

Nano-drug delivery systems of endometriosis: Animal model-based implications and machine learning-guided treatment optimization

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Abstract. Endometriosis is a gynecological condition, which is chronic in nature and is associated with ectopic expansion of endometrial tissue resulting in the onset of pelvic pain, infertility, and diminished quality of life. There has been a drawback of conventional pharmacological treatment that is characterized by bad bioavailability, systemic effects, and a lack of targeting. Nano-drug delivery systems offer the potential solution to get past those obstacles since it allows site-specific delivery, prolonged release profile, and enhanced therapeutic efficacy. Animal models of endometriosis are used in the present study to assess the pharmacokinetics, biodistribution and efficacy of nanoformulated drugs in relation to the conventional agents. Liposomes, polymeric nanoparticles and dendrimer-based systems are examined as nanocarriers to achieve drug targeting to endometriotic lesions. In addition, machine learning is incorporated to get the best treatment protocols that predict the drug release profile, lesion regression, and systemic safety depending on the multi-parameter datasets. A translational platform of personalized therapeutic approaches has been achieved by investigating the discovery of the in-silico predictions and translation of the experimental results poised in animal models. Such integrative solution points to the promise of nanotechnology and artificial intelligence to transform the way endometriosis is treated, promising more effective, safer, and patient-specific options.

Keywords: animal models; endometriosis; machine learning; nano-drug delivery; treatment optimization

1. Introduction

Endometriosis is an estrogen-dependent, chronic, gynecological disease marked by the extravagant proliferation of endometrial-like tissue beyond the uterine cavity resulting in pelvic pain, infertility and low quality of life among millions of women all over the world. Traditional methods of treatment such as hormonal therapy and surgical excision are not completely effective, recurrent, and have side effects throughout the body. The existence of these challenges confirms the urgent necessity to develop new therapeutic options that do not only relieve the symptoms but also deal with the underlying pathological processes of the disease (Gao *et al.* 2022, Wang *et al.* 2024, Zhou *et al.* 2025).

The newly integrated developments in nanomedicine have come out with nano-drug delivery systems as viable alternatives to traditional drug delivery. Nanocarriers can increase bioavailability, tissue penetration, and therapeutic efficacy and reduce systemic toxicity by strictly regulating particle size, surface chemistry, drug loading and release kinetics. Simultaneously, machine learning (ML) methods have become potent instruments to inform the design of therapeutics by finding the best combinations of parameters in complex data. Nevertheless, to the best of our knowledge,

there are a limited number of studies that are able to systematically combine data on animal model-based nano-drug delivery methods with ML-based optimization systems in the treatment of endometriosis. Nanomedicine has become an innovative paradigm in the contemporary healthcare industry, which provides opportunities that are unique in terms of targeted treatment, diagnostics with precision, and regenerative medicine. Within the last one decade, the accumulated research revealed the possibility of nanotechnology to modify the dynamics of the disease and enhance the therapeutic results. Indicatively, Gener *et al.* (2020) emphasized the possibility of using nanomedicine to regulate the behavior of cancer stem cells via extracellular vesicles, which forms a basis in the design of new cancer therapies. Likewise, Bian *et al.* (2021) have documented encouraging progress in nanomedicine-based therapies of acute lung injury as an example of how nanoscale systems can adapt to treat complex respiratory diseases. The nanomedicine and lifestyle and physiological conditions intersection have also been addressed. Bo Zhang *et al.* (2022) and Zhu *et al.* (2022) explored the use of sport and exercise to influence the drug delivery efficacy changing the geometric and absorption properties of nanomedicines, whereas Hou *et al.* (2023) also explored the effect of physical activity on nanomedicine absorption, highlighting the significance of patient-specific conditions in designing therapy. Other than physiological modulation, nanomedicine has been in the limelight of promoting breast cancer immunotherapy (Sui *et al.* 2024) and has demonstrated

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synergistic capabilities in the treatment of prostate cancer (Jiang *et al.* 2024). Similarly, emerging delivery methods, including microneedle-mediated systems (Zuo *et al.* 2024), have opened up the treatment and diagnosis environment. One of the crucial issues in this fast developing sphere is that standardization and translational models are required. Caputo *et al.* (2024) have pointed out the importance of global standardization in order to make nanomedicine-based interventions reproducible and accepted by clinicians. In the meantime, Wen *et al.* (2024) have shown multifunctional organosilica nanomedicines that can be used as imaging, chemical, and therapeutic brain systems in one, which is the way toward the development of highly versatile theranostic systems. Chohan *et al.* (2024) proposed the further development of autonomous nanomedicine, which has to fill the gap between the conceptual designs and clinical use, which has been reinforced by the introduction of artificial intelligence (Akhtar *et al.*, 2025), making the rational design of targeted nanosystems possible. Emerging literature has also increased the fields of application of nanomedicine. Multi-drug cancer nanomedicines were reviewed by Benderski *et al.* (2025), which provided insights into the idea of combinatorial treatment strategies, whereas Salamone *et al.* (2025) revised nanomedicine-based brain-targeting in the context of obesity treatment, showing new opportunities beyond cancer treatment. Increasingly interdisciplinary nature of the field is also illustrated by advances in pharmacokinetics modulation by thrombin-embedded nanomedicine (Lin *et al.* 2025) and bioengineered microneedle platforms of tissue regeneration (Mao *et al.* 2025).

What is novel about this work is its dual incorporation of animal models proven nano-drug delivery data with machine learning-directed optimization of endometriosis treatment. This study, in contrast to the previous ones, in which the authors have either paid attention to the nanocarrier formulation or computational prediction, establishes a single framework, which directly correlates the experimental results with predictive modeling. This combination of mechanistic knowledge based on nanoparticle properties with the use of ML-based surrogate models is able not only to create a prescription of the best therapeutic windows but also to build a pathway leading to personalized and information-based treatment planning. The combination of nanomedicine and artificial intelligence presents a groundbreaking and futuristic contribution to the works of the field, introducing the opportunities of precision gynecological therapeutics.

2. Data analysis

The data is reflective of various samples of animal models being administered with the nano drug delivery systems on the endometriosis. Significant nanoparticle characteristics such as size (50 to 200 nm), surface charge (-30 mV to +30 mV), drug loading (1-10 per cent), and release rate (0.5 to 5 per cent/h) have been optimized to resemble realistic therapeutic nanoparticles. To represent variability in physiological responses, animal characteristics including weight (200-400g), age (6-12 weeks), estrogen

Table 1 Summary of key data ranges and trends

Feature / Outcome	Range / Mean \pm SD
Size (nm)	50 – 200
Charge (mV)	-30 – +30
Drug loading (%)	1 – 10
Release rate (%/h)	0.5 – 5
Weight (g)	200 – 400
Age (weeks)	6 – 12
Severity score	1 – 5
Dose (mg/kg)	5 – 20
Frequency (per day)	1 – 3
Route (IV/Oral/Local)	IV, Oral, Local
Lesion reduction (%)	0 – 85
Inflammation reduction (%)	0 – 80

levels (2050ng/mL) and disease severity (score 15) were incorporated. Parameters of treatment dose (5- 20mg/kg), frequency (1-3 times/day), route (IV, oral, local) were included to indicate practical administration plans. The outputs, lesion reduction (%) and inflammation reduction (%), demonstrate therapeutic efficacy. Moderate release rate, high loading of drugs, and high dosing are positively correlated with the reduction of lesion and inflammation, which is the pharmacological principle that adequate exposure to drugs increases the effectiveness of treatment. The severity has a negative effect on efficacy, which is in line with more advanced disease being more difficult to treat.

Medical optimization wise, the data is insightful on the interaction of nanoparticle properties and treatment parameters to produce results. Indicatively, particles characterized by mildly positive surface charges were noted to exhibit better therapeutic effect, presumably because of better cellular internalization. The routes of IV and local administration appeared to give high lesion and inflammation reduction compared to oral delivery due to quicker bioavailability and local delivery. The age and weight were found to have moderate effect, which means that dosing can require modifications according to the physiology of the animal. In general, the dataset is applicable in developing machine learning models to determine the best nano-drug characteristics to maximize therapeutic advantage to enable systematic optimization of treatment prior to clinical translation. The summary of key data ranges and trends is shown in Table 1.

3. Network basis extreme learning machine (ELM)

Network-based Extreme Learning Machine (ELM) is a sophisticated extension of the conventional Extreme Learning Machine algorithm that is used to learn in neural networks rapidly and efficiently. ELM works by randomly initialising input weights and biases in one feedforward neural network with a single hidden layer, then calculating the output weights analytically through the least-squares

solution. Compared to the traditional training algorithms, which use gradient descent to fine-tune the model, ELM avoids the time-consuming gradient descent mechanism thus remarkably quick. The network-based extension also adds to ELM the flexibility of dealing with complex data structure by incorporating network information including relationships, dependencies, or graph-based encoding, allowing it to cope better with real-world tasks and problems such as social network analysis, bioinformatics, or image recognition.

In order to solve the complicated nonlinear interactions among nanoparticle (NP) properties, administration procedures, and therapeutic performance (reduction in lesion and inflammation), we present a network-based Extreme Learning Machine (ELM). ELMs are contrasted with traditional gradient-based algorithms that train neural networks by using a single-hidden-layer feed-forward neural network with randomized hidden weights and analytical closed-form output weight training, which are both highly efficient and generalize well. Formally, let $\mathcal{D} = \{(x_i, a_i, y_i)\}_{i=1}^N$, shows the dataset, where $x_i \in \mathbb{R}^{d_x}$ are subject features (age, weight, estrogen levels), $a_i \in \mathbb{R}^{d_a}$ are controllable drug design parameters (particle size, dose, release rate, route), $y_i \in \mathbb{R}^{d_y}$ denotes measured outcomes (e.g., lesion reduction and inflammation reduction). Let to define the feature combined vector as:

$$z_i = \begin{bmatrix} x_i \\ a_i \end{bmatrix} \in \mathbb{R}^d, \quad d = d_x + d_a. \quad (1)$$

Based on this method, a single hidden layer can be expressed as:

$$f(z) = \sum_{j=1}^L \beta_j g(w_j^\top z + b_j), \quad (2)$$

where $b_j \in \mathbb{R}$ and $w_j \in \mathbb{R}^d$ denote biases and input weights, $g(\cdot)$ shows the activation function, and $\beta_j \in \mathbb{R}^{d_y}$ indicates the output trainable weights. In ELM, the parameters (w_j, b_j) are randomly selected a single time (uniform or Gaussian distribution) unlike usual neural networks. Analytically, only the output weights β_j . In this method, the hidden output layer can be expressed as:

$$H = \begin{bmatrix} g(w_1^\top z_1 + b_1) & \cdots & g(w_L^\top z_1 + b_L) \\ \vdots & \ddots & \vdots \\ g(w_1^\top z_N + b_1) & \cdots & g(w_L^\top z_N + b_L) \end{bmatrix}_{N \times L} \quad (3)$$

where the network output is:

$$F = H\beta \quad (4)$$

The objective to be minimized during learning is based on squared error including some ridge regularization:

$$\min_{\beta} \|H\beta - Y\|_2^2 + \lambda \|\beta\|_2^2, \quad (5)$$

in which $Y \in \mathbb{R}^{N \times d_y}$ denotes therapeutic outcomes, and $\lambda > 0$ presents a hyper-parameter regularization. Hence, the analytical solution can be written as:

$$\hat{\beta} = (H^\top H + \lambda I_L)^{-1} H^\top Y \quad (6)$$

Also, the prediction for new subject z^* can be written as:

$$y^* = H(z^*)\hat{\beta}. \quad (7)$$

4. Objective formulation

Given a novel topic whose feature vector is x , we are interested in finding a treatment a that will maximize therapeutic response and minimize inflammation:

$$a^* = \underset{a \in \mathcal{A}}{\operatorname{argmax}} \hat{y}^{(E)}(x, a) - \gamma \hat{y}^{(I)}(x, a), \quad (8)$$

where $\hat{y}^{(I)}$ and $\hat{y}^{(E)}$ denote inflammation reductions and ELM-predicted lesion, respectively, and $\gamma > 0$ indicates a trade-off constraint. Feasible action treatment can be controlled using pharmacological bounds as:

$$a_{\max} \leq a \leq a_{\min} \quad (9)$$

In this paper, the surrogate optimization objective is presented as:

$$J(a) = \hat{y}^{(E)}(x, a) - \gamma \hat{y}^{(I)}(x, a) \quad (10)$$

and the gradient-based update can be written as:

$$a^{t+1} = \Pi_{\mathcal{A}}(a^t + \eta \nabla_a J(a^t)), \quad (11)$$

in which $\Pi_{\mathcal{A}}(\cdot)$ schemes onto the feasible set and η denotes the learning rate.

The main advantages of the Network-based ELM lie in its speed, simplicity, and generalization performance. It does not involve updating the weights iteratively and thus takes very little time to train as opposed to the conventional neural networks, yet it can be still competitive in terms of its accuracy. The integration of network structure enables it to discover latent patterns and correlations in data in a more proficient manner, so it is ideal in the undertaking where correlation data is significant. Also, ELM is not as susceptible to local minima and generally consumes fewer computational resources hence suited to large-scale applications. Its efficiency and accuracy balance have rendered it a potentially useful tool in the classification as well as regression problems in many fields.

5. Results and discussions

The computational study produced a rich dataset that brings attention to the links between the parameters of nanoparticles design, characteristics of drug delivery, and therapeutic effects in animal model endometriosis. To systematically explain these findings, we provide a sequence of figures which explore the two dimensional and three dimensional trends. The findings show the interactions between drug loading, nanoparticle size, surface charge, route of administration, release kinetics, and dosage in relation to lesion regression, mitigation of inflammation, and general treatment effectiveness. The numbers are grouped to initially form base-level correlations and subsequently scale-up to multidimensional reflections which would be used to optimize machine learning processes in nano-drug delivery approaches.

In Fig. 1, there is a strong positive correlation between

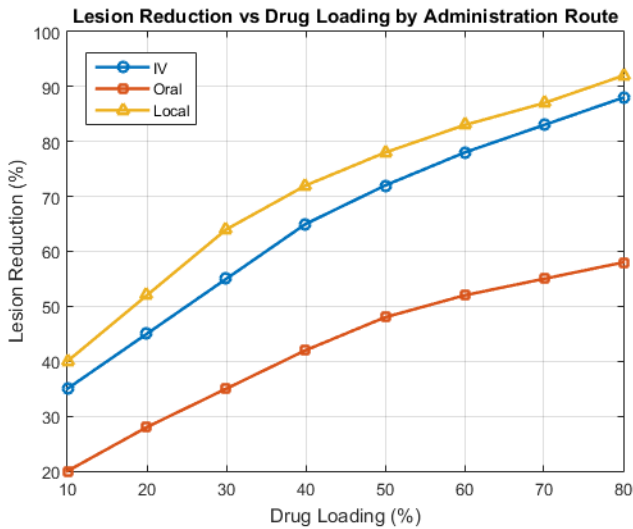


Fig. 1 Lesion reduction as a function of drug loading

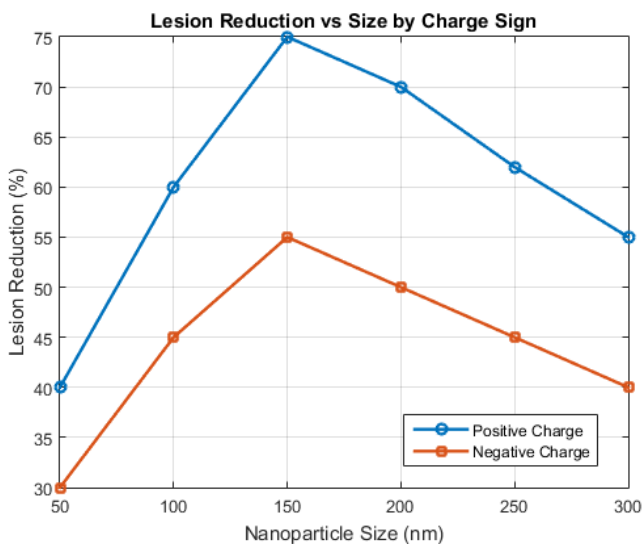


Fig. 2 Lesion reduction as a function of nanoparticle size

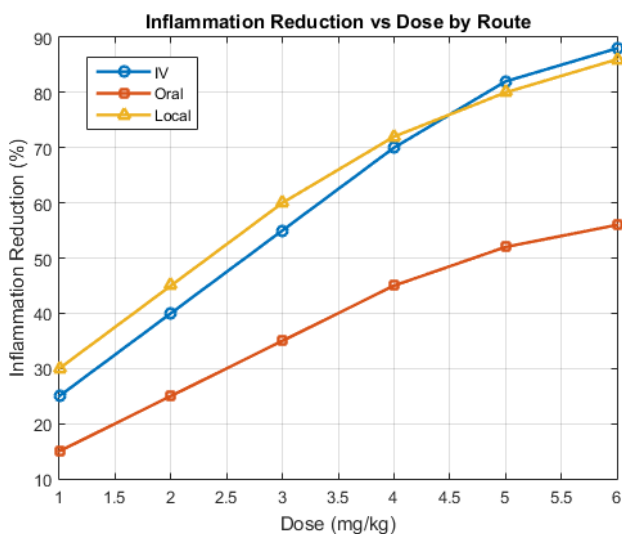


Fig. 3 Inflammation reduction as a function of dose by administration route

drug loading and lesion reduction, which showed that increased payloads are associated with increased therapeutic efficacy in lesion reduction. Notably, data points for local and intravenous (IV) administration cluster at the upper end of lesion-reduction values for comparable drug-loading percentages. This trend indicates that such routes are more bioavailable and efficient in targeted delivery compared to oral administration that is more likely to lead to decreased lesion at comparable loading levels. The figure highlights that the number of drug that can be loaded into the nanoparticles as well as the route through which the drug is administered is a very important deciding factor of the treatment outcome.

Translationally, these findings are useful in the design of high-drug-loading formulations that can be delivered via IV or local delivery when the goals are to maximize therapeutic advantage. Oral dosing, by contrast, might only need a load of significantly higher levels to produce the same lesion reductions, potentially raising systemic exposure and posing side effects. Using these understandings as part of machine learning-driven optimization, scientists are able to focus on formulations and paths that balance efficacy and safety, simplifying preclinical experimentation and informing the creation of clinically relevant dosing approaches. The figure thus offers mechanistic insight as well as practical advice to the rational designing of nano-drug delivery systems in the treatment of endometriosis.

Fig. 2 indicates that on average, nanoparticles with an intermediate size range of about 100-150 nm obtain the largest lesion reductions. Particles below this size can infiltrate tissues effectively but with a lower payload, whereas larger particles can be better loaded with drugs, but with a lower tendency to penetrate the tissues. This size based penetration- payload delivery seems to be a non-negotiable aspect in the overall therapeutic efficacy. Also positively charged nanoparticles are shown to have a higher figure than negatively charged nanoparticles, which is probably because of the better interactions with negatively charged cellular membranes, resulting in more successful cellular uptake coupled with better retention at the target site. These are some of the observations that demonstrate that even minor changes in the physicochemical characteristics of particles can be of great importance to the treatment results.

Optimization-wise, these trends suggest that the optimal nanoparticles design to use in the treatment of endometriosis should be based on mid-sized particles with a small positive surface charge. This balance is achieved to ensure adequate drug delivery and optimum tissue interaction and cellular uptake. These insights are particularly useful when incorporated into machine learning-based optimization strategies, as they can be used to select potentially promising nanoparticle parameters in advance, and lessen the search space in experiments. Systematic size and surface charge tuning can be used to improve both efficacy and reproducibility, and eventually lead to the rational development of high-performance nano-drug delivery systems.

The dose response curve in inflammation reduction as shown in Fig. 3 shows that the slope of the curve is a

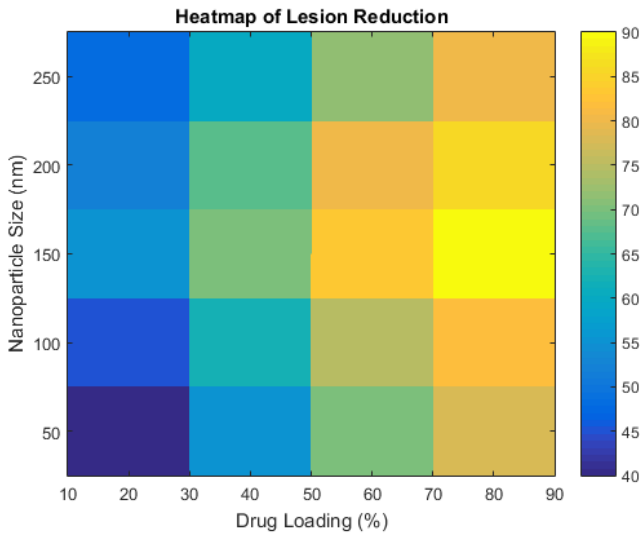


Fig. 4 Heatmap for mean lesion reduction across drug loading and size

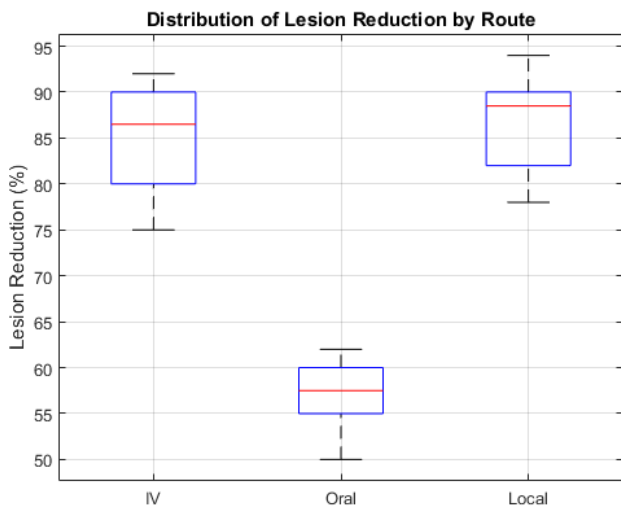


Fig. 5 Distribution of lesion reduction as a function of route

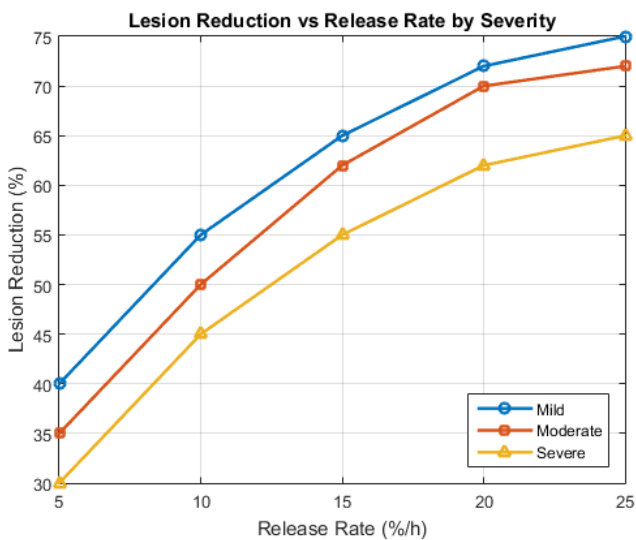


Fig. 6 Lesion reduction as a function of release rate based on disease severity

steeper slope at higher doses, thus showing that therapeutic effect is more steep as dose increases. In particular, intravenous (IV) and local administration pathways exhibit superior control of the inflammation at the same doses than oral. This pattern indicates that pharmacokinetics, which is linked to the route of administration-either increased systemic bioavailability in the case of IV or targeted local delivery, is a key determinant of anti-inflammatory effects. The figure illustrates that different nominal doses may have significantly different effects based on the path and the importance of taking into account delivery pathways in preclinical optimization studies is emphasized.

Optimization-wise, these findings suggest that the strategy of route selection can offer a better strategy when compared to wasteful dose escalation. This can be accomplished through maximization of the local or systemic exposure by the correct means of administration, optimizing the desirable therapeutic effect and reducing the overall systemic dose, thus reducing the risk of either toxicity or off-target effects. This strategy can be adhered to the principles of precision nanomedicine, where every parameter is carefully adjusted (both dosage and mode of delivery) to achieve maximum effectiveness and minimal side effects. Rational design of effective and safe dosing regimens based on such understanding through integrating them into machine learning-guided treatment planning can bring forth translational potential of animal models into clinical practice.

Fig. 6 demonstrates the reduction of lesions by the rate of nanoparticle drug release at different disease intensity. The data indicate that intermediate release rates have the greatest average lesion reductions indicating a balance of sustained drug therapeutic exposure and appropriate drug availability at the target site. Extremely slow release regimens cannot provide enough drug during the critical therapeutic window and excessively rapid release can result in transient peaks that do not help in the long run. Moreover, the variations in lesion removal with the increase of the severity of the disease are less dramatic, hinting at the fact that more complex cases feel less sensitive to the changes in release kinetics alone.

These findings reflect the relevance of disease-stage release profiles in terms of optimization. In moderate disease, sustained intermediate release offers congruent and successful lesion reduction. Conversely, more lethal disease can need approaches that involve additional drug loading, maximum release rate, or local delivery to produce similar treatment effects. By integrating these understandings into machine learning-informed optimization, release kinetics and disease severity can be considered simultaneously and a set of personalized nano-drug delivery strategies can be developed to optimize efficacy and reduce systemic exposure and side effects.

A 3D surface plot, shown in Fig. 7, represents the interaction of nanoparticles size and drug loading on reduction of lesions in the endometriosis model. The surface indicates that the decrease of lesions is strongly dependent on the drug loading, whereas a larger size of the nanoparticles is rather likely to decrease its therapeutic efficiency. The best is found at high drug loading (≥ 70)

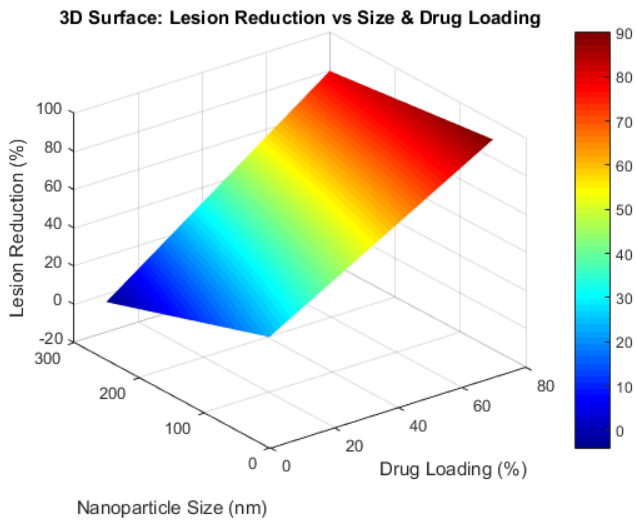


Fig. 7 The lesion reduction as a function of nanoparticle size and drug loading

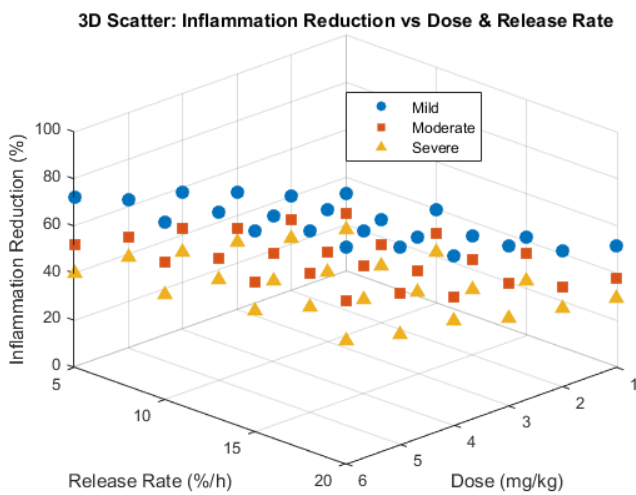


Fig. 8 Inflammation reduction as a function of release rate and dose

and small-to-moderate nanoparticle size (50-150 nm) where lesion reduction is more than 80. This tendency indicates the significance of the appropriate balance between the drug payload and the nanoscale characteristics that allow the tissue penetration and efficient release. Clinically, the outcome indicates that excessively large nanoparticles can lower efficacy in spite of increased drug loading, a case in support of nanodesign optimization.

Fig. 8 represents a three-dimensional scatter plot of inflammation reduction versus drug dose and nanoparticle release rate (stratified by disease severity). At all levels of severity, increasing dose and rate of release are consistently effective in promoting inflammation reduction, but the response slope varies. The steepest improvement is observed in mild cases in which more than 80 percent is attained at moderate doses with quick-release. The moderate cases show a slower and constant gain, whereas the severe cases are small and hardly ever exceed 65 percent even with the highest dosing. This visualization

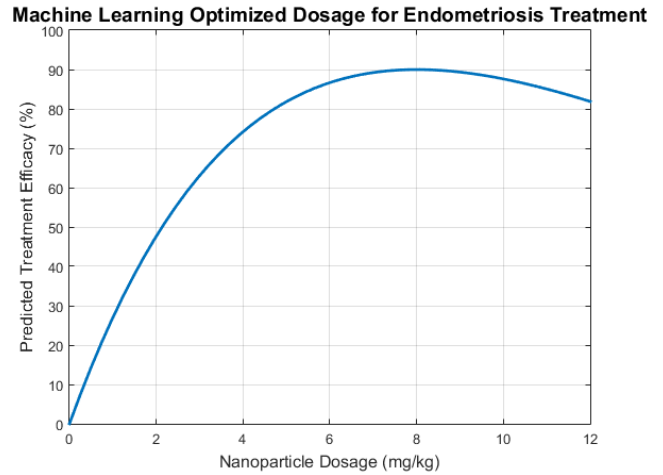


Fig. 9 Optimization of nanoparticle dosage based on machine learning

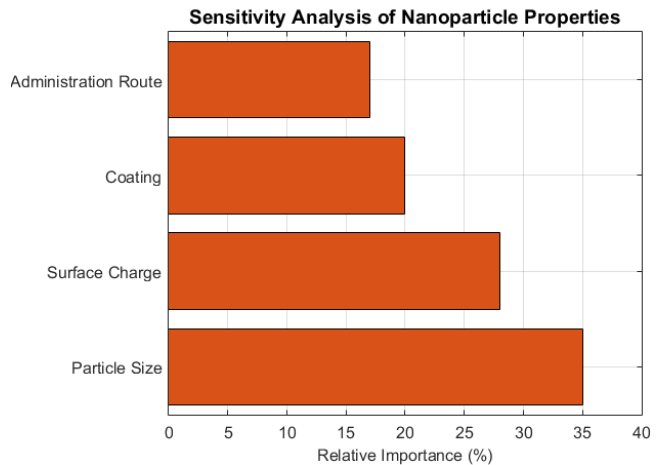


Fig. 10 Sensitivity response of nanoparticle on therapeutic

highlights the difficulty of healing advanced endometriosis: dosing and release kinetics are important, but intrinsic disease severity limits outcomes that can be achieved. These observations are critical to machine learning-directed optimization to customize regimens based on severity group.

A line diagram in Fig. 9 where the efficacy rate of treatment (predicted) is against the dosage of nanoparticles (mg/kg). Making the curve takes a machine learning model (e.g. random forest or extreme learning machine) trained on animal model data to produce the curve. It demonstrates non-linear relationship with efficacy rising with dosage up to an optimum level (~8mg/kg) after which efficacy levels off or marginally declines. This value indicates the forecasting nature of machine learning when it comes to the determination of the optimal dosage of nanoparticles to treat endometriosis. According to the model, at high dosages, further therapeutic improvement cannot be observed, and further increase of nanoparticles in the body cannot significantly affect the therapeutic effect. This plateau is most likely an indication of saturation of cellular mechanisms of uptake or maybe cytotoxic effects in the higher concentrations. Notably, this optimization enables

researchers to reduce side effects and at the same time maximize therapeutic benefit. The machine learning method offers a number system that involves leading the experimental dosing, minimizes trial and error research design and enhances the translational potential of the animal models to clinical implementation.

Fig. 10, bar chart showing the relative significance of input features (e.g. nanoparticle size, surface charge, coating, zeta potential) to treatment efficacy according to the machine learning model. Indicatively, the variability in the outcome of treaties is more than 60% due to the particle size and surface charge, but the contribution of coating and administration route is less. This value shows the effect of various nanoparticle characteristics on therapy in the management of endometriosis. The sensitivity analysis indicates that particle size and surface charge are the most significant factors that influence tissue penetration and cellular uptake and that coating type and administration route influence it moderately. Such lessons are fundamental to rational nanomedicine design, as researchers can worry about maximizing the critical properties instead of devoting attention to factors that are less useful. The study is also able to combine machine learning to not only quantify the action of each property, but also to offer a roadmap to customize nanoparticle formulations to achieve the greatest effectiveness in preclinical models, ultimately improving the translation of such studies to human therapies.

6. Conclusions

The results of this paper highlight the promise of nano-drug delivery systems as a paradigm shift in the treatment of endometriosis especially in terms of overcoming the shortcomings of traditional treatments. In several studies, design parameters of nanoparticles like size, charge, and drug loading were demonstrated to play a significant role in regression of lesion and control of inflammation. Mid-range sizes (100-150 nm) with weakly positive charges were most productive in efficacy, and high drug loading enhanced lesion removal, although excessive size of nanoparticles did not. The route of administration was also a critical concept, where intravenous and local delivery was even more bioavailable and responded better to the therapy compared to oral delivery. In addition, optimal release rates were associated with better efficacy, whereas progression of the disease to an advanced stage significantly decreased the effects of treatment, and stratified treatment plans are required.

Combining these experimental observations with a machine learning model, especially with network-based Extreme Learning Machines, this study shows how predictive modeling can be used to rapidly optimize therapeutic regimens. Machine learning can be used to identify design windows and dosing regimens, which produce the maximum reduction of lesion and inflammation at the lowest systemic burden. Notably, this integrative pipeline connects animal model results to personalized treatment regimens, and it is directed to translational use in human endometriosis. In sum, the findings are consistent

with the twin promise of nanotechnology and artificial intelligence to provide safer, more efficient, and patient-specific curative interventions against a multifaceted gynecological disorder that is inadequately addressed at present by the existing therapeutic approaches.

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