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Optimizing Complex Pharmaceutical Formulations Using Lexicographic Goal Programming: A Case Study on Ultradeformable Liposomes

Optimización de Formulaciones Farmacéuticas Complejas Mediante Programación por Metas Lexicográficas: Un Caso de Estudio en Liposomas Ultradeformables

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Resumen

Introducción: La optimización de formulaciones farmacéuticas requiere enfoques de estudio avanzados para garantizar calidad, seguridad y eficacia. Entre ellos, aunque la función de deseabilidad y la Programación por Metas Ponderada equilibran múltiples respuestas, carecen de priorización jerárquica. La Programación por Metas Lexicográfica supera esta limitación al optimizar objetivos de forma secuencial. Este estudio presenta a este tipo de programación como un enfoque innovador para optimizar nanoliposomas ultradeformables.

Método: El estudio sigue seis etapas estructuradas, incluyendo la identificación de factores clave, el desarrollo de un Diseño de Experimentos, la definición de niveles de aspiración, la asignación de prioridades y la optimización secuencial. Se enfocó en parámetros críticos como tamaño de vesícula, potencial zeta y eficacia de encapsulación, asegurando una visión jerárquica integral.

Resultados: La Programación por Metas Lexicográfica priorizó primero el potencial zeta y la eficacia de encapsulación, seguidos por el tamaño de vesícula y las respuestas de menor prioridad. Preservó los atributos críticos sin compromisos, minimizando eficientemente las desviaciones tanto para objetivos de maximización como de minimización.

Conclusiones: La Programación por Metas Lexicográfica proporciona un marco jerárquico sólido para la optimización de formulaciones en el campo farmacéutico, gestionando eficazmente los compromisos entre objetivos. Al garantizar que los objetivos clave se cumplen primero, se alinea con los principios de Calidad por Diseño. Este método es especialmente ventajoso para formulaciones complejas, como los sistemas de administración de fármacos liposomales, que requieren un control preciso sobre la estabilidad de las vesículas, su tamaño y la encapsulación del fármaco.

Palabras clave: Toma de decisiones asistida por ordenador; Técnicas de Apoyo para la Decisión; Diseño de Medicamentos; Liposomas

Abstract

Introduction: Optimizing pharmaceutical formulations requires advanced approaches to ensure quality, safety, and efficacy. While the desirability function and Weighted Goal Programming balance multiple responses, they lack hierarchical prioritization. Lexicographic Goal Programming overcomes this limitation by optimizing objectives sequentially. This study introduces this tool as an innovative approach for optimizing ultradeformable nanoliposomes.

Method: The study follows six structured steps, including identifying key factors, developing a Design of Experiments, defining aspiration levels, assigning priorities, and sequential optimization. It focuses on critical parameters such as vesicle size, zeta potential, and encapsulation efficiency, ensuring a comprehensive hierarchical approach.

Results: Lexicographic Goal Programming prioritized zeta potential and encapsulation efficiency first, followed by vesicle size and lower-priority responses. It preserved critical attributes without compromise, efficiently minimizing deviations for both maximization and minimization objectives.

Conclusions: Lexicographic Goal Programming provides a robust hierarchical framework for optimization in the pharmaceutical field, effectively managing trade-offs. Ensuring key objectives are met first, it aligns with Quality-by-Design principles. This method is particularly advantageous for complex formulations, such as liposomal drug delivery systems, requiring precise control over vesicle stability, size, and drug encapsulation.

Keywords: Decision Making Computer-Assisted, Decision Support Techniques; Pharmaceutical Design; Liposomes.

Highlights

The optimization of formulations in Pharmaceutical Technology, which have multiple responses, is typically approached using multi-objective techniques, frequently using the desirability function or Weighted Goal Programming as a global criterion. However, these techniques do not capture hierarchical optimization priorities in responses, which could be a requirement in practice.

To our knowledge, this is the first time that the Lexicographic Goal Programming technique has been applied to the optimization of pharmaceutical formulations.

The optimization of pharmaceutical formulations using Lexicographic Goal Programming improves decision-making by prioritizing critical objectives, ensuring stability and efficacy without compromising

essential attributes in complex formulations such as ultra-deformable nanoliposomes. This methodology could be applied and standardized in the optimization of other formulations where this optimization process is complicated.

Introduction

No borrar esta línea (sub-sección del nivel 1 tiene 2 líneas en blanco después) Optimization of nano pharmaceutical formulations often involves multiple, potentially conflicting objectives such as maximizing drug entrapment, minimizing particle size, ensuring adequate stability, and meeting regulatory criteria[1,2]. Quality-by-design (QbD) principles promote systematic design and risk assessment to ensure robust and high-quality drug products[3–5]. Conventional optimization techniques, including Weighted Goal Programming (WGP), typically aggregate all objectives simultaneously, which may not adequately reflect the importance hierarchy among different responses[6].

Lexicographic Goal Programming (LGP) addresses this shortcoming by introducing a tiered approach. To each objective is assigned a distinct priority, and higher-priority goals are optimized first. The method proceeds to subsequent objectives only after fully or nearly satisfying higher-priority objectives. This study explores the application of LGP to timolol-loaded ultra-deformable nanoliposomes, which are eye drop formulations designed to enhance ocular bioavailability by improving permeability across corneal barriers[7]. By prioritizing critical parameters such as zeta potential (to maintain stability) and drug entrapment efficiency (to ensure therapeutic efficacy), the approach ensures that the final formulation meets stringent performance requirements.

Timolol, a beta-blocker commonly used for glaucoma management, can be formulated into ultra deformable liposomes to enhance ocular penetration and reduce systemic absorption[8]. These vesicles often require balancing size distribution, surface charge and drug encapsulation efficiency to achieve optimal therapeutic effects while minimizing side effects[9]. WGP-based optimization has been used in earlier studies to strike a compromise among these parameters[10]. However, the lexicographic method offers a more decision-driven approach[11]. By systematically addressing the highest-priority responses, such as preventing vesicle aggregation (via stable zeta potential) and maximizing drug entrapment, LGP can yield a more robust solution.

This research aimed to demonstrate the effectiveness of LGP in resolving multi-objective conflicts for QbD-based timolol-loaded ultra-deformable nanoliposomes. The approach highlights how sequential decision-making can achieve lower deviations in high-priority objectives and potentially improve overall performance. Additionally, adaptability of the method to incorporate both minimization (z_1, z_2) and maximization goals (z_3, z_4, z_5, z_6), is showcased.

Methods

The methodology follows a structured, step-by-step process, detailed below.

Identifying Factors and Responses

According to González-Rodríguez et al.[12], five key formulation factors influence the quality attributes of liposomes, including cholesterol amount (F_1), edge activator amount (F_2), the phase in which timolol is added (F_3), the presence of stearylamine (F_4), and the type of edge activator (F_5). This study focuses on optimizing six critical responses: minimizing vesicle size (z_1) to enhance ocular penetration and polydispersity index (z_2) to ensure uniform particle distribution, while maximizing zeta potential (z_3) for colloidal stability, deformability index (z_4) to facilitate transit through ocular membranes, phosphorus content (z_5) to maintain bilayer integrity, and drug entrapment efficiency (z_6) to enhance therapeutic efficacy.

Design of Experiments (DoE)

A fractional factorial Taguchi L16 orthogonal array (see Table 1) was employed to systematically analyze the impact of formulation factors on each response[13].

Table 1. Taguchi L16 orthogonal array. T20: Tween® 20, Deo: sodium deoxycholate.

Run	F_1 Cholesterol (µmol)	F_2 EA (mg)	F_3 TM Phase	F_4 SA	F_5 Edge-activator
1	20	10	Lipid	Yes	T20
2	20	10	Aqueous	No	Deo
3	20	12	Lipid	Yes	Deo
4	20	12	Aqueous	No	T20
5	27	10	Lipid	No	Deo
6	27	10	Aqueous	Yes	T20
7	27	12	Lipid	No	T20
8	27	12	Aqueous	Yes	Deo
9	20	10	Lipid	Yes	Deo
10	20	10	Aqueous	No	T20
11	20	12	Lipid	No	T20
12	20	12	Aqueous	Yes	Deo
13	27	10	Lipid	No	T20
14	27	10	Aqueous	Yes	Deo
15	27	12	Lipid	Yes	Deo
16	27	12	Aqueous	No	T20

Each experimental run measured (z_1–z_6), and regression models were developed to quantify their dependencies on formulation factors. Adjusted R-squared values confirmed model accuracy, and any anomalies were addressed to ensure data reliability.

Defining Aspiration Levels

The aspiration levels for each response were set based on the decision maker's preferences to serve as a guide for the optimization process and ensure the best possible performance of the liposomal formulation. Table 2 presents the target values for each response, defining whether they should be minimized or maximized based on their impact on formulation quality (e.g., using "≤" or "≥"). Zeta potential was set to be maximized above 12 mV to maintain colloidal stability, preventing particle aggregation. Drug entrapment efficiency was prioritized for maximization, requiring values above 4.5 % to ensure enough drug loading. Vesicle size was targeted for minimization, with an aspiration level below 160 nm to facilitate ocular penetration. Similarly, polydispersity index was set to be minimized below 0.155 to ensure uniform size distribution and improve formulation consistency. The deformability index was aimed to be maximized above 0.24 ml/min to enhance vesicle flexibility, improving penetration through biological membranes. Lastly, phosphorus content was maximized above 30 mg to maintain bilayer integrity, ensuring structural stability.

Table 2. Aspiration levels.

Response	Criterion	Target
Vesicle size (z_1)	Minimize (≤)	≤ 160 nm
Polydispersity index (z_2)	Minimize (≤)	≤ 0.155
Zeta potential (z_3)	Maximize (≥)	≥ 12 mV
Deformability index (z_4)	Maximize (≥)	≥ 0.24 ml/min
Phosphorus content (z_5)	Maximize (≥)	≥ 30 mg
Drug entrapment efficiency (z_6)	Maximize (≥)	≥ 4.5 %

These aspiration levels provide a structured reference for optimization, ensuring that key formulation attributes align with pharmaceutical quality standards, even if they are not fully met. In such cases, LGP finds the closest possible solution while respecting the priority hierarchy.

Assigning Priorities

In LGP, the highest-priority goals are satisfied first, ensuring that no solution compromises the top-tier objectives while optimizing lower-tier ones. The primary goal is zeta potential (z_3), which ensures stability, followed by drug entrapment efficiency (z_6) to maintain therapeutic efficacy. Next, vesicle size (z_1) is prioritized as it influences bioavailability, while the deformability index (z_4) assists in ocular penetration. Phosphorus content (z_5) reflects bilayer integrity, and finally, the polydispersity index (z_2) contributes to sample uniformity. This hierarchical approach guarantees that critical formulation attributes are preserved before addressing secondary considerations.

Optimization

LGP solves a series of optimization problems in a predetermined hierarchy. Therefore, if response i (for the set of m responses) has a higher priority than response i+1, i.e. $P_i >> P_{i+1}$, the model can be summarized as follows:

$$\text{Lexmin } G = [d_{P_1}, d_{P_2}, \ldots d_{P_n}] = [n_3, n_6, p_1, n_4, n_5, p_2]$$

Subjected to:

$$z_i(\mathbf{F}) + n_i - p_i = T_i, \forall i \in m$$

$$n_i, p_i \geq 0, \forall i \in m$$

$$F_1, F_2 \in R \text{ and } F_3, F_4, F_5 \in \{0, 1\}$$

where F = (F_1, ..., F_5) represents the sets of decision variables (factors) and z_i(F) represents the actual function value for the i-th goal. The variables n_i and p_i represent the negative and positive deviations (d_{pj}) from the aspiration level T_i and priority j.

Since z_1 and z_2 are minimization responses, their positive deviations p_i (excess over T_i) are minimized. Conversely, for maximization responses z_3 to z_6, their negative deviations n_i (shortfall from T_i) are minimized.

The objective function G first minimizes the deviation associated with the highest-priority goal, then proceeds to the second priority, and so forth[11]. The final solution ensures that higher priorities remain as close as possible to their targets, with lower priorities optimized within that feasible boundary. This stepwise approach is particularly valuable in multi-objective formulation scenarios, where exceeding or missing certain targets can drastically affect product quality[14].

LINGO software was used for solving sequential optimization problems, employing a global solver to ensure optimum solutions for each priority level[15]. Alternative tools could handle the problem similarly, but the robust capability of LINGO for non-linear and mixed-integer programming made it well-suited for these liposomal models.

Results

According to the methodology, the results obtained based on the established priorities are presented below.

Achieving Priority 1: Zeta Potential (z_3)

The first objective minimized n_3, the negative deviation from the zeta potential aspiration level. See z_3 in Figure 1 and Figure 2. The solution yielded a zeta potential above 12 mV (e.g., 12.91 mV in one itera-

tion), confirming that the highest-priority stability requirement was met. All subsequent optimizations locked $n_3 = 0$, meaning no further compromise on zeta potential was allowed.

Achieving Priority 2: Drug Entrapment Efficiency (z_6)

Next, n_6 was minimized to increase entrapment above 4.5 %. The final optimized solution reached or exceeded this threshold (e.g., 4.52 %), ensuring adequate drug delivery. With zeta potential already set, the second priority had to meet its target without reducing z_3 below 12 mV, exemplifying the strength of the hierarchical approach.

Achieving Priority 3: Vesicle Size (z_1)

Subsequently, p_1 was minimized to keep vesicle size below 160 nm. While the solution approached this target, slight deviations were allowed only if they did not compromise the first two priorities. This often resulted in sizes around 152–155 nm, close to the aspiration level, highlighting the trade-off management inherent to LGP.

Remaining Goals

After fixing the first three responses, the model minimized deviations in deformability (z_4), phosphorous content (z_5), and polydispersity index (z_2) in sequence. Minor fluctuations were noted, but overall, each metric remained within acceptable limits. For example, polydispersity might have a slight deviation if optimizing it would conflict with maintaining the higher-priority goals[6]. This structured step-by-step optimization demonstrates the power of lexicographic approaches for managing complex, multi-objective problems.

The evolution of each response over the steps is shown in Figure 1.

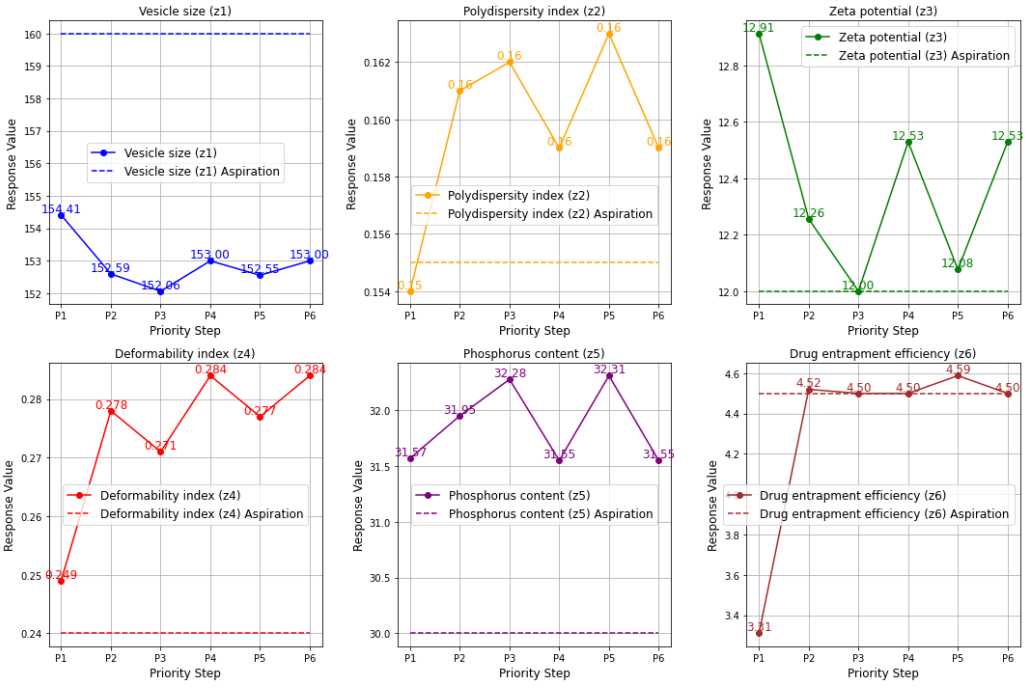

Figure 1. z_i evolution through priority steps in optimization.

In addition, Figure 2 shows the deviations on each response through the priority steps.

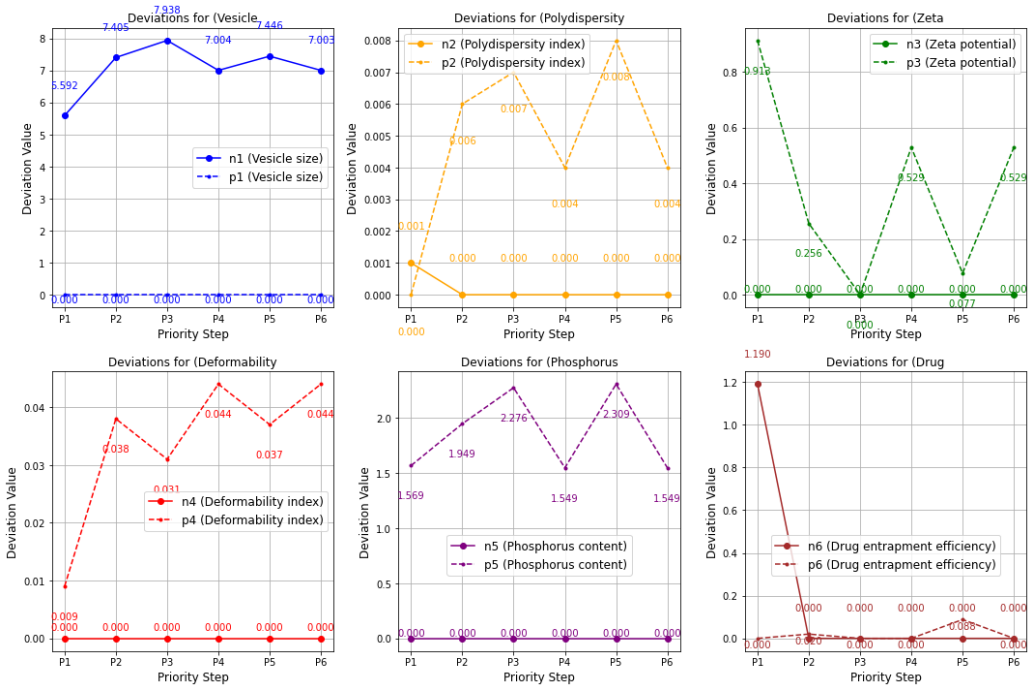

Figure 2. Deviations n_i and p_i evolution through priority steps in optimization.

Discussion

The sequential, hierarchical nature of LGP highlights its utility in tackling complex pharmaceutical optimization challenges, particularly when critical formulation objectives cannot be compromised. Consistent with prior research, emphasizing high-impact parameters—such as zeta potential (z_3) for stability and drug entrapment efficiency (z_6) for therapeutic efficacy—ensures that key formulation attributes are maintained throughout the optimization process[16]. This ensures that the most essential parameters, particularly those linked to colloidal stability and therapeutic potency, achieve near-ideal or acceptable levels before the process attends to lower-priority goals. As a result, the system avoids the simultaneous balancing of all objectives at once, which could dilute the emphasis on crucial variables. The lock-in of high-priority achievements (e.g., $n_3 = 0$ for z_3) provides a stable baseline upon which subsequent optimizations can be executed without eroding earlier successes.

While higher-priority goals often converge fully to their aspiration levels, lower-priority responses may display small deviations due to inherent constraints[11]. For instance, polydispersity index (z_2) may exceed its nominal threshold if pushing it further risks undermining drug entrapment efficiency or colloidal stability. These minor compromises underscore the real-world relevance of LGP. In practice, decision-makers may tolerate slight trade-offs in less critical attributes so long as primary objectives remain intact. Crucially, this stepwise acceptance of lower-priority deviations reflects a pragmatic understanding of limited resources, mechanical constraints, and time or cost considerations.

From a QbD perspective, LGP aligns well with risk-based frameworks that emphasize systematic identification and control of critical process parameters[1]. Because LGP assigns strict priorities and satisfies

them in an orderly, tiered fashion, it readily fits into the QbD approach of defining design spaces that reflect actual manufacturing priorities and constraints. This feature becomes especially relevant in liposomal formulations, where small shifts in composition or process conditions can produce outsized changes in vesicle stability or drug release profiles[14]. By directing resources toward high-impact attributes and locking them in place before refining lower-priority features, LGP creates a robust path for developers to meet their most pressing objectives while still optimizing ancillary characteristics. Ultimately, the integration of LGP into QbD methodologies offers a powerful synergy, enabling structured and evidence-based decision-making that reflects both scientific insights and regulatory expectations.

Conclusions

LGP presents a structured, sequential optimization methodology that aligns well with real-world pharmaceutical development, where certain product attributes cannot be compromised. This study confirms that a hierarchical approach—focusing first on essential responses like zeta potential and drug entrapment—can yield robust, near-optimal solutions for complex, multi-parameter formulations such as timolol-loaded ultra deformable liposomes.

By ensuring minimal deviations for top-tier objectives, LGP preserves stability and therapeutic efficacy while allowing secondary goals to be fine-tuned under fewer constraints. This hierarchical method stands in contrast to WGP, where simultaneous optimization may risk suboptimal performance in critical responses. Overall, LGP is a valuable tool in QbD-driven formulation design, effectively balancing the myriad objectives inherent to pharmaceutical product optimization.

Although the case study focused on timolol-loaded ultra-deformable liposomes, LGP can be generalized to other nanoparticles, micellar systems, or advanced platforms. Potential enhancements include integrating machine learning algorithms to refine the search space or coupling LGP with Bayesian approaches for improved uncertainty management[17]. Such expansions could further streamline pharmaceutical optimization processes.

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