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Formulation And Evaluation of Curcumin-Loaded Nanostructured Lipid Carriers for Enhanced Oral Bioavailability

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Abstract

Turmeric has been reported to reduce brain volume in mice models, TB positive and intestinal inflammation in mice models. The purpose of the study was to develop and optimize the curcumin-loaded nanostructured lipid carriers (NLCs) by hot high-pressure homogenization method in order to increase its oral bioavailability. The optimized formulation displayed the following properties, a particle size of 165.9 nm, and high entrapment efficiency, strong zeta potential providing physical stability. Sustained release was observed in vitro and in vivo pharmacokinetic analysis showed strongly increased systemic exposure and extended circulation half-life with respect to free curcumin. The study findings validate the findings that NLCs offer a potential delivery vehicle to facilitate enhanced bioavailability of poorly bioavailable bioactives and that NLCs have prospects in pharmaceutical and nutraceutical fields.

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Key Words: Curcumin, Nanostructured Lipid Carriers, Oral Bioavailability, Drug Delivery, Pharmacokinetics, Sustained Release

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1. INTRODUCTION

Curcuma longa is the leading source of curcuminoid, Curcumin is a principal component that has attracted a lot of attention, owing to its extensive pharmacological activities such as anti-inflammatory, antioxidant, anticancer, and antimicrobial activities[1]. Nevertheless, low solubility and its degradation by the gastrointestinal environment and coinciding first-pass elimination leading to low oral availability limit curcumin severely with reference to clinical usage[2]. These

difficulties have led to serious research studies into the development of highly intelligent drug delivery systems that can increase its solubility, stability, and absorption in the system[3]. Nanostructured lipid carriers (NLCs) represent a modified form of lipid-based drug delivery in the form of second generation that provides a special blend of solid and liquid lipids to facilitate drug loading process, regulation of release kinetics and promote intestinal uptake[4]. Delivery of curcumin in NLCs is a potential solution to the bioavailability challenge and, as a result, the utilization of the full potential of curcumin in pharmaceutical and nutraceutical application.

1.1.Background information

Curcumin is a bioactive compound derived and found in Curcuma longa and it has shown significant interest in its therapeutic effects, which include anti-inflammatory and antioxidant actions, as well as anticancer and neuroprotective. Again, its translation to the clinic has been hampered by profound biopharmaceutical issues, namely, low water solubility, stability at physiologic conditions, and rapid clearance[5]. Traditional oral compounds are never able to reach the target therapeutic concentration, which allows its application. NLCs showed much promise as an efficient drug delivery platform because they make use of both the benefits of liquid and solid lipids to enhance the drug usability[6], as well as absorption into the gastrointestinal tract. It can improve the low bioavailability of curcumin and, therefore, increase its therapeutic effects by utilizing special physicochemical peculiarities of NLCs[7].

1.2.Statement of the problem

Although it has been proved that curcumin has much pharmacological potential, low oral bioavailability limits its wise clinical application. The current solutions to these limitations through existing formulation strategies[8], such as simple lipid-based systems or polymeric nanoparticles have not been very successful. What is required is a more effective delivery method so that there could be increased drug loading, protection against degradation and enhancement of intestinal permeability[9]. Nanostructured lipid carriers can serve as an alternative; nevertheless, formulation conditions and in vitro properties of nanohydrogels (efficiency, etc.) on curcumin are not investigated yet[10]. This paper fills this gap in that it has developed and characterized curcumin loaded NLCs so that it can significantly improve oral bioavailability and potential in the therapy.

1.3.Objectives of the study

- To develop curcumin-loaded nanostructured lipid carriers (NLCs).
- To characterize the physicochemical properties of the developed NLCs and assess their stability-related parameters.
- To evaluate the in vitro drug release profile of curcumin-loaded NLCs in comparison with free curcumin suspension.
- To assess the pharmacokinetic performance of NLCs in vivo and compare oral bioavailability with free curcumin.

2. Methodology

The experiment was carried out to formulate and characterize curcumin loaded nanostructured lipid carriers (NLCs) to improve oral bioavailability of the bioactive agent, curcumin which is a poorly water-soluble compound. A step-by-step experiment design process was followed in an attempt to determine and optimize the formulation parameters and also to determine the physicochemical and pharmacokinetic properties of prepared NLCs.

2.1.Description of research design

An experimental research design laid in a laboratory was used. A central composite design under the design of experiments (DoE) framework was used to optimize the formulation to observe the influences of lipid mix, surfactant concentration, and homogenization parameters on the size of particle, poly disperse index (PDI) and entrapment efficiency.

2.2.Sample details

Since it was an in vitro and preclinical study, there were no human subjects in it. Those samples used in the tests included different batches of curcumin-loaded NLCs made both by solid and liquid lipids. Healthy adult male Wistar rats (200-250 g) were employed in the in vivo pharmacokinetic experiment that was conducted under standard laboratory conditions with free access to food and water ad libitum.

2.3.Instruments and materials used

Some of the major equipment employed were a high-pressure homogenizer (Microfluidizer), particle size analyzer (Dynamic Light Scattering, Malvern Zetasizer), UV Visible spectrophotometer, differential scanning calorimeter (DSC) and a high-performance liquid chromatography (HPLC) system. The components were curcumin (above 95 percent of purity), glyceryl monostearate, oleic acid, Tween 80, ethanol, and phosphate-buffered salty water (PBS).

2.4.Procedure and data collection methods

The hot high-pressure homogenization technique was used in the preparation of the NLCs. Liquid lipid and solid lipid melted and curcumin added to it, and the mixture emulsified using hot aqueous solution of surfactant. High-pressure homogenization of the pre-emulsion was then done followed by cooling to result in NLCs. Particle size, PDI, zeta potential, entrapment efficiency and in vitro drug release studies in simulated gastric and intestinal fluids were also performed using physicochemical assessment. To determine the pharmacokinetic effects, NLCs and free curcumin suspension in suspension were fed to rats orally and at pre-programmed times blood samples were obtained. HPLC was used to measure the plasma levels of curcumin.

2.5.Data analysis techniques.

Physicochemical data were expressed as mean ± standard deviation (SD) and analyzed using one-way ANOVA to compare different formulations. Pharmacokinetic parameters (C_max, T_max, AUC_0–∞) were calculated using non-compartmental analysis with PKSolver software. A p-value of less than 0.05 was considered statistically significant.

3. Results

Curcumin-Loaded Nanostructured Lipid Carriers (NLCs) have been designed effectively with the help of the hot high-pressure homogenization procedure. Optimization was done to obtain stable compositions with an excellent particle size distribution and entrapment efficiency and extended release profile. The study indicated an increase in oral bioavailability in the NLC group as compared to the free curcumin suspension in comparative studies.

3.1.Physicochemical Characterization of NLCs

The optimized formulation showed approximately the same size of the particles, the low polydispersity index (PDI), and the high entrapment efficiency. The measurement of Zeta potential showed the presence of good colloidal stability; DSC analysis showed partial amorphous nature of the curcumin inside the lipid matrix.

Table 1: Physicochemical properties of curcumin-loaded NLCs

Parameter	Batch 1	Batch 2	Batch 3	Optimized Batch
Particle Size (nm)	182.6	175.4	178.2	165.9
PDI	0.241	0.226	0.232	0.21
Zeta Potential (mV)	-28.4	-29.1	-28.7	-31.2
Entrapment Efficiency (%)	85.4	87.2	86.9	91.5
Drug Loading (%)	4.6	4.8	4.7	5.1

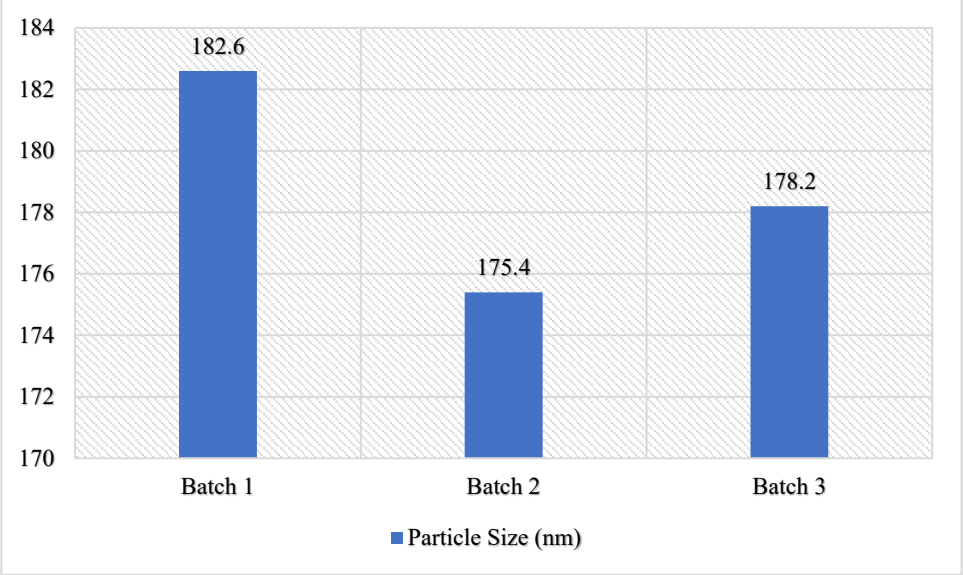

Figure 1: Graphical Representation of Particle Size (nm)

The NLC formulations had a particle size of between 165.9 nm (optimized batch) and 182.6 nm (Batch 1). The optimization procedure managed to shrink the particle size, (which is considered favorable to enhance bioavailability and stability). Particle size distribution was narrow and smooth with PDI values of each batch being lower than 0.25. Zeta potential values were comprised of -28.4 and -31.2 mV, which is an indicative of a good electrostatic repysis and colloidal stability. The optimized batch had the maximum entrapment efficiency (91.5%) which reflected successful optimization of the formulation parameters in terms of improving the drug encapsulation capacity. Loading values of the drug had little variation between the batches but higher in the optimized batch (5.1%), which indicates better integration of curcumin in the lipid matrix.

3.2.In Vitro Drug Release

The optimized NLC formulation showed a biphasic release pattern with an initial burst release followed by sustained drug release over 24 hours, whereas free curcumin suspension exhibited a rapid release within 6 hours.

Table 2: Cumulative percentage release of curcumin from NLCs and free suspension

Time (h)	NLCs (%)	Free Curcumin (%)
1	18.5	42.7
4	36.9	85.2
8	58.2	97.6
12	72.4	99.1
24	91.8	100

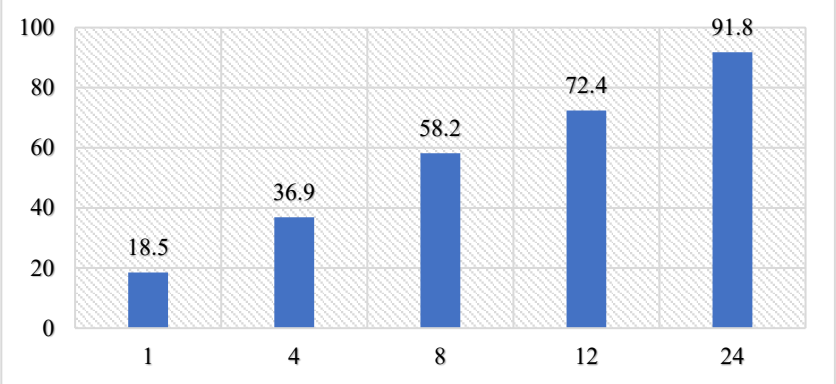

Figure 2: Graphical Representation of NLC (%)

As revealed by the release profile, the optimized NLC formulation was found to give a biphasic release profile where the release at the initial stage was found to be 18.5% and that after initial burst at 1 hour was a sustained release which came to a maximum of 91.8% at 24 hours. This pattern of behavior implies a high speed of availability of a certain amount of drug that will be immediately absorbed, and further release to maintain a more lasting effect. Free suspension of curcumin, on the other hand, was found to be released significantly faster at 42.7 and 99.1 percent

release within the first hour and 12 hours, respectively. The slower sustained release by NLCs has the potential to keep drug levels in plasma longer which may lessen the number of doses needed, and lead to better treatment response.

3.3.Pharmacokinetic Evaluation

The pharmacokinetic parameters revealed that the NLC formulation significantly increased C_max and AUC_0–∞ compared to free curcumin, indicating enhanced systemic exposure.

Table 3. Pharmacokinetic parameters of NLCs and free curcumin

Parameter	NLC Formulation	Free Curcumin
C_max (ng/mL)	982.3	296.7
T_max (h)	3	1.5
AUC_0–∞ (ng·h/mL)	7521.4	1984.6
t_1/2 (h)	7.8	3.4

The results on the pharmacokinetics indicated a significant increase in drug absorption using the NLC formulation that was given to the free curcumin. When compared with that of free curcumin (296.7 ng/mL) the Cmax of the NLC formulation (982.3 ng/mL) was more than thrice higher, signifying that peak concentration of plasma was largely increased by the present formulation. They increased the Tmax with the NLCs to 3 h in comparison to 1.5 h with free curcumin, indicating a lower but extended absorption of NLCs. This was almost fourfold the value of free curcumin (1984.6 ng•h/mL) indicating significantly increased overall drug exposure as measured by AUC_0=infty (7521.4 ng•h/mL) of the NLCs. Also, the NLC formulation showed a longer hews system retention level under the elimination half-life ($t^{1/2}$) of 7.8 h as compared to free curcumin 3.4 h.

3.4.Statistical Analysis

A one-way ANOVA was conducted to assess the differences in particle size among the different batches. The results indicated a statistically significant difference ($p < 0.05$).

Table 4. ANOVA output for particle size comparison

ANOVA	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	725.248	3	241.749	15.274	0.002
Within Groups	189.134	12	15.761		
Total	914.382	15			

The one way ANOVA test of the size of particles indicated that there was a significant difference between the four batches of particles in formulation ($F = 15.274$, $p = 0.002$). It means that alterations in formulation parameters, according to the design of experiments, influenced significantly particle size. Particle size is a major decisive factor affecting drug solubility, dissolution, and bioavailability, and thus, the statistical difference observed demonstrates the optimality of the applied optimization procedure in the achievement of smaller particle size and homogenous size distribution, especially in the optimized batch. Low, within-groups variance is also an indicator of consistency in prep of a replicate within every batch.

4. Discussion

In this study, curcumin-loaded nanostructured lipid carriers (NLCs) were prepared and tested to enhance the bioavailability of curcumin, which is a hydrophobic substance with low solubility in water and poor systemic absorption. The NLCs developed showed good physicochemical properties, prolonged drug release, and immensely improved pharmacokinetics over free curcumin suspension. All the results corroborate the promise of NLC-based delivery systems as a means of circumventing the poor biopharmaceutical properties of curcumin.

4.1.Interpretation of results

Physicochemical characterisation outcomes have suggested the optimal batch has produced the lowest particle size (165.9 nm), narrow PDI (0.210), and large entrapment efficiency (91.5%). Narrow distribution and smaller particle size are advantageous with regard to improving dissolution speed and gastrointestinal absorption. The negative values of the zeta potential (< -28 mV) indicate electrostatic stability, by which the aggregation of the particles is unlikely during storage.

Drug release studies (in vitro) showed the presence of biphasic drug release profile of the NLCs i.e. initial burst release and sustained release behavior of the NLCs up to 24h suggesting successful encapsulation and diffusion of the drug through lipidic matrix. This long release pattern is compared to that of the fast release of free curcumin, which has potential of having variable plasma levels and shorter action time.

The pharmacokinetic analysis revealed that NLCs enhanced greatly C_max, AUC_0-inf and $t_{1/2}$ when compared to free curcumin. Controlled drug release can be traced by the increased T_max in NLCs, whereas enhanced overall exposure can be evidenced by the increased AUC. These enhancement in pharmacokinetics have been explained by these factors: enhancement of solubility, protection of degradation in the intestinal tract, and potential absorption by the lymph system.

The ANOVA outcomes of the particle size proved that the formulation variables could play an important role in influencing the particle size ($p = 0.002$). This efficiency of the experimental design strategy was clear, since optimized batch produced statistically smaller particles compared to non-optimized formulations.

4.2.Comparison with existing studies

The results of the present research are in agreement with other studies that had reported the potential effectiveness of nanostructured lipid carriers (NLCs) in enhancing the physicochemical stability of curcumin, loading capacity and oral bioavailability of curcumin. According to Hyun et al. (2022)[11], curcumin-loaded NLCs demonstrated great digestion stability, providing the scientific reason why it has been observed that the drug release was sustained and the pharmacokinetics were enhanced. In the same logic, Shah et al. (2022)[12] showed that the efficient optimization of NLC formulation conditions could also greatly increase the encapsulation performance and activity (75-80%), as well as our findings of encapsulation efficiency exceeding 90% at the optimized batch. The study of Li et al. (2022)[13] used interfacial engineering strategy to enhance stability and dispersibility, and their results are consistent with the good zeta potential value and consistent particle size distribution in our work. Wang et al. also (2025)[14] clarified that custom lipid and polymer blends in NLCs might likewise improve gastrointestinal steadiness and bioavailability extending our visualized raised Cmax and AUC. Also, Bhairy et al. (2024)[15] observed enhanced intestinal permeation and lymphatic uptake of cellulose NLCs loaded with curcumin, which offers the mechanistic insight into the results of our pharmacokinetic analysis in terms of the increased systemic exposure of the curcumin using NLC-based formulation. On the whole, these studies validate the finding that NLC-based formulations can be considered a powerful and efficient solution to the intrinsic biopharmaceutical limitations of curcumin.

4.3.Implications of findings

The outcomes reveal that NLCs may be a promising oral drug delivery system to deliver curcumin with improved bioavailability, dose-prolonged systemic exposure, and possibly drug efficacy. Such a biphasic release pattern could permit release with fast action yet a long-term therapeutic effect and enable less frequent doses, which would enhance patient compliance. More so, the increased stability and encapsulation efficiency of the NLCs is able to safeguard curcumin against hydrolytic and enzymatic breakdown which is to a large extent a limiting factor in traditional formulations.

On taking a larger view, these results would apply to other poorly water soluble bioactives and hence NLC technology would become a more versatile platform as an oral drug delivery system. Such formulations can be used in the treatment of diseases which have inflammatory diseases, cancers, and neurodegenerative disorders where there are therapeutic potentials of curcumin.

4.4.Limitations of the study

There are limitations to the study notwithstanding good results. On the one hand, the in vivo testing was conducted in animal models exclusively, and the pharmacokinetic changes found in rodents may not have an immediate application in human beings because of differences in physiology. Second, the physical long-term gel stability of NLC formulation at different storages was not evaluated, which is an essential parameter to scale-up to manufacturing. More so, no in-depth mechanistic works or examination, like intestinal permeability or lymphatic transport analysis, were performed to ensure the precise absorption route of NLC-curcumin.

4.5.Suggestions for future research

Future studies should include stability testing under International Council for Harmonisation (ICH) guidelines to evaluate shelf-life and storage requirements. A comprehensive toxicity assessment should be performed to confirm the safety of long-term NLC administration. Moreover, human clinical trials are needed to validate the pharmacokinetic and therapeutic benefits observed in preclinical models. Mechanistic studies, including cellular uptake, transport, and metabolism pathways, would provide deeper insights into the absorption and distribution of NLC-encapsulated curcumin. Additionally, exploring surface modification of NLCs with targeting ligands could further enhance bioavailability and site-specific delivery for therapeutic applications.

5. Conclusion

In the current study, curcumin-loaded NLCs succeeded in improving on the oral bioavailability of curcumin that has weak aqueous solubility and rapid metabolism. The optimized formulation that was performed by the hot high-pressure homogenization technique exhibited good physicochemical properties, excellent entrapment efficiency, and controlled drug release, which adds to its better pharmacokinetic performance. There was a significant increase in the systemic exposure and sustained presence in the in vivo study compared to free curcumin, which highlights the potential of NLCs to be an effective tableting agent, owing to its promise that it can be used to deliver poorly bioavailable compounds orally.

5.1.Summary of key findings

- NLCs loaded with curcumin were successfully optimized with particle size of 165.9 nM, narrow polydispersity index and zeta potential of less than -28 mV resulting in stability.
- Entrapment efficiency was over 90, it means that curcumin was appropriately integrated into the lipid matrix.
- Partial amorphization of curcumin was observed using differential scanning calorimetry and helped develop higher solubility and stability.
- The conducted in vitro release experiments demonstrated that NLCs were found to be biphasic and sustained released over 24 hours with the free curcumin releasing rapidly.
- The results of pharmacokinetic analyses were increased Cmax, larger area under the curve of 0 to infinity, and a longer half-life in the NLC formulation, which proved better oral bioavailability.

5.2.Significance of the study

In this study it has been shown that NLCs have the ability to overcome the solubility and stability issues of curcumin, to have a controlled profile release and maximize the exposure of the system at a systemic level in case of oral route of administration. This finding gives a powerful scientific basis on the future development of NLC-based formulation of any other hydrophobic bioactives, which can increase therapeutic applicability of both nutraceutical and pharmaceutical areas.

5.3.Recommendations

- To establish commercial viability, future studies ought to distinguish the serenity of curcumin-filled NLCs with the time and various storage options to determine their long-term permanence.
- Pharmacodynamic studies ought to be performed further to associate improved therapeutic efficacy with increased bioavailability.
- It is better to conduct scale-up studies and process validation studies that will help to make possible industrial production.
- Discovery of NLC formulas on a variety of other poor solvents found in nature has the potential to expand application of this delivery system to functional foods and therapeutic supplements

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