RESEARCH PAPER

Development and Optimization of Exemestane-Loaded PLGA–Glyceryl Monostearate Polymer–Lipid Hybrid Nanoparticles Using Box–Behnken Design

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ABSTRACT

Background: Exemestane is an orally active steroidal aromatase inhibitor, but its formulation performance can be influenced by aqueous solubility, dissolution and gastrointestinal absorption. Polymer–lipid hybrid nanoparticles offer a combined architecture in which a biodegradable polymer can provide structural integrity and controlled release while a lipid component can modify interfacial and drug-partitioning behavior. The present work investigated the development and optimization of exemestane-loaded polymer–lipid hybrid nanoparticles using poly(D,L-lactide-co-glycolide) (PLGA), glyceryl monostearate (GMS) and polyvinyl alcohol (PVA).

Methods: Exemestane was incorporated into a PLGA–GMS matrix stabilized with PVA. A three-factor, three-level Box–Behnken design was applied to investigate PLGA, GMS and PVA as formulation variables. The formulations were evaluated for particle size, polydispersity index (PDI), zeta potential and other critical quality attributes. The selected formulation was further characterized by microscopy, FTIR, DSC and X-ray diffraction.

Results and discussion: The optimized formulation, EF15, contained the formulation components at the selected design condition and showed a particle size of 181.9 ± 2.9 nm, PDI of 0.196 ± 0.009 and zeta potential of −31.4 ± 1.6 mV. TEM and SEM observations supported predominantly spherical, discrete nanosized particles. The optimized formulation retained substantial drug in simulated gastrointestinal conditions and produced 91.7 ± 1.2% release at 12 h.

Conclusion: The results demonstrate the feasibility of producing a nanosized exemestane carrier using a PLGA–GMS–PVA platform. EF15 combined a small particle size, relatively narrow size distribution and favorable surface charge with controlled drug release, providing a rational basis for subsequent biological and pharmacokinetic evaluation.

Keywords: exemestane; PLGA; glyceryl monostearate; polymer–lipid hybrid nanoparticles; PVA; Box–Behnken design; controlled release; oral drug delivery

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INTRODUCTION

Oral administration remains one of the most widely accepted approaches for delivering therapeutic agents because of its convenience, non-invasive nature, ease of administration and suitability for long-term treatment. These advantages are particularly relevant in chronic diseases such as cancer, where prolonged pharmacotherapy may be required. Despite these benefits, the oral route presents several physiological and biopharmaceutical barriers that can restrict drug exposure. After administration, a drug must undergo disintegration and dissolution in gastrointestinal fluids before becoming available for absorption. The dissolved drug may subsequently encounter variations in gastrointestinal pH, enzymatic degradation, intestinal epithelial barriers, efflux mechanisms and presystemic metabolism. Consequently, compounds with inadequate aqueous solubility or dissolution characteristics may exhibit incomplete and variable absorption, ultimately limiting their therapeutic performance [1,2].

Nanotechnology-based drug delivery systems have emerged as an important approach for addressing some of these limitations. Reducing drug or carrier dimensions to the nanometer range can increase the interfacial surface area available for interaction with

biological fluids and may improve dispersion of poorly water-soluble substances. Nanocarriers can additionally provide a protective microenvironment for the incorporated drug and permit modification of drug release, surface characteristics and interaction with biological membranes. Polymeric nanoparticles are particularly attractive because their composition and structure can be adjusted to achieve specific physicochemical and drug-release characteristics [2,3].

Among biodegradable polymers, poly(lactic-co-glycolic acid) (PLGA) has received extensive attention for pharmaceutical and biomedical applications. PLGA is composed of lactic acid and glycolic acid units and undergoes hydrolytic degradation to relatively low-molecular-weight products that can subsequently enter normal metabolic pathways. Its biodegradability, biocompatibility, formulation flexibility and established processing techniques make it a suitable material for the development of controlled and sustained drug-delivery systems [3,4]. The degradation characteristics of PLGA can be influenced by factors such as the lactic acid-to-glycolic acid ratio, molecular weight, particle dimensions, crystallinity and formulation environment. These characteristics permit adjustment of drug retention and release according to the requirements of a particular therapeutic agent. Recent developments have further extended PLGA-based systems toward surface-engineered and hybrid nanocarriers designed to improve stability, drug loading and biological performance [5].

Although polymeric nanoparticles offer important advantages, combining a polymer with a lipid component provides an opportunity to obtain complementary characteristics from two different classes of materials. Polymer–lipid hybrid nanoparticles are generally designed around a polymeric matrix or core associated with a lipid component at the particle interface or within the matrix. Such systems can integrate the structural integrity and controlled-release characteristics of polymeric nanoparticles with the hydrophobicity, interfacial behavior and drug-partitioning properties associated with lipid materials [6,7]. Depending on the formulation strategy, the lipid component can influence particle organization, drug incorporation, surface characteristics and release kinetics. Hybrid systems are therefore increasingly investigated as versatile platforms for poorly soluble and therapeutically challenging compounds.

The performance of a polymer–lipid hybrid nanoparticle depends strongly on the composition and relative concentration of its individual components. Polymer concentration can influence matrix formation, particle size, drug entrapment and release behavior. The amount and nature of lipid can affect the internal organization of the particle, hydrophobic interactions and drug partitioning. Similarly, a stabilizer is generally required during nanoparticle preparation to reduce interfacial tension and minimize particle aggregation. Poly(vinyl alcohol) (PVA) is frequently employed as an aqueous-phase stabilizer during preparation of polymeric nanoparticles because it can facilitate particle formation and improve dispersion stability. Thus, the final characteristics of the nanoparticles are not determined by a single ingredient but arise from interactions among polymer, lipid, stabilizer, drug concentration, solvent composition, mixing conditions and solvent-removal processes [6,8].

Glyceryl monostearate (GMS) is a lipid excipient of interest for the development of lipid-containing drug-delivery systems. Incorporation of GMS into a PLGA-based system provides an opportunity to modify the hydrophobic environment surrounding the drug and consequently influence drug distribution and release. Lipid–polymer matrices have been reported to provide high drug entrapment and physicochemical stability while allowing release characteristics to be tailored through appropriate selection of lipid, polymer and surfactant concentrations [8]. In the present formulation strategy, PLGA was selected as the principal biodegradable polymer, GMS as the lipid component and PVA as the stabilizing agent. The resulting formulation was designed as an integrated polymer–lipid nanocarrier rather than as a simple physical mixture of the individual components.

Exemestane was selected as the model drug for the present investigation. Exemestane is a third-generation, steroidal, irreversible aromatase inhibitor used in the hormonal management of estrogen-dependent breast cancer in postmenopausal women. It acts as a steroidal aromatase inactivator and inhibits the conversion of androgenic substrates into estrogens, thereby reducing estrogen biosynthesis [9,10]. Its pharmacological activity and oral therapeutic use make it an appropriate candidate for investigating advanced oral drug-delivery approaches.

From a formulation perspective, exemestane presents challenges associated with its physicochemical and biopharmaceutical characteristics. Published studies have reported limited aqueous solubility and relatively high lipophilicity, characteristics that can contribute to inadequate dissolution and variable oral absorption. One investigation reported an aqueous solubility of approximately 0.08 mg/mL and a log P value of about 4.22 [11]. Another study specifically attributed the relatively low oral bioavailability of exemestane, reported at approximately 5% in that formulation context, to poor water solubility and extensive first-pass metabolism [12]. These findings provide a

rationale for exploring formulation approaches capable of increasing the effective surface area of the drug, improving dispersion and dissolution, and potentially modifying its absorption behavior.

Several formulation strategies have previously been investigated to improve the oral delivery of exemestane. Proliposomal formulations were developed with the objective of improving solubility, dissolution and intestinal permeability [13]. Similarly, self-microemulsifying drug-delivery systems have demonstrated the ability to enhance the oral bioavailability of exemestane in experimental studies [14]. Cyclodextrin-based formulations have also been investigated and were reported to improve dissolution and apparent permeability [12]. More recently, nanosizing approaches have attracted attention because reduction of particle dimensions can substantially influence dissolution kinetics. In a Box–Behnken-optimized exemestane nanosuspension, nanocrystallization produced improved dissolution and increased pharmacokinetic exposure compared with untreated drug [15]. These findings collectively demonstrate the potential of nanoscale formulation strategies for addressing the dissolution and absorption limitations associated with exemestane.

For the present study, a PLGA–GMS polymer–lipid hybrid nanoparticle approach was selected to combine the advantages of a biodegradable polymeric matrix with those of a lipid component. The polymeric fraction is expected to provide structural integrity and contribute to controlled drug release, whereas GMS may modify the hydrophobic microenvironment and drug–matrix interactions. PVA serves as the stabilizing component during particle formation, assisting in the generation of a stable nanoscale dispersion. Such a hybrid architecture may provide an alternative to conventional nanosuspensions, lipid systems or polymeric nanoparticles by integrating multiple formulation functions within a single nanostructured carrier [6,7].

Analytical and preformulation studies are essential before systematic nanoparticle development. In the present investigation, phosphate-buffered saline (PBS) at pH 7.4 was selected as an analytical medium, and the maximum absorption wavelength of exemestane was established at 240 nm. A concentration-dependent spectrophotometric response was obtained within the investigated range of 2–10 µg/mL, providing a basis for quantitative estimation during subsequent formulation studies. Evaluation of powder characteristics and solubility in different media further established the physicochemical foundation for formulation development. Such preliminary investigations are important because formulation variables must be interpreted in relation to the intrinsic properties of the active pharmaceutical ingredient.

Optimization is a critical component of nanoparticle development because formulation variables frequently exert simultaneous and sometimes opposing effects on the critical quality attributes of the finished product. An increase in polymer concentration, for example, may improve matrix formation and drug entrapment but can also increase particle size and formulation viscosity. Increasing lipid concentration may alter drug partitioning and release, while excessive stabilizer concentration may modify interfacial characteristics and particle growth. Consequently, optimization based solely on changing one variable at a time may not adequately describe interactions among formulation factors.

Design of Experiments (DoE) provides a systematic approach for investigating several formulation variables simultaneously. Response surface methodology can identify significant main effects, interaction effects and nonlinear relationships between independent variables and formulation responses [16]. Among the available experimental designs, the Box–Behnken design is particularly useful when three or more formulation factors are to be investigated at different levels. It requires fewer experimental combinations than a full factorial design while permitting estimation of quadratic effects and interactions. DoE-based optimization has therefore become an important strategy for developing nanocarriers with reproducible and controlled quality attributes [16].

In the present work, a Box–Behnken experimental design was employed to systematically investigate the influence of selected formulation variables, particularly the concentrations of PLGA, GMS and PVA, on the characteristics of exemestane-loaded polymer–lipid hybrid nanoparticles. Critical responses may include particle size, polydispersity, surface charge, drug-entrapment efficiency and drug-release behaviour. Establishing mathematical relationships between the formulation variables and these responses enables identification of an optimized composition rather than relying on empirical formulation trials.

Thus, the present study was undertaken to develop and optimize exemestane-loaded PLGA–GMS polymer–lipid hybrid nanoparticles using a Box–Behnken design. The investigation integrates preformulation characterization, analytical method development, nanoparticle preparation, physicochemical characterization, drug-entrapment assessment, in-vitro release evaluation and statistical optimization. The overall objective is to establish a rational nanotechnology-based formulation approach capable of addressing the physicochemical limitations of exemestane while providing a controlled and systematically optimized oral drug-delivery platform.

The present study was designed around a three-factor, three-level Box–Behnken experimental design. PLGA, GMS and PVA were treated as independent variables, while particle size, PDI, zeta potential and entrapment efficiency were considered important formulation responses. The optimized formulation was then subjected to complementary physicochemical evaluation and release testing. The central hypowork was that an appropriately balanced PLGA–GMS–PVA composition could generate a stable nanosized system with a controlled release profile suitable for further oral-delivery investigation.

Nanoliposomes are the vesicles containing concentric bilayers of phospholipids with both hydrophobic and hydrophilic regions. Hydrophilic drugs are entrapped in the aqueous section and hydrophobic and amphiphilic drugs are found position in concentric bilayer of phospholipids [17].

Nanoliposomes are a new concept, whether liposomes carry a past of more than five decades. First time Bangham et al were described liposomes in 1961 [18]. There are many nano based lipid formulations have shown higher therapeutic efficacy by giving quick transport of the drug from nasal mucosa to brain . Among these, nanoliposomes (NLs) vesicles found to be effective delivery system to enhance permeability and reduce drug dose [19].

Polymeric nanoparticles (PNPs) are the most common among various polymer-based nanocarriers. During the past few decades, the significance of PNPs has increased exponentially in oncology. PNPs represent a large diversity in both structure and physiochemical properties. The main reason for its versatility is the huge variety of monomers that may be used to build up the polymer architectures. The polymers selected for the drug delivery system must full fill a number of requirements including biocompatibility, suitable biodegradation kinetics, and non-immunogenic, can load various chemotherapeutics [20].

Microneedle patches have emerged as promising alternatives to conventional injections for vaccine administration. These patches can deliver vaccines painlessly into the skin, where a high concentration of immune cells is present, resulting in enhanced immune responses. AI-based optimization techniques can help determine the optimal microneedle design, vaccine dosage, and release profile for improved immunization efficiency [21].

Nanoemulsions offer several pharmaceutical and biopharmaceutical benefits. Their nanosized droplets increase the surface area available for absorption, resulting in improved drug dissolution and permeation. They also provide protection against degradation and facilitate sustained drug release profiles [22].

Micro-balloons also known as hollow microsphere are that system that tends to be one the most suitable approach for gastric retention micro balloons drug delivery system can be explained as it is containing empty particles of spherical shape without core identically having a size than 200micrometers. The floating micro balloons showed a mechanism in which drug is floating in the gastric fluid which in turns increases its bioavailability. Micro-balloons are one of the most like approving floating systems with the unique advantage of multiple unit's system as well as better floating properties, because there is a central hollow space within the microsphere [23].

At present, nanoparticles are extensively synthesized and utilized owing to their diverse and versatile applications. The presence of a large surface area with tunable size and properties makes them prospective candidates for a wide spectrum of applications such as drug delivery, pharmaceuticals, food packaging and biotechnology [24].

Nanotechnology-based drug delivery systems have emerged as promising approaches to improve the performance of poorly water-soluble drugs. Nanoparticles provide increased surface area, enhanced dissolution rate, improved permeation, sustained release behavior, and better therapeutic efficacy [25].

Nanoparticle-loaded metal complexes: Encapsulation in polymeric nanoparticles, liposomes, or metallic nanocarriers improves solubility, bioavailability, and controlled release characteristics [26].

Recent advances in nanomaterials, enzyme immobilization strategies, and microfluidic paper-based analytical devices (μPADs) have further enhanced the sensitivity, stability, and analytical performance of paper-based enzymatic biosensors. The incorporation of nanoparticles, conductive materials, and signal amplification techniques has enabled lower detection limits and improved operational stability, facilitating real-time pesticide monitoring in diverse sample matrices [27].

Nanotechnology has revolutionized heavy metal detection by enabling the development of highly sensitive and selective Nano sensors. Nanomaterials such as gold nanoparticles, silver nanoparticles, carbon nanotubes, graphene, and quantum dots possess unique properties, including high surface area, enhanced conductivity, and strong catalytic activity [28].

MATERIALS AND METHODS

Materials

Table 1. Composition and design range used for exemestane-loaded hybrid nanoparticles.

Component	Role	Level/description

Exemestane	Active pharmaceutical ingredient	10 mg per batch
PLGA	Polymeric matrix	50–100 mg
GMS	Lipid component	10–30 mg
PVA	Stabilizing surfactant	0.5–1.5% w/v

The formulation procedure described in the work used an organic phase containing exemestane, PLGA and GMS and an aqueous phase containing PVA. The organic phase was introduced into the aqueous phase under stirring, followed by high-speed homogenization and sonication. Solvent removal produced the hybrid nanoparticles, after which the dispersion was separated, washed and redispersed. The work indicates that selected dispersions could subsequently be converted into dry material by lyophilization where required.

Analytical and preformulation studies

UV-visible spectrophotometry was used for quantitative estimation of exemestane. In PBS pH 7.4, the maximum absorption wavelength was 240 nm. The reported calibration concentrations were 2, 4, 6, 8 and 10 µg/mL, with absorbance values of 0.149, 0.299, 0.473, 0.654 and 0.833, respectively. The formulation investigation also included organoleptic evaluation, powder-flow assessment, solubility studies and drug–excipient compatibility assessment.

Experimental design and optimization

After preliminary screening, 75 mg PLGA, 20 mg GMS and 1.0% w/v PVA were selected as intermediate levels for the three-factor, three-level Box–Behnken design. Fifteen experimental runs were generated. The independent variables were PLGA concentration (X1), GMS concentration (X2) and PVA concentration (X3). The principal response variables were particle size, PDI, zeta potential and entrapment efficiency; in-vitro release was also considered during final formulation selection. The design was used to identify a formulation region producing small, relatively uniform particles with acceptable surface charge and drug retention.

Preparation of nanoparticles

For each experimental batch, the specified quantities of exemestane, PLGA and GMS were incorporated into the organic phase. PVA was separately dissolved in purified water. The organic phase was added gradually to the aqueous stabilizer phase with continuous stirring. The resulting emulsion was subjected to high-speed homogenization followed by sonication. Solvent evaporation was then allowed to proceed under controlled conditions. The resulting dispersion was centrifuged where required, washed and redispersed. The optimized system was retained for physicochemical, release and biological studies.

Characterization

Particle size and PDI were evaluated as measures of hydrodynamic diameter and size distribution. Zeta potential was determined as an indicator of surface electrostatic behavior. Morphology was assessed by TEM and SEM. FTIR was used to examine characteristic spectral features and potential major chemical incompatibility. DSC was used to evaluate thermal behavior, while XRD was used to assess changes in the crystalline characteristics of the drug after incorporation into the carrier.

In-vitro release and gastrointestinal stability

EF15 was evaluated under the release conditions described in the work. Cumulative release was monitored through 12 h. Gastrointestinal stability was examined sequentially in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 6.8), with drug retention and physical appearance monitored during exposure.

RESULTS AND DISCUSSION

Analytical response and preformulation

The analytical response showed progressive increases in absorbance with increasing exemestane concentration. The reported values provide a simple quantitative basis for routine formulation assays. The selected 240-nm wavelength was therefore used for subsequent drug-estimation work. The preformulation findings were also favorable from a handling perspective. Carr's index, Hausner ratio and angle of repose were consistent with satisfactory powder flow, which is useful during accurate weighing and mixing. Solubility varied across the investigated media. The highest reported value was 16.65 mg/mL in 0.1 N HCl, while PBS pH 4.7 produced the lowest value among the tested buffer systems at 8.96 mg/mL . Tween 20 produced a progressive increase from 11.16 to 13.13 mg/mL as concentration increased from 0.5 to 2% w/v. Such variation demonstrates that the medium can materially affect apparent solubilization and therefore must be considered when interpreting dissolution and release data.

Formulation optimization

Among the 15 experimental batches, EF13, EF14 and EF15 showed comparatively favorable particle characteristics. EF15 displayed the smallest particle size and lowest PDI of the three selected batches, together with the largest magnitude of negative zeta potential. These characteristics supported its progression to subsequent studies. The work emphasizes that final optimization should consider all

critical quality attributes rather than particle characteristics alone.

Table 3. Particle characteristics of the selected formulations.

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	Selection observation
EF13	198.3 ± 3.4	0.216 ± 0.011	−27.8 ± 1.2	Small size; narrow distribution
EF14	187.6 ± 3.1	0.203 ± 0.010	−30.1 ± 1.5	Small size; low PDI
EF15	181.9 ± 2.9	0.196 ± 0.009	−31.4 ± 1.6	Smallest size; lowest PDI

The progressive reduction in particle size from EF13 to EF15 may reflect the combined effect of formulation composition and stabilization conditions. A PDI below 0.25 in all three selected batches suggests comparatively narrow distributions. The negative zeta potential indicates that the particle surfaces possessed measurable electrostatic charge, which can contribute to repulsive interactions and dispersion stability. EF15 was consequently selected for deeper characterization.

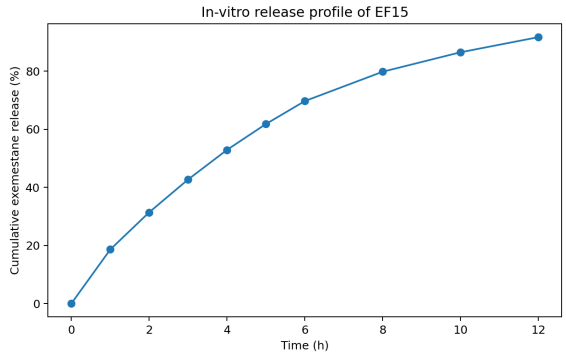


Fig.1 In-vitro release profile of EF15 based on the values reported in the work.

Gastrointestinal stability and controlled release

Table 4. Gastrointestinal stability of EF15.

Time/medium	Drug retained or released (%)
SGF 0 h	100.0 ± 1.2 retained
SGF 1 h	98.1 ± 1.0 retained
SGF 2 h	96.8 ± 1.1 retained
SIF 3 h	95.7 ± 1.0 retained
SIF 4 h	94.8 ± 0.9 retained
SIF 6 h	94.1 ± 1.1 retained

EF15 retained approximately 96.8% of drug after 2 h in SGF and approximately 94.1% after 6 h of subsequent SIF exposure. No pronounced precipitation or aggregation was reported. The relatively high retention during acidic exposure indicates that the hybrid matrix was able to protect a substantial proportion of incorporated drug during the simulated gastric phase. The gradual decrease during intestinal exposure is compatible with progressive hydration and diffusion of drug from the carrier.

Table 5. In-vitro release profile of EF15.

Time (h)	Cumulative release (%)
0	0.00 ± 0.00
1	18.6 ± 1.2
2	31.4 ± 1.5
3	42.7 ± 1.4
4	52.9 ± 1.3
5	61.8 ± 1.5
6	69.7 ± 1.2
8	79.8 ± 1.1
10	86.5 ± 1.0
12	91.7 ± 1.2

The release curve displayed an early phase followed by a slower phase. Approximately 18.6% of drug was released during the first hour, whereas 91.7% was released by 12 h. The early fraction can be associated with drug located near the particle surface or in readily accessible domains. The subsequent slower phase is consistent with diffusion through the hydrated polymer matrix and gradual matrix hydration or erosion. GMS may contribute an additional hydrophobic barrier that limits rapid penetration of the aqueous medium.

CONCLUSION

The study established the feasibility of preparing exemestane-loaded PLGA–GMS polymer–lipid hybrid nanoparticles using PVA as stabilizer and a Box–Behnken design for formulation optimization.

EF15 showed a particle size of 181.9 ± 2.9 nm, PDI of 0.196 ± 0.009 and zeta potential of −31.4 ± 1.6 mV. The formulation exhibited predominantly spherical morphology, retained substantial drug under simulated gastrointestinal conditions and released 91.7 ± 1.2% drug over 12 h. These findings support EF15 as a suitable optimized formulation for further biological and pharmacokinetic investigation.

DECLARATIONS

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conflict of interest

No conflict of interest to be disclosed.

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Data Availability

All data generated or analyzed during this study are included in the manuscript. Further inquiries can be directed to the corresponding author.

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