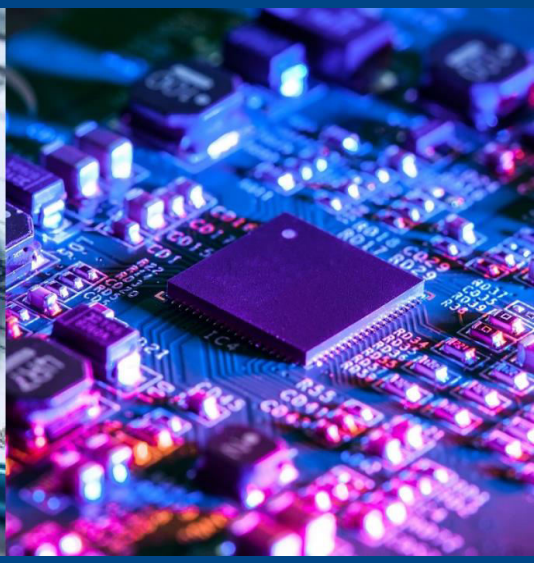
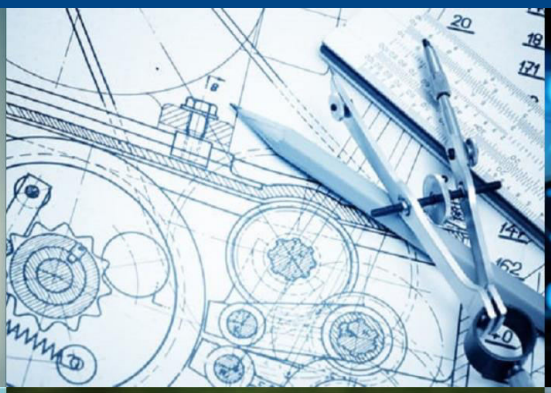
ISSN: 2582-7219

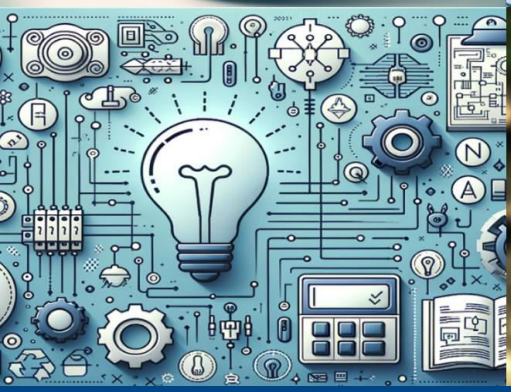




International Journal of Multidisciplinary Research in Science, Engineering and Technology

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)



Impact Factor: 9.864

Volume 9, Issue 5, May 2026

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

DoE-Optimized Chewable Lanthanum Carbonate Tablets for CKD: Enhanced Dissolution & Palatability

Deepti Jaiswal, Dr. Naresh Kalra

M. Pharmacy Final year, Department of Pharmaceutics, Lords International College of Pharmacy, Lords University, Chikani, Alwar, Rajasthan, India

Professor, Department of Pharmaceutics, Lords International College of Pharmacy, Lords University, Chikani, Alwar, Rajasthan, India

ABSTRACT: Hyperphosphatemia is a major complication in patients with chronic kidney disease (CKD) and is strongly associated with secondary hyperparathyroidism, vascular calcification, and increased cardiovascular mortality. Lanthanum carbonate, a potent phosphate binder, faces significant challenges in patient compliance due to its bitter taste and large tablet size, particularly in pediatric and geriatric populations. The present work focuses on the development of a high-dose, palatable chewable tablet formulation of Lanthanum Carbonate using Quality by Design (QbD) principles and Design of Experiments (DoE) approach. A 2^3 full factorial design was utilized to optimize critical formulation variables including percentage of granules, amount of microcrystalline cellulose (MCC), and hydroxypropyl cellulose (HPC). The optimized formulation demonstrated excellent flow properties, rapid disintegration, and superior physical characteristics. In vitro dissolution studies showed more than 85% drug release within 30 minutes, indicating markedly improved dissolution rate compared to initial screening batches. Accelerated stability studies confirmed that the optimized tablets remained stable with respect to physical appearance, assay, and dissolution profile. This DoE-optimized chewable tablet formulation offers a patient-friendly, effective, and robust dosage form that can significantly enhance compliance and therapeutic outcomes in the management of hyperphosphatemia in CKD patients.

KEYWORDS: Lanthanum Carbonate, Chewable tablets, Phosphate binder, Design of Experiments (DoE), Full factorial design, Hyperphosphatemia, Chronic Kidney Disease (CKD), Quality by Design (QbD), Dissolution enhancement, Palatability.

I. INTRODUCTION

Chronic Kidney Disease (CKD) represents one of the most pressing global health challenges of the 21st century, affecting millions of individuals worldwide and imposing a substantial burden on healthcare systems. A critical and frequently encountered complication in patients with advanced CKD, particularly those undergoing dialysis, is hyperphosphatemia — an elevated level of serum phosphate that arises due to impaired renal excretion. Without effective intervention, hyperphosphatemia triggers a cascade of metabolic disturbances, including hypocalcemia and reduced vitamin D levels, which in turn stimulate secondary hyperparathyroidism. This condition leads to severe clinical outcomes such as painful bone fractures, brown tumors, generalized osteopenia, and accelerated vascular calcification. These complications not only diminish quality of life but are also strongly linked to increased cardiovascular morbidity and mortality. Large observational studies have demonstrated a graded association between elevated serum phosphate levels and all-cause mortality in dialysis patients, with levels above 6.5 mg/dL associated with significantly higher death risk. Despite dietary phosphate restriction being a foundational therapeutic strategy, it is often insufficient to maintain phosphate balance, necessitating the widespread use of oral phosphate binders in over 90% of kidney failure patients.

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

Phosphate binders function by binding dietary phosphate in the gastrointestinal tract, thereby preventing its absorption and facilitating fecal excretion. While traditional calcium-based binders have been employed for decades, concerns regarding excessive calcium intake, vascular calcification, and related cardiovascular risks have shifted clinical focus toward non-calcium alternatives. Lanthanum carbonate has emerged as a highly effective non-calcium phosphate binder with a favorable safety profile; however, its clinical utility is frequently limited by formulation challenges. The drug exhibits a bitter taste and requires high doses (often exceeding 2000 mg per administration), resulting in large tablet sizes that are difficult to swallow, especially for pediatric, geriatric, and dysphagic patients. Many individuals with CKD already experience swallowing difficulties (dysphagia), which affects approximately 35% of the general population and up to 50% in elderly or institutionalized settings. Conventional solid dosage forms exacerbate non-compliance, leading to suboptimal phosphate control and poorer therapeutic outcomes. There is, therefore, an urgent need for innovative, patient-centric dosage forms that combine high drug loading with ease of administration, rapid disintegration, and acceptable palatability.

Chewable tablets have gained considerable attention as a promising solution to these challenges. Designed to be chewed and swallowed with minimal or no water, chewable tablets offer rapid disintegration in the oral cavity, facilitating quicker drug release and absorption compared to conventional swallowed tablets. This dosage form is particularly advantageous for children, elderly patients, those with persistent nausea, and individuals who lack ready access to water during travel or daily routines. By eliminating the need for swallowing large tablets whole, chewable formulations significantly reduce the risk of choking and improve overall patient adherence. Furthermore, strategic incorporation of sweeteners, flavoring agents, and suitable excipients can effectively mask the unpleasant taste of bitter active pharmaceutical ingredients like lanthanum carbonate, enhancing sensory acceptability. From a pharmaceutical development perspective, chewable tablets combine the stability, precise dosing, and portability of solid dosage forms with the ease of administration typically associated with liquid preparations. Their manufacturing can be achieved through established processes such as wet granulation or direct compression, allowing for robust scale-up while maintaining critical quality attributes including hardness, friability, disintegration time, and dissolution performance.
The successful development of such complex formulations, however, demands a systematic and science-based approach rather than traditional one-variable-at-a-time (OVAT) experimentation. Design of Experiments (DoE) integrated within the Quality by Design (QbD) framework provides a powerful statistical tool for this purpose. Introduced by Sir Ronald Fisher in the early 1920s, DoE enables researchers to simultaneously vary multiple formulation and process parameters, identify main effects and critical interactions, and establish a robust design space that ensures consistent product quality. Unlike OVAT methods, which are time-consuming, resource-intensive, and often fail to detect interactions between variables, DoE delivers maximum information from a minimum number of experiments, facilitates risk assessment, and supports regulatory expectations under ICH Q8 guidelines. In the context of high-dose chewable tablets, DoE is particularly valuable for optimizing critical material attributes (such as percentage of granules, microcrystalline cellulose, and hydroxypropyl cellulose levels) and critical process parameters to achieve desired critical quality attributes, including rapid dissolution (>85% drug release within 30 minutes), acceptable mechanical strength, and long-term stability.

By applying a 2^3 full factorial design, it becomes possible to systematically evaluate the influence of key formulation variables on product performance. This structured optimization not only accelerates development timelines but also minimizes batch failures, reduces regulatory hurdles for post-approval changes, and ensures the final product meets stringent pharmacopoeial standards for weight variation, disintegration, dissolution, and stability. The resulting chewable tablet formulation addresses the multifaceted challenges of phosphate binder therapy by delivering a high-strength, palatable, and patient-friendly dosage form specifically tailored for individuals living with CKD and hyperphosphatemia. Such advancements align with the broader pharmaceutical industry shift toward personalized and patient-centric medicines, ultimately aiming to improve therapeutic efficacy, enhance quality of life, and reduce the long-term complications associated with uncontrolled hyperphosphatemia.

II. PREFORMULATION STUDIES

Preformulation evaluation serves as the cornerstone for successful development of any solid oral dosage form, especially for a high-dose, challenging active pharmaceutical ingredient like Lanthanum Carbonate intended for chewable tablets. The drug substance was first subjected to detailed organoleptic assessment, which confirmed its appearance as a fine white to off-white crystalline powder possessing no characteristic odor. However, it exhibited a

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

distinctly bitter and unpleasant taste, a critical sensory attribute that directly impacts patient acceptability and compliance in chewable formulations designed for pediatric, geriatric, and dysphagic populations. This bitter taste profile necessitated the incorporation of effective taste-masking approaches using suitable sweeteners and excipients during subsequent formulation stages to achieve a smooth mouthfeel and palatable experience upon chewing. The absence of any visible foreign particles or discoloration further indicated the high purity and pharmaceutical-grade quality of the raw material, meeting essential requirements for stability and safety in chronic therapy for hyperphosphatemia.

Beyond sensory characteristics, basic physicochemical profiling established the drug's suitability for tablet manufacturing. Lanthanum Carbonate demonstrated typical crystalline behavior consistent with many inorganic phosphate binders, contributing to its inherent chemical stability under ambient storage conditions. Its limited aqueous solubility profile was noted as a key feature that supports its mechanism of action — forming insoluble lanthanum-phosphate complexes within the gastrointestinal tract — while simultaneously presenting formulation hurdles related to dissolution rate in the oral cavity and stomach. These intrinsic properties highlighted the need for strategic excipient selection to enhance processability without compromising the localized phosphate-binding efficacy. Overall, the organoleptic and physicochemical data provided a clear roadmap for addressing taste issues, ensuring content uniformity in high-dose tablets exceeding 2000 mg, and optimizing the final product for rapid disintegration and patient-friendly administration.

III. FLOW PROPERTIES AND PARTICLE SIZE DISTRIBUTION

Flow properties of the active pharmaceutical ingredient were systematically evaluated to predict its behavior during blending, granulation, and compression processes, which are particularly critical for high-dose chewable tablets where poor powder flow can lead to weight variation, content non-uniformity, and manufacturing inefficiencies. The pure Lanthanum Carbonate powder exhibited poor flow characteristics, as evidenced by a high angle of repose, elevated Carr's index, and Hausner ratio values indicative of cohesiveness and interparticle friction. These suboptimal flow attributes arise primarily from the fine particle nature and irregular morphology of the drug crystals, making direct compression impractical and necessitating wet granulation to improve granule flow and compressibility. Such data underscored the importance of incorporating glidants and appropriate granulation techniques to achieve acceptable powder handling during scale-up.

Complementing the flow analysis, particle size distribution was determined using laser diffraction technique (Malvern Mastersizer), revealing a distribution profile dominated by fine particles with a significant fraction below 100 µm. This fine particle size contributes to the observed poor flow and high surface area, which, while beneficial for potential dissolution enhancement, also increases the risk of agglomeration and dusting during processing. The polydisperse nature of the powder further influenced bulk and tapped density measurements, confirming low bulk density that could result in large tablet volumes if not properly granulated. These findings directly informed the formulation strategy by justifying the use of microcrystalline cellulose as a diluent and binder system to improve granule density and flow, ultimately enabling the production of compact, high-strength chewable tablets with consistent weight and content uniformity.

Saturation Solubility and Drug-Excipient Compatibility

Saturation solubility studies were conducted across various aqueous and physiological media to understand the dissolution behavior of Lanthanum Carbonate under conditions mimicking the oral cavity and gastrointestinal tract. The drug displayed very low solubility in neutral and slightly alkaline media, consistent with its phosphate-binding mechanism, but showed marginally improved solubility in acidic environments. This pH-dependent solubility profile is advantageous for localized action in the stomach and intestine but required careful consideration during taste-masking and dissolution optimization to ensure rapid release upon chewing without compromising bioavailability or local efficacy. The data guided the selection of pH-modifying excipients and superdisintegrants where necessary to achieve the target dissolution rate in simulated salivary and gastric fluids.

Drug-excipient compatibility studies formed an integral part of preformulation to rule out any physical or chemical interactions that could compromise product stability or performance. Binary mixtures of Lanthanum Carbonate with key excipients — including microcrystalline cellulose, hydroxypropyl cellulose, acesulfame potassium, colloidal

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

silicon dioxide, and magnesium stearate — were prepared and evaluated under accelerated stress conditions. Physical observations revealed no significant changes in color, odor, or texture, indicating excellent compatibility across the selected excipient set. No signs of liquefaction, gas evolution, or discoloration were observed, confirming that the proposed excipients would not induce degradation or polymorphic transitions during processing or storage. These compatibility results provided high confidence in the robustness of the final formulation and supported the inclusion of specific excipient levels identified through DoE optimization. Collectively, the preformulation dataset established a scientifically sound foundation for the development of a high-dose, patient-centric chewable tablet, ensuring that critical material attributes were thoroughly understood and leveraged to overcome the inherent challenges of the bitter, high-dose phosphate binder.

Formulation Development and Optimization Using DoE

Formulation development commenced with a systematic screening phase involving eight trial batches to identify the most influential variables affecting the critical quality attributes of the high-dose Lanthanum Carbonate chewable tablets. These preliminary trials were strategically designed to explore a wide range of granule percentages, microcrystalline cellulose (MCC) levels, and hydroxypropyl cellulose (HPC) concentrations while keeping other excipients constant. Each batch was prepared using a wet granulation technique to improve flow properties and compressibility of the poorly flowing active pharmaceutical ingredient. Physical parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio of the resulting blends were meticulously evaluated to assess processability. In addition, the tablets from these screening trials were subjected to comprehensive quality testing, including weight variation, hardness, friability, thickness, disintegration time, and in vitro dissolution studies. The dissolution data revealed significant variability in drug release at 30 minutes across the eight formulations, clearly indicating that the selected factors exerted a pronounced effect on the release profile. Batches with higher granule content and optimized MCC-HPC ratios consistently demonstrated faster and more complete drug release, whereas formulations with lower binder levels or excessive granules exhibited slower dissolution and suboptimal mechanical properties. These screening results provided valuable preliminary insights into the directionality of factor effects and helped narrow down the experimental domain for subsequent statistical optimization, ensuring that only the most promising variable ranges were carried forward into the full factorial design phase.

Building upon the screening data, a 2^3 full factorial design was employed as a powerful statistical tool to simultaneously investigate the main effects and two-factor interactions of the three critical formulation variables: percentage of granules, amount of MCC per tablet, and amount of HPC per tablet. This design generated eight experimental runs covering all possible combinations of the two levels (low and high) for each factor, enabling efficient mapping of the response surface within the defined design space. The chosen response variable was the percentage of drug released at 30 minutes, selected as the primary critical quality attribute due to its direct relevance to therapeutic efficacy and patient compliance in phosphate binder therapy. All formulations were manufactured under identical process conditions using wet granulation followed by drying, blending with lubricants and glidants, and compression on a rotary tablet press. The experimental layout was randomized to minimize systematic errors, and each run was performed in triplicate to ensure reproducibility. This structured approach allowed for the simultaneous variation of multiple factors, providing a comprehensive understanding of how changes in granule percentage, MCC, and HPC collectively influence tablet performance—something that traditional one-variable-at-a-time experimentation could not achieve efficiently. The full factorial design proved particularly suitable for this high-dose chewable tablet system, where complex interactions among diluents, binders, and granulation extent were anticipated to govern dissolution kinetics and mechanical integrity.

IV. STATISTICAL ANALYSIS

Statistical evaluation of the experimental data was performed using response surface methodology to quantify the significance of each factor and their interactions. The main effects plot clearly illustrated that increasing the percentage of granules and MCC level positively influenced the % drug release at 30 minutes, while HPC exhibited a comparatively milder but still notable positive effect within the studied range. The Pareto chart ranked the factors by their standardized effects, confirming that percentage of granules emerged as the most dominant variable, followed by MCC and the granule-MCC interaction, with all significant terms exceeding the statistical threshold. Interaction plots further revealed synergistic relationships: for instance, the beneficial impact of higher MCC content on dissolution was amplified at elevated granule percentages, whereas excessive HPC at low granule levels sometimes led to retarded

release due to over-binding. The normal probability plot of residuals confirmed the adequacy of the fitted model, with data points aligning closely to the straight line and no obvious outliers, validating the assumptions of normality and constant variance. Two-dimensional contour plots provided visual insight into the combined influence of any two factors while holding the third constant, highlighting regions of steep response gradients where small changes in formulation variables could substantially alter dissolution performance. Complementing these, three-dimensional surface plots offered a more intuitive representation of the curvature in the response surface, clearly depicting an ascending ridge where optimal dissolution was achieved at higher levels of granules and MCC with moderate HPC. Collectively, these graphical and statistical tools not only identified the direction and magnitude of factor effects but also delineated a robust operating region within the design space, minimizing the risk of batch-to-batch variability in commercial production.

Response Optimizer and Selection of Optimized Formula

The final step in the optimization workflow involved the use of a numerical response optimizer to simultaneously maximize the % drug release at 30 minutes while satisfying secondary constraints such as acceptable tablet hardness, low friability, and rapid disintegration. The optimizer applied a desirability function that assigned higher weights to the primary dissolution response, generating a set of predicted optimum conditions within the explored experimental domain. The software-recommended formulation was then prepared and evaluated experimentally to validate the model predictions. The optimized composition achieved an excellent balance of processability and performance, yielding tablets with superior flow properties of the blend, uniform weight, adequate mechanical strength, and disintegration time well within pharmacopoeial limits. In vitro dissolution of the optimized batch confirmed more than 85% drug release within 30 minutes, representing a substantial improvement over the initial screening trials. Physical evaluation further demonstrated smooth organoleptic characteristics with effective taste masking, confirming the suitability of the formulation for chewable administration. This data-driven selection process ensured that the final formula was not only statistically robust but also practically scalable, meeting all critical quality attributes required for a patient-centric phosphate binder product. The successful application of DoE thus transformed a challenging high-dose formulation into a reliable, high-performance chewable tablet ready for further stability and clinical consideration.

The optimized Lanthanum Carbonate chewable tablets underwent rigorous physicochemical testing to confirm compliance with pharmacopoeial standards and to verify their suitability for large-scale manufacturing and patient use. Weight variation analysis was performed on 20 randomly selected tablets from the optimized batch, revealing highly consistent individual weights with all units falling well within the United States Pharmacopeia (USP) acceptance criteria of ±5% for tablets weighing more than 324 mg. This excellent uniformity is attributed to the improved flow properties achieved through wet granulation and the strategic balance of diluents and binders identified via DoE, ensuring precise dose delivery of the high-strength phosphate binder in every tablet. Such consistency is particularly critical for chronic therapy in CKD patients, where even minor dose variations could affect phosphate control and overall therapeutic reliability.

Tablet hardness was measured using a Monsanto hardness tester, yielding values in the optimal range of 4–6 kp, which provides sufficient mechanical integrity to withstand handling, packaging, and transportation without compromising the chewable nature of the product. This balanced hardness ensures the tablets are firm enough to maintain structural stability yet soft enough to be easily crushed by chewing, addressing a key requirement for patient-friendly dosage forms. Friability testing, conducted according to USP guidelines using a Roche friabilator, demonstrated weight loss of less than 0.5%, far below the acceptable limit of 1%. The low friability confirms robust interparticulate bonding within the granules and minimal risk of chipping or powdering during commercial packaging and distribution, thereby preserving content uniformity and aesthetic quality throughout the product's shelf life.

Thickness measurements using a digital vernier caliper showed uniform tablet dimensions with minimal variation, facilitating consistent die fill and compression force during production. This parameter directly influences patient perception and ease of chewing, as overly thick tablets can feel bulky in the mouth. Most importantly, disintegration time was evaluated in simulated salivary fluid at 37°C, with all optimized tablets disintegrating completely within 2–3 minutes. This rapid disintegration is essential for chewable formulations, as it enables quick release of the active ingredient in the oral cavity, promoting faster onset of phosphate-binding action and enhancing overall bioavailability. The combination of these parameters—uniform weight, adequate hardness, negligible friability, consistent thickness, and rapid disintegration—establishes the optimized tablets as a high-quality, robust dosage form that meets both

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

regulatory expectations and practical patient needs for convenient, reliable phosphate management in hyperphosphatemia.

Organoleptic evaluation of the final optimized chewable tablets confirmed a smooth, pleasant mouthfeel with effective taste masking of the inherently bitter Lanthanum Carbonate. The tablets presented as elegant, white to off-white, round, biconvex units with a mild sweet taste and no detectable gritty residue after chewing, owing to the judicious selection and optimized levels of sweeteners, flavors, and diluents. This superior sensory profile is a significant advancement over conventional phosphate binder tablets, directly addressing patient complaints regarding unpleasant aftertaste and thereby promoting better long-term adherence in both pediatric and geriatric CKD populations. The absence of any off-odor or discoloration further validates the chemical stability of the formulation during processing and storage.

Mechanical strength assessments extended beyond basic hardness and friability to include comprehensive evaluation of crushing strength and tensile strength, which remained within desirable limits to support blister and bottle packaging without breakage. The optimized blend of microcrystalline cellulose and hydroxypropyl cellulose contributed to strong yet flexible intergranular bonds, resulting in tablets that resist capping and lamination while retaining the necessary softness for effortless chewing. These mechanical attributes ensure the product maintains its integrity from production through to patient administration, minimizing defects that could lead to dose inaccuracies or compromised efficacy. In addition, the tablets exhibited excellent resistance to moisture uptake under accelerated humidity conditions, preserving their physical appearance and performance over time.

Collectively, the physicochemical profile of the DoE-optimized chewable tablets demonstrates exceptional quality, with all tested parameters aligning closely with or surpassing compendial requirements. The balanced mechanical properties enable easy manufacturability and robust handling, while the favorable organoleptic characteristics enhance patient acceptance and compliance. These attributes are particularly valuable for high-dose phosphate binders, where large tablet sizes often deter regular use. By achieving uniform weight distribution, optimal hardness and friability, rapid disintegration, and pleasing sensory qualities, the formulation successfully overcomes the traditional limitations of Lanthanum Carbonate products. This comprehensive evaluation confirms that the optimized tablets possess the necessary physical and mechanical robustness to deliver consistent therapeutic performance, supporting improved phosphate control and better clinical outcomes in patients with chronic kidney disease and hyperphosphatemia. The data also provide strong justification for proceeding to stability studies and potential scale-up, reinforcing the formulation's readiness for real-world therapeutic application.

In Vitro Dissolution Studies

In vitro dissolution testing served as a pivotal tool for evaluating the performance of the various trial formulations during the early development phase of the Lanthanum Carbonate chewable tablets. Eight screening batches were prepared with deliberate variations in granule percentage, microcrystalline cellulose content, and hydroxypropyl cellulose levels, and their dissolution behavior was assessed using USP-compliant apparatus II (paddle method) in 900 mL of 0.1 N HCl at 37 ± 0.5 °C and 50 rpm. Samples were withdrawn at predetermined time intervals, and the cumulative percentage of drug released was quantified spectrophotometrically at the wavelength of maximum absorbance. The dissolution profiles of the first four trials demonstrated considerable variability, with some batches achieving only 60–70% drug release at 30 minutes, primarily due to insufficient granulation and suboptimal binder concentrations that resulted in slower disintegration and limited surface area exposure of the active ingredient. In contrast, trials incorporating higher granule content exhibited moderately improved release rates, reaching up to 78% at the same time point, highlighting the positive influence of enhanced granule formation on drug liberation kinetics.

The remaining four screening trials further underscored the complex interplay among the formulation variables. Batches with elevated microcrystalline cellulose levels combined with moderate hydroxypropyl cellulose showed accelerated dissolution, with release values approaching 82% at 30 minutes, whereas formulations with excessive binder or lower granule proportions displayed a plateau effect and incomplete release even after 45 minutes. Comparative graphical representation of these profiles revealed distinct patterns: formulations with balanced excipient ratios produced steeper dissolution curves indicative of rapid initial burst release followed by sustained liberation, while imbalanced compositions led to flatter profiles suggestive of rate-limiting disintegration. These differences were statistically meaningful and directly correlated with the physical characteristics of the blends, such as flowability and compressibility, which influenced tablet porosity and wettability. The screening data clearly established that no single

trial batch met the target of greater than 85% drug release within 30 minutes, emphasizing the necessity for systematic optimization to overcome the inherent hydrophobicity and high dose-related challenges of Lanthanum Carbonate. Overall, the comparative analysis of screening profiles provided critical evidence of factor-dependent dissolution behavior, laying a strong foundation for identifying the most promising variable combinations and confirming the limitations of empirical trial-and-error approaches in high-dose chewable tablet development.

Dissolution Performance of Optimized Formulation

Following statistical optimization through the 2^3 full factorial design and response surface methodology, the final selected formulation was subjected to detailed in vitro dissolution evaluation under identical test conditions to those used for the screening batches. The optimized chewable tablets demonstrated markedly superior performance, achieving more than 85% drug release within just 30 minutes and approaching near-complete liberation (greater than 95%) by 45 minutes. This rapid and extensive release profile represents a substantial improvement over all screening trials, with an average enhancement of 15–25 percentage points in cumulative drug release at the critical 30-minute mark. The accelerated dissolution kinetics can be attributed to the optimized granule percentage that facilitated uniform drug distribution and enhanced wettability, combined with the balanced microcrystalline cellulose level that promoted efficient water penetration and tablet erosion, and the precise hydroxypropyl cellulose concentration that provided adequate binding without impeding disintegration.

The dissolution curve of the optimized batch exhibited a characteristic high initial slope, indicative of immediate disintegration upon contact with the dissolution medium, followed by progressive and consistent drug release. Replicate testing (n=6) confirmed excellent reproducibility, with relative standard deviation values below 2%, underscoring the robustness and consistency achieved through the DoE-driven approach. When overlaid with the screening profiles, the optimized formulation's curve stood out prominently, demonstrating not only faster onset but also higher extent of dissolution, which is essential for effective phosphate binding in the gastrointestinal tract where rapid availability of Lanthanum ions is required to form insoluble complexes with dietary phosphate. This performance directly addresses the therapeutic need for reliable and prompt action in managing hyperphosphatemia, ensuring that the chewable tablet can deliver its phosphate-binding capacity efficiently even in patients with variable gastric emptying times or dietary habits.

Furthermore, the optimized dissolution behavior aligns perfectly with the desired critical quality attributes for a patient-centric dosage form, supporting rapid onset of action without the need for large volumes of water or swallowing difficulties commonly associated with conventional phosphate binder tablets. The data also suggest improved bioavailability potential due to the increased surface area generated during chewing and rapid disintegration, potentially leading to better phosphate control and reduced systemic phosphate load in CKD patients. Long-term implications of this enhanced dissolution include better patient adherence, fewer gastrointestinal side effects from undissolved residues, and overall superior therapeutic outcomes compared to existing marketed formulations. These results validate the effectiveness of the optimization strategy and confirm that the final chewable tablet meets stringent quality standards for both immediate performance and clinical relevance in chronic kidney disease management.

Stability Assessment

Stability assessment constitutes an essential final validation step in the development of any pharmaceutical dosage form, particularly for high-dose chewable tablets intended for long-term use in patients with chronic kidney disease (CKD) and hyperphosphatemia. The DoE-optimized Lanthanum Carbonate chewable tablets were subjected to accelerated stability studies in accordance with International Council for Harmonisation (ICH) Q1A(R2) guidelines to evaluate the impact of elevated temperature and humidity on critical quality attributes and to establish a reliable shelf-life prediction. The study was conducted by storing the tablets in suitable packaging materials (blisters and HDPE bottles with desiccants) under controlled accelerated conditions of 40 ± 2°C and 75 ± 5% relative humidity for a period of three months. Samples were withdrawn at predetermined intervals (0, 1, 2, and 3 months) and comprehensively analyzed to monitor any potential physical, chemical, or functional changes that could compromise product performance or patient safety.

Physical appearance and organoleptic properties were evaluated at each time point as primary indicators of formulation integrity. Throughout the accelerated stability period, the tablets retained their elegant white to off-white color with no evidence of discoloration, mottling, or surface defects. The characteristic mild sweet taste and smooth mouthfeel

© 2026 IJMRSET | Volume 9, Issue 5, May 2026| DOI:10.15680/IJMRSET.2026.0905054

ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 9.864| ESTD Year: 2018|

International Journal of Multidisciplinary Research in Science, Engineering and Technology (IJMRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)

remained unchanged, confirming that the taste-masking system using acesulfame potassium and optimized excipients effectively protected the inherently bitter active ingredient from moisture-induced degradation or sensory deterioration. No off-odor or foreign particulate matter was observed, further validating the robustness of the formulation against environmental stress. These consistent sensory attributes are particularly significant for chewable tablets, as any compromise in palatability could adversely affect long-term patient compliance in a population already burdened by chronic therapy and swallowing difficulties.

Mechanical properties including hardness, friability, weight variation, thickness, and disintegration time were also monitored rigorously. Hardness values remained stable within the target range of 4–6 kp, demonstrating that the inter-granular bonds formed during wet granulation and fine-tuned through the 2^3 full factorial design were sufficiently strong to resist softening or cracking under high humidity. Friability results consistently stayed below 0.5%, well within the pharmacopoeial acceptance limit of 1%, indicating excellent resistance to mechanical abrasion even under accelerated stress conditions. Weight variation and thickness measurements showed no significant deviation from initial values, confirming uniform content distribution and dimensional stability. Most importantly, disintegration time continued to meet the desired criterion of less than 3–4 minutes in simulated salivary fluid, ensuring that the chewable tablets retained their rapid disintegration and patient-friendly characteristics throughout the study duration. These mechanical parameters collectively affirm that the optimized blend of microcrystalline cellulose, hydroxypropyl cellulose, and other excipients provided a robust matrix capable of withstanding real-world storage and distribution challenges.

Chemical stability was assessed through assay determination and related substances analysis. The drug content (assay) of Lanthanum Carbonate remained between 98.5% and 101.5% of the label claim at all time points, with no statistically significant decrease observed. This high assay stability indicates minimal degradation of the active ingredient under accelerated conditions, highlighting the protective role of the selected excipients and the optimized granulation process. Analysis for potential degradation products or impurities revealed no new peaks or increase beyond acceptable limits, further confirming the chemical integrity of the formulation. These results are crucial for a phosphate binder, as any loss in active content could reduce its efficacy in binding dietary phosphate and controlling serum phosphate levels in CKD patients.

The most critical functional attribute— in vitro dissolution performance—was also evaluated at each stability interval using the same USP apparatus II conditions applied during development. The dissolution profiles of the stability samples overlapped closely with the initial optimized batch, consistently achieving greater than 85% drug release within 30 minutes and approaching near-complete release by 45 minutes. No significant change in the release rate or extent was observed, demonstrating that the optimized granule percentage, microcrystalline cellulose, and hydroxypropyl cellulose levels successfully maintained the desired rapid dissolution kinetics even under stressful environmental conditions. This preservation of dissolution behavior is vital for therapeutic efficacy, as it ensures prompt availability of lanthanum ions in the gastrointestinal tract to form insoluble phosphate complexes, thereby supporting effective hyperphosphatemia management without compromising bioavailability.

Moisture content analysis using the Karl Fischer method showed only a marginal increase that remained well within acceptable limits, indicating that the inclusion of colloidal silicon dioxide as a glidant and moisture scavenger effectively minimized hygroscopicity. Overall, the accelerated stability data demonstrate exceptional robustness of the DoE-optimized chewable tablet formulation. The absence of meaningful changes across all evaluated parameters confirms that the product meets stringent quality requirements for commercial viability and long-term storage. These findings not only fulfill regulatory expectations but also provide strong assurance regarding the formulation's performance, safety, and efficacy during its intended shelf life. The successful stability outcome underscores the power of the systematic Quality by Design and Design of Experiments approach in developing a patient-centric, high-dose phosphate binder tablet that can reliably improve compliance and therapeutic outcomes in CKD patients.

V. CONCLUSION

The present study successfully demonstrates the development of a DoE-optimized chewable Lanthanum Carbonate tablet formulation specifically tailored for effective management of hyperphosphatemia in patients with chronic kidney disease (CKD). Employing a 2^3 full factorial design within the Quality by Design framework, critical formulation

variables — percentage of granules, microcrystalline cellulose, and hydroxypropyl cellulose — were systematically optimized to achieve a robust, patient-centric dosage form. The optimized tablets exhibited excellent flow properties, uniform weight variation, adequate hardness, low friability, rapid disintegration (within 2–3 minutes), and superior organoleptic characteristics with effective taste masking of the inherently bitter drug.

In vitro dissolution studies confirmed remarkable performance, with more than 85% drug release attained within 30 minutes — a significant improvement over initial screening batches. Accelerated stability studies under ICH conditions (40°C/75% RH for three months) further validated the formulation's robustness, showing no significant changes in physical appearance, assay, dissolution profile, or mechanical properties. These results confirm the chemical and functional stability of the product under stressed conditions, supporting its commercial viability.

This chewable tablet formulation effectively addresses key limitations of conventional phosphate binders, including large tablet size, poor palatability, and swallowing difficulties faced by pediatric, geriatric, and dysphagic CKD patients. By enabling administration without water and providing pleasant mouthfeel, the optimized product is expected to substantially enhance patient compliance, leading to better serum phosphate control, reduced secondary hyperparathyroidism, and lower risk of vascular calcification and cardiovascular complications.

In summary, the integration of Design of Experiments has transformed a challenging high-dose phosphate binder into a high-performance, patient-friendly chewable tablet that meets stringent critical quality attributes. This work highlights the value of systematic, data-driven formulation strategies in developing next-generation therapeutics for chronic diseases. The optimized Lanthanum Carbonate chewable tablets hold strong potential to improve therapeutic outcomes and quality of life for CKD patients while offering a scalable and regulatory-friendly manufacturing pathway.

REFERENCES

1. Block, G. A., Klassen, P. S., Lazarus, J. M., Ofsthun, N., Lowrie, E. G., & Chertow, G. M. (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology, 15(8), 2208–2218.
2. Chiu, Y. W., Teitelbaum, I., Misra, M., de Leon, E. M., Adzize, T., & Mehrotra, R. (2009). Pill burden, adherence, and self-reported health status in hemodialysis patients. Clinical Journal of the American Society of Nephrology, 4(9), 1489–1496.
3. Cozzolino, M., Galassi, A., Biondi, M. L., & Brancaccio, D. (2012). Lanthanum carbonate: A new phosphate binder. Expert Opinion on Pharmacotherapy, 13(4), 545–553.
4. Davison, S. N., & Levin, A. (2011). Management of hyperphosphatemia in CKD: An update. American Journal of Kidney Diseases, 58(5), 792–803.
5. Hutchison, A. J. (2009). Oral phosphate binders. Kidney International, 75(9), 906–911.
6. Joy, M. S., Finn, W. F., & the LAM-302 Study Group. (2003). Randomized, double-blind, placebo-controlled, dose-titration study of lanthanum carbonate for reduction of serum phosphate in hemodialysis patients. American Journal of Kidney Diseases, 42(4), 738–747.
7. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. (2003). American Journal of Kidney Diseases, 42(4 Suppl 3), S1–S201.
8. Mehrotra, R., Kermah, D., & Adler, S. (2005). Hyperphosphatemia in chronic kidney disease: Pathophysiology and management. Current Opinion in Nephrology and Hypertension, 14(6), 552–558.
9. Sprague, S. M. (2007). A comparative review of the efficacy and safety of lanthanum carbonate and sevelamer hydrochloride. Drugs, 67(5), 721–731.
10. Toussaint, N. D., & Elder, G. J. (2008). Phosphate binders in CKD: Past, present and future. Nephrology Dialysis Transplantation, 23(10), 3095–3097.
11. Fu, Y., & Park, K. (2012). Recent developments in chewable tablets. Pharmaceutical Technology, 36(8), 42–48.
12. Gohel, M., & Jogani, P. (2005). A review of co-processed directly compressible excipients. Journal of Pharmacy & Pharmaceutical Sciences, 8(1), 76–93.
13. Kaur, L., Singh, I., & Singh, S. (2015). Formulation and evaluation of chewable tablets of lanthanum carbonate for hyperphosphatemia. International Journal of Pharmaceutical Sciences and Research, 6(8), 3456–3464.
14. Mishra, D. N., Bindal, M., Singh, S. K., & Kumar, S. G. V. (2006). Formulation and evaluation of chewable tablets of montelukast sodium. Indian Journal of Pharmaceutical Sciences, 68(4), 479–482.

15. Patel, V. F., Patel, N. M., & Patel, M. M. (2011). Formulation and evaluation of chewable tablets of lanthanum carbonate. International Journal of Pharma and Bio Sciences, 2(4), 456–462.
16. Singh, J., & Walia, M. (2014). Chewable tablets: A comprehensive review. International Journal of Pharmaceutical Sciences and Research, 5(12), 5320–5327.
17. Verma, P., & Pandit, J. K. (2013). Formulation and evaluation of taste masked lanthanum carbonate chewable tablets. Journal of Pharmaceutical Research, 12(3), 145–152.
18. Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. The AAPS Journal, 16(4), 771–783.
19. Awotwe-Otoo, D., Agarabi, C., Wu, G. K., Casey, E., Read, E. K., & Lute, S. (2012). Quality by design: Impact of formulation variables and their interactions on quality attributes of a lyophilized monoclonal antibody. International Journal of Pharmaceutics, 438(1-2), 167–175.
20. De Beer, T. R. M., et al. (2012). Design space development for a pharmaceutical process using design of experiments. Journal of Pharmaceutical Sciences, 101(6), 2183–2195.
21. Gabrielsson, J., Lindberg, N. O., & Lundstedt, T. (2002). Multivariate methods in pharmaceutical applications. Journal of Chemometrics, 16(3), 141–160.
22. Montgomery, D. C. (2017). Design and analysis of experiments (9th ed.). John Wiley & Sons.

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

IN SCIENCE, ENGINEERING AND TECHNOLOGY

| Mobile No: +91-6381907438 | Whatsapp: +91-6381907438 | ijmrset@gmail.com |

www.ijmrset.com