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Original Article

Quality by Design Based Formulation and Development of a Novel Bi-Compound Pharmaceutical Capsule: An Innovative Approach for the Treatment of Hypertension

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ABSTRACT

Objectives: This study aimed to develop a novel bi-compound pharmaceutical capsule containing nifedipine gastro-retentive floating microspheres and telmisartan immediate-release solid dispersions using a Quality by Design (QbD) approach. **Materials and Methods:** QbD methodology was applied to optimize the formulations and ensure product quality. Risk assessment tools identified the Critical Material Attributes (CMA) and Critical Process Parameters (CPP). A Plackett-Burman screening design was applied to examine the impact of these factors on Critical Quality Attributes (CQA), followed by a Box-Behnken optimization design to establish the design space. The optimized formulation was analyzed, and drug-excipient compatibility was confirmed using FTIR, DSC, and XRD analyses. **Results and Discussion:** The results demonstrated that the optimized nifedipine microspheres remained buoyant for over 12 hr with 95.15% drug release at 12 hr. Telmisartan solid dispersions exhibited 97.83% drug release within 1 hr. Particle size analysis revealed the size range of 200-300 µm for bi-compound pharmaceutical formulation. The drug entrapment efficiency was 80-90% for both components. *In vivo* gamma scintigraphy in rats confirmed the gastro-retentive properties over 12 hr. Stability studies demonstrated <5% change in critical quality attributes over 12 months of storage, confirming the robustness of this formulation. **Conclusion:** The QbD-guided development of this bi-compound pharmaceutical capsule presents a promising approach for effective hypertension management, with the potential for improved patient compliance and therapeutic outcomes.

Keywords: Hypertension, Combination therapy, Quality by Design (QbD), Bi-compound pharmaceutical capsule, Gamma scintigraphy.

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INTRODUCTION

Hypertension is a major global health concern that increases the risk of cardiovascular disease threefold compared to normal blood pressure, contributing to approximately 7.5 million deaths annually.[1,2] According to the NICE guidelines, hypertension is diagnosed when the blood pressure is ≥140/90 mmHg.[3,4] The JNC-8 suggests a target BP of <150/90 mmHg for individuals aged ≥60 years and <140/90 mmHg for those with diabetes or chronic kidney disease.[5,6] The treatment guidelines from the ESC/ESH and ACC/AHA suggest starting monotherapy for low-risk CV groups or frail elderly patients.[3-7] Increasing monotherapy doses can reduce coronary and cerebrovascular events by 29% and 40%, respectively, whereas using two antihypertensive agents can reduce these events by 40% and 54%, respectively. Using a combination of medications with distinct mechanisms of action can lower Blood Pressure (BP) five-fold compared with escalating the dosage of a single antihypertensive medication.[8,9] Various effective combinations are available, but the most preferred combination is an Angiotensin Receptor Blocker (ARB) with a Calcium Channel Blocker (CCB). This combination reduces BP and alleviates side effects, such as pedal edema, from dihydropyridine CCBs.[10,11] Nifedipine is an arteriolar vasodilator and CCB that primarily affects blood vessels without affecting heart rate. The Shanghai Trial found that long-acting nifedipine reduced blood pressure in hypertensive patients, lowering morning systolic blood pressure by 2 mmHg and diastolic blood pressure by 1 mmHg, while increasing the pulse rate by 1 bpm, compared with amlodipine.[12] Telmisartan is an effective antihypertensive agent belonging to the ARB class that inhibits angiotensin II activity and reduces blood pressure. A previous study showed that telmisartan 80 mg provides better control of systolic and diastolic blood pressure over 6 h than losartan 50 mg and telmisartan 40 mg.[13] It also outperformed valsartan, likely due to its longer half-life, which improves glycemic and lipid levels.[14] Combining nifedipine

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extended-release (GITS) with telmisartan is recommended for patients at high cardiovascular risk. Nifedipine is metabolically neutral and slows atherosclerosis, whereas telmisartan effectively targets the AT1 receptor for a prolonged duration of action.[15] The TALENT study further supports that low-dose nifedipine GITS with telmisartan leads to quicker blood pressure control without significantly increasing the adverse events. However, the TALENT study involved the sequential addition of nifedipine and telmisartan rather than a single-pill combination. Consequently, no fixed-dose combination is currently available in the market.[16] A fixed-dose combination of nifedipine and telmisartan may not exist because of formulation challenges, such as differences in their physicochemical properties and drug release profiles. Additionally, regulatory hurdles, including the need for extensive clinical trials to ensure safety and efficacy, could contribute to the absence of such a combination. Interestingly, studies have shown that combining nifedipine and telmisartan can provide greater and earlier blood pressure reduction than monotherapy with either drug. The oral route of administration is generally the most favorable. However, conventional oral delivery systems have poor solubility, low bioavailability, and short half-lives, leading to frequent dosing and plasma concentration fluctuations. These challenges are addressed by advanced medication delivery mechanisms, including Gastro-Retentive Drug Delivery Systems (GRDDS) and Super-Saturable Drug Delivery Systems (SDDS).[17,18] Nifedipine, a calcium channel blocker for high blood pressure, is rapidly released due to its short half-life and spikes the plasma concentration, resulting in adverse events. Sustained-release nifedipine is preferred for hypertension management because it minimizes these spikes and improves patient compliance. Gastro retentive systems enhance nifedipine delivery by providing a sustained release and consistent plasma concentrations.[19] Floating microspheres improve the oral bioavailability and therapeutic efficacy by ensuring prolonged gastric retention and controlled drug release. This formulation maintains therapeutic plasma levels, enhances patient compliance, and reduces side effects.[20] The oral bioavailability of poorly water-soluble medications, such as telmisartan, is enhanced by SDDS. This system maintains the drug in a supersaturated state within the gastrointestinal tract.[21] In ternary solid dispersions, telmisartan is uniformly incorporated into a hydrophilic polymer matrix with a surfactant to improve its dissolution and prevent precipitation. Studies have demonstrated that these systems lead to rapid dissolution, prolonged supersaturation, and better bioavailability than binary systems or pure drugs, offering the potential to optimize the delivery of telmisartan and similar antihypertensive medications.[22] Combination therapy is well tolerated and has fewer side effects than high-dose monotherapy.[23,24]

Combining drugs with different release profiles in a single dosage form presents challenges due to distinct physicochemical properties. This study addresses these challenges by formulating a bi-compound pharmaceutical capsule incorporating nifedipine gastro-retentive floating microspheres for sustained release and telmisartan immediate-release solid dispersions. A Quality by Design (QbD) approach with risk assessment and design of experiments was employed.[25] Ethyl cellulose in nifedipine microspheres controlled the release rate, while soluplus and poloxamer 188 in telmisartan solid dispersions enhanced dissolution. This strategy successfully integrates immediate and sustained release profiles into a single capsule, potentially improving patient adherence and therapeutic outcomes. This novel QbD-assisted formulation demonstrated superior bioavailability, patient compliance, and therapeutic efficacy compared with conventional antihypertensive formulations.

MATERIALS AND METHODS

Materials

Nifedipine was received as a complementary sample from Cipla Ltd., Mumbai and Telmisartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad, India. Ethyl cellulose and Hydroxypropyl Methyl Cellulose (HPMC) were obtained from Loba Chemie Pvt. Ltd., (Mumbai, India). Soluplus and Poloxamer 188 were obtained from BASF Corporation (Mumbai, India; headquarters in Ludwigshafen, Germany). Polyvinyl Alcohol (PVA), dichloromethane, and ethanol were obtained from Merck Ltd., (Mumbai, India). Magnesium stearate and talc were purchased from SD Fine Chemicals. Ltd., (Mumbai, India). All other ingredients, chemicals, reagents, and solvents were of analytical grade and used as received.

Methods

Defining the QTPP and identification of CQAs

The Quality Target Product Profile (QTPP) is the primary step in Quality by Design (QbD) as it outlines the ideal characteristics that ensure the desired quality and safety of pharmaceutical products. This parameter was defined in the early development phase. Critical Quality Attributes (CQAs) were derived from the QTPP using preliminary studies and literature reviews. These attributes represent the characteristics of the final product, and monitoring them ensures consistent product performance and stability. CQAs offer a more technical perspective for product and process understanding.[26,27]

Risk Assessment Studies

To proceed with the Design of Expert software, risk assessment studies were conducted to identify the potential high-risk critical material attributes and critical process parameters for bi-compound pharmaceutical formulation that affect the critical quality attributes of drug product.[26-28]

Preparation of Formulations

Preparation of gastro-retentive floating microspheres of Nifedipine

Nifedipine microspheres were synthesized via an emulsification (o/w) solvent evaporation method. The internal phase was prepared by dissolving ethyl cellulose and hydroxypropyl methylcellulose in dichloromethane and ethanol, followed by drug incorporation. The aqueous phase was prepared by heating a polyvinyl alcohol emulsifier in distilled water at 50°C. The internal phase was added dropwise to the aqueous phase and stirred at 40°C for 3 hr. After the evaporation of the organic solvent and filtration, the floating microspheres were washed using 0.1N HCl and subsequently dried for further analysis.

Preparation of Immediate-release solid dispersions of Telmisartan

Telmisartan solid dispersions were prepared using a solvent evaporation method. The drug compound, polymer, and surfactant were quantified and dissolved in an appropriate organic solvent (ethanol) to produce a homogeneous solution of each. The concentrations were optimized based on solubility and compatibility parameters. The solution was agitated and heated at 50°C for 6 hr to ensure complete dissolution of the drug and polymer. Subsequently, the organic solvent was evaporated to yield a solid dispersion of the drug, polymer, and surfactant mixture.

Screening Study (Plackett-Burman Design)

A Plackett-Burman design was employed to screen for potential high-risk factors from the results of the risk assessment step, facilitating the efficient identification of significant factors affecting CQAs. Six factors were evaluated at low and high levels over 12 runs. Design Expert®13 software was used to generate the experimental plan and perform statistical analyses. Twelve formulations were prepared in triplicate, and their effects on the CQAs were analyzed using multilinear regression and ANOVA. Pareto charts were used to study the influence of the factors on the responses, with the bar length representing the magnitude of the impact. These charts highlight the most significant factors affecting the critical quality attributes to focus on improvement.[28,29]

Optimization Study (Box-Behnken Design)

Box-Behnken design was employed to optimize the bi-compound pharmaceutical formulation. Seventeen batches were prepared at low, intermediate, and high levels. Design Expert®13 software was used for matrix generation and statistical analyses to evaluate the various CQAs of the formulation. Each formulation was prepared in triplicates. Model significance was assessed by identifying the correlation between adjusted R^2 and predicted R^2 values, *p*-value of the suggested model, and lack of fit, followed by regression analysis to establish polynomial equations and evaluate the significance of factors using *p*-values. Three-dimensional response surface plots illustrated the influence of factors on the responses, and an overlay plot was generated to optimize the formulation.[28,29]

Establishment of the Design Space

This study employed response surface methodology and optimization to define the design space for a bi-compound pharmaceutical formulation. The objective was to minimize particle size and drug release in 12 hr while maximizing buoyancy, 1-hr drug release, percentage yield, and drug entrapment efficiency. Overlay plots incorporating the responses were generated. To determine the optimal formula, a desirability function (d-value) was constructed based on the target response. A d-value approaching 1 indicates desirable results, whereas 0 signifies detrimental outcomes. Successful operating ranges were established as follows: drug release in 12 hr (80-90%), buoyancy (85-95%), particle size (210-220 µm), drug release in 1 hr (85-100%), percentage yield (85-95%), and drug entrapment efficiency (80-90%).[28,29]

Confirmation test of the model

A confirmation test was conducted for all three factors to evaluate the accuracy and robustness of the proposed model. The bi-compound pharmaceutical formulations with these compositions were prepared in triplicate and analyzed to determine their responses (CQAs). A comparison was made between the actual responses and the responses predicted using the design-space model.[28,29]

Evaluation/Characterization of Formulations

Particle Size

The particle size of the bi-compound pharmaceutical formulation was evaluated using an optical microscope fitted with a calibrated eyepiece micrometer. A minute quantity of each formulation was spread on a clean glass slide with a drop of liquid paraffin separately, and a cover slip was positioned on the top. The average particle size was calculated and determined by measuring 100 particles of each batch using Edmondson's equation.[30,31]

$$d_{mean} = \frac{\Sigma nd}{\Sigma n}$$

where "n" represents the number of quantified microspheres or solid dispersions, and "d" represents the average particle diameter.

Surface Morphology

The surface morphology of the optimized bi-compound pharmaceutical formulation was examined using Scanning Electron Microscopy (SEM). Each sample was placed on an aluminum stub and covered with a thin gold-palladium coating using an auto fine coater (JEOL, JEC-1601, Japan). A scanning electron microscope (JEOL, JSM-6362A, Japan) operating at an

acceleration voltage of 10 kV was used to analyze each sample individually.[30,31]

Percentage Yield

The percentage yield of the bi-compound pharmaceutical formulation was calculated separately to determine the efficiency of the method.[32,33] The percentage yield was calculated as follows:

$$Percentage\ yield = \frac{Weight\ of\ microspheres\ or\ solid\ dispersions\ recovered}{Theoretical\ weight\ of\ the\ polymer\ and\ drug} \times 100$$

Drug Entrapment Efficiency

The entrapment efficiency of the bi-compound pharmaceutical formulation was determined independently. Ten milligrams of each formulation was dissolved in ethanol (10 mL), and the volume was adjusted using 0.1 N HCl. After filtration, the solutions were analyzed by spectrophotometry (Shimadzu UV-1700 S, Japan) at 238 nm for floating microspheres and 296 nm for solid dispersions, using a calibration curve. Drug content analysis was performed in triplicate for each batch.[32,33] The entrapment efficiency was determined using the following formula:

$$Drug\ Entrapment\ Efficiency = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

In vitro Buoyancy Study

An *in vitro* buoyancy study was conducted using a USP type II dissolution apparatus (paddle type). Nifedipine floating microspheres (100 mg) were spread on the surface of the apparatus filled with 900 mL of 0.1 N HCl solution (pH 1.2) containing Tween 80 (0.02 w/v %) to simulate gastric fluid. The mixture was agitated using a paddle rotating at 100 rpm and 37±0.5°C for 12 hr. Subsequently, the floating and sunken microspheres were collected and weighed separately.[34] The buoyancy percentage of the dried microspheres was calculated using the following formula:

$$\%\ Buoyancy = \frac{W_f}{W_f + W_s} \times 100$$

Where W_f and W_s are the weights of the floating and sinking microspheres.

In vitro Dissolution Study

An *in vitro* dissolution study of the bi-compound pharmaceutical formulation was conducted using a USP Type II Dissolution apparatus (paddle type) at 37±0.5°C and a speed of 100 rpm. A total of 900 mL of simulated gastric fluid (0.1N HCl) was used as the medium. The use of 0.1N HCl as a dissolution medium for both nifedipine and telmisartan is justified because it simulates gastric conditions and offers valuable insights into their dissolution behavior in the stomach, which is crucial for oral absorption and bioavailability. For nifedipine, floating microspheres equivalent to 50 mg were added to the medium. Aliquots (2 mL) were withdrawn every hour for 12 hr. For telmisartan, solid dispersions equivalent to 50 mg were used. Aliquots (2 mL) were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min. The sink condition was maintained by replacing the equivalent volume of the medium. The samples were filtered and analyzed using a UV spectrophotometer (UV 1800, Shimadzu, Kyoto, Japan) at 238 nm for nifedipine and 296 nm for telmisartan.[35,36]

Determination of the drug release mechanism

To understand the drug release mechanism, *in vitro* release data of the optimized formulation were fitted to various kinetic models. The most appropriate model was selected based on goodness-of-fit criteria.

Drug-Excipient Compatibility Study

Fourier Transform Infrared (FT-IR) analysis

FT-IR spectroscopy was used to analyze the drug-polymer interactions and formulation stability. Samples (2-3 mg) were combined with an equivalent mass of anhydrous potassium bromide and compressed into KBr discs. An FT-IR spectrophotometer (Shimadzu 1700 S, Japan) was used to obtain the spectra of pure nifedipine and the optimized formulation. Similarly, FT-IR spectra of pure telmisartan and the optimized formulation were obtained using the same methodology.[35,36]

Differential Scanning Calorimetry (DSC) analysis

Thermal analysis of the bi-compound pharmaceutical formulation was performed using a Differential Scanning Calorimeter (DSC-60, Shimadzu, Japan). Samples were weighed, sealed in aluminum pans, and heated from 20 to 350°C at 10°C/min under nitrogen purge. An empty pan was used as the reference pan. The DSC thermogram of the pure drug was compared with that of the microspheres. Similarly, thermal analysis of the drug and selected solid dispersion formulation was conducted using the same calorimeter and compared.[31-37]

X-ray Diffraction (XRD) analysis

Powder X-ray Diffraction (XRD) analysis of pure nifedipine and the optimized floating microspheres was conducted using an X-ray diffractometer (Bruker AXS D8 Advance, GmbH, Germany). The samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed at 2θ between 2° and 40°C, with a voltage of 30 kV and a current of 30mA. Analogous XRD analysis was performed on pure telmisartan and optimized solid dispersions.[33-35]

Micromeritics

Bulk Density

The bulk density was determined by placing a predetermined quantity of dried microspheres or solid dispersions in a graduated cylinder. After levelling the powder, the bulk volume was recorded.[33-37] The bulk density was calculated using the following formula:

$$Bulk\ density = \frac{Mass\ of\ microspheres\ or\ solid\ dispersions}{Bulk\ volume\ of\ microspheres\ or\ solid\ dispersions}$$

Tapped Density

The tapped density is the ratio of the mass of the microspheres or solid dispersions to the volume occupied after a standardized tapping procedure. A measured quantity of microspheres or solid dispersions was placed in a cylinder and subjected to 300 taps from a 1-inch height at 2-sec intervals.[33-37] The resulting tapped volume was recorded and calculated using the following equation:

$$Tapped\ density = \frac{Mass\ of\ microspheres\ or\ solid\ dispersions}{Tapped\ volume\ of\ microspheres\ or\ solid\ dispersions}$$

Hausner's ratio

Hausner's ratio was used to predict the flow characteristics of the microspheres and solid dispersions.

$$Hausner's\ ratio = \frac{Tapped\ density}{Buk\ density}$$

Compressibility Index

The Compressibility Index (CI) is a quantitative measure of the capacity of a powder for compression and volume retention under applied pressure. The CI was determined for both microspheres and solid dispersions.[33-37]

Angle of Repose

The Angle of Repose (AOR) represents the tendency of a powder to flow and its resistance to gravitational forces. The funnel was secured to a stand 3 cm above the horizontal plane. Microspheres or solid dispersions were introduced into the funnel and allowed to flow freely, after which the height and radius of the resultant heap of the microspheres/solid dispersions were measured separately.[33-37]

$$\theta = \frac{tan^{-1}\,h}{r}$$

Where, 'h' is the height of heap and 'r' is the radius of heap of microspheres/solid dispersions.

Formulation and Evaluation of Novel Dual Drug-Loaded Delivery System

Formulation of novel dual-drug loaded delivery system

Bi-compound pharmaceutical capsules were prepared by filling the 00-size hard gelatin capsule with the optimized formulation of floating microspheres equivalent to 20 mg of nifedipine and solid dispersions equivalent to 80 mg of telmisartan with talc and magnesium stearate to improve its flow properties.

Evaluation of novel dual-drug loaded delivery system

Weight variation and Content uniformity test

The weight variation and content uniformity of the capsules containing drug-loaded microspheres and solid dispersions were also evaluated. Ten empty capsules were individually weighed, filled with microspheres and solid dispersion powders, and reweighed to determine their gross weight. The drug content in each capsule was quantified, and the content uniformity was assessed by determining the drug content of all 10 capsules. The drug concentrations were measured at 238 nm for nifedipine and 296 nm for telmisartan using a UV-visible spectrophotometer.[38,39]

Disintegration Time

The disintegration test utilized an apparatus comprising a basket rack with six glass tubes (7.75 cm long, 2.15 mm diameter) and a #10 mesh sieve at the bottom. Six capsules were placed in each tube, and the basket was raised and lowered 28-32 times per minute in 900 mL of 0.1N HCl at 37±2°C. The disintegration time was measured as the time required for capsule fragments to pass through the mesh.[38,39]

In vitro Drug Release Study

Drug release from the optimized capsule was evaluated using a USP dissolution apparatus type II with 0.1 N HCl (900 mL) as the dissolution medium. Drug release was quantified over 60 min for immediate-release telmisartan solid dispersions and over 12 hr for sustained-release nifedipine floating microspheres. The temperature was maintained at 37±0.5°C and agitated at 50 rpm. Aliquots were withdrawn at predetermined intervals and filtered through Whatman paper, and their absorbance was measured at 238 nm for nifedipine and 296 nm for telmisartan using a UV-visible spectrophotometer. The cumulative percentage of drug release was calculated using a standard curve.[38,39]

Drug Release Kinetics Study

The mechanism of drug release from the bi-compound pharmaceutical capsules was investigated by fitting the dissolution data of the optimized formulation to the following models: zero-order, first-order, Higuchi square root law, and Korsmeyer.

Stability Studies

Stability testing of bi-compound pharmaceutical capsules was conducted under accelerated (40±2°C/75% RH±5% RH) and intermediate conditions (30±2°C/65% RH±5% RH) for 6 months and long-term conditions (25±2°C/60% RH±5% RH) for 12 months, as per the ICH Q1A(R2) guideline. The physical characteristics, particle size distribution, percentage yield, drug entrapment efficiency, and drug release of the capsules were assessed.

Comparison of test preparation with marketed preparation

Nifedipine capsules and the commercial product Adalat retard (20 mg) were evaluated for dissolution. The studies were conducted using the United States Pharmacopeia (USP) standard dissolution apparatus II, equipped with a paddle stirrer (75 rpm, 37°C, 900 mL dissolution medium). The capsules and tablets were subjected to a dissolution medium for 12 hr. At predetermined intervals, 5 mL samples were withdrawn using a syringe fitted with a pre-filter. The withdrawn volume was replenished with fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 238 nm using a UV-visible spectrophotometer after appropriate dilution. All the studies were conducted in triplicate. The dissolution medium was a hydrochloric acid buffer (pH 1.2). Similarly, telmisartan capsules and the marketed formulation, Telma™ 80 mg, were assessed using an identical apparatus and conditions for 90 min. Samples were withdrawn and analyzed by measuring the absorbance at 296 nm using a UV-visible spectrophotometer after dilution. All experiments were performed in triplicates.

In vivo Evaluation of Gastric Retention Ability of Optimum Formulation

The experimental protocol (CCSEA/IAEC/P'Ceutics/60/2023-24/195) was approved by the Institutional Animal Ethics Committee, Y.B. Chavan College of Pharmacy, Aurangabad, India, on 27/04/2024, adhering to standard guidelines.

Gamma scintigraphy studies were conducted at Spect Labs (Pune, India). Nine adult male Wistar rats (12-13 weeks old, 250-300 g) were housed under controlled conditions and provided access to RO-treated water and a standard diet. The rats were allocated into three groups, each comprising three rats (treated and untreated), in accordance with standard practices in preclinical research. This approach balances statistical power with ethical considerations aimed at minimizing the use of animals. Studies have investigated the transit of radiolabelled microspheres through the gastrointestinal tract following oral administration. These microspheres, labelled with radioactive samarium-153 oxide ($^{153}Sm_2O_3$), underwent neutron activation in a nuclear reactor and were subsequently analyzed 24 h later by gamma spectroscopy. They were stored to allow for the decay of undesired byproducts. Following a 12-hr fasting period, the rats received microspheres via a feeding tube, followed by water. A gamma camera monitored the gastrointestinal location at various time points from 1 to 12 hr after administration. The rats were allowed unrestricted movement during the scans. A region of interest was established around the stomach, and the radioactivity was quantified using specialized software. The microsphere preparation included 10 mg of ^{153}Sm, with its release indicating the release of nifedipine.[40]

RESULTS

Defining the QTPP and identification of CQAs

The QTPP for a bi-compound pharmaceutical formulation was determined. Several Critical Quality Attributes (CQAs) influence the desired once-daily dosing regimen and therapeutic efficacy of the selected formulations.

Risk Assessment Studies

The Ishikawa fishbone diagram identifies the potential risk factors affecting the CQAs of a bi-compound pharmaceutical formulation, as shown in Figure 1. The Risk Estimation Matrix (REM) provided a comprehensive risk assessment through ordinal scores, and Failure Mode and Effects Analysis (FMEA) prioritized the factors by assigning Risk Priority Number (RPN) scores, further highlighting the significant risk factors with the elimination of low-risk factors.

Preparation of Formulations

Gastro-retentive floating microspheres of nifedipine and immediate-release solid dispersions of telmisartan were successfully prepared.

Screening Study (Packett-Burman Design)

The results present the significant model terms with Analysis of Variance (ANOVA), where a *p*-value of less than 0.05 was considered statistically significant. The Pareto charts were used to determine the number of factors that significantly influenced responses, with values exceeding the t-value limit and crossing the Bonferroni limit.

Optimization Study (Box-Behnken Design)

The model selection process prioritized the maximization of adjusted R^2 and predicted R^2 values, demonstrating minimal differences of less than 0.2, with a statistically significant model *p*-value of <0.05 and a non-significant lack of fit (Table 1). The minimal discrepancy between the actual and predicted values confirmed the efficacy of this design. Response surface plots, including three-dimensional representations were used to elucidate the interactions between the significant factors and their effects on the response variables.

Evaluation of the Design Space

The established operating ranges were effective in the design space. The overlay plot demonstrates that all response goals were achieved, further defining the overlap of ranges for the six CQAs, indicating the fulfilment of all criteria.

Confirmation test of the model

A strong correlation was observed between the model predictions and experimental observations; consequently, a desirability value of 0.976 was obtained. Therefore, the model was confirmed, and

the formulation and process variables were robust within the design space.

Evaluation of Formulations

Particle size analysis

The particle size analysis revealed a range of 200-300 µm, unveiling the microstructure of the formulations. An increase in particle size was observed with a high amount of polymers, while the surfactant concentration and stirring speed notably reduced the particle size of the formulations.

Percentage yield

The percentage yield of the nifedipine floating microspheres increased with increasing polymer concentration and was found to be 95.24±0.31. Similarly, telmisartan solid dispersions exhibited a high yield of 96.24±0.37, which increased with increasing polymer and surfactant concentrations. Furthermore, the percentage yield improved with increasing stirring speed up to a certain threshold value. These findings demonstrate the efficacy of the preparation technique for floating microspheres and solid dispersions.

Drug entrapment efficiency

The drug entrapment efficiency of the nifedipine floating microspheres was 91.79±0.26 and exhibited a positive correlation with higher concentrations of EC and HPMC and a negative correlation with stirring speed. For telmisartan solid dispersions, the entrapment efficiency of 89.29±0.35 showed improvement with higher soluplus concentrations, whereas increased poloxamer 188 concentrations and stirring speed resulted in a decreased yield. This study achieved a drug entrapment efficiency of 80-90% for both drugs. This finding is comparable to those of previous studies. For example, the study by Chalamalasetty *et al*., (2019) reported entrapment efficiencies ranging from 75% to 85% for nifedipine microspheres.[37]

In vitro buoyancy study

The optimized nifedipine microspheres in this study remained buoyant for over 12 hr, which is better than that reported in some previous studies on floating drug delivery systems. For example, a study by Chalamalasetty *et al*., (2019) on nifedipine floating microspheres reported a maximum floating time of 10 hr.[37] Microspheres containing higher concentrations of Ethyl Cellulose (EC) demonstrated superior buoyancy compared with those containing Hydroxypropyl Methylcellulose (HPMC), which can be attributed to the insolubility of EC in gastric fluid (pH 1.2).

Surface morphology

The morphology of the nifedipine floating microspheres revealed a spherical shape with a hollow cavity and smooth surface, indicating complete drug entrapment. The solid dispersions of telmisartan resulted in large spherical amorphous particles, suggesting the molecular dispersion of the drug within the carrier.

In vitro dissolution study

An *in vitro* dissolution study of nifedipine floating microspheres demonstrated that drug release was sustained throughout the duration, and no burst effect was observed. The telmisartan solid dispersions in this study exhibited 97.83% drug release within

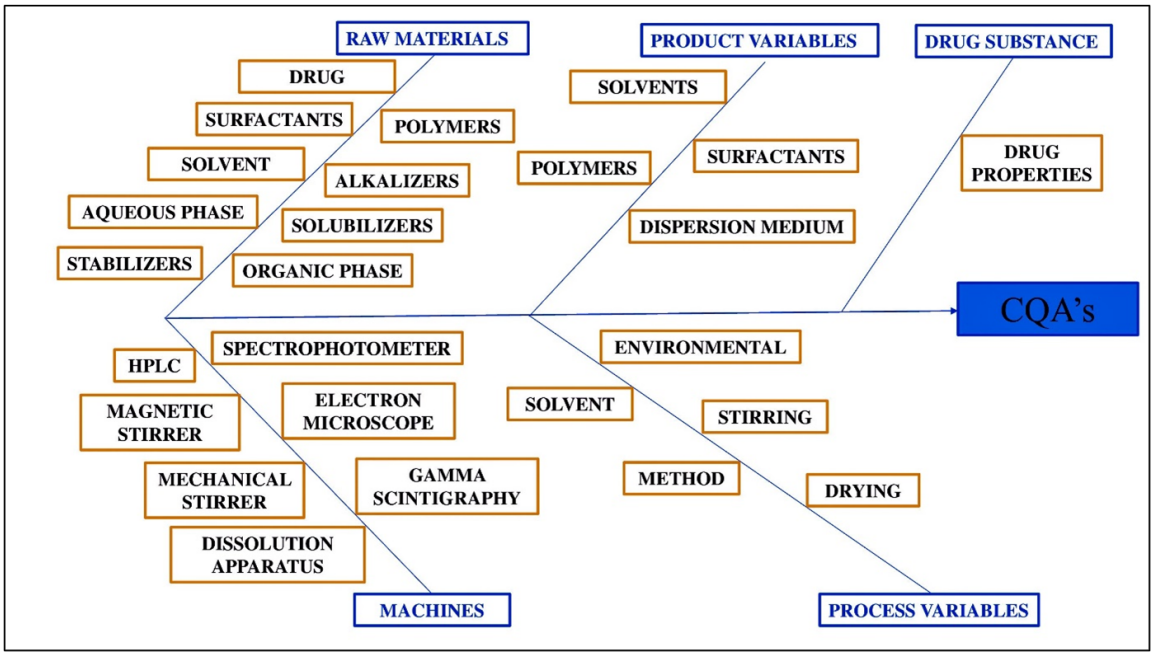

Figure 1: Ishikawa fish-bone diagram illustrating the interrelationships among variables for the formulation of bi-compound pharmaceutical formulation.

1 hr. This is a significant improvement over previous study. For instance, a study by Paul (2019) on telmisartan solid dispersions reported a maximum drug release of approximately 85% in 1 hr.[36] For solid dispersions, higher concentrations of the polymer and surfactant enhanced drug release through improved wettability and reduced interfacial tension.

Drug release kinetics

The most appropriate model was determined by comparing the correlation coefficients (r^2). The zero-order plots for all nifedipine formulations demonstrated linearity in an acidic medium (pH 1.2). The highest r^2 values were observed for the zero-order model, indicating that diffusion was the primary mechanism of drug release. These zero-order kinetics demonstrated the controlled release of the prepared microspheres. For telmisartan solid dispersions, the drug release kinetic data exhibited the best fit to the Higuchi model, with a regression coefficient (r^2) of 0.9714. The Korsemeyer-Peppas equation indicated a super case-II transport mechanism with n exceeding 0.89.

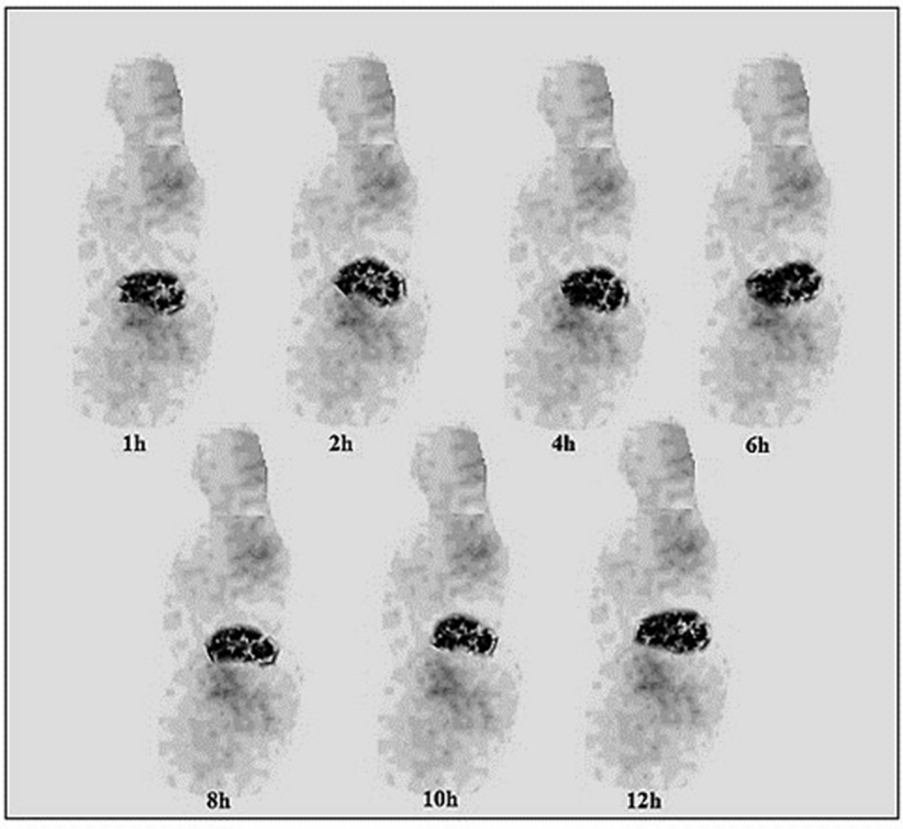

Figure 2: Gamma scintigraphy images of rat stomach following oral administration of nifedipine microspheres.

Table 1: Statistical data values for dependent variables in Box-Behnken design.

Parameters	Values for Dependent Variables					
	Drug release in 12 hr (%)	Buoyancy (%)	Particle size (µm)	Drug release in 1 hr (%)	Percentage yield (%)	Drug entrapment efficiency (%)
Model F value	74.63	95.87	51.80	27.18	40.55	104.00
Model *p*-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Lack of fit F value	0.3018	0.2999	0.7766	3.25	1.01	0.2784
Lack of fit *p*-value	0.9374	0.9384	0.6557	0.1343	0.5376	0.9486
R^2	0.9451	0.9568	0.9228	0.8625	0.9035	0.9600
Adjusted R^2	0.9325	0.9468	0.9050	0.8308	0.8812	0.9508
Predicted R^2	0.9168	0.9354	0.8787	0.7625	0.8264	0.9399

Table 2: Evaluation of Bicompound Pharmaceutical Capsule.

	Weight variation (mg)	Disintegration time (mins)	Drug content	Drug release
Nifedipine	500±0.11	6.7±0.29	97.36±0.33	95.93±0.36
Telmisartan			98.26±0.31	97.85±0.25

Drug-Excipient Compatibility Study

Fourier Transform Infrared (FT-IR) analysis

Drug-polymer compatibility was evaluated using FT-IR peak matching. A comparison of the IR spectra of the drugs and their formulations revealed no significant peak shifts, indicating the absence of chemical interactions during formulation development. The absence of additional peaks confirmed the compatibility and integrity of the physicochemical properties of the systems.

Differential Scanning Calorimetry (DSC) analysis

Nifedipine exhibited a peak at 173°C, while the optimized nifedipine microspheres did not exhibit a nifedipine peak (173°C), indicating the transformation of the drug to an amorphous form. Telmisartan displayed a sharp endothermic peak at 278°C, and the optimized batch of telmisartan solid dispersions demonstrated the absence of a telmisartan peak (278°C), indicating the conversion of the drug from a crystalline to an amorphous form.

X-ray diffraction (XRD) analysis

Nifedipine exhibited diffraction peaks at 2θ values of 8.14°, 11.82°, 16.38°, 19.55°, and 24.49°. The optimized microsphere formulation did not display sharp peaks, producing a halo pattern typical of amorphous compounds. Telmisartan exhibited sharp diffraction peaks at 6.27°, 10.14°, and 25.24°. The optimized solid dispersions showed a significant reduction in crystalline peaks, indicating conversion to the amorphous form.

Micromeritics

The bulk and tapped densities of the nifedipine floating microspheres were 0.41 and 0.47 g/cm^3, respectively, with a corresponding Hausner's ratio of 1.15 and a compressibility index of 12.77%. The angle of repose was measured as 29.74°. For telmisartan solid dispersions, the bulk and tapped densities were 0.46 g/cm^3 and 0.52 g/cm^3, respectively, with a Hausner's ratio of 1.13, a compressibility index of 11.54%, and an angle of repose of 26.57°.

Formulation and Evaluation of Novel Dual Drug-Loaded Delivery System

Bicompound pharmaceutical capsules were successfully prepared and evaluated. The evaluation parameters are listed in Table 2.

Stability Studies

Stability testing of the bi-compound pharmaceutical capsules demonstrated consistent results under accelerated, intermediate, and long-term conditions. These findings confirm the stability of this novel formulation and indicate its potential for long-term storage and use.

Comparison of test preparation with marketed preparation

The findings of this study demonstrated that the drug release percentage for the nifedipine test formulation (floating microspheres) was 95.15±0.22, compared to 98.86±0.25 for the marketed formulation after 12 hr. Additionally, the drug release percentage for the telmisartan test formulation (solid dispersions) was 97.83±0.28 within 1 hr, whereas the marketed formulation achieved 90.65±0.39 in the same timeframe. This suggests that the optimized formulation exhibited a release profile similar to that of a marketed preparation. Hence, it can be concluded that the developed test formulations of nifedipine and telmisartan have the potential to serve as effective dosage forms.

In vivo Evaluation of Gastric Retention Ability of Optimum Formulation

In vivo drug behavior was monitored using gamma scintigraphy. Figure 2 shows the location of the optimized microsphere formulation in the gastrointestinal tract of rats over time. The results indicated that the formulation remained buoyant, gradually releasing the drug over 12 hr, thereby demonstrating the role of ethyl cellulose in controlling the release. This finding supports the potential for improved bioavailability through prolonged gastric retention. Regarding the labeling efficiency, $^{153}Sm_2O_3$ proved to be ideal for use in controlled-release formulations because of its uniform distribution within the microspheres, making its release indicative of drug release. Additionally, $^{153}Sm_2O_3$ is chemically stable and water-insoluble, preventing its absorption into the GI tract or blood plasma. It is excreted from the body through feces and eventually decays into a stable nuclide (^{153}Eu). This clearance mechanism ensures minimal radiation exposure and eliminates the need for specialized radioactive waste management. The *in vivo* findings correlated with the *in vitro* results, confirming that the gastro-retentive properties of the optimized formulation were unaffected by gastric retention.

DISCUSSION

This study presents a novel bi-compound pharmaceutical capsule containing nifedipine gastro-retentive floating microspheres and telmisartan immediate-release solid dispersions for hypertension treatment, developed using a Quality by Design (QbD) approach. The findings of this study represent a significant advancement in hypertension management, potentially improving patient adherence and therapeutic outcomes compared with existing treatments. Maggy L demonstrated that the combination of atenolol (a beta-blocker) and nifedipine (a calcium channel blocker) synergistically reduced blood pressure. However, the telmisartan-nifedipine combination provides better blood pressure control and metabolic benefits than the atenolol-nifedipine combination. Telmisartan, an angiotensin receptor blocker, enhances glucose metabolism and improves lipid profiles. Its longer half-life compared to atenolol allows for sustained antihypertensive effects, resulting in improved blood pressure management and decreased risk of fluctuations. The dual cardiovascular and metabolic benefits of telmisartan make it particularly valuable for patients with diabetes or metabolic syndrome, providing enhanced organ protection.[41]

STUDY LIMITATIONS

The study lacked long-term clinical trials to assess the efficacy and safety of the bi-compound pharmaceutical capsule in human subjects.

CONCLUSION

The present study developed a novel bi-compound pharmaceutical capsule containing nifedipine gastro-retentive floating microspheres and telmisartan immediate-release solid dispersions using a Quality-by-Design (QbD) approach. QbD principles optimize the formulation and process parameters, ensuring consistent product quality. Risk assessment tools identified critical material attributes and process parameters, which were evaluated using Plackett-Burman and Box-Behnken designs for screening and optimization of the process. The optimized formulation exhibited excellent floating properties, with the nifedipine microspheres remaining buoyant for over 12 hr, whereas the telmisartan solid dispersions demonstrated rapid drug release. Various characterization techniques were used to confirm the desired properties. Drug-excipient compatibility was verified using FTIR, DSC, and XRD analyses, ensuring the integrity of the physicochemical properties. The *in vivo* gastric retention ability was evaluated using gamma scintigraphy in rats, confirming the gastroretentive properties observed *in vitro*. Stability studies indicated the robustness of the formulation under various storage conditions. In conclusion, the QbD-guided development of this bi-compound pharmaceutical capsule presents a promising approach for effective management of hypertension. This formulation has the potential to improve patient adherence and enhance the therapeutic outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACC: American College of Cardiology; **ACEI:** Angiotensin Converting Enzyme Inhibitor; **AHA:** American Health Association; **ANOVA:** Analysis of Variance; **AOR:** Angle of Repose; **ARB:** Angiotensin Receptor Blocker; **BP:** Blood Pressure; **CCB:** Calcium Channel Blocker; **CCSEA:** Committee for Control and Supervision of Experiments on Animals; **CI:** Compressibility Index; **CMA:** Critical Material Attributes; **CPP:** Critical Process Parameters; **CPS:** Counts Per Second; **CQA:** Critical Quality Attributes; **CVD:** Cardiovascular Disease; **DBP:** Diastolic Blood Pressure; **DOE:** Design of Experiments; **DSC:** Differential Scanning Calorimetry; **EC:** Ethyl Cellulose; **ESC:** European Society of Cardiology; **ESH:** European Society of Hypertension; **FDA:** Food and Drug Administration; **FMEA:** Failure Mode and Effect Analysis; **FTIR:** Fourier Transform Infrared Spectroscopy; **GIT:** Gastrointestinal tract; **GITS:** Gastrointestinal Therapeutic System; **GRDDS:** Gastro-Retentive Drug Delivery Systems; **HPMC:** Hydroxypropyl Methylcellulose; **HR:** Hausner ratio, HTN Hypertension; **IAEC:** Institutional Animal Ethics Committee; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **JNC:** Joint National Committee; **KBr:** Potassium bromide; **nm:** Nanometre; **NICE:** National Institute for Health and Care Excellence; **PVA:** Polyvinyl Alcohol; **QBD:** Quality by design; **QTPP:** Quality Target Product Profile; **REM:** Risk Estimation Matrix; **RPN:** Risk Priority number; **SBP:** Systolic Blood Pressure; **SDDS:** Supersaturated Drug Delivery Systems; **SEM:** Scanning Electron Microscope; **SR:** Sustained Release; **STONE:** Shanghai Trial of Nifedipine in the Elderly; **UV:** Ultra-violet; **XRD:** X-ray diffraction.

ETHICS COMMITTEE APPROVAL

The experimental protocol (CCSEA/IAEC/P'Ceutics/60/2023-24/195) was approved by the Institutional Animal Ethics Committee, Y.B. Chavan College of Pharmacy,

Aurangabad, India, on 27/04/2024, adhering to the standard guidelines.

AUTHOR CONTRIBUTIONS

Concept and design, Data acquisition, Data analysis/ interpretation, Critical revision of manuscript, Final approval- Aiman Rabiya, Mohamed Hassan Dehghan. Drafting manuscript, Statistical analysis- Aiman Rabiya, Supervision-Mohamed Hassan Dehghan.

SUMMARY

This article describes the development of a novel bi-compound pharmaceutical capsule containing nifedipine gastro-retentive floating microspheres and telmisartan immediate-release solid dispersions for the treatment of hypertension. The formulation was optimized using Quality by Design (QbD) principles, including risk assessment and design of experiments. The optimized formulation demonstrated excellent floating properties, with the nifedipine microspheres remaining buoyant for over 12 hr, whereas the telmisartan solid dispersions exhibited rapid drug release. Characterization techniques confirmed the desired properties and drug-excipient compatibility. *In vivo* studies in rats using gamma scintigraphy validated the gastroretentive properties. Stability studies indicated robustness under various storage conditions. The authors concluded that QbD-guided development presents a promising approach for effective hypertension management, potentially improving patient adherence and therapeutic outcomes.

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