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Central Composite Design Approach for Enhanced Alfuzosin Hydrochloride Extended Release Matrix Tablets: Promising Solutions for Benign Prostatic Hyperplasia Management

Kumara Swamy Samanthula[1*], Chandrashekar Thalluri[1], Satya Obbalareddy[2], Daniel Kothapally[3], Agaiah Goud Bairi[4]

[1]Faculty of Pharmaceutical Science, Assam Downtown University, Guwahati, 781026, Assam, India, [2]Department of Health System Management Studies, JSS Academy of Higher Education and Research, Mysuru-570004, India, [3]Chaitanya Deemed to be University, Hanamkonda, Warangal, Telangana, 506001, India, [4]SRR College of Pharmaceutical Sciences, Valbhapur, Warangal, Telangana, 505476, India. *Corresponding Author's Email: kumar4koty@gmail.com

Abstract

Alfuzosin hydrochloride targets benign prostatic hypertrophy (BPH) in older men. This study aimed to produce matrix compositions with 24-hour extended-release tablets to reduce the requirement to provide three 2.5-mg Alfuzosin hydrochloride tablets daily. Wet granulation blended hydrophilic (Hydroxypropyl methylcellulose, HPMC K15M) and hydrophobic (Ethyl Cellulose, EC) polymers to develop the tablets. QbD employed a Randomised, Non-block, Central Composite Design using a quadratic model, response surface study style, and version 13.0. We methodically created eleven different formulas. A three-level-two factorial design was used, with independent variables HPMC K15 X_1 and EC and X_2 concentrations and dependent variables t_{25} and t_{90}% drug release. Extended-release points were chosen based on % drug releases at 2, 4, 12, 16,20 and 24 hours. The formulation F8 displayed the highest drug release, approximately 99.95±1.84 percent within the specified time at 24 hours. The dissolution data were fitted into several release kinetics. Drug release was caused by the diffusion mechanism. The ANOVA data showed a regression coefficient value (R^2) of 0.9502, suggesting a high level of excellence of fit. The calculated p-value of 0.002 falls below the significance threshold of $p<0.05$. It appears that the current model had a notable impact on the t_{90}% drug release by utilizing a specific bio-degradable polymer. A combined polymers mixer extended Alfuzosin release over 24 hours, suggesting that the formulations are appropriate for a once-daily dosing. This approach optimizes the best, controlled release batch within the defined period, and F8 received the highest attractiveness rating of 1.00, highlighted in blue.

Keywords: Alfuzosin Hydrochloride, Alpha-1 Antagonist, Benign Prostatic Hyperplasia (BPH), Central Composite Design, Quality by Design (QbD).

Introduction

A novel method of administering drugs as well as biologically active medications has emerged within the last few decades. Extended-release, sustained-release, or controlled releases are terms used to describe this method of medication delivery. The idea is to insert a special polymeric carrier material into the body, which will act as a reservoir for the medications (1). Following physical injection, implant, or oral administration, the primary objective is for the medication and carrier material to be released at a specified pace for a given duration (2). Because time-release technology is a relatively young discipline, research in this area has been exceedingly fruitful, yielding several discoveries. New and more advanced sustained-release medication delivery methods have been proposed and tested all the time (3). A quinazoline derivative called Alfuzosin is a selective alpha-1 antagonist that has been used to treat high blood pressure as well as benign prostatic hyperplasia. Alfuzosin works by blocking vascular smooth muscle's postsynaptic alpha-1 adrenoceptors (4). By blocking the vasoconstrictor effects of catecholamines (epinephrine and norepinephrine) in circulation and in the body, this medicine produces peripheral vasodilation. The patient has urinary retention due to the enlargement of the prostate gland in benign prostatic hyperplasia. A time-release dose form that induces sufficient necrosis to allow the prostate to shrink as the body recycles the diseased tissue is the main goal of the therapies, with the hope of relieving the obstruction of the urinary system (5).

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The standard dose of Alfuzosin for BPH patients is 2.5 mg immediate-release dosage forms twice or thrice daily, 5 mg extended-release dosage forms twice daily, or 10 mg extended-release dosage forms once daily.In order to more slowly achieve the optimum plasma concentration, the absorption properties of the prolonged-release formulation are modified (C_{max}). By preventing excessive plasma concentration peaks, this promotes a stable plasma concentration over a 20-hour period, enabling once-daily dosage and increasing tolerability (6). Alfuzosin hydrochloride is a component in the prescription medication Alfoo (Dr. Reddy's Laboratories Ltd) 10 mg Tablet PR Extended-release formulations was designed to minimize pill burden and improve patient compliance. It is administered for the management of male BPH symptoms. In BPH, the prostate gland enlarges, resulting in urinary issues such as difficulty urination, frequent urination, weak urine stream, etc. This medication relaxes the muscles in the urinary bladder, urethra, and prostate. As a result, it aids in the relief of BPH symptoms. However, it has no effect on prostate size (7, 8). The ideal pharmacokinetic coverage over 24 hours may be achieved using a once-daily formulation of Alfuzosin that is administered via a unique prolonged-release technology. This formulation also improves dosing convenience. The medicine's high solubility in water poses the greatest challenge to the development of a controlled-release formulation (BCS class 1 drug). The reference listed drug that is now on the market managed the release of the very soluble Alfuzosin from its dosage forms using several pharmaceutical rate-controlling polymers (9, 10).
Therefore, for readily soluble medications like Alfuzosin, a high amount of HPMC is necessary to control the release, resulting in a difficult-to-swallow tablet. The solution to the issue is to use water-insoluble polymers in the formulation. For the preparation of tablets, ethylcellulose was combined with HPMC in the current investigation (11, 12). According to a literature review, an extended-release drug delivery method for Alfuzosin hydrochloride was developed to sustain effective plasma concentrations throughout the first 3-6 hours after administration, corresponding to the middle of the average sleep time. In this work, a combination of isopropyl alcohol and ethylcellulose, hydrogenated castor oil, and hydroxypropyl methylcellulose in different amounts were used to manufacture prolonged release matrix tablets containing Alfuzosin hydrochloride (13). This study aimed to develop and test Alfuzosin hydrochloride extended-release matrix tablets to increase patient compliance and therapeutic action. The goal of prolonged-release preparation is to alter the absorption properties so that the maximum plasma concentration is reached more slowly (C_{max}). This supports a stable plasma concentration over a period of 24 hours, allowing for once-daily dosage and increased tolerability by avoiding excessive plasma concentration peaks.

Materials and Methods

Alfuzosin hydrochloride was obtained as a gift sample from Hetero Drugs Pvt. Ltd, Hyderabad. Hydroxypropyl methylcellulose and ethylcellulose are obtained from Chemi-nova Remedies, Balanagar, Hyderabad. Lactose monohydrate, polyvinyl pyrrolidone (PVP K30), magnesium stearate, and aerosil were obtained from Nihal Trader's private limited, Hyderabad, and all other materials were analytical and pharmaceutical grade.

Formulation of Extended-Release Matrix Tablets

The wet granulation approach was used to prepare tablet formulations. Alfuzosin HCl extended-release tablets were made using a wet granulation method. Table 1 shows the proportion of excipients in the tablet's formulation. Using a sieve having a number 40 opening, the ingredients were sifted until they were all of a moderately fine, homogeneous size. The final blend was formed by mixing Alfuzosin HCl, lactose monohydrate, HPMC K15 and EC. Wet granulation of the final mixture was done with PVP K30 dissolved in isopropyl alcohol (5 per cent w/v). Wet granules were subsequently dried in an oven at 50°C for 30 minutes after passing the wet mass through sieve number 12. Dried granules were sized with the aid of passing them through sieve number 22 and blended with magnesium stearate and aerosil. A rotary tablet punching machine was used to compress the tablets with a trendy concave punch.

Experiment Design (Central Composite Design/Response Surface Methodology)

We used a method called the response surface technique, specifically a three-level, two-factor central composite design, along with Design Expert® (Version 10.0.1, State-Ease Inc., India), to improve the design and formulation of matrix tablets that release their ingredients slowly. In this study, Central Composite Design (CCD) within the Response Surface Methodology (RSM) framework was selected over other Design of Experiments (DoE) approaches such as full factorial, Box-Behnken, and Plackett–Burman designs due to its efficiency and suitability for capturing both curvature and interaction effects, making it ideal for optimization studies. Allowed for process optimization with the fewest feasible runs, which were 11 runs total, including three duplicated center points. Below is a computer-generated quadratic equation representing a three-factor, three-level model that is non-linear and polynomial.

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

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}. Additionally, 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_1^2 and X_2^2, on the other hand, indicate the quadratic models of the independent variables. These quadratic models introduce curvature effects into the study's analysis (14).

Table 1: Composition of 3^2 Factorial Design Formulations of Alfuzosin Hydrochloride Extended-Release Matrix Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Alfuzosin hydrochloride	10	10	10	10	10	10	10	10	10	10	10
HPMC K 15M	150	100	125	100	150	125	125	125	100	150	125
Ethyl Cellulose	50	25	25.0	50.0	25.0	37.5	37.5	50.0	37.5	37.5	37.5
Lactose monohydrate	30	105	80	80	55	67.5	67.5	55	92.5	42.5	67.5
PVP K30	30	30	30	30	30	30	30	30	30	30	30
Magnesium-stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of Alfuzosin Hydrochloride Extended Release Matrix Tablets

Pre-Compression Characteristics: The granular properties such as poured density, tapped density, Carr's index, Hausner's ratio, and angle of repose for the batches were determined according to the standard tests specified by the pharmacopoeia (15, 16).

Fourier Transform Infrared Spectroscopy (FTIR) Compatibility Studies: The I.R. spectra of the drug were compared to those from the physical mixture. The tablets were crushed and ground into powder. For FTIR experiments, the palletized powder and KBr were both employed. An IR-spectrophotometer was used to record the IR spectra for the pure drug, EC, HPMC K15, and optimum formulation (17, 18).

Post-Compression Parameters: The bulk and tapped density, Carr's index, Hausner's ratio, and angle of repose of the granules were all measured. In addition, the thickness test, hardness test, friability test, weight variation test, the drug content, and in vitro release studies of the tablets were all analyzed. The following unofficial and official assessments were performed for the entire matrix tablets prepared (19, 20).

Hardness: A Monsanto hardness instrument was used to determine the hardness of tablets. The standard error and mean were calculated and reported. It has measured in kilograms per square meter (21).

Friability: For the purpose of determining the tablet's friability, the Roche friabilator was used. A percentage, or %, is used to quantify it. Initially, 10 tablets were dropped in the friabilator after being pre-weighed and placed there. It was spun at 25 revolutions per minute for a period of four minutes. Even after four minutes had passed, the samples were reweighed once again. Following that, the formula was used in order to compute the Friability (22, 23).

$$\text{Friability (\%)} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} x\ 100 \quad [2]$$

Weight Variation Test: A random selection of twenty tablets were picked from each batch and individually weighed. The average weight of 20 tablets was calculated, along with its standard deviation. The weights of individual tablets do not deviate by at least two from the average weight. As a result, the batch weight successfully meets the criteria for weight variation. As per the guidelines set by the USP, the standard percentage difference allowed for the tablet is provided in Table 2 (24).

Table 2: Weight Variation Tolerance for Uncoated Tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 (or less)	10%
130 - 324	7.5%
> 324	5%

Drug Content: Weighing 10 tablets allowed us to determine the average mass of the tablets. Each and every one of the 10 tablets was smashed apart using a mortar. After shaking the mixture for fifteen to twenty minutes, the powder that was equal to ten milligrams of Alfuzosin hydrochloride was dissolved in two hundred and fifty milliliters of 0.1N hydrochloric acid and phosphate buffers with a pH of 6.8. After filtering the solution, 0.1N HCl and buffer were used to dilute 5ml of the solution filtrate to 100ml volume. The resultant solution's 'absorbance' was measured at 254nm using 0.1N HCl and pH 6.8 phosphate buffers as references. Finally, the amount of drug in the tablet was determined (25).

Dissolution Study: The tablet dissolving process for each batch was carried out with the assistance of U.S.P. type-II equipment that included a paddle. Afterward 900 millilitres of 0.1N hydrochloric acid with a pH of 1.2 was maintained at 37±0.5^{0}C for two hours, the remaining dissolving media consisted of phosphate buffers with a pH of 6.8. Each dissolution vessel had one tablet, and the paddle rotational motion was set to 50rpm, at 1, 2, 4, 8, 12,16, 20 and 24 hours, 5ml of the dissolute sample was taken and replaced with the same amounts of the fresh medium. The data needed to determine the concentration of Alfuzosin hydrochloride in the samples was acquired using the double beam UV-visible spectroscopy (Shimadzu) at a wavelength of 254 nm (26, 27).

Treatment of Dissolution Data with Different Kinetic Models: Some scientists have proposed that a zero-order kinetic equation could be used to describe the dosage forms of drugs that do not break down and release slowly. Some scientists have proposed that a zero-order kinetic equation could be used to describe the dosage forms of drugs that do not break down and release slowly. It is common practice in systems where pure diffusion maintains drug release to assess the quantity of drug released from matrix tablets based on the passage of time, as stated by others. Hence, a versatile model capable of detecting contributions to the whole dynamics of the equation suggested by Korsmeyer-Peppa's model is required for drug release analysis using bulging matrices. The suitability of the many equations presented in this work to characterize the processes by which drugs dissolve was considered

in relation to the publication date. In order to ascertain the matrix tablets' release pattern, the results from the drug release trials were examined using the following equations.

Zero-order model (K_0): [$Q = K_0 t$] [3]
The first-order kinetics model: -kt in (1-Q) [4]
Higuchi model (K_H): [$Q = KH\ t½$] [5]
Korsmeyer-Peppa's model: $F = (M_t/M) = Km\ t^n$ [6]

When working with mathematical equations, certain variables are used to represent different aspects of drug release. For example, Q represents the amount of drug released at a specific time, Mt represents the drug released at that time, and M represents the total amount of drug in the dosage form. Other variables like F, K_0, K_H, K_m, and n are used to describe specific characteristics of the drug release process. When n is at or below 0.45, it suggests Fickian diffusion. On the other hand, if n falls between 0.45 and 0.89, it points towards anomalous transport. Lastly, when n exceeds 0.89, it indicates case-II transport (28, 29).

Results and Discussion

Preliminary formulation trials were conducted to identify suitable ranges for the independent variables, specifically HPMC K15M and Ethyl Cellulose, which play a critical role in modulating the drug release profile and ensuring matrix integrity in extended-release tablets. In these trials, varying concentrations of HPMC K15M (80–160 mg) and Ethyl Cellulose (20–50 mg) were tested. Formulations with lower polymer concentrations exhibited faster drug release and poor matrix integrity, while those with higher concentrations provided extended drug release but resulted in excessively rigid matrices. Based on these observations, the ranges of HPMC K15M (100–150 mg) and Ethyl Cellulose (25–50 mg) were selected for the Central Composite Design (CCD) optimization, ensuring an appropriate balance between sustained release and tablet robustness. These selections are also in alignment with values reported in relevant literature, further supporting their use in the design space.

Evaluation of Granules

The findings for batches F1-F11 were presented in Table 3, which shows granular attributes such as tapped density, poured density, angle of repose, Carr's index, and Hausner's ratio. The formulation yielded the equations necessary for granule production. The continual release of medication from matrix-type particles is required by many dosage forms, and granulation is an essential stage in their production. Bonds of limited strength hold the particles that make up a granule together. The fact that the angle of repose for several formulations was less than 30 demonstrated the granules' excellent flow characteristics. Lower compressibility indexes backed up this theory. Israr examined the precompression properties of a cefuroxime axetil matrix system and noted good to exceptional powder flow (30). All of these findings suggest that the granules have good flow characteristics.

Table 3: Evaluation of the Alfuzosin Hydrochloride-Containing Granules' Characteristics (F1-F11)

Formulation code	Poured density* (gm/ml)	Tapped density* (gm/ml)	Carr's index (%)	Hausner's ratio (%)	The angle of repose*
F1	0.51±0.06	0.42±0.04	12.83	1.15	23±1.57
F2	0.46±0.07	0.52±0.08	13.46	1.16	25±2.64
F3	0.47±0.03	0.41±0.35	14.63	1.17	26±0.46
F4	0.36±0.02	0.42±0.07	14.28	1.17	24±2.61
F5	0.52±0.04	0.43±0.05	12.81	1.13	23±1.54
F6	0.47±0.04	0.42±0.33	14.62	1.16	26±0.42
F7	0.42 ±0.04	0.55±0.05	13.74	1.31	23±2.16
F8	0.36±0.15	0.43±0.06	16.05	1.19	23±1.16

F9	0.38±0.06	0.45±0.07	16.99	1.2	25±2.52
F10	0.53±0.04	0.42±0.05	12.84	1.14	23±1.56
F11	0.38±0.06	0.44±0.03	11.16	1.13	23±1.52

Notes: * Indicates Average Reading ± SD (n = 3)

Pre-Compression Characteristics

FTIR Compatibility Studies: The FTIR spectra confirmed that the medication and physical combination did not interact with the excipients. The drug complied with the preliminary identification test. All of the excipients are compatible with the drug, according to IR spectroscopic investigations. It was confirmed that there was no drug-component interaction because the IR spectra of the optimized formulation contained all of Alfuzosin's characteristic peaks, as shown in Figure 1(A) and Figure 1(B).

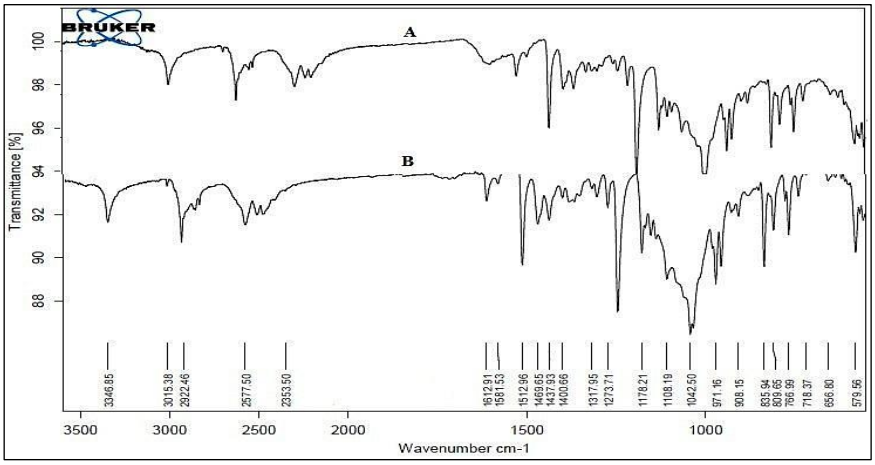

Figure 1: The FTIR Spectra of (A) Pure Alfuzosin Hydrochloride, and (B) Optimized Formulation

Post-Compression Parameters: The characters of tablets like thickness, hardness and Friability for the formulations F1-F11 (Alfuzosin hydrochloride tablets) were determined, and the results were reported, as shown in Table 4. The tablets were discovered to have a thickness of 3-4mm. The weight of each tablet formulation was determined to be within the specified limits, which indicates that all compositions passed the weight variation test according to the official requirements. The drug content was more than 98%, and there was good uniformity across all formulations. The average weight was 302 mg, and the standard deviation was ±1.66% to ±2.15% (less than 7.5%). The tablets hardness was found to be between 5.5 and 6.6 kg/cm^2. Parmar found that the matrix formulations for a sustained-release system with paroxetine HCl met the pharmacopoeia standards for post-compression values, showing they had excellent compression qualities (31). Out of the eleven formulations, the F8 formulation was chosen as the sustained-release tablet for Alfuzosin because it had good physical compression properties that met the standards set by pharmacopoeias. This could be due to the influence of isopropyl alcohol, which causes a tablet's hardness to increase. A tablet's hardness isn't a good indicator of its strength. Friability is another indicator of a tablet's strength. Traditional compressed tablets with a weight loss of less than 1% are generally regarded as acceptable, as well as within the prescribed limitations.

Table 4: Properties of Tablets Containing Alfuzosin Hydrochloride (F1-F11)

Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F1	3.7±0.14	6.6±0.55	0.42
F2	3.3±0.07	5.5±0.51	0.64
F3	3.6±0.15	5.6±0.76	0.66
F4	3.4±0.16	5.5±0.65	0.48

F5	3.5±0.09	6.6±0.45	0.65
F6	3.5±0.16	5.9±0.33	0.33
F7	3.5±0.14	5.8±0.36	0.47
F8	3.5±0.09	5.7±0.57	0.39
F9	3.4±0.12	6.2±0.13	0.55
F10	3.6±0.07	6.5±0.12	0.65
F11	3.5±0.13	5.9±0.18	0.53

Notes: Data are expressed as Mean ± SD (n = 3)

We investigated and reported the values of drug content homogeneity and weight variation fluctuation for the formulations F1-F11 (Alfuzosin hydrochloride), as shown in Table 5. All of the formulations had drug content percentages close to 100, ranging from 98.55±0.54 to 99.78±0.92% in 0.1N HCl and 97.98±0.63 to 100.15±0.33% in pH 6.8 phosphate buffers, showing that the preparation process was consistent.

Table 5: Drug Content Uniformity and Weight Variation

Formulation	**Drug content uniformity(mg)**		**Weight -Variation (mg)**
	0.1N HCl	**pH 6.8 phosphate buffers**	
F1	98.58±0.18	97.98±0.63	276±1.55
F2	98.55±0.54	99.66±0.42	277±1.68
F3	99.78±0.92	98.13±0.55	274±1.66
F4	99.65±0.35	98.16±0.21	275±1.88
F5	99.28±0.66	99.33±0.33	276±2.15
F6	99.45±0.82	100.15±0.33	275±1.33
F7	98.83±0.79	98.25±0.66	274±1.97
F8	99.49±0.41	99.69±0.85	276±1.66
F9	98.56±0.36	99.85±0.73	275±1.63
F10	98.89±0.46	99.33±0.89	276±1.33
F11	99.75±0.73	98.57±0.48	275±1.54

Notes: Data are Expressed as Mean ± SD (n = 3)

In-Vitro Dissolution Studies

Tablets containing Alfuzosin hydrochloride (F1-F11) were prepared. The *in-vitro* release study qualities were examined using the USP type-II dissolution apparatus, at 50 rpm, in simulated stomach for first 2 hours and intestinal fluid for 20 hours. The results of the dissolution studies indicated that the formulations F1 to F11 released 10.23±1.62% to 25.80±2.51% of Alfuzosin hydrochloride at the end of 2 hours in the simulated stomach fluid (acidic medium). The results of the dissolution studies indicated that the formulations F1, F5, and F10 released 55.58±2.09%, 61.98±1.91%, and 69.51±2.52% of Alfuzosin hydrochloride at the end of 20 hours, respectively, in the simulated intestinal fluid. The formulations F2, F3, F6, F7, F9, and F11 released 98.52±2.17%, 92.42±2.38%, 90.86±2.52%, 91.78±1.83%, 93.42±2.89%, and 92.65±1.99% of the drug after 20 hours in the simulated intestinal fluid. Figure 2 shows the formulations that exhibit different remarkable cumulative percentage drug releases. Gangolu and Elsayed brought attention to the fact that the release pattern improved with increasing concentrations of ethylcellulose and HPMC polymer polymers, suggesting that the polymer played a crucial role in Clarithromycin release from the extended-release tablets (32-34).

The release rate went up when the amounts of ethylcellulose and HPMC K15M in these formulations were reduced.

The enlargement of the HPMC K15M polymer, which facilitates diffusion within the polymer, may be the cause. However, as the concentration of gelling HPMC K15M polymer increased with decreasing the ethylcellulose polymer, the release pattern raised, confirming the swellable hydrophilic polymer's major involvement in releasing Alfuzosin hydrochloride from matrix tablets. In addition, ethylcellulose's high polymer concentration shows an extended drug release at the end of 20 hours. The dissolution profiles show that the hydrating polymer HPMC K15M dominated the ethylcellulose polymer due to the high viscosity in extending the release of Alfuzosin hydrochloride from the matrix tablets.

According to the findings, formulation F8 is the best formulation based on in-vitro drug release studies. The optimized formulation F8 was compared with the innovator (Alfoo) and the prepared matrix tablets release was 21.23±1.66% at the end of 2h in the stomach fluid (acidic medium) and 84.82±1.13% at the end of 20h in the intestinal fluid,and the innovator (Alfoo) tablet release was 18.55±1.25% at the end of 2h in the stomach fluid (acidic medium) and 81.53±1.55% at the end of 20h in the intestinal fluid, this could be due to the water-loving nature of the formulation, which makes it swell up like a gel and helps the medication to be released effectively (Figure 3). The results shown that 80% of the drug was released at 20 hours, with the remaining 20% perhaps released at the very end. The results indicate that once compared to the marketed product, the developed formulation satisfies the once-daily extended-release dose form.

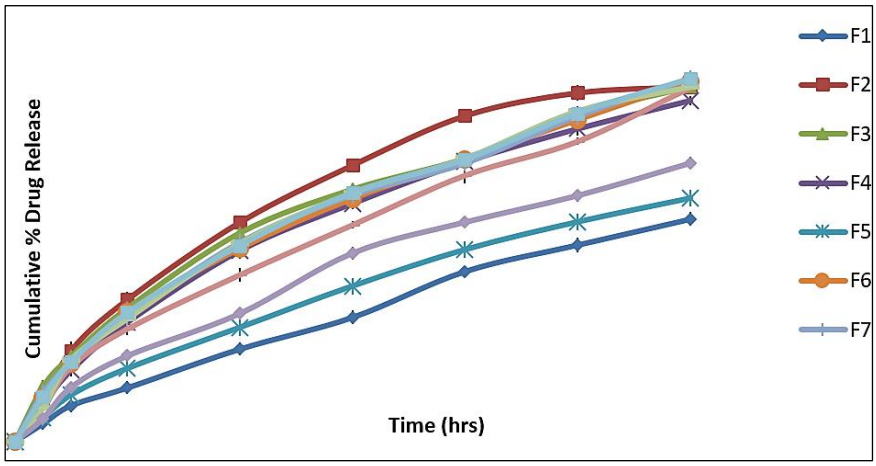

Figure 2: *In-Vitro* Release Profiles of Alfuzosin Hcl Matrix Tablets in pH 1.2 Acidic Medium (2hr) and pH 6.8 Phosphate Buffers (Data Presented as Mean±SD, N=3)

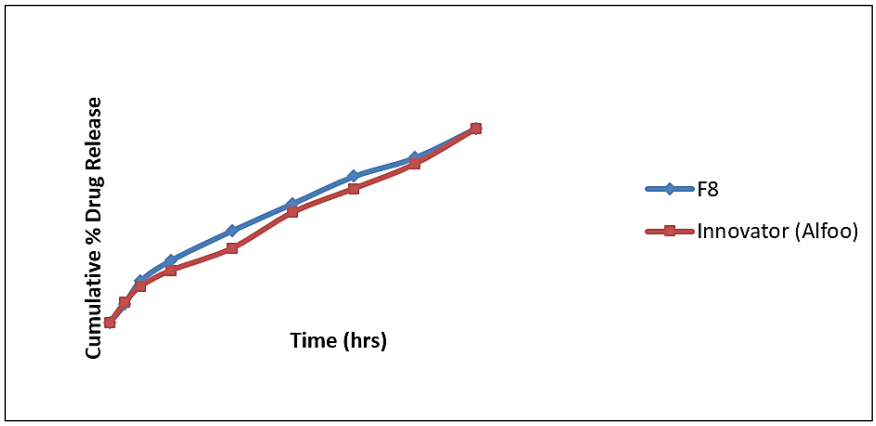

Figure 3: Comparative Dissolution Profile of Optimized Formulation and Innovatorin pH 1.2 Acidic Medium (2hr) and pH 6.8 Phosphate Buffers (Data Presented as Mean ±SD, N=3)

In-Vitro Dissolution Profile of Matrix-Extended Tablets

One mathematical approach for developing models, CCD seeks to maximise the number of independent variables. In the study of matrix-extended tablets (F1-F11), *in-vitro* dissolution experiments were conducted in accordance with established standards. The percentage of drug released from all formulations (except three) exceeded over 80 percentages at 20 hours, falling within the acceptable range. Notably, a significant percentage of drug release was observed between F1–F11 at 24 hours, as identified by the authors (35). This phenomenon could potentially be attributed to the influence of key independent variables, namely HPMC K15 (X_1), and EC (X_2).

Among the formulations, F1, F5 and F10 exhibited the lowest drug, with 62.89±1.95 percent 68.65±1.48 percent and 78.65±1.69 at 24 hours. Conversely, formulation F8 displayed the highest drug release, approximately 99.95±1.84 percent within the specified time at 24 hours. Based on these observations, the authors found the significant variations in drug release pattern to achieve the present objective due to the matrix formation and swelling properties of both polymers can form a matrix when they are hydrated. In extended-release formulations, the drug is dispersed or dissolved within this matrix. As the matrix hydrates, it forms a gel-like structure that controls the diffusion of the drug out of the dosage form and also this swelling behavior contributes to the formation of the gel matrix and also helps in maintaining the integrity of the dosage form during the release process. The degree of swelling can be controlled by varying the composition and molecular weight of the polymers. The concentration and molecular weight of HPMC K15 and EC in the formulation can be adjusted to tailor the drug release profile according to the desired therapeutic effect. Higher polymer concentrations and molecular weights typically result in slower drug release rates due to increased viscosity and matrix strength. A graphical representation of the results can be found in Figure 4. Hydroxypropyl methylcellulose and ethyl cellulose are commonly used in the formulation of extended-release pharmaceutical dosage forms to modulate drug release kinetics. They achieve this through various mechanisms:

Application of Factorial Design for Optimization of Matrix- Extended Tablets

Time requires for 25 percentage drug release (t_{25}) Y_1: The "t_{25} percentage drug release" refers to the time it takes for 25% of the drug to be released from an extended-release dosage form. This parameter is often used to characterize the release profile of a drug from a pharmaceutical formulation, particularly for extended-release formulations.

The time requires for 25 percentage drug release (t_{25}) of all formulations of matrix-extended release tablets (F1-F11) were carefully recorded, and all values range of 1.86±0.17 to 7.33±1.37 hours. Based on the observations, it became evident that the chosen amount of both polymers (combination of HPMC K15 with EC) had a noteworthy impact on the t_{25} percentage drug release, 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.

$$t_{25} \text{ percentage drug release } (Y_1) = +42.21 - 12.14\,X_1 - 6.39\,X_2 + 0.005X_{12} + 0.555X_1^2 + 0.575X_2^2 \quad [7]$$

The ANOVA data revealed a regression coefficient value (R^2) of 0.964, indicating strong goodness of fit. The p-value was calculated to be 0.0013, which is smaller than the threshold of $p<0.05$. This indicates that the current model significantly influenced the disintegration time through the use of the polymer thickeners.

Based on the polynomial equation, the coefficient value of X_1 (HPMC K15) exhibited a larger value of 12.14 compared to other matrix polymer such as Ethyl cellulose X_2. Notably, X_1 had a negative coefficient sign with an impact on t_{25} percentage drug release (t_{25}) and 2 folds times greater than X_2. This suggests that increasing the concentration of both polymers thickeners results in a reduction in time require for percentage drug to be released. This effect can be attributed to matrix hydration forms gel, controlling drug diffusion and maintaining form integrity. Swelling regulates gel formation, adjustable by polymer properties. Modifying polymer concentrations and molecular weights tailors drug release. Higher concentrations and weights slow release by enhancing viscosity and matrix strength. The

hydration of the matrix forms a gel-like structure that controls drug diffusion and contributes to the integrity of the dosage form during release. The degree of swelling, crucial for gel matrix formation, can be regulated by adjusting polymer composition and molecular weight. To tailor the drug release profile for the desired therapeutic effect, concentrations and molecular weights of HPMC K15 and EC in the formulation can be varied. Typically, higher polymer concentrations and molecular weights lead to slower drug release rates owing to increased viscosity and matrixstrength. The results were depicted in Figure 5.

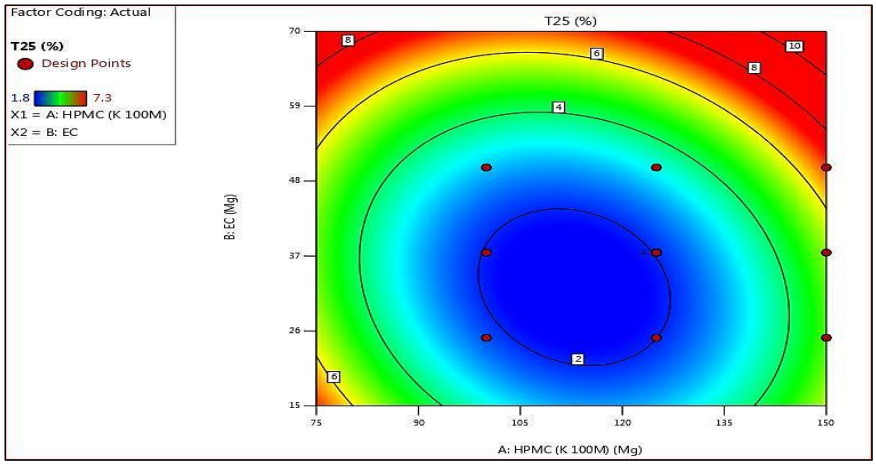

Figure 4: 2D Contour Plot for T_{25} Percentage Drug Release (Y_1)

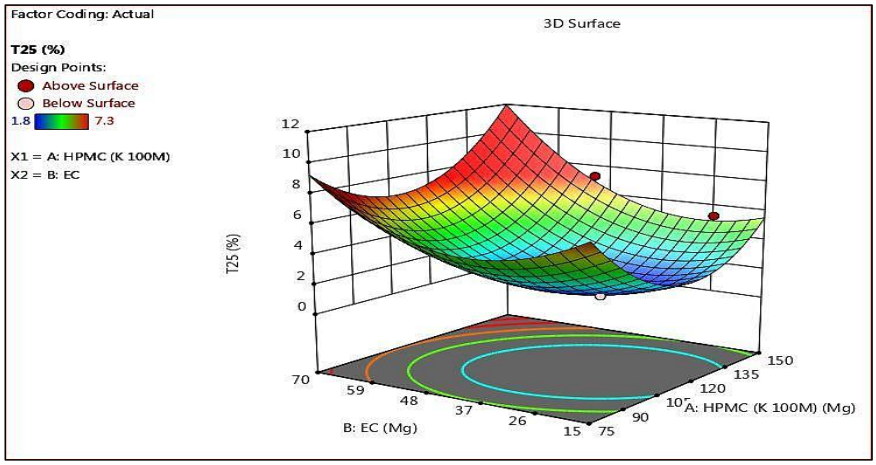

Figure 5: 3D RSM Plot for T_{25} Percentage Drug Release (Y_1)

Time requires for 90 percentage drug release (t_{90}) Y_2: The determination of t_{90} percentage indicates the time taken for 90% of the drug to be released, which can be crucial for drugs with a narrow therapeutic window or where achieving a specific plasma concentration is critical for efficacy and safety and also essential for controlled release formulations as it helps ensure the sustained release of the drug over the desired period, maintaining therapeutic levels within the body for longer durations.

The time requires for 90 percentage drug release (t_{90}) of all formulations of matrix-extended release tablets (F1-F11) were carefully recorded, and all values range of 17.06±0.17 to 37.28±1.37 hours. Based on the observations, it became evident that the chosen amount of both polymers (combination of HPMC K15 with EC) had a noteworthy impact on the t_{90} percentage drug release, denoted as Y_2. To analyze this relationship, a quadratic model was employed. The mathematical representation of the quadratic regression coefficient equation is provided below.

$$t_{90} \text{ percentage drug release } (Y_2) = +147.14 - 27.28\,X_1 - 8.41\,X_2 + 0.059\,X_{12} + 0.957\,X_1^2 + 0.418X_2^2 \quad [8]$$

The ANOVA data revealed a regression coefficient value (R^2) of 0.9502, indicating strong goodness of fit. The p-value was calculated to be 0.002, which is smaller than the threshold of $p<0.05$. This indicates that the current model significantly influenced the t_{90} percentage drug release through the use of the selective bio-degradable polymer.

Based on the polynomial equation, the coefficient value of X_1 (HPMC K15) exhibited a greater value of 27.28 over EC as another independent variable in the present study X_2. Notably, X_1 had a negative coefficient sign with an impact on t_{90} percentage drug release (t_{90}) and approximately 3 folds times greater than X_2. It meant that, as increasing the concentration of both polymer thickeners leads to a decrease in the time required for drug release percentage. This phenomenon occurs because the hydrated matrix forms a gel, which controls drug diffusion and preserves the integrity of the formulation. The swelling process regulates the formation of the gel, which can be adjusted based on the properties of the polymers. By modifying polymer concentrations and molecular weights, the release of the drug can be tailored. Higher concentrations and molecular weights slow down the release by increasing viscosity and strengthening the matrix. A graphical representation of the results can be found in Figure 6 and 7.

Matrix hydration forms a gel, controlling drug release and maintaining form integrity. Swelling adjusts gel formation, regulated by polymer properties. Modifying polymer concentrations and molecular weights tailors drug release. Higher concentrations and weights slow release by enhancing viscosity and matrix strength.

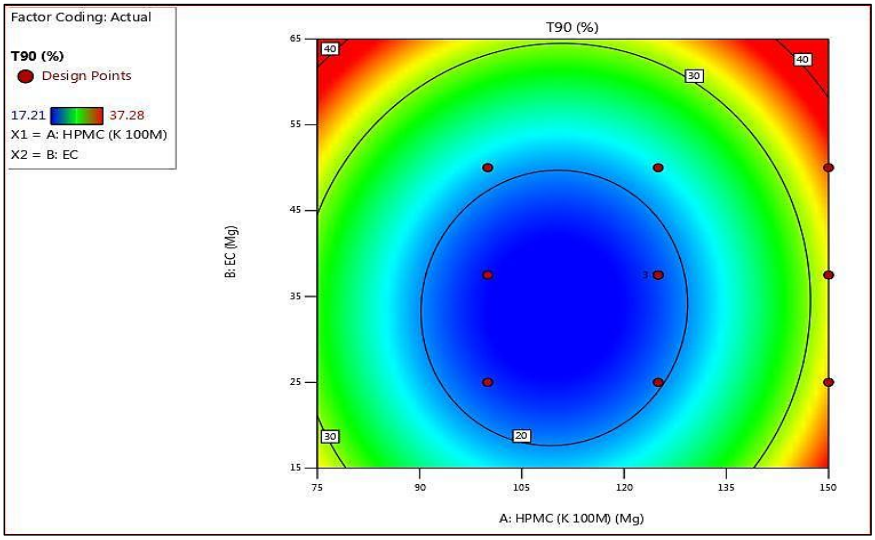

Figure 6: 2D Contour Plot for T_{90} Percentage Drug Release (Y_2)

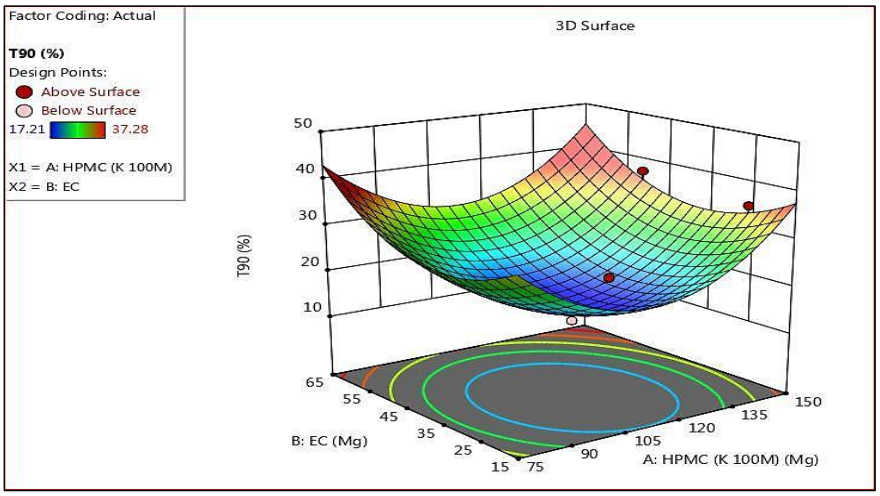

Figure 7: 3D RSM Plot for T_{90} Percentage Drug Release (Y_2)

Selection of Optimized Batch as Function of Desirability of All Response Variables

The desirability response from Design Expert Software was crucial in choosing the optimal formulation. To select the most trustworthy formulation, this method was vital. The software's desirability graph, which incorporated several answers from dependent variables, made it easy to create an ideal formulation with the necessary physicochemical characteristics. The desirability scale was from 0 to 1 for optimization reasons. The software evaluated each formulation from F1 to F11, standardizing the values of the individual response variables. A desirability rating near zero indicated undesirable circumstances for the responses, thereby making the formulations more appealing. On their side, the formulation grew much more appealing and desired as the value got closer to one. The findings informed a software-based visual comparison of the formulations' appeal. In the allotted time frame, this method showed promise in determining the optimal controlled release batch. Figures 8 and 9 display the information visually using desirability and overlay plots. Figure 8 clearly showed that F8 was the best formulation, with a blue circle indicating its greatest desirability value of 1.00. The development of an optimized extended-release (ER) matrix tablet of Alfuzosin Hydrochloride offers several clinical advantages. By enabling sustained drug release over a 12–24 hour period, the ER formulation supports once-daily dosing, which can significantly improve patient compliance—particularly important for individuals with benign prostatic hyperplasia (BPH), who are often elderly and managing multiple medications. Moreover, the controlled release mechanism helps maintain consistent plasma drug levels, thereby minimizing peak-trough fluctuations that are commonly associated with immediate-release formulations. This can reduce the incidence of adverse effects such as first-dose hypotension or orthostatic hypotension, which are concerns with α1-blockers like Alfuzosin. Overall, the proposed ER design aligns well with the therapeutic goals of BPH management by improving convenience, safety, and tolerability in real-world clinical use (36, 37).

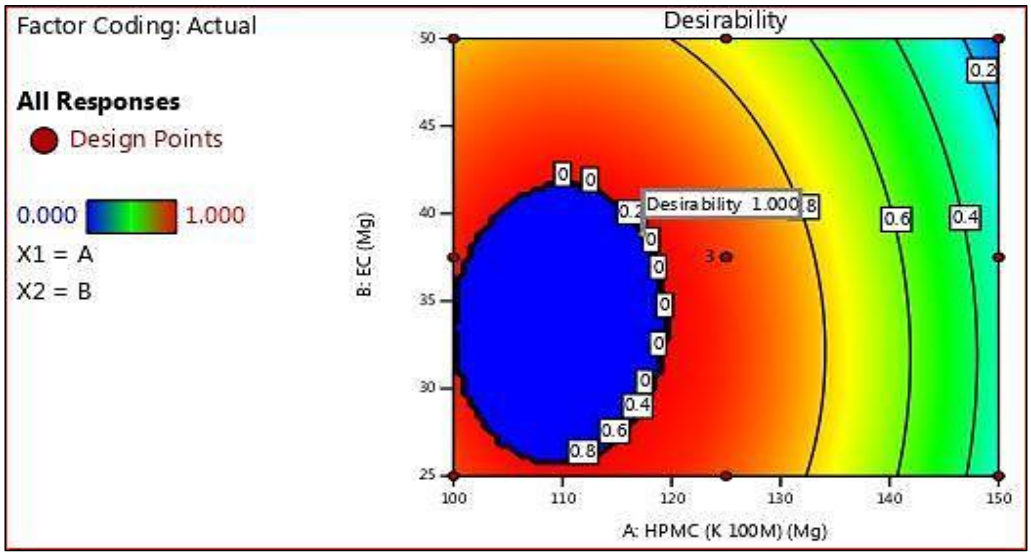

Figure 8: Desirability Plot for All Response Variables

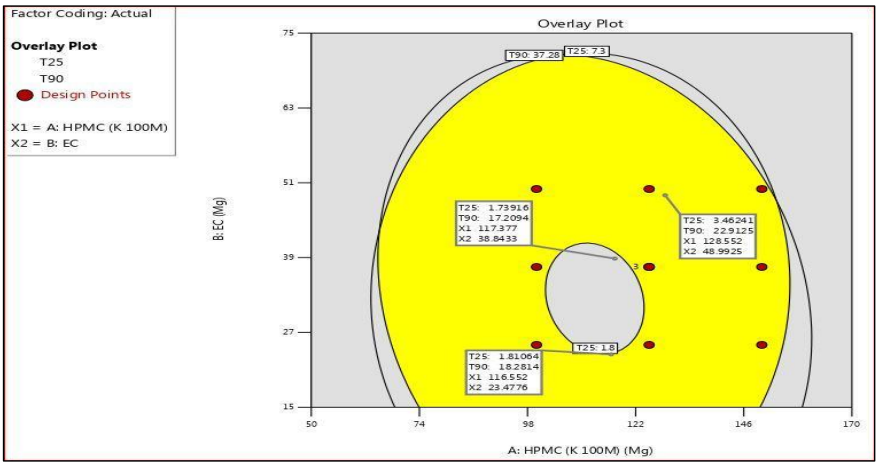

Figure 9: Overlay Plot for All Response Variables

The DD solver model software evaluated the matrix-extended formulations produced in batches F1–F11 for release orders. To interpret the complex release patterns, the DD solver model software was an invaluable tool. The research team found important results by using different mathematical models, especially with the F8s, which showed a strong link between the model and the real data, as indicated by the high R^2 value of 0.9099 from the zero-order model. In the same vein, we got an MSC value of 2.15 and an AIC value of 55.75. The F8 formulation confirmed the model's robust fit with an improved R^2 value of 0.9719 in the setting of first-order studies. Both the AIC and MSC values were measured at 44.43 and 3.32, respectively. As we turn our attention to the Higuchi Model, we find that formulation F8 demonstrates excellent agreement between the model and the experimental data (R^2 = 0.9638). We found an MSC value of 3.06 and an Akaike Information Criterion score of 46.45. The Korsmeyer-Peppas equation allowed us to delve more into formulation F8 as we continued our inquiry. The model's predicted R^2 value of 0.9967 is highly congruent with the observed data. With an MSC of 5.21 and an Akaike Information Criterion of 29.28, the results were as expected. The release was governed by a non-Fickian diffusion-type mechanism, as shown by the exponent release (n) value of 0.658, which is noteworthy (Table 6).

Table 6: Release Kinetics of the Formulations

Type of release order	R^2	R^2 Adjusted	Akaike Information Criterion (AIC)	Model selection criterion (MSC)	Exponent release value, n (Sphere)
Zero order	0.9099	0.9099	53.17	2.157	0.658
First order	0.9719	0.9719	44.43	3.321	Non-Fickian
Higuchi Model	0.9638	0.9638	46.45	3.069	diffusion-
Korsmeyer-Peppas	0.9967	0.9962	29.28	5.215	type mechanism

Conclusion

The drug Alfuzosin hydrochloride could be formulated in an extended-release dosage form using an optimum amount of isopropyl alcohol and ethylcellulose and hydroxypropyl methylcellulose. The drug can dissolve in water and stays in the body for a long time, but it spreads too quickly through the water-loving gel, which makes it hard to use in water-loving systems, especially for this type of medication. To create extended-release dosage forms for these medications, a hydrophilic matrix and hydrophobic polymers work well. The findings clearly show that the best method for once-daily extended-release tablets of Alfuzosin hydrochloride is matrix tablets made with the right proportions of isopropyl alcohol, ethyl cellulose, and hydroxypropyl methylcellulose.

The dissolution investigations revealed that after 20 hours, the formulation F8 released

84.82±1.13% of Alfuzosin hydrochloride and was selected as an optimized formulation. Hence, it can be concluded that the formulation F8 tablets are promising as they extended the drug delivery, which is almost equal to the innovator Alfoo tablets and confirms the appropriateness of the formulations for once-daily dose. Overall, choosing t_{90} instead of cumulative percentage drug release has several benefits in terms of therapeutic relevance, control over release kinetics, comparative analysis, optimization of patient compliance, and regulatory compliance. With the help aforementioned mechanisms, formulators in the pharmaceutical industry can develop extended-release formulations that offer precise control over the release of drugs. This enables them to achieve optimized therapeutic outcomes and ensure better patient compliance.

Abbreviations

AIC: Akaike Information Criterion, BPH: Benign Prostatic Hypertrophy, EC: Ethyl Cellulose, FTIR: Fourier Transform Infrared Spectroscopy, HPMC K15M: Hydroxy Propyl Methyl Cellulose, MSC: Model selection criterion, PVP K30: Poly Vinyl Pyrrolidone, QbD: Quality by Design, USP: United States Pharmacopeia.

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Author Contributions

Kumara Swamy Samanthula: Study conception, design, planning, securing funding and management, Data collection, analysis, interpretation of results, Chandrashekar Thalluri: Study conception, design, planning, securing funding and management, Data collection, analysis, interpretation of results, Satya Obbalareddy: Study conception, design, planning, securing funding and management, Data collection, analysis, interpretation of results, Daniel Kothapally: Draft manuscript preparation, reviewed the study, suggested modifications, Agaiah Goud Bairi: Draft manuscript preparation, reviewed the study, suggested modifications.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Approval

Ethical clearance was not necessary for this research since it did not include any human or animal

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