ORIGINAL ARTICLE

Integrating Quality by Design Principles for Elevating Bioavailability of Candesartan Cilexetil in Fast-dissolving Tablets

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Abstract

Aim: The present research was aimed to increase the bioavailability of Candesartan cilexetil by integrating efficient super disintegrating agents applying the principles of quality by design. **Materials and Methods:** This study optimized fast dissolving tablets containing Candesartan cilexetil by integrating efficient super disintegrating agents (Isabgol husk, Potato starch, F melt C) through a direct compression method. Utilizing Design of Expert version 13.0 with a response surface methodology, formulations (CC1-CC15) were systematically developed. The influence of super disintegrates on key parameters - disintegration time (Y1), drug release at 15 min (Y2), and drug release at 30 minutes (Y3) - was extensively studied to enhance Candesartan cilexetil's dissolution properties. **Results and Discussion:** Comprehensive evaluation of pre- and post-compressional factors, coupled with robust in-vitro dissolution analysis, highlighted formulation CC12's excellence, featuring rapid disintegration and maximal drug release within specified timeframes. Utilizing the DD solver guided by regression coefficients (r2), Akaike Information Criterion (AIC), and model selection criteria (MSC), kinetics and release mechanisms were elucidated. CC12 exhibited a fickian diffusion mechanism, substantiating its robust drug release profile. Additionally, shelf-life evaluation as per ICH guidelines and a comparative analysis employing the similarity factor (f2) with Atacand were conducted. Stability studies, assessed via ANOVA, indicated insignificant differences ($P > 0.05$) during storage. In summary, this research optimally enhanced Candesartan cilexetil's dissolution via proficiently formulated fast dissolving tablets. The strategic integration of super disintegrating agents, driven by Design of Expert version 13.0, yielded CC12 as an optimal candidate with rapid disintegration and superior drug release. Elucidation of release kinetics and mechanisms further fortified performance assessment. Thorough stability and similarity evaluations underscored the potential of this optimized formulation for improved therapeutic outcomes. **Conclusion:** Fast dissolving tablets of C and esartan cilexetil were developed by optimizing selected independent variables to improve the dissolution profile. The presence of soluble polymers like Isabgol husk, potato starch and F melt C, acting as super disintegrants, played a significant role in enhancing solubility..

Key words: Fast-dissolving tablets, release kinetics, response surface methodology, stability studies, super disintegrating agents

INTRODUCTION

Fast-dissolving tablets (FDTs) represent a distinctive dosage form designed to facilitate rapid diffusion of the active pharmaceutical ingredient (API) upon exposure in the oral cavity, ensuring swift onset of action without necessitating water consumption.[1] The contemporary landscape underscores the significance of FDTs as a viable and promising formulation strategy,[2] particularly

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Received: April 2024
Revised: June 2024
Accepted: July 2024

advantageous for specific patient cohorts such as pediatric and geriatric populations who encounter challenges with conventional dosage forms including tablets, capsules, and bulk powders.[3,4] Furthermore, FDTs find utility in exigent situations wherein immediate therapeutic intervention is warranted, exemplified by the amelioration of intense pain, mitigation of inflammation/itching, alleviation of motion sickness, and sudden onset of coughing. Notably, FDTs are characterized by their expedited disintegration, favorable mouthfeel, and facile administration.[5,6]

However, an extensive review of the literature reveals that a substantial fraction, around 40%, of pharmaceutically active compounds grapple with solubility and bioavailability-related challenges.[7,8] Consequently, the swift disintegration characteristic of FDTs presents a paradox, wherein achieving desirable drug bioavailability becomes a formidable task. Various strategies have been explored to enhance solubility and dissolution profiles, encompassing techniques, such as drug incorporation into soluble salt forms,[9] particle size modulation,[10] prodrug derivatization,[11] conversion to amorphous states,[12] integration of co-solvents and cyclodextrin complexes, and preparation of polymer-embedded solid dispersions (SDs) with suitable polymers.[13] Additional methodologies include co-processing with soluble polymers,[14] self-micro emulsifying chewable tablets,[15] manipulation of polymorphs such as entacapone,[16] lipid-based SDs integrated with Gelucire,[17] Novel Applications of Hot Melt extrusion technology,[18] and development of Fast Dissolving by solvent evaporation[19] and gold nanoparticles.[20] This diversification extends to the fabrication of FDTs for an array of drug categories, encompassing ketoprofen,[21] glyburide,[22] itopride,[23] torsemide,[24] piroxicam,[25] promethazine HCl[26] among others.

In the context of the present research endeavor, novel super-disintegrating agents were judiciously selected to enhance drug solubility through diverse mechanisms, including capillary action, wicking, and swelling, the efficacy of which is influenced by the preparation methodology and choice of disintegrating agents.[27] Accordingly, the development of FDTs emerges as a compelling technique, offering the prospect of optimizing API release from the dosage form and concomitantly augmenting bioavailability, thus bolstering pharmacological efficacy.[28]

Candesartan cilexetil is an angiotensin II receptor antagonist and chemically known as 2-ethoxy-1-({4-[2-(2H-1, 2, 3, 4-tetrazol-5-yl) phenyl] phenyl} methyl)-1H-1,3benzodiazole-7-carboxylic acid. Developing candesartan cilexetil as FDTs holds scientific merit based on several key considerations. Candesartan cilexetil, an angiotensin II receptor blocker used for hypertension and heart failure, faces challenges stemming from its poor aqueous solubility.[29] The adoption of FDTs can enhance drug solubility through rapid disintegration and dissolution in the oral cavity, potentially improving absorption and bioavailability. FDTs offer an opportunity for rapid drug absorption through the oral mucosa and gastrointestinal tract, thereby potentially bypassing first-pass metabolism and leading to increased bioavailability. Furthermore, FDTs can provide a quicker onset of action, particularly beneficial for hypertensive emergencies, aligning well with candesartan cilexetil's relatively long half-life (9–12 h).[30] By leveraging fast-dissolving technology (FDT technology), the formulation aims to overcome solubility challenges, optimize drug delivery, and potentially offer expedited therapeutic benefits.

The Design of Expert software (Model 13.0) serves as a valuable statistical tool utilized for the optimization of the current FDTs formulation. This software facilitates the creation of various design models for formulations, aiming to streamline and expedite processes while conserving time, resources, and materials. Employing a factorial design approach, this study systematically investigates and characterizes the significance of simulated variables, enabling the prediction of their collective impacts on diverse response parameters.[31] The factorial design methodology is a well-established technique for comprehensively studying variable interactions and their effects. Particularly, the response surface method emerges as an efficacious approach for efficiently developing a suitable model, circumventing the need for extensive trial periods. In the present investigation, a 3^3 factorial design was employed to assess the influence of distinct concentrations of super-disintegrating agents, considered as independent variables, on key response parameters such as disintegration time (DT) Y_1, percentage drug release at 15 min (Q15 min) Y_2, and percentage drug release at 30 min (Q30 min) Y3, which are the dependent variables under scrutiny.[32]

MATERIALS AND METHODS

The selected API candesartan cilexetil was collected gift sample from Orchid Health-Care Pvt. Ltd., Hyderabad; Microcrystalline cellulose (PH101) and Lactose monohydrate, Accent micorcel Industries, Mumbai; Frieslands Foods Domo, Isabgol husk, FMC Biopolymer, Hyderabad, Potato starch from HiMedia Pvt. Lab, Ahmedabad; F melt C ISP International chemical Ltd., Colloidal silicon dioxide from Wacker, Mumbai; and Aspartame flavor from IBIS Chemi International and Magnesium Stearate Nitika Chemicals/ Sunshine Organics Pvt. Ltd., Hyderabad. The quality of all excipients was found in analytical reagent grades.

Designing of fast-dissolving loaded candesartan cilexetil tablets by factorial design approach 3^3

Based on preliminary investigational trials, Isabgol husk, potato starch, and F melt C (5–15 mg) were identified as suitable super-disintegrating agents for the formulation of FDTs[33] containing candesartan cilexetil. Employing a 3^3 factorial design approach, a total of 15 formulations (CC1–CC15) of FDTs were systematically devised, with varying

Table 1: Candesartan cilexetil fast-dissolving tablets by 2^3 factorial design

Name of the component	CC1	CC2	CC3	CC4	CC5	CC6	CC7	CC8	CC9	CC10	CC11	CC12	CC13	CC14	CC15
Candesartan cilexetil	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
Isabgol husk	10	15	5	10	15	15	15	15	10	5	5	10	5	5	10
potato starch	10	5	5	15	15	15	5	10	5	15	10	10	5	15	10
F melt C	15	15	5	10	15	5	5	10	10	5	10	10	15	15	5
MCC (PH 101)	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
Lactose	113.9	113.9	133.9	113.9	103.9	103.9	123.9	113.9	123.9	123.9	123.9	118.9	123.9	113.9	123.9
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Silicon-di-oxide	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aspartame	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight/ tablet (mg)	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

quantities of the chosen super disintegrating agents [as outlined in Table 1]. In this factorial design, Isabgol husk (X_1), potato starch (X_2), and F melt C (X_3) were designated as independent variables, while the responses of the FDTs, including DT (Y_1), percentage drug release at 15 min (Y_2), and percentage drug release at 30 min (Y_3), served as the dependent variables. These responses were evaluated at three levels of super-disintegrating agent concentrations, representing low (−1), central (0), and high (+1) values, as specified by the experimental design.

Candesartan cilexetil FDTs by direct compression

Measure the required quantities of candesartan cilexetil, lactose monohydrate, and microcrystalline cellulose (PH101) based on the desired tablet size and strength then incorporate the selected super disintegrants into the mixture in appropriate amounts. Thereafter, mix these ingredients for a specific period of time to ensure even distribution and pass the mixture through a #40 sieve to achieve an exceptionally fine powder. Then, add the required quantity of F melt C to the fine powder mixture and pass this mixture through a #12 sieve to ensure thorough blending. After that, pre-lubricate the above-dried blend with suitable lubricants and glidants and mix well for a specified time according to the relevant standards. After proper pre-lubrication, collect the powder blend and use a 9-mm round shape standard concave punch to compress the blend into tablets. This compression helps shape the tablets and gives them the desired hardness.

Statistical analysis using the design of expert software

In this study, Design of Expert version 13.0 from India was utilized for statistical analysis. The analysis involved several important steps.[34] First, a one-way analysis of variance (ANOVA) test was performed. This test was chosen to assess any significant differences among various groups or treatments. The level of significance, represented by a $P = 0.05$, was used to determine whether the observed differences were statistically meaningful. Alongside this, a 95% confidence interval (95% CI) was calculated to provide an estimation of the precision of the results.

Furthermore, the analysis included the use of the F-test, a statistical technique employed to evaluate variances. Quadratic models were integrated into the analysis as well. These models aimed to establish relationships and understand the impact of individual parameters.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Interpreting polynomial equations

In the provided polynomial equations, the variable Y represents the measured responses associated with individual factors at different levels. These responses could arise from the combined effects of various factors across these levels. The study's independent variables are denoted as X_1, X_2, and X_3. The intercept of the polynomial equation is represented by b_0, while the regression coefficients are represented by b_1, b_2, and b_{12}.

In addition, the terms X_1X_2, X_1X_3, and X_2X_3 reflect the main effects of the individual factors and their interactions at each level. The terms X_{12} and X_{22}, on the other hand, indicate the quadratic models of the independent variables. These quadratic models introduce curvature effects into the study's analysis.

In summary, the polynomial equations provide insights into the relationships between the independent variables, their main effects, interactions, and quadratic curvature effects. Understanding these equations aids in comprehending the multifaceted nature of the factors and their impacts on the measured responses. This interpretation is in line with the reference.

ASSESSMENT OF POWDER BLEND CHARACTERISTICS

Fourier-transform infrared spectroscopy (FTIR) studies

The physical properties of a powder mixture containing candesartan cilexetil.[35] were analyzed using an FTIR spectrophotometer (Shimadzu model 1205). Figure 1 represents the pure candesartan cilexetil spectrum, and Figure 2 shows the spectrum when combined with excipients. Peaks in these spectra reveal key details about the composition and properties of the substances under investigation.

Differential scanning calorimetry (DSC)

DSC thermograms were obtained for pure and optimized formulation (CC12) FDTs using a Shimadzu DSC-60 instrument. Nitrogen gas at 20 psi ensured an inert atmosphere within the aluminum sample holder, preventing oxidation. Calibration was performed with indium metal, and the sample, sealed in an aluminum pan, was scanned from 10 to 200°C at a rate of 10°C/min.

In addition to that, a comprehensive evaluation of the pre-compressional properties of each powder blend was carried out using an established standard procedure. This procedure

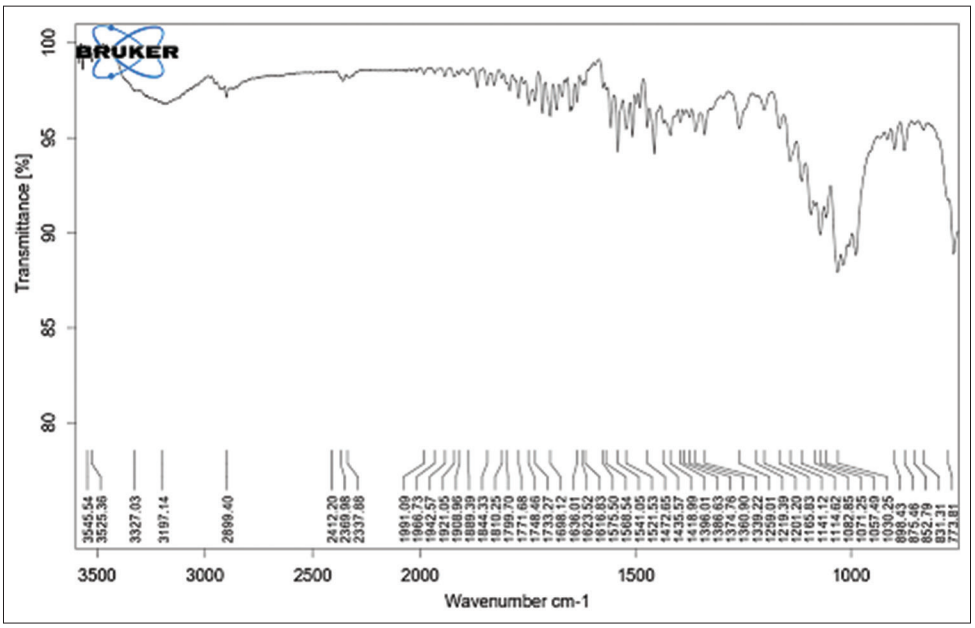

Figure 1: Fourier-transform infrared spectroscopy-spectra pure candesartan cilexetil

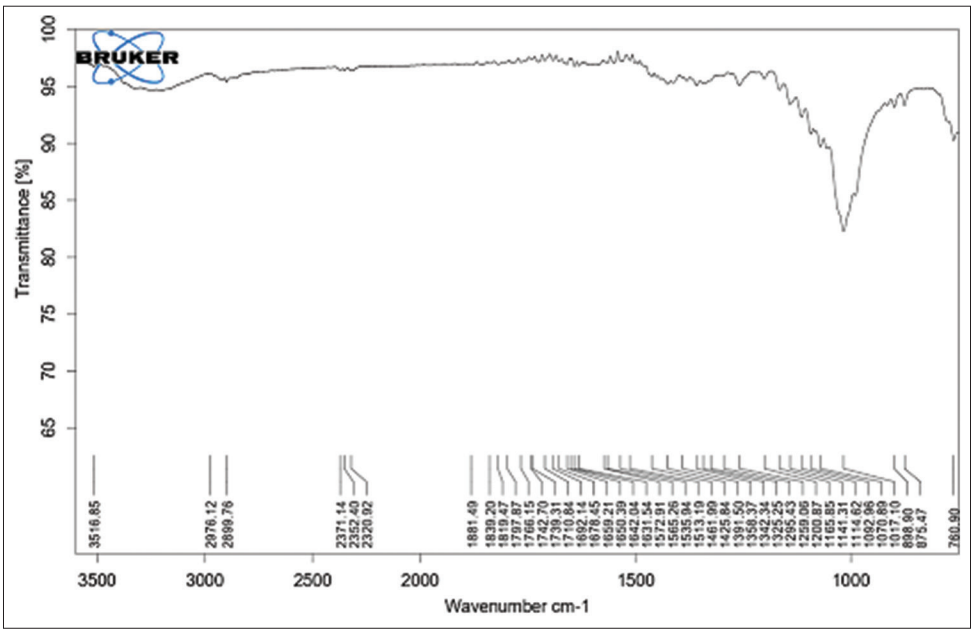

Figure 2: Fourier-transform infrared spectroscopy-spectra candesartan cilexetil fast-dissolving tablets (CC12)

encompassed key parameters including bulk and true density, which were measured to understand the flow behavior of the powder blend. In addition, the angle of repose (θ), Hausner's ratio, and Carr's Index were determined to provide insights into the blend's flow properties.

Evaluation of candesartan cilexetil FDTs

In accordance with the standard procedure outlined in the Indian pharmacopeia (IP), a thorough assessment of various aspects of candesartan cilexetil FDTs formulations was conducted. The evaluation covered essential factors such as the tablet's physical appearance, thickness, hardness, friability, variations in tablet weight, and the content of the drug substance.

The findings obtained from these evaluations were compiled and are presented in Table 2 for easy reference. This table encapsulates the results of the analyses, providing a consolidated overview of the observed outcomes.

In vitro dissolution study

For the *in vitro* dissolution study, a USP dissolution test apparatus of type I (Basket) was employed. A single tablet was placed into the apparatus, and the temperature was carefully maintained at 37°C ± 0.5°C. During the study, at specific time intervals, 5 mL of the sample solution was extracted from the dissolution medium, which contained a total of 900 mL. This extracted sample underwent filtration through a 0.45 µm membrane filter to achieve clarity. Subsequently, the filtered liquid was diluted to the necessary volume using the dissolution medium (0.1N HCl). To assess the drug dissolution, a spectrophotometer set to a wavelength of 216 nm was utilized. This analysis provided the percentage of the drug dissolved from the candesartan cilexetil tablets. This procedure offers valuable insights into the release behavior of the active ingredient from the tablets.[36]

Drug release kinetics and mechanism analysis

To elucidate the drug release kinetics and mechanisms of candesartan cilexetil FDTs, the *in vitro* dissolution profiles for all formulations were systematically evaluated. These profiles were subjected to a range of appropriate models, including zero-order kinetics, first-order kinetics, Higuchi's plot, and the Korsmeyer–Peppas (K-P) model. The statistical tool DD solver software was employed for this analysis.[37]

In this assessment, crucial parameters such as the adjusted regression values (r^2 adjusted), the range of akaike information criterion (AIC), and the model selection criterion (MSC) values played a pivotal role. These parameters generated distinct values that formed the basis of comparison. By analyzing these values, it became possible to determine the best-fitting models that elucidate the release order mechanism for the various formulations ranging from CC1 to CC15. This systematic approach provides insights into the kinetics and mechanisms governing the drug release from the different formulations.[38-40]

Stability studies according to ICH guidelines

In accordance with the ICH guidelines, stability studies were undertaken to determine the true shelf-life of the optimized

Table 2: Evaluation of pre-compressional parameters of candesartan cilexetil physical mixture

Formulation	Bulk density (mg/mL)	Tapped density (mg/mL)	Angle of repose (θ)	Hausner ratio (Hr)	Compressibility index (%)
CC1	0.715±0.11	0.812±0.17	25.32±0.15	1.13±0.17	12.28±0.11
CC2	0.724±0.15	0.846±0.16	26.47±0.18	1.17±0.14	14.25±0.15
CC3	0.719±0.14	0.812±0.23	23.34±0.15	1.15±0.16	14.17±0.14
CC4	0.718±0.16	0.844±0.18	26.18±0.11	1.14±0.16	13.66±0.13
CC5	0.714±0.16	0.823±0.17	25.17±0.14	1.18±0.14	13.57±0.17
CC6	0.716±0.08	0.836±0.13	23.27±0.13	1.14±0.16	13.88±0.12
CC7	0.721±0.17	0.816±0.16	24.28±0.13	1.17±0.17	13.87±0.15
CC8	0.733±0.14	0.835±0.10	23.65±0.51	1.16±0.13	13.59±0.17
CC9	0.724±0.13	0.818±0.18	26.73±0.14	1.15±0.14	12.55±0.19
CC10	0.710±0.17	0.814±0.14	25.44±0.18	1.16±0.15	13.58±0.16
CC11	0.721±0.14	0.824±0.13	24.27±0.17	1.14±0.12	12.28±0.17
CC12	0.727±0.10	0.826±0.13	23.51±0.31	1.15±0.13	13.21±0.13
CC13	0.713±0.16	0.814±0.14	24.25±0.27	1.66±0.14	13.17±0.14
CC14	0.713±0.14	0.817±0.31	23.19±0.14	1.18±0.16	13.45±0.18
CC15	0.725±0.23	0.825±0.27	26.18±0.32	1.16±0.11	13.78±0.19

SD values *n*=3

candesartan cilexetil FDTs (CC12). These tablets were subjected to controlled conditions, specifically maintained at a temperature of 40°C and a relative humidity of 75%, over a span of 90 days. The objective of these studies was to gain insight into the tablets' stability and to ascertain their potential performance and quality over an extended period under these specified conditions.[41]

Comparison of *in vitro* dissolution profiles by *similarity factor (f_2)*

The primary objective of this study was to conduct a comparative analysis between the *in vitro* dissolution profiles of the optimized formulation of candesartan cilexetil FDTs (CC12) and the commercially available Atacand tablets. To achieve this, a model-independent method was employed. Mathematically expressed, this method allows for a robust comparison of the dissolution behaviors of the two formulations. The focus was on understanding the release patterns of both formulations and drawing meaningful comparisons, facilitating insights into their respective performance characteristics.[42]

$$f_2 = 50 \times \log \{[1+(1/n) \Sigma | R_t - T_t |^2]^{-0.5} \times 100\} \quad (2)$$

Here, similarity index factor *(f_2),* observations in number *(n)*, R_t, and T_t indicate the percentage amount of drug to be dissolved from both formulations (reference and test).

RESULTS AND DISCUSSION

The FTIR spectrum of pure candesartan cilexetil reveals distinct characteristic peaks, including C-O-C asymmetric stretching at 1785.24 cm^{-1}, symmetric stretching of (C-O-C) at 1025.36 cm^{-1}, C-O-H stretching at 1027.13 cm^{-1}, C = O stretching at 1741.28 cm^{-1}, and C-H bending at 796.47 cm^{-1}. When comparing this to the optimized formulation (CC12), two similar peaks were identified in both spectra, specifically O-H bending and C-H stretching at 1044.23 cm^{-1}, along with asymmetric C-O-C stretching at 1217.34 cm^{-1}. In addition, characteristic peaks related to excipients, such as the C-H stretching of the ethanol group at 2832.29 cm^{-1} and O-H stretching at 3317.38 cm^{-1}, were evident. This analysis leads to the conclusion that there is no significant interaction between candesartan cilexetil and the formulation's excipients, as evidenced by the preservation of functional groups in both spectra.

DSC is useful for understanding a substance's physical and energetic properties. When a guest molecule interacts with a pure drug (candesartan cilexetil), it can alter the substance's melting, boiling, or sublimation points, often causing them to shift or disappear within the pure substance decomposition range.

In the DSC thermogram [Figures 3 and 4] of the drug, a sharp endothermic peak at 166.7°C indicates its high crystallinity. However, the optimized formulation (CC12) displayed a broad peak at 145.60°C, confirming its amorphous nature. This amorphous nature led to a reduction in its melting point to 42°C.

This could be attained due to the incorporation of highly efficient super-disintegrating agents that can create layers on the surface of APIs and get adsorbed onto aggregated particles during the disintegration process. This helps enhance drug solubility through mechanisms, such as capillary action, swelling, and wicking.

Evaluation of formulations

All formulations, denoted as CC1 to CC15, underwent comprehensive parameter evaluation, yielding favorable outcomes as presented in Table 2. Upon careful analysis of the observations, it was found that the bulk and true density values across the CC1 to CC15 formulations were well within the acceptable range.

Flow properties and compressibility

The angle of repose measurements across all formulations was observed to range from 23.19 ± 0.14 to 26.73 ± 0.14.

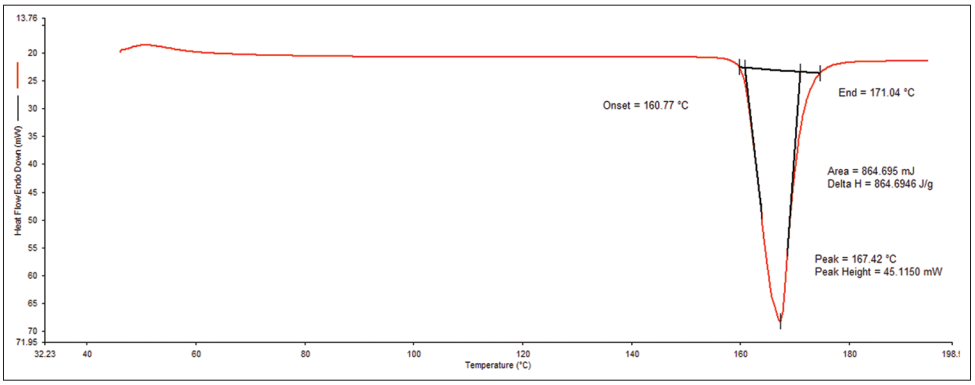

Figure 3: DSC-spectra pure candesartan cilexetil

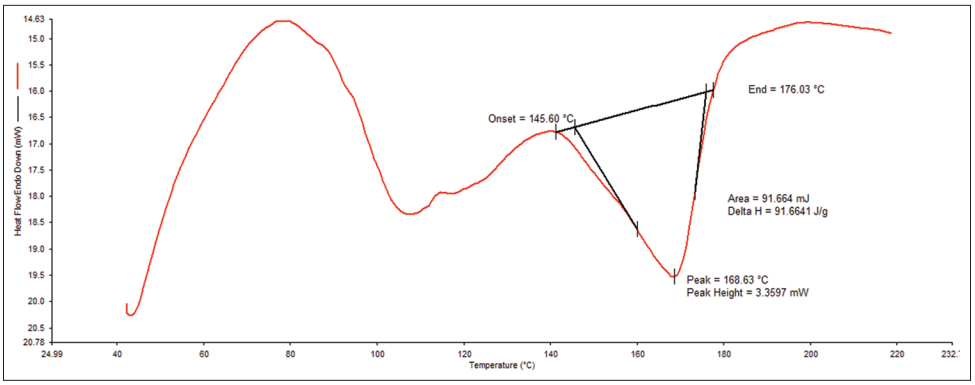

Figure 4: DSC spectra of Candesartan cilexetil fast-dissolving tablets (CC12)

This range signifies that all formulations possess excellent flow properties, which is promising for processing. Similarly, the Hausner ratio, an indicator of compressibility, exhibited values from 1.14 ± 0.12 to 1.17 ± 0.17 across the formulations. This aligns with the acceptable limits for compressibility. In addition, the compressibility index readings spanned from 12.28 ± 0.11 to 14.25 ± 0.15 for all formulations, indicating good compressibility.

In summary, the comprehensive evaluation of formulations CC1 to CC15 revealed consistently acceptable results across various parameters. These results highlight excellent flow properties, suitable compressibility, and promising potential for further processing and development.

The physical parameters, including thickness, hardness, friability, and weight variation, were assessed for all three formulations (n = 3). The results of these tests demonstrated that the values were within the limits specified by the pharmacopeia. The drug content analysis for each formulation also indicated that the concentrations were within acceptable ranges. The collected data were organized and presented in Table 3. Overall, the evaluation of the prepared formulations concluded that they met the required criteria, leading to satisfactory outcomes.

In vitro dissolution profile of candesartan cilexetil FDTs

In the study of candesartan cilexetil fast-dissolving tablets (CC1-CC15), *in vitro* dissolution experiments were conducted in accordance with established standards. The percentage of drug released from all formulations exceeded (Q_{85}) percentage, falling within the acceptable range. Notably, a significant percentage of drug release was observed between $Q_{15\ min}$ and $Q_{30\ min}$, as identified by the authors. This phenomenon could potentially be attributed to the influence of key independent variables, namely Isabgol husk (X_1), potato starch (X_2), and F melt C (X_3).

Among the formulations, CC7 and CC10 exhibited the lowest drug release, with 26 ± 1.25% at $Q_{15\ min}$ and 86 ± 0.146% at $Q_{30\ min}$. Conversely, formulation CC12 displayed the highest drug release, approximately 50 ± 0.29% at $Q_{15\ min}$ and an impressive 98 ± 0.16% within $Q_{30\ min}$. Based on these observations, it can be inferred that an increase in the concentration of the super-disintegrating agents enhances tablet swelling properties. This, in turn, facilitates greater water penetration into the tablet, improving wetting ability, and reducing the time required for tablet disintegration, consequently enhancing drug release. A graphical representation of the results can be found in Figure 5.

Application of factorial design for optimization of candesartan cilexetil FDTs

DT (Y_1)

The DTs of all formulations of FDTs (CC1-CC15) were carefully recorded, and all values fell within the acceptable range of 135 ± 0.17–190 ± 1.37 s. Based on the observations, it became evident that the chosen amount of super disintegrate had a noteworthy impact on the DT, denoted as Y_1. To analyze this relationship, a quadratic model was employed. The mathematical representation of the quadratic regression coefficient equation is provided below.

$$DT\ (Y_1) = +\ 334.05 - 22.57X_1 - 4.13X_2 - 35.35X_3 + 0.005X_{12} - 1.43X_{13} + 0.195X_{23} + 0.555X_1^2 + 0.575X_2^2 + 0.555X_3^2$$

The ANOVA data revealed a regression coefficient value (r^2) of 0.986, indicating strong goodness of fit. The *P*-value was calculated to be 0.011, which is smaller than the threshold of $P < 0.05$. This indicates that the current model significantly influenced the DT through the use of the super-disintegrating agent.

Based on the polynomial equation, the coefficient value of X_3 (F melt C) exhibited a larger value of 35.35 compared to the other super-disintegrating agents, Isabgol husk X_1, and Potato starch X_2. Notably, X_3 had a negative coefficient sign with an impact on DT. This suggests that increasing the concentration of F melt C results in a reduction in DT. This effect can be attributed to its remarkable hydrophilic properties, which lead to rapid water imbibition. This, in turn,

Table 3: Evaluation of post-compressional parameters of candesartan cilexetil fast-dissolving tablets

Formulation	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Drug content (%)
CC1	3.37±0.12	4.51±0.17	0.56±0.15	251.11±0.16	97.12±0.13
CC2	3.34±0.13	4.47±0.12	0.58±0.14	250.06±0.14	96.15±0.11
CC3	3.27±0.14	4.61±0.11	0.54±0.12	251.33±0.12	99.11±0.12
CC4	3.35±0.15	4.71±0.14	0.53±0.16	249.14±0.18	98.15±0.13
CC5	3.28±0.13	4.57±0.12	0.55±0.13	250.16±0.16	97.23±0.14
CC6	3.62±0.14	4.68±0.13	0.56±0.16	250.57±0.13	98.24±0.10
CC7	3.46±0.16	4.58±0.15	0.57±0.17	248.25±0.16	98.18±0.17
CC8	3.38±0.14	4.61±0.16	0.60±0.14	250.56±0.15	99.14±0.11
CC9	3.41±0.15	4.64±0.14	0.72±0.15	250.55±0.10	98.21±0.17
CC10	3.42±0.11	4.45±0.14	0.61±0.11	252.42±0.15	99.32±0.12
CC11	3.35±0.15	4.42±0.14	0.66±0.16	251.27±0.16	98.24±0.14
CC12	3.37±0.13	4.62±0.14	0.51±0.14	251.25±0.14	98.12±0.23
CC13	3.33±0.11	4.47±0.14	0.53±0.15	252.44±0.14	99.13±0.17
CC14	3.34±0.14	4.52±0.14	0.57±0.17	251.53±0.13	99.16±0.16
CC15	3.36±0.16	4.43±0.14	0.56±0.18	252.57±0.17	98.15±0.21

SD values *n*=3

greatly enhances the swelling mechanism by a significant factor (5–8 times) in a matter of seconds. Consequently, this promotes water penetration into the tablet core, weakening the intra-molecular forces between particles. Ultimately, this phenomenon facilitates swift and efficient disintegration, as illustrated in Figure 6.

Percentage drug release at 15 min (Y_2)

To analyze the relationship between the chosen amount of super disintegrant and the percentage drug release (denoted as Y2), the percentage drug release for all formulations (CC1-CC15) was assessed at the 15-min mark. The values observed fell within an acceptable range of 26 ± 0.12–50 ± 0.29% release. It was evident from these observations that, the amount of super disintegrant had a significant impact on DT. For this analysis, a quadratic model was employed, and the mathematical representation of the quadratic regression coefficient equation is provided below.

Percentage drug release at Q 15 min (Y_2) = 51.133 + 18.666X_1 + 7.726X_2 + 35.786X_3–0.020X_{12} + 3.040X_{13}–0.020X_{23}–0.253X_1^2–0.273X_2^2–0.453X_3^2

According to the ANOVA data, the regression coefficient value (r^2) was determined to be 0.978, indicating a strong level of fit. In addition, the *P*-value was calculated as 0.021, which is lower than the established threshold of $P < 0.05$. As a result, it can be concluded that the current model significantly affects DT through the influence of the super-disintegrating agent.

According to the polynomial equation, the coefficient value of X_3 (F melt C) exhibited a larger value of 35.78, which

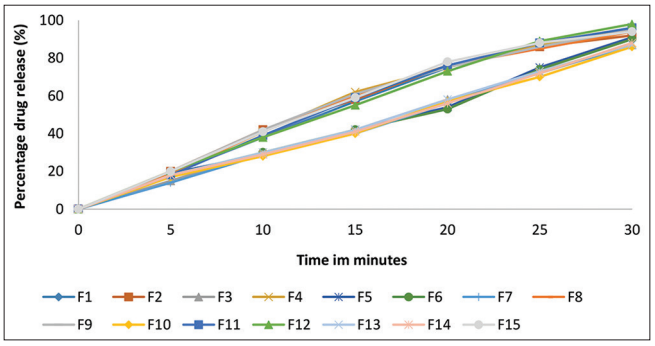

Figure 5: *In vitro* dissolution profile of candesartan cilexetil fast-dissolving tablets (CC1-CC15)

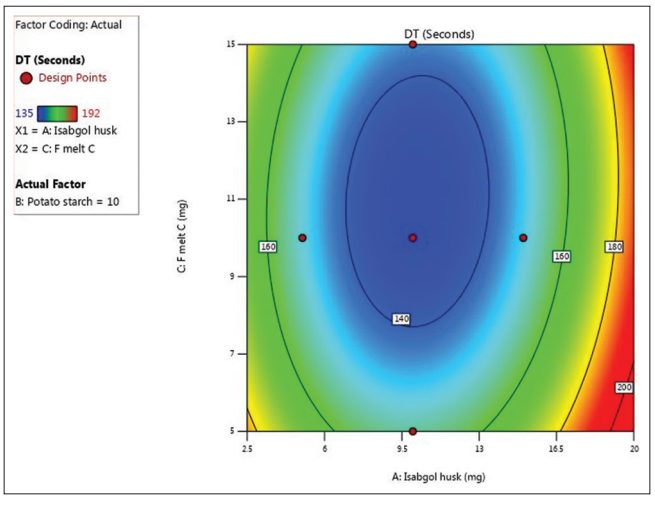

Figure 6: 2D contour plot for disintegration time

was twice as large as that of the super-disintegrating agent Isabgol husk X_1 and 5 times greater than potato starch X_2. Notably, this coefficient showed a significant positive effect

on the percentage of drug release at the 15-min mark. This suggests that as the concentration of F melt C increases, the drug release also increases. This effect can be attributed to the compound's extensive hydrophilic properties, which enable it to take in larger amounts of water and exhibit significant swelling. In addition, it reduces the inter-particle attraction within the tablet's internal matrices. These essential properties collectively lead to a decrease in DT and promote maximum drug release from the dosage form. Consequently, this facilitates the dissolution of a larger amount of drug in the liquid medium, resulting in rapid release. This phenomenon is illustrated in Figures 7 and 8.

Percentage drug release at 30 min (Y_3)

The drug release percentages for all formulations (CC1-CC15) were assessed at the 30-min mark and were found to be within the acceptable range of 86 ± 0.29–98 ± 0.87. These observations highlighted the significant influence

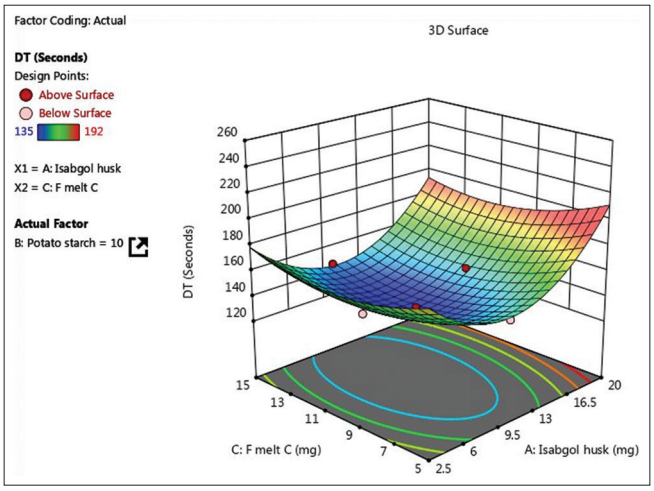

Figure 7: 3D response surface method plot for disintegration time

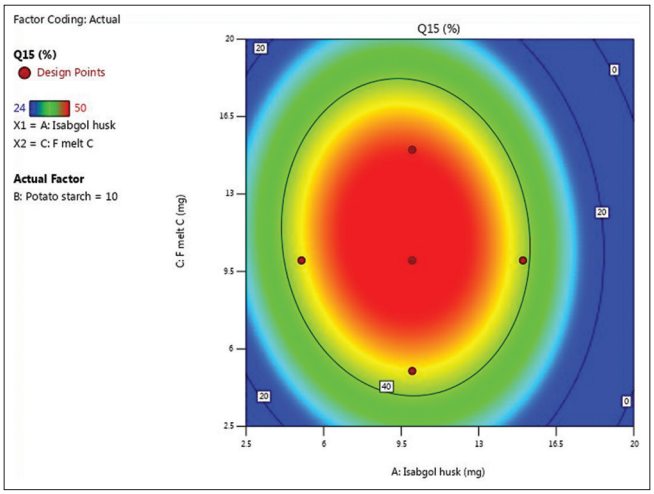

Figure 8: 2D contour plot for percentage drug release at 15 min (Y2)

of the chosen super-disintegrant amount on the drug release percentage, denoted as Y_3. To examine this relationship, a quadratic model was used, and the mathematical representation of the quadratic regression coefficient equation is presented below.

Percentage drug release Q at 30 min (Y_3)

$$Y_3 = 56.788 + 12.402X_1 + 4.682X_2 + 25.742X_3 + 0.015X_{12} + 2.025X_{13} + 0.020X_{23} - 1.1315X_1^2 - 1.131X_2^2 - 1.131X_3^2$$

The ANOVA data analysis revealed that the regression coefficient value (r^2) was measured at 0.989, signifying a strong level of fit between the model and the data. Moreover, the *P*-value obtained was 0.03, indicating statistical significance as it is smaller than the pre-defined threshold of $P < 0.05$. Consequently, it can be concluded that the current model effectively influences the DT through the incorporation of the super-disintegrating agent F melt C (X_3).

In line with the polynomial equation, the coefficient value of X_3 (F melt C) exhibited a larger value of 25.74, which was nearly equivalent to the coefficient value of the other super-disintegrating agent, Isabgol husk X_1 as well as potato starch X_2. Notably, this coefficient demonstrated a substantial positive effect on the percentage of drug release at the 30-min interval. This indicates that increasing the concentration of F melt C led to a corresponding increase in the amount of drug released. Interestingly, the authors observed a similar impact of both super-disintegrating agents on the percentage of drug release. The outcomes of these experiments are visually presented in Figure 8.

Selection of optimized batch as a function of desirability of all response variables

The selection of the best and optimized formulation relied on the desirability response, a key function in Design Expert software. This approach played a crucial role in identifying the most reliable formulation. The desirability graph in the software combined various responses from dependent variables, thus facilitating the creation of an ideal formulation with the desired physicochemical properties.

For optimization purposes, the desirability scale ranged from 0 to 1. It aligned the values of individual response variables and was applied to evaluate each formulation from CC1 to CC15. A desirability value close to zero indicated unfavorable and unacceptable conditions for the responses, rendering a formulation undesirable. Conversely, as the value approached one, the formulation became highly preferable and desirable.

In light of the results, the desirability of all formulations was compared graphically using software. This approach offered potential solutions for optimizing the FDTs batch. The information was illustrated through desirability and

overlay plots, showcased in Figures 9 and 10. Notably, from Figure 9, it was evident that CC12 stood out as the most desirable formulation, given its highest desirability value of 0.984, highlighted by a blue circle.

In the assessment of release orders for the fabricated candesartan cilexetil fast-dissolving formulations from batches CC1–CC15, the DD solver model software was employed. This software served as a powerful tool for deciphering the intricate release patterns. By utilizing a range of mathematical models, the study yielded insightful results is shown in Figures 11-15.

From the zero-order model, the CC12 formulation exhibited a notable r^2 value of 0.9765, indicating a robust correlation between the model and the observed data. Correspondingly, the AIC value was calculated as 32.48, while the MSC value reached 3.53. In the context of first-order studies, the model CC12 formulation resulted in a higher r^2 value of 0.9852, confirming the model's strong fit. The recorded AIC value was 28.15, and the MSC value stood at 4.62

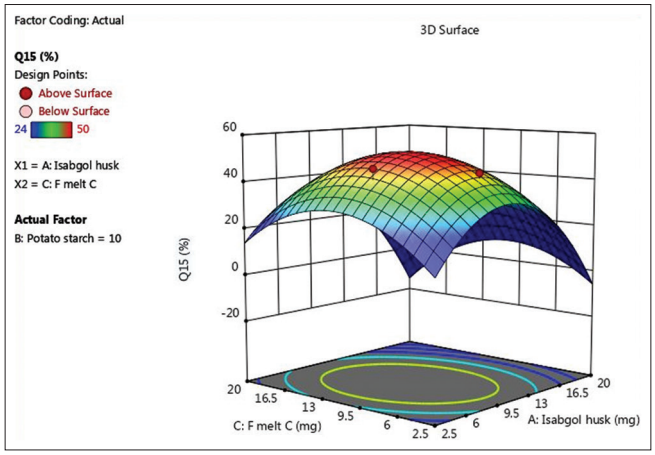

Figure 9: 3D response surface method plot for percentage drug release at 15 min (Y2)

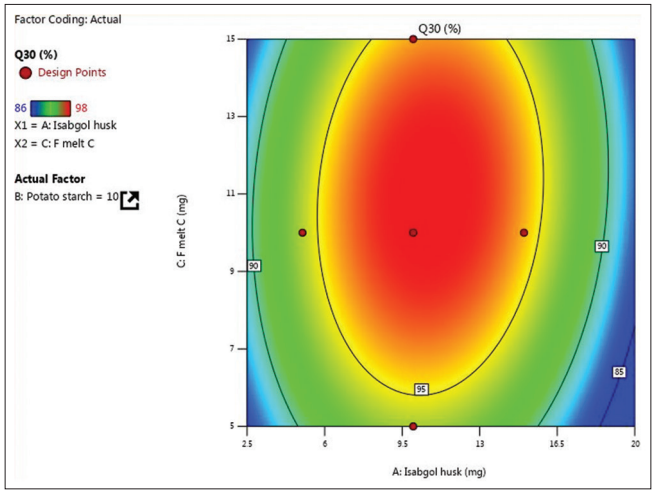

Figure 10: 2D contour plot for percentage drug release at 30 min (Y3)

Shifting focus to the Higuchi model, formulation CC12 demonstrated an r^2 value of 0.9731, signifying the model's excellent alignment with the experimental data. The AIC value was determined as 30.27, while the MSC value reached

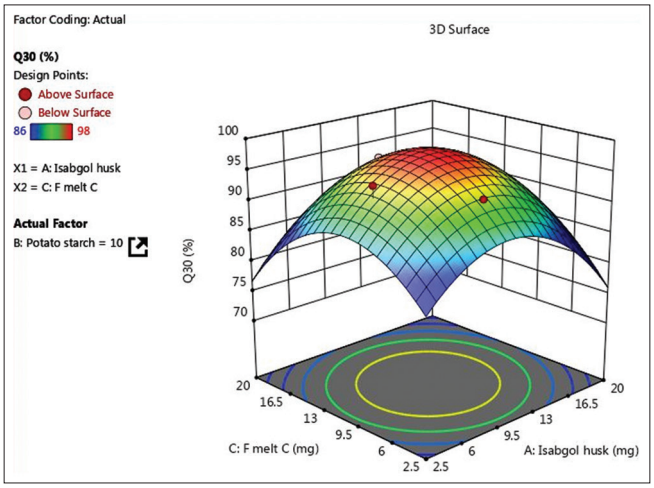

Figure 11: 3D response surface method plot for percentage drug release at 30 min (Y3)

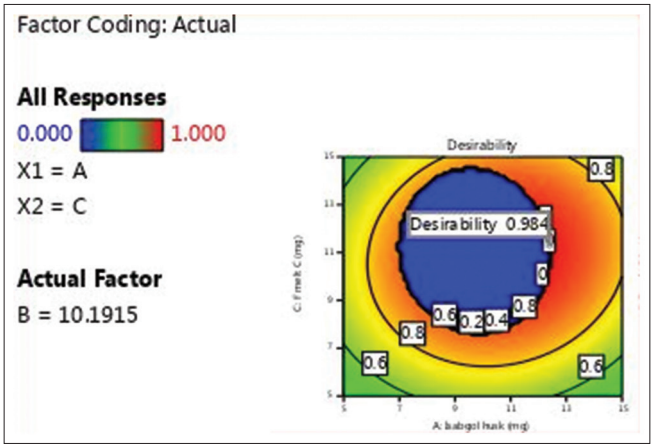

Figure 12: Desirability plot for all response variables

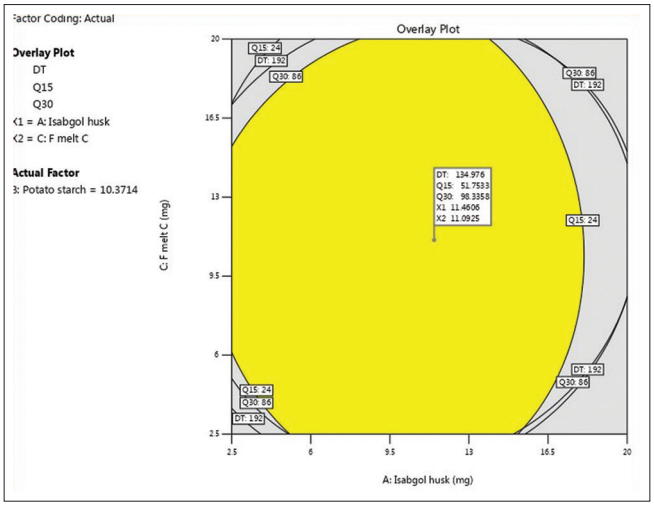

Figure 13: Overlay plot for all response variables

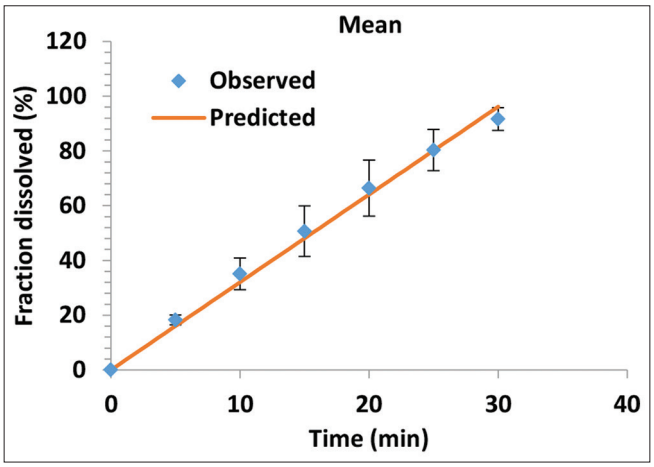

Figure 14: Zero-order plot

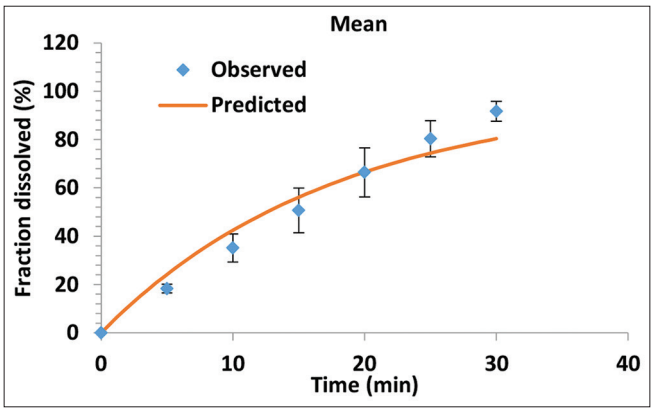

Figure 15: First-order plot

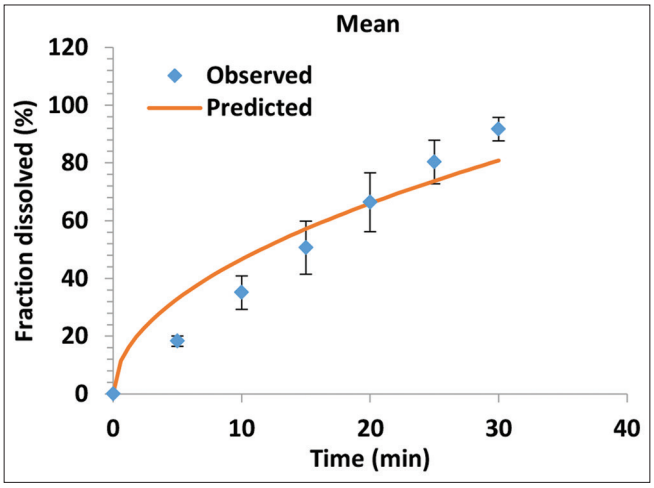

Figure 16: Higuchi plot

4.85. Notably, the inclusion of Hixson-Crowell release order analyses revealed that for formulation CC12, the r^2 value was 0.9871, the AIC value was 35.43, and the MSC value was 5.24.

Extending the investigation, the Korsmeyer–Peppas equation provided deeper insights into formulation F5. The model suggested an r2 value of 0.9841, in strong agreement with the

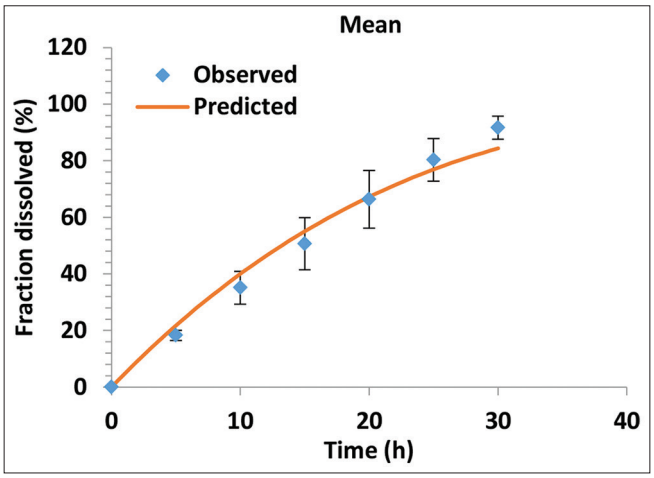

Figure 17: Hixon–Crowell plot

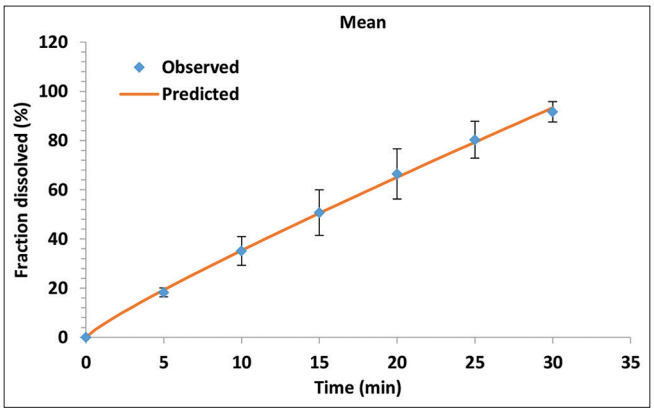

Figure 18: Korsmeyer–Peppas plot

data. The calculated AIC value was 30.14, while the MSC value was 5.96. Notably, the exponent release (n) value stood at 0.346, indicating a Fickian diffusion-type mechanism governing the release.

In this comprehensive study, various mathematical models were used to explore and explain the complex patterns of drug release from different formulations of candesartan cilexetil. Through detailed analysis, these models offered detailed insights into the release kinetics. As a result, a better understanding of how the formulations release their contents over time was achieved [Figures 16-18].

Stability studies were conducted to ascertain the true shelf-life of the optimized candesartan cilexetil fast-dissolving tablets. Formulation CC12 underwent these tests at 40°C and 75% relative humidity (RH) conditions. Over 3 months, the formulations underwent comprehensive analysis, evaluating overall tablet properties, such as hardness, friability, and drug content. The study also included *in vitro* dissolution evaluations.

In the *in vitro* dissolution studies, an ANOVA was performed. The obtained $P = 0.926$ surpassed the threshold of $P > 0.05$, indicating insignificant variation in the *in vitro* dissolution

parameters. Furthermore, the optimized CC12 formulation's performance was compared to the commercial Atacand 16 mg. This comparison utilized the similarity factor *(f2)* assessment, resulting in an impressive *f2* value of 78. This value highlighted a remarkable resemblance between the dissolution profiles of the CC12 formulation and Atacand 16 mg.

The thorough stability studies highlighted the positive characteristics of the optimized CC12 formulation for 3 months under controlled temperature and humidity. Remarkably, the dissolution behavior of CC12 closely mirrored that of the established Atacand 16 mg, suggesting a promising equivalence between the two formulations.

CONCLUSION

FDTs of candesartan cilexetil were developed by optimizing selected independent variables to improve the dissolution profile. The presence of soluble polymers, such as Isabgol husk, potato starch, and F melt C, acting as super disintegrants, played a significant role in enhancing solubility. Furthermore, these super disintegrants were statistically optimized through the Design of Expert software using response surface methodology.

The statistical designs unveiled that the concentration of the super disintegrating agent had a notable impact on DT and percentage drug release at both 15 and 30 min. Formulation CC12 emerged as the optimized choice, aligning with the requirements of FDTs as per IP standards and the study's objectives.

Utilizing the DD solver as a statistical tool, the *in vitro* dissolution data of formulations CC1-CC15 were analyzed, unveiling insights into kinetics, release mechanisms, and similarity factors (f2). Adhering to ICH guidelines, stability studies under stress conditions were conducted for 90 days. Notably, the results highlighted minimal alterations in the physical and chemical properties of the prepared candesartan cilexetil FDTs, confirming their enhanced quality.

ACKNOWLEDGMENT

We express our sincere gratitude to Assam Downtown University, Guwahati, Assam, Chaitanya Deemed to be University, Warangal, and Vaageswari College of Pharmacy, Karim Nagar, India, Department of Pharmaceutics, Sreedattha Institute of pharmacy, Sheriguda, Ibrahimpatnam, R.R.Dist, Hyderabad, Telangana, for providing the necessary resources and facilities for conducting this research. Special thanks are due to the research team members for their invaluable contributions. This work was made possible through the collaborative efforts of all involved parties.

AUTHORS' CONTRIBUTIONS

Dr. V. Mallikarjun: Contributed to the literature review and manuscript preparation and analyzed the data and interpreted the results. Dr. U. Sambamoorthy: Investigation, Data curation, Writing - original draft and editing. Mrs. Jyothi Muddagoni: Revision, Software, and Writing – reviewing and editing. Dr. Yedurukrishnareddy: Provided expertise in pharmaceutical formulation and quality by design principles. Dr. Chandrashekar Thalluri: Conceptualized the study and designed the research methodology and conducted the experiments and collected the data.

ETHICS APPROVAL

Not applicable.

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Source of Support: Nil. **Conflicts of Interest:** None declared.