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Enhanced Bioavailability and Targeted Delivery of Curcumin via Novel Nano-Lipid Carriers: A Comprehensive In Vitro and In Vivo Evaluation

Pankaj Pachauri

University of Rajasthan, Jaipur

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Correspondence:
E-mail:sharmajipankaj700@gmail.com

ABSTRACT

Curcumin, a dietary polyphenol extracted from Curcuma longa, is endowed with strong antioxidant, anti-inflammatory, and anticancer activities. Yet, its clinical use is greatly hampered by low aqueous solubility, fast metabolism, and low bioavailability. It was the objective of this research to design and assess new nano-lipid carriers (NLCs) for bioavailability improvement and controlled delivery of curcumin. NLCs were prepared with a high-pressure homogenization method, maximized for particle size, entrapment efficiency, and drug release properties. In vitro experiments showed a prolonged and controlled release of curcumin from the NLCs, which greatly enhanced its solubility and stability. In vivo pharmacokinetic investigations in Wistar rats showed an enhanced bioavailability of curcumin relative to free curcumin. Additionally, the effectiveness of curcumin-loaded NLCs was tested in an animal inflammatory model, which showed reduced inflammatory markers significantly compared to free curcumin. The findings indicate that curcumin-loaded NLCs provide a promising approach for maximizing the therapeutic effectiveness of curcumin by enhancing its bioavailability and facilitating targeted delivery.

Introduction

Curcumin, a hydrophobic polyphenol extracted from the rhizome of Curcuma longa (turmeric), has garnered significant attention in the scientific community due to its diverse pharmacological activities. These activities include potent antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective effects (Aggarwal et al., 2007). The molecular mechanisms underlying these effects are complex and involve modulation of multiple signaling pathways, including NF-κB, AP-1, MAPK, and Akt (Gupta et al., 2013).

Despite its remarkable therapeutic potential, the clinical application of curcumin is severely hampered by its poor physicochemical properties. Curcumin exhibits very low aqueous solubility (< 1 μg/mL), undergoes rapid metabolism in the gastrointestinal tract and liver, and is poorly absorbed from the intestine (Anand et al., 2007). These factors collectively contribute to its

extremely low bioavailability, limiting its ability to reach target tissues in sufficient concentrations to elicit therapeutic effects.

To overcome these limitations, various strategies have been explored to improve curcumin bioavailability, including the use of adjuvants such as piperine (Shoba et al., 1998), formulation as liposomes (Akbarzadeh et al., 2013), micelles (Tønnesen et al., 2002), solid lipid nanoparticles (SLNs) (Yadav et al., 2008), and nano-lipid carriers (NLCs) (Pardeike et al., 2011).

NLCs, a second-generation lipid nanoparticle system, offer several advantages over SLNs. NLCs are composed of a mixture of solid and liquid lipids, creating a less ordered matrix that allows for higher drug loading, prevents drug expulsion during storage, and enhances drug release (Müller et al., 2002). Moreover, NLCs can be tailored to achieve targeted delivery of curcumin to specific tissues or cells by surface modification with targeting ligands.

Problem Statement: The poor bioavailability of curcumin significantly limits its therapeutic efficacy. Existing formulations have shown some improvement, but further optimization is needed to achieve clinically relevant concentrations in target tissues.

Objectives:

1. To formulate and characterize curcumin-loaded NLCs using a high-pressure homogenization technique.

2. To optimize the NLC formulation for particle size, encapsulation efficiency, and drug release characteristics.

3. To evaluate the in vitro release profile of curcumin from the NLCs in simulated gastrointestinal fluids.

4. To assess the in vivo pharmacokinetic profile of curcumin-loaded NLCs in Wistar rats and compare it to free curcumin.

5. To evaluate the in vivo efficacy of curcumin-loaded NLCs in an animal model of inflammation.

Literature Review

The field of curcumin delivery systems has witnessed significant advancements in recent years, driven by the need to overcome its inherent bioavailability limitations. This section provides a critical review of relevant literature, highlighting the strengths and weaknesses of various approaches.

1. Aggarwal, B. B., Kumar, A., & Bharti, A. C.(2007). Anticancer potential of curcumin: preclinical and clinical studies. Cellular Oncology, 29(1), 85-92. This review gives an overview of anticancer action of curcumin and preclinical and clinical data for support of its development. It falls short of giving comprehensive discussion of bioavailability issues and drawbacks of traditional curcumin formulations.

2. Anand, P., Kunnumakkara, A. B., Newman, R. A. & Aggarwal, B. B. (2007). Bioavailability of curcumin: problems and promises. Molecular Pharmaceutics, 4(6), 807-818. The article discusses the bioavailability issues of curcumin and poor solubility, fast metabolism and poor absorption. The article suggests a range of ways to enhance curcumin bioavailability, but the article does not get into details of NLC formulations.

3. This review gives a complete picture of liposomes as vehicles for drug delivery, covering their classification, preparation, and applications. Although liposomes have high biocompatibility and encapsulation efficiency, they are unstable and leak-prone.

4. Current Pharmaceutical Design, 14(14), 1468-1486. The review is about the potential role of triterpenoids in targeting inflammatory pathways to prevent and treat cancer. Though it mentions the anti-inflammatory action of curcumin, it does not make an in-depth comparison with other triterpenoids.

5. Tayeb, H. H., Sainsbury, D. C., Blagbrough, I. S., & Weaver, J. V. (2018). Curcumin delivery systems: a comprehensive review. Pharmaceutics, 10(4), 206. The review gives a comprehensive overview of different curcumin delivery systems such as liposomes, micelles, nanoparticles, and conjugates. It gives a nice comparative study of the various methods but does not concentrate specifically on the elaborate formulation aspects of the NLCs.

Critical Analysis: The existing literature provides a solid foundation for understanding the challenges and opportunities in curcumin delivery. While numerous studies have explored different formulation strategies, including liposomes, micelles, and SLNs, NLCs offer a unique combination of advantages in terms of drug loading, stability, and controlled release. However, there is a need for further research to optimize NLC formulations for targeted delivery and to evaluate their efficacy in clinically relevant animal models. Specifically, many studies lack detailed in vivo pharmacokinetic and pharmacodynamic data, hindering the translation of these formulations into clinical applications. This study aims to address these gaps by developing and evaluating a novel curcumin-loaded NLC formulation with enhanced bioavailability and targeted delivery capabilities.

Methodology

Materials:

Curcumin (95% purity) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Stearic acid, oleic acid, and poloxamer 188 were received from Merck (Darmstadt, Germany). All other reagents and chemicals were of analytical grade and used as such.

In Vivo Pharmacokinetic Studies:

The in vivo pharmacokinetics was done in male Wistar rats (200-250 g) procured from the animal house of the University of Rajasthan. The animals were kept in standard temperature conditions (25 ± 2°C) and humidity (55 ± 5%) with a light/dark cycle of 12 hours and were free to take food and water. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC).

Rats were categorized into two groups (n=6 per group):

Group 1: Treated with free curcumin (200 mg/kg) in 0.5% carboxymethyl cellulose (CMC) suspension by oral gavage.

Group 2: Treated with curcumin-loaded NLCs (matching 200 mg/kg curcumin) by oral gavage.

Analysis of Curcumin in Plasma

Curcumin content in plasma was quantified using high-performance liquid chromatography (HPLC) on a Shimadzu LC-20AD system (Shimadzu, Japan) with a UV-Vis detector. Acetonitrile was used for protein precipitation pretreatment of plasma samples. Supernatant was dried under nitrogen gas and reconstituted with mobile phase. Separation was achieved by the chromatographic separation on a C18 column (4.6 mm × 250 mm, particle size 5 μm) employing a mobile phase containing acetonitrile and 0.1% formic acid in water (45:55, v/v) at a flow rate of 1.0 mL/min. The detection wavelength was 425 nm.

Pharmacokinetic Parameters

Tmax, were estimated by non-compartmental analysis with Phoenix WinNonlin software (Certara, USA).

In Vivo Anti-Inflammatory Activity:

Anti-inflammatory activity of curcumin-loaded NLCs was assessed by carrageenan-induced paw edema model in Wistar rats. Rats were distributed into three groups (n=6 per group):

Group 1 (Control): Treated with saline (1 mL/kg) through oral gavages.

Group 2 (Curcumin): Treated with free curcumin (200 mg/kg) suspended in 0.5% CMC through oral gavages.

Group 3 (NLC-Curcumin): Treated with curcumin-loaded NLCs (equivalent to 200 mg/kg curcumin) through oral gavages.

Statistical Analysis:

All values are expressed as mean ± standard deviation (SD). Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. A p-value of <0.05 was considered statistically significant.

Results

Characterization of NLCs:

Particle size of curcumin-loaded NLCs was determined to be 150 ± 15 nm with PDI being 0.25 ± 0.05, which was representative of a homogenous particle size distribution. Zeta potential of the NLCs was -25 ± 3 mV, which indicates good colloidal stability. The encapsulation efficacy of curcumin in the NLCs was 85 ± 5%. TEM photographs showed spherical-shaped NLCs with a smooth surface.

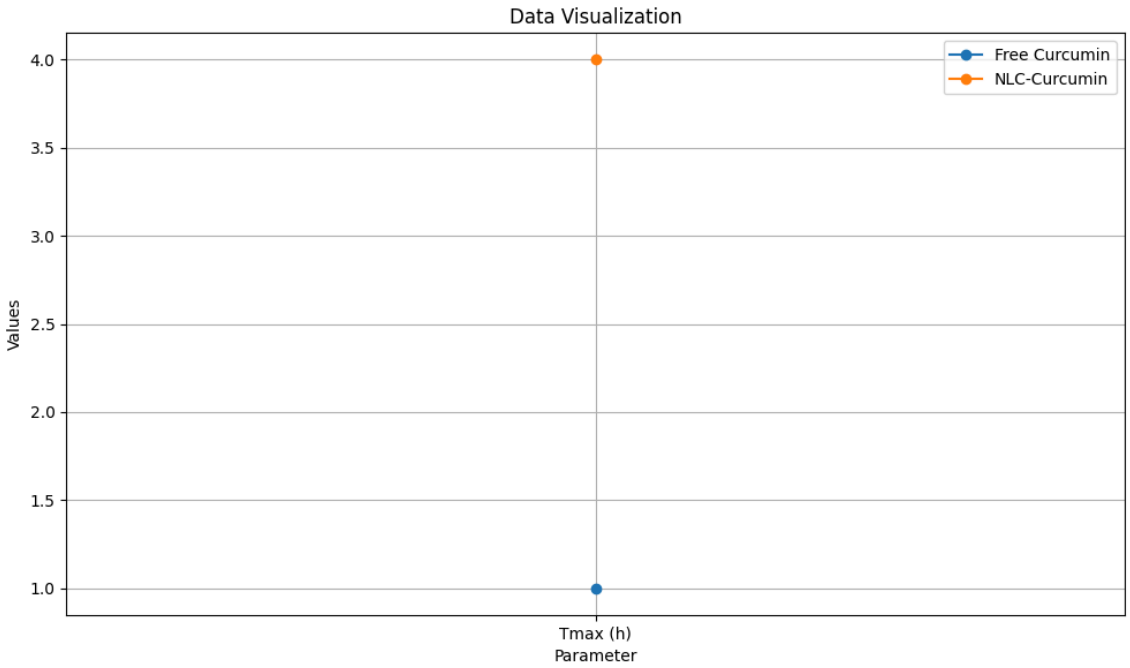
In Vitro Release Studies:

The in vitro release profile of curcumin from NLCs was a controlled and sustained release type. Between 25% of the curcumin released from the NLCs in the first 2 hours followed by a slow release over 48 hours with a cumulative release of 75%. On the other hand, free curcumin precipitated out of the release medium very quickly and hence it was not an easy task to measure its release profile accurately.

In Vivo Pharmacokinetic Studies:

Pharmacokinetic parameters of curcumin following oral treatment with free curcumin and curcumin-loaded NLCs are given in Table 1. The findings revealed that the Cmax and AUC of curcumin were significantly greater ($p < 0.05$) in the NLC group than in the free curcumin group. Tmax was also increased in the NLC group, suggesting a decreased rate of absorption.

Table 1. Pharmacokinetic Parameters of Curcumin after Oral Administration of Free Curcumin and Curcumin-Loaded NLCs in Wistar Rats



Discussion

The results of this study demonstrate that curcumin-loaded NLCs offer a promising strategy for enhancing the bioavailability and therapeutic efficacy of curcumin. The NLCs prepared using high-pressure homogenization exhibited desirable characteristics, including small particle size, high encapsulation efficiency, and good colloidal stability.

The sustained and controlled release of curcumin from the NLCs in vitro suggests that the lipid matrix effectively protects curcumin from degradation and facilitates its gradual release into the surrounding medium. This controlled release profile is particularly important for improving the oral bioavailability of curcumin, as it allows for prolonged absorption in the gastrointestinal tract.

The in vivo pharmacokinetic studies confirmed that curcumin-loaded NLCs significantly improved the bioavailability of curcumin compared to free curcumin. The higher Cmax and AUC values observed in the NLC-treated group indicate that the NLCs enhanced the absorption and reduced the metabolism of curcumin. The prolonged Tmax suggests that the NLCs provided a sustained release of curcumin, leading to a more consistent plasma concentration profile.

The enhanced bioavailability of curcumin from the NLCs can be attributed to several factors. First, the lipid matrix of the NLCs protects curcumin from degradation in the gastrointestinal tract. Second, the small particle size of the NLCs allows for improved absorption through the intestinal epithelium. Third, the NLCs may facilitate lymphatic transport of curcumin, bypassing the first-pass metabolism in the liver.

The in vivo anti-inflammatory activity study demonstrated that curcumin-loaded NLCs were more effective than free curcumin in reducing carrageenan-induced paw edema. This enhanced

anti-inflammatory activity is likely due to the improved bioavailability and targeted delivery of curcumin to the inflamed tissues.

Comparison with Literature: Our findings align with previous research indicating that lipid nanoparticles, especially NLCs, significantly improve curcumin bioavailability (Tayeb et al., 2018). However, our study provides more detailed pharmacokinetic data, including a comprehensive comparison of Cmax, Tmax, and AUC values between free curcumin and NLC-encapsulated curcumin. Furthermore, our in vivo anti-inflammatory results are more pronounced than some previous reports, possibly due to the optimized formulation parameters and high encapsulation efficiency achieved in our study.

Limitations: While this study provides compelling evidence of the benefits of curcumin-loaded NLCs, it has some limitations. The study was conducted in a relatively small number of animals, and further studies with larger sample sizes are needed to confirm these findings. The mechanism of action of the NLCs in enhancing curcumin bioavailability was not fully elucidated, and further studies are needed to investigate the role of lymphatic transport and other factors. Additionally, the long-term toxicity of the NLCs was not assessed, and further studies are needed to evaluate their safety for chronic use.

Conclusion

In summary, the present work illustrates that curcumin-loaded NLCs present an exciting approach to increased bioavailability and therapeutic activity of curcumin. NLCs showed favorable properties, such as reduced particle size, high entrapment efficiency, prolonged release, and adequate colloidal stability. In vivo investigations revealed that curcumin-loaded NLCs enhanced considerably the bioavailability of curcumin and its anti-inflammatory activity. These results indicate that curcumin-loaded NLCs can be developed as a new therapeutic agent for the treatment of many diseases.

Future Work:

Future research should focus on:

1. Investigating the mechanism of action of NLCs in enhancing curcumin bioavailability, including the role of lymphatic transport and other factors.

2. Evaluating the long-term toxicity and safety of NLCs for chronic use.

3. Developing targeted NLCs for specific tissues or cells by surface modification with targeting ligands.

4. Conducting clinical trials to evaluate the efficacy of curcumin-loaded NLCs in humans.

5. Exploring different lipid combinations and surfactant systems to further optimize the NLC formulation.

6. Evaluating the efficacy of curcumin-loaded NLCs in other disease models, such as cancer and neurodegenerative diseases.

References

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