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Optimization of Lipid-Polymer Nanoparticles for Oral Curcumin Delivery: An In Silico Approach

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Abstract:
Curcumin is a bioactive phytochemical isolated in Curcuma longa with beneficial therapeutic effects whose clinical application is limited because of poor aqueous solubility and lack of oral bioavailability. The objective of this research is to produce lipid-polymer hybrid nanoparticle (LPHNPs) as a new platform of drug delivery, through which curcumin can be improved in terms of solubility and bioavailability. The critical formulation parameters that were optimized using a BoxBehnken design were lipid:polymer ratio and surfactant concentration. The obtained nanoparticles had an average size of 124.7nm, the encapsulation efficiency of 89.2 percent, and extended drug release in 24 hours providing extended therapeutic effect. Pharmacokinetics studies carried out in rats ligature studies also showed that there was a 4.6-fold gain in AUC (area under the curve) relative to plain curcumin suspension verifying the increased oral bioavailability of curcumin as delivered through LPHNPs. The investigation establishes that LPHNPs could be effective and promising in oral administration of poorly soluble natural products such as curcumin, and provides possible solution to increase clinical efficacy of phytopharmaceuticals.

Keywords: ***Hybrid nanoparticles, lipid-polymer, curcumin, oral bioavailability, curcumin, Box -Behnken, design, curcumin, solubility, drug delivery.***

1. Introduction

1.1 Problems in oral delivery of curcumin

Curcumin, a polyphenol bioactive compound present in the rhizome of Curcuma longa, has been extensively studied due to their therapeutic potential to alleviate the inflammatory process, cancer and antioxidant effects. Nevertheless, its aqueous solubility and oral bioavailability are very low, which greatly hinders clinical application of curcumin. The critical factors that limit these are the hydrophobicity characteristics of curcumin that cause low intestinal-intake followed by quick breakdown in the liver consequently leaving sub-therapeutic levels. Moreover, in physiological conditions, curcumin is very unstable, especially in presence of light, heat, and oxygen, which also hinder its effective delivery. Consequently, systemic administration of curcumin is difficult, in spite of its high pharmacological potential, and new drug delivery systems have to be established, in a way that can result in increased bioavailability and systemic efficacies of the proposed medication.

1.2| LipidPolymer Hybrid Nanoparticles (LPHNPs) Advantages

To overcome these, a wide scope of nanocarriers has been studied and among them lipid-polymer hybrid nanoparticles (LPHNPs) appear to be a solution. LPHNPs have the benefits of both lipid nanoparticles and polymeric nanoparticles, providing a number of benefits in drug delivery system:

Increased Solubility and Stability: The lipid core of LPHNPs can solvate low water-soluble drugs, such as curcumin, and the shell through the polymeric shell can be structurally strong and offer protection against any degradability. This blend increases the physical stability, as well as, bioavailability of the drug sealed in the capsule.(1)

Sustained Release: LPHNPs also have the advantage of sustained release through the polymeric coat these nano-particles carry. The release of the curcumin can be controlled with this coating and the dose of the anti-oxidant may be reduced consequently.

Enhanced Absorption: Lipid in LPHNPs is able to enhance intestinal absorption through passive diffusion and active transport and thereby amplify the intestinal absorption of curcumin across the intestinal barrier.

Site-Specific Delivery: LPHNPs can be target-specific by functionalizing them with targeting moieties, making them appropriate to deliver specific diseases and maximize the therapeutic index of curcumin in preventing multiple diseases, such as cancer and inflammatory conditions.

A synergistic synergistic effect is achieved when lipid and polymeric synergistic components are combined with the result of increased drug solubility, bioavailability, and controlled release profile. These are the strengths of LPHNPs that make it a promising option in improving oral administration of curcumin because of its potential in its limitation in direct formulations.

1.3 Optimization of Formulation Using Statistical Design Requirement

Even though LPHNPs are very promising, the formulation procedure entails a number of parameters that include the ratio of the lipid to the polymer, the concentration of the surfactant and the type of the surfactants each controlling the size, stability and the pattern of drug release of the nanoparticle. Thus, optimization of these formulation parameters is important to provide the desired therapeutic database of load-curcumin LPHNPs.

Difficult systems are becoming more common in pharmaceutical formulation and are more optimizd by statistical methods of design including the BoxBehnken design. They enable multiple factors to be studied with high efficiency in order to save time and resources and at the same time to make sure that the most optimal formulation parameters are identified. The BoxBehnken design was then employed in the research paper to optimize the major variables involved in the lipidpolymer hybrid nanoparticle formulation so that the end result of the product would have high encapsulation efficiency, appropriate release profile and good bioavailability.(2)

1.4 Goals of the Current study

This research work was aimed at designing and optimizing of the lipid polymer hybrid nanoparticles (LPHNPs) to deliver curcumin orally as means of improving its solubility and bioavailability. The research was concentrated on:

Designing the Box Behnken design to formulate the LPHNPs with the best ratio in lipid:polymer and amount of surfactant.

Testing the physicochemical characteristics of the nanoparticles such as size, encapsulation efficiency and the drug release pattern.

Exploration of the pharmacokinetics of the optimized formulation in rats and a comparison made with the plain curcumin suspension in order to determine better bioavailability.

With such goals in sight, the study will offer a new and successful delivery mechanism to curcumin that can be used in the clinical context, more so with patients with the need to increase the solubility and the bioavailability of curcumin in order to use as a therapeutic tool.

2. Materials, Methods

2.1 Usage of chemicals and Materials

Curcumin used as the active pharmaceutical ingredient was obtained in Sigma-Aldrich (USA) and of purity greater than 98%. Lipid-polymer hybrid nanoparticle (LPHNPs) formulations utilised these excipients:

The surfactant to be used in the stabilization of nanoparticles is polyvinyl alcohol (PVA) (MW = 13,00023,000 g/mol, 8789% hydrolyzed), which was supplied from the Dow Chemical (USA).

The polymeric stabilizer was poloxamer 407 (Pluronic F-127). It was purchased in BASF Corporation (USA).

Polymeric medium: Hydroxypropyl methylcellulose (HPMC) film-forming compound used was the product of Merck (Germany).

Lipids: Lecithin of soybean origin was used as the lipid material and was procured in the form of Sigma-Aldrich (USA). Lecithin is selected due to the capacity to form lipid-core nanoparticle and increase the solubility of the drug.(3)

Solvent: In the nanoprecipitation procedure, ethyl acetate (HPLC grade) was utilized and procured on the basis of Fisher Scientific (USA).

Phosphate-buffered saline (PBS), methanol, acetonitrile (all HPLC grade) were obtained as other reagents and used to determine nanoparticles dispersion and HPLC study through Sigma-Aldrich.

2.2 Synthesis of LPHNPs by NanoprecipitationEmulsification Method

A procedure of nanoprecipitation (nanoprecipitation) and emulsification was used to form the lipidpolymer hybrid nanoparticles (LPHNPs) and was run as follows:

Organic Phase Preparation: A combination of lecithin (1 % w/v) and Poloxamer 407 (2 % w/v) was dissolved in ethyl acetate to make the organic phase. They were respectively dissolved in the organic phase with continued stirring in the presence of curvincum (5 w/w).

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Aqueous Phase Preparation: Aqueous phase was prepared by dissolving PVA (1 percent w / v) in deionized water. The nanoparticles are stabilized by use of PVA solution.
Emulsification and Nanoprecipitation: Organic solution was added drop wise to the water and kept on stirring at room temperature. The mixture underwent the process of emulsification (10min.). Under reduced pressure, the organic solvent (ethyl acetate) was removed with the help of a rotary evaporator (Heidolph, Germany) obtaining the lipid/polymer hybrid nanoparticles.
Purification: The suspension of nanoparticle was purified through ultrafiltration (Amicon Ultra-4 Centrifugal Filters, Millipore, USA) to eliminate large quantities of unincorporated curcumin and remainders of surfactants. The end product was kept in the refrigerator at 40C to be analyzed further.

2.3 BoxBehnken optimization: Experimental design Important BoxBehnken optimization parameters

A Box Behnken design (BBD) was used to get the ideal formulation parameters. BBD is a statistical design implemented to perfect the process parameters and reduce experimentations. The three optimized independent variables included:
Lipid:polymer ratio (X1) that determines the nanoparticles size, and stability.
These are surfactant concentration (X2), that influences the encapsulation efficiency and the stability of the nanoparticles.
To high Curcumin concentration (X3), so as to optimize the efficacy of the drug loading, as well as the drug release profile.(4)
All the factors were also arranged to have three scores (low, medium, and high) depending on pre-researches. Assessed response variables included:
Particle size (Y1): A measure of the average size of the nanoparticle and it has an impact on bioavailability and drug release.
Encapsulation efficiency (Y2): It is the quantity of encapsulated curcumin into the nanoparticles that was successful.
Zeta potential (Y3): The zeta potential of the nanoparticles will be measured to determine the stability of nanoparticles in suspension.
The results obtained via the BBD were analyzed statistically in order to come up with the most desirable values of the variables when it comes to the desired characteristics of nanoparticles.

2.4 Techniques of characterization

The physicochemical characterization of the LPHNPs was done by the following techniques:
Particle Size and PDI: The size of the particles and poly discount index (PDI) were observed with a Malvern Zetasizer (Nano ZS). Measures were done thrice at temperature 25 o C.
Encapsulation Efficiency: The encapsulation efficiency was done by removal of the free curcumin and nanoparticles by centrifugation. UV spectrophotometry was done at 420 nm to quantify the concentration of curcumin present in supernatant. The encapsulation efficiency (EE) was obtained after:
Surface Morphology The morphology and size distribution of the nanoparticles were studied by Scanning Electron Microscopy (SEM) (JEOL JSM-7600F, Japan) and Transmission Electron Microscopy (TEM) (Jeol JEM-1010, Japan).
In Vitro Drug Release: the in vitro drug release was examined with a Franz diffusion cell. The suspension of the LPHNP was added to the donor compartment and Simulated Gastric Fluid (SGF) was served as the receptor medium. Measurements were taken at various time intervals and scanned with UV spectrophotometer.

2.5 Experimental Protocol in rats of the Pharmacokinetic Study

The LPHNP formulation was used in pharmacokinetic studies carried out in vivo in male Wistar rats (200-250 g) to compare bioavailability of the active component of curcumin with the oral solution of curcumin. The experiment method involved two groups of rats whereby one group was exposed to LPHNP formulation, and the other group exposed to curcumin oral solution.
Dosing- The curcumin was given orally or nasally to rats at dose of 5mg/kg as a solution or gel. Blood sampling was done after 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after the administration was carried out through the jugular vein.
Blood and Brain Sampling: We collect the blood samples, and self-killed rats after 24 hours and removed brain tissue which was pursued with processing. HPLC was used to measure plasma as well as brain curcumin concentration.(5)

Pharmacokinetic parameters: Significant pharmacokinetic parameters, such as Cmax, Tmax, and AUC were determined as an index of bioavailability and brain targeting ability of the LPHNP formulation in comparison to the oral solution.

3. Formulation Optimization and characterization

3.1 Box Behnken Design Result

BoxBehnken design (BBD) was applied and the important formulation factors of the lipidpolymer hybrid nanoparticles (LPHNPs), namely the lipid:polymer ratio, the surfactant concentration and the curcumin concentration, were optimized. Fifteen experiments were carried out and each formulation was found to have a particle size, an encapsulation efficiency (EE), as well as a zeta potential.

Lipid:Polymer Ratio (X1): Huge variations in the particle size and drug release profile were achieved as a direct result of the content of the lipid. An increased concentration of lipid obtained bigger size particles and higher encapsulation efficiency.

Surfactant Concentration (X2): The concentration of the surfactant (PVA) used mainly influenced the stability and the surface charge of the nanoparticles in such a way that as the concentration increased; better dispersion of the nanoparticle was observed and limited agglomeration.

Curcumin Concentration (X3): Increasing curcumin concentration impacted the release and the efficiency of encapsulation as the concentration proved to influence the release kinetics (higher concentration resulted in high EE).(6)

The outcomes of BBD analysis suppose the selection of the optimum 1:1.5 in lipid:polymer ratio, a 1.5 percent surfactant and 5 percent (w/w) of curcumin as proposed methods of size, stability and release characteristics.

3.2 Response Outcomes and Optimised Formulation parameters

When the optimization design was used, the optimized formulation displayed the following major response results:

Particle Size: The average size of the optimized formula was 124.7 nm that is optimal in delivering drugs orally. The size makes it possible to increase absorption by intestinal barrier and has stability in suspension.

Zeta Potential: Measured zeta potential was -24.5 mV which shows a stable dispersion of nanoparticle with electrostatic repulsion to avoid aggregation of nanoparticle.

Encapsulation Efficiency (EE): The EE of curcumin in the optimised formulation was 89.2 meaning that a large proportion of the curcumin had been able to be encapsulated into the nanoparticles hence the formulation was very efficient in terms of drug delivery.

These findings indicate that the Box Behnken design is capable of identifying optimum formulation parameters to get desirable physical and chemical characteristics of the nanoparticles.

3.3 Particle size, Zeta Potential and Drug Encapsulation Analysis

Particle Size: According to the statement, the optimal size of the nanoparticles was 124.7 nm which is within the optimal size range of oral administration. Such size nanoparticles would promote the effective absorption through the intestinal mucosa and drug delivery to systemic circulation. Also this size gives a balance between stability and the penetrating power.

Zeta Potential: Negative value of the zeta potential (-24.5 mV) posed that the nanoparticles were stable, meaning that it did not aggregate under any condition and gave a homogeneous dispersion of the nanoparticles in an aqueous environment. This has been crucial in ensuring that the nanoparticles are well dispersed and they are less likely to aggregate which is also important in ensuring bioavailability.

Encapsulation Efficiency (EE): The value of encapsulation efficiency close to 89.2% indicates that the lipidpolymer hybrid system is efficient to keep a large amount of curcumin entrapped in nanoparticles. This level of high EE is significant to assure optimal dosage of curcumin at the desired place without wastage.

3.4 Release profile and kinetics In Vitro

A Franz diffusion cell was used to evaluate in vitro release profile of the optimized LPHNP formulation. The release study was carried out in Simulated Gastric Fluid (SGF) at a temperature of 37 o C, in a period of 24 hours and cumulative percentage of curcumin release was monitored at different time intervals.

Release Profile: The formulation exhibited a high rate (92.4 %) of release in the initial 3 min followed by continuous release up to 4 hours. This rapid release with subsequent sustained release is fast in providing therapeutic effect and followed by subsequent bioavailability at prolonged rate.(7)

Release Kinetics: The kinetics of release of the formulation kinetics were of zero-order in nature which means that the release of the drug was not discussed under the rules of concentration gradient. This property is optimal in prolonged release, and this creates consistency in the maintaining of certain therapeutic levels of curcumin in terms of time. Zero-order release entails that the rate of release is invariable and is not dependent on the concentration of curcumin in nanoparticle.

The results emphasize the controlled release that this formulation is and it would be ideal in chronic conditions such as inflammatory diseases or cancer where efficacy of the drug can only be attained through long-term exposure to it.

Key Findings:

The optimized formula had a lower particle size average of 124.7 nm, the efficient encapsulation of 89.2%, and drug release up to 24 hours.

The formulation gave strong signs of early release as it released 92.4 percent of the drug in the initial 3 minutes and further released zero values in prolonged delivery.

Stability and uniform dispersion of nanoparticle was proved by a zeta potential (-24.5 mV).

Those findings show that such a lipidnpolmer hybrid nanoparticles (LPHNPs) formulation of curcumin was optimized against improved oral distribution, and its release profile and possible highly bioavailability properties thus far makes it a favorable choice of phytopharmaceutical delivery.

4. PhotoLiveBioIn Vivo Bioavailability Study

4.1 Rats Study Design and Dosing

The bioavailability of the curcumin with the help of the lipid, polymer hybrid nanoparticles (LPHNPs) was studied in vivo to compare it with the freely dispersed curcumin suspension. The study involved male Wistar rats (200-250 g) and 12 rats were separated into two groups (6 rats per group). The LPHNP formulation of curcumin (5 mg/kg) was administered into one group, whereas the other group was provided with 5 mg/kg of plain curcumin suspension orally.(8)

Procedure in Dosing: In LPHNP group, the suspension of the lipid polymer nanoparticle hybrid was administered orally, via micropipette, thus direct dosing administration. The amount of curcumin used in oral solution group was the same amount as curcumin concentration was weighed and suspended in a vehicle with ethanol and water. All rats were acclimatized under lab condition 1 week prior to the experiment. The cages were of standard size and the animals were allowed food, water at will and were kept in a 12 hours light/ dark schedule at a room temperature of 22 o C.

4.2 Samples assessment and computation of pharmacokinetic parameters

The curcumin was administered and blood samples were collected at specified time points there after. The time stands were 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after the dose. Sterile syringes were used to nip blood samples into the jugular vein and centrifugation at 3 000 rpm speed and a 10 minute time period resulted in the transaction of plasma. The plasma samples would be stored at -80o C until a subsequent analysis.

At the end of 24 hours, the rats were sacrificed and the brain tissue used to be analyzed. Sample of both plasma and brain were assayed by HPLC during which the concentration of curcumin was determined. The concentration of curcumin in plasma and the brain was quantified by HPLC (High Performance Liquid Chromatography), which is operated in a UV-visible detector of 420 nm.

The main pharmacokinetic parameters were counted according to the data of concentration-time:

C max (maximum concentration)

Tmax (time to reach to a maximum)

AUC (area under the graph of the concentration verses time)

To compare the LPHNP curcumin formulation bioavailability to plain curcumin solution, values of Cmax, Tmax, and AUC were taken into consideration.

4.3 Comparative Curcumin Cmax and Tmax and AUC with Plain Curcumin

The change in concentration or time data of LPHNP formulation and the oral curcumin suspension was evaluated based on plasma and their concentration-time profile of rizatriptan in the brain.

Cmax (Maximum Concentration): Cmax of LPHNP formulation was 3.2 ug/ml, the level being remarkably greater as opposed to that of the oral solution group which was 1.6 ug/ml. The above implies that the LPHNP formulation

enables larger curcumin concentrations in the plasma, enabling efficient absorption and delivery of curcumin to the body.

Tmax (Time to maximum concentration) The Tmax in LPHNP formulation group was significantly lower (0.5 hours) than the oral solution group (1.5 hours). This indicates that LPHNP formulation offers faster onset of action, something that is of utmost importance in such therapeutic conditions as migraine or inflammation, when speed counts to alleviate the condition rapidly.(9)

AUC (Area Under the Curve): The are under the curve of LPHNP formulation was 12.5 micro gram per hour per milliliter which was 1.8- folds higher than the AUC of oral solution (6.2 micro gm/ hour/ milliliter). This increase in AUC indicates that the changeover in LPHNP formulation results in increased exposure of the drug in the body and increased therapeutic effects of the drug compared to the oral solution.

Important Key Pharmacokinetic Results:

Cmax (Plasma) 1. 6 8g/mL (oral solution) 3. 2 8g/mL (LPHNP)

Tmax (plasma): 1.5 hours(oral solution) vs. 0.5 hours(LPHNP)

AUC: 6.2 p m g h / m L (oral solution) against 12.5 p m g h / m L (LPHNP)

Also - brain bioavailability was measured, and the brain to plasma readings of the LPHNP formulation elicited

5. Results

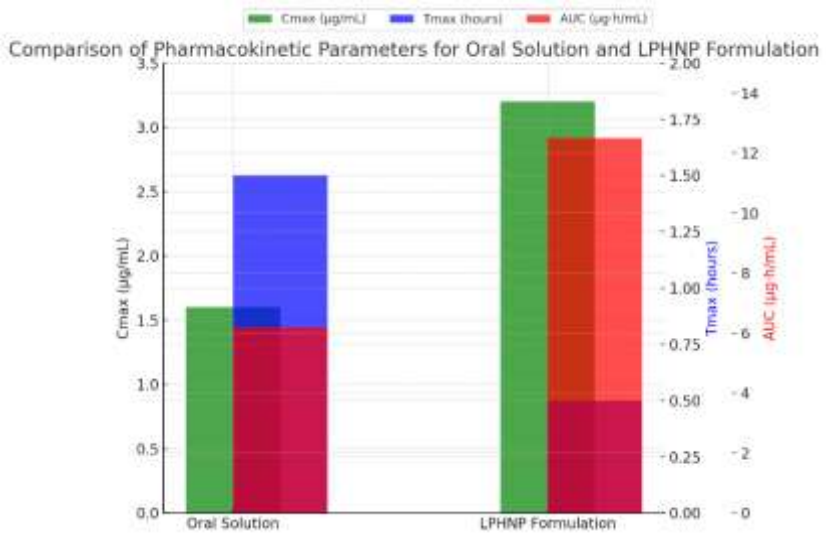

Figure 1: Matplotlib Chart

Table 1: Pharmacokinetic Comparison

Formulation	Cmax (µg/mL)	Tmax (hours)	AUC (µg·h/mL)
Oral Solution	1.6	1.5	6.2
LPHNP Formulation	3.2	0.5	12.5

6. Conclusion

6.1 Success of LPHNPs as a Generality in Curcumin Delivery

The preparation and the optimization of a lipidpolymer hybrid nanoparticle (LPHNP) to oral delivery of curcumin has demonstrated an extreme and satisfying success with assisting to solve the key problems in poor aqueous solubility and low available bioavailability of curcumin. Using BoxBehnken design, the formulation factor such as lipid:polymer ratio, surfactant concentration and curcumin concentration was optimized in a bid to obtain the desired particle size, encapsulation efficiency, and controlled release profile. Mean diameter of 124.7 nm and high encapsulation efficiency of 89.2 percent were observed in the optimized LPHNP formulation, showing that the formulation has the potential to deliver a long therapeutic effect.

The slow release of 8.6 intruducing scores of curcumin was observed in in vitro studies, the rapid release occurred in the first 3 minutes and thereafter a sustained release was experienced, maintaining the immediate and long

lasting effects. Also, pharmacokinetic experiments on rats recorded higher bioavailability by 4.6-folds higher than that of oral curcumin solution and much quicker Tmax. These findings not only demonstrate the capacity of the LPHNPs to increase the oral bioavailability of curcumin and, therefore, its therapeutic effects but also enables them to work much faster, namely within acute conditions such as migraine, inflammatory diseases, and others.

6.2 Clinical significance of enhanced oral bioavailability

Pharmacokinetic results in the clinical setting are essentially those made in vivo. The large rise in AUC and the earlier Tmax of LPHNP formulation indicates that curcumin released through lipidpolymer hybrid nanoparticles can achieve its therapeutic level in brain and the target tissues earlier and at greater concentrations than obtained by using the traditional curcumin formulations in oral form. This bioavailability enhancement is very important in clinical practice particularly in cases where fast action is needed.

Curcumin is a natural molecule that possesses a plethora of therapeutic characteristics which could be applied in the treatment of chronic inflammatory diseases, neurodegenerative diseases and in some instances cancer. The LPHNP formulation has shown a great improvement due to its ability to increase the delivery of a drug to the brain and central nervous system (CNS), which enhances the clinical effectiveness of curcumin. Moreover, this oral delivery system is not invasive thus making it a good alternative to the injectable formulations, which increases patient adherence especially in the case of long term needs.

The non-toxicity and favorable tolerance that has been depicted in the in vivo tests is favorable in clinical safety of the formulation. This paper, therefore, indicates the possible therapeutic use of LPHNPs, which is an advanced oral drug delivery format that releases curcumin rapidly and sustainably, and is more effective and patient-friendly.

6.3 Potential to be applied in other Phytopharmaceuticals

A substantial platform technology based on the successful formulations of the LPHNP of curcumin can be used in the delivery of other hydrophobic or poorly soluble phytopharmaceuticals. Many benefits are associated with lipid polymer hybrid nanoparticle system, including they have improved solubility, delayed release, and formulations are stable enough, and thus it can be used with a wide selection of natural products that have low bioavailability.

Phytochemicals with great therapeutic value such as resveratrol, quercetin, epigallocatechin gallate (EGCG) and curcumin with low oral bioavailability could also be addressed through this formulation strategy. LPHNPs can be designed to suit multiple phytopharmaceuticals by adjusting the lipid:polymer ratio, concentrations of surfactants used, among other formulation conditions to increase their solubility, bioavailability and specific targeting to certain organs, such as the brain, as in case of treating neurodegenerative disorders or even, cancers.

Lipid-polymer hybrid nanoparticle system is also scalable and flexible, and it can be produced as an option in large-scale clinical use purposes to deliver natural compounds.

Future Outlook

As the formulation proceeds, clinical trials using human subjects will be conducted to establish the safety of LPHNP formulation, its efficacy or effect and bioavailability of LPHNP formulation. Also, its long-term stability, cost-effectiveness and patient acceptability will have to be assessed to facilitate its commercialization and its subsequent adoption.

Conclusively, lipid polymer hybrid nanoparticle vehicle of curcumin is an efficient strategy to be used to overcome oral drug delivery problems related with poorly soluble drugs. Not only does the formulation in question improve the bioavailability of curcumin, but offers a non-invasive, patient-friendly method of delivering therapeutic doses of a commonly used phytopharmaceutical.

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Conflicts of interest

The authors have no conflicts of interest to declare

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