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QUALITY BY DESIGN–BASED DEVELOPMENT AND OPTIMIZATION OF NANOSTRUCTURED LIPID CARRIERS FOR ENHANCED ANTIHYPERTENSIVE DRUG DELIVERY

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ABSTRACT

Hypertension is a major chronic cardiovascular disorder requiring long-term pharmacological management. Although several antihypertensive drugs are clinically effective, their therapeutic performance may be limited by poor aqueous solubility, low oral bioavailability, extensive first-pass metabolism, variable gastrointestinal absorption, and the requirement for repeated administration. Nanostructured lipid carriers (NLCs), composed of a mixture of solid and liquid lipids stabilized by suitable surfactants, have emerged as promising lipid-based nanocarriers for improving drug solubilization, gastrointestinal permeability, drug protection and controlled release. The present research proposes a systematic Quality by Design (QbD)-based approach for the development and optimization of NLCs intended for enhanced antihypertensive drug delivery. The development strategy involves defining the Quality Target Product Profile (QTPP), identifying critical quality attributes (CQAs), screening critical material attributes (CMAs) and critical process parameters (CPPs), performing risk assessment, and applying Design of Experiments (DoE) for formulation optimization. Important formulation variables may include the concentrations and ratios of solid lipid, liquid lipid and surfactant, while process variables may include homogenization pressure, homogenization cycles, sonication time and processing temperature. The optimized

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formulation should be evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, morphology, crystallinity, drug–excipient compatibility, in vitro drug release and physical stability. Advanced characterization using dynamic light scattering, transmission electron microscopy, Fourier-transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction can provide comprehensive information regarding the physicochemical characteristics of the developed system. Previous QbD-based studies involving antihypertensive drugs such as isradipine and lacidipine have demonstrated that optimized NLC systems can improve drug entrapment, intestinal permeation, oral bioavailability and antihypertensive performance. The proposed QbD framework is therefore expected to provide a scientifically justified, robust and reproducible strategy for developing NLCs with improved drug delivery characteristics and potential for enhanced therapeutic performance.

Keywords:- Nanostructured lipid carriers, Quality by Design, antihypertensive drug, Design of Experiments, optimization, lipid nanoparticles, oral bioavailability, drug delivery.

I. INTRODUCTION

Hypertension is one of the most important risk factors associated with cardiovascular morbidity and mortality. Persistent elevation of blood pressure contributes to the development of myocardial infarction, stroke, heart failure, renal impairment and other cardiovascular complications. Pharmacological treatment of hypertension commonly involves calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and other therapeutic agents. Despite the availability of effective antihypertensive drugs, conventional dosage forms may not always provide optimal therapeutic outcomes because of physicochemical and biopharmaceutical limitations associated with individual drugs.

A considerable number of antihypertensive drugs possess poor aqueous solubility and variable gastrointestinal absorption. Some drugs are also subjected to extensive first-pass metabolism, resulting in reduced systemic availability after oral administration. These limitations may necessitate higher or repeated doses and can contribute to fluctuations in plasma drug concentrations. Therefore, development of advanced drug-delivery systems capable of enhancing solubility, improving intestinal absorption, protecting the drug from degradation and providing controlled release has received substantial attention.

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Lipid-based nanocarriers represent an important class of advanced drug-delivery systems. Among these, nanostructured lipid carriers are considered second-generation lipid nanoparticles. Unlike solid lipid nanoparticles, which primarily contain a solid lipid matrix, NLCs generally combine solid and liquid lipids. The presence of liquid lipid disrupts the highly ordered structure of the solid lipid matrix, creating imperfections that can accommodate greater amounts of drug and potentially improve drug loading and release characteristics.

NLCs may improve the delivery of poorly water-soluble drugs through several mechanisms, including enhanced apparent solubility, increased interfacial area, protection of the encapsulated drug, improved interaction with gastrointestinal membranes and, for suitable systems, enhanced lymphatic transport. Their nanometric size and lipidic composition can also influence drug release and absorption. Consequently, NLC technology has been investigated for several therapeutic classes, including antihypertensive drugs.

For example, an NLC system developed for isradipine using a QbD approach demonstrated optimized particle size, high entrapment efficiency and favorable drug-release characteristics. The optimized formulation also showed improved gastrointestinal stability and greater in vitro gut permeation compared with an isradipine suspension. Another study involving isradipine-NLCs reported an improvement in oral bioavailability and prolonged antihypertensive performance in an experimental model. Similarly, lacidipine-loaded NLCs optimized through Box–Behnken design demonstrated high entrapment efficiency, controlled drug release, improved intestinal permeation and increased relative oral bioavailability compared with drug dispersion.

However, the development of nanocarrier systems using conventional trial-and-error methods can require considerable time, materials and experimental resources. Formulation variables often interact with each other, making it difficult to identify their individual and combined effects through one-factor-at-a-time experimentation. Quality by Design provides a systematic alternative by integrating scientific understanding, risk assessment, experimental design and statistical modeling into pharmaceutical development. ICH Q8 describes QbD as a systematic approach involving prior knowledge, quality risk management and Design of Experiments to develop products with predefined quality characteristics.

The application of QbD to lipid-based nanosystems has been reported to facilitate the

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identification of formulation and process variables affecting particle size, polydispersity, zeta potential, drug entrapment and drug-release behavior. More recent literature further emphasizes the importance of QTPP, CQAs, CMAs, CPPs and DoE in achieving reproducible and scalable lipid-nanoparticle development.

Therefore, the present research focuses on the QbD-based development and optimization of NLCs for enhanced antihypertensive drug delivery, with particular emphasis on systematic formulation development, risk assessment, statistical optimization, physicochemical characterization and evaluation of drug-release and delivery performance.

II. THEORETICAL BASIS OF NANOSTRUCTURED LIPID CARRIERS

Nanostructured lipid carriers (NLCs) are advanced lipid-based nanocarrier systems developed to overcome several limitations associated with conventional pharmaceutical dosage forms and first-generation lipid nanoparticles. They are particularly useful for the delivery of poorly water-soluble and lipophilic drugs because they provide a lipidic environment capable of incorporating therapeutic molecules and modifying their release and absorption. NLCs generally consist of a combination of solid lipid and liquid lipid stabilized by one or more surfactants. The theoretical foundation of NLC technology is based on the ability of this mixed lipid matrix to provide improved drug accommodation, enhanced physical stability, controlled drug release and, for suitable drugs, improved bioavailability. In the context of antihypertensive drug delivery, NLCs are especially relevant because several antihypertensive agents exhibit poor aqueous solubility, low or variable oral bioavailability and extensive first-pass metabolism. The development of NLCs therefore provides a rational strategy for improving the biopharmaceutical performance of such drugs.

The concept of NLCs evolved from solid lipid nanoparticles (SLNs). SLNs were developed as alternatives to polymeric nanoparticles and traditional colloidal carriers, using physiologically acceptable solid lipids as the principal matrix material. Although SLNs provide several advantages, their highly crystalline lipid matrix can have limitations, particularly with respect to drug incorporation. During storage, lipid molecules may undergo polymorphic transitions toward more stable crystalline forms, which can reduce the available space for drug molecules and potentially result in drug expulsion. NLCs were developed to overcome these limitations by incorporating a liquid lipid into the solid lipid matrix. The resulting matrix has a greater degree of structural disorder and can provide additional

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accommodation sites for drug molecules. Thus, the fundamental theoretical principle of NLCs is the creation of a less ordered lipid structure that improves drug incorporation while retaining the advantages of a lipid-based nanocarrier.

The lipid matrix is the central component of an NLC system. It generally contains a solid lipid and a liquid lipid in a suitable ratio. Solid lipids provide structural integrity and help maintain the particulate state of the carrier at room and physiological temperatures. Examples include glyceryl monostearate, stearic acid, glyceryl behenate and related pharmaceutically acceptable lipids. Liquid lipids, such as oleic acid and medium-chain or long-chain lipidic excipients, disrupt the ordered arrangement of the solid lipid molecules. The choice and ratio of these two components directly influence particle size, drug loading, entrapment efficiency, crystallinity and release behavior. Therefore, lipid selection is not merely an excipient-selection step but a fundamental part of the theoretical design of NLCs.

Three principal structural models have commonly been proposed to explain drug incorporation within NLCs: the imperfect crystal model, the amorphous model and the multiple-oil-in-fat model. According to the imperfect crystal model, incorporation of liquid lipid produces imperfections in the solid lipid crystal lattice. These imperfections create additional spaces into which drug molecules can be accommodated. This model is particularly useful for explaining increased drug-loading capacity. The amorphous model proposes that the lipid matrix is maintained in a less crystalline or amorphous state, thereby reducing the likelihood of drug expulsion during storage. The multiple-oil-in-fat model suggests the formation of small oil compartments within the solid lipid matrix. These compartments provide additional regions for solubilization of lipophilic drug molecules. In practice, the internal structure of NLCs may involve characteristics of more than one model depending on the composition and manufacturing process.

Surfactants are another essential component of NLC formulations. They reduce interfacial tension between the lipid and aqueous phases and facilitate the formation of nanosized particles during homogenization or other manufacturing processes. Surfactants also stabilize the newly formed particles against aggregation by providing steric and/or electrostatic stabilization. Commonly investigated surfactants include Tween 80, Poloxamer 188 and related pharmaceutical surfactants. The concentration of surfactant must be carefully optimized because insufficient surfactant may result in particle aggregation and increased

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particle size, whereas excessive surfactant may influence drug release, membrane interactions and formulation tolerability.

The nanoscale dimension of NLCs is another important theoretical component. Reduction of particle size substantially increases the specific surface area of the formulation. A larger surface area can facilitate interaction between the formulation and the gastrointestinal environment and may influence dissolution and drug-release behavior. For poorly water-soluble drugs, the lipid matrix can maintain the drug in a solubilized or molecularly dispersed state within the carrier. After administration, interaction of the lipid carrier with gastrointestinal fluids can facilitate drug transfer from the lipid matrix toward the absorption interface. Consequently, NLCs may improve the apparent solubility and dissolution behavior of poorly water-soluble drugs.

NLCs can also influence oral drug absorption through several potential mechanisms. Following oral administration, lipid digestion and interaction with bile salts can result in the formation of colloidal structures capable of maintaining lipophilic drug molecules in a solubilized state. Depending on the formulation and drug properties, lipid digestion products may promote drug partitioning toward the intestinal membrane. Certain lipid-based formulations may additionally promote lymphatic transport, potentially reducing hepatic first-pass metabolism. These mechanisms are particularly important for drugs with high lipophilicity and substantial first-pass metabolism. However, the extent of these effects is highly dependent on lipid composition, drug physicochemical properties and gastrointestinal conditions.

Controlled drug release represents another theoretical advantage of NLC systems. Drug molecules located near the surface of the nanoparticles may be released relatively rapidly, whereas drug incorporated deeper within the lipid matrix may require longer diffusion or matrix erosion processes before release. Consequently, the composition and internal structure of the NLC can be manipulated to obtain an appropriate release profile. Factors such as lipid type, solid-to-liquid lipid ratio, surfactant concentration, drug loading and particle size can substantially influence release kinetics. For antihypertensive drugs requiring sustained therapeutic exposure, controlled release may potentially contribute to maintaining drug concentrations over an extended period and reducing fluctuations associated with conventional immediate-release formulations.

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The surface characteristics of NLCs also influence their stability and biological behavior. Zeta potential provides information about the electrical potential at the particle surface and can be used as one indicator of colloidal stability. Steric stabilization provided by non-ionic surfactants may also be important, particularly when the magnitude of surface charge is not sufficiently high to prevent aggregation. Particle size and polydispersity index are similarly important quality characteristics. A smaller and relatively uniform particle population generally provides greater formulation consistency and predictable behavior. However, the optimum particle characteristics must be established experimentally because excessively small particles or high surfactant concentrations may not necessarily provide the best pharmaceutical performance.

The theoretical basis of NLC development is closely connected with the principles of Quality by Design (QbD). QbD considers product quality as a consequence of formulation composition and manufacturing-process understanding rather than as something achieved solely through final-product testing. In NLC development, the Quality Target Product Profile (QTPP) defines the desired characteristics of the final formulation. Critical Quality Attributes (CQAs), such as particle size, PDI, zeta potential, entrapment efficiency, drug loading and drug-release characteristics, are then identified. Critical Material Attributes (CMAs), including lipid type, lipid ratio and surfactant concentration, and Critical Process Parameters (CPPs), such as homogenization pressure, homogenization cycles, processing temperature and sonication time, can subsequently be evaluated. Design of Experiments (DoE) allows interactions among these variables to be investigated systematically.

For antihypertensive drug delivery, the theoretical significance of NLCs lies in their potential to improve the biopharmaceutical properties of drugs with unfavorable physicochemical characteristics. Drugs such as isradipine, lacidipine and olmesartanmedoxomil have been investigated using lipid-based nanocarriers, with studies reporting improvements in drug entrapment, intestinal permeation, release characteristics and/or oral bioavailability. These findings provide a scientific basis for applying NLC technology to antihypertensive drug delivery, although the magnitude of improvement depends on the individual drug and formulation composition. the theoretical basis of nanostructured lipid carriers is founded on the combination of solid and liquid lipids to create a structurally imperfect and relatively flexible lipid matrix capable of efficiently incorporating drug molecules.

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Their nanoscale size, large surface area, lipid-mediated solubilization, controlled-release potential and possible effects on intestinal absorption make NLCs attractive systems for enhancing the delivery of poorly water-soluble antihypertensive drugs. Integration of NLC technology with Quality by Design further provides a systematic framework for understanding the relationships among formulation variables, process parameters and critical quality attributes. Thus, NLCs represent a scientifically rational and potentially robust platform for developing improved antihypertensive drug-delivery systems.

III. FOURIER-TRANSFORM INFRARED SPECTROSCOPY

Fourier-Transform Infrared Spectroscopy (FTIR) is an important analytical technique widely used in pharmaceutical research for the identification of chemical compounds, characterization of functional groups, evaluation of molecular interactions, and assessment of drug–excipient compatibility. In the development of nanostructured lipid carriers (NLCs), FTIR spectroscopy is particularly useful for investigating the compatibility of the selected antihypertensive drug with solid lipids, liquid lipids, surfactants, and other formulation components. The technique is based on the principle that molecules absorb infrared radiation at specific frequencies corresponding to the vibrational movements of their chemical bonds. Different functional groups, such as hydroxyl, carbonyl, amino, methyl, methylene, and aromatic groups, exhibit characteristic absorption bands. Therefore, the infrared spectrum obtained from a substance provides a characteristic molecular fingerprint that can be used for identification and structural interpretation.

The basic principle of FTIR involves the interaction of infrared radiation with the molecules present in a sample. When infrared radiation is directed toward the sample, specific frequencies are absorbed by the chemical bonds present within the molecules. These absorptions cause molecular vibrations such as stretching, bending, rocking, and twisting. The resulting signal is processed mathematically through Fourier transformation to produce an infrared spectrum, generally represented as transmittance or absorbance against wavenumber. The position and intensity of absorption bands provide useful information about the functional groups and molecular environment of the analyzed material. FTIR is therefore considered a rapid and reliable technique for determining whether the chemical characteristics of an active pharmaceutical ingredient remain unchanged after incorporation into a pharmaceutical formulation.

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In the present study, FTIR spectroscopy can be employed to evaluate the chemical compatibility of the selected antihypertensive drug with the excipients used for the preparation of NLCs. Initially, the FTIR spectrum of the pure drug should be recorded to identify its characteristic functional-group peaks. Subsequently, the spectra of the selected solid lipid, liquid lipid, surfactant, physical mixture, and optimized NLC formulation should be obtained under identical or appropriately standardized conditions. The spectra can then be compared to determine whether any major changes occur following formulation. The characteristic peaks of the pure drug should ideally remain identifiable in the physical mixture and optimized NLC formulation. Minor changes in peak position, intensity, or band broadening may occur because of changes in the molecular environment, hydrogen bonding, or interactions between the drug and lipid matrix. Such changes do not necessarily indicate chemical incompatibility and should be interpreted in combination with other characterization studies.

FTIR analysis is particularly significant during the preformulation stage because drug–excipient compatibility is an essential requirement for developing a stable pharmaceutical formulation. If the selected antihypertensive drug exhibits substantial chemical interaction with a lipid or surfactant, it may affect drug stability, potency, release behavior, or therapeutic performance. FTIR can provide preliminary evidence regarding such interactions before extensive formulation development is undertaken. In a Quality by Design (QbD)-based development strategy, this information contributes to the scientific understanding of formulation components and supports rational selection of suitable excipients. Consequently, FTIR analysis can be considered an important characterization step for establishing the compatibility and quality of the proposed NLC formulation.

The FTIR spectrum of the pure antihypertensive drug is expected to show characteristic absorption bands corresponding to its specific functional groups. After incorporation into the NLC, these bands may remain unchanged, shift slightly, decrease in intensity, or become broader depending on the interactions between the drug and the lipid matrix. If the characteristic functional-group peaks of the drug remain present without the appearance of significant new peaks or major disappearance of important peaks, the formulation can generally be considered to show no evidence of substantial chemical incompatibility. However, interpretation should not be based solely on the presence or absence of individual peaks because lipid and surfactant components can produce overlapping absorption bands.

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Careful comparison of the complete spectra of the pure drug, physical mixture, and optimized formulation is therefore necessary.

Attenuated Total Reflectance (ATR)-FTIR is particularly suitable for pharmaceutical and lipid-based formulations because it requires little sample preparation. In ATR-FTIR, the sample is placed directly on an ATR crystal, and infrared radiation interacts with the sample at the crystal surface. This approach is convenient for analyzing powders, solid lipids, liquid excipients, physical mixtures, and dried NLC samples. It also reduces sample-preparation requirements and allows rapid analysis. The technique can therefore be effectively incorporated into the characterization workflow of the optimized nanostructured lipid carrier.

In NLC research, FTIR can also provide supportive information regarding the incorporation of the antihypertensive drug within the lipid matrix. When the drug is incorporated into the carrier, changes in the chemical environment surrounding its functional groups may lead to modifications in the FTIR spectrum. These changes can provide evidence that the drug is associated with or incorporated into the lipid system. Nevertheless, FTIR cannot independently establish the exact physical state of the drug within the NLC. Whether the drug remains crystalline, becomes amorphous, or is molecularly dispersed should be investigated using complementary techniques such as Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD).

For the proposed QbD-based NLC formulation, FTIR analysis should therefore be performed as part of comprehensive physicochemical characterization. The pure drug, individual excipients, physical mixture, and optimized NLC should be analyzed and their spectra compared. The major absorption bands should be identified and appropriately interpreted. The absence of significant changes or new characteristic bands would provide supportive evidence of satisfactory drug–excipient compatibility, whereas substantial changes should be further investigated using complementary analytical techniques. FTIR findings can subsequently be correlated with other critical quality attributes such as particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, crystallinity, and in vitro drug release.

Fourier-Transform Infrared Spectroscopy provides a rapid, sensitive, and non-destructive approach for investigating the chemical characteristics of antihypertensive drug-loaded nanostructured lipid carriers. Its ability to identify functional groups and detect changes in the

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molecular environment makes it valuable for preformulation studies and final formulation characterization. In the present research, FTIR will help establish the compatibility of the antihypertensive drug with the selected lipid and surfactant components and provide supportive evidence regarding the chemical integrity of the optimized NLC formulation. When integrated with DSC, XRD, particle-size analysis, zeta-potential measurement, microscopy, drug-release studies, and stability testing, FTIR contributes to a comprehensive understanding of the formulation and supports the QbD-based development of a robust and reproducible NLC system for enhanced antihypertensive drug delivery.

IV. IN VIVO PHARMACOKINETIC EVALUATION

In vivo pharmacokinetic evaluation is an important stage in the development and characterization of nanostructured lipid carriers (NLCs) because it provides information about the absorption, distribution, metabolism, and elimination of the antihypertensive drug following administration of the optimized formulation. The primary purpose of pharmacokinetic evaluation is to determine whether incorporation of the drug into the NLC system improves systemic drug exposure, enhances oral bioavailability, and modifies the duration of drug availability compared with the conventional drug formulation. For the proposed study, the optimized antihypertensive NLC formulation should be compared with a suitable reference formulation, such as the pure drug suspension or marketed conventional formulation. The study should be conducted according to an approved animal protocol and applicable institutional and regulatory requirements.

For pharmacokinetic investigation, an appropriate laboratory animal model may be selected based on the physicochemical and pharmacological characteristics of the antihypertensive drug. Animals should be appropriately acclimatized and randomly allocated into experimental groups. Before administration, animals may be fasted for a predefined period where scientifically justified, while allowing free access to water. The optimized NLC formulation and reference formulation should be administered through the intended route, with oral administration being particularly relevant when the objective is to evaluate enhancement of oral drug delivery. The administered dose should be scientifically justified from available pharmacological and toxicological information and should be identical or appropriately dose-normalized between treatment groups to permit meaningful comparison.

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Following administration, blood samples should be collected at predetermined time intervals appropriate to the pharmacokinetic profile of the selected drug. Samples should be processed to obtain plasma or serum and stored under validated conditions until analysis. The concentration of the antihypertensive drug in biological samples should be determined using a suitable validated bioanalytical method, preferably a sensitive chromatographic technique such as high-performance liquid chromatography (HPLC) or liquid chromatography coupled with mass spectrometry (LC–MS/MS), depending on the analytical requirements of the drug. The analytical method should demonstrate appropriate specificity, accuracy, precision, sensitivity, and stability to ensure reliable quantification of drug concentrations.

The plasma drug concentration versus time data obtained from the NLC and reference formulation should be used to construct pharmacokinetic profiles. Important pharmacokinetic parameters include maximum plasma concentration (Cmax), time required to reach maximum plasma concentration (Tmax), area under the plasma concentration–time curve (AUC), elimination half-life (t½), mean residence time (MRT), clearance, and apparent volume of distribution where applicable. Cmax provides an indication of the maximum systemic drug exposure achieved after administration, whereas Tmax represents the time required to reach that concentration. AUC is particularly important for evaluating the overall systemic exposure to the drug and is commonly used for assessing relative oral bioavailability. The elimination half-life provides information about the persistence of the drug in the systemic circulation, while MRT indicates the average time the drug molecules remain within the body.

The pharmacokinetic performance of the optimized NLC is expected to differ from that of the conventional formulation if the nanocarrier successfully improves drug solubilization and absorption. A higher AUC for the NLC formulation would indicate increased systemic exposure and potentially improved oral bioavailability. An increase in Cmax may indicate enhanced absorption, although an excessively rapid increase in drug concentration is not necessarily desirable for an antihypertensive formulation. A prolonged Tmax and increased MRT or half-life may suggest sustained drug availability. However, the interpretation of these parameters should be based on the complete pharmacokinetic profile rather than on individual parameters alone.

Relative bioavailability can be calculated by comparing the AUC of the optimized NLC with that of the reference formulation using the following equation:

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Relative Bioavailability (%) = ($AUC_{nl}c$ / AUC_{ref}) × ($Dose_{ref}$ / $Dose_{nl}c$) × 100

When the same dose is administered to both groups, the dose ratio becomes one and relative bioavailability can be expressed primarily as the ratio of the respective AUC values. A higher relative bioavailability for the NLC formulation would provide evidence that the formulation improves systemic drug exposure compared with the reference formulation.

The improved pharmacokinetic performance of NLCs may be attributed to several mechanisms. The lipid matrix can improve the apparent solubility of poorly water-soluble antihypertensive drugs and maintain them in a solubilized or molecularly dispersed state. The nanosized particles provide a large surface area that can facilitate interaction with gastrointestinal fluids and absorption surfaces. Following oral administration, digestion of lipid components may generate lipid digestion products and colloidal structures that can assist in maintaining lipophilic drug molecules in a solubilized state. Depending on the lipid composition and physicochemical characteristics of the drug, lipid-based delivery may also influence intestinal lymphatic transport and potentially reduce the impact of hepatic first-pass metabolism. These mechanisms can collectively contribute to improved systemic exposure.

Previous research provides support for investigating antihypertensive drugs using NLC systems. QbD-based development of isradipine NLCs has demonstrated improved formulation characteristics and enhanced intestinal permeation compared with conventional drug suspension. Other investigations of isradipine-loaded NLCs have reported improved oral bioavailability and prolonged antihypertensive activity. Similarly, lacidipine-loaded NLCs have demonstrated enhanced oral delivery characteristics, including improved intestinal permeation and bioavailability compared with conventional drug dispersion. These findings provide a scientific rationale for evaluating the optimized formulation through in vivo pharmacokinetic studies.

Pharmacokinetic parameters should be statistically compared between the NLC and reference groups using an appropriate statistical method. Continuous variables may be expressed as mean ± standard deviation, and the statistical test should be selected according to the experimental design and distribution of the data. Pharmacokinetic parameters such as AUC and Cmax may require log-transformed analysis when conducting formal bioavailability comparisons. Tmax, being a time-to-event parameter, may require a non-parametric approach

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depending on the data distribution. Statistical significance should be established using a predefined significance level, commonly **$p < 0.05$**.

The results of the pharmacokinetic investigation should ultimately be correlated with the physicochemical characteristics of the optimized NLC. For example, reduced particle size, satisfactory PDI, high entrapment efficiency, appropriate lipid composition, and controlled drug release may contribute to improved systemic drug exposure. Such correlations can strengthen the mechanistic understanding developed through the Quality by Design framework. Nevertheless, an improvement in pharmacokinetic parameters should not automatically be interpreted as improved therapeutic efficacy; pharmacodynamic evaluation is necessary to determine whether increased drug exposure translates into a meaningful antihypertensive response. in vivo pharmacokinetic evaluation provides critical evidence regarding the performance of the optimized NLC formulation after administration.

Comparison of Cmax, Tmax, AUC, t½, MRT, clearance, and relative bioavailability between the NLC and conventional formulation can establish whether the nanocarrier improves drug absorption and systemic exposure. When integrated with in vitro drug-release, ex vivo intestinal-permeation, physicochemical characterization, and pharmacodynamic studies, pharmacokinetic evaluation can provide a comprehensive assessment of the potential of NLCs as an advanced delivery system for antihypertensive drugs. Thus, the study can establish whether the QbD-optimized NLC formulation provides a scientifically meaningful improvement over conventional drug delivery while maintaining reproducible pharmaceutical quality.

V. CONCLUSION

The Quality by Design approach provides a systematic and scientifically justified framework for the development and optimization of nanostructured lipid carriers for antihypertensive drug delivery. NLCs offer several potential advantages over conventional drug-delivery systems because their combination of solid and liquid lipids can improve drug incorporation, modify release characteristics and potentially enhance gastrointestinal absorption and oral bioavailability. Existing research involving antihypertensive drugs such as isradipine, lacidipine and olmesartanmedoxomil supports the feasibility of applying QbD principles to NLC development.

The proposed development strategy begins with establishment of the QTPP and identification

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of CQAs, followed by systematic evaluation of CMAs and CPPs through risk assessment. Screening and response-surface DoE can then be used to understand the individual and interactive effects of formulation and process variables and to identify an optimized formulation. Comprehensive physicochemical, in vitro, ex vivo and, where appropriate, in vivo evaluation can establish whether the optimized NLC provides meaningful improvement over the conventional drug formulation.

Importantly, QbD moves formulation development from empirical trial-and-error experimentation toward a knowledge-based development process. The resulting understanding of formulation composition, manufacturing parameters and product performance can contribute to improved reproducibility, robustness and scalability. Therefore, QbD-based NLC development represents a promising strategy for designing advanced antihypertensive drug-delivery systems with improved pharmaceutical performance and potential therapeutic benefits.

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