylor, S. Sharma, et al., Vaginal pharmacomicrobiomics modulates risk of persistent and recurrent bacterial vaginosis, NPJ Biofilms Microbiomes 11 (2025) 115, https://doi.org/10.1038/s41522-025-00748-0.
[32] A.T. Gustin, A.R. Thurman, N. Chandra, L. Schifanella, M. Alcaide, R. Fichorova, et al., Recurrent bacterial vaginosis following metronidazole treatment is associated with microbiota richness at diagnosis, Am. J. Obstet. Gynecol. 226 (2022) 225.e1–225.e15, https://doi.org/10.1016/j.ajog.2021.09.018.
[33] T. Hoang, E. Toler, K. DeLong, N.A. Mafunda, S.M. Bloom, H.C. Zierden, et al., The cervicovaginal mucus barrier to HIV-1 is diminished in bacterial vaginosis, PLoS Pathog. 16 (2020) e1008236, https://doi.org/10.1371/journal.ppat.1008236.
[34] G. Lacroix, V. Gouyer, F. Gottrand, J.-L. Desseyn, The cervicovaginal mucus barrier, Int. J. Mol. Sci. 21 (2020) 8266, https://doi.org/10.3390/ijms21218266.
[35] L.M. Ensign, R. Cone, J. Hanes, Nanoparticle-based drug delivery to the vagina: a review, J. Control. Release 190 (2014) 500–514, https://doi.org/10.1016/j.jconrel.2014.04.033.
[36] B. Valamla, P. Thakor, R. Phuse, M. Dalvi, P. Kharat, A. Kumar, et al., Engineering drug delivery systems to overcome the vaginal mucosal barrier: current understanding and research agenda of mucoadhesive formulations of vaginal delivery, J. Drug Deliv. Sci. Technol. 70 (2022), https://doi.org/10.1016/j.jddst.2022.103162.
[37] E. Taneva, S. Sinclair, P.M.M. Mesquita, B. Weinrick, S.A. Cameron, N. Cheshenko, et al., Vaginal microbiome modulates topical antiretroviral drug pharmacokinetics, JCI Insight 3 (2018), https://doi.org/10.1172/jci.insight.99545.
[38] A.R. Thurman, J. Ravel, P. Gajer, M.A. Marzinke, L.A. Ouattara, T. Jacot, et al., Vaginal microbiota and mucosal pharmacokinetics of tenofovir in healthy women using a 90-day tenofovir/levonorgestrel vaginal ring, Front. Cell. Infect. Microbiol. 12 (2022), https://doi.org/10.3389/fcimb.2022.799501.

[39] R. Donahue Carlson, A.N. Sheth, T.D. Read, M.B. Frisch, C.C. Mehta, A. Martin, et al., The female genital tract microbiome is associated with vaginal antiretroviral drug concentrations in Human Immunodeficiency Virus–infected women on antiretroviral therapy, J. Infect. Dis. 216 (2017) 990–999, https://doi.org/10.1093/infdis/jix420.
[40] N.R. Klatt, R. Cheu, K. Birse, A.S. Zevin, M. Perner, L. Noël-Romas, et al., Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women, Science 356 (2017) 938–945, https://doi.org/10.1126/science.aai9383, 1979.
[41] R.M. Machado, A. Palmeira-de-Oliveira, C. Gaspar, J. Martinez-de-Oliveira, R. Palmeira-de-Oliveira, Studies and methodologies on vaginal drug permeation, Adv. Drug Deliv. Rev. 92 (2015) 14–26, https://doi.org/10.1016/j.addr.2015.02.003.
[42] P. Mirmonsef, A.L. Hotton, D. Gilbert, D. Burgad, A. Landay, K.M. Weber, et al., Free glycogen in vaginal fluids is associated with lactobacillus colonization and low vaginal pH, PLoS One 9 (2014) e102467, https://doi.org/10.1371/journal.pone.0102467.
[43] K. Godha, K.M. Tucker, C. Biehl, D.F. Archer, S. Mirkin, Human vaginal pH and microbiota: an update, Gynecol. Endocrinol. 34 (2018) 451–455, https://doi.org/10.1080/09513590.2017.1407753.
[44] E. Szymańska, M. Wojasiński, J. Dąbrowska, M. Krzyżowska, M. Nowicka, T. Ciach, et al., Chitosan-poly(ethylene oxide) nanofibrous mat as a vaginal platform for tenofovir disoproxyl fumarate – the effect of vaginal pH on drug carrier performance, Int. J. Biol. Macromol. 222 (2022) 856–867, https://doi.org/10.1016/j.ijbiomac.2022.09.207.
[45] V. Agrahari, S. Putty, C. Mathes, J.B. Murowchick, B.C. Youan, Evaluation of degradation kinetics and physicochemical stability of tenofovir, Drug Test Anal. 7 (2015) 207–213, https://doi.org/10.1002/dta.1656.
[46] V.M. Golla, M. Kurmi, K. Shaik, S. Singh, Stability behaviour of antiretroviral drugs and their combinations. 4: characterization of degradation products of tenofovir alafenamide fumarate and comparison of its degradation and stability behaviour with tenofovir disoproxil fumarate, J. Pharm. Biomed. Anal. 131 (2016) 146–155, https://doi.org/10.1016/j.jpba.2016.08.022.
[47] Y.P. Lin, W.C. Chen, C.M. Cheng, C.J. Shen, Vaginal ph value for clinical diagnosis and treatment of common vaginitis, Diagnostics 11 (2021), https://doi.org/10.3390/diagnostics11111996.
[48] R. Romero, S.S. Hassan, P. Gajer, A.L. Tarca, D.W. Fadrosh, L. Nikita, et al., The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women, Microbiome 2 (2014) 4, https://doi.org/10.1186/2049-2618-2-4.
[49] A.C. Freitas, B. Chaban, A. Bocking, M. Rocco, S. Yang, J.E. Hill, et al., The vaginal microbiome of pregnant women is less rich and diverse, with lower prevalence of mollicutes, compared to non-pregnant women, Sci. Rep. 7 (2017) 9212, https://doi.org/10.1038/s41598-017-07790-9.
[50] R.J. Levin, VIP, vagina, clitoral and periurethral glans — an update on human female genital arousal, Exp. Clin. Endocrinol. 98 (1991) 61–69, https://doi.org/10.1055/s-0029-1211102.
[51] E.R. Boskey, T.R. Moench, P.S. Hees, R.A. Cone, A self-sampling method to obtain large volumes of undiluted cervicovaginal secretions, Sex. Transm. Dis. 30 (2003) 107–109, https://doi.org/10.1097/00007435-200302000-00002.
[52] J.P. Semmens, Estrogen deprivation and vaginal function in postmenopausal women. JAMA: the, JAMA 248 (1982) 445, https://doi.org/10.1001/jama.1982.03330040033027.
[53] D.A. Eschenbach, S. Hillier, C. Critchlow, C. Stevens, T. DeRouen, K.K. Holmes, Diagnosis and clinical manifestations of bacterial vaginosis, Am. J. Obstet. Gynecol. 158 (1988) 819–828, https://doi.org/10.1016/0002-9378(88)90078-6.
[54] P. Wølner-Hanssen, Clinical manifestations of vaginal trichomoniasis. JAMA: the, JAMA 261 (1989) 571, https://doi.org/10.1001/jama.1989.03420040109029.
[55] D.H. Owen, D.F. Katz, A vaginal fluid simulant, Contraception 59 (1999) 91–95, https://doi.org/10.1016/S0010-7824(99)00010-4.
[56] C. Mitchell, K. Paul, K. Agnew, R. Gaussman, R.W. Coombs, J. Hitti, Estimating volume of cervicovaginal secretions in cervicovaginal lavage fluid collected for measurement of genital HIV-1 RNA levels in women, J. Clin. Microbiol. 49 (2011) 735–736, https://doi.org/10.1128/JCM.00991-10.
[57] S.J. Usala, G.F.B. Schumacher, Volumetric self-sampling of cervicovaginal fluid: a new approach to ovulation timing, Fertil. Steril. 39 (1983) 304–309, https://doi.org/10.1016/S0015-0282(16)46876-7.
[58] K. Vermani, S. Garg, The scope and potential of vaginal drug delivery, Pharm. Sci. Technol. Today 3 (2000) 359–364, https://doi.org/10.1016/S1461-5347(00)00296-0.
[59] T.W. Wong, M. Dhanawat, M.J. Rathbone, Vaginal drug delivery: strategies and concerns in polymeric nanoparticle development, Expert Opin. Drug Deliv. 11 (2014) 1419–1434, https://doi.org/10.1517/17425247.2014.924499.
[60] Z. Izadifar, J. Cotton, S. Chen, V. Horvath, A. Stejskalova, A. Gulati, et al., Mucus production, host-microbiome interactions, hormone sensitivity, and innate immune responses modeled in human cervix chips, Nat. Commun. 15 (2024) 4578, https://doi.org/10.1038/s41467-024-48910-0.
[61] D.J. Delgado-Diaz, B. Jesaveluk, J.A. Hayward, D. Tyssen, A. Alisoltani, M. Potgieter, et al., Lactic acid from vaginal microbiota enhances cervicovaginal epithelial barrier integrity by promoting tight junction protein expression, Microbiome 10 (2022) 141, https://doi.org/10.1186/s40168-022-01337-5.
[62] M. Pandey, H. Choudhury, A. Abdul-Aziz, S.K. Bhattamisra, B. Gorain, T. Carine, et al., Promising drug delivery approaches to treat microbial infections in the vagina: a recent update, Polymers (Basel) 23 (2021) 1–65, https://doi.org/10.3390/polym13010026.
[63] B.C. Herold, B.A. Chen, R.A. Salata, M.A. Marzinke, C.W. Kelly, C.S. Dezzutti, et al., Impact of Sex on the Pharmacokinetics and Pharmacodynamics of 1% Tenofovir Gel, 2015.
[64] B. Grace, L.A. Wise, M. Nieroda, J. Egbunike, N.O. Usman, Digital health technologies to transform women's health innovation and inclusive research, BMJ 391 (2025) e085682, https://doi.org/10.1136/bmj-2025-085682.
[65] A. Carballo-Diéguez, R. Giguere, C. Dolezal, B.A. Chen, J. Kahn, G. Zimet, et al., "Tell juliana": acceptability of the candidate microbicide VivaGel® and two placebo gels among ethnically diverse, sexually active young women participating in a phase 1 microbicide study, AIDS Behav. 16 (2012) 1761–1774, https://doi.org/10.1007/s10461-011-0028-6.
[66] L.M. Ensign, B.C. Tang, Y.Y. Wang, T.A. Tse, T. Hoen, R. Cone, et al., Mucus-penetrating nanoparticles for vaginal drug delivery protect against herpes simplex virus, Sci. Transl. Med. 4 (2012), https://doi.org/10.1126/scitranslmed.3003453.
[67] M. Mohideen, E. Quijano, E. Song, Y. Deng, G. Panse, W. Zhang, et al., Degradable bioadhesive nanoparticles for prolonged intravaginal delivery and retention of elvitegravir, Biomaterials 144 (2017) 144–154, https://doi.org/10.1016/j.biomaterials.2017.08.029.
[68] M. Yang, S.K. Lai, T. Yu, Y.-Y. Wang, C. Happe, W. Zhong, et al., Nanoparticle penetration of human cervicovaginal mucus: the effect of polyvinyl alcohol, J. Control. Release 192 (2014) 202–208, https://doi.org/10.1016/j.jconrel.2014.07.045.
[69] Y. Wu, N. Wang, P. Xiong, R. Wang, J. Deng, D. Ouyang, Artificial intelligence for drug delivery: yesterday, today and tomorrow, Acta Pharm. Sin. B (2025), https://doi.org/10.1016/j.apsb.2025.09.022.
[70] A. Gupta, K. Vaidya, N. Boehnke, AI and machine learning in pharmaceutical formulation and manufacturing of personalized medicines, in: Artificial Intelligence for Drug Product Lifecycle Applications, Elsevier, 2024, pp. 121–167, https://doi.org/10.1016/B978-0-323-91819-0.00006-3.
[71] S. Wang, J. Di, D. Wang, X. Dai, Y. Hua, X. Gao, et al., State-of-the-art review of artificial neural networks to predict, characterize and optimize pharmaceutical formulation, Pharmaceutics 14 (2022) 183, https://doi.org/10.3390/pharmaceutics14010183.
[72] S. Aghajanpour, H. Amiriara, M. Esfandyari-Manesh, P. Ebrahimnejad, H. Jeelani, A. Henschel, et al., Utilizing machine learning for predicting drug release from polymeric drug delivery systems, Comput. Biol. Med. (2025) 188, https://doi.org/10.1016/j.compbiomed.2025.109756.
[73] S. Joshi, S. Sheth, Artificial intelligence (AI) in pharmaceutical formulation and dosage calculations, Pharmaceutics 17 (2025) 1440, https://doi.org/10.3390/pharmaceutics17111440.
[74] A. Dedeloudi, E. Weaver, D.A. Lamprou, Machine learning in additive manufacturing & microfluidics for smarter and safer drug delivery systems, Int. J. Pharm. (2023) 636, https://doi.org/10.1016/j.ijpharm.2023.122818.
[75] P. Bannigan, M. Aldeghi, Z. Bao, F. Häse, A. Aspuru-Guzik, C. Allen, Machine learning directed drug formulation development, Adv. Drug Deliv. Rev. (2021) 175, https://doi.org/10.1016/j.addr.2021.05.016.
[76] G. Obaido, I.D. Mienye, O.F. Egbelowo, I.D. Emmanuel, A. Ogunleye, B. Ogbuokiri, et al., Supervised machine learning in drug discovery and development: algorithms, applications, challenges, and prospects, Mach. Learn. Appl. 17 (2024) 100576, https://doi.org/10.1016/j.mlwa.2024.100576.
[77] Y. Yang, Z. Ye, Y. Su, Q. Zhao, X. Li, D. Ouyang, Deep learning for in vitro prediction of pharmaceutical formulations, Acta Pharm. Sin. B 9 (2019) 177–185, https://doi.org/10.1016/j.apsb.2018.09.010.
[78] K.A. Ali, S. Mohin, P. Mondal, S. Goswami, S. Ghosh, S. Choudhuri, Influence of artificial intelligence in modern pharmaceutical formulation and drug development, Futur. J. Pharm. Sci. (2024) 10, https://doi.org/10.1186/s43094-024-00625-1.
[79] S. Patil, Artificial Intelligence in Pharmacy: Applications, Challenges, and Future Directions in Drug Discovery, Development, and Healthcare, Deep Science Publishing, 2025, https://doi.org/10.70593/978-93-7185-204-3.
[80] R.N. Woodring, E.G. Gurysh, T. Pulipaka, K.E. Shilling, R.T. Stiepel, E.S. Pena, et al., Supervised machine learning for predicting drug release from acetalated dextran nanofibers, Biomater. Sci. 13 (2025) 2806–2823, https://doi.org/10.1039/D5BM00259A.
[81] Z. Zhang, B. Zhang, R. Chen, Q. Zhang, K. Wang, The prediction of the in vitro release curves for PLGA-based drug delivery systems with neural networks, Pharmaceutics 17 (2025) 513, https://doi.org/10.3390/pharmaceutics17040513.
[82] S. Dong, H. Yu, P. Poupart, E.A. Ho, Gaussian processes modeling for the prediction of polymeric nanoparticle formulation design to enhance encapsulation efficiency and therapeutic efficacy, Drug Deliv. Transl. Res. 15 (2025) 372–388, https://doi.org/10.1007/s13346-024-01625-7.
[83] N. Hanari, S. Mihandoost, S. Rezvantalab, Intelligence prediction of microfluidically prepared nanoparticles, Sci. Rep. 15 (2025) 37512, https://doi.org/10.1038/s41598-025-21471-y.
[84] C. Protopapa, A. Siamidi, A.A. Eneli, M. Elbadawi, M. Vlachou, Machine learning predicts drug release profiles and kinetic parameters based on tablets formulations, AAPS J. 27 (2025) 124, https://doi.org/10.1208/s12248-025-01101-1.
[85] J. Deng, Z. Ye, W. Zheng, J. Chen, H. Gao, Z. Wu, et al., Machine learning in accelerating microsphere formulation development, Drug Deliv. Transl. Res. 13 (2023) 966–982, https://doi.org/10.1007/s13346-022-01253-z.
[86] A. Mendyk, J. Szlęk, R. Jachowicz, R. Lau, A. Paclawski, Heuristic modeling of macromolecule release from PLGA microspheres, Int. J. Nanomedicine (2013) 4601, https://doi.org/10.2147/IJN.S53364.

[87] J.T. Moreira-Filho, D. Ranganath, R.S. Tieghi, R. Patton, V. Sutherland, C. Schmitt, et al., Automating data extraction from scientific literature and general <scp>PDF</scp> files using large language models and <scp>KNIME</scp> : an application in toxicology, WIREs Comput. Mol. Sci. 15 (2025), https://doi.org/10.1002/wcms.70047.
[88] H. Oka, A. Yoshizawa, H. Shindo, Y. Matsumoto, M. Ishii, Machine extraction of polymer data from tables using XML versions of scientific articles, Sci. Technol. Advan. Mater. 1 (2021) 12–23, https://doi.org/10.1080/27660400.2021.1899456.
[89] P. Shetty, A.C. Rajan, C. Kuenneth, S. Gupta, L.P. Panchumarti, L. Holm, et al., A general-purpose material property data extraction pipeline from large polymer corpora using natural language processing, npj Comput. Mater. 9 (2023) 52, https://doi.org/10.1038/s41524-023-01003-w.
[90] L. Cao, D. Russo, K. Felton, D. Salley, A. Sharma, G. Keenan, et al., Optimization of formulations using robotic experiments driven by machine learning DoE, Cell Rep. Phys. Sci. 2 (2021) 100295, https://doi.org/10.1016/j.xcrp.2020.100295.
[91] C. Shen, M. Zhang, M. Lu, E. Chang, Z. Gao, W. Ban, et al., Machine learning empowered formulation design, optimization and characterization of nanoparticulate drug delivery systems: current applications, challenges, and future perspectives, Acta Pharm. Sin. B (2025), https://doi.org/10.1016/j.apsb.2025.12.011.
[92] P. Bannigan, Z. Bao, R.J. Hickman, M. Aldeghi, F. Häse, A. Aspuru-Guzik, et al., Machine learning models to accelerate the design of polymeric long-acting injectables, Nat. Commun. 14 (2023) 35, https://doi.org/10.1038/s41467-022-35343-w.
[93] A.D. Woolfson, M.L. Umrethia, V.L. Kett, R.K. Malcolm, Freeze-dried, mucoadhesive system for vaginal delivery of the HIV microbicide, dapivirine: optimisation by an artificial neural network, Int. J. Pharm. 388 (2010) 136–143, https://doi.org/10.1016/j.ijpharm.2009.12.042.
[94] E. Tsanaktsidou, M. Krestenitis, C. Karavasili, C.K. Zacharis, D.G. Fatouros, C. K. Markopoulou, *In vitro* and *in silico* computational methods for assessing vaginal permeability, Drug Dev. Ind. Pharm. 49 (2023) 249–259, https://doi.org/10.1080/03639045.2023.2199071.
[95] L. Simon, M. Fernandes, Neural network-based prediction and optimization of estradiol release from ethylene–vinyl acetate membranes, Comput. Chem. Eng. 28 (2004) 2407–2419, https://doi.org/10.1016/j.compchemeng.2004.06.002.
[96] G. Al-Kharusi, N.J. Dunne, S. Little, T.J. Levingstone, The role of machine learning and design of experiments in the advancement of biomaterial and tissue engineering research, Bioengineering 9 (2022) 561, https://doi.org/10.3390/bioengineering9100561.
[97] I.M. Fukuda, C.F.F. Pinto, C. dos S. Moreira, A.M. Saviano, F.R. Lourenço, Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD), Braz. J. Pharm. Sci. 54 (2018), https://doi.org/10.1590/s2175-97902018000001006.
[98] Ł. Pałkowski, M. Karolak, B. Kubiak, J. Błaszczyński, R. Słowiński, Application of dominance-based rough set approach in vaginal dosage forms optimization, Acta Pol. Pharm. Drug Res. 81 (2024) 331–343, https://doi.org/10.32383/appdr/187795.
[99] Y. Lee, A. Khemka, G. Acharya, N. Giri, C.H. Lee, A cascade computer model for mocrobicide diffusivity from mucoadhesive formulations, BMC Bioinformatics 16 (2015) 263, https://doi.org/10.1186/s12859-015-0684-z.
[100] D. McKinley, S.K. Patel, G. Regev, L.C. Rohan, A. Akil, Delineating the effects of hot-melt extrusion on the performance of a polymeric film using artificial neural networks and an evolutionary algorithm, Int. J. Pharm. 571 (2019) 118715, https://doi.org/10.1016/j.ijpharm.2019.118715.
[101] V.M.K. Ndesendo, V. Pillay, Y.E. Choonara, L.C. du Toit, P. Kumar, E. Buchmann, et al., Optimization of a polymer composite employing molecular mechanic simulations and artificial neural networks for a novel intravaginal bioadhesive drug delivery device, Pharm. Dev. Technol. 17 (2012) 407–420, https://doi.org/10.3109/10837450.2010.546406.
[102] M.O. Ilomuanya, R.F. Elesho, A.N. Amenaghawon, A.O. Adetuyi, V. Velusamy, A. S. Akanmu, Development of trigger sensitive hyaluronic acid/palm oil-based organogel for in vitro release of HIV/AIDS microbicides using artificial neural networks, Futur. J. Pharm. Sci. 6 (2020), https://doi.org/10.1186/s43094-019-0015-8.
[103] M.O. Ilomuanya, B.B. Salako, M.O. Ologunagba, O.O. Shonekan, K. Owodeha-Ashaka, E.S. Osahon, et al., Formulation and optimization of metronidazole and *Lactobacillus* spp. layered suppositories via a three-variable, five-level central composite design for the management of bacterial vaginosis, Pharmaceutics 14 (2022) 2337, https://doi.org/10.3390/pharmaceutics14112337.
[104] K.O. Oyediran, I.M. Cardoso-Daodu, P.O. Bassey, D.A. Ogundemuren, R. Muhammed, O.E. Ojo, et al., Artificial neural network guided optimization of tenofovir and Cyanovirin-N multipurpose preventive hydrogel formulation developed using the box behnken design model, Pharmaceut. Sci. Advan. 3 (2025) 100079, https://doi.org/10.1016/j.pscia.2025.100079.
[105] Y. Lee, A. Khemka, J. Yoo, C. Lee, Assessment of diffusion coefficient from mucoadhesive barrier devices using artificial neural networks, Int. J. Pharm. 351 (2008) 119–126, https://doi.org/10.1016/j.ijpharm.2007.09.032.
[106] R. Shaikh, T. Raj Singh, M. Garland, Ad Woolfson, R. Donnelly, Mucoadhesive drug delivery systems, J. Pharm. Bioallied Sci. 3 (2011) 89, https://doi.org/10.4103/0975-7406.76478.
[107] J. Leal, H.D.C. Smyth, D. Ghosh, Physicochemical properties of mucus and their impact on transmucosal drug delivery, Int. J. Pharm. 532 (2017) 555–572, https://doi.org/10.1016/j.ijpharm.2017.09.018.
[108] Y. Abdalla, M. Taub, E. Hilton, P. Akkaraju, A. Milanovic, M. Orlu, et al., A Variationally Encoded Generative Model for Overcoming Data Scarcity in, Pharmaceutical Science (2025), https://doi.org/10.48550/arXiv.2501.08995.
[109] J. das Neves, M.H. Amaral, M.F. Bahia, Performance of an in vitro mucoadhesion testing method for vaginal semisolids: influence of different testing conditions and instrumental parameters, Eur. J. Pharm. Biopharm. 69 (2008) 622–632, https://doi.org/10.1016/j.ejpb.2007.12.007.
[110] I. Zainol Abidin, E. Murphy, G.W. Fehrenbach, E. Rezoagli, N. Gately, I. Major, A systematic review of mucoadhesive vaginal tablet testing, Drug Target Insights 17 (2023) 5–30, https://doi.org/10.33393/dti.2023.2477.
[111] M.H. Elkomy, M. Elmowafy, K. Shalaby, A.F. Azmy, N. Ahmad, A. Zafar, et al., Development and machine-learning optimization of mucoadhesive nanostructured lipid carriers loaded with fluconazole for treatment of oral candidiasis, Drug Dev. Ind. Pharm. 47 (2021) 246–258, https://doi.org/10.1080/03639045.2020.1871005.
[112] Y. Zhang, S. Li, K. Loch, G.A. Duncan, L. Kaler, R. Pangeni, et al., PH-responsive mucus-penetrating nanoparticles for enhanced cellular internalization by local administration in vaginal tissue, ACS Macro Lett. 12 (2023) 446–453, https://doi.org/10.1021/acsmacrolett.2c00639.
[113] C. Liu, X. Jiang, Y. Gan, M. Yu, Engineering nanoparticles to overcome the mucus barrier for drug delivery: design, evaluation and state-of-the-art, Med. Drug Discov. 12 (2021) 100110, https://doi.org/10.1016/j.medidd.2021.100110.
[114] L. Kaler, K. Joyner, G.A. Duncan, Machine learning-informed predictions of nanoparticle mobility and fate in the mucus barrier, APL Bioeng. 6 (2022), https://doi.org/10.1063/5.0091025.
[115] Y.-Y. Wang, S.K. Lai, L.M. Ensign, W. Zhong, R. Cone, J. Hanes, The microstructure and bulk rheology of human cervicovaginal mucus are remarkably resistant to changes in pH, Biomacromolecules 14 (2013) 4429–4435, https://doi.org/10.1021/bm401356q.
[116] S.K. Lai, Y.-Y. Wang, D. Wirtz, J. Hanes, Micro- and macrorheology of mucus, Adv. Drug Deliv. Rev. 61 (2009) 86–100, https://doi.org/10.1016/j.addr.2008.09.012.
[117] M. Tjakra, K. Lidayová, C. Avenel, C.A.S. Bergström, S. Hossain, Machine learning framework for investigating nano- and micro-scale particle diffusion in colonic mucus, J. Nanobiotechnol. 23 (2025) 583, https://doi.org/10.1186/s12951-025-03659-6.
[118] T. Zhang, C. Zhang, V. Agrahari, J.B. Murowchick, N.A. Oyler, B.-B.C. Youan, Spray drying tenofovir loaded mucoadhesive and pH-sensitive microspheres intended for HIV prevention, Antivir. Res. 97 (2013) 334–346, https://doi.org/10.1016/j.antiviral.2012.12.019.
[119] J.-W. Yoo, N. Giri, C.H. Lee, PH-sensitive eudragit nanoparticles for mucosal drug delivery, Int. J. Pharm. 403 (2011) 262–267, https://doi.org/10.1016/j.ijpharm.2010.10.032.
[120] J. Meng, V. Agrahari, M.J. Ezoulin, S.S. Purohit, T. Zhang, A. Molteni, et al., Spray-dried thiolated chitosan-coated sodium alginate multilayer microparticles for vaginal HIV microbicide delivery, AAPS J. 19 (2017) 692–702, https://doi.org/10.1208/s12248-016-0007-y.
[121] J. Meng, T. Zhang, V. Agrahari, M.J. Ezoulin, B.-B.C. Youan, Comparative biophysical properties of tenofovir-loaded, thiolated and nonthiolated chitosan nanoparticles intended for HIV prevention, Nanomedicine 9 (2014) 1595–1612, https://doi.org/10.2217/nnm.13.136.
[122] K. Maisel, M. Reddy, Q. Xu, S. Chattopadhyay, R. Cone, L.M. Ensign, et al., Nanoparticles coated with high molecular weight PEG penetrate mucus and provide uniform vaginal and colorectal distribution in vivo, Nanomedicine 11 (2016) 1337–1343, https://doi.org/10.2217/nnm-2016-0047.
[123] V. Agrahari, C. Zhang, T. Zhang, W. Li, T.K. Gounev, N.A. Oyler, et al., Hyaluronidase-sensitive nanoparticle templates for triggered release of HIV/AIDS microbicide in vitro, AAPS J. 16 (2014) 181–193, https://doi.org/10.1208/s12248-013-9546-7.
[124] S.O. Ekama, M.O. Ilomuanya, C.P. Azubuike, J.B. Ayorinde, O.C. Ezechi, C. I. Igwilo, et al., Enzyme responsive vaginal microbicide gels containing maraviroc and tenofovir microspheres designed for acid phosphatase-triggered release for pre-exposure prophylaxis of HIV-1: a comparative analysis of a bigel and thermosensitive gel, Gels 8 (2021) 15, https://doi.org/10.3390/gels8010015.
[125] V. Singh, S. Sinha, J. Verma, Bioinformatics models in drug delivery: predicting biomaterial-biological interactions for targeted therapies, Next Nanotechnol. 9 (2026) 100335, https://doi.org/10.1016/j.nxnano.2025.100335.
[126] E. Cheong, D.C. Radford, A.J. Gormley, Automated active learning to optimize hydrogel drug release profiles, J. Control. Release 391 (2026) 114602, https://doi.org/10.1016/j.jconrel.2026.114602.
[127] W. Qian, X. Wang, Y. Kang, P. Pan, T. Hou, C.-Y. Hsieh, A general model for predicting enzyme functions based on enzymatic reactions, J. Chemother. 16 (2024) 38, https://doi.org/10.1186/s13321-024-00827-y.
[128] D. Minh, H.X. Wang, Y.F. Li, T.N. Nguyen, Explainable artificial intelligence: a comprehensive review, Artif. Intell. Rev. 55 (2022) 3503–3568, https://doi.org/10.1007/s10462-021-10088-y.
[129] A.J. Gormley, Machine learning in drug delivery, J. Control. Release 373 (2024) 23–30, https://doi.org/10.1016/j.jconrel.2024.06.045.
[130] E.A. Miller, D.E. Beasley, R.R. Dunn, E.A. Archie, Lactobacilli dominance and vaginal pH: why is the human vaginal microbiome unique? Front. Microbiol. 7 (2016) https://doi.org/10.3389/fmicb.2016.01936.
[131] G. Nunziata, D. Pollonio, E. Lacroce, F. Rossi, Smart pH-responsive polymers in biomedical applications: nanoparticles, hydrogels, and emerging hybrid platforms, Mater. Today Chem. 49 (2025) 103063, https://doi.org/10.1016/j.mtchem.2025.103063.

[132] R. AlAnsari, B. Hasan, G.R. Deen, U. Torsten, Hydrogel- and nanocomposite-based drug-delivery strategies in the treatment of vaginal infections, Polymers (Basel) 16 (2024), https://doi.org/10.3390/polym16060775.
[133] Y. Sun, S. Qin, Y. Li, N. Hasan, Y.V. Li, J. Liu, Machine learning integrated with in vitro experiments for study of drug release from PLGA nanoparticles, Sci. Rep. 15 (2025) 4218, https://doi.org/10.1038/s41598-024-82728-6.
[134] S. Kim, Y.L. Traore, E.A. Ho, M. Shafiq, S.H. Kim, S. Liu, Design and development of pH-responsive polyurethane membranes for intravaginal release of nanomedicines, Acta Biomater. 82 (2018) 12–23, https://doi.org/10.1016/j.actbio.2018.10.003.
[135] G. Zucca, B. Vigani, C. Valentino, A. Civra, D. Lembo, M. Ruggeri, et al., Electrospun hydrogel-forming nanofibres embedded in a pH-responsive film for the prevention of sexually transmitted infections, Int. J. Pharm. X 10 (2025) 100456, https://doi.org/10.1016/j.ijpx.2025.100456.
[136] R. Cazorla-Luna, A. Martín-Illana, F. Notario-Pérez, L.M. Bedoya, A. Tamayo, R. Ruiz-Caro, et al., Vaginal polyelectrolyte layer-by-layer films based on chitosan derivatives and Eudragit® S100 for pH responsive release of tenofovir, Mar. Drugs 18 (2020) 44, https://doi.org/10.3390/md18010044.
[137] S. Fathi-karkan, A. Rahdar, M. Shirzad, Integrating machine-learning and nanotechnology to quantify pH-modulated oxaliplatin release, Sci. Rep. 15 (2025) 42190, https://doi.org/10.1038/s41598-025-26145-3.
[138] V. Agrahari, M.M. Peet, N. Chandra, P. Ramalingam, P.K. Gupta, S. Jonnalagadda, et al., Formulation development of dual-compartment topical inserts combining tenofovir alafenamide and elvitegravir for flexible on-demand HIV prevention, J. Control. Release 377 (2025) 842–854, https://doi.org/10.1016/j.jconrel.2024.11.062.
[139] M. Lal, M. Lai, S. Ugaonkar, A. Wesenberg, L. Kizima, A. Rodriguez, et al., Development of a vaginal fast-dissolving insert combining griffithsin and carrageenan for potential use against sexually transmitted infections, J. Pharm. Sci. 107 (2018) 2601–2610, https://doi.org/10.1016/j.xphs.2018.06.002.
[140] McCoy CF, X. Zhao, X. Shen, Y.H. Dallal Bashi, D.J. Murphy, P. Boyd, et al., Advances in drug-releasing vaginal rings, J. Drug Deliv. Sci. Technol. 115 (2026) 107813, https://doi.org/10.1016/j.jddst.2025.107813.
[141] E.M. Pacheco-Quito, L.M. Bedoya, J. Rubio, A. Tamayo, R. Ruiz-Caro, M.D. Veiga, Layer-by-layer vaginal films for acyclovir controlled release to prevent genital herpes, Int. J. Pharm. 627 (2022), https://doi.org/10.1016/j.ijpharm.2022.122239.
[142] N.J. Alexander, E. Baker, M. Kaptein, U. Karck, L. Miller, E. Zampaglione, et al., Why consider vaginal drug administration? Mod. Trends Fertil. Steril. 82 (2004) https://doi.org/10.1016/j.fertnstert.2004.
[143] B.T. Chappell, B.L. Griffin, B. Howard, Mechanisms of action of currently available woman-controlled, vaginally administered, non-hormonal contraceptive products, Ther. Adv. Reprod. Health 16 (2022), https://doi.org/10.1177/26334941221107120.
[144] K. Ridgeway, E.T. Montgomery, K. Smith, K. Torjesen, A. van der Straten, S. L. Achilles, et al., Vaginal ring acceptability: a systematic review and meta-analysis of vaginal ring experiences from around the world, Contraception 106 (2022) 16–33, https://doi.org/10.1016/j.contraception.2021.10.001.
[145] J. Veen, M. Engberts, M. Wiegerinck, H. van der Vaart, User acceptability and ease of use of the MedRing, a new personalized vaginal drug delivery and monitoring device, Expert Opin. Drug Deliv. (2026) 1–8, https://doi.org/10.1080/17425247.2026.2619095.
[146] N.D. Laborde, J. Leslie, E. Krogstad, N. Morar, P. Mutero, J. Etima, et al., Perceptions of the "fabric" - an exploratory study of a novel multi-purpose technology among women in sub-Saharan Africa, PLoS One 13 (2018), https://doi.org/10.1371/journal.pone.0204821.
[147] N.R. Marasine, G. Kunwar, M. Chaudhary, A. Adhikari, S. Sankhi, Assessment of patient perception and administration technique of vaginal tablets at a tertiary care women's hospital, Explor. Res. Clin. Soc. Pharm. 19 (2025) 100632, https://doi.org/10.1016/j.rcsop.2025.100632.
[148] M.J. Minkin, S. Reiter, Maamari, Improved compliance and patient satisfaction with estradiol vaginal tablets in postmenopausal women previously treated with another local estrogen therapy, Int. J. Women's Health 133 (2013), https://doi.org/10.2147/IJWH.S41897.
[149] G.S.F. Vitral, C.C.V. Silva, H.C. Polonini, M.A.F. Brandão, N.R.B. Raposo, Vaginal films as a patient-Centered dosage form: evaluation of preferences, acceptability, and applicability in personalized drug delivery, Int. J. Pharm. Compd. 30 (2026) 78–87.
[150] M. Ghazwani, U. Hani, Determination of disintegration time using formulation data for solid dosage oral formulations via advanced machine learning integrated optimizer models, Sci. Rep. 15 (2025) 30118, https://doi.org/10.1038/s41598-025-15996-5.
[151] M. Ghazwani, U. Hani, Prediction of tablet disintegration time based on formulations properties via artificial intelligence by comparing machine learning models and validation, Sci. Rep. 15 (2025) 13789, https://doi.org/10.1038/s41598-025-98783-6.
[152] A. Moin, F. Fatima, F. Alqahtani, Z.A.A. Asiri, N.A. abo Sahba, H.S. Alqahtani, et al., Development of machine learning models for estimation of disintegration time on fast-disintegrating tablets, Eur. J. Pharm. Sci. 211 (2025) 107141, https://doi.org/10.1016/j.ejps.2025.107141.
[153] M. Momeni, M. Afkanpour, S. Rakhshani, A. Mehrabian, H. Tabesh, A prediction model based on artificial intelligence techniques for disintegration time and hardness of fast disintegrating tablets in pre-formulation tests, BMC Med. Inform. Decis. Mak. 24 (2024) 88, https://doi.org/10.1186/s12911-024-02485-4.
[154] S. Jiménez-Jiménez, S. Cordero-Sánchez, R. García, J. Hernández, J. Villegas-Cortez.The effect of bcc lattices on the drug release kinetics in inert systems by monte carlo simulation, J. Mex. Chem. Soc. 69 (2025), doi:https://doi.org/10.29356/jmcs.v69i1.2295.
[155] R. Cazorla-Luna, R. Ruiz-Caro, M.D. Veiga, R.K. Malcolm, D.A. Lamprou, Recent advances in electrospun nanofiber vaginal formulations for women's sexual and reproductive health, Int. J. Pharm. (2021) 607, https://doi.org/10.1016/j.ijpharm.2021.121040.
[156] B.O. Omiyale, A. Ogbeyemi, A.A. Rasheed, T.M. Adamolekun, W.C. Zhang, Influence of electrospinning parameters on the development of high-quality electrospun nanofibers: a brief critical assessment, Next Nanotechnol. 8 (2025) 100295, https://doi.org/10.1016/j.nxnano.2025.100295.
[157] F.J. López-Flores, J.A. Ornelas-Guillén, A. Pérez-Nava, J.B. González-Campos, J. M. Ponce-Ortega, Data-driven machine learning approach for modeling the production and predicting the characteristics of aligned electrospun nanofibers, Ind. Eng. Chem. Res. 63 (2024) 9904–9913, https://doi.org/10.1021/acs.iecr.4c00075.
[158] A. Shabani, G.A. Al, N. Berri, B. Castro-Dominguez, H.S. Leese, U. Martinez-Hernandez, Electrospinning technology, machine learning, and control approaches: a review, Adv. Eng. Mater. (2025) 27, https://doi.org/10.1002/adem.202401353.
[159] P. Jiang, Y. Dai, Y. Hou, J. Stein, S.S. Lin, C. Zhou, et al., Artificial intelligence-assisted design, synthesis and analysis of smart biomaterials, BMEMat (2025), https://doi.org/10.1002/bmm2.70004.
[160] J. Vamathevan, D. Clark, P. Czodrowski, I. Dunham, E. Ferran, G. Lee, et al., Applications of machine learning in drug discovery and development, Nat. Rev. Drug Discov. 18 (2019) 463–477, https://doi.org/10.1038/s41573-019-0024-5.
[161] A. Blanco-González, A. Cabezón, A. Seco-González, D. Conde-Torres, P. Antelo-Riveiro, Á. Piñeiro, et al., The role of AI in drug discovery: challenges, opportunities, and strategies, Pharmaceuticals 16 (2023) 891, https://doi.org/10.3390/ph16060891.
[162] R.L. Shapiro, K. DeLong, F. Zulfiqar, D. Carter, M. Better, L.M. Ensign, In vitro and ex vivo models for evaluating vaginal drug delivery systems, Adv. Drug Deliv. Rev. (2022) 191, https://doi.org/10.1016/j.addr.2022.114543.
[163] J.M. McCracken, G.A. Calderon, A.J. Robinson, C.N. Sullivan, E. Cosgriff-Hernandez, J.C.E. Hakim, Animal models and alternatives in vaginal research: a comparative review, Reprod. Sci. 28 (2021) 1759–1773, https://doi.org/10.1007/s43032-021-00529-y.
[164] M.H. Karami, M. Abdouss, M. Karami, Evaluation of in vitro and ex vivo models for studying the effectiveness of vaginal drug systems in controlling microbe infections: a systematic review, Clin. J. Obst. Gynecol. 6 (2023) 201–215, https://doi.org/10.29328/journal.cjog.1001151.
[165] P.R. de Araújo, G.M.F. Calixto, I.C. da Silva, L.H. de Paula Zago, J.A. Oshiro Junior, F.R. Pavan, et al., Mucoadhesive in situ gelling liquid crystalline precursor system to improve the vaginal administration of drugs, AAPS PharmSciTech 20 (2019) 225, https://doi.org/10.1208/s12249-019-1439-3.
[166] C. Huang, S.J. Soenen, E. van Gulck, G. Vanham, J. Rejman, S. Van Calenbergh, et al., Electrospun cellulose acetate phthalate fibers for semen induced anti-HIV vaginal drug delivery, Biomaterials 33 (2012) 962–969, https://doi.org/10.1016/j.biomaterials.2011.10.004.
[167] M. Kaur, K.M. Gupta, A.E. Poursaid, P. Karra, A. Mahalingam, H.A. Aliyar, et al., Engineering a degradable polyurethane intravaginal ring for sustained delivery of dapivirine, Drug Deliv. Transl. Res. 1 (2011) 223–237, https://doi.org/10.1007/s13346-011-0027-1.
[168] D.A. Ogundemuren, P.-O.O. Bassey, K.O. Oyediran, O.G. Nmesoma, D. Tsamos, A. Tsamis, et al., Innovative multilayered electrospun fiber systems for dual-action HIV prophylaxis and nonhormonal contraception, Adv. Pharmacol. Pharm. Sci. (2025) 2025, https://doi.org/10.1155/adpp/4749211.
[169] K.M. Tyo, H.R. Vuong, D.A. Malik, L.B. Sims, H. Alatassi, J. Duan, et al., Multipurpose tenofovir disoproxil fumarate electrospun fibers for the prevention of HIV-1 and HSV-2 infections in vitro, Int. J. Pharm. 531 (2017) 118–133, https://doi.org/10.1016/j.ijpharm.2017.08.061.
[170] R. Campos, S.F. Bittencourt, J.A. Rojas-Moscoso, L. Pissinatti, L.S. Chen, M. Porto, et al., The rabbit vagina as an in vivo model for vaginal fenticonazole permeability and toxicity, J. Pharmacol. Toxicol. Methods 94 (2018) 14–18, https://doi.org/10.1016/j.vascn.2018.04.001.
[171] C.A. Squier, M.J. Mantz, P.M. Schlievert, C.C. Davis, Porcine vagina ex vivo as a model for studying permeability and pathogenesis in mucosa, J. Pharm. Sci. 97 (2008) 9–21, https://doi.org/10.1002/jps.21077.
[172] M. Merbah, A. Introini, W. Fitzgerald, J. Grivel, A. Lisco, C. Vanpouille, et al., Cervico-vaginal tissue ex vivo as a model to study early events in HIV-1 infection, Am. J. Reprod. Immunol. 65 (2011) 268–278, https://doi.org/10.1111/j.1600-0897.2010.00967.x.
[173] E. Tsanaktsidou, A.-T. Chatzitaki, A. Chatzichristou, D.G. Fatouros, C. K. Markopoulou, A comparative study and prediction of the ex vivo permeation of six vaginally administered drugs across five artificial membranes and vaginal tissue, Molecules 29 (2024) 2334, https://doi.org/10.3390/molecules29102334.
[174] N. Hettikankanamage, N. Shafiabady, F. Chatteur, R.M.X. Wu, F. Ud Din, J. Zhou, EXplainable artificial intelligence (XAI): a systematic review for unveiling the black box models and their relevance to biomedical imaging and sensing, Sensors 25 (2025) 6649, https://doi.org/10.3390/s25216649.
[175] S. Wu, Y. Liu, X. Fan, Y. Shen, H. Qu, Trends and new process analytical technologies in pharmaceutical manufacturing, Int. J. Pharm. 682 (2025) 125957, https://doi.org/10.1016/j.ijpharm.2025.125957.
[176] M. Yafout, A. Ousaid, J. Akrim, Y. Khayati, Integrating artificial intelligence with process analytical technology for real time pharmaceutical process monitoring: a comprehensive review, Asian J. Res. Med. Pharmaceut. Sci. 14 (2025) 139–151, https://doi.org/10.9734/ajrimps/2025/v14i3326.

[177] I. Walsh, M. Myint, T. Nguyen-Khuong, Y.S. Ho, S.K. Ng, M. Lakshmanan, Harnessing the potential of machine learning for advancing "quality by design" in biomanufacturing, MAbs 14 (2022), https://doi.org/10.1080/19420862.2021.2013593.
[178] G. Gerzon, Y. Sheng, M. Kirkitadze, Process analytical technologies – advances in bioprocess integration and future perspectives, J. Pharm. Biomed. Anal. 207 (2022) 114379, https://doi.org/10.1016/j.jpba.2021.114379.
[179] G. Lenarczyk, T. Minssen, N. Price, A. Rai, The future of AI regulation in drug development: a comparative analysis, J. Law Biosci. 12 (2025), https://doi.org/10.1093/jlb/lsaf028.
[180] S.K. Niazi, Regulatory perspectives for AI/ML implementation in pharmaceutical GMP environments, Pharmaceuticals 18 (2025) 901, https://doi.org/10.3390/ph18060901.
[181] F. Hasanzadeh, C.B. Josephson, G. Waters, D. Adedinsewo, Z. Azizi, J.A. White, Bias recognition and mitigation strategies in artificial intelligence healthcare applications, NPJ Digit. Med. 8 (2025) 154, https://doi.org/10.1038/s41746-025-01503-7.
[182] M.F. Byrne, J. Rittscher, J.E. East, Synergies among clinicians, academia, and industry in the age of artificial intelligence, Gastroenterology 169 (2025) 531–544, https://doi.org/10.1053/j.gastro.2025.05.007.
[183] L.H. Goetz, N.J. Schork, Personalized medicine: motivation, challenges, and progress, Fertil. Steril. 109 (2018) 952–963, https://doi.org/10.1016/j.fertnstert.2018.05.006.
[184] S. Dharani, R. Kamaraj, A review of the regulatory challenges of personalized medicine, Cureus (2024), https://doi.org/10.7759/cureus.67891.
[185] K.B. Johnson, W. Wei, D. Weeraratne, M.E. Frisse, K. Misulis, K. Rhee, et al., Precision medicine, AI, and the future of personalized health care, Clin. Transl. Sci. 14 (2021) 86–93, https://doi.org/10.1111/cts.12884.
[186] F.A. McAlister, A. Laupacis, P.W. Armstrong, Finding the right balance between precision medicine and personalized care, CMAJ 189 (2017) E1065–E1068, https://doi.org/10.1503/cmaj.170107.
[187] J.L. Karim, R. Wan, R.S. Tabet, D.S. Chiu, A. Talhouk, Person-generated health data in womens health: scoping review, J. Med. Internet Res. 26 (2024) e53327, https://doi.org/10.2196/53327.
[188] A.K. Nulty, E. Chen, A.L. Thompson, The ava bracelet for collection of fertility and pregnancy data in free-living conditions: an exploratory validity and acceptability study, Digit. Health 8 (2022), https://doi.org/10.1177/20552076221084461, 205520762210844.
[189] N. Thigpen, S. Patel, X. Zhang, Oura ring as a tool for ovulation detection: validation analysis, J. Med. Internet Res. 27 (2025) e60667, https://doi.org/10.2196/60667.
[190] S. Moghimikandelousi, L. Najm, Y. Lee, F. Bayat, A. Prasad, S. Khan, et al., Advances in biomonitoring technologies for women's health, Nat. Commun. 16 (2025) 8507, https://doi.org/10.1038/s41467-025-63501-3.
[191] A. Paghi, M. Corsi, A.A. La Mattina, G. Egri, L. Dähne, G. Barillaro, Wireless and flexible optoelectronic system for in situ monitoring of vaginal pH using a bioresorbable fluorescence sensor, Adv. Mater. Technol. 8 (2023), https://doi.org/10.1002/admt.202201600.
[192] G.M. Stojanović, S. Qureshi, H. Zafar, D. Dimitrijević, I. Tomić, Tampon-based sensors for monitoring intravaginal pH levels, IEEE Sens. Lett. 9 (2025) 1–4, https://doi.org/10.1109/LSENS.2025.3549185.
[193] J.H. Elnaggar, J.W. Lammons, C.M. Ardizzone, K.J. Aaron, C. Jacobs, K.J. Graves, et al., Predicting Bacterial Vaginosis Development using Artificial Neural Networks, 2025, https://doi.org/10.1101/2025.05.02.25326872.
[194] C. Huang, C. Gin, J. Fettweis, B. Foxman, B. Gelaye, D.A. MacIntyre, et al., Meta-analysis reveals the vaginal microbiome is a better predictor of earlier than later preterm birth, BMC Biol. 21 (2023) 199, https://doi.org/10.1186/s12915-023-01702-2.
[195] O. Bar, S. Vagios, O. Barkai, J. Elshirbini, I. Souter, J. Xu, et al., Harnessing vaginal inflammation and microbiome: a machine learning model for predicting IVF success, NPJ Biofilms Microbiomes 11 (2025) 95, https://doi.org/10.1038/s41522-025-00732-8.
[196] M.T. France, B. Ma, P. Gajer, S. Brown, M.S. Humphrys, J.B. Holm, et al., VALENCIA: a nearest centroid classification method for vaginal microbial communities based on composition, Microbiome 8 (2020) 166, https://doi.org/10.1186/s40168-020-00934-6.
[197] D. Fernández-Edreira, J. Liñares-Blanco, P. V.-del-Río, C. Fernandez-Lozano, VIBES: a consensus subtyping of the vaginal microbiota reveals novel classification criteria, Comput. Struct. Biotechnol. J. 23 (2024) 148–156, https://doi.org/10.1016/j.csbj.2023.11.050.