

Nano-Structured Lipid Carriers for Co-Delivery of Linagliptin and Canagliflozin in Type 2 Diabetes: A Critical Review and Conceptual Framework

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ABSTRACT

Type 2 diabetes mellitus (T2DM) affects 537 million adults worldwide, a figure projected to reach 783 million by 2045, necessitating novel combinatorial therapeutic strategies. Dipeptidyl peptidase-4 (DPP-4) and sodium-glucose cotransporter-2 (SGLT2) inhibitors act via complementary mechanisms, yet co-encapsulation of linagliptin and canagliflozin within nanostructured lipid carriers (NLCs) has not previously been reported. This review is structured to critically evaluate existing NLC formulation strategies using the Quality by Design (QbD) methodology, assess the pharmacological rationale for dual-agent delivery, and propose a biphasic dual-drug NLC framework addressing the marked disparity in elimination half-lives and lipophilicity between the two agents. Preclinical evidence for individually formulated NLCs demonstrates 3-5-fold bioavailability enhancement and sustained release extending to 96 hours; however, no experimental data exist for the proposed combination. Drug-drug-lipid interactions, long-term stability, and clinical translational feasibility are identified as critical uncertainties. A conceptual framework is presented, positioning this dual-drug NLC as a theoretically justified but experimentally unvalidated formulation strategy.

Keywords: Nanostructured lipid carriers, type 2 diabetes mellitus, linagliptin, canagliflozin, DPP-4 inhibitors, SGLT2 inhibitors.

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1. INTRODUCTION

The management of type 2 diabetes mellitus has changed substantially over the last two decades, advancing from glycaemic control as the main goal to a more integrated understanding of the disease as a multi-organ metabolic disorder. This change has occurred with advancements in pharmaceutical delivery science, with nanocarrier-based systems being increasingly explored as vehicles that can overcome the pharmacokinetic limitations inherent to conventional oral antidiabetic formulations. However, before the rationale for a dual-drug nanostructured lipid carrier system can be established, the scale of the clinical problem and the physiological basis for combination therapy must first be explained.

1.1 The Global Burden and Pathophysiology

T2DM is a worldwide epidemic that happens when insulin resistance and β -cell malfunction create high blood sugar levels. The International Diabetes Federation says that 537 million adults have diabetes today. This number is predicted to increase to 783 million by 2045 [1]. These losses currently amount to \$327 billion annually in the US alone, and there is a critical demand for new therapeutic alternatives [2]. DeFronzo's ominous octet forebodes T2DM aetiology via eight interdependent failures- β -cell failure, hepatic insulin resistance, muscle insulin resistance,

adipocyte dysfunction, incretin deficit, hyperglucagonemia, renal reabsorption of glucose, and suboptimal CNS function

(Figure 1) [3]. This complexity explains why monotherapy frequently fails, as combination regimens are required in some 50% of patients within the 3 years after diagnosis [4].

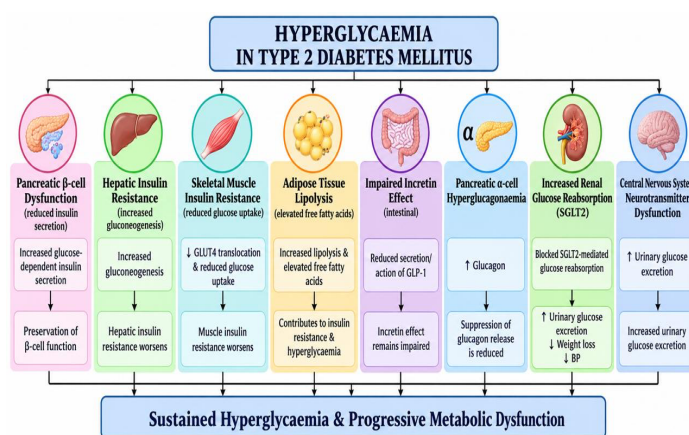


Figure 1. Multi-Targeted Therapy Addressing T2DM Pathophysiology

DPP-4 inhibitors and SGLT2 inhibitors in combination act on two different nodes in the pathogenic network of type 2 diabetes mellitus [5]. Inhibition of DPP-4 prevents enzymatic degradation of GLP-1 and GIP, which results in increased biological half-life and, consequently, increased glucose-dependent insulinotropic secretion and decreased glucagon output. SGLT2 inhibition is insulin-independent and reduces proximal tubular glucose reabsorption, resulting in glucosuria of 70–120 g/day with decreased adiposity (2–3 kg within three weeks) and systolic blood pressure [6]. Since these agents act on different molecular substrates rather than a common pathway, their combination results in additive rather than redundant efficacy. In Asian populations, dual therapy reduced HbA1c by 0.57% compared with DPP-4 monotherapy and by 0.46% compared with SGLT2 monotherapy, without a concomitant increase in hypoglycemic incidence [5]. However, this evidence is based on a fixed-dose, single-tablet regimen, and information on dose adaptability or long-term outcomes is not available.

1.2 Pharmacological Profiles of Linagliptin and Canagliflozin

Linagliptin (Tradjenta®) is a xanthine-based DPP-4 inhibitor with a terminal half-life of >100 h and concentration-dependent protein binding. Elimination is mainly faecal (85%) only 5% is excreted renally [6]; therefore, no dose adjustment is required in hepatic or renal impairment. The dose of 5 mg once daily maintains inhibition of DPP-4 for at least 24 hours and shows selectivity for DPP-4 over related enzymes of greater than 10,000-fold [7]. Oral bioavailability is limited to approximately 30% due to P-glycoprotein-mediated efflux and the first-pass hepatic metabolism. Canagliflozin (Invokana®) was the first SGLT2 inhibitor to be approved for clinical use. It inhibits both SGLT1 and SGLT2 (K_i 770.5 nM and 4.0 nM, respectively) to delay intestinal glucose absorption and increase incretin secretion. Oral bioavailability is approximately 65%. Protein binding is >99%. Hepatic clearance is via O-glucuronidation (UGT1A9, UGT2B4). 60% of elimination is faecal and 33% renal. In the CANVAS and CREDENCE studies, cardiovascular and renal protection has been demonstrated, the latter including patients with eGFR down to 60 mL/min/1.73 m² [8, 9]. The pharmacokinetic and pharmacodynamic parameters of the two agents are summarized in **Table 1**, as are the implications of differences in lipophilicity for choice of dosage form.

Table 1. Pharmacokinetic and Pharmacodynamic Comparisons of Linagliptin and Canagliflozin

Parameter	Linagliptin	Canagliflozin	References
Mechanism	DPP-4 inhibitor	SGLT2/SGLT1 inhibitor	[7,8]
Molecular Weight	472.54 g/mol	444.52 g/mol	[7,8,11]
Log P	~3.0	~4.2	[11,12]
Oral Bioavailability	~30%	~65%	[11,13]
Tmax	1.5 hours	1-2 hours	[14]
Protein Binding	99% (low conc.) To 75-89% (high conc.)	>99%	[15]
Volume of Distribution	~1,110 L	83.5-119 L	[14]
Terminal Half-life	>100 hours	10.6-13.1 hours	[15]
Elimination	84.7% fecal, 5.4% renal	60% fecal, 33% renal	[8,12]
Renal Impairment	No adjustment needed	Adjust if eGFR <60	[9,16]
Standard Dose	5 mg once daily	100-300 mg once daily	[16,17]
HbA1c Reduction (monotherapy)	0.5-0.8%	0.7-1.0%	[16,18]
Hypoglycaemia Risk	Very low	Very low	[18,19]

1.3 Nanostructured Lipid Carriers (NLCs): An Overview of the Technology

NLCs are the second generation of lipid nanoparticles and were developed to overcome the main limitations of solid lipid nanoparticles (SLNs), such as low drug-loading capacity, drug expulsion during storage and burst release [20-22]. They are solid and liquid lipids mixed in an imperfect crystal matrix which can accommodate more drug load than SLNs alone (**Figure 2**). Three structural forms of NLCs were described [23]. The imperfect-crystal NLCs, generated from the mixing of structurally different lipids, include lattice defects that

provide voids for the incorporation of drug molecules. Amorphous NLCs stop crystallisation at the point of lipid saturation, which maximises drug loading and prevents drug expulsion during storage. Multiple oil-in-fat-in-water (O/F/W) NLCs disperse nanoscale oil droplets in a solid lipid matrix and are designed to improve solubilisation and retention of highly lipophilic drugs [24-26]. The structural spectrum provides formulators with a range of options to match the carrier design to the physicochemical properties and therapeutic needs of the drug.

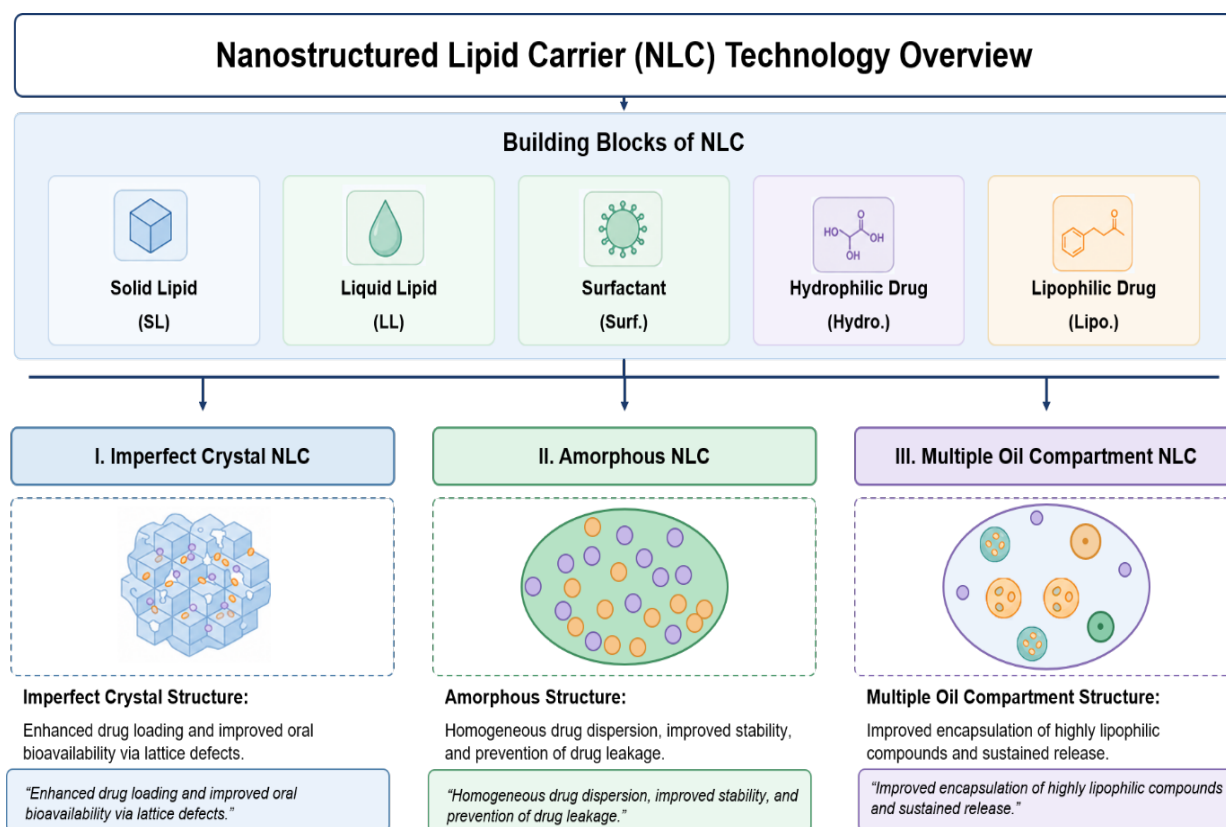


Figure 2. Nanostructured Lipid Carrier (NLC) Structures

Previous studies on oral antidiabetic agents revealed that the lymphatic uptake may offer an alternative route for absorption bypassing the hepatic first-pass effect, limiting the enzymatic degradation, enhancing the permeability across membranes, and maintaining the sustained release of drugs. Excipients with a generally-recognised-as-safe (GRAS) status also contribute to ease of regulatory approval.

Currently, no study has reported the co-encapsulation of linagliptin and canagliflozin in a nanostructured lipid carrier (NLC) system, although there is a pharmacological rationale for their combination. That is the question this review answers. It discusses the rationale and limitations of codelivering the two agents, reviews the preclinical evidence for a dual-drug NLC system, proposes such a system on that basis and considers the obstacles and clinical translational prospects for nanocarrier-based combination therapies of this type. It examines current NLC formulation approaches using Quality by Design (QbD) methodology.

2. QbD methods for improving NLC

2.1 QbD Framework

The ICH Q8-Q11 guidance created the QbD model, which says that drug development should be done in a systematic and risk-based way (**Figure 3**). One begins with the definition of a quality target product profile (QTPP), which includes the desired clinical performance and quality attributes [27]. Using failure mode and effects analysis (FMEA) to assess risk helps find critical quality attributes (CQAs) like particle size and distribution, surface charge, crystallinity, drug load, release kinetics, and stability. Homogenisation conditions are what make critical process parameters (CPPs) work, while lipid ratios and drug-lipid miscibility are what make critical material attributes (CMAs) work [28]. The logical QbD methodology is employed to create process maps for systematic NLC formation. **Table 2** shows the order of all the experiments based on a pre-defined screening strategy.

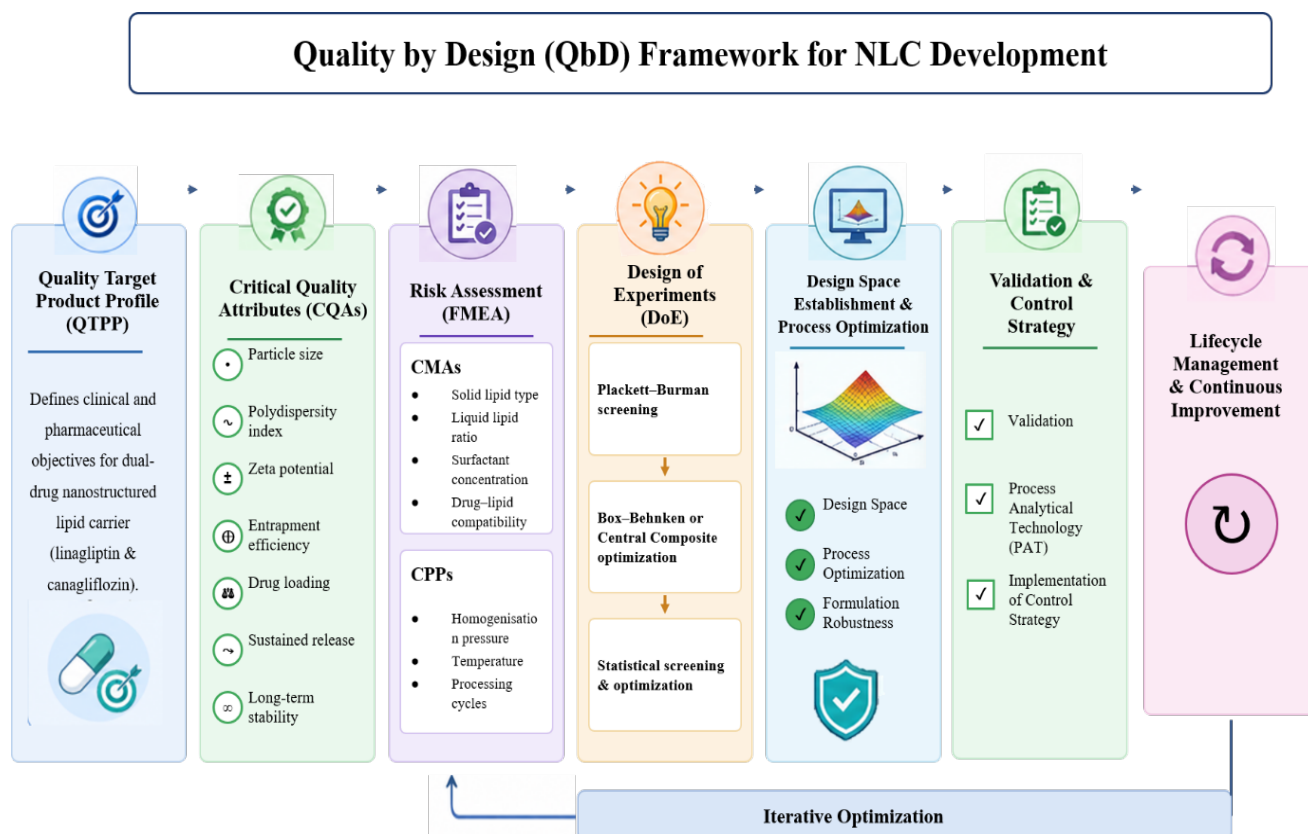


Figure 3. A framework for development based on integrated QbD

2.2 Optimising the Design of Experiments

Based on this formulation rationale, systematic optimization starts with screening designs such as the Plackett-Burman and fractional factorial designs, which assess the effect of several factors in a minimum number of experimental runs, and eliminate variables that have insignificant influence [29]. The retained factors after screening are then modeled using response surface methodology (RSM) generally with a Box-Behnken design (BBD) or central composite design (CCD) to establish the mathematical relationships between formulation variables and critical quality attributes (CQAs) [30]. The two approaches are increasingly combined in sequence, with a Plackett-Burman design initially identifying the important factors from a larger candidate set, and followed by BBD or CCD optimisation. The CQA targets can be achieved at the same time with the formulations obtained using desirability functions applied to the generated polynomial equations [31]. Monte Carlo simulation takes this approach a step further by defining a design space within which

manufacturers can have formulation flexibility without compromising product quality [32].

3. State of the Art: NLCs as Antidiabetic Drug Formulation

These optimisation methods form the basis of a growing body of work on NLC-based antidiabetic drug delivery. In preclinical studies, NLCs have enhanced oral bioavailability, therapeutic activity and patient adherence of several classes of antidiabetic drugs including DPP-4 inhibitors, SGLT2 inhibitors and older antidiabetic agents. The following sections review this evidence, with a focus on formulation parameters, release and solubility profiles.

3.1 DPP-4 and SGLT2 inhibitors containing NLC formulations

Table 2 summarizes the benefits of DPP-4 inhibitors delivered using NLCs that have been reported in several studies.

Table 2. Typical NLC Formulations of Antidiabetic Drugs.

Drug	Solid Lipid	Liquid Lipid	Surfactant	Particle Size (nm)	Polydispersity index (PDI)	Millivolt (mV)	Entrapment Efficiency (EE) (%)	Bioavailability Enhancement	Reference
Sitagliptin	Glyceryl Monostearate (GMS)	Medium-Chain Triglycerides (MCT)	Poloxamer 188	142	0.221	-28.4	86.3	3.2×	[33]
Vildagliptin	Compritol 1888	Oleic acid	Tween 80	168	0.214	-26.1	84.7	3.8×	[34]
Saxagliptin	Precirol ATO	Capryol 90	Pluronic F-127	155	0.245	-24.3	79.5	2.9×	[35]
Dapagliflozin	Glyceryl behenate	Squalene	Poloxamer 188 + Lecithin	178	0.198	-31.2	88.4	3.5×	[36]
Empagliflozin	Stearic acid	Oleic acid	Tween 80/Span 80	192	0.267	-22.7	81.9	3.1×	[37]
Metformin	Compritol 1888	Labrafac	Poloxamer 407	134	0.189	-27.8	76.2	2.8×	[38]
Pioglitazone	Precirol ATO	MCT	Poloxamer 188	163	0.224	-29.5	85.6	4.2×	[39]
Glimepiride	GMS	Oleic acid	Tween 20	147	0.236	-25.9	83.1	3.7×	[40]

All reported NLC-based antidiabetic formulations have a particle size in the range of 130–195 nm. The entrapment efficiency (EE) is usually more than 75%, and the oral bioavailability is increased by 2–4 times in comparison to free drug in animal models. All this evidence is based on single-drug systems, but its applicability to dual-drug platforms has not been confirmed [41]. DPP-4 inhibitors such as sitagliptin NLCs (142 nm, zeta potential –28.4 mV, EE 86.3%) increase bioavailability 3.2-fold and have a biphasic release profile, with 28% of the drug being released in the first 2 hours and the rest being released slowly over 72 hours, resulting in a 58% decrease in glucose levels during an oral glucose tolerance test, compared to a 32% decrease with the free drug [41,42]; vildagliptin NLCs (168 nm, EE 84.7%) similarly increase bioavailability 3.8-fold and have a sustained release over 96 hours, which is long enough to allow once-daily dosing of a drug that is normally dosed twice daily [43]; and saxagliptin NLCs similarly improve the dissolution rate, but the supporting studies are based on streptozotocin-induced diabetic models that do not reproduce the progressive β -cell decline or the

insulin resistance that is characteristic of human type 2 diabetes mellitus [44]. Among the SGLT2 inhibitors, dapagliflozin NLCs (178 nm, EE 88.4%, zeta potential –31.2 mV) result in a 3.5-fold increase in bioavailability and sustained-release kinetics leading to enhanced renal glucose elimination and reduced glycaemic load [36], while empagliflozin NLCs (192 nm, EE 81.9%) result in a 3.1-fold increase mediated by a Tween 80/Span 80 surfactant combination that increases gastrointestinal permeability and prolongs systemic exposure [37]. Critically, the capacity to enhance bioavailability is not limited to DPP-4 and SGLT2 inhibitors but also applies to structurally distinct antidiabetic drugs: metformin NLCs, despite the drug being hydrophilic, attain 76.2% EE and a 2.8-fold enhancement in bioavailability due to stabilization by Poloxamer 407, demonstrating the continued utility of the NLC platform for poorly lipophilic compounds [38]; pioglitazone NLCs exhibit the greatest improvement among the studied agents, with a 4.2-fold increase, 85.6% EE, and a particle size of 163 nm, aligning with the drug's favorable lipophilicity and solubility in the lipid matrix [39]; and

glimepiride NLCs (147 nm, EE 83.1%) show a 3.7-fold increase in bioavailability, where oleic acid, the liquid-lipid component, significantly contributes to drug solubilization and intestinal absorption [40]. Together, these results validate a consistent, mechanism-rationalized trend of NLC-mediated bioavailability enhancement across chemically diverse classes of antidiabetic drugs and provide a compelling, but currently preclinically unproven, rationale for the extension of this platform to co-encapsulation of linagliptin and canagliflozin.

3.2 SGLT2 Inhibitor Nano Formulations

SGLT2 inhibitors had similar solubility and bioavailability issues that led to the development of NLCs for DPP-4 inhibitors, and nanoformulation work on this class has followed a similar trajectory. Dapagliflozin in solid lipid nanoparticulate or nanoemulsion formulations demonstrated a 3.5-fold increase in bioavailability [45, 46], while 3D-printed nano-emulsifying tablets improved its dissolution rate and permeation in the gastrointestinal tract, and mesoporous silica nanoparticles enabled targeted delivery that preserved its cardioprotective activity, expanding the argument for nanocarrier platforms within this class of drugs [47]. A similar 3.1-fold increase was observed for empagliflozin NLCs (192 nm, EE 81.9%), confirming the suitability of lipid nanoparticles for SGLT2 inhibitors with moderate lipophilicity. Canagliflozin is the outlier. No NLC formulation has been reported for it despite a log P of ~ 4.2 , which should favor efficient lipid encapsulation. This gap is addressed by the present review (Table 1). Canagliflozin has a high lipophilicity and low aqueous solubility and is therefore in principle well suited for encapsulation within NLCs, but this remains untested and provides the pharmaceutical basis for the here proposed formulation strategy [48].

3.3 Dual-Drug Delivery Systems

Dual-drug nanoparticulate systems for antidiabetic therapy are also poor, even though the limited available work is promising. Electrospayed trilayer PLGA nanoparticles co-releasing hellicid and PEG exhibited stable *in vitro* release, improved pharmacokinetics, and prolonged systemic retention in rabbits. Co-loading of sitagliptin and dapagliflozin in a self-nanoemulsifying drug delivery system (SNEDDS) improved bioavailability of both drugs. There is no study of co-delivery of linagliptin and canagliflozin based on NLC. This provides up several practical questions such as the most effective ratio of the two drugs, the influence of the lipid composition on the co-loading capacity, the long-term stability, and whether the *in vivo* performance can be comparable to the existing fixed-dose combinations [49].

3.4 Assessment of Study Quality

The bioavailability gains reported here are consistent with the literature, but the evidence base has real limitations.

Stability data rarely extend more than six months, far short of the 24–36 month profile required for pharmaceutical products [50]. Most *in vivo* studies have employed streptozotocin-induced diabetic models, which are not reliable predictors of the human glycaemic response [51]. Only a few studies have directly compared NLC formulations with optimized conventional ones [52], and lab-scale batches (10–100 mL) are rarely successfully transferred to commercial manufacturing without significant reformulation [52]. The end result: Under 5% of NLC formulations make it to human trials, despite the amount of preclinical publications behind them [53].

4. Developing a Conceptual Framework for Biphasic Dual-Drug NLCs

Despite these limitations, the formulation rationale presented in the previous sections supports the development of a biphasic dual-drug NLC system incorporating linagliptin and canagliflozin, a pharmacologically coherent but technically challenging combination to realise. The theoretical basis, the formulation considerations, and a stepwise conceptual approach to establishing this co-delivery system are as follows [54–56].

4.1 Justification and Theoretical Benefits

The co-encapsulation of linagliptin and canagliflozin in NLCs is anticipated to offer a number of advantages. [57] Combined into a single dosage form, the regimen would be simplified for patients; the large difference in elimination half-life between the two drugs (>100 hours for linagliptin versus 10–13 hours for canagliflozin) presents an opportunity for a standardization of their pharmacokinetics via controlled release; and systemic exposure for both compounds may be improved by lymphatic uptake and avoidance of P-glycoprotein-mediated efflux. These remain theoretical projections without empirical confirmation. Mechanistically, linagliptin increases glucose-dependent insulin secretion, and canagliflozin promotes insulin-independent glucose elimination, thereby addressing two of the eight pathophysiological defects that comprise the so-called ominous octet of type 2 diabetes. Whether co-encapsulation within a common lipid nanostructure enhances, reduces, or leaves unchanged this established clinical synergy [54, 55] remains to be resolved.

4.2 Critical Formulation Considerations

The development of a functional dual-drug NLC system requires careful consideration of drug-lipid compatibility, the selection of lipid and surfactant, drug-loading capacity, and the design of release kinetics, which together determine the stability and therapeutic efficacy of the final product [55, 58]. The significant difference in lipophilicity of linagliptin (log P ~ 3.0) and canagliflozin (log P ~ 4.2), which is expected to lead to an uneven distribution of the two drugs within a lipid matrix, is the first step in the assessment, but this does not exclude their functional

coexistence within a single NLC architecture (Figure 2), a possibility that needs to be verified using differential scanning calorimetry, FTIR, and XRD, the standard techniques for evaluating drug-lipid compatibility and identifying formulation challenges at the early stage [58]. Based on this compatibility profile, lipid selection is guided by the precedent set by comparable single-drug formulations, with the preference for an intermediate-polarity solid lipid such as glyceryl behenate (Compritol) and a moderately polar liquid phase of medium-chain triglycerides and oleic acid where a solid-to-liquid ratio of 90:10/95:5 is expected to stabilise the nanostructure while permitting adequate drug loading, although the exact ratio will have to be determined experimentally [59]. In this lipid setting, the clinical doses required (5 mg linagliptin and 100–300 mg canagliflozin) are within the normal NLC loading window of 5–15% w/w. This equates to an estimated volume of oral formulation of 2–6 g per dose, which remains a separate question for future optimisation studies [60]. However, the ultimate success of the formulation depends on the ability to coordinate the release kinetics of the two drugs: sustained delivery over 24 hours, and hence once-a-day dosing, is possible in principle, but the differing physicochemical properties of the two drugs complicate this in practice, requiring careful tuning of the lipid ratio, surfactant system, and particle size, with the relative merits of simultaneous versus staggered release still unresolved [61]. The clinical determinant to overcome these challenges is adherence. Once-daily regimens enhance adherence in diabetes management to 79% in comparison to lower rates for three-times-daily dosing [62],

and fixed-dose combinations improve adherence by 10–13% compared with separate-pill regimens and also provide superior glycaemic control (mean HbA1c difference - 0.53%, $P < 0.001$) [63], indicating the practical value of overcoming the formulation challenges.

4.3 Proposed Quality by Design Optimization Strategies

The workflow shown in **Figure 3** is built upon a typical Quality by Design (QbD) development cycle. It starts with risk assessment: Critical quality attributes (CQAs) for both drugs were determined using Failure Mode and Effects Analysis (FMEA) [64], namely particle size in the range of 100–200 nm required for efficient absorption, acceptable polymorphic form, polydispersity index (PDI), 24-hour drug release, and stability [65]. A screening phase is then carried out using Plackett-Burman or fractional factorial design to test 8–10 candidate factors, including lipid type and concentration, surfactant type and level, and homogenisation conditions, and to narrow these down to the three or four parameters with the greatest effect on formulation performance [65]. The remaining factors are then optimised using a response surface methodology, where Box-Behnken or central composite designs generate regression equations correlating formulation variables with performance outcomes, and desirability functions applied to these equations identify the formulation that best meets all target responses simultaneously. **Table 3** shows the typical three-factor, three-level Box-Behnken design, which is frequently utilized in this stage [66, 67].

Table 3. Box-Behnken Model for Optimisation of Dual-Drug-Loaded NLCs (Theoretical)

Run	Factor A: Solid Lipid (% w/v)	Factor B: Surfactant (% w/v)	Factor C: Homogenization Cycles	Target Responses	Reference
1-4	3.0 (-1) / 5.0 (+1)	1.0 (-1) / 3.0 (+1)	5 (centre)	Y1: Particle size 100-200 nm	[68-72]
5-8	3.0 (-1) / 5.0 (+1)	2.0 (centre)	3 (-1) / 7 (+1)	Y2: Linagliptin EE >80%	
9-12	4.0 (centre)	1.0 (-1) / 3.0 (+1)	3 (-1) / 7 (+1)	Y3: Canagliflozin EE >80%	
13-17	4.0 (centre)	2.0 (centre)	5 (centre)	Y4: PDI <0.3	

4.4 Identification of the Design Space

The last phase of this QbD process, design space identification, uses Monte Carlo simulation to define a formulation space that is robust to variability in manufacturing. The sequence above describes an idealised path and not a guaranteed one. Optimisation in practice is iterative, and several unsuccessful formulations are likely before a viable candidate is found [73].

5. Comprehensive Framework for Characterization and Evaluation

Such a dual-drug NLC requires a sufficiently thorough characterisation programme to show its quality, safety, and therapeutic efficacy. In addition to confirming physical and chemical stability, this characterisation work shows how the drugs interact with the lipid matrix, how they are released and how they are likely to perform once administered. The proposed strategy for this co-encapsulation system is as follows [74].

5.1 Principal Characterization Parameters

Physicochemical characterisation includes particle size distribution, PDI and zeta potential by dynamic light scattering and electrophoretic mobility, and morphological assessment by TEM, SEM, and AFM. DSC, XRD, and FTIR determine drug-excipient interaction and crystallinity of matrix. Validated HPLC determines drug content and entrapment efficiency [75]. Performance characterisation is concerned with release behaviour, assessed by multi-compartmental pH-gradient dissolution testing reflecting gastrointestinal transit (pH 1.2 gastric, 6.8 duodenal, 7.4

intestinal) and release mechanisms identified by fitting zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models [76]. Stability testing is carried out as per ICH Q1A(R2): 24 months at long-term storage conditions (25°C/60% RH), 12 months at intermediate storage conditions (30°C/65% RH), and 6 months at accelerated stress conditions (40°C/75% RH) [77, 78]. The proposed critical quality attributes, target specifications, their justification, and the required analytical methods to fully characterize the formulation are given in **Table 4**.

Table 4. Key Quality Attributes for dual-drug NLCs

CQA	Target Specification	Justification	Analytical Method	References
Particle Size	100-200 nm	Optimal intestinal absorption	Dynamic light scattering	[79]
Polydispersity Index (PDI)	≤0.300	Narrow distribution, batch reproducibility	Dynamic light scattering	[79,80]
Zeta Potential	−20 to −40 mv	Colloidal stability	Electrophoretic mobility	[80,81]
Linagliptin Content	90-110% of label claim	Accurate dosing (5 mg)	Validated RP-HPLC	[82]
Canagliflozin Content	90-110% of label claim	Accurate dosing (100-300 mg)	Validated RP-HPLC	[82]
Linagliptin Entrapment	≥80%	Formulation efficiency	Ultracentrifugation + HPLC	[82]
Canagliflozin Entrapment	≥80%	Formulation efficiency	Ultracentrifugation + HPLC	[82]
Drug Loading	8-15% (w/w)	Therapeutic dose in an acceptable volume	Gravimetric + HPLC	[79,81]
Release at 2h (both drugs)	20-30%	Moderate burst, avoid dose dumping	Dialysis + HPLC	[83]
Release at 24h (both drugs)	70-90%	Sustained release, once-daily dosing	Dialysis + HPLC	[83]
pH	6.0-7.4	Drug stability, GI compatibility	pH electrode	[81]
Morphology	Spherical, smooth	Proper formulation	TEM, SEM	[80,81]
Crystallinity	Reduced vs. Bulk	Matrix disruption, drug accommodation	DSC, XRD	[84]
Stability (6 month, 25°C)	≤15% Δ size; ≥90% active drug content	Adequate shelf life	DLS, HPLC	[91,92]

5.2 Preclinical Evaluation Approach

Characterization data alone cannot determine clinical viability. Before clinical work can begin, however, graded *in vitro*, *ex vivo*, and *in vivo* studies are needed to confirm the safety, efficacy, and translational potential of the dual-drug NLC system [85].

***In vitro* studies:** Studies in different cell lines to determine biocompatibility and to understand the uptake of formulation at the cellular level [93, 94]. Caco-2 monolayer assays provide apparent permeability coefficients (Papp) and in combination with a well characterized efflux inhibitor, such as verapamil, the contribution of P-glycoprotein-mediated transport can be estimated. Testing for cytotoxicity on Caco-2 cells, HepG2 hepatocytes, and

normal fibroblasts helps to establish safety margins and identify off-target effects in different tissue types [87]. This work allows us to evaluate the safety and absorption behaviour prior to the use of any animal.

In vivo testing: Piperine-loaded NLC and solid lipid nanoparticle formulations provide a precedent here, having demonstrated improved oral bioavailability in streptozotocin-induced diabetic rats [88]. Pharmacokinetic assessment should include C_{max}, T_{max}, AUC, t_{1/2}, and relative bioavailability. Pharmacodynamic assessment should comprise oral glucose tolerance testing and 28-day monitoring of fasting glucose, HbA_{1c}, body weight, and organ function [89]. Safety assessment should be conducted according to OECD guidelines, including haematology, clinical chemistry, and histopathology [90].

A major caveat is that streptozotocin models are very different from how type 2 diabetes actually behaves in humans, so bioavailability gains seen in rats will not necessarily translate to people due to differences in intestinal physiology, lymphatic architecture, and disease progression between species [91]. The improvements in bioavailability reported in rodent studies are summarised in **Table 2**, but whether these translate across species remains undetermined.

6. Regulatory considerations and the route to clinical translation

Based on preclinical evidence alone, this formulation will not make it to the clinic. The translation from bench to bedside is also dependent on the extent to which the programme is compatible with a regulatory environment for nanomedicines that is still in development at the national and international levels.

6.1. Legal structure

The FDA's nanomaterial guidance was released in April 2022, and the corresponding EMA guidelines set out clear pathways for nanomedicine development. There are already about 700 nanotechnology products on the market, so lipid-based nanocarriers are not new, with liposomal formulations such as Doxil® (1995) being a precedent. The Platform Technology Designation Program, announced in May 2024, indicates that regulators are increasingly receptive to nanoparticle platforms in general, but oral NLC formulations are still not extensively studied. Bioequivalence to existing products will not likely be sufficient in itself, as regulators now expect demonstrated efficacy and safety benefit, not just marginal gains in bioavailability [92].

6.2 Chemistry, Manufacturing, and Control (CMC) Requirements

A comprehensive CMC package includes detailed characterization of particle size distribution by dynamic

light scattering and nanoparticle tracking analysis, surface and morphological properties by electron microscopy, and determination of crystalline form. Critical process parameters must be defined and in-process controls put in place to ensure consistency of the manufacturing process. Certificates of analysis for excipients must include purity, fatty acid profile, peroxide value, and assay; impurity and degradation methods must be validated under ICH Q2(R1). At least three validation batches have shown a batch-to-batch consistency and a comparison between manufacturing scales. Stability studies have to support the proposed shelf life considering any observed degradation [93].

6.3 Considerations for Clinical Development

Clinical development should be carried out in a phased program that sequentially builds the evidence of safety, pharmacokinetics and efficacy.

Phase I is a parallel group, single-ascending-dose study in healthy volunteers to establish maximum tolerated dose and pharmacokinetic parameters and includes routine bioequivalence testing and assessment of the effect of food on absorption.

Phase IIa (proof-of-concept) is a double-blind, randomised study in 120–150 patients with type 2 diabetes inadequately controlled on metformin, with the primary endpoint being change in HbA_{1c} from baseline to weeks 12–16. Comparator arms, the co-loaded NLC, the dual free-drug combination, each single-drug NLC alone, and the placebo are necessary for proving that any beneficial effect is derived from the nanoformulation per se and not simply the two drugs being administered together [95].

Dosing, safety, and efficacy confirmed in Phase IIb/III trials. Phase III will enroll 500-1000 patients per arm over 24-52 weeks, testing non-inferiority and superiority where data support it against standard-of-care fixed-dose combinations, with extension phases tracking long-term durability and safety. FDA guidance here calls for adjudicated MACE (major adverse cardiovascular event) endpoints, which will be critical for excluding unacceptable cardiovascular risk [96]. The programme's primary challenge will be to prove that the new formulation is better than, or at least as good as, the fixed-dose combinations currently on the market, while incurring development costs of between \$500 million and \$1 billion. Regulators and payers generally require at least a 0.3-0.5% reduction in HbA_{1c} as a rationale for market entry, which increases the pressure to indicate a lower risk of hypoglycaemia or some other specific clinical advantage [97].

7. Critical areas of future investigation and directions for research

A theoretical framework regarding the safety of the two NLCs, linagliptin and canagliflozin, significant gaps remain

concerning drug-drug interactions between these agents and the specifics of blood compatibility, particularly in the context of treating a large population, prior to initiating clinical trials with this dual-drug NLC in humans. It is now essential that these deficiencies are rectified through definitive, rigorous preclinical and clinical studies to substantiate the scientific rationale and therapeutic advantage of this co-delivery principle.

7.1 Identified Knowledge Gaps

The reviewed literature demonstrates a current deficiency in understanding dual-drug nanostructured formulations. To begin, there is no evidence of synergistic pharmacological interactions; specifically, there are no documented cases of stable co-encapsulation of canagliflozin and linagliptin at clinically significant concentrations, while simultaneously preserving the efficacy of both drugs. Second, competitive partitioning into lipid phases and possible incompatibilities that affect encapsulation efficiency are two drug-drug-lipid interactions that are not yet well understood in nanoconfinement. Third, the fact that the elimination half-lives (linagliptin >100 h; canagliflozin 10–13 h) or physicochemical properties (log P, solubility) do not match makes it difficult to achieve a synchronised 24-hour therapeutic effect profile from a single carrier. This complicates pharmacokinetic optimisation [98]. Fourth, regulatory approval necessitates a shelf life of 24 to 36 months, ensuring the maintenance of drug content (≥ 90 –110%), particle size distribution (polydispersity index <0.3), and release kinetics. Nonetheless, the most extended evaluation documented in the literature lasted merely six months, indicating a significant deficiency in long-term stability data. Fifth, translational superiority cannot be substantiated owing to the absence of relative *in vivo* efficacy against optimized standard fixed-dose combinations in established diabetic models (db/db mice, Zucker diabetic fatty rats). Lastly, there is no rational platform selection available apart from empirically guided screening, as there are no systematic direct comparisons between NLCs and alternative nanocarriers (polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, and liposomes) contained in standardised evaluation criteria [99].

7.2 Proposed Research Directions

Based on these considerations, there are a number of research directions that are worth systematically exploring to move this formulation from concept to clinical reality. This should be preceded by a rigorous Quality by Design (QbD) approach addressing risk assessment, multivariate optimisation, design space definition, and formulation development tolerant to raw material variability, substantiated by preparatory studies including drug–drug compatibility studies and lipid phase behaviour characterisation through differential scanning calorimetry (DSC) or phase diagrams [100]. This should be

complemented by advanced characterisation platforms, such as cryo-transmission electron microscopy (cryo-TEM) for observing the native ultrastructure in a re-hydrated state, small-angle X-ray scattering (SAXS) for explaining the internal nanoarchitecture, solid-state nuclear magnetic resonance (ssNMR) for probing drug–lipid molecular interactions, confocal Raman micro-spectroscopy for mapping the spatial drug distribution, and molecular dynamics simulations for predicting the long-term stability trajectories [101]. Additional parallel mechanistic pharmacology studies would be required: perfusion and confocal imaging of fluorescently labelled NLCs to determine tissue distribution; mesenteric lymph duct cannulation to quantify absolute lymphatic transport; target engagement validation by pancreatic dipeptidyl peptidase-4 (DPP-4) activity and renal sodium–glucose cotransporter-2 (SGLT2) expression; and population pharmacokinetic/pharmacodynamic (PK/PD) modelling to correlate formulation characteristics with glycaemic outcomes in progressive diabetes models such as db/db mice and Zucker diabetic fatty rats [102]. To move toward clinical application, translation would require GMP-compliant scale-up with full process validation, development of an Investigational New Drug (IND) application and Chemistry, Manufacturing, and Controls (CMC) package, and pre-IND regulatory discussions, built upon IND-enabling toxicity studies including 90-day repeat-dose, genotoxicity (Ames and micronucleus), and reproductive toxicology assessments, and Phase I protocol development including patient-reported outcome measures (PROMs) [103]. In the longer term, next-generation NLC architectures may allow further therapeutic refinement by means of stimuli-responsive systems based on pH-sensitive polymers or glucose-responsive phenylboronic acid moieties, hybrid platforms incorporating mucoadhesive polymers with NLCs, or freeze-dried powder-in-capsule formulations for improved shelf stability [104]. Finally, the incorporation of precision medicine principles, pharmacogenomic classification based on uridine diphosphate-glucuronosyltransferase (UGT) variants that impact canagliflozin glucuronidation and DPP-4 polymorphisms, algorithm-based dose individualisation that considers renal function, body mass index, and diabetes duration, and connection with digital therapeutics that allow for real-time dose adjustment through continuous glucose monitoring feedback loops could ultimately enable a more personalised and clinically responsive therapeutic strategy [105].

8. Limitations and Critical Uncertainties

8.1 Theoretical Nature of the Proposed System

The present review provides a model derived from a literature search of discrete components and therefore, several important limitations should be noted. First of all, there are no experimental data: there are currently no experimental data supporting the co-encapsulation of linagliptin and canagliflozin in NLCs and the attainment of

therapeutic doses (5 mg + 100–300 mg) in stable nanoformulations with acceptable particle characteristics and release kinetics [106]. Secondly, the pharmacodynamic synergy needs to be established. Although clinical studies have shown increased effects when individual formulations are combined, it is not clear if a real synergistic effect would be observed due to NLC co-delivery. This is especially since the co-therapy of binary drugs in nanoformulations can modulate chronopharmacodynamics by altering T_{max}, C_{max} and AUC (area under the curve) levels at target sites [107]. Third, potential drug–drug–lipid interactions are yet to be characterised. No reports are available addressing possible physicochemical interactions of linagliptin and canagliflozin in a confined lipid matrix. The pronounced difference in lipophilicity of the two agents (log P 3.0 vs. 4.2) could in fact lead to phase separation in situ, competition for lipid binding sites, and unexpected storage instabilities [108].

8.2 Barriers to Translation

Although dual-drug NLC systems demonstrate great potential theoretically, a series of obstacles needs to be solved in further clinical translation. The challenges are, as shown below, limitations of preclinical models, challenges with formulation, challenges with regulatory and manufacturing scalability, and so on.

8.2.1 Limitations of Animal Models:

Streptozotocin (STZ) is a well-known diabetes model that rapidly triggers β -cell toxicity. However, in patients with T2DM, insulin resistance and β -cell failure develop slowly over time. The principal translational limitations arise because disease progression is rapid in the STZ model but slow in human T2DM, the model reflects insulin deficiency rather than the insulin resistance characteristic of human disease, obesity-related metabolic changes are absent, and incretin physiology differs between species. The variations in the functionality of the lymphatic systems among species and the operation of the intestines complicate the extrapolation of these findings to humans. The increased bioavailability noted in rodent studies may not be replicated in humans due to variations in bile content, gastrointestinal transit time, lymphatic drainage, and P-glycoprotein expression patterns between species [109].

8.2.2 Manufacturing and Scale-Up Challenges:

NLCs that were made in the lab (10–100 mL) often lose their stability when they are made on a larger scale (100–1000 L) because moving from a small to a large scale is a difficult process. Different cooling rates in labs and factories can affect the kinetics of lipid crystallisation in different ways. This can change how particles form and how polymorphs change shape. At the industrial level, long readings of high-pressure homogenisation can cause processes that make particles or aggregates bigger because of energy-driven coalescence mechanisms. Some of the

differences between batches are due to the fact that lipid raw material formulations are not always the same. This is especially true when it comes to changes in fatty acid profiles and purity standards, which make them less stable. Because of differences in conditions, the high-pressure orifice homogeniser used in labs and industrial-scale processing equipment are not always in balance, which limits the experimental methods that can be used. Because most NLC literature is confined to small-scale formulations, translation to commercial scale is difficult in the absence of dedicated scale-up studies. Commercialisation under GMP requires extensive advance planning, including determination of facility and equipment requirements, which carries high upfront costs (\$/L 1000–5000) and a lengthy process validation timeline [110].

8.2.3 Long-Term Stability Challenges:

There are many ways that NLC goods cannot last on store shelves for 24 to 36 months. This energy might not be obvious at first, but unlike electrostatic and steric repulsion, which both get stronger right away with smaller particles, Van der Waals forces slowly take over over time. This leads to Ostwald ripening, which is when drugs move from small bodies to big bodies in storage environments. Unsaturated lipids can oxidise, which means they can go through lipid peroxidation even when antioxidants are present. Colloidal instability is shown by phase separation in liquid formulations, which can happen through creaming, sedimentation, or stratification. Polymorphic transitions are a very important way to destabilise things. When solid lipids change from the metastable α -form to the thermodynamically stable β -form, they form a more uniform crystalline physical state that eventually releases the drug molecules that were bound to them. This polymorphic change from a high-energy disordered to a low-energy ordered configuration during storage affects the retention of therapeutic payloads, which leads to drug ejection and precipitation. Most of the studies on NLC stability look at accelerated condition testing for 6 to 12 months. This may not be enough for long-term commercial products that also need to be validated for a long shelf life [111].

8.3 Clinical Translation Uncertainties

8.3.1 Clinical Translational Efficacy Uncertainties

There are unresolved concerns regarding the clinical translation of NLC-enhanced formulations in relation to their essential efficacy inquiries. It is possible to determine if NLC-based bioavailability enhancement leads to superior glycemic control compared to dose-optimised conventional formulations through equivalence clinical trials. The potential for attaining therapeutic equivalence between once-daily NLC therapy and twice-daily immediate-release formulations remains uncertain due to significant inter- and inpatient variability in lipid digestion and lymphatic absorption kinetics. Certain patient-specific factors,

including meal composition, fluctuations in gastric pH, bile salt availability and micellar solubilization capacity, as well as the activity of pancreatic lipase, can induce unpredictable variations in drug absorption and therapeutic outcomes. Furthermore, it is imperative to critically evaluate the justification for employing sustained-release technology for agents with exceptionally prolonged elimination half-lives (e.g., linagliptin $t_{1/2} > 100$ h) to enhance complexity and potentially foster a perception of superior pharmacology or mere pharmacological refinements [112].

8.3.2 Safety Concerns

Changes in pharmacokinetic profiles resulting from NLC formulation may affect the occurrence of adverse events. There are known risk relationships between SGLT2 inhibitors and genitourinary infections, but DPP-4 inhibitors have a lower risk of pancreatitis. This will be complemented by a careful analysis of the potential health impacts subsequent to chronic exposure of human populations as the long-term safety profiles of the CS lipid nanoparticle develop. The lipids most commonly used as excipients are generally accepted as safe (GRAS), but prolonged administration in chronic disease individuals may lead to unforeseen toxicological responses, including inflammation, immune reactions or metabolic disorders. In addition, drug-drug interactions in nanoconfinement could produce new metabolites that are not present in the free drug family of compounds and thus require increased metabolic profiling/genotoxicity assessment [113].

8.3.3 The complexities of the regulatory pathway

There are almost 700 nanotechnology products that are now allowed to be sold, but there are still a lot of regulatory problems to solve when it comes to oral NLC formulations. To get regulatory approval, you need to show that the clinical benefits are greater than the benefits of the higher bioavailability. These benefits must be real and have to do with better efficacy, safety margins, or outcomes that are important to the patient. The rules for CMC documentation are much stricter than those for on-the-shelf formulations. For example, they need to define and understand CQAs like the particle size distribution (PSD), polydispersity index (PDI), zeta potential, morphological evaluation, and release kinetics under physiologically relevant conditions, which must be characterised in more detail. In the United States (US), one active drug ingredient may lead to device oversight. However, products that contain two different active drug ingredients and use new delivery methods may face more regulatory scrutiny and longer approval times if they fall under the jurisdiction of the Office of Combination Products (OCP). Post-market surveillance requirements make it necessary to keep an eye on the safety of nanomedicines, which makes it even harder to comply and make money [114].

8.4 Barriers to the development of NLCs for clinical and market use

A systematic examination has demonstrated that fewer than 5% of the published NLC formulations undergo preclinical evaluation, highlighting numerous translational barriers. Manufacturing costs remain a significant barrier, ranging between \$500 and \$2000 per kilogram compared with \$50–200 per kilogram for conventional tablets, constraining commercial viability. Scale-up presents a further obstacle; more than 60% of laboratory-tested formulations fail at the pilot stage owing to inconsistent process parameters and poor reproducibility. Limited lipid nanoparticle production capacity at Good Manufacturing Practice (GMP)-compliant contract manufacturing organisations, together with more stringent storage and transportation stability requirements, further constrains commercial feasibility. Clinical benefits frequently remain constrained, as enhanced bioavailability does not always equate to a clinically significant therapeutic advantage, and the incremental efficacy attained is insufficient to surmount market entry barriers. NLC clinical development programs inadequately reflect patient-assessed outcomes, including quality of life and treatment satisfaction, while health economic analyses frequently reveal unfavourable cost-effectiveness ratios that prevent adoption [115]. The current competitive environment is not beneficial, as the established formulation options (immediate release, extended release, and fixed dose combinations) adequately address clinical requirements for the majority of indications. Generic competition on products whose patents have expired limits pricing flexibility and market penetration opportunities. Physician inertia with established therapies that have become fixed in the treatment pathway and payer reluctance to pay for premium-priced treatments without demonstrable superior clinical benefit are significant barriers to access. Intellectual property risks would make developmental risks worse. For example, a complicated patent thicket with lots of claims that overlap could make it hard to act freely. It is hard to get composition-of-matter patents on formulations that contain well-known, non-novel excipients, which makes it harder to protect against competition. Regulatory pathways that favour generic and biosimilar products over new formulation design are sped up by shorter development and review programs like the 505(b) (United States) and hybrid application (European Union). There is a lack of clear rules and guidelines for nanomedicine characterisation standards, and the rules are not the same in all regions. The necessity for a challenging demonstration of "additional clinical benefit" relative to standard treatments, coupled with a negative, risk-averse stance towards nanomedicines and stringent post-marketing pharmacovigilance, serves to dissuade investments in NLC development programs [116].

8.5 Statement of Intent

This study is designed as a concept paper, and the proposed formulation methods, optimization strategies, and characterization protocols are substantiated through logical

extensions of existing literature, which require further controlled experimental validation. The transition of a linagliptin-canagliflozin NLC concept to clinical application is improbable and necessitates the surmounting of considerable technical, regulatory, and commercial challenges elucidated in this article. Scientists who are thinking about going down this path for drug design need to know that it has a high-risk/high-reward profile and that they need to be experts in a variety of fields, including pharmaceuticals, analytical chemistry, pharmacology, and clinical development. The costs of getting Phase IIa clinical trials will be between \$10 million and \$50 million. This is because the translation pipeline depends a lot on these costs. There also needs to be an honest look at the problems with translation and the ability to stop projects when important development goals are not accomplished. These kinds of requirements show how important it is to have structured team science methods and decision-making frameworks that cover the whole process of bringing therapeutic nanomedicine from idea to clinic [117, 118].

CONCLUSION

The literature survey suggested co-encapsulating linagliptin and canagliflozin in NLCs (nanostructured lipid carriers) as a new way to treat T2DM. This would be a smart way to combine the drugs' pharmacological effects with cutting-edge drug delivery technology. Clinical studies that show proof-of-concept show that DPP-4 and SGLT2 inhibitors will lower HbA1c by 0.5–0.6% more than monotherapy. However, this has only been proven so far using conventional separate tableting formulations. In contrast, for NLC of individual antidiabetic agents, bioavailability increases of 3-fold to 5-fold have been reported, achieving 48–96 hour sustained release via lymphatic transport, P-glycoprotein bypass, and protection against enzymatic degradation. Nonetheless, a significant knowledge deficit exists, as no experimental studies have investigated the co-encapsulation of linagliptin and canagliflozin in NLCs. It remains uncertain whether both drugs can be safely co-encapsulated at therapeutic concentrations without drug-drug-lipid interactions that compromise stability, exhibit pharmacokinetics that enhance clinical efficacy, and ensure that pharmaceutical-scale dose manufacturing adheres to regulatory standards. While QbD principles have been beneficial for the development of single-drug NLCs, and approximately 700 nanotechnology formulation products have received approval, with lipid-based carriers having regulatory precedence since 1995, significant translational barriers temper any enthusiasm: Most laboratory testing successes do not translate to commercial viability; achieving a 24–36 month shelf life remains challenging; while bioavailability enhancement may be possible, clinically beneficial outcomes may not materialise; combination products offering low-cost fixed-dose therapy are already on the market; and development costs (\$500M–\$1B) frequently surpass market returns and stakeholder expectations. Important questions for future research.

Future research must systematically examine the fundamental feasibility, comparative effectiveness in direct trials, characterisation of the safety profile, patient-relevant outcomes such as medication adherence and glycaemic control, economic viability relative to generic alternatives, and long-term performance over extended treatment durations. This requires validation of the underlying experimental assumptions, a realistic appraisal of translational barriers, rigorous comparison with existing therapies, and thorough economic evaluation. Researchers must be prepared to discontinue development if predefined objectives are not met. This is a hypothesis-generating exercise rather than a demonstration of clinical efficacy, and cost-effectiveness relative to existing therapies remains an open question requiring further evidence.

Declaration section

Ethics approval statement

Not applicable

Conflict of interest disclosure

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Not applicable

Declaration of AI utilization

AI models such as Grammarly and Quillbot have been used for the refinement of the English language in the manuscript.

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