

Development, Optimization, and Characterization of Wet-Granulated Curcumin Nanostructured Lipid Carrier Tablets

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ABSTRACT: Curcumin has been widely recognized for its broad therapeutic potential, including its emerging role as an antiviral agent. However, its clinical translation is limited by poor aqueous solubility, rapid metabolism, and low oral bioavailability. To address these challenges, nanostructured lipid carriers (NLCs) have been proposed as a promising delivery system to enhance curcumin stability and systemic availability. This study aimed to formulate curcumin-loaded NLCs, optimize their physicochemical characteristics, and develop an oral tablet dosage form using the wet granulation method with super-disintegrant variation. The optimized NLC formulation was prepared and subsequently freeze-dried prior to compression into tablets. Particle size, polydispersity index (PDI), zeta potential, morphology, entrapment efficiency (EE), and loading capacity (LC) were evaluated. Tablets were formulated using starch, croscarmellose sodium (2% and 3%), PVP, aerosil, and Avicel PH 102, followed by assessment of physical quality parameters including weight uniformity, hardness, friability, disintegration, and dissolution profile. The optimized NLCs exhibited desirable nanoscale characteristics, with particle size of 70.95 nm, PDI 0.379, zeta potential -23.9 mV, spherical morphology, EE 99.75%, and LC 9.93%. The resulting tablets were yellow, bitter, and odorless, with acceptable pharmacopeial quality. Weight and size uniformity were within limits, hardness was 3.81 kg/cm² and 4.38 kg/cm², friability 1.45% and 0.50%, and disintegration times 1.86 min and 1.28 min for 2% and 3% super-disintegrant, respectively. Dissolution profiles indicated 26.12% and 25.79% release within the test period. Curcumin can be successfully formulated into stable NLCs with excellent encapsulation efficiency and incorporated into wet-granulated tablets meeting pharmacopeial standards. The use of 3% croscarmellose sodium provided the most favorable disintegration profile, suggesting its potential as an optimized oral dosage form to improve curcumin delivery and bioavailability.

KEYWORDS: Curcumin; Nanostructured Lipid Carrier (NLC); Oral Tablet; Wet Granulation; Dissolution.

1. INTRODUCTION

Nanotechnology has become one of the most transformative innovations in modern pharmaceutical sciences, particularly in the development of advanced drug delivery systems. Over recent decades, nanoparticle-based formulations have been increasingly explored to overcome challenges associated with conventional dosage forms, such as poor solubility, instability, and low oral bioavailability of many therapeutic agents. Oral dosage forms remain the most convenient and preferred route of administration, but their effectiveness depends on rapid and consistent drug release followed by adequate absorption. For compounds categorized as Biopharmaceutics Classification System (BCS) Class II—with good membrane permeability but poor aqueous solubility—nanoparticle technologies offer a promising solution to improve therapeutic outcomes [1-3].

Curcumin, the principal bioactive constituent of *Curcuma longa* L. (turmeric), is a prime example of such a compound. Traditionally used both as a culinary spice and herbal remedy, curcumin has attracted wide scientific interest for its diverse pharmacological activities, including anti-inflammatory, antioxidant, anticancer, antimicrobial, and particularly antiviral properties. During the COVID-19 pandemic, curcumin

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gained renewed attention due to its potential immunomodulatory effects, such as regulating the expression of angiotensin-converting enzyme 2 (ACE2) and modulating cytokine release, which could theoretically mitigate viral infection and progression. These findings highlight curcumin's therapeutic promise as both a direct antiviral and a supportive immunomodulator [2,3].

Despite these benefits, the pharmaceutical use of curcumin is severely constrained. Curcumin is poorly soluble in water, chemically unstable under light and alkaline conditions, and rapidly metabolized through glucuronidation and sulfation. Its absorption in the gastrointestinal tract is minimal, and systemic elimination occurs quickly, leading to extremely low oral bioavailability even at high doses. Consequently, conventional dosage forms such as capsules, suspensions, or herbal extracts fail to deliver sufficient plasma concentrations for consistent therapeutic effects [2,3,8].

To address these challenges, numerous formulation strategies have been attempted, including liposomes, polymeric nanoparticles, micelles, and solid dispersions. Among these, Nanostructured Lipid Carriers (NLCs) have emerged as one of the most advanced and effective systems. NLCs are second-generation lipid nanoparticles composed of a mixture of solid and liquid lipids, producing a less ordered crystalline structure that allows high drug loading, reduced risk of drug expulsion during storage, and enhanced physical stability. Importantly, NLCs protect curcumin against chemical degradation and promote its solubilization during lipid digestion in the gastrointestinal tract, facilitating absorption via enterocytes and enhancing lymphatic uptake. This process can partially bypass hepatic first-pass metabolism, leading to higher systemic exposure compared with conventional formulations [4,5].

The pharmaceutical versatility of NLCs has been demonstrated in various routes of administration, including oral, dermal, ocular, and pulmonary delivery. In the oral route, they are particularly advantageous for poorly water-soluble natural compounds such as curcumin. Previous studies have attempted to incorporate curcumin NLCs into dosage forms such as sublingual tablets; however, some reported limitations included inadequate mechanical strength and suboptimal hardness, which reduced the practicality of the formulation. These findings highlight the importance of excipient selection and processing methods to ensure that nanocarrier-based dosage forms achieve the required physical and biopharmaceutical standards [4,6].

The present study therefore focuses on the formulation of curcumin-loaded NLCs into oral tablets using the wet granulation method. This method is widely applied in pharmaceutical manufacturing to achieve tablets with consistent weight, uniformity, and mechanical strength. The formulation incorporates excipients such as starch, polyvinylpyrrolidone (PVP), aerosil, and Avicel PH 102. To optimize disintegration and dissolution, croscarmellose sodium is employed as a superdisintegrant, leveraging its swelling and wicking properties to accelerate water penetration and tablet breakup without compromising hardness. This excipient is expected to balance the need for sufficient mechanical robustness with rapid disintegration, ultimately improving drug release profiles [7-12].

Accordingly, the aim of this study is to develop and evaluate oral tablets containing curcumin-loaded NLCs prepared via wet granulation. The objectives are to: (i) characterize the physicochemical properties of curcumin NLCs, (ii) formulate oral tablets using different concentrations of superdisintegrant, and (iii) assess the physical quality parameters and dissolution profiles of the resulting tablets. By integrating NLC technology with optimized excipient systems, this research seeks to establish a practical and pharmaceutically acceptable dosage form that enhances the stability, bioavailability, and therapeutic potential of curcumin for antiviral and other clinical applications.

2. MATERIALS AND METHODS

2.1. Material

Curcumin (PT. Phytochemindo Reksa), Stearic acid, Virgin Coconut Oil, Propylen glicol, Cremophor RH 40 (PT. Mega Setia Agung Kimia), Tween 80, Etanol 96%, Avicel pH 102, Amylum Manihot, Croscarmellose Sodium, PVP, Aerosil, Magnesium Stearat, dan Aquadest.

Glassware (Pyrex), Analytical balance (AND GR-200), Magnetic stirrer (Cimarec 2), Ultraturrax (IKA T25, USA), Ultrasonic processor (QSONICA sonicator, USA), Ice box, Particle size analyzer (Beckman Coulter),

Zeta sizer (Malvern, UK), Transmission Electron Microscope (TEM) (JEOL JEM-1010), Centrifuge (Kokusan, H-103n), Ultraviolet-visible spectrophotometer (UV-Vis) (Shimadzu UV-1900), Freezer, Freeze dryer (Heto), Single punch tablet press machine (Rimek Mini Press-II), Vernier caliper (TRICLE), Stopwatch, Granule flow tester (Autonics LE35), Particle size distribution tester (Testing sieve TSUTSUI), Compressibility tester (Bulk density tester IMF BDT M3-100), Tablet hardness tester (Flight YD-3), Tablet friability tester (Erweka Friabilator), Tablet disintegration tester (Flight BJ-2), Dissolution tester Type II (Paddle apparatus), Volumetric apparatus.

2.2. Procedure

2.2.1. Preparation of Curcumin-Loaded Nanostructured Lipid Carriers (NLCs)

Curcumin-loaded NLCs were prepared using the high-shear homogenization and ultrasonication method with three formulations (F1–F3) as listed in Table 1. Solid lipid (stearic acid) and liquid lipid (virgin coconut oil) were melted in a water bath at 5–10 °C above the lipid melting point. Separately, distilled water containing Cremophor RH 40 and Tween 80 (3:1, w/w) was heated to the same temperature. Curcumin, previously dissolved in propylene glycol, was incorporated into the lipid phase (oil mass). The lipid phase was then added to the aqueous surfactant solution under stirring at 500 rpm for 10 min at 40 °C to form a coarse emulsion. The emulsion was homogenized using an Ultraturrax at 15,000 rpm for 30 min at 40 °C, followed by further homogenization at 5,000 rpm for 5 min while cooling to approximately 4 °C. The resulting nanoemulsion was sonicated at 50 amplitude for 10 min, maintaining the temperature at 4–5 °C.

The obtained NLC dispersions were subjected to physicochemical characterization, including particle size, polydispersity index, zeta potential, and morphology, for each formulation (F1–F3) [13–17].

Table 1. Composition of Curcumin-Loaded NLC Formulations

Ingredient	F1 (% w/v)	F2 (% w/v)	F3 (% w/v)
Curcumin	2.0	2.5	3.0
Stearic acid	4.0	4.0	4.0
Virgin coconut oil	3.0	3.0	3.0
Propylene glycol	5.0	5.0	5.0
Cremophor RH 40	3.0	3.0	3.0
Tween 80	1.0	1.0	1.0
Distilled water	ad 100	ad 100	ad 100

2.2.2. Characterization of Curcumin-Loaded Nanostructured Lipid Carriers (NLCs)

All NLC formulations (F1–F3) were characterized for particle size, polydispersity index (PDI), and zeta potential. The optimized formulation was further analyzed for particle morphology using TEM, as well as entrapment efficiency (EE) and loading capacity (LC). Samples were stored under refrigeration prior to analysis.

2.2.3. Particle size and polydispersity index (PDI):

Measurements were performed using a dynamic light scattering technique (Malvern Particle Size Analyzer, UK). One drop of NLC dispersion was diluted with 50 mL of distilled water and mixed. Ten milliliters of the diluted sample were transferred into a clean cuvette, placed in the sample holder, and analyzed. PDI values < 0.3 were considered indicative of good homogeneity.

2.2.4. Zeta potential

Electrophoretic mobility was determined using a Zetasizer (Malvern, UK). One drop of NLC dispersion was diluted with 50 mL distilled water, loaded into a specialized cuvette with two electrodes, and analyzed. Zeta potential values exceeding ± 30 mV were considered to indicate stable dispersions.

2.2.5. Particle morphology (TEM)

Morphological examination was conducted using a Transmission Electron Microscope (JEOL JEM-1010, Japan) at 100,000 $\times$ magnification. Copper grids (400 mesh) pre-coated with 0.5% Formvar in chloroform were immersed in the NLC dispersion for 1 min, followed by staining with 1% uranyl acetate for 1 min. Excess stain was removed and grids were air-dried before imaging.

2.2.6. Determination of Entrapment Efficiency (EE) and Loading Capacity (LC) of NLC-Curcumin

A total of 1.5 mL of NLC-Curcumin was pipetted into a centrifuge tube, dispersed with 15 mL of distilled water, and centrifuged at 10,000 rpm for 30 minutes. This process separated the supernatant (clear nanosuspension of free curcumin) from the pellet. The supernatant was collected and its absorbance measured using a UV-Vis spectrophotometer at the optimized wavelength. Absorbance data were then used to calculate the amount of free curcumin based on a linear regression equation from the calibration curve. The weight of free curcumin obtained was used to calculate the entrapment efficiency (EE) and loading capacity (LC) of NLC-Curcumin.

2.2.7. Preparation of Oral NLC-Curcumin Tablets

Tablets were prepared by wet granulation using a single-punch tablet press. Two formulations were developed, differing in superdisintegrant concentration, as shown in Table 2.

Table 2. Oral NLC-Curcumin Tablet Formulation

Ingredient	Formula I (% b/b)	Formula II (% b/b)
NLC-Curcumin	150 mg	150 mg
Starch	10	10
Croscarmellose sodium	2	3
PVP	3	3
Aerosil	1	1
Avicel pH 102	ad 300 mg	ad 300 mg
Tablet weight: 300 mg; batch size: 150 tablets.		

- NLC-Curcumin was mixed with starch, PVP, and Avicel pH 102 until homogeneous (C1).
- Ethanol 96% was added dropwise to C1 until wet mass formed.
- The compact mass was sieved through mesh no. 12 to obtain moist granules.
- Granules were dried in an oven at 60 °C for 2 h.
- Dried granules were sieved through mesh no. 16.
- External phase (Croscarmellose sodium and Aerosil) was blended with dried granules until uniform.
- The final blend was compressed into tablets using a single-punch press.

2.2.8. Determination of Curcumin Content in Tablets

Powder equivalent to 10 mg curcumin was dissolved in 0.1 M phosphate buffer (pH 6.8) and transferred into a 100 mL volumetric flask. An aliquot of 0.5 mL was further diluted to 25 mL. Absorbance was measured at 429 nm using a UV-Vis spectrophotometer [8].

3. RESULTS AND DISCUSSION

Variation of curcumin concentration in NLC formulations (F1: 2%, F2: 2.5%, F3: 3%) was performed to evaluate its effect on nanoparticle characteristics. Visually, all formulations appeared homogeneous, with no undissolved curcumin observed.

Table 3. Effect of Curcumin Concentration on NLC-Curcumin Characteristics

Formula	Curcumin Concentration	Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)
I	2%	122.6	0.579	-27.2
II	2.5%	110.2	0.444	-24.8
III	3%	70.95	0.379	-23.9

Among the three formulations, F3 demonstrated the most favorable characteristics, with the smallest particle size and lowest PDI, indicating better homogeneity. Although its zeta potential was slightly lower than F1, it remained within the acceptable stability range. Thus, F3 was selected as the optimal formulation, as it showed the highest potential to maintain curcumin stability and minimize degradation compared to F1 and F2.

The entrapment efficiency and loading capacity of curcumin-loaded NLC were determined to evaluate the formulation's ability to encapsulate and retain curcumin within the lipid matrix.

Table 4. Entrapment Efficiency of Curcumin-Loaded NLC

Initial Curcumin Weight (mg)	Absorbance	Free Curcumin (mg)	Entrapment Efficiency (%)
10	0.2960	0.0249	99.75
10	0.3010	0.0252	99.75
10	0.3100	0.0259	99.74
Average	—	—	99.75

The results in Table 4 indicate that the entrapment efficiency averaged 99.75%, confirming that almost all of the curcumin was successfully encapsulated within the nanoparticles. High entrapment efficiency ensures sufficient drug retention, enhances drug stability, and prolongs drug availability at the target site, which is essential for effective therapeutic outcomes.

The loading capacity of a nanoparticle drug delivery system is a crucial parameter that directly reflects how much of the active pharmaceutical ingredient can be incorporated into the carrier relative to the total weight of the formulation. In the case of curcumin-loaded nanostructured lipid carriers (NLCs), the loading capacity achieved in this study was 9.93% on average, which demonstrates a highly favorable drug-to-carrier ratio. This result, in conjunction with the remarkably high entrapment efficiency of 99.75%, suggests that the formulation strategy applied here is not only efficient but also highly reliable in ensuring maximum drug utilization with minimal loss during the formulation process.

Loading capacity is critical because it defines the actual therapeutic payload that the delivery system can transport to the target site. A higher loading capacity means that a greater concentration of curcumin can be delivered per unit mass of the nanoparticle, reducing the number of excipients needed while maximizing the drug concentration in the final dosage form. For poorly soluble drugs like curcumin, which inherently suffer from low bioavailability due to poor solubility, rapid metabolism, and limited absorption in the gastrointestinal tract, achieving a high loading capacity provides a substantial advantage. It ensures that more curcumin is available to be released in vivo, thereby increasing the likelihood of achieving effective therapeutic levels in systemic circulation [13-16].

In the context of curcumin's pharmacological potential, particularly its roles as an anti-inflammatory, antioxidant, anticancer, and antiviral agent, ensuring sufficient drug load in the delivery system is essential. A nanoparticle system with low loading capacity may require higher dosages to achieve the same therapeutic effects, which can complicate the manufacturing process, increase patient pill burden, and potentially introduce issues related to formulation stability. Thus, the nearly 10% loading capacity observed here highlights the suitability of NLCs for optimizing curcumin therapy [17-24].

NLCs are considered an advanced generation of lipid-based nanoparticles that combine both solid and liquid lipids in their matrix. This unique composition provides several benefits that make NLCs more effective than earlier lipid-based systems such as solid lipid nanoparticles (SLNs). Some of the key advantages include: (1) **Enhanced Drug Loading Capacity:** The imperfect crystalline structure of NLCs, created by mixing solid lipids with liquid lipids, leaves more space within the matrix to accommodate drug molecules. This structural imperfection directly contributes to the higher loading capacity observed in curcumin-NLCs. In contrast, SLNs often suffer from drug expulsion during storage because their highly crystalline lipid matrices tend to expel entrapped drugs. (2) **Improved Physical Stability:** The combination of solid and liquid lipids also prevents the system from undergoing undesirable crystallization during storage, which reduces the risk of drug leakage or instability. This stability ensures that the encapsulated curcumin remains intact over extended periods, maintaining both its therapeutic potential and product shelf life. (3) **Controlled and Sustained Release:** NLCs provide the advantage of controlled drug release, which helps in maintaining steady therapeutic levels of curcumin in systemic circulation. Sustained release is particularly beneficial for drugs like curcumin that undergo rapid metabolism and clearance, as it can prolong their half-life and therapeutic effects. (4) **Versatility in Administration Routes:** NLCs have been studied for multiple routes of administration, including oral, topical, ocular, pulmonary, and parenteral delivery. This versatility broadens their applicability across

different therapeutic areas. In oral delivery, NLCs can improve lymphatic uptake of lipophilic drugs like curcumin, thereby bypassing first-pass metabolism and enhancing bioavailability. (5) **Biocompatibility and Safety:** NLCs are typically composed of physiologically acceptable lipids and surfactants, making them generally recognized as safe (GRAS) excipients. This reduces the risk of toxicity and ensures that the system is well-tolerated by patients [19-30].

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Curcumin presents several formulation challenges, including poor solubility in aqueous environments, rapid degradation in the gastrointestinal tract, and extensive first-pass metabolism. These limitations contribute to its extremely low oral bioavailability, which has hampered its clinical application despite its vast therapeutic potential. NLCs address many of these challenges simultaneously. Improved Solubility: By incorporating curcumin into the lipid matrix, its apparent solubility is enhanced, making it more bioavailable upon oral administration. Protection from Degradation: The lipid matrix shields curcumin from chemical degradation due to pH fluctuations, enzymatic action, and exposure to light, thereby preserving its pharmacological activity. Enhanced Absorption: The nano-sized particles increase the surface area for absorption and improve permeability across biological membranes. In addition, the lipid-based nature of NLCs facilitates lymphatic transport, which bypasses hepatic first-pass metabolism. Targeted and Sustained Release: By adjusting the lipid composition and surfactant concentration, NLCs can be engineered to release curcumin in a controlled manner, ensuring a sustained therapeutic effect [28-33].

The observed loading capacity of 9.93% is particularly meaningful because it directly influences the therapeutic efficacy of curcumin-NLC tablets. A higher drug load ensures that a sufficient amount of curcumin is encapsulated to exert pharmacological effects even at lower dosing frequencies. This reduces the need for frequent administration, enhances patient compliance, and potentially lowers treatment costs. Moreover, higher loading capacity enables better scalability for industrial production. Formulations with higher active content minimize the need for excessive excipients, thereby reducing production costs, tablet size, and overall manufacturing complexity. This is critical for ensuring that curcumin-based NLC formulations can progress from the laboratory stage to commercial pharmaceutical products [20,27,30-33].

The findings of this study suggest that curcumin-loaded NLCs with high entrapment efficiency and favorable loading capacity could serve as a promising platform for clinical applications. Beyond oral delivery, such a system could be adapted for other administration routes where curcumin's therapeutic potential may be beneficial, such as topical formulations for wound healing or dermal inflammation, ocular drops for eye disorders, or parenteral formulations for systemic diseases like cancer. In addition, the concept demonstrated here can be applied to other hydrophobic bioactive compounds that face similar challenges of low solubility and bioavailability. By leveraging the structural advantages of NLCs, future research could explore broader applications in phytopharmaceuticals and natural product-based drug delivery.

4. CONCLUSION

Curcumin was successfully formulated into a nanostructured lipid carrier (NLC), with Formula III identified as the optimal composition. This formulation contained 3% curcumin, 4% stearic acid, 3% virgin coconut oil, 5% propylene glycol, 3% Cremophor RH 40, and 1% Tween 80 in 100 mL of distilled water. Characterization showed favorable nanoparticle properties: particle size 70.95 nm, polydispersity index (PDI) 0.379, zeta potential -23.9 mV, spherical morphology, entrapment efficiency 99.75%, and loading capacity 9.93%. These findings confirm that curcumin can be efficiently incorporated into NLCs with stable physicochemical characteristics, supporting their potential as effective drug delivery systems. The NLC-curcumin was further developed into oral tablets using the wet granulation method. The best-performing formulation (Formula II) consisted of 150 mg NLC-curcumin, 10% starch, 3% croscarmellose sodium, 3% PVP, 1% Aerosil, and Avicel pH 102 (q.s. to 300 mg). Evaluation showed that both Formula I and II met quality standards.

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