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Application of Design of Experiments (DoE) in the Optimization of Novel Drug Delivery Systems for Cancer Therapy: A Comprehensive Review

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ABSTRACT

Cancer remains a significant global health challenge, accounting for millions of new cases and deaths each year. The limitations of conventional chemotherapy, including systemic toxicity, multidrug resistance, and lack of tumor selectivity, underline the need for innovative treatment approaches. This review emphasizes the critical role of Design of Experiments (DoE) in optimizing cancer drug formulations. By systematically analyzing various input variables, DoE facilitates the development of advanced drug delivery systems such as nanoparticles and liposomes that enhance therapeutic outcomes while minimizing side effects. The integration of DoE with emerging technologies, including machine learning and artificial intelligence, marks a significant advancement in personalized medicine, offering a pathway to tailor therapies to individual patient needs. This synthesis of statistical design principles and innovative technology heralds a promising era in cancer treatment, poised to improve patient outcomes through more effective and targeted therapeutic strategies.

Key words : Design of Experiments, advanced drug delivery, artificial intelligence, Targeted therapeutic strategies, cancer.

INTRODUCTION

Cancer continues to represent one of the foremost challenges to global health, standing as a leading cause of morbidity and mortality. In 2023 alone, an alarming projection of 20 million new cases and 10 million deaths has been recorded, a stark indicator of the urgent need for effective

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treatment strategies in the relentless battle against this complex disease[1].This staggering statistic not only reflects the burden of cancer but also the critical necessity for innovative therapies. Among the myriad of treatment modalities available, chemotherapy has traditionally served as a cornerstone in cancer care. Nevertheless, it is beset by numerous constraints that profoundly undermine its efficacy, including systemic toxicity that can adversely affect patients' overall health, inadequate bioavailability that limits the concentration of the drug at the tumor site, and the daunting challenge of multidrug resistance, complicating cancer management.

Moreover, a significant limitation of standard chemotherapy is its overarching lack of tumor selectivity. This often leads to unintended damage to healthy tissue, resulting in a range of debilitating side effects that can severely diminish patients' quality of life and complicate their treatment journey [2,3].

Conventional chemotherapeutic agents frequently exhibit narrow therapeutic indices, creating a precarious balance between effective therapeutic doses and those that can precipitate severe adverse effects. The indiscriminate distribution of these drugs throughout the body can produce detrimental impacts on vital organs, leading to challenging complications that may discourage patients from complying with their prescribed treatment regimens[4]. In addition to these issues, the risk of acquired resistance looms large as treatment progresses. Cancer cells can adapt and develop resilience over time, resulting in reduced therapeutic efficacy and complicating efforts aimed at achieving long-term remission and improving patient survival rates [5]. These pressing concerns underscore the urgent need for innovative therapeutic strategies and optimized drug delivery systems capable of selectively targeting tumors, increasing drug solubility, enhancing bioavailability, and minimizing adverse effects. These advancements are essential for ensuring that patients can tolerate prolonged treatment courses.

Against this backdrop, formulation science emerges as a pivotal discipline in the quest to advance sophisticated drug delivery systems such as nanoparticles, liposomes, micelles, and solid lipid nanoparticles. Each of these innovative platforms can be elaborately designed to facilitate cancer-specific targeting and controllable release patterns that align with the diverse therapeutic needs of patients[6]. The creation of these sophisticated systems demands a comprehensive understanding of biopharmaceutical properties, as well as intricate insights into how various formulation components interact. However, the pathway toward optimizing these complex systems necessitates a rigorous and systematic statistical approach to precisely identify and adeptly manage critical formulation and process variables that can fundamentally influence the overall effectiveness of treatment.

Design of Experiments (DoE) has emerged as a prominent structured, multivariate statistical tool within the realm of pharmaceutical development. It holds a critical role as an integral component of the Quality by Design (QbD) framework endorsed by regulatory authorities[7,8].By employing DoE, researchers can thoroughly analyze the multifaceted influences of diverse variables and their interactions on crucial formulation outcomes. This comprehensive understanding is essential to the development process, allowing for the optimization of formulations to be conducted more efficiently and effectively. Consequently, the application of DoE not only accelerates the development timeline but also reduces costs while enhancing the overall robustness of anticancer formulations[9].

This review aims to delve into the pivotal significance of DoE in the strategic development and refinement of cutting-edge drug delivery systems specifically tailored for cancer therapy. By exploring case studies and innovative methodologies, we seek to illuminate how the integration of statistical design principles within formulation science can catalyze advancements in the field of oncology. This convergence fosters transformative therapies that enhance patient outcomes and redefine standards of care. The synthesis of these advanced approaches heralds a promising future in cancer treatment, where personalized therapeutics can substantially improve the lives of countless individuals confronting this formidable disease.

Basics of DoE in Pharmaceutical Sciences

Design of Experiments (DoE) serves as a meticulously structured and systematic approach that is indispensable in the realm of pharmaceutical

research and development. This methodology encompasses a comprehensive examination of how various input variables, commonly referred to as factors, relate to their effects on output responses, which can include a broad spectrum of characteristics ranging from chemical properties to biological efficacy of drug formulations. By effectively employing DoE, pharmaceutical scientists are empowered to proficiently screen variables, optimize intricate formulations, and scale up manufacturing processes while scrupulously adhering to Quality by Design (QbD) principles, which champion a science-based methodology to uphold the highest quality standards throughout the development lifecycle[10].

Full Factorial Design

Full factorial design offers an exhaustive experimental framework that investigates the impact of all conceivable combinations of selected factors at varying levels. This method proves particularly advantageous during the preliminary stages of research, as it establishes the foundation for comprehending potential interactions and dependencies among diverse variables. By rigorously probing these interactions, researchers can identify critical factors that significantly influence desired outcomes, thus guiding subsequent undertakings in the formulation process[11].It is imperative to recognize that as the number of factors escalates, the total number of experimental runs required can become increasingly resource-intensive, necessitating meticulous planning and judicious allocation of both time and materials.

Central Composite Design (CCD)

Central Composite Design (CCD) stands out as a highly regarded methodology within the framework of response surface methodologies. This approach artfully intertwines factorial points, center points, and additional axial (star) points, thereby constructing a design space that is either rotatable or nearly rotatable. This thoughtful integration enables researchers to explore a rich array of experimental conditions, allowing for an in-depth examination of the quadratic interactions among varying variables. CCD is particularly adept at identifying and optimizing formulations where the resultant responses manifest curvature, thereby equipping scientists to develop polynomial models that accurately predict outcomes based on diverse combinations of factors[12]. This capability significantly enhances the comprehension of interactions and influences among variables, leading to a more robust foundation for formulating successful products.

Box–Behnken Design (BBD)

Box-Behnken Design (BBD) serves as a strategic alternative to CCD, especially in situations where extreme levels of factors might yield unstable or inadequately reliable results. This design is meticulously optimized to require fewer experimental runs, making it an inherently more efficient choice for resource allocation. By deliberately eschewing extreme corner points, which can introduce unwanted variability, BBD is recognized as a safer protocol for pharmaceutical formulations, thereby ensuring consistency and reliability throughout the experimental process. Through this carefully structured design, researchers can extract valuable insights while maintaining a streamlined and effective experimental approach[13].

Taguchi Method

The Taguchi Method, conceived by the distinguished Genichi Taguchi, has emerged as a pivotal strategy for achieving design robustness across a myriad of disciplines, including pharmaceuticals. This method leverages orthogonal arrays to deftly identify optimal conditions while concurrently striving to minimize variability within the resulting experimental outcomes. By focusing on enhancing quality with a limited number of experimental runs, the Taguchi Method provides a pragmatic pathway for both formulation development and quality enhancement initiatives[14]. Nonetheless, it remains crucial to acknowledge that this methodology does not facilitate interaction analysis among factors, which may restrict its versatility in comparison to more comprehensive approaches offered by response surface methodologies.

Mixture Designs

Mixture designs are distinctly specialized for scenarios where all components in a formulation must collectively sum to 100%. This characteristic renders them essential for refining formulations that involve multiple ingredients, such as the ratios of excipients in tablets or nanoparticle assemblies. In these contexts, the specific proportions of individual components can profoundly influence the overall attributes of the final product. By implementing mixture designs, researchers can systematically

evaluate how varying these proportions affect vital quality attributes, including solubility, stability, and bioavailability, thereby significantly enhancing the effectiveness of drug delivery systems[15].

Through the strategic application of these diverse DoE models, formulators construct a resilient foundation for developing statistically credible, reproducible, and regulatory-compliant drug delivery systems. This practice becomes particularly vital when addressing the complexities of diseases, such as cancer, where the challenges associated with formulation and production can have profound implications on treatment effectiveness. By diligently employing these methodologies, the reliability of pharmaceutical applications is fortified, paving the way for groundbreaking advancements in the field.

Formulation strategies for cancer treatment

Advanced drug delivery strategies targeting cancer therapy have evolved as a critical area of exploration in the medical research landscape, with the overarching objective of augmenting drug concentration at tumor sites while concurrently reducing systemic toxicity that could adversely affect patient well-being. These pioneering formulation techniques are meticulously designed not only to enhance pharmacokinetics and improve targeting precision but also to significantly elevate therapeutic outcomes, granting patients access to more effective treatment modalities and ultimately enriching their quality of life.

Nanocarriers for Passive and Active Targeting

Nanocarriers encompass a diverse array of advanced delivery systems, including liposomes, solid lipid nanoparticles (SLNs), polymeric micelles, dendrimers, and nanogels, which have profoundly transformed the domain of anticancer therapy. Functioning as sophisticated vehicles, these carriers adeptly encapsulate anticancer drugs, providing them with protection against premature degradation in the bloodstream and ensuring their targeted delivery to malignant cells.

Passive Targeting

This approach strategically harnesses the enhanced permeability and retention (EPR) effect, a distinctive phenomenon evident in the vascular architecture of tumors. Tumor blood vessels typically exhibit heightened permeability and compromised lymphatic drainage, conditions that facilitate the preferential accumulation of nanoparticles in the dimensions of 100–200 nm within tumor tissues. This unique biological response is ingeniously exploited to optimize drug localization in the challenging tumor microenvironment, markedly increasing the concentration of therapeutic agents precisely where they are most critically required, while simultaneously minimizing exposure to healthy tissues. This is of paramount importance for mitigating the adverse side effects frequently associated with conventional chemotherapy treatments [16,17].

Active Targeting: In contrast, active targeting employs meticulous modifications to nanocarriers by conjugating specific ligands such as folic acid, transferrin, antibodies, or peptides that can selectively bind to an array of receptors which are often over expressed on tumor cells. This targeted delivery method profoundly enhances the efficiency of receptor-mediated endocytosis, ensuring superior cellular uptake of the nanocarrier-entrapped drugs. Through careful refinement of these targeting strategies, researchers can amplify therapeutic efficacy while further minimizing off-target effects, rendering treatment modalities more personalized and impactful for patients[18].

pH-Sensitive, Thermosensitive, and Redox-Responsive Systems

The distinctive conditions prevalent in the tumor microenvironment present both challenges and remarkable opportunities for the development of innovative stimuli-responsive drug delivery strategies.

pH-Sensitive Systems: These systems are ingeniously engineered to leverage the acidic milieu characteristically found in tumor tissues, where the pH typically ranges from approximately 6.5 to 6.8 standing in stark contrast to the neutral pH observed in healthy tissues (around 7.4). Moreover, endosomal compartments demonstrate even more acidic conditions, hovering around pH 5.0–6.0. By developing drug delivery systems that are responsive to these pH variations, researchers can create mechanisms that trigger precise drug release specifically within these acidic environments, culminating in enhanced therapeutic efficacy. This often employs acid-cleavable linkers or pH-responsive polymers that undergo disassembly or

release their drug contents in response to the unique pH levels that characterize tumor environments[19].

Thermosensitive Formulations: These cutting-edge drug delivery systems are adeptly designed to respond to slight elevations in temperature, typically around 40-42°C. Such localized temperature increases can be achieved through techniques including external heating or tumor hyperthermia, a strategic approach that effectively raises the temperature of tumor tissues to enhance treatment effectiveness. Thermosensitive formulations commonly incorporate temperature-responsive lipids or polymers, such as poly(N-isopropylacrylamide) (PNIPAM), which undergo a phase transition from soluble to gel-like states in response to heat, facilitating localized drug release. This targeted release mechanism not only amplifies the efficacy of the treatment but also reduces the systemic exposure of healthy tissues to cytotoxic agents, thereby minimizing potential side effects associated with chemotherapy [20].

Redox-Responsive Carriers: These carriers exploit the unique biochemical landscape characterized by cancer cells, frequently exhibiting elevated levels of intracellular glutathione (GSH)-reaching concentrations of up to 10 mM-when compared to the significantly lower concentrations (approximately 2 μM) found in extracellular fluids. By utilizing disulfide bond-based linkers or redo-sensitive polymers, these systems can facilitate the selective release of therapeutic agents once inside cancer cells, effectively taking advantage of the higher GSH levels that enable targeted intracellular release. This strategic approach allows for precise drug delivery, thereby enhancing therapeutic effectiveness while substantially reducing systemic toxicity [21].

Surface Modification of Nanocarriers

Surface modifications of nanocarriers play a crucial role in shaping their pharmacokinetic properties, circulation durations, biodistribution, and overall targeting efficacy within the body.

PEGylation

One prevalent technique is PEGylation, which involves the strategic attachment of polyethylene glycol (PEG) chains to the surfaces of nanocarriers. This modification results in a hydrophilic "stealth" layer that effectively cloaks the nanocarriers from the vigilant immune system, thereby diminishing opsonization (the process by which particles are marked for clearance by phagocytotic cells) and prolonging their residence in systemic circulation. The increased blood retention time vastly enhances the probability of the drug successfully reaching and penetrating tumor tissues, thereby yielding improved therapeutic outcomes [22].

Ligand Conjugation

Furthermore, ligand conjugation emerges as an influential strategy geared towards active targeting of nanocarriers. By attaching specific ligands, such as folate or RGD peptides that target integrins, alongside antibodies directed against over expressed receptors on tumor cells (for instance, the folate receptor or EGFR), researchers can considerably improve the efficiency of chemotherapeutic delivery to intended sites. This targeted delivery framework is instrumental in maximizing drug uptake by cancer cells, ensuring that therapeutic benefits are accentuated while minimizing impacts on non-cancerous cells-a crucial consideration in devising treatments for cancers where the preservation of healthy tissue is vital [23].

Other modifications could involve cationic surface alterations aimed at bolstering cellular uptake or the implementation of pH-labile linkers designed to facilitate drug release in the acidic environments characteristic of tumors.

By meticulously optimizing these advanced formulation techniques through the application of methodologies such as Design of Experiments (DoE), researchers can attain precise control over pivotal parameters, including drug loading capacities, release profiles, and overall targeting capabilities. Collectively, the breakthroughs in these innovative drug delivery technologies herald the promise of significantly enhancing therapeutic efficacy in cancer treatments, marking the dawn of a new era where more effective and personalized therapies are systematically tailored to align with the unique molecular and cellular characteristics of individual tumors.

Advantges of DoE in Cancer formulation

The development of anticancer drug delivery systems represents a sophisticated undertaking,

characterized by a plethora of formulation and process variables that are instrumental in achieving optimal product quality, safety, and therapeutic efficacy. Within this complex milieu, Design of Experiments (DoE) emerges as a highly advanced statistical framework that rigorously investigates these diverse factors and their intricate interrelationships. This systematic approach facilitates the creation of robust, reproducible, and finely-tuned formulations that adhere closely to contemporary regulatory standards and benchmarks.

Efficient Screening of Multiple Variables

One of the most compelling advantages of DoE is its extraordinary capability to simultaneously assess multiple independent variables, thereby distinguishing it from the conventional one-factor-at-a-time (OFAT) methodology that has historically dominated the field. By employing sophisticated methodologies such as factorial, fractional factorial, and response surface designs, researchers can meticulously identify and analyze critical formulation parameters including polymer concentration, surfactant levels, stirring speed, and drug loading. Each of these factors plays a pivotal role in determining crucial outcomes, such as particle size, entrapment efficiency, and drug release kinetics. This multi factorial strategy empowers researchers with invaluable insights into the complex interplay among these variables, which are often overlooked in simpler OFAT approaches. Such insights are particularly vital in the nuanced design of advanced nanocarriers for targeted cancer therapies, given that even minor adjustments in formulation can lead to substantial variations in therapeutic effectiveness and, consequently, patient outcomes [24,25].

Cost-Effective and Reproducible Development

The ability of DoE to markedly reduce the number of experiments required for the optimization of formulations constitutes another major benefit of this approach, all while maximizing the wealth of data extracted from each experimental run. For instance, experimental designs such as Box–Behnken Design (BBD) or Central Composite Design (CCD) allow formulation scientists to delve into the effects of multiple factors with far fewer experimental trials than would be necessary under traditional exhaustive testing protocols. This enhanced efficiency not only conserves critical financial and material resources but also accelerates the formulation development process, which is particularly essential in the realm of cancer research, where active pharmaceutical ingredients (APIs) can be both prohibitively expensive and often available only in limited quantities. Additionally, the predictive models produced through the DoE framework aid in elucidating optimal conditions for desired outcomes, thereby significantly enhancing the reproducibility and scalability of anticancer formulations, whether they are liposomes, polymeric micelles, or solid lipid nanoparticles. This strategic approach to optimization not only reinforces the foundation for innovative therapeutic strategies but also fosters improvements in patient care [26,27].

Regulatory Acceptance and QbD-Driven Development

Beyond its methodological enhancements, DoE serves as a cornerstone of Quality by Design (QbD), a regulatory-endorsed paradigm in pharmaceutical development that is backed by guidelines such as ICH Q8 (R2), Q9, and Q10. Regulatory bodies, including the US FDA and EMA, actively champion the integration of QbD frameworks, which are rooted in scientific principles and risk-based strategies attuned to the complexities of pharmaceutical development. By leveraging DoE, researchers are empowered to delineate what is termed the design space a multidimensional combination of input variables that collectively ensure and uphold product quality. When thoroughly documented, the design space and associated control strategies not only streamline regulatory approval processes but also substantially mitigate the risk of post-approval modifications, thereby establishing a pathway for continuous refinement and enhancement of cancer drug formulations. This congruence with regulatory expectations underscores the critical role that DoE plays in advancing drug delivery systems from conceptual stages in the laboratory to practical applications in clinical settings[28,29].

In conclusion, the suite of advantages presented by DoE positions it as an indispensable instrument in the rational design, optimization, and regulatory compliance of anticancer drug delivery systems. Its application not only accelerates the transition of pioneering laboratory breakthroughs into effective clinical therapies but also enriches the therapeutic choices and quality of care accessible

to patients confronting cancer. This comprehensive understanding of DoE accentuates its vital significance within contemporary pharmaceutical sciences, particularly in the evolving landscape of oncology.

Challenges and Limitations

Complex Biological Models

Cancer is characterized by its heterogeneous and dynamically evolving nature, posing significant challenges in our efforts to both understand the disease and develop effective treatment modalities. A primary concern in formulation development, particularly when utilizing Design of Experiments (DoE), is the navigation of highly intricate tumor micro environments. These environments are not static; they continuously adapt to a multitude of factors, including fluctuations in blood perfusion, which fundamentally impacts the delivery and overall efficacy of therapeutic agents. Moreover, tumors cunningly employ numerous immune evasion strategies, thereby complicating treatment outcomes as they deftly maneuver to escape detection by the immune system. The additional challenge of multidrug resistance further complicates the therapeutic landscape, creating formidable barriers to successful intervention. Although DoE is a robust methodology for optimizing both formulation and process variables, it predominantly draws upon simplified in vitro or animal testing models. While these models offer valuable insights, they often fail to encapsulate the full spectrum of biological complexities faced in human oncology. The encouraging results observed in laboratory settings frequently do not translate seamlessly into the multifaceted context of human patients. This disconnect is particularly pronounced in the case of nanocarriers optimized through DoE methodologies. While these carriers may exhibit promising outcomes in controlled in vitro experiments, they typically confront substantial obstacles when applied in vivo, including reticulo endothelial system (RES) clearance that leads to premature elimination from circulation, unintended off-target accumulation, or inconsistencies in enhanced permeability and retention (EPR) effects in human tumors—factors that cumulatively diminish therapeutic effectiveness when contrasted with initial findings from laboratory evaluations[30,31].

Translational Hurdles

The transition from laboratory-scale development to clinical-scale production introduces a plethora of challenges that significantly hinder the full realization of DoE's potential in oncology. Formulations that are meticulously refined and optimized under controlled laboratory conditions may encounter numerous issues when scaled up to clinical applications. A major concern is equipment variability, as the technologies and methodologies utilized at the research level often differ markedly from those employed in production environments. Such discrepancies can lead to critical process instability, ultimately resulting in alterations to the physicochemical properties of the formulations, thereby undermining both efficacy and safety. Notably, the scaling-up process involves a complex interplay of variables that can significantly influence the characteristics of the final product, thereby complicating the development trajectory. Furthermore, unless DoE models are thoroughly constructed with parameters that thoughtfully account for the challenges inherent in the scale-up process, they risk neglecting critical considerations related to process-induced variability that can manifest during the production of larger batch sizes. This oversight can consequently yield formulations that underperform in clinical contexts. In addition to these translational hurdles, the regulatory landscape governing the development of nanomedicines and cancer therapies is often intricate and rigorous. The incorporation of novel excipients or unapproved materials adds layers of complexity that can further delay or obstruct the clinical advancement of DoE-optimized systems, exposing them to stringent regulatory scrutiny[32,33].

Model Predictability vs. Real-World Efficacy

While DoE is highly regarded for its capacity to deliver mathematical and statistical predictions regarding experimental responses, it is essential to recognize that these models are fundamentally empirical. This empirical focus may introduce limitations, as such models might not fully encapsulate the complex dynamics evolving within biological systems. For instance, a model may accurately predict a high entrapment efficiency or an optimal drug release profile; however, these favorable statistics do not necessarily correlate with enhanced therapeutic outcomes or substantial tumor

regression in real-world human cases[34]. The disparity between model projections and actual clinical results can be quite profound. Additionally, the interaction terms among various formulation factors can create confusion, as those terms deemed statistically insignificant in the framework of the model may hold significant biological relevance in practical, in vivo situations. As a result, researchers are encouraged to adopt an integrative approach, delving deeper into their findings and complementing DoE outputs with extensive mechanistic insights, thorough pharmacokinetic evaluations, and comprehensive assessments of clinical relevance. This holistic methodology is crucial for bridging the gap between theoretical models and practical clinical applications, ultimately enhancing the likelihood of achieving successful translational outcomes[35].

Despite these multifaceted obstacles, it is vital to accentuate that the strategic application of DoE when effectively integrated with robust biological validation, meticulous quality risk management practices, and a comprehensive awareness of regulatory requirements remains an invaluable asset in optimizing the development of effective cancer therapies. This integrative strategy has the potential to play a critical role in advancing therapeutic interventions in the increasingly complex and nuanced field of oncology.

Formulation insights from doe-based cancer studies

Table 1 presents a meticulous summary of 30 carefully scrutinized research studies that exemplify the successful application of Design of Experiments (DoE) in the sophisticated development and optimization of various anticancer drug formulations. This table serves as an invaluable resource for researchers and pharmaceutical developers alike, illuminating the innovative methodologies employed in the formulation of advanced drug delivery systems. The selected studies encompass a broad spectrum of cutting-edge drug delivery platforms, including liposomes, widely acclaimed for their ability to encapsulate and safeguard therapeutic agents; solid lipid nanoparticles (SLNs), celebrated for their unique combination of solid lipid matrices and nano scale technology; nanostructured lipid carriers (NLCs), specifically designed to enhance drug solubility and stability; polymeric nanoparticles (NPs), esteemed for their biocompatibility and precise control over release mechanisms; as well as diverse formulations such as micelles, nanogels, hydrogels, and transdermal patches, each presenting distinct mechanisms for effective drug targeting and release.

In the context of these studies, a variety of DoE models were skillfully employed, including Box–Behnken Design (BBD), Central Composite Design (CCD), Full Factorial Design, Taguchi Orthogonal Array, and Response Surface Methodology (RSM). These methodologies play a pivotal role in systematically examining and optimizing the critical formulation and process parameters that are essential for the development of effective cancer therapies. The key variables investigated across these studies are extensive and include polymer concentration, which is vital for maintaining the structural integrity of the formulations; surfactant ratio, necessary for stabilizing the drug delivery systems; lipid composition, which significantly influences drug release kinetics; particle size, a crucial factor directly impacting the distribution and absorption efficiency of the drug; sonication time, essential for achieving the desired nanoparticle sizes; and pH, a critical parameter that can heavily affect both the stability and efficacy of the therapeutic agents.

The insights presented in the table underscore that DoE not only markedly reduces the experimental workload, thus expediting the research timeline, but also tremendously enhances the reliability, reproducibility, and overall efficacy of the resulting formulations. A majority of the studies reported significant advancements such as increased drug loading capacity, translating into more potent therapeutic options; extended release profiles, enabling sustained therapeutic action; improved bioavailability, ensuring that a greater proportion of the drug effectively reaches systemic circulation; targeted delivery to tumor sites, minimizing collateral damage to healthy tissues; and dramatically reduced off-target toxicity, thereby enhancing the safety profile of treatment regimens.

This compilation serves not merely as an indispensable reference but also highlights the crucial importance of DoE as a fundamental component in Quality by Design (QbD)-oriented pharmaceutical development specifically tailored for

Table 1:Formulation strategies developed by Design of experiments [DoE]

S. No.	Formulation Type	Drug	DoE Model Used	Optimized Parameters	Key Outcome	Ref.
1	Liposomes	Doxorubicin	BBD	Lipid:drug ratio, cholesterol %, hydration time	↑Entrapment, ↑Burst release	36
2	SLNs	Curcumin	Full Factorial	Lipid %, surfactant %, stirring speed	↑Bioavailability	37
3	Polymeric NP	Paclitaxel	CCD	Polymer %, emulsifier, stirring rate	Optimal size, ↑DL	38
4	NLCs	Tamoxifen	BBD	Solid:liquid lipid ratio, sonication time	Sustained release	39
5	Micelles	5-FU	Taguchi	Drug:polymer ratio, solvent volume	pH-sensitive release	40
6	Nanogels	Cisplatin	CCD + RSM	Crosslinking density, pH, reaction time	Tumor-triggered release	41
7	Lipid-polymer NP	Docetaxel	CCD	Polymer type, lipid %, surfactant	Dual-targeted delivery	42
8	Nanosponges	Methotrexate	Full Factorial	Polymer:crosslinker ratio	High drug loading	43
9	PEGylated NP	Camptothecin	CCD	PEG %, size, loading efficiency	Long-circulation	44
10	Solid Dispersion	Sorafenib	BBD	Carrier ratio, solvent mix, drying temp	↑Solubility	45
11	Transfersomes	Gemcitabine	BBD	Phospholipid: surfactant ratio	↑Skin penetration	46
12	Gold NP	Epirubicin	Full Factorial	Particle size, stabilizer %, pH	Targeted imaging	47
13	Polymeric Micelles	Quercetin	CCD	PEG ratio, drug %, micelle size	↑Tumor accumulation	48
14	Hydrogels	5-FU	Taguchi	Polymer %, pH, crosslinker	Controlled release	49
15	Mesoporous silica NP	Cisplatin	BBD	Pore size, loading %, surface charge	Tumor-specific release	50
16	Lipid NP	Erlotinib	CCD	Surfactant %, particle size, sonication	↑Bioavailability	51
17	Thermosen sitive Gel	Doxorubicin	BBD	Polymer ratio, temp sensitivity	Sustained depot delivery	52
18	Carbon NP	Curcumin	Full Factorial	Particle size, zeta potential	↑Cell uptake	53
19	Niosomes	Tamoxifen	CCD	Span ratio, cholesterol %, hydration time	↑Encapsulation	54
20	PLGA NP	Gefitinib	BBD	Polymer %, stirring speed, solvent	Controlled release	55
21	Polyplexes	siRNA	CCD	Charge ratio, N/P ratio, pH	Gene knockdown	56

22	Albumin NP	Doxorubicin	BBD	Albumin %, stirring speed	Tumor targeting	57
23	Cyclodextrin complex	Topotecan	CCD	Cyclodextrin %, drug %, solvent	↑Solubility	58
24	SLNs	Resveratrol	BBD	Lipid %, surfactant %, particle size	Antiangiogenic effect	59
25	In-situ gel	Mitomycin C	Taguchi	Polymer %, gelling agent	Mucoadhesive retention	60
26	Transdermal Patch	Letrozole	Full Factorial	Polymer blend %, enhancer type	Prolonged delivery	61
27	Nanoemulsion	Lapatinib	CCD	Oil %, surfactant %, droplet size	↑Oral absorption	62
28	Polymeric NP	Curcumin-piperine	BBD	Dual drug %, polymer ratio	Synergistic cytotoxicity	63
29	Chitosan NP	Imatinib	CCD	Chitosan %, TPP %, pH	Enhanced tumor uptake	64
30	Lipid-based NP	Bicalutamide	CCD	Lipid %, PEG %, particle size	Improved lymphatic delivery	65

cancer therapies. By fostering rational formulation designs and adopting systematic approaches, DoE accelerates the translation of promising nanomedicines from the laboratory bench to clinical application, thus holding significant potential to transform patient care and enhance clinical outcomes. Each study emphasizes the importance of strategic planning and rigorous experimentation in the relentless pursuit of optimizing cancer therapeutics, illustrating a dynamic and vibrant field of research dedicated to amplifying therapeutic efficacy and enriching the quality of life for patients

Future Perspectives

The horizon of anticancer drug formulation is increasingly marked by the dynamic convergence of Design of Experiments (DoE) with state-of-the-art technologies such as machine learning (ML) and artificial intelligence (AI). DoE exemplifies an essential methodology for systematically optimizing a diverse array of formulation variables, while its collaboration with AI introduces remarkable predictive capabilities. This synergistic partnership not only streamlines the intricate process of drug development but also facilitates the rapid creation of more personalized therapies, ultimately enhancing the efficacy of cancer treatments designed to address the specific needs of individual patients [66,67].

Integration with Machine Learning

In this innovative landscape, machine learning emerges as a pivotal force, adept at scrutinizing complex, multivariate datasets generated through DoE methodologies. By harnessing sophisticated computational algorithms, ML can uncover nonlinear relationships and hidden interactions among formulation components, bringing to light insights that may remain obscured in traditional analytical frameworks[68]. Notably, advanced ML techniques such as support vector machines, random forests, and deep neural networks have demonstrated remarkable accuracy in forecasting critical parameters, including nanoparticle performance, drug release kinetics, and cytotoxicity profiles, by leveraging extensive training datasets amassed from previous experimental endeavors[69]. This powerful capability not only reduces the time and resources traditionally consumed through trial-and-error approaches but also significantly enhances the overall efficiency and effectiveness of the formulation processes.

AI-Assisted DoE Models

The advent of AI-augmented DoE models marks a monumental shift in the realm of pharmaceutical research. Innovative approaches such as Bayesian optimization, reinforcement learning, and genetic algorithms empower researchers to engage in real-time learning through iterative experiments, progressively refining their predictive accuracy at each stage of the investigation[70]. These advanced AI systems

excel at recommending the next most informative experimental undertaking, thereby optimizing the allocation of resources and maximizing research outcomes. Furthermore, the seamless integration with cloud-based infrastructures and automated laboratory arrangements such as robotic synthesis not only signifies a remarkable convenience but also represents a fundamental reimagining of experimental design and execution. Such advancements lay a robust foundation for closed-loop optimization frameworks that promise to significantly streamline drug formulation initiatives[71].

Toward Personalized Cancer Nanomedicine

At the forefront of these technological breakthroughs is the ambitious pursuit of personalized nanomedicine. This forward-thinking concept seeks to leverage patient-specific data—including tumor biomarkers, genetic profiles, and receptor densities—to engineer highly customized drug delivery systems attuned to the individual nuances of each patient's condition[72,73]. For instance, sophisticated AI algorithms are capable of processing vast amounts of multi-omic data, thereby guiding the selection of ligands for targeted delivery and recommending optimal particle size and drug release profiles suited for particular tumor microenvironments[74]. This personalized strategy aims not only to amplify therapeutic efficacy but also to minimize systemic toxicity, ultimately enhancing the overall therapeutic experience and increasing the likelihood of favorable treatment outcomes for cancer patients.

As these revolutionary technologies continue to advance and mature, the integration of AI-assisted DoE is on the brink of redefining the pharmaceutical formulation landscape. This transformation heralds an optimistic future in which the rational design and personalized crafting of robust nanomedicine solutions for cancer therapy become standardized, thereby improving survival rates and enriching the quality of life for patients engaged in the battle against cancer [75].

CONCLUSION

The urgent global challenge posed by cancer necessitates innovative therapeutic strategies that effectively target tumor cells while minimizing adverse effects on healthy tissues. Design of Experiments (DoE) offers a systematic and robust framework that facilitates the optimization of anticancer drug formulations. By employing various statistical models like Central Composite Design,Box-Behnken Design, and others, researchers can efficiently screen multiple variables that influence formulation outcomes. This multi factorial approach leads to enhanced therapeutic efficacy, improved bioavailability, and reduced off-target toxicity, thereby ensuring better patient care.

As we move toward more personalized cancer therapies, integrating advanced methodologies such as machine learning and artificial intelligence with DoE promises to revolutionize cancer treatment. This convergence enables real-time insights and the optimization of drug delivery systems tailored to individual patient profiles. The future of anticancer formulations rests on these sophisticated innovations, which aim to significantly enhance the quality of life and survival rates of individuals battling this complex disease.

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Conflict of interst

The author declare no conflict of interest, financial or other wise

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