REVIEW ARTICLE

A Review on Nanostructured Lipid Carriers in Tyrosine Kinase Inhibitor Therapy: Formulation, Characterization, and Artificial Intelligence Perspectives

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Abstract

Tyrosine kinase inhibitors (TKIs) have revolutionized targeted cancer therapy by selectively inhibiting aberrant signaling pathways involved in tumor growth and progression. Despite their clinical success, the majority of TKIs exhibit significant biopharmaceutical limitations, including poor aqueous solubility, low and variable bioavailability, extensive first-pass metabolism, and the development of drug resistance. These challenges often result in suboptimal therapeutic outcomes and dose-related toxicity. Nanostructured lipid carriers (NLCs), as advanced lipid-based nanocarrier systems, have emerged as a promising strategy to overcome these limitations by enhancing drug solubility, improving pharmacokinetics, enabling controlled release, and facilitating targeted delivery. This review provides a comprehensive overview of TKIs with emphasis on their physicochemical and pharmacokinetic properties, followed by a detailed discussion on formulation strategies, preparation methods, optimization approaches, and characterization of NLCs. Furthermore, recent advancements in targeted delivery, co-delivery systems, and smart nanocarriers are highlighted. The integration of artificial intelligence (AI) in formulation design and optimization is also discussed as a transformative approach in nanomedicine. Finally, challenges associated with clinical translation, regulatory considerations, and future perspectives are critically addressed. The convergence of nanotechnology and AI holds significant promise for enhancing the therapeutic efficacy and clinical performance of TKI-based therapies.

Key words: Artificial intelligence, lipid-based nanocarriers, nanostructured lipid carriers, quality by design, tyrosine kinase inhibitors

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a substantial burden on global healthcare systems.[1] The increasing incidence of cancer is attributed to multiple factors including aging populations, environmental exposures, lifestyle changes, and genetic predispositions.[2] Despite significant advances in conventional treatment modalities such as chemotherapy, radiotherapy, and surgery, these approaches often lack specificity, leading to systemic toxicity, off-target effects, and suboptimal therapeutic outcomes. In this context, the emergence of targeted therapy has revolutionized cancer treatment by focusing on specific molecular pathways involved in tumor growth and progression.[3]

Among targeted therapies, tyrosine kinase inhibitors (TKIs) represent a major breakthrough in oncology. Tyrosine kinases are enzymes that play a critical role in signal transduction pathways regulating cell proliferation, differentiation, metabolism, and apoptosis.[4] TKIs function by selectively inhibiting aberrant kinase activity, thereby blocking downstream signaling pathways essential for tumor survival

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and growth. Clinically, TKIs have demonstrated remarkable success in the management of various malignancies, including chronic myeloid leukemia (CML), non-small cell lung cancer (NSCLC), breast cancer, and renal cell carcinoma (RCC).[5]

However, despite their therapeutic potential, the clinical application of TKIs is significantly limited by several pharmacokinetic and pharmacodynamic challenges. A large proportion of TKIs belong to Biopharmaceutics Classification System Class II or IV, characterized by poor aqueous solubility and low oral bioavailability.[6] Their hydrophobic nature leads to erratic absorption profiles and high inter-individual variability. In addition, extensive first-pass metabolism and efflux by transporters such as P-glycoprotein further reduce systemic drug availability.[7] These limitations often necessitate higher dosing, which in turn increases the risk of adverse effects [Figure 1].

Another major challenge associated with TKI therapy is the development of drug resistance, which can be either primary (intrinsic) or acquired. Resistance mechanisms include mutations in kinase domains, activation of alternative signaling pathways, drug efflux, and tumor microenvironment-mediated protection.[8] This significantly compromises long-term therapeutic efficacy and remains a critical barrier in cancer management. Furthermore, many TKIs exhibit dose-limiting toxicities such as hepatotoxicity, cardiotoxicity, and dermatological adverse effects, which further complicate treatment regimens.[9]

To overcome these limitations, considerable research efforts have been directed toward the development of advanced drug delivery systems. Among these, nanostructured lipid carriers (NLCs) have emerged as a promising platform for improving the delivery of poorly soluble anticancer drugs, including TKIs.[10] NLCs are second-generation lipid nanoparticles composed of a blend of solid and liquid lipids, designed to enhance drug loading capacity, improve stability, and provide controlled release. Their biocompatibility, ability to enhance solubility, and potential for targeted delivery make them highly suitable for TKI formulation.[11]

In recent years, the integration of artificial intelligence (AI) in pharmaceutical development has further accelerated the optimization of such nanocarrier systems. AI-driven approaches enable predictive modeling, formulation optimization, and efficient screening of excipients, thereby reducing development time and improving formulation performance.[12] Therefore, the convergence of targeted therapy, nanotechnology, and AI represents a transformative approach in modern oncology, offering the potential to overcome existing limitations and improve therapeutic outcomes of TKIs.

TKIs

However, genetic mutations, amplifications, and chromosomal rearrangements often result in constitutive activation of these kinases, leading to uncontrolled proliferation, evasion of apoptosis, angiogenesis, and metastasis. TKIs are rationally designed small molecules that inhibit these aberrant kinases, thereby suppressing tumor growth at the molecular level.[13]

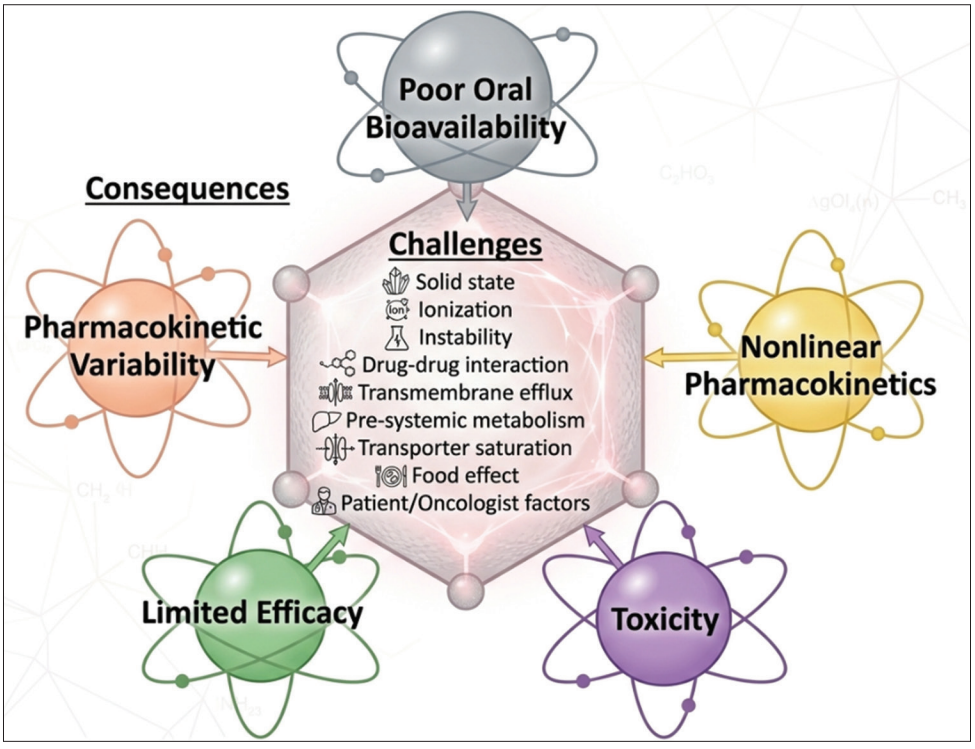

Figure 1: Schematic representation of the challenges associated with poor oral bioavailability and their pharmacological consequences

Classification of TKIs

Epidermal growth factor receptor (EGFR) inhibitors

EGFR is a transmembrane receptor tyrosine kinase (RTKs) belonging to the ErbB family and plays a crucial role in regulating epithelial cell growth and survival. Mutations and overexpression of EGFR are commonly observed in NSCLC, glioblastoma, and colorectal cancers.[14] EGFR inhibitors function by blocking ATP binding at the intracellular kinase domain, thereby preventing receptor autophosphorylation and downstream signaling activation.

First-generation EGFR inhibitors such as gefitinib and erlotinib are reversible inhibitors, while second-generation agents like afatinib form irreversible covalent bonds with the receptor. Third-generation inhibitors such as osimertinib are specifically designed to overcome resistance mutations (e.g., T790M mutation). Despite their clinical success, resistance development and dermatological toxicities remain major challenges.[15]

BCR-ABL TKIs

The BCR-ABL fusion protein results from the Philadelphia chromosome translocation and is the hallmark of CML. This constitutively active kinase drives uncontrolled proliferation of hematopoietic cells. Imatinib, the first clinically successful TKI, revolutionized CML treatment by selectively inhibiting BCR-ABL kinase activity.[16]

Subsequent generations of inhibitors, such as dasatinib and nilotinib, were developed to overcome resistance associated with point mutations in the kinase domain. Ponatinib, a third-generation inhibitor, is effective against the T315I mutation, which confers resistance to earlier drugs. These agents have significantly improved survival outcomes in leukemia patients, although long-term therapy may still be associated with resistance and adverse effects.[17]

Vascular endothelial growth factor receptor (VEGFR) inhibitors

VEGFR plays a central role in tumor angiogenesis by promoting the formation of new blood vessels that supply nutrients and oxygen to tumors. Overexpression of VEGF signaling is a hallmark of many solid tumors, including RCC, hepatocellular carcinoma (HCC), and colorectal cancer.[18]

Anaplastic lymphoma kinase (ALK) inhibitors

ALK gene rearrangements are implicated in a subset of NSCLC and certain lymphomas. Crizotinib was the first ALK inhibitor approved for clinical use, demonstrating significant efficacy in ALK-positive lung cancer patients. However, resistance develops rapidly due to secondary mutations and poor central nervous system (CNS) penetration.

Second- and third-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib have improved potency, selectivity, and CNS activity. These agents are now widely used in advanced-stage lung cancer, significantly improving progression-free survival.[19]

Multi-targeted TKIs

Multi-targeted TKIs inhibit multiple signaling pathways simultaneously, making them effective against heterogeneous tumors with complex signaling networks. Agents such as lenvatinib, regorafenib, and cabozantinib target a combination of VEGFR, FGFR, RET, and other kinases.

These drugs are particularly useful in cancers where multiple pathways contribute to tumor progression. However, their lack of selectivity often results in increased toxicity, necessitating careful dose optimization and monitoring.[20]

Cyclin-dependent kinase (CDK) inhibitors

CDKs regulate cell cycle progression, and their dysregulation is a hallmark of cancer. CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib are widely used in hormone receptor-positive breast cancer.[21]

Mechanism of action of TKIs

Tyrosine kinases function by transferring phosphate groups from ATP to tyrosine residues on target proteins, thereby activating intracellular signaling cascades. These cascades include pathways such as PI3K/AKT, RAS/RAF/MEK/ERK, and JAK/STAT, all of which contribute to tumor cell survival and proliferation. Mechanism of action of TKIs targeting RTKs. The binding of growth factors to RTKs such as EGFR, VEGFR, PDGFR, ABL, and SRC activates downstream signaling cascades, including MAPK, JAK/STAT, and PI3K/AKT pathways, which regulate cell proliferation, angiogenesis, and metastasis.[22] TKIs competitively inhibit ATP binding at the kinase domain, thereby blocking receptor activation and subsequent intracellular signaling [Figure 2].

TKIs inhibit these processes through multiple mechanisms

- ATP-competitive inhibition: Most TKIs bind to the ATP-binding pocket of the kinase domain, preventing phosphorylation and downstream signaling.
- Allosteric inhibition: Some TKIs bind to sites other than the ATP-binding region, inducing conformational changes that inactivate the enzyme.
- Irreversible inhibition: Certain TKIs form covalent bonds with cysteine residues in the kinase domain, leading to prolonged inhibition.[23]

Based on binding modes, TKIs are classified as:

- Type I inhibitors: Bind active kinase conformation
- Type II inhibitors: Bind inactive conformation
- Type III/IV inhibitors: Allosteric inhibitors.

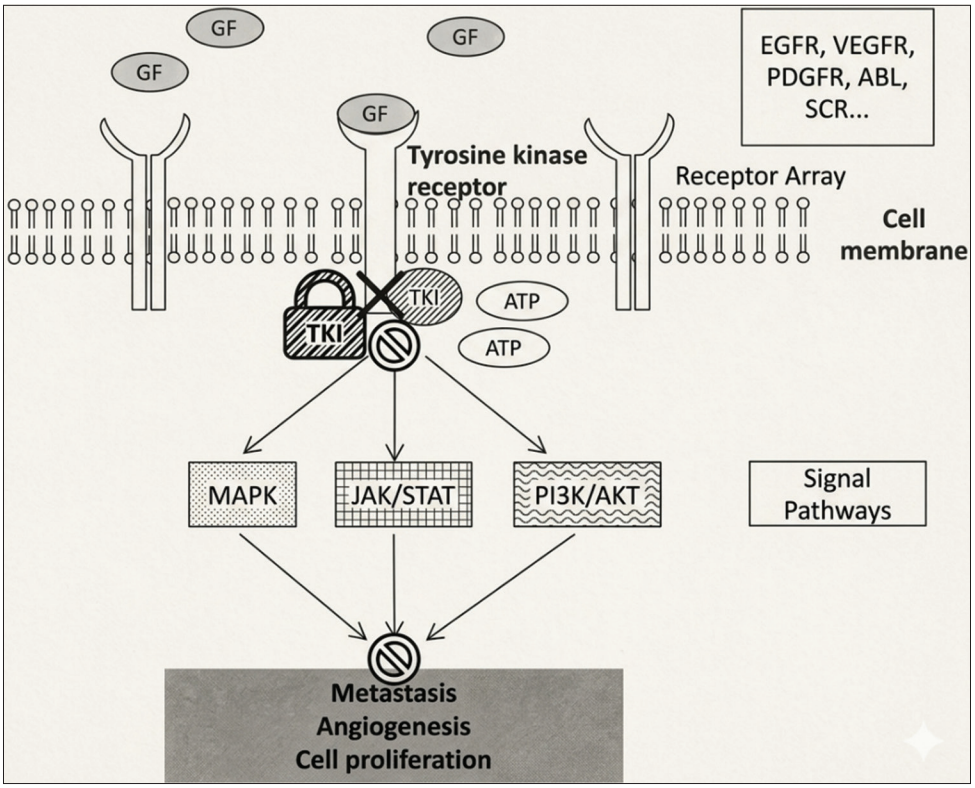

Figure 2: Mechanism of tyrosine kinase inhibitors

The net effect of these interactions is:

- Inhibition of tumor cell proliferation
- Induction of apoptosis
- Suppression of angiogenesis
- Reduced metastatic potential.

Clinical applications of TKIs

TKIs have significantly improved therapeutic outcomes across a wide range of cancers and are now integral components of standard treatment protocols.

- Hematological malignancies: TKIs such as imatinib have transformed CML from a fatal disease into a manageable chronic condition. Long-term remission is achievable in many patients, demonstrating the success of targeted therapy.[24]
- NSCLC: EGFR and ALK inhibitors are widely used in NSCLC patients harboring specific genetic mutations. Personalized medicine approaches involving biomarker testing have enabled the selection of appropriate TKIs, improving survival rates and reducing unnecessary toxicity.[25]
- Breast cancer: CDK4/6 inhibitors, in combination with hormonal therapy, have become the standard of care for hormone receptor-positive breast cancer. These agents significantly improve progression-free survival and delay disease progression.[26]
- RCC: VEGFR inhibitors such as sunitinib and pazopanib are commonly used in RCC, where angiogenesis plays a critical role in tumor progression. These agents have demonstrated improved survival outcomes compared to conventional therapies.[27]
- HCC: Sorafenib and regorafenib are approved for advanced liver cancer and function by inhibiting multiple kinases involved in tumor growth and angiogenesis.[28]
- Thyroid cancer and other solid tumors: Lenvatinib and other multi-target TKIs are used in thyroid cancers and other malignancies where multiple signaling pathways contribute to disease progression.[29]

CHALLENGES IN ORAL AND SYSTEMIC DELIVERY OF TKIs

The clinical effectiveness of TKIs is profoundly influenced by their pharmacokinetic limitations, which arise from intrinsic physicochemical properties as well as complex biological barriers. Despite their high specificity and potency, the majority of TKIs exhibit suboptimal absorption and systemic exposure, thereby restricting their therapeutic potential. These limitations are multifactorial, involving poor aqueous solubility, extensive first-pass metabolism, efflux transport, low and variable bioavailability, dose-dependent toxicity, and the emergence of drug resistance.[30]

Furthermore, the solubility of many TKIs is highly pH-dependent, with greater solubility observed in acidic gastric conditions but a marked decrease in solubility at intestinal pH. This often results in supersaturation followed by rapid precipitation, thereby reducing the effective concentration of

the drug available for absorption. Consequently, variability in gastrointestinal pH, food intake, and physiological conditions further exacerbate inconsistencies in drug exposure.[31]

The situation is further complicated by the involvement of efflux transporters such as P-glycoprotein and breast cancer resistance protein, which actively transport drug molecules back into the intestinal lumen. The combined effect of metabolic degradation and efflux transport constitutes a formidable barrier to drug absorption, often described as a "dual barrier effect," which significantly limits oral bioavailability.[32]

As a result, achieving optimal plasma concentrations becomes challenging, often necessitating higher doses or therapeutic drug monitoring.[33]

However, increasing the dose to compensate for poor bioavailability introduces another significant issue dose-related toxicity. TKIs are associated with a narrow therapeutic index, where small variations in plasma concentration can lead to adverse effects. Off-target inhibition of kinases and interactions with non-specific biological pathways result in toxicities such as hepatotoxicity, cardiotoxicity, gastrointestinal disturbances, and dermatological reactions.[34]

LIPID-BASED DRUG DELIVERY SYSTEMS

Lipid-based drug delivery systems have emerged as a promising strategy to address the limitations associated with poorly soluble drugs such as TKIs. These systems are designed to enhance drug solubilization, improve absorption, and facilitate targeted delivery by leveraging the physiological pathways of lipid digestion and transport. The fundamental principle underlying lipid-based formulations lies in their ability to maintain drugs in a solubilized state within the gastrointestinal tract, thereby enhancing dissolution and promoting absorption across biological membranes.[35]

On oral administration, lipid-based systems undergo enzymatic digestion by pancreatic lipases, resulting in the formation of monoglycerides and free fatty acids. These digestion products interact with bile salts to form mixed micelles, which serve as carriers for solubilized drug molecules. This process significantly enhances the transport of lipophilic drugs across the intestinal epithelium. Moreover, highly lipophilic drugs can associate with chylomicrons and enter the lymphatic system, thereby bypassing hepatic first-pass metabolism and improving systemic availability.[36]

Several types of lipid-based delivery systems have been developed, each with distinct structural and functional characteristics. Solid lipid nanoparticles (SLNs) represent one of the earliest lipid-based systems and consist of a solid lipid core stabilized by surfactants. While SLNs offer advantages such as controlled drug release and protection against degradation, their highly ordered crystalline structure often leads to drug expulsion during storage.[37] Other lipid-based systems include liposomes and nanoemulsions. Liposomes are vesicular structures composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs, offering versatility in drug delivery. However, their clinical application is sometimes limited by stability issues and rapid clearance by the reticuloendothelial system. Nanoemulsions, on the other hand, are thermodynamically stable systems that enhance drug solubilization and absorption but may require high surfactant concentrations, which can pose toxicity concerns.[38]

Overall, lipid-based drug delivery systems offer significant advantages over conventional formulations, including enhanced solubility, improved bioavailability, protection from degradation, and the potential for targeted delivery. These systems also have the ability to modulate drug release and reduce toxicity, making them particularly suitable for the delivery of TKIs.

NLCS: CONCEPT AND DESIGN

NLCs represent a significant advancement in lipid-based drug delivery systems, specifically designed to overcome the limitations of SLNs. NLCs are composed of a combination of solid and liquid lipids, forming a heterogeneous lipid matrix with reduced crystallinity.[11] This structural modification introduces imperfections within the lipid lattice, which enhances drug loading capacity and prevents drug expulsion during storage [Figure 3].

The design of NLCs is based on the principle of creating a less ordered lipid matrix that can accommodate higher amounts of drug molecules. The solid lipid component provides structural integrity and contributes to sustained drug release, while the liquid lipid component disrupts the crystalline arrangement, increasing the free volume within the matrix.[10] Surfactants play a crucial role in stabilizing the nanoparticle system, reducing surface tension, and preventing aggregation. The interplay between these components determines the physicochemical properties, stability, and performance of the NLC formulation.

Based on their internal structure, NLCs can be classified into different types, including imperfect, amorphous, and multiple types. Imperfect-type NLCs are characterized by structural defects in the lipid matrix, which create spaces for drug incorporation. Amorphous-type NLCs are designed to prevent crystallization altogether, thereby eliminating the risk of drug expulsion and improving long-term stability.[39]

FORMULATION STRATEGIES FOR TKI-LOADED NLCS

The successful development of NLCs for TKIs requires a rational and systematic formulation approach that integrates

Figure 3: Comparative illustration of structural organization and drug loading behavior in solid lipid nanoparticles and nanostructured lipid carriers

physicochemical properties of the drug with lipid matrix design and processing parameters.[40]

Selection of lipids and surfactants

Surfactants are equally important, as they stabilize the nanoparticle system by reducing interfacial tension and preventing aggregation. Commonly used surfactants include polysorbates (Tween 80), poloxamers, and lecithin. The choice and concentration of surfactant influence particle size, polydispersity index, and zeta potential. A balanced surfactant system ensures the formation of uniform nanoparticles with high physical stability while minimizing toxicity. In some formulations, a combination of surfactants is used to achieve optimal stabilization through synergistic effects.[41]

Drug incorporation techniques

Efficient incorporation of TKIs into the lipid matrix is essential for achieving high entrapment efficiency and controlled drug release. The method of drug incorporation depends on the physicochemical properties of the drug and the composition of the lipid system. In general, TKIs are incorporated into NLCs using techniques such as hot homogenization, cold homogenization, solvent emulsification, or ultrasonication.[42]

In hot homogenization, the drug is dissolved in the molten lipid phase, followed by dispersion in an aqueous surfactant solution at the same temperature. The distribution of the drug within the NLC matrix can follow different models, including homogeneous matrix distribution, drug-enriched shell, or drug-enriched core. These models significantly influence drug release kinetics. For instance, a drug-enriched shell may result in an initial burst release, whereas a homogeneous matrix provides sustained release. Therefore, controlling the incorporation technique is essential for tailoring the release profile of TKIs.[43]

Solubility enhancement approaches

The use of co-solvents and solubilizers during formulation can further enhance drug incorporation. In addition, amorphization of the drug within the lipid matrix reduces crystallinity, thereby improving dissolution behavior. The inclusion of liquid lipids plays a significant role in this context, as they disrupt the ordered crystalline structure of solid lipids, creating a more accommodating environment for drug molecules.[10]

Surface modification and functionalization of NLCs

Surface modification of NLCs is a powerful strategy to enhance their biological performance, particularly in terms of circulation time, targeting efficiency, and cellular uptake. One of the most widely used approaches is PEGylation, which involves the attachment of polyethylene glycol (PEG) chains to the surface of nanoparticles. PEGylation provides a hydrophilic steric barrier that reduces recognition by the reticuloendothelial system, thereby prolonging systemic circulation and enhancing accumulation at tumor sites via the enhanced permeability and retention (EPR) effect.[44]

In addition to PEGylation, active targeting can be achieved by conjugating specific ligands to the surface of NLCs. These ligands may include antibodies, peptides, folic acid, or other molecules that recognize overexpressed receptors

on cancer cells. Such targeted systems facilitate receptor-mediated endocytosis, leading to increased intracellular drug concentration and improved therapeutic efficacy.[45]

METHODS OF PREPARATION OF NLCS

The preparation method plays a decisive role in determining the physicochemical characteristics, stability, and performance of NLCs. Parameters such as particle size, polydispersity index, drug loading, and release behavior are highly dependent on the selected manufacturing technique. Therefore, the choice of preparation method must be aligned with the physicochemical properties of the drug, lipid composition, and intended application.[46]

High-pressure homogenization (HPH)

HPH is one of the most widely employed and scalable techniques for the production of NLCs. This method involves forcing a coarse pre-emulsion through a narrow gap under high pressure (typically 100–2000 bar), resulting in intense shear stress and cavitation forces that reduce particle size to the nanometer range.[47]

The major advantages of HPH include its industrial scalability, reproducibility, and ability to produce narrow particle size distributions. However, limitations such as high energy input, potential degradation of thermolabile drugs, and equipment cost must be considered during formulation development [Figure 4].

Ultrasonication technique

Ultrasonication is a widely used laboratory-scale technique that utilizes high-frequency sound waves to generate cavitation forces, leading to the breakdown of lipid particles into nanoscale droplets. In this method, the lipid phase is first melted and dispersed in an aqueous surfactant solution to form a coarse emulsion. The application of ultrasonic energy induces the formation and collapse of microbubbles, generating localized high shear forces that reduce particle size.

This technique is particularly advantageous due to its simplicity, cost-effectiveness, and suitability for small-scale production. It allows rapid preparation of NLCs with relatively uniform particle sizes. However, ultrasonication has certain limitations, including potential contamination from the probe, limited scalability, and difficulty in achieving consistent results at larger production volumes.[48] In addition, prolonged exposure to ultrasonic energy may lead to degradation of sensitive drug molecules [Figure 5].

Solvent emulsification-evaporation method

This method offers precise control over particle size and drug loading, as the drug is molecularly dispersed in the lipid phase prior to nanoparticle formation. It is particularly beneficial for heat-sensitive drugs, as it avoids exposure to high temperatures. However, the use of organic solvents introduces concerns related to toxicity, residual solvent content, and environmental impact.[49] Therefore, complete solvent removal and regulatory compliance are critical considerations in this approach [Figure 6].

Microemulsion technique

The microemulsion technique involves the formation of a thermodynamically stable microemulsion composed of lipid, surfactant, co-surfactant, and water. The lipid phase containing the drug is mixed with surfactants to form a clear microemulsion at elevated temperatures. This system is then rapidly dispersed in cold water under stirring, resulting in the formation of NLCs due to lipid crystallization [Figure 7].

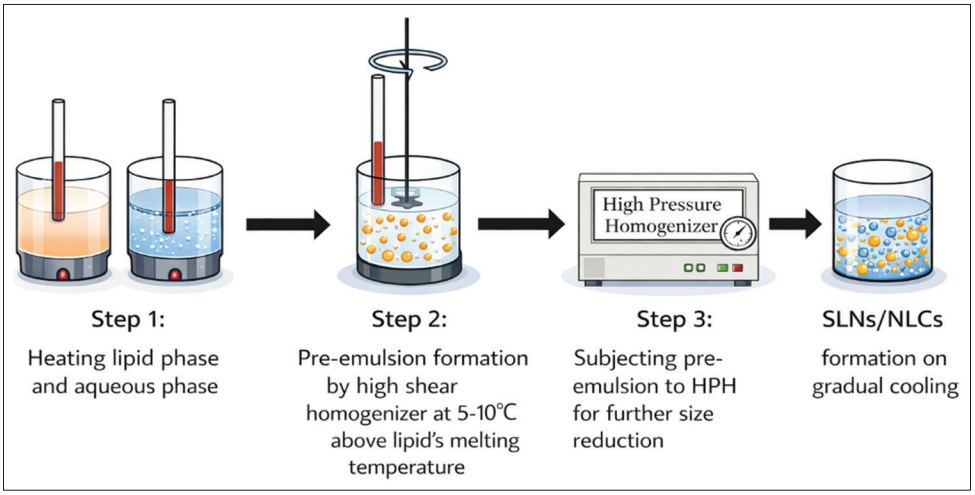

Figure 4: High-pressure homogenization

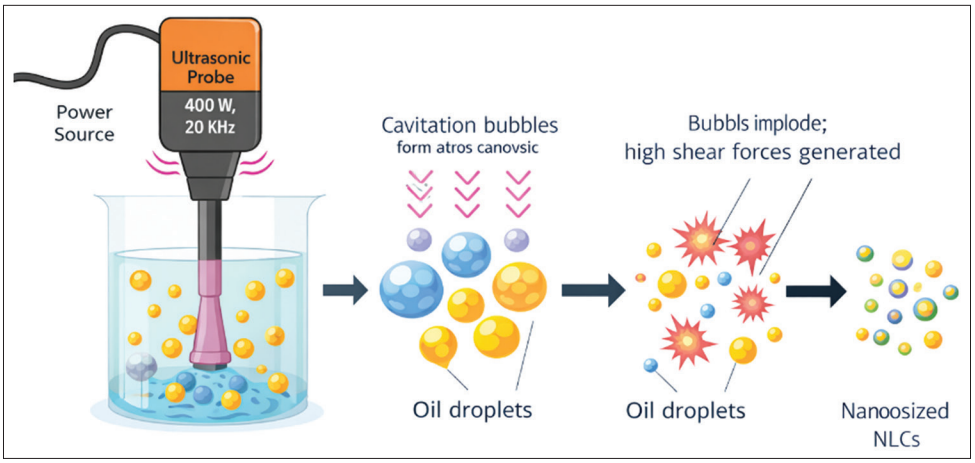

Figure 5: Ultrasonication technique

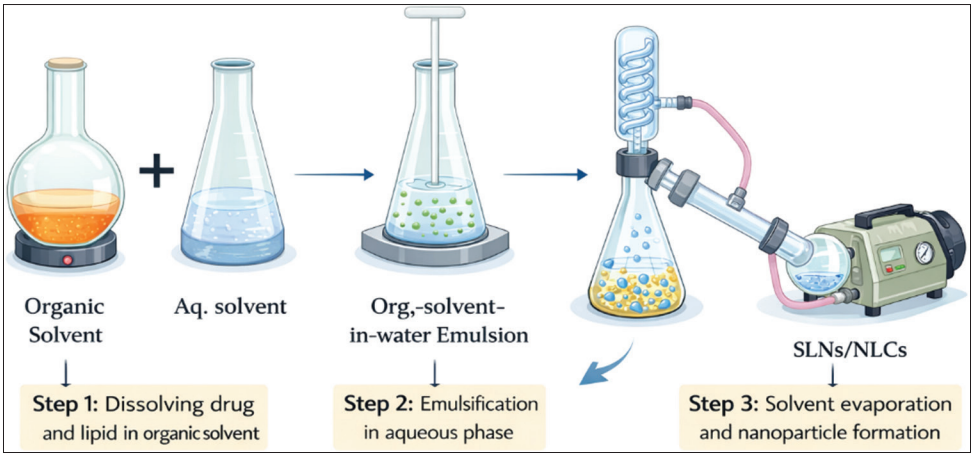

Figure 6: Solvent emulsification–evaporation method

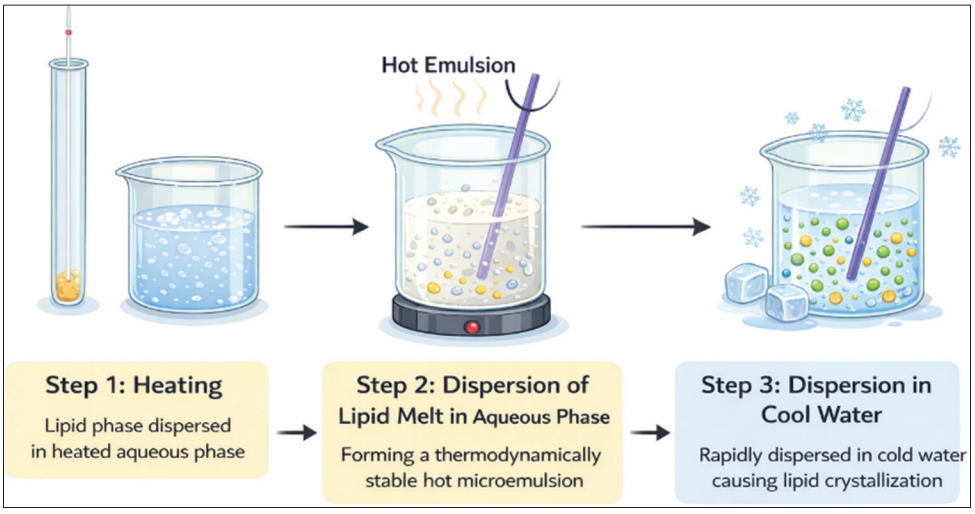

Figure 7: Microemulsion technique

OPTIMIZATION OF NLC FORMULATIONS

The optimization of NLC formulations is a critical step in ensuring consistent product quality, enhanced therapeutic performance, and successful translation from laboratory to clinical application. Given the complex interplay between formulation variables and process parameters, a systematic and science-based approach is essential.[50] In recent years, the adoption of the quality by design (QbD) framework has transformed the development of lipid-based nanocarriers by emphasizing a thorough understanding of formulation and process dynamics rather than reliance on empirical methods [Figure 8].

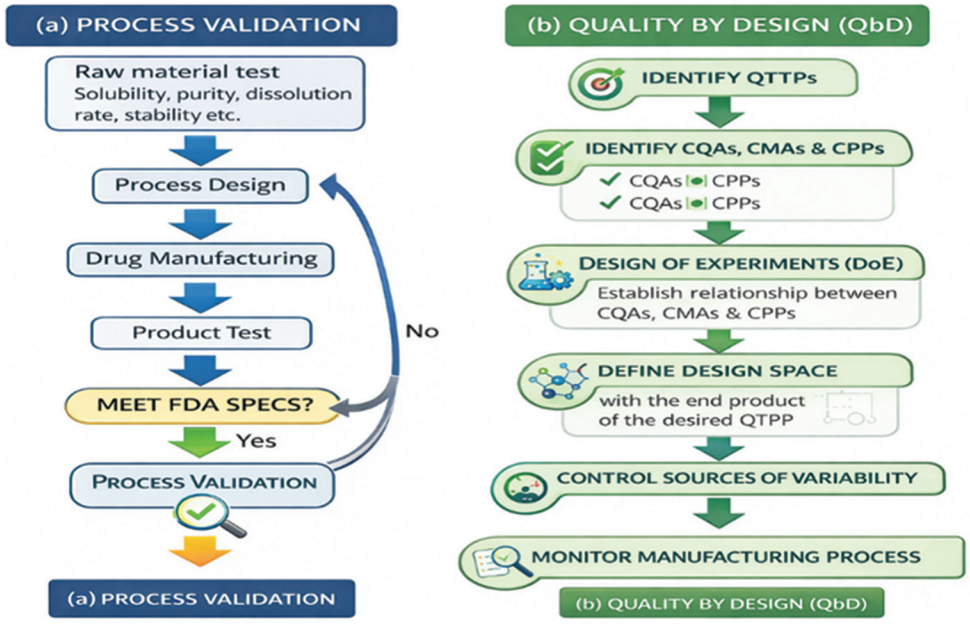

Figure 8: Optimization of nanostructured lipid carrier

QbD approach

QbD represents a paradigm shift in pharmaceutical development, focusing on designing quality into the product from the earliest stages of formulation. In the context of NLC-based delivery of TKIs, QbD begins with the definition of the quality target product profile, which outlines the desired characteristics of the final formulation, including particle size, drug loading, release kinetics, stability, and route of administration.[50]

A systematic risk assessment is subsequently performed to identify factors that may influence product quality. This is followed by establishing a relationship between formulation variables and critical quality attributes (CQAs), such as particle size distribution, zeta potential, and entrapment efficiency. By applying QbD principles, researchers can develop robust formulations with reduced variability and improved reproducibility. Furthermore, QbD facilitates regulatory acceptance by providing a comprehensive understanding of the formulation design space and ensuring consistent product performance throughout its lifecycle.[51]

Critical material attributes (CMAs)

CMAs refer to the inherent properties of raw materials that significantly impact the quality of NLC formulations. These attributes include the physicochemical characteristics of lipids, surfactants, and the drug molecule itself. Parameters such as lipid melting point, chain length, degree of saturation, and solubilization capacity directly influence the internal structure of NLCs and their ability to encapsulate TKIs effectively.[52]

Critical process parameters (CPPs)

CPPs are the operational variables that influence the manufacturing process and ultimately determine the quality of the final NLC formulation. These include homogenization pressure, temperature, mixing speed, sonication time, and cooling rate. Each of these parameters plays a crucial role in controlling particle size, polydispersity, and drug encapsulation efficiency.[53]

Design of experiments (DoE)

DoE is a statistical and mathematical tool that enables systematic evaluation of multiple variables and their interactions. Within the QbD framework, DoE plays a central role in optimizing NLC formulations by identifying critical factors and establishing their influence on key responses such as particle size, entrapment efficiency, and drug release profile.

Experimental designs such as factorial design, Box-Behnken design, and central composite design are commonly employed to construct predictive models. These models allow the identification of optimal formulation conditions and the establishment of a design space within which the formulation consistently meets predefined quality criteria. The use of DoE significantly reduces experimental workload while enhancing the robustness and predictability of the formulation process.[54]

TARGETED DRUG DELIVERY USING NLCS

Targeted drug delivery represents a major advancement in nanomedicine, enabling selective accumulation of therapeutic

agents at the tumor site while minimizing systemic toxicity. NLCs offer a versatile platform for targeted delivery of TKIs due to their nanoscale size, biocompatibility, and modifiable surface properties.

Passive targeting (EPR effect)

Passive targeting relies on the EPR effect, a phenomenon observed in tumor tissues characterized by leaky vasculature and impaired lymphatic drainage. NLCs, typically in the size range of 50–200 nm, can preferentially accumulate in tumor tissues through these permeable blood vessels.[55]

Active targeting (ligand-mediated delivery)

Active targeting involves the functionalization of NLC surfaces with ligands that can specifically bind to receptors overexpressed on cancer cells. These ligands may include antibodies, peptides, folic acid, transferrin, or aptamers. On binding to target receptors, the NLCs undergo receptor-mediated endocytosis, resulting in enhanced intracellular drug delivery.[56]

Stimuli-responsive systems

Stimuli-responsive NLCs represent an advanced strategy in targeted drug delivery, where drug release is triggered by specific internal or external stimuli. Internal stimuli include pH variations, enzymatic activity, and redox gradients, while external stimuli may involve temperature, light, or magnetic fields.[57]

Recent advances in NLC-based TKI delivery

Recent years have witnessed significant advancements in NLC-based delivery systems, driven by the need to overcome resistance, enhance therapeutic efficacy, and enable personalized medicine approaches.

Co-delivery systems

Co-delivery systems involve the simultaneous encapsulation of multiple therapeutic agents within a single NLC formulation. This approach allows synergistic interactions between drugs, improving treatment outcomes and reducing the likelihood of resistance. For example, the co-delivery of a TKI with a chemotherapeutic agent or siRNA can target multiple pathways simultaneously, enhancing anticancer efficacy.[58]

Combination therapy

Combination therapy using NLCs enables the integration of different therapeutic modalities, such as chemotherapy, immunotherapy, and targeted therapy. By delivering multiple agents in a controlled manner, NLCs can enhance therapeutic synergy while minimizing systemic toxicity. This strategy is particularly useful in overcoming tumor heterogeneity and resistance mechanisms.[59]

Smart nanocarriers

Smart NLCs incorporate advanced functionalities such as stimuli responsiveness, self-regulation, and real-time monitoring. These systems can adapt to physiological conditions and release drugs in a controlled manner based on environmental triggers. Integration with AI and nanotechnology further enhances the design and optimization of such systems, paving the way for precision medicine.[60]

CLINICAL TRANSLATION AND REGULATORY CONSIDERATIONS

Despite promising preclinical outcomes, the clinical translation of NLC-based TKI delivery systems remains challenging due to manufacturing, regulatory, and safety considerations.

Scale-up challenges

Scaling up NLC production from laboratory to industrial level requires maintaining consistency in particle size, drug loading, and stability. Variability in process parameters, equipment limitations, and batch-to-batch inconsistencies pose significant challenges. Advanced manufacturing techniques such as HPH and continuous processing are being explored to address these issues.[61]

Regulatory guidelines (Food and Drug Administration/European Medicines Agency [FDA/EMA] considerations)

Regulatory agencies such as the U.S. FDA and EMA have established guidelines for the development of nanomedicines, emphasizing safety, quality, and efficacy. Comprehensive characterization of nanocarriers, including particle size, surface properties, and stability, is required for regulatory approval.[62]

Safety and toxicity considerations

The safety profile of NLCs is influenced by their composition, size, and surface characteristics. Although lipid-based systems are generally considered biocompatible, potential concerns include:

- Cytotoxicity of surfactants
- Accumulation in non-target tissues
- Immunogenic responses.

Comprehensive *in vitro* and *in vivo* studies are essential to evaluate toxicity, biodistribution, and long-term safety. Understanding these factors is crucial for successful clinical translation and commercialization of NLC-based TKI delivery systems.[63]

AI IN THE DESIGN AND OPTIMIZATION OF NLC-BASED TKI DELIVERY SYSTEMS

AI has emerged as a transformative paradigm in pharmaceutical sciences, fundamentally reshaping the design, optimization, and evaluation of complex drug delivery systems such as NLCs. In the context TKIs, which present multifaceted formulation challenges, including poor solubility, variable bioavailability, and resistance development, AI-driven methodologies provide a data-centric and predictive framework that surpasses traditional empirical approaches. Conventional formulation strategies, often reliant on iterative trial-and-error experimentation, are time-consuming and inefficient in capturing nonlinear relationships among formulation variables. AI enables systematic exploration of multidimensional datasets, facilitating rapid and rational formulation development.[64]

Machine learning (ML) models in NLC formulation design

ML algorithms play a central role in modeling the complex relationships between formulation variables and CQAs. Supervised learning techniques such as artificial neural networks, support vector machines, and random forests are widely applied to predict key parameters, including particle size, polydispersity index, zeta potential, drug loading, and release kinetics.[65]

AI-based prediction of drug–lipid compatibility

One of the critical challenges in NLC formulation is the selection of suitable lipid matrices that ensure optimal drug solubilization and stability. AI-based approaches utilize molecular descriptors such as lipophilicity, molecular weight, hydrogen bonding potential, and polar surface area to predict drug–lipid compatibility.

Quantitative structure–property relationship and quantitative structure–activity relationship models are increasingly employed to estimate drug solubility within lipid systems and to predict formulation behavior. These *in silico* methods allow rapid screening of multiple lipid candidates, significantly reducing experimental workload and enabling rational formulation design.[63]

Integration of AI with QbD and DoE

The integration of AI with QbD frameworks represents a significant advancement in pharmaceutical formulation optimization. While DoE provides a structured methodology for evaluating formulation variables, its predictive capability is often limited by linear assumptions. AI models enhance DoE by capturing nonlinear interactions and complex dependencies among variables.

By combining AI with DoE-generated datasets, researchers can develop predictive models that define a robust design space within which the formulation consistently meets predefined quality criteria. This hybrid approach improves formulation robustness, reduces variability, and aligns with regulatory expectations for systematic product development.[66]

In silico modeling of drug release and pharmacokinetics

AI-driven computational models are increasingly used to simulate drug release behavior and pharmacokinetic profiles of NLC formulations. These models integrate mechanistic understanding of drug diffusion, lipid matrix degradation, and physiological conditions to predict *in vivo* performance.

Physiologically based pharmacokinetic modeling, when combined with AI, enables the prediction of drug absorption, distribution, metabolism, and elimination. Such models facilitate the translation of preclinical findings to clinical outcomes, reducing the need for extensive *in vivo* studies and accelerating drug development timelines.[67]

AI in personalized nanomedicine for TKI therapy

The application of AI in personalized medicine represents a paradigm shift in cancer therapy. By analyzing patient-specific data such as genetic profiles, tumor characteristics, and metabolic parameters, AI algorithms can guide the design of customized NLC formulations tailored to individual patient needs.[68]

Deep learning and advanced data analytics in formulation development

Deep learning techniques, including CNNs and recurrent neural networks, extend the capabilities of traditional ML by enabling advanced pattern recognition in large and complex datasets. These models can identify hidden correlations and extract meaningful features from experimental data, facilitating improved formulation design and optimization.

In addition, deep learning approaches can be applied to imaging-based characterization of nanoparticles, enabling automated analysis of morphology, size distribution, and structural properties. This integration of data analytics with experimental techniques enhances the overall efficiency of formulation development.[69]

Automation and AI-driven formulation platforms

The integration of AI with automation and robotics has led to the development of autonomous formulation platforms capable of iterative optimization. These systems utilize real-time data analysis and feedback mechanisms to continuously refine formulation parameters.

Such closed-loop systems significantly reduce human intervention, improve reproducibility, and accelerate the development process. The combination of AI, robotics, and high-throughput screening represents a significant advancement toward fully automated pharmaceutical development.[70]

CLINICALLY APPROVED TKIs: DRUG-SPECIFIC PROPERTIES AND FORMULATION CHALLENGES

TKIs are predominantly small, lipophilic molecules with complex pharmacokinetic profiles. A detailed understanding of their physicochemical and biopharmaceutical parameters, such as molecular weight, log P, solubility, bioavailability, and half-life, is essential for rational formulation design. Examples are Imatinib, Dasatinib, Nilotinib, and Gefitinib.

FUTURE PERSPECTIVES

The future of TKI delivery is expected to be shaped by the convergence of nanotechnology, AI, and precision medicine. While NLCs have demonstrated significant potential in improving the solubility and bioavailability of TKIs, further advancements are required to fully realize their clinical applicability. One of the key directions involves the development of multifunctional and stimuli-responsive nanocarriers capable of delivering drugs in a controlled and site-specific manner. The incorporation of pH-sensitive, enzyme-responsive, and redox-responsive elements into NLCs can enable precise drug release within the tumor microenvironment, thereby enhancing therapeutic efficacy while minimizing systemic toxicity.

Another promising area is the integration of active targeting strategies, where NLCs are functionalized with ligands such as antibodies, peptides, or small molecules that recognize tumor-specific receptors. This approach can significantly improve cellular uptake and intracellular drug accumulation, particularly in resistant cancer cells. Additionally, the design of co-delivery systems capable of simultaneously delivering TKIs along with chemotherapeutic agents, gene therapies, or immunomodulators is expected to address tumor heterogeneity and overcome resistance mechanisms.

The application of AI in formulation development is anticipated to revolutionize the field by enabling predictive modeling, rapid optimization, and personalized drug delivery. AI-driven platforms can analyze large datasets to identify optimal formulation parameters, predict drug-excipient interactions, and simulate *in vivo* behavior, thereby reducing development time and cost. Furthermore, the integration of AI with high-throughput screening and automated formulation systems may lead to the emergence of fully autonomous drug development pipelines.

From a translational perspective, efforts must be directed toward improving scalability, reproducibility, and regulatory compliance of NLC formulations. Advances in manufacturing technologies, such as continuous processing and microfluidics, are expected to facilitate large-scale production with consistent quality. In addition, the establishment of standardized regulatory guidelines for nanomedicines will be crucial for accelerating clinical approval.

Overall, the future of NLC-based TKI delivery lies in the development of smart, targeted, and patient-specific nanocarrier systems, supported by advances in computational modeling and regulatory science. These innovations have the potential to significantly improve therapeutic outcomes and redefine the landscape of cancer treatment.

CONCLUSION

TKIs have significantly transformed the management of various cancers by providing a targeted approach to therapy. However, their clinical effectiveness is often limited by inherent physicochemical and pharmacokinetic challenges, including poor solubility, low bioavailability, metabolic instability, and the emergence of drug resistance. These limitations highlight the need for advanced drug delivery strategies capable of enhancing therapeutic performance.

NLCs have emerged as a promising platform for addressing these challenges due to their ability to improve drug solubility, enhance bioavailability, enable controlled release, and facilitate targeted delivery. The flexibility in their design allows for the incorporation of various functional modifications, including surface engineering and stimuli-responsive elements, further enhancing their therapeutic potential.

The integration of systematic formulation approaches such as QbD, along with emerging technologies like AI, has further strengthened the development of NLC-based delivery systems. These advancements enable a deeper understanding of formulation variables and their impact on product quality, leading to more robust and efficient drug delivery systems.

Despite these promising developments, challenges related to large-scale manufacturing, regulatory approval, and long-term safety remain to be addressed. Continued research and interdisciplinary collaboration will be essential to overcome

these barriers and facilitate the successful translation of NLC-based systems into clinical practice.

The combination of nanotechnology and targeted therapy represents a powerful strategy for improving the delivery and efficacy of TKIs. With ongoing advancements in formulation science, computational modeling, and regulatory frameworks, NLC-based drug delivery systems are poised to play a pivotal role in the future of cancer therapy.

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