



Glyceryl Monostearate-Based Nanostructured Lipid Carriers: A Comparative Review of Formulation Strategies and Performance Evaluation

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Abstract

Nanostructured lipid carriers (NLCs) represent a second-generation lipid nanocarrier technology designed to address the limitations of solid lipid nanoparticles (SLNs), particularly their low drug-loading capacity and instability. This comprehensive review evaluates the role of glyceryl monostearate (GMS) as the primary solid lipid component in NLC systems. It analyzes formulation strategies, physicochemical characteristics, and performance outcomes of GMS-based NLCs. Relevant literature published between 2015 and 2025 was systematically collected from prominent scientific databases and critically assessed based on formulation composition, particle size, polydispersity index (PDI), zeta potential (ZP), entrapment efficiency (EE), drug loading (DL), and biological performance. The reviewed studies underscore the significant influence of lipid ratios, surfactant selection, and preparation methods on NLCs characteristics. GMS forms a semi-crystalline matrix that facilitates drug accommodation and minimizes drug expulsion. In summary, GMS-based NLCs exhibit substantial potential to enhance the bioavailability, stability, and controlled-release properties of lipophilic compounds for pharmaceutical and cosmeceutical applications.

Keywords: Formulation strategies, glyceryl monostearate, nanostructured lipid carriers, physicochemical characteristics.

1. Introduction

Advancements in pharmaceutical science have propelled the development of innovative drug delivery systems to circumvent the limitations of conventional dosage forms, such as poor solubility, permeability, and stability [1]. Nanostructured lipid carriers (NLCs) have emerged as a second-generation lipid-based nanocarrier that enhances drug loading capacity, entrapment efficiency, and long-term stability [2]. Glyceryl monostearate (GMS), a biocompatible and biodegradable solid lipid form, create a semi-crystalline matrix that improves drug encapsulation and prevents expulsion during storage [3]. This review elucidates formulation strategies and physicochemical characteristics of GMS-based NLCs to achieve stable, efficient, and controlled-release drug delivery systems [4,5].

The escalating interest in GMS-based NLCs is evidenced by the growing number of studies investigating their application for oral, topical, transdermal, and targeted drug delivery [6]. Numerous active pharmaceutical ingredients, including flavonoids, antihyperlipidemic agents, antidiabetic drugs, anticancer compounds, and phytoconstituents, have been successfully incorporated into GMS-based NLCs formulations [6]. Nevertheless, the available evidence remains fragmented across various therapeutic compounds, formulation compositions, and evaluation approaches, rendering it challenging to establish a comprehensive understanding of the contribution of GMS to NLCs performance.

Although several review articles have discussed NLCs in general, a focused review specifically evaluating the formulation strategies and performance of GMS-based NLCs remains limited [3]. Furthermore, the relationship

between formulation variables, physicochemical characteristics, encapsulation performance, and biological outcomes has not been comprehensively summarized. Therefore, this review aims to critically evaluate how GMS influences formulation characteristics, encapsulation performance, and biological outcomes of NLCs based on evidence published between 2015 and 2025. To provide a comprehensive understanding of GMS-based NLCs, this review discusses the rationale for NLCs development, the role of GMS as a solid lipid, formulation strategies, physicochemical characteristics, encapsulation performance, biological evaluations, current challenges, and future perspectives for pharmaceutical and cosmeceutical applications.

2. Rationale for the Use of NLCs in Drug Delivery

Nanostructured lipid carriers (NLCs) represent a significant advancement in modern drug delivery systems, particularly for bioactive compounds with poor solubility or stability. The first generation of lipid-based nanocarriers, known as solid lipid nanoparticles (SLNs), offered advantages such as biocompatibility and protection of drugs from degradation. However, SLNs (Fig. 1a) were limited by low drug-loading capacity and potential drug expulsion during storage due to their highly ordered crystalline structure [6]. During storage, SLNs may undergo polymorphic transitions from the metastable α form to the more thermodynamically stable β' and β forms. This transition increases lipid crystal ordering and packing density, which can result in drug expulsion or redistribution from the lipid matrix [7].

To overcome these limitations, NLCs (Fig. 1b) were introduced as a second-generation system by incorporating liquid lipids into the solid lipid matrix. This modification introduced structural imperfections that improved encapsulation efficiency and increased drug-loading capacity [1,6]. Compared with SLNs, this lipid combination results in a less ordered matrix that improves retention of encapsulated drugs and reduces drug expulsion during storage [7].

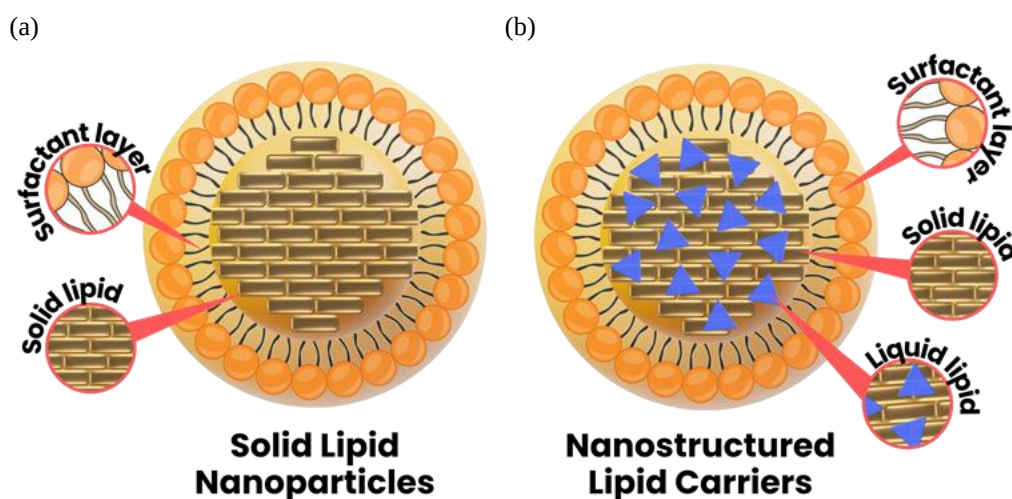


Figure 1 Structural comparison between (a) Solid Lipid Nanoparticles (SLNs) and (b) Nanostructured Lipid Carriers (NLCs)

Recent studies have demonstrated the broad applicability and therapeutic potential of NLCs across both oncological and non-oncological applications. For instance, apigenin-loaded NLCs significantly enhanced the solubility and cytotoxic activity of apigenin against non-small-cell lung cancer (NSCLC) cells compared with the free drug [6]. Similarly, anastrozole-loaded NLCs exhibited nanoscale particle size, high stability, and controlled drug release profiles, supporting their potential for breast cancer therapy [7]. Furthermore, *Ficus deltoidea*-loaded NLCs demonstrated improved antioxidant activity, enhanced skin permeation, and favorable biocompatibility, underscoring the broader applicability of NLCs in dermatological and cosmeceutical formulations [1].

Collectively, these findings support the use of NLCs as an advanced drug delivery platform. Compared with conventional formulations and first-generation SLNs, NLCs offer improved encapsulation efficiency, enhanced bioavailability, controlled drug release, greater protection of labile compounds, and reduced systemic side effects through targeted delivery, making them particularly suitable for therapeutic agents with challenging pharmacokinetic and biopharmaceutical properties [1,6,7].

3. Role of GMS as Solid Lipid in NLCs Systems

The monoacylglycerol moiety in GMS consists of a glycerol backbone bearing two free hydroxyl groups and one stearyl acyl chain attached through an ester bond. This structure gives GMS its amphiphilic character, in which the fatty acyl chain acts as the hydrophobic region, while the glycerol hydroxyl groups act as the hydrophilic region. In Figure 2, the long hydrophobic C18 hydrocarbon chain on the left represents the stearyl monoacyl chain, while the red oxygen-containing region on the right represents the ester-linked glycerol headgroup. Therefore, the monoacylglycerol chain should be indicated in the figure by labeling the stearyl acyl chain, ester linkage, and glycerol headgroup to clarify the structural region responsible for lipid packing and amphiphilic behavior [8].

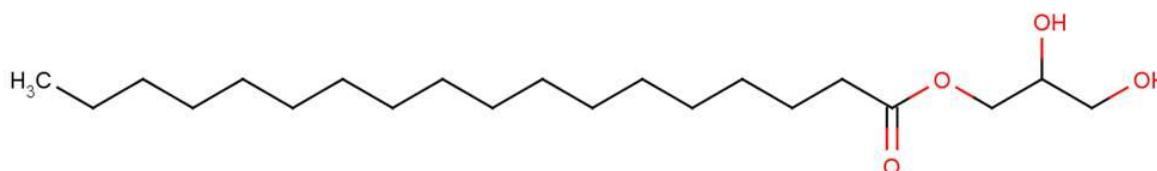


Figure 2 2D structure of glyceryl monostearate

Glyceryl monostearate (GMS) has emerged as a widely utilized solid lipid in the development of Nanostructured Lipid Carriers (NLCs). Its exceptional physicochemical stability, biocompatibility, and ability to form a semi-crystalline matrix capable of encapsulating a diverse range of active compounds contribute to its prominence in this field. Structurally, GMS comprises monoesterified glycerol with stearic acid, exhibiting amphiphilic properties that enable effective interaction with both hydrophilic and lipophilic drug molecules [9]. This dual affinity facilitates the stabilization of emulsified systems and promotes the self-assembly of nanoparticles with robust structural integrity.

One of the key roles of GMS (Fig. 2) in NLCs systems lies in its ability to form a rigid yet partially disordered crystalline network when blended with liquid lipids. This imperfect crystallization minimizes drug expulsion during storage and increases drug accommodation within the lipid matrix [10]. Mechanistically, drug expulsion in lipid nanoparticles usually occurs when the solid lipid matrix becomes more ordered during storage. In highly crystalline systems, lipid molecules pack tightly and reduce the free volume available for drug molecules, forcing the entrapped drug to migrate toward the particle surface or external aqueous phase. In GMS-based NLCs, the incorporation of liquid lipids disrupts the regular packing of the saturated stearyl chains of GMS. This disruption reduces crystallinity, increases lattice imperfections, and creates amorphous or less ordered regions that can accommodate drug molecules more effectively [3,11].

The presence of monoacylglycerol chains allows GMS molecules to align within the lattice structure of NLCs, producing lattice defects that provide additional void spaces for drug molecules [12]. More specifically, the single stearyl chain of GMS contributes to hydrophobic packing inside the lipid core, while the glycerol headgroup supports interfacial orientation with surfactants and the aqueous phase. When a compatible liquid lipid such as oleic acid, medium-chain triglycerides, Capryol®90, glyceryl triacetate, or vegetable oils is incorporated, the difference in chain length, saturation, and molecular mobility between the liquid lipid and GMS prevents the formation of a perfect crystal lattice. As a result, drug molecules are not compressed out of the matrix during lipid recrystallization. This cause-and-effect relationship may be summarized as follows: GMS-liquid lipid blending produces a less ordered lipid matrix; the less ordered matrix generates more defects and free volume; these defects increase drug accommodation and reduce drug migration; consequently, drug expulsion during storage is minimized [11,13]. Such a property is particularly advantageous compared to other solid lipids like stearic acid or tristearin, which tend to recrystallize into highly ordered forms, resulting in reduced encapsulation efficiency.

Moreover, GMS contributes significantly to the physical stability and surface charge properties of NLCs dispersions. Due to its amphiphilic nature, GMS can orient itself at the lipid-water interface, thereby reducing interfacial tension and supporting the formation of smaller and more stable nanoparticles [14]. The resulting zeta potential values often exceed ± 30 mV, an indicator of strong electrostatic repulsion that prevents particle aggregation. In addition, the high melting point of GMS (approximately 58-60°C) allows it to maintain nanoparticle integrity under varying storage or physiological conditions, improving thermal and colloidal stability [15]. However, GMS alone may still undergo crystallization into more ordered polymorphic forms; therefore, its combination with liquid lipids is essential to maintain matrix disorder and reduce drug leakage over time.

Another critical role of GMS is its contribution to the controlled release behavior of NLCs formulations. The crystalline arrangement of GMS slows the diffusion of entrapped drugs, enabling a sustained-release profile that enhances therapeutic efficacy and reduces dosing frequency [16]. This controlled release mechanism occurs as the drug diffuses through both the solid lipid matrix and the liquid lipid compartments. The solid GMS matrix

provides a diffusion barrier, whereas the liquid lipid phase can act as a drug-solubilizing nano compartment. Therefore, an initial release may occur from drug molecules located near the particle surface, followed by prolonged release from the internal lipid core. This explains why many GMS-based NLCs exhibit a biphasic release pattern consisting of an initial burst followed by sustained release. Furthermore, in topical formulations, GMS also exhibits occlusive and emollient properties that improve drug penetration through the stratum corneum. It enhances skin hydration by reducing trans epidermal water loss, which consequently facilitates higher drug permeation rates [17].

From a mechanistic standpoint, GMS-NLCs also demonstrate enhanced entrapment efficiency (EE%) and drug loading capacity (DL%) due to their semi-solid matrix architecture. Studies have reported EE values ranging from 80-95% when GMS is combined with liquid lipids such as oleic acid or medium-chain triglycerides [18]. This is attributed to the formation of amorphous regions within the lipid matrix, which can physically entrap drug molecules and prevent their migration to the particle surface. Additionally, GMS provides chemical stability by shielding drugs from oxidation or hydrolysis-particularly beneficial for unstable or photosensitive drugs [10]. For example, lutein-loaded NLCs prepared from GMS and vegetable oils showed that increasing oil loading reduced particle size, produced a less ordered lipid matrix, and increased entrapment efficiency. The same study also reported slower lutein release from NLCs compared with nanoemulsions, supporting the role of the GMS-containing solid matrix in restricting drug diffusion and protecting unstable compounds [13].

Empirical findings further support the role of GMS as a functional solid lipid rather than merely an inert carrier. Apigenin-loaded NLCs prepared using GMS, glyceryl triacetate, and poloxamer 188 achieved high entrapment efficiency of $88.22 \pm 1.61\%$ and drug loading of $4.22 \pm 0.13\%$, while also improving the inhibitory activity of apigenin against NSCLC cells compared with free apigenin [6]. This result indicates that the GMS-liquid lipid matrix can retain lipophilic flavonoids efficiently and improve biological performance. Similarly, 6-gingerol-loaded NLCs using GMS and medium-chain triglycerides produced nanosized particles and improved pharmacokinetic performance, suggesting that the mixed lipid matrix could enhance oral delivery of poorly water-soluble compounds [19]. Carvedilol-loaded GMS-based NLCs also demonstrated high entrapment efficiency and improved oral delivery potential, showing the importance of GMS in stabilizing lipophilic cardiovascular drugs within the lipid matrix [20].

Beyond physical and chemical functions, GMS also plays a biopharmaceutical role by enhancing bioavailability. Its lipophilic nature promotes lymphatic uptake when administered orally, bypassing the first-pass metabolism and improving systemic absorption of poorly water-soluble drugs [9]. When used in topical and transdermal delivery, GMS enhances local deposition of the active compound through lipid-lipid interaction with the skin barrier, while minimizing irritation due to its GRAS (Generally Recognized as Safe) status. These multifaceted roles make GMS a superior solid lipid choice for NLCs development compared to other lipids like cetyl palmitate or stearic acid, which may provide good stability but lack the same encapsulation and release-modulating capabilities.

4. Formulation Strategies of GMS-NLCs

Formulating an efficient GMS-NLCs requires careful consideration of several interdependent parameters, including lipid composition, surfactant selection, preparation method, and optimization of processing conditions. The ratio of GMS to liquid lipids is one of the most critical factors influencing physicochemical characteristics such as particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency [17]. An excess of GMS can lead to a highly crystalline matrix that restricts drug accommodation, whereas insufficient solid lipid content may result in particle instability or drug leakage. Therefore, maintaining an optimal balance-typically around 60-80% GMS of total lipid content-has been reported to enhance both stability and encapsulation efficiency [18]. However, the optimal proportion of GMS may vary depending on the physicochemical properties of the active compound and the selected liquid lipid. For example, in apigenin-loaded NLCs prepared using GMS, glyceryl triacetate, and Poloxamer 188, according to a previous study, optimizing the formulation using central composite design-response surface methodology (CCD-RSM) used an emulsifier concentration of 1.33%, a lipid-drug ratio of 20, and a solid-liquid lipid ratio of 9.52, producing an entrapment efficiency of $88.22 \pm 1.61\%$ and drug loading of $4.22 \pm 0.13\%$ [6]. The predicted errors for EE and DL were only 2.12% and 4.09%, respectively, indicating that the experimental design accurately predicted the optimized formulation. For example, in apigenin-loaded NLCs prepared using GMS, glyceryl triacetate, and Poloxamer 188, optimized the formulation using central composite design-response surface methodology (CCD-RSM) [19]. The optimized formulation used an emulsifier concentration of 1.33%, a lipid-drug ratio of 20, and a solid-liquid lipid ratio of 9.52, producing an entrapment efficiency of $88.22 \pm 1.61\%$ and drug loading of $4.22 \pm 0.13\%$. The predicted errors for EE and DL were only 2.12% and 4.09%, respectively, indicating that the experimental design accurately predicted the optimized formulation.

The type of liquid lipid chosen also affects the degree of miscibility with GMS, where medium-chain triglycerides or oleic acid are often preferred to introduce lattice imperfections that support higher drug loading

[15]. Experimental data support this mechanism because the incorporation of liquid lipids disrupts the regular packing of the GMS matrix and improves drug accommodation. According to a previous study reported that lutein-loaded NLCs composed of GMS and vegetable oils, including virgin coconut oil, rice bran oil, and palm oil, were successfully prepared with particle sizes of approximately 105-160 nm and PDI values below 0.35 [13]. Increasing the oil loading from 5% to 20% significantly decreased particle size ($p < 0.05$), indicating that higher liquid lipid content reduced matrix viscosity and facilitated particle size reduction. The same study also showed that NLCs containing 20% oil loading had significantly higher lutein retention after storage than formulations containing 5% or 10% oil loading ($p < 0.05$), suggesting that liquid lipid incorporation helped maintain an imperfect matrix and reduce lutein expulsion from the lipid core.

In addition to lipid composition, surfactant type and concentration greatly influence NLCs stability and drug release. Surfactants such as Poloxamer 188 and Tween 80 are frequently used to reduce interfacial tension and stabilize GMS-NLCs dispersions [21]. A higher surfactant concentration can decrease particle size and improve homogeneity but may also lead to surfactant-induced toxicity or excessive micelle formation that interferes with drug entrapment. Hence, optimization through factorial design or response surface methodology (RSM) is often employed to determine the ideal surfactant level that ensures both stability and safety [22]. This need for optimization was demonstrated in the AP-NLCs study, where the CCD-RSM model for EE was statistically significant ($p < 0.0001$) with an R^2 value of 0.9669, while the model for DL was also statistically significant ($p < 0.0001$) with an R^2 value of 0.9953. Among the tested variables, emulsifier dosage significantly affected EE ($p = 0.0009$) and DL ($p = 0.0004$), while the solid-liquid lipid ratio showed a highly significant effect on both EE and DL ($p < 0.0001$). These findings indicate that surfactant concentration and lipid ratio should not be selected empirically but should be optimized statistically to achieve reproducible NLCs performance [6].

Furthermore, the preparation technique such as high-pressure homogenization, ultrasonication, or microemulsion methods affects the crystalline behavior and morphology of NLCs. The use of hot homogenization combined with sonication is widely favoured for GMS-based systems, as it allows uniform dispersion and minimizes lipid recrystallization [16]. In the AP-NLCs formulation, melt sonication produced spherical or oval nanoparticles with a particle size of 47.77 ± 1.79 nm, PDI of 0.217 ± 0.015 , and zeta potential of -18.5 ± 0.96 mV. Stability testing for two months at 4°C showed only a slight increase in particle size and PDI, while zeta potential remained relatively stable, indicating that the preparation method contributed to acceptable colloidal stability [6]. Similarly, 6-gingerol-loaded NLCs prepared using optimized GMS-based formulation exhibited a mean particle size of 63.59 ± 5.54 nm, zeta potential of -12.18 ± 1.06 mV, EE of $76.71 \pm 1.11\%$, and DL of $1.17 \pm 0.35\%$. The optimized formulation also produced sustained release and significantly higher serum concentration, mean residence time, and AUC compared with free 6-gingerol suspension, demonstrating that formulation optimization can translate into improved pharmacokinetic performance [19].

Recent research trends emphasize the incorporation of bioactive lipids or co-surfactants in GMS-NLCs to further modulate release kinetics and enhance bioavailability. For instance, the addition of phosphatidylcholine or stearic acid has been reported to improve the interfacial packing between GMS and liquid lipid components, resulting in improved long-term stability and controlled drug diffusion [23]. Likewise, using natural lipids such as shea butter or mango seed oil in combination with GMS can enhance biocompatibility and provide additional antioxidant or moisturizing effects for topical applications [24].

Optimization of these formulation parameters not only improves encapsulation efficiency and release control but also tailors NLCs performance for specific routes of administration, including dermal, oral, and ocular delivery. Overall, the strategic formulation of GMS-NLCs integrates principles of lipid chemistry, colloidal stability, and process optimization to achieve a system that offers superior drug loading, prolonged release, and enhanced therapeutic efficacy. The available experimental evidence indicates that successful GMS-NLCs development depends on four connected formulation decisions: selecting a compatible liquid lipid, adjusting the GMS-liquid lipid ratio to maintain matrix imperfections, optimizing surfactant concentration statistically, and applying a preparation technique that produces small and homogeneous particles. Continuous exploration of GMS interactions with different lipid matrices and surfactant systems will enable the development of next-generation lipid nanocarriers with improved functionality and stability suitable for various pharmaceutical and cosmeceutical applications.

5. Methodology

This review employed a structured narrative review approach to identify and evaluate studies related to glyceryl monostearate (GMS)-based NLCs. Literature searches were performed using PubMed, ScienceDirect, and Google Scholar databases between August and September 2025. The search strategy employed combinations of the following keywords: “glyceryl monostearate”, “GMS”, “nanostructured lipid carrier”, “NLC”, “solid lipid”, “drug delivery system”, “encapsulation efficiency”, “drug loading”, “particle size”, “zeta potential”, and “controlled release”. Boolean operators (AND, OR) were applied to broaden or narrow the search results as appropriate. The inclusion criteria consisted of: (1) original research articles published in peer-reviewed journals;

(2) studies involving GMS as the primary solid lipid component in NLCs formulations; (3) articles reporting physicochemical characteristics such as particle size, PDI, ZP, EE, DL, or drug release behavior; and (4) articles published in English between 2015 and 2025. The exclusion criteria included: (1) review articles, conference abstracts, editorials, and book chapters; (2) studies not utilizing GMS as a major solid lipid component; (3) articles lacking sufficient formulation or characterization data; and (4) duplicate publications retrieved from multiple databases. After removing duplicate records, the titles and abstracts of the retrieved articles were screened for relevance. Full-text evaluation was subsequently performed to determine eligibility according to the predefined inclusion and exclusion criteria. The selected studies were analyzed and categorized according to formulation strategy, physicochemical characterization, encapsulation performance, drug release behavior, and pharmaceutical applications. Data extracted from the eligible studies were summarized and critically compared to identify formulation factors influencing the performance of GMS-based NLCs.

6. Physicochemical Characterization of GMS-NLCs

The physicochemical characterization of glyceryl monostearate (GMS)-based nanostructured lipid carriers (NLCs) is strongly influenced by formulation composition, particularly the solid-to-liquid lipid ratio, surfactant type, and processing conditions. Among the key parameters, particle size (PS), polydispersity index (PDI), zeta potential (ZP), encapsulation efficiency (EE), and drug loading (DL) are essential indicators of formulation performance and colloidal stability (Table 1). These parameters collectively determine the quality, stability, and therapeutic potential of NLCs systems.

Table 1 Summary of GMS-NLCs formulations reported in previous studies

No	Formulation				Test Results					Reference
	API	GMS (%)	Liquid lipid	Surfactants	PS (nm)	PDI	ZP (mV)	EE (%)	DL (%)	
1	6-Gingerol	2.5	MCT	Tween 80 + Poloxamer 188	63.59 ± 5.54	0.243 ± 0.039	-12.18 ± 1.06	76.71 ± 1.11	1.17 ± 0.35	[19]
2	Carvedilol	0.6	Oleic acid	Tween 80 + Poloxamer 188	110.1 ± 1.3	0.373 ± 0.03	-30.0 ± 0.9	85.11 ± 3.7	16.76 ± 0.93	[20]
3	Apigenin	90.6 (of the lipid phase)	Glyceryl triacetate	Poloxamer 188	47.77 ± 1.79	0.217 ± 0.015	-18.5 ± 0.96	88.22 ± 1.61	4.22 ± 0.13	[6]
4	Anastrozole	200 mg (83.3% of the lipid phase)	Oleic acid	Tween 80, Poloxamer 407, Lecithin	166 ± 3.86	0.271 ± 0.04	-23.7 ± 2.65	42.43 ± 3.9	1.23 ± 0.35	[7]
5	Ficus deltoidea	2	Virgin Coconut Oil	Soy lecithin, Tween 80	158.0 ± 1.3	0.15 ± 0.02	-42.3 ± 1.5	87.4 ± 1.3	8.5 ± 1.2	[1]
6	Ceftriaxone	70 (of the lipid phase)	Capryol-90	Tween 80	126.78 ± 6.54	0.26 ± 0.07	-29.14 ± 3.47	46.98 ± 7.48	8.56 ± 0.86	[25]
7	Repaglinide	-	Medium-chain triglyceride	Poloxamer 188, Tween 80	75.935 – 331.39	0.069-0.279	-14.89 to -8.55	96.28-98.86	3.04 - 4.413	[4]
8	Rosuvastatin	1.4	Transcutol HP	Poloxamer 188 + Tween 80	126.4 ± 2.6	0.36 ± 0.03	-9.5 ± 3.7	63 ± 2	3.15 ± 0.16	[26]
9	Pioglitazone	4	Oleic acid	Tween 80 + Soy lecithin	158.6 ± 2.9	0.192 ± 0.014	-28.4 ± 1.7	86.1 ± 2.2	9.4 ± 0.7	[2]
10	Lutein	8.0-9.5	VCO / RBO / PO	Poloxamer 188	105-160	< 0.35	-26 to -38	94-99.5	-	[13]

Particle size (PS) is a critical quality attribute of nanostructured lipid carriers (NLCs) that reflects the efficiency of nanoparticle formation and directly influences formulation homogeneity. In the reviewed studies, PS ranged from 47 to 166 nm, confirming the nanoscale characteristics of GMS-based NLCs systems. Variations in particle size were primarily attributed to differences in the solid-to-liquid lipid ratio and surfactant composition [1]. A higher proportion of liquid lipid combined with optimized surfactant systems, such as Tween 80, Poloxamer 188, and lecithin, generally resulted in smaller particle sizes due to reduced lipid crystallinity and improved interfacial stabilization [6, 16]. Conversely, larger particle sizes were associated with less optimized lipid ratios and incomplete surfactant coverage at the particle interface [7, 19]. Overall, particle size reflects the effectiveness of

formulation parameters in controlling nanoparticle formation and structural uniformity across different GMS-based NLCs systems.

The polydispersity index (PDI) indicates the homogeneity of particle size distribution within NLCs formulations. Most formulations exhibited PDI values below 0.3, indicating a relatively narrow size distribution and acceptable system uniformity [1,6,16]. However, certain formulations, such as carvedilol-loaded NLCs, showed slightly higher PDI values (0.373 ± 0.03), suggesting a broader size distribution [17]. Variations in PDI are mainly influenced by lipid composition, surfactant concentration, and homogenization efficiency during preparation. Overall, lower PDI values contribute to improved physical stability and more consistent formulation performance.

Zeta potential (ZP) values of GMS-based NLCs ranged from approximately -12 to -42 mV, indicating moderate to strong electrostatic repulsion between particles [1, 12, 19]. Higher absolute ZP values (≥ 25 mV) are generally associated with improved colloidal stability due to reduced particle aggregation. Among the formulations, Ficus deltoidea-loaded NLCs exhibited the highest ZP (-42.3 mV), indicating strong electrostatic stabilization [1], whereas 6-gingerol formulations showed lower ZP values (-12.18 mV) but remained physically stable when combined with steric stabilization mechanisms [16]. Nonionic surfactants such as Tween 80 and Poloxamer 188 contribute to steric stabilization, while lecithin may increase negative surface charge due to ionizable phosphate groups [11, 15]. Therefore, the stability of GMS-based NLCs is governed by the combined effects of electrostatic repulsion and steric hindrance.

Table 2 Influence of GMS Characteristics on the Physicochemical and Functional Properties of NLCs

GMS characteristics	Influence on NLCs characteristics	Advantages of GMS in NLCs systems	Reference
Amphiphilic molecular structure	Facilitates interaction with lipid and aqueous phases	Promotes nanoparticle self-assembly and emulsion stability	[8], [11]
Biocompatible and biodegradable solid lipid	Provides safe lipid matrix	Suitable for pharmaceutical and cosmeceutical applications	[3], [8], [12]
Semi-crystalline lipid matrix	Forms partially ordered structure with defects	Enhances drug encapsulation and reduces drug expulsion	[3], [9], [10]
Lattice imperfections with liquid lipids	Creates void spaces in lipid core	Improves drug loading and entrapment efficiency	[9], [10], [15]
Compatibility with liquid lipids (oleic acid, MCT, Capryol-90, natural oils)	Produces less ordered lipid structure	Enhances stability and controlled release	[12], [14], [15]
Compatibility with surfactants (Tween 80, Poloxamer 188, lecithin)	Reduces interfacial tension and stabilizes interface	Results in reduced particle size and lower PDI	[11], [15], [16], [17]
High melting point	Maintains structural integrity	Improves thermal and storage stability	[12], [14]
Crystalline matrix slows diffusion	Controls drug release rate	Enables sustained and biphasic release	[13], [16], [20]
Lipophilic nature	Enhances drug solubilization	Improves bioavailability	[8], [19], [24]
Occlusive/emollient property	Enhances stratum corneum hydration	Enhances topical drug delivery	[5], [12], [14]

As shown in Table 2, the performance of GMS in NLC systems is closely related to its intrinsic physicochemical properties. The amphiphilic structure of GMS enables interaction with both hydrophilic and lipophilic components, supporting interfacial stabilization and nanoparticle formation [8,11]. In addition, GMS forms a semi-crystalline lipid matrix that becomes partially disordered when combined with liquid lipids, generating lattice imperfections that significantly enhance drug accommodation [3,9,10]. This structural feature directly contributes to improved encapsulation efficiency, increased drug loading, and reduced drug expulsion during storage.

The compatibility of GMS with various liquid lipids and surfactants further enhances formulation performance. Liquid lipids disrupt the ordered crystalline structure of GMS, producing a more flexible lipid matrix, while surfactants reduce interfacial tension and provide steric stabilization [11,15,16,17]. These combined effects result in nanosized particles with improved homogeneity and colloidal stability, consistent with the data summarized in Table 1.

Furthermore, the solid lipid nature of GMS supports controlled drug release by slowing diffusion through the lipid matrix, leading to a biphasic release profile characterized by an initial burst release followed by sustained release [13,16,20]. This behavior is beneficial for maintaining therapeutic drug levels over extended periods. In topical applications, the occlusive property of GMS enhances skin hydration and improves drug permeation through the stratum corneum [5,12,14]. Overall, GMS acts not only as a structural lipid but also as a multifunctional excipient that governs nanoparticle formation, colloidal stability, drug encapsulation, and release behavior in NLCs systems.

7. Encapsulation Efficiency and Drug Loading

Encapsulation efficiency (EE%) of GMS-based NLCs is highly dependent on the physicochemical nature of the drug, the solid–liquid lipid ratio, and the surfactant composition. Previous studies have suggested that solid lipid concentration and surfactant composition may influence EE; however, quantitative comparison among the reviewed studies was limited due to differences in formulation composition and experimental conditions. Among the formulations studied, lutein-loaded GMS-based NLCs achieved the highest EE values (94–99.5%), reflecting the strong lipophilic affinity of lutein toward both the GMS matrix and liquid lipids such as virgin coconut oil (VCO), rice bran oil (RBO), and palm oil (PO). Similarly, repaglinide exhibited very high EE (96.28–98.86%) with moderate Drug Loading (DL%) (3.04–4.41%), indicating optimal encapsulation efficiency due to good chemical compatibility with medium-chain triglycerides (MCT). Pioglitazone-loaded NLCs, using a combination of GMS and oleic acid, yielded an EE of $86.1 \pm 2.2\%$ and a high DL of $9.4 \pm 0.7\%$, showing balanced drug retention and lipid matrix stability.

In contrast, rosuvastatin-loaded GMS NLCs demonstrated relatively low EE ($63 \pm 2\%$, reported 48–73%) and DL ($3.15 \pm 0.16\%$), attributed to the drug's hydrophilic character and poor solubility within the Transcutol HP lipid phase. Carvedilol and 6-gingerol exhibited only moderate EE ($76.71 \pm 1.11\%$ and $85.11 \pm 3.7\%$, respectively) and low DL ($1.17 \pm 0.35\%$ for 6-gingerol; $16.76 \pm 0.93\%$ for carvedilol), reflecting the influence of molecular lipophilicity and lipid compatibility on entrapment performance. Interestingly, despite being hydrophobic, 6-gingerol displayed reduced thermodynamic stability in the MCT-Tween-Poloxamer system, leading to partial drug loss during encapsulation. Conversely, apigenin achieved high EE ($88.22 \pm 1.61\%$) and moderate DL ($4.22 \pm 0.13\%$), consistent with its lipophilic flavonoid structure and favorable solubility in the GMS–glyceryl triacetate matrix.

Ceftriaxone, a hydrophilic molecule, showed moderate EE ($46.98 \pm 7.48\%$) but relatively high DL ($8.56 \pm 0.86\%$), suggesting drug partitioning toward the aqueous phase during emulsification. Anastrozole presented the lowest EE ($42.43 \pm 3.9\%$) and DL ($1.23 \pm 0.35\%$) among the lipophilic drugs, likely due to suboptimal drug–lipid interactions and the complex surfactant mixture (Tween 80, Poloxamer 407, and lecithin) used. Meanwhile, Ficus deltoidea NLCs exhibited favorable values (EE $87.4 \pm 1.3\%$, DL $8.5 \pm 1.2\%$), demonstrating efficient retention of phytoconstituents within a simple lipid system. The reviewed studies employed various liquid lipids, including oleic acid, Capryol®90, medium-chain triglycerides, and natural oils, and generally reported moderate to high EE and DL values. However, the specific contribution of each liquid lipid could not be directly compared because formulation compositions differed substantially among studies. These results collectively confirm that encapsulation efficiency and drug loading capacity in GMS-NLCs are governed by the interplay between drug lipophilicity, lipid phase solubility, and surfactant balance, with optimal systems achieving both high drug entrapment and thermodynamic stability.

Overall, the reviewed studies indicate that the performance of GMS-based NLCs is influenced by the interplay between drug physicochemical properties, lipid composition, and surfactant system. Lipophilic compounds generally exhibited higher encapsulation efficiency than hydrophilic drugs, although the extent of drug loading varied considerably among formulations. Because substantial differences existed in formulation composition, surfactant concentration, and preparation methods, direct comparisons between studies should be interpreted cautiously. Nevertheless, the available evidence supports the potential of GMS as a versatile solid lipid for the development of stable NLCs systems with favourable encapsulation characteristics [27].

8. Performance Evaluation of GMS Based NLCs

Overall, GMS-based NLCs demonstrated favourable physicochemical characteristics and diverse performance profiles, including prolonged or controlled drug release, improved drug retention, enhanced permeability, and increased chemical stability (Table 3). These outcomes were influenced by particle size, lipid composition, and the structural organization of the lipid matrix. Importantly, EE alone does not appear to be a definitive predictor of NLC performance, as formulations with moderate EE may still demonstrate favorable release and permeability profiles. Therefore, EE and DL should be interpreted together with other formulation and performance parameters when evaluating the effectiveness of GMS-based NLCs.

Table 3 Comparative Characteristics and Performance of GMS-Based NLCs

API	GMS-NLCs characteristics	Performance	Reference
6-Gingerol	NLCs containing two mixed lipids	Sustained release NLC formulation could availably improve the water solubility and enhance the oral bioavailability of 6-Gingerol	[19]
Carvedilol	GMS-based NLCs	Increased lipid concentration prolongs drug release and enhances bioavailability partly due to reduced first-pass metabolism while also ensuring good storage stability.	[20]
Apigenin	GMS-based NLCs	Drug-release curves fitted using mathematical kinetic models	[6]
Anastrozole	GMS-based NLCs	GMS-based NLC provided strong drug retention under simulated GI conditions and pH-sensitive release, supporting its potential as a controlled-release carrier	[7]
Ficus deltoidea	GMS-based NLCs combining solid and liquid lipid phase	GMS-based NLC of Ficus deltoidea show higher permeability with very short lag period after application, indicating that steady state permeation was reached quickly	[1]
Ceftriaxone	GMS-based NLCs	Strong permeability and brain-targeting performance despite moderate EE	[25]
Repaglinide	GMS-based NLCs	Sustained release and smaller NLCs showed higher intestinal absorption and more consistent hypoglycemic effects	[4]
Rosuvastatin	GMS-based NLCs	Slow drug release for up to 24 hours and improved oral bioavailability through enhanced gastrointestinal solubilization	[26]
Pioglitazone	GMS-based NLCs	Controlled release and improved glycemic control compared with conventional suspension	[2]
Lutein	GMS-based NLCs compared with nanoemulsion	Vegetable oil type had minimal effect on physical stability but significantly influenced lutein chemical stability, drug release, and skin permeation	[13]

9. Challenges and Limitations of GMS Based NLCs

GMS based NLCs have been proposed as an advanced alternative to solid lipid nanoparticles (SLNs), particularly because of their enhanced drug loading capacity and reduced risk of drug expulsion. Nevertheless, the translation of these systems into practical applications remains limited by persistent challenges related to formulation development and large-scale implementation. A fundamental limitation lies in the structural stability of the GMS containing lipid matrix. The incorporation of liquid lipids into SLNs has been proposed to overcome low drug loading and drug leakage by creating an imperfect crystalline matrix with increased accommodation space for drug molecules [25]. However, differences in lipid compatibility and molecular packing hinder uniform mixing at the molecular level, resulting in poor miscibility between GMS and liquid lipids. As a result, formulations are largely developed empirically. Poor miscibility can lead to phase separation during storage, promoting lipid recrystallization into more ordered structures, which reduces matrix imperfections and ultimately causes drug expulsion and decreased encapsulation efficiency [30]. The absence of standardized criteria for selecting compatible lipid combinations further highlights a gap in rational NLCs design [31].

In addition to miscibility-related challenges, the polymorphic behavior of GMS represents an intrinsic source of instability. As a high-melting lipid, GMS undergoes time-dependent transitions from metastable α - and β' -forms toward the thermodynamically stable β -form during storage [32]. While energetically favourable, these transitions increase matrix crystallinity and reduce the free volume available for drug incorporation. Consequently, drug leakage and alterations in release kinetics may occur, particularly during prolonged storage. The difficulty in controlling these polymorphic transformations raises concerns regarding the long-term physical stability and batch-to-batch reproducibility of GMS-based NLCs formulations. This observation further suggests that the theoretical advantages of NLCs over SLNs may diminish over time if structural transitions are not adequately controlled [29].

Another major challenge is the multifactorial optimization of formulation parameters, which remains highly formulation-specific and lacks universal design principles. The ratio of solid to liquid lipids is crucial in maintaining structural disorder; however, imbalance can significantly reduce performance. Excess solid lipid increases crystallinity similar to SLNs, while excess liquid lipid may cause phase separation and oil leakage, compromising stability. In addition, surfactant type and concentration strongly influence system stability. Poor optimization can lead to particle aggregation, increased size, broader polydispersity index (PDI), and reduced entrapment efficiency, ultimately affecting reproducibility. This highlights the need for more systematic and model-based approaches in NLCs design. From a safety perspective, although GMS-based NLCs formulations generally exhibit a pH within the acceptable skin range (7.3–7.4) and GMS is widely regarded as biocompatible, their safety profile warrants further evaluation. High concentrations of GMS and surfactants may induce cytotoxicity, membrane disruption, oxidative stress, or local irritation, particularly in topical and parenteral applications [11]. Furthermore, the application of GMS-based NLCs for delivering large biomolecules, including proteins, peptides, and nucleic acids, remains limited because of the inherent incompatibility between hydrophilic macromolecules and lipid matrices. This limitation restricts their utility in advanced biopharmaceutical delivery

and underscores the need for formulation strategies, such as surface modification or hybrid carrier systems, to expand their therapeutic applications [29].

Manufacturing, reproducibility, and regulatory considerations remain major barriers to the clinical translation of GMS-NLCs. While small-scale formulations can be tightly controlled in the laboratory, scaling up production often results in variability in particle attributes and reduced stability [34]. Achieving consistent nanoparticle batches with stable colloidal properties during storage is challenging, highlighting the importance of implementing Quality by Design strategies early in development. Furthermore, formulation sensitivity can lead to inconsistent therapeutic outcomes at larger scales, and long-term safety concerns, including surfactant or excipient toxicity, remain under-explored [35]. Addressing these issues related to stability, scalability, and regulatory compliance is critical for the successful clinical translation of GMS-NLCs formulations.

10. Development Prospects of GMS Based NLCs in Pharmaceutical Applications

GMS-NLCs exhibit broad applicability across various administration routes due to their high drug loading capacity and favorable safety profile. They are particularly effective in enhancing the solubility and permeability of poorly soluble drugs, thereby improving bioavailability [31]. Studies have demonstrated NLCs use via oral, parenteral (e.g. IV), topical (transdermal), pulmonary, ocular, and intranasal routes [29]. This versatility allows targeting a wide spectrum of diseases, NLCs formulations have been investigated for cancer, infections, neurodegenerative disorders, diabetes, hypertension, and pain management [11]. By improving drug stability and biodistribution, GMS-NLCs can overcome limitations of traditional dosage forms in challenging therapeutic areas.

The potential of GMS-NLCs is further highlighted by their ability to support multi-drug delivery systems. Research has shown that co-delivery strategies, such as combining chemotherapeutic agents with natural compounds, can enhance therapeutic efficacy while reducing adverse effects. For example, the co-delivery of phytochemicals in cancer treatment has demonstrated synergistic effects, improving outcomes and minimizing toxicity [36]. Similarly, combining NLC-based delivery with conventional therapies such as chemotherapy or immunotherapy may provide synergistic benefits while mitigating side effects. Continued innovation in co-delivery strategies, advanced formulation approaches including ligand targeting or hybrid systems, and rigorous clinical validation will be critical to fully harness the pharmaceutical potential of GMS-NLCs [34].

Notably, GMS performs effectively across both natural and synthetic active ingredients, though through somewhat different mechanisms. Natural compounds such as apigenin achieve high entrapment efficiency and improved cytotoxic activity within the GMS matrix [6]. Similarly, *Ficus deltoidea* extract loaded into GMS-based NLCs shows high entrapment efficiency and strong antioxidant activity [1]. In contrast, synthetic drugs such as anastrozole show lower entrapment efficiency due to suboptimal drug–lipid interaction [7]. Carvedilol, however, achieves high entrapment efficiency owing to more favorable lipid compatibility [20]. This indicates that GMS-NLC performance depends more on drug–lipid compatibility than on whether the active ingredient is natural or synthetic. Such dual capacity supports GMS-NLCs as a versatile platform for natural synthetic co-delivery systems [36]. These structural advantages are also consistent with comparative reviews affirming the superiority of NLCs over first-generation SLNs [3].

Despite their promising applications, the clinical translation of GMS-NLCs faces several challenges. Manufacturing scalability remains a major hurdle, as scaling up production often introduces variability in particle characteristics and compromises stability. Implementing Quality by Design principles during development is essential to ensure consistent product quality and performance. Additionally, long term safety, including potential toxicity associated with surfactants or excipients, remains insufficiently explored [37]. Addressing these challenges through optimized formulation strategies, improved manufacturing processes, and regulatory frameworks tailored to complex lipid nanocarriers will be critical. With continued research and technological advancement, GMS-NLCs are expected to transition from experimental systems to practical pharmaceutical solutions, broadening their clinical applications and transforming drug delivery in the coming decade.

11. Conclusion

Glycerol monostearate (GMS) forms a semi-crystalline matrix in nanostructured lipid carriers (NLCs), which enhances drug accommodation and bioavailability for poorly water-soluble compounds. GMS-based NLCs typically exhibit sizes of 47–166 nm, high encapsulation efficiency (up to 99.5%), and sustained-release profiles, which are heavily influenced by lipid ratios, surfactants, and preparation methods. Although promising for therapeutic applications, barriers such as polymorphic transitions, manufacturing scalability, and long-term stability hinder clinical translation. Future developments must leverage systematic Quality by Design (QbD) optimization and comprehensive stability evaluations to facilitate successful commercialization.

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13. Author Contributions

Ainurofiq A.: Conceptualization, Funding acquisition, Supervision; Anvorismasra RP.: Investigation, Formal analysis, Data curation; Veronikasari P.: Software, Writing – review & editing; Febyaningrum VD.: Resources, Project administration; Azizah FSN.: Validation, Writing – review & editing; Herawardhani N.: Methodology, Visualization; Purbowati D.: Writing – original draft, Project administration.

14. Conflicts of interest

There are no conflicts of interest.

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