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Original Article

DEVELOPMENT AND OPTIMIZATION OF LASER-DRILLED OSMOTICALLY CONTROLLED NIFEDIPINE EXTENDED-RELEASE TABLETS BY RESOLUTION IV 2^{4-1} FRACTIONAL FACTORIAL DESIGN

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ABSTRACT

Objective: The purpose of this investigation was to create a tablet containing nifedipine for extended-release by laser drilling technique using a resolution IV 2^{4-1} fractional factorial design.

Methods: The extended-release tablet formulation bearing nifedipine was developed by the wet granulation method. The A resolution IV 2^{4-1} fractional factorial design was employed to optimize the nifedipine extended-release tablets. The ratio of sodium chloride (NaCl) to polyox water soluble resin (WSR) NEO, the ratio of NaCl to polyox WSR Coagulant LEO in the push layer, the ratio of polymer and plasticizer in extended release (ER) coat, and % weight gain in the extended-release coat were taken as independent variables, and the percentage of drug dissolved was taken as the dependent variable. The resolution IV 2^{4-1} fractional factorial design was utilized to optimize the formulation, which was subsequently assessed for its performance such as mean weight, thickness, hardness, and friability. Finally, optimized laser-drilledtablets were compared with the undrilled nifedipine extended-release tablets for percent drug release.

Results: The mean weight of the optimized formulation was found to be 718±2.5 mg, the mean thickness was measured to be 7.51±0.2 mm, the hardness of the tablet was found to be 130±5 N, tablet friability was measured as 0.9±0.1% and finally the drug release study of tablets having précised orifice shows controlled drug release over a period of time.

Conclusion: The developed nifedipine extended-release formulation demonstrated controlled drug release following laser drilling. The laser-drilled tablets exhibited a sustained release profile over the study period. The results indicate that laser drilling is a feasible approach for modulating drug release from extended-release tablets.

Keywords: Nifedipine, Tablet, Osmotically controlled, Laser-drilling, Extended release, Factorial design

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INTRODUCTION

Hypertension (HTN) is a chronic health condition and a major global public health problem characterized by elevated high blood pressure. It is estimated that over 1.13 billion peoples suffer from hypertension worldwide [1-3]. The treatment of hypertension often requires lifelong therapy with antihypertensive medications, including calcium entry blockers such as nifedipine [4]. Nifedipine is a potent calcium channel blocker that works by blocking the entry of calcium ions into cells, leading to vasodilation and decreased blood pressure levels. Nifedipine is available in immediate-release (IR) and ER formulations [5]. The pharmaceutical industry has widely used osmotic control and laser drilling technologies to manufacture ER dosage forms. These techniques offer precise control over the drug release profile and help to achieve consistent drug levels in the body. The goal of the ER formulations is to deliver a prolonged, sustained release of the medication, thereby maintaining consistent drug levels in the body and improving patient compliance [6, 7]. The treatment of hypertension requires lifelong therapy, and ER formulations play a critical part in the treatment of this illness. ER has become increasingly important in the treatment of various diseases as they offer several advantages over conventional IR tablets. They provide a controlled medication release over an extended time period leading to improved patient compliance, reduced dosing frequency, and enhanced therapeutic efficacy. Various methods for preparing ER tablets include the osmotic-controlled release oral delivery system (OROS) method and laser drilling nifedipine is a calcium channel blocker used to treat hypertension, angina, and other cardiovascular conditions [8]. Nifedipine ER tablets have been developed using various techniques, including osmotic control, to achieve a controlled release. However, these formulations often suffer from incomplete drug release, leading to suboptimal therapeutic outcomes. Conventional osmotic systems often suffer from limitations such as coating defects, lag time before drug release, and variability in mechanically formed orifices, which can lead to inconsistent drug release profiles; laser drilling overcomes these shortcomings by enabling precise and reproducible orifice formation. By creating micro-channels or pores in the tablet coating, laser drilling can enhance the drug release rate and improve the overall performance of the ER formulation [9, 10].

However, the effectiveness of ER formulations depends on their ability to achieve a controlled release of the medicament over an extended time. Osmotic control has been widely used to achieve this objective by creating a semipermeable membrane around the drug core, which controls the rate of drug release by osmosis [11]. Despite its advantages, osmotic control often suffers from incomplete drug release, leading to suboptimal therapeutic outcomes. Laser drilling has emerged as a promising technique for enhancing the drug release rate of ER formulations. By creating micro-channels or pores in the tablet coating, laser drilling can improve the permeability of the membrane and enhance the drug release rate. Laser drilling can also help to overcome the limitations of osmotic control by providing a more precise and controllable drug release profile [12, 13]. The poor aqueous solubility of nifedipine reduces its absorption and bioavailability. Compare with ordinary preparation, the bioavailability of the drug is about 45-56% whereas, with the use of advanced techniques like laser drilling, the bioavailability of the drug increases to 90-99% [14, 15]. Hence, in the present investigation osmotically controlled laser drilled extended-release tablets of nifedipine were prepared and optimized by using fractional factorial experimental design involving four independent variables at three levels (low, medium, and high).

MATERIALS AND METHODS

Materials

Obtained a complimentary sample of nifedipine from Moehs Fine Chemicals, Barcelona, Spain. Polyox WSR N80 lEO and Methocel E5 Premium was procured from the Chem Point, Barcelona, Spain. Sodium chloride powder United State Pharmacopoeia (USP) was procured from Annexe Chem, Vadodara, Gujarat, magnesium stearate was purchased from ChemiGnition laboratory, Gujarat. Hydroxy propyl cellulose was obtained from the Nippon Soda, Gurgaon, Haryana. Other chemicals and reagents used in the development of tablets were of analytical grade.

Methods

Compatibility studies

Fourier transform infrared spectroscopy (FTIR) analysis

FTIR of pure drug, physical mixture, and final tablets formulation was carried out to identify any potential physicochemical incompatibilities between the drug and excipients that could affect formulation stability and performance. FTIR transmission spectra were obtained using Perkin Elmer 1600 spectrophotometer. Potassium Bromide (KBr) discs were used to prepare the samples using a hydrostatic press. The resolution was 4 cm-1 and the scanning range was 500 to 4,000 cm^{-1}. The distinctive summits were noted [16, 17].

Differential scanning calorimetry (DSC)

The pure drug sample and physical mixture of nifedipine were exposed in a standard aluminium pan and scanned at a speed of 5ºC/min and heat flow from 30 to 330 °C on a DSC (Shimadzu, Japan), and crystal transformation and thermal behavior were studied. Ni was used as a reference material to calibrate the device for temperature and heat flow at 5 °C per min prior to measurement. Five to ten milligram's of sample material were placed in sealed, non-hermetic aluminium pans for each measurement [18, 19].

Method of preparation

Nifedipine extended-release tablets with dosage strength of 99 mg (extra 10% of the drug compared to the indicated dosage was taken because about 10% of the drug is retained within the tablet and cannot be discharged by the expanding osmotic push layer) were formulated using the wet granulation process. The development process involves the preparation of the drug layer by wet granulation using granulation technique. The drug substance was present in the drug mix along with excipients and the consequent mixture was granulated using a blend of alcohol (10.5 ml) and purified water (1.5 ml) for 100 tablets. Nifedipine contribution concerning drug product claim was 20.6% w/w of total drug layer weight. The direct compression process was considered unsuitable for formulation having low drug content and poor flowable drug substance. Hence, the wet granulation process was employed for the development of both the medicament layer and the push layer for better drug uniformity and flowability. A wet granulation process was adopted for blend preparation followed by bi-layer core tablet compression. Bilayer tablets were compressed using a Korsch XT 6000 rotary bilayer tablet press (53-station). A pre-compression force of approximately 3-5 kN was applied to remove entrapped air, followed by a main compression force of 18–22 kN to achieve tablets with adequate mechanical strength and uniformity. The bi-layer core tablet was coated with a seal coat followed by ER coat. The seal coat was applied using hydroxypropyl cellulose (HPC-SSL) with polyethylene glycol (PEG 400) to protect the tablet core and prevent moisture ingress, while the film coat was applied using Opadry® to provide a uniform outer coating and improve tablet appearance and handling. Laser drilling (0.4, 0.5, and 0.7 mm) was performed on the drug layer side of tablets followed by film coating. Laser drilling of the tablets was performed using a carbon dioxide (CO_2) laser system. The laser was operated at a power setting of 20–30 W, with pulse duration of 100–200 µs. The entire coating process took place using a coating pan that had complete perforation [20, 21]. The "undrilled" control tablets were prepared using the same formulation and the same manufacturing batch as the laser-drilled tablets without laser-drilling step.

Optimization using design of experiment (DOE) by resolution IV 2^{4-1}fractional factorial design

A systematic Quality by Design (QbD) approach was adopted for the development and optimization of nifedipine extended-release tablets in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH Q8) (R2) guidelines. The Quality Target Product Profile (QTPP) was defined to ensure the desired therapeutic performance and product quality. The QTPP included dosage form (extended-release tablet), route of administration (oral), strength, release profile (controlled release over specified duration), assay, content uniformity, and stability parameters. An initial risk assessment was performed to identify potential formulation and process variables affecting drug release. An Ishikawa (fishbone) diagram was constructed to systematically evaluate the influence of material attributes and process parameters on the critical quality attribute, i. e., percent drug release. Based on preliminary studies and literature reports, formulation variables such as NaCl ratio, polymer concentration in drug layer, push layer polymer ratio, ER coating composition, and % weight gain were identified as high-risk variables. Nifedipine drug product is a complex formulation consisting of multiple components, including the drug layer, push layer, and extended-release layer coating layer. The drug release from this product is affected by various formulation variables such as polymer content and sodium chloride content in the drug layer, the polymer in ER coating, plasticizer in ER coating, and ER coating % weight gain. Total 11 runs were generated and details of the variables employed for development of nifedipine tablets by resolution IV 2^{4-1}fractional factorial designare given in table 1 and response recorded for each run is given table 3. However, studying individual factors can be time-consuming and challenging when dealing with several factors simultaneously, as is the case here. Therefore, a few factors are combined into one factor for ease of evaluation. To understand the individual factor effects and interactions between them, we applied the DOE approach using specifically a resolution IV 2^{4-1}fractional factorial design using Design Expert 11 (32-bit) software (Stat-Ease Inc., Minneapolis, United States of America (USA) [22, 23]. This approach provides an efficient and effective means of investigating the relationships between multiple factors simultaneously. The DOE approach was used to identify the critical quality attributes (CQAs) that affect drug release from the product [23-25]. The partial factorial design has several advantages over the full factorial design. Firstly, it reduces the number of experimental runs required to evaluate the factors, which ultimately saves time and resources. Secondly, it allows the identification of the most critical factors that affect the CQAs of the product while also accounting for the interactions between the factors. This information is essential for process optimization and product development. Finally, the partial factorial design provides an efficient means of evaluating multiple factors simultaneously while keeping the number of experiments manageable [26, 27]. In this study ratio of NaCl and polyox WSR N80 in drug layer, ratio of NaCl and polyox WSR Coagulant LEO in push layer, ratio of ethyl acetate and polyethylene glycol, and percentage weight gain in the ER coat were selected as the independent variables and percent drug release was selected as the dependent variable. The selection of the coded levels (−1, 0,+1) for each independent variable was based on preliminary formulation trials, literature reports, and functional performance requirements of the osmotic extended-release system. The levels of independent variables were fixed within experimentally feasible and pharmaceutically relevant ranges, ensuring measurable effects on *in vitro* drug release. These ranges allowed systematic evaluation of both linear and interaction effects of the variables within the design space. Based on the statistical analysis and response surface evaluation, a design space was established within the studied ranges of independent variables where the desired drug release profile was achieved. The optimized formulation was selected within this multidimensional design space ensuring consistent product performance. A control strategy was proposed based on the optimized design space, wherein critical material attributes such as NaCl ratio, polymer ratios, and ER coating weight gain were maintained within statistically established limits to ensure consistent drug release performance.

Table 1: List of independent variables for optimization by using experimental design

Independent variables					
Factors	**Description**	**Level −1**	**Level 0**	**Level+1**	**Unit**
A	NaCl: Polyox WSR N80 lEO ratio in drug layer	0.039	0.052	0.065	Ratio
B	NaCl: Polyox WSR Coagulant LEO ratio in push layer	0.083	0.111	0.138	Ratio
C	Polymer: Plasticizer ratio in ER coat (CA: PEG)	4.5	9	13.5	% w/w
D	Weight gain in ER coat	7.5	9.0	10.5	%

+1 correspond to low, medium, and high settings, respectively. ER = Extended release. CA= Cellulose acetate, PEG= Polyethylene glycol

Table 2: Dependent variable and optimization goal

Dependent variable	Optimization goal
Percent drug release (Y_1)	Maximize

Table 3: Formulation composition of the DOE trials to study the interaction of formulation variables

Composition	Run I	Run II	Run III	Run IV	Run V	Run VI	Run VII	Run VIII	Run IX	Run X	Run XI
Nifedipine	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00
Polyox WSR N80	341.13	332.71	341.13	332.71	341.13	332.711	341.13	332.711	336.87	336.87	336.87
Hypromellose 5cps	24.00	24.00	24.000	24.000	24.000	24.000	24.000	24.000	24.000	24.000	24.00
Sodium chloride	13.46	21.88	13.46	21.88	13.46	21.88	13.46	21.88	17.73	17.73	17.73
Magnesium stearate	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
Drug layer weight (mg)	480	480	480	480	480	480	480	480	480	480	480
Polyox coagulant	207.29	207.29	197.18	197.18	207.29	207.29	197.18	197.18	202.11	202.11	202.11
Sodium chloride	17.27	17.27	27.38	27.38	17.27	17.27	27.38	27.38	22.45	22.45	22.45
Hypromellose 5cps	12.97	12.97	12.97	12.97	12.97	12.97	12.97	12.97	12.97	12.97	12.97
Iron oxide red	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73
Magnesium stearate	0.724	0.724	0.724	0.724	0.724	0.724	0.724	0.724	0.724	0.724	0.724
Push Layer weight (mg)	240.0	240.0	240.0	240.0	240.0	240.0	240.0	240.0	240.0	240.0	240.0
Tablet weight (mg)	720.0	720.0	720.0	720.0	720.0	720.0	720.0	720.0	720.0	720.0	720.0
Hydroxypropyl cellulose SSL	17.10	17.10	17.10	17.10	17.10	17.10	17.10	17.10	17.10	17.10	17.10
PEG 400	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90
Seal coated tablet weight (mg)	738	738	738	738	738	738	738	738	738	738	738
Cellulose	45.287	63.402	63.402	45.287	72.143	51.531	51.531	72.143	59.778	59.778	59.778
PEG 3350	10.063	14.088	14.088	10.063	5.347	3.819	3.819	5.347	6.642	6.642	6.642
Tablet weight (mg)	793.350	815.490	815.490	793.350	815.490	793.350	793.350	815.490	804.420	804.42	804.420
Opadry pink 20H54007	31.734	32.620	32.620	31.734	32.620	31.734	31.734	32.620	32.177	32.177	32.177
% Drug dissolved at 24 h	97.78	94.44	96.12	95.42	68.44	89.14	90.23	79.11	98.32	96.15	99.99

PEG-Polyethylene glycol, WSR-Water soluble resin, mg-milligram (99 mg per tablet), cps-Centipoise

Evaluation

Pre-compression parameters

After the lubrication and blending process, the pre-compression parameters were determined to evaluate the flow characteristics of the granules. The bulk density was evaluated by determining the weight of a known volume of granules. Tapped density was obtained by measuring the mass of the granules after subjecting them to tapping. The hausner's ratio was determined by dividing the tapped density by the bulk density while indicating the degree of packing and cohesion. The compressibility index, obtained by comparing the bulk and tapped densities, provided insights into the flowability of the granules [28, 29].

Post-compression parameters

Thickness, hardness, weight variationand friability

The measurement of thickness was conducted using a vernier caliper to ensure uniformity of thickness. Hardness was evaluated using a Monsanto hardness tester, which measures the force required to break the tablet. Hardness is an essential parameter, as it determines the tablet's ability to withstand mechanical stress during transportation and handling. The weight of each tablet was recorded to assess dosage accuracy. 20 tablets were measured to determine their weight and the percentage difference in weight was computed. The friability, which refers to the ability of the tablet to resist breakage or chipping when subjected to mechanical stress, was measured using Roche Friabilator [30-32].

***In vitro* drug release**

The study was performed using a USP type I basket apparatus with a #20 mesh at 100 rotation per minute (RPM) and 37±0.5 °C in 900 ml (simulated gastric fluid) without enzyme (pH 1.2) containing 0.5% sodium lauryl sulfate (SLS) and analyzed by high performance liquid chromatography (HPLC).

Acetonitrile, methanol, and water were combined in a ratio of 35:35:30 v/v/v to create the mobile phase which was then sonicated to degas. [33]. Chromatographic analysis was performed using an HPLC equipped with a waters X-terra RP18 column (250 x 4.6 mm, 5 µm) or equivalent, with a flow rate of 1.5 ml/min, a UV/PDA detector, and a wavelength of 338 nm. The sample compartment was kept at 25 °C, the column oven temperature was kept at 30 °C, and the injection volume was 10 µl. The standard stock solution was prepared by dissolving 50 mg of nifedipine in 50 ml of methanol, which was then sonicated and diluted to a final concentration of 1 mg/ml. The dissolution medium pH 1.2 was prepared by dissolving 20 g of NaCl in 8000 ml of water, adding 70 ml of hydrochloric acid, and diluting it to 10,000 ml. To this, 50 g of SLS was added and sonicated to dissolve, and the pH was adjusted to 1.2±0.05 with NaOH or HCl solution. The test preparation was performed by transferring 900 ml of dissolution medium into the basket, placing one tablet, and operating the apparatus for a specified time interval. The resulting solution was filtered through a 0.45 µ Polyvinylidene Fluoride (PVDF)/nylon filter after discarding the first 2 ml of filtrate. Finally, 10 µl of the test preparation, standard solution, and blank (dissolution medium) were separately injected into the chromatographic system, and the chromatograms were recorded. The peak area counts for the nifedipine peak was measured, and the retention time (RT) of the peak was about 3 min. The method presented here is a reliable and reproducible approach to evaluate the *in vitro* dissolution of tablets using HPLC, which is widely accepted in the pharmaceutical industry [34, 35].

In vitro drug release kinetics

To evaluate the drug release kinetics of the optimized formulation, the obtained data from the drug release study were analyzed using different mathematical models. These models included the zero-order, first-order, Korsmeyer-Peppas, Higuchi, and Hixson-Crowell release kinetics. By fitting the data to these models we aimed to understand the pattern and mechanism of drug release of the optimized formulation [36].

Morphology of laser-drilled nifedipine ER tablet

The scanning electron microscope (SEM) (JEOL JSM IT 500) was utilized to evaluate the orifice size of laser-drilled tablets. For analysis, tablets were placed on a stainless-steel stub and wrapped with carbon tape. Furthermore, the tablet was stacked in it before being placed under a microscope. The samples were then analyzed at an accelerating voltage of 3 kV and a working distance of 10 mm [37, 38].

Accelerated stability study

The stability studies of the optimized nifedipine extended-release tablets were performed according to the guidelines of Q1A (R2) set by the ICH. The optimized formulation was placed in a designated quarantine area and subjected to storage conditions of 40 °C±2 °C and relative humidity (RH) of 75%±5% for duration of 3 mo in a high-density polyethylene (HDPE) bottle. The samples were withdrawn in 1st month, second month, and third month and further evaluated for potential changes in their physical appearance, color, *in vitro* drug release, and overall product integrity [39].

RESULTS AND DISCUSSION

Compatibility studies by using FTIR and DSC

The principle peaks of nifedipine (fig. 1) were recorded at 3329.10 cm^{-1} for N-H stretching, 2953.81 cm^{-1} for C-H stretching, 1625.49 cm-1 for C=O stretching, 1677.73 cm^{-1} for C=C stretching, 1494.24 cm^{-1} for C-H bending, and 1184.25 cm^{-1} for C-N stretching. These peaks were characteristics of the molecular structure of nifedipine and can be used to confirm its presence and purity in the sample analyzed by FTIR.

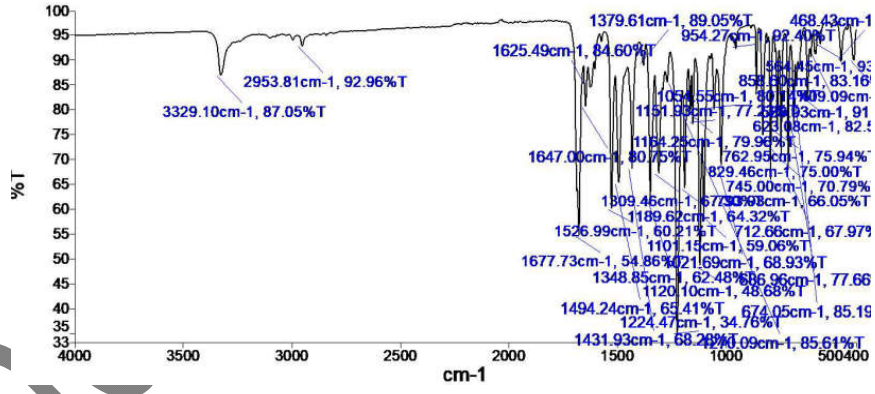

Fig. 1: FTIR spectrum of pure nifedipine showing characteristic peaks corresponding to its functional groups, confirming the identity and structural integrity of the drug

The principal peaks of nifedipine in the physical mixture (fig. 2) were recorded at 3328.24 cm^{-1} for N-H stretching, 2889.60 cm^{-1} for C-H stretching, 1678.12 cm-1 for C=C stretching, 1646.68 cm^{-1} for C=O stretching, 1494.37 cm^{-1} for C-H bending, and 1151.90 cm^{-1} for C-N stretching. In the physical mixture the FTIR spectra had all characteristics peaks of nifedipine hence the drug was found to be compatible and does not show any interaction with the components used in the physical mixture.

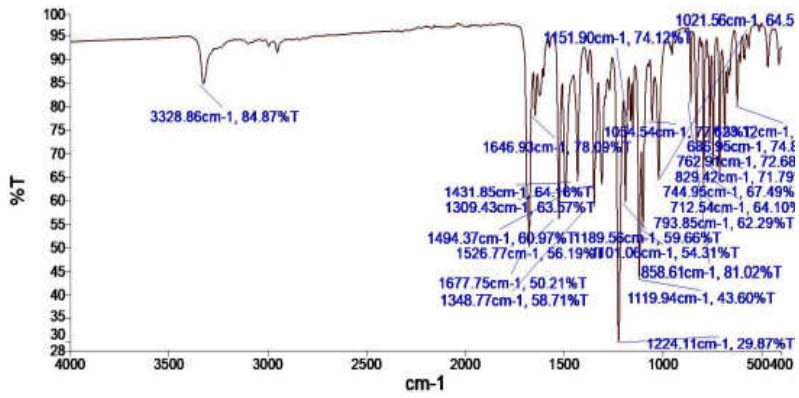

Fig. 2: FTIR spectrum of the physical mixture of nifedipine with formulation excipients. The characteristic peaks of nifedipine were retained without significant shift, broadening, or disappearance, indicating absence of chemical interaction between the drug and polymers

The DSC thermograph of nifedipine exhibited a well-defined endothermic peak at 173.46 °C (fig. 3) which corresponds to its melting point. The distinct natures of the peak in the physical mixture and in optimized formulation confirm the compatibility of the drug with the other components used in the formulation.

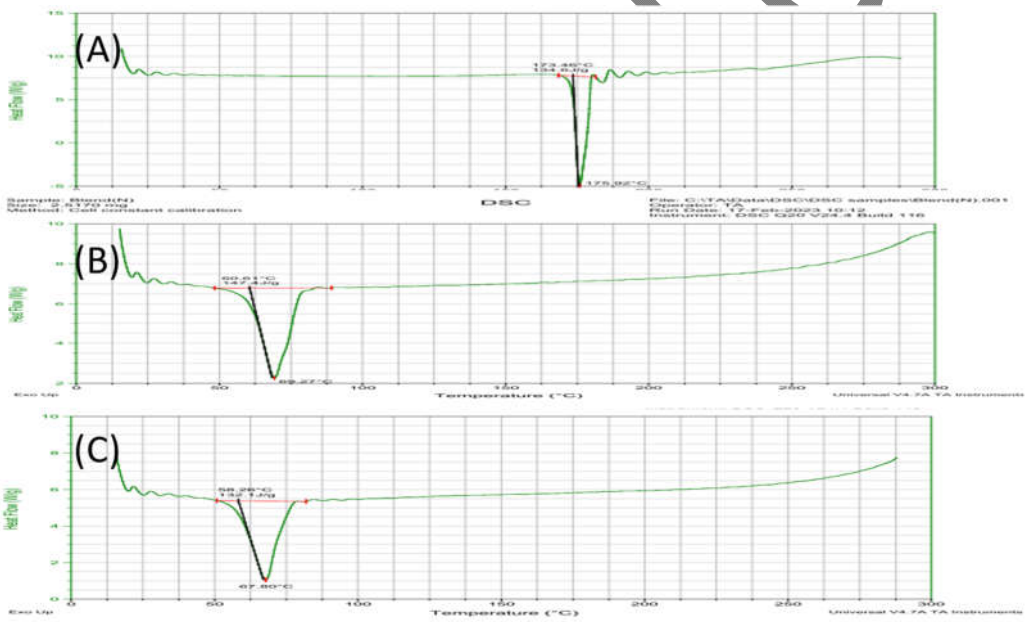

Fig. 3: DSC thermograms of pure nifedipine (A), physical mixture (B), and optimized formulation (C). The characteristic endothermic peak of nifedipine was preserved in both the physical mixture and optimized formulation with no significant shift, suggesting compatibility of the drug with excipients and absence of drug–polymer interaction

Pre-compression parameters

The drug layer of the tablets exhibits a bulk density of 0.515 g/cm^3, a tapped density of 0.588 g/cm^3, and a compressibility index of 12.414%. The push layer exhibits a bulk density of 0.415 g/cm^3, a tapped density of 0.462 g/cm^3, and a compressibility index of 10.173%. Both layers exhibit moderate flowability based on their hausner's ratios as mentioned in table 4.

Table 4: Observations for pre-compression parameters

Drug layer blend	Push layer blend
Bulk density	Bulk density
0.517±0.002	0.357±0.004
Tapped density	Tapped density
0.594±0.003	0.441±0.002
Compressibility index (%)	Compressibility index (%)
12.962±0.001	19.04±0.001

Hausner ratio	Hausner ratio
1.148±0.002	1.235±0.002

Results are expressed as mean±SD (n=3)

Optimization of formulation using design of experiment by resolution IV 2^{4-1}fractional factorial design

A study was conducted using a resolution IV 2^{4-1}fractional factorial designto examine how formulation variables affect the percentage of drug release. The ratio of NaCl to polyox WSR NEO, the ratio of NaCl to polyox WSR Coagulant LEO in the Push Layer, the ratio of polymer and plasticizer in ER coat, and % weight gain in the ER coat were considered as independent variables and the % drug release as dependent variables used in optimization. An experiment was conducted, consisting of 11runs, with the responses recorded in table 3. The study aimed to assess the presence of significant differences among the independent variables A, B, C, and D, using analysis of variance (ANOVA). If the Prob>F value is below 0.050 indicated that the model term is statistically significant table 5.

Table 5: Statistical summary of model for *in vitro* drug release

Responses	**% drug release (Y)**
Model F-value	17.38
Lack of fit F-value	1.96
p-value	0.019
R^2	0.8816
Adjusted R^2	0.8309
PredictedR^2	0.7273
% CV	5.46
Adequate precision	10.367

The ANOVA indicated that the model was significant with F-value17.38 and p value 0.019, with model degrees of freedom (df) i. e. 4 and residual df was found to be 6. The lack-of-fit was insignificant with F value of 1.96 and p value of 0.214 confirming that the model adequately fits the experimental data. Since the Prob>F value was less than 0.05 for the model and greater than 0.05 for lack-of-fit, the regression model was considered statistically valid and predictive. The predicted R^2 value was found closely match with the adjusted R^2 value, which was0.7273 and 0.8309 respectively, for the response as mentioned in table 5. The response had an adequate precision of 10.367, which exceeded the desired value. A polynomial equation was used to relate the independent variables to the responses and statistical analysis was conducted using design software (32 bit Stat-Ease Inc. in Minneapolis, USA).

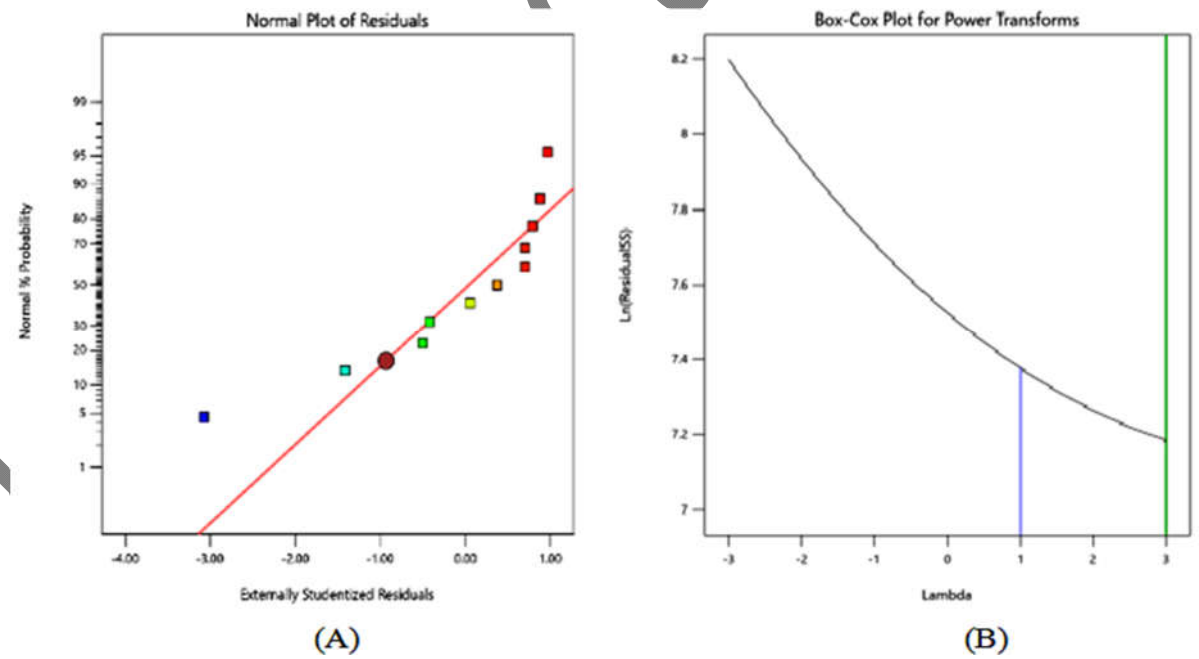

Fig. 4: Diagnostic plots for the statistical model developed to optimize percent drug release at 24 h: (A) Normal probability plot of residuals indicating normal distribution and model adequacy; (B) Box–Cox plot suggesting appropriate data transformation and confirming suitability of the model for 24-h drug release optimization

The results show that after 24 h the maximum drug release was observed with the NT11 (99.99±1.2%) than compared to the other combination. The ratio of sodium chloride to polyox had the least impact on controlling drug release as we can see in the responses in fig. 5. Since the 24 h time point best captures the formulation's stability and sustained release performance, it was chosen as the critical response. NT11 was found to be the formulation with the highest projected response and desirability when the model equation was utilized to forecast the ideal combination of factors.

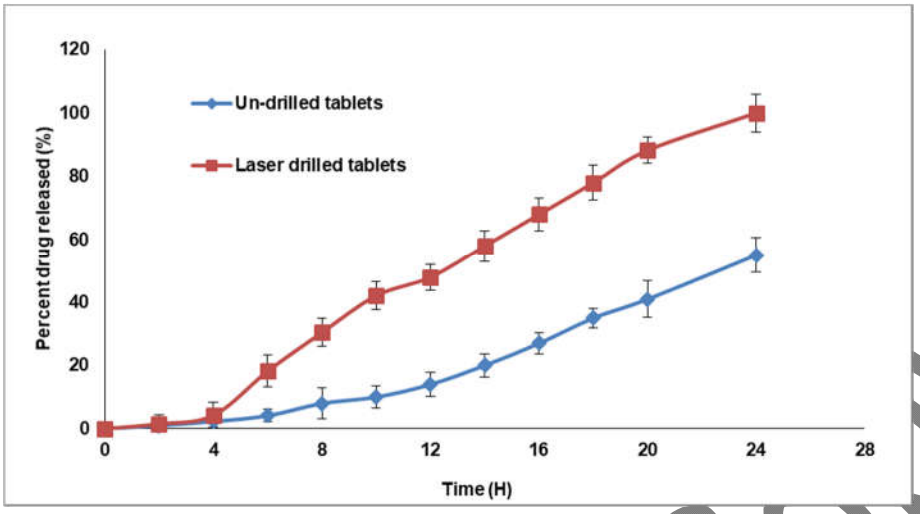

Fig. 5: Comparison of release profile of optimized laser-drilled versus undrilled tablets, results are expressed as mean±SD (n=3)

The *in vitro* release kinetics data for osmotically controlled laser-drilled tablets were analyzed by using various mathematical models. The value with a high R^2value was found the best-fit model for drug release. The R^2value for First order, Hixson, Korsmeyer-Peppas, Zero-order, and Higuchi was found to be 0.8654, 0.9592, 0.9341, 0.9842, and 0.8981 respectively. The optimized formulation exhibiting zero-order kinetics shows a strong correlation with an R^2value of 0.984 and an n value of 0.43 which indicates nifedipine extended-release tablet follows the fickian diffusion. Results indicated that diffusion via polymeric matrix is the major contributor to drug release. Additionally, osmotic drug delivery often shows a combination of release mechanisms including diffusion. Thus, although the n value indicates Fickian diffusion as the dominant mechanism, the overall release behavior may be governed by mixed mechanisms inherent to osmotic-controlled systems.

Based on the results obtained from the design, NT11 was selected for further evaluation. The mean weight of the optimized formulation was found to be 718±2.5 mg indicating dosage accuracy was within the acceptable range. The mean thickness was measured to be 7.51± 0.2 mm, which demonstrated the uniformity of the tablets. The optimized tablet's hardness was found to be130±5 N suggesting that it can withstand mechanical stress during transportation and handling. The optimized tablets friability was measured as 0.9±0.1% which confirmed that they could resist breakage or chipping when subjected to mechanical stress.

SEM analysis of laser-drilled nifedipine tablet

The surface morphology and orifice diameter of the optimized nifedipine ER tablet were examined using SEM (JEOL JSM IT 500). The SEM image (fig. 6) revealed a well-defined circular orifice with an average diameter of approximately 589.1 µm (≈0.59 mm), corresponding to the 0.5 mm laser-drilling condition used for the optimized batch. The orifice margins were uniformly smooth, well-defined, and showed no signs of uneven melting or cracking, according to the SEM results. This suggests accurate laser drilling without damage to the polymeric membrane.

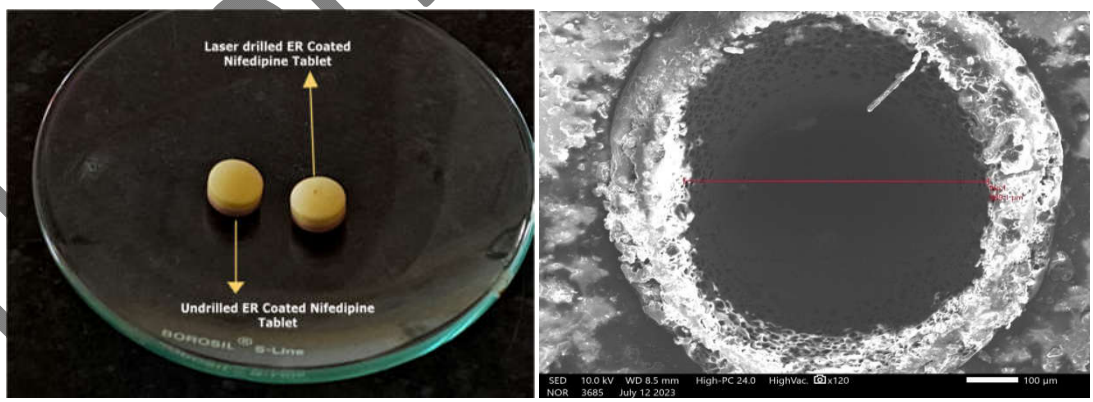

Fig. 6: SEM images of laser-drilled osmotically controlled nifedipine tablets

Acceleratedstudy of the optimized formulation

The stability of optimized nifedipine extended-release tablets was evaluated according to ICH guidelines Q1A (R2) by storing them at 40 °C±2 °C and 75%±5% relative humidity for duration of 3 mo. After the storage period, the tablets were assessed for alterations in their visual characteristics such as physical appearance, color, and efficacy in terms of *in vitro* drug release. The formulation exhibited good physical and chemical stability under accelerated conditions for 3 mo, suggesting suitability for further long-term studies.

DISCUSSION

The findings of the present study are in agreement with previously published studies on osmotic-controlled release systems employing mechanically prepared delivery orifices. For instance, Tiwari *et al.* 2025 demonstrated that customized notch-enabled tooling can successfully substitute conventional laser drilling in osmotic tablet manufacturing, offering a cost-effective and industrially realistic alternative. In their study on Metformin HCl osmotic tablets, drug release was successfully developed by optimizing core composition and coating parameters, particularly the plasticizer concentration and coating weight gain. Similar to their investigation, the present study confirms that membrane characteristics-especially the polymer-to-plasticizer ratio and ER coating weight gain play a decisive role in governing water influx, osmotic pressure, and drug diffusion. The current work systematically elucidates the statistical significance and interaction effects of formulation variables using a resolution IV 2^{4-1} fractional factorial design [40]. In the present investigation nifedipine extended-release tablets were prepared and optimized by using resolution IV 2^{4-1}fractional factorial design to improve the therapeutics effectiveness of the drug. Compatibility studies using the FTIR and DSC were performed to investigate the existence of any interaction between the drug and formulation excipients. The results indicated that the drug is compatible with the various excipients used in the formulation of the extended-release tablets. The nifedipine extended-release tablets were prepared by wet granulation methods and optimized by the resolution IV 2^{4-1}fractional factorial design. Total 11 runs were generated with the different combinations of the excipients and investigated for the drug release studies. The pre compression parameters were determined for various parameters and found to be optimum for the compression. The release of nifedipine after 2 h was impacted by the ratio of CA to PEG 3350 and ER weight gain but these factors did not interact. The effect of the ratio of CA to PEG 3350 was more significant than ER weight gain. A higher ER weight gain and polymer-to-plasticizer ratio in ER coats resulted in decreased drug release. Factor A and B had an interaction effect, but the impact of NaCl was not significant. Factor C (ratio of CA to PEG) had the most significant impact on drug release at 4 h, followed by ER weight gain. All trials, except those with a lower weight gain of 7.5% and a polymer-to-plasticizer ratio of 4.5, were out of specifications for drug release at 4 h. At 12 h, Factors C and D (ER coating weight gain) were critical factors affecting drug release. Formulation with higher ER weight gain and polymer-to-plasticizer ratios showed slower drug release. At 24 h, Factors C and D were determined to be the most significant in determining drug release. The drug release study of tablets having précised orifice shows-controlled drug release over a specific duration. The pronounced effect of the polymer: plasticizer ratio can be attributed to its direct control over membrane flexibility and porosity, which governs water influx and drug diffusion. By reducing the free volume within the coating matrix, an increase in the polymer-to-plasticizer ratio limits the amount of water that can enter the core and lowers membrane permeability. Drug diffusion rate and osmotic pressure generation are thereby decreased by reduced water penetration. On the other hand, a higher plasticizer concentration improves the micro porosity and flexibility of the membrane, enabling regulated osmotic pumping. This explains why, at all-time points, Factor C had the strongest effect on drug release. Pharmacopeial requirements for extended-release systems that need sustained and controlled drug administration during the dosing interval without dosage dumping were met by the improved formulation NT11, which showed near-complete drug release at 24 h (99.99±1.2%). In addition, the consistent performance under stability conditions and the observed zero-order release behaviour imply that the system combines orifice-mediated modulation and osmotic pressure-driven release, offering better release linearity and robustness than traditional matrix-based extended-release formulations. No significant alterations were observed during the stability studies and NT11 formulation was found to be stable under the stressed condition. The developed system demonstrates improved performance relative to previously reported laser-drilled osmotic tablets. The observed release profile is consistent with osmotic pumping–controlled systems and is comparable to previously reported laser-drilled osmotic ER formulations, while offering improved release linearity and reduced formulation complexity. These findings confirm that the developed system effectively integrates osmotic principles with controlled orifice-mediated release to achieve robust extended drug delivery.

CONCLUSION

The study evaluated the effectiveness of laser drilling in enhancing the drug release rate of osmotically controlled nifedipine ER tablets. Using a resolution IV 2^{4-1}fractional factorial design the critical quality attributes affecting drug release were identified and the optimal formulation was determined. The findings indicated that the drug release rate of nifedipine ER tablets was significantly improved through laser drilling with a more consistent drug release profile compared to previous-generation ER tablets. These findings suggest that laser drilling may be a valuable technique for improving the performance of osmotically controlled ER tablets and enhancing the therapeutic outcomes of patients with hypertension. This study highlights the potential benefits of using laser drilling in the manufacturing of ER tablets particularly for drugs that require precise control over their release rate.

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AUTHORS CONTRIBUTIONS

Abhishek Sharma contributed to the conceptualization, study design, data analysis, and manuscript writing. Atul Kabra was involved in the literature search, data collection, statistical analysis, and drafting of the manuscript. Md. Khalid Anwer, Mohammed F. Aldawsari contributed to methodology development, quality assessment, and critical review of the manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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