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Research Article

FORMULATION AND OPTIMIZATION OF FLOATING SUSTAINED RELEASE TABLETS OF ATAZANAVIR SULFATE THROUGH BOX-BEHNKEN DESIGN

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ABSTRACT

Objective: Atazanavir (ATZ) sulfate is widely prescribed as an antiretroviral drug belonging to BCS class II with low solubility. This research aims to design, formulate, and optimization of floating sustained-release tablets of ATZ through Box-Behnken design (BBD).

Method: The formulation parameters were optimized using the BBD. Methocel K100M (A) was chosen as the primary release-retarding polymer, Sodium Bicarbonate (B) served as the gas-generating agent, Ethyl Cellulose (C) was utilized as an additional release-retarding polymer, and Cetyl Alcohol as a floating assistant. In this design, A, B, and C were designated as independent variables, while three response variables floating lag time (FLT) (Y1), swelling index (Y2), and percentage drug release (Y3) were selected as the dependent variables. The compatibility of the drug and excipients was evaluated through Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and morphology by scanning electron microscopy. Tablets were prepared through the direct compression method and subsequently evaluated for parameters including FLT, flotation time, swelling index, hardness, drug content, friability, *in vitro* drug release, and drug release kinetics.

Results: FTIR and DSC investigations revealed no interaction between the drug and the excipients, physical mixture of the drug and the excipients indicated the amorphous state of ATZ. All the evaluated tablets showed satisfactory results. The drug release from the validated optimized tablets was gradual and sustained over 12 h (99.76±0.75) following zero-order kinetics.

Conclusion: The optimized tablets with desirable formulation characters were determined through a statistical optimization model and the optimized formulation remarkably sustained the drug release for up to 12 h, indicating its improved therapeutic potential for the treatment of HIV.

Keywords: Floating time, Fourier-transform infrared spectroscopy, Scanning electron microscopy, Differential scanning calorimetry, Optimization, Sustained release.

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INTRODUCTION

The gastro-retentive drug delivery system (GRDDS) is designed to retain the drug in the gastrointestinal tract, specifically in the stomach for an extended period. In the commercialization of novel drug entities, complexities have increased substantially; consequently, considerable attention has been directed toward the improvement of sustained or controlled drug delivery systems. The primary objective of designing a sustained drug release system is to reduce the dosing frequency or enhance the drug's efficacy by localizing at the target site, thereby providing uniform drug delivery. Certain limitations in the oral drug delivery system must be overcome using GRDDS [1,2]. In addition to the continuous release of drugs to the small intestine, GRDDS offers several advantages, including (a) achievement of a prolonged therapeutic effect; (b) reduction in the frequency of drug dosing; and (c) effective treatment for proximal gastric disorders [3,4].

Atazanavir (ATZ) is an antiretroviral drug used to treat human immunodeficiency virus (HIV) [5]. It inhibits the processing of viral gag-pol proteins in HIV-1-infected cells, thereby controlling the maturation of infectious virions. It is characterized by rapid absorption, with a T_{max} of approximately 2.5 h and exhibits non-linear pharmacokinetics, demonstrating supra-proportional enhancement in AUC and C_{max} over the dosage range of 200–800 mg administered per day. The drug contains a plasma half-life of 6.5 h. ATZ solubility was pH-dependent, reaching maximum solubility at pH 1.9, which aligns with the acidic environment of the stomach with increased solubility in acidic conditions such as the stomach pH [6,7].

The floating tablets offer a novel strategy for improving ATZ pharmacokinetics by avoiding premature drug release into the intestine and keeping it in the acidic gastric environment for a longer period, hence enhancing drug absorption. Sustained-release floating matrix tablet formulations address major issues in HIV treatment such as medication resistance, adherence, and side effects induced by changing drug levels so we may expect high patient compliance [8,9]. Floating tablets were developed with a unique formulation to ensure sustained drug release and optimized buoyancy characteristics. To optimize the formulation parameters for floating tablets of ATZ, Box-Behnken design (BBD) was used. BBD proved to be a robust tool for optimizing formulation parameters and assessing the effects of formulae components on the efficacy of ATZ sustained-release floating tablets [10].

MATERIALS AND METHODS

Materials

ATZ sulfate was provided by Laurus Labs Ltd, Unit 3, Visakhapatnam. Sodium hydrogen carbonate, Methocel K100M, EC, and, Supratab 11 SD were obtained from Merck Life Science Pvt. Ltd., Mumbai. Further, cetyl alcohol, talc, hydrochloric acid, and magnesium stearate were obtained from Yarrow Chem Products Mumbai.

Method of preparation of floating tablets

The tablet was prepared by the direct compression method using BBD as the basis for the experimental design. Seventeen formulations of ATZ tablets have been formulated employing different combinations of matrix-forming agents (Methocel K100M, Ethyl cellulose), filler

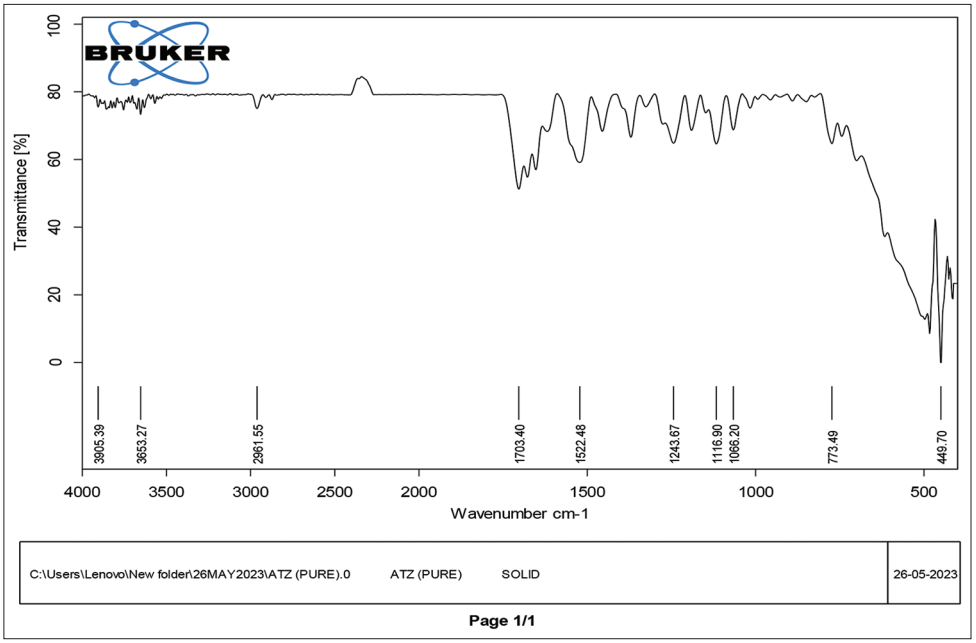

Fig. 1: Fourier transform infrared of atazanavir pure drug

Table 1: Formulae of ATZ floating sustained-release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
ATZ	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
EC	85	77.5	70	85	85	77.5	70	70	77.5	77.5	85	70	77.5	77.5	77.5	78	77.5
Sodium bicarbonate	60	70	65	70	60	60	70	65	65	65	65	60	60	65	70	65	65
Methocel K100M	190	170	190	180	180	190	180	170	180	180	170	180	170	180	190	180	180
Cetyl alcohol	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Supratab 11 SD	5	22.5	15	5	15	12.5	20	35	17.5	17.5	20	30	32.5	17.5	2.5	18	17.5
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight of tab (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

ATZ: Atazanavir, EC: Ethylcellulose

(Supratab 11 SD), gas-generating agents shown in Table 1 (sodium bicarbonate), cetyl alcohol as floating assistant, talc as a glidant, and Mg stearate as lubricant. All of the materials were weighed precisely following the formula and combined in symmetrical proportions with pestle and mortar. The resulting mixture has been filtered through sieve no.80 and properly stirred in a polythene bag. The powdered blending was then mixed with talc and magnesium stearate and subsequently compacted into a tablet using a Tablet press machine Mini-8 D.

Experimental design

In this design, a statistical approach employing BBD with (3×3, i.e., three factors at three levels) has been used to analyze the primary, interaction, and quadratic effects of independent variables on the dependent variables [11,12]. A second-order polynomial equation was generated using Design-Expert software (Version 13, Stat-Ease Inc., USA) to facilitate statistical optimization of formulation variables. This method was selected intentionally instead of the Central Composite Design because it requires fewer experiments to be conducted to carry out an adequate analysis of the effects of three variables. The design matrix had 17 runs of experiments, which provided a sequential analysis of the formulation factors and their impact on the product. Methocel K100M (Factor A) was selected as a release-retarding polymer, sodium bicarbonate (Factor B) as the gas-generating agent, and ethyl cellulose (Factor C) as a secondary release-retarding polymer. In this design, factors A, B, and C were designated as independent variables, while three response variables floating lag time (FLT) (Y_1), swelling index (Y_2), and percentage drug release (Y_3) were selected as the dependent variables [13,14]. Model evaluation parameters, including

Table 2: Factors and their levels employed in the Box-Behnken design

Factors	Level: Low (−1)	Level: Medium (0)	Level: High (+1)
Methocel K100M (A)	170	180	190
Sodium bicarbonate (B)	60	65	70
Ethyl cellulose (C)	70	77.5	85

the coefficient of variation (CV), coefficient of determination (R^2), adjusted R^2, predicted R^2 (Pred. R^2), adequate precision, optimization, and along desirability, have been analyzed using Design-Expert software (Version 13, Stat-Ease Inc., USA) to identify the best-fit model.

Analysis of variance (ANOVA) was conducted to determine the significance of regression coefficients and their impact on the responses, based on p-values and F-values [15,16]. The selected factors and their levels, as well as their respective quantities are detailed in Table 2. The 17 combinations of factors generated by a statistical approach employing BBD along with their corresponding measured responses are presented in Table 3 [17,18].

Drug excipient compatibility studies

Fourier-transform infrared (FTIR) analysis

An ALPHA-Brooker FTIR Spectrophotometer with KBR disk FTIR spectra recorded an ATZ and its combination with various excipients,

Table 3: Independent and dependent variable responses as per Box-Behnken design

Independent variables			Dependent variables		
Methocel K100 (A)	**Sodium bicarbonate (B)**	**Ethyl cellulose (C)**	**Floating lag time (sec) (Y1)**	**Swelling Index (%) (Y2)**	**% drug release in 12 h (Y3)**
190	65	85	30±0.6	42.06±2	75.1±2.19
170	70	77.5	27±0.3	44.0±3	85.1±0.22
190	65	70	21±0.5	51.54±4	80.50±0.60
180	70	85	30±0.1	40.32±6	75.30±0.24
180	60	85	45±0.3	46.72±2	74.76±0.44
190	60	77.5	31±0.4	49.43±6	80.15±0.38
180	70	70	33±0.8	47.62±5	84.88±0.10
170	65	70	30±0.7	43.23±8	90.30±0.42
180	65	77.5	33±0.9	44.23±4	85.2±0.24
180	65	77.5	33±0.6	45.09±6	85.2±0.24
170	65	85	29±0.7	47.69±5	75.20±0.21
180	60	70	38±0.8	46.26±8	85.2±0.44
170	60	77.5	36±0.9	45.98±4	89.6±0.44
180	65	77.5	33±0.5	44.32±3	85.2±0.44
190	70	77.5	20±0.9	44.53±7	80.6±0.44
180	65	77.5	33±0.4	44.23±4	85.25±0.84
180	65	77.5	33±0.8	44.23±5	85.2±0.77
180	65	71.33	30±0.6	66.52±3	100±0.40

*n=3, Mean±standard deviation

such as methocel K100 M, sodium bicarbonate, cetyl alcohol, and ethyl cellulose. The resolution was 2 cm^{-1}, and scanning was 400–4000 cm^{-1} [19,20].

Differential scanning calorimetry (DSC)

The thermal behavior of ATZ and various excipients (methocel K100M, ethyl cellulose, cetyl alcohol, and sodium bicarbonate) was tested in terms of their melting endotherm. This was performed with a combined thermal analysis system, Hitachi Japan, with about 1–5 mg of the sample placed in a sealed aluminium pan. The samples were scanned at 30–350°C at a constant rate of 10°C/min under nitrogen [21].

X-ray diffraction (XRD)

Analysis powder diffractometer was performed under the following experimental conditions: CuK using a beta filter; voltage 40 kV; suitable electric current 30 mA; and scan range 5–90° in continuous scan mode at speed of 10°/min at 2θ angle position [22].

Scanning electron microscopy (SEM)

The specimens which were coated with a thin layer of gold were mounted on Al stub. The images were photographed at 10 kV voltage using Joel, JSM 6360.

Post-compression evaluation

Floating tablets were developed with a unique formulation to ensure sustained drug release and optimized buoyancy characteristics.

Buoyancy test (in vitro floating behavior studies)

The *in vitro* floating behavior of the tablets was assessed by measuring two critical parameters: FLT and total floating time (TFT). The evaluation was conducted in an electrically controlled water bath maintained at 37°C. A 200 mL borosilicate beaker with 100 mL of 0.1N HCl solution served as the dissolving medium, simulating gastric conditions. FLT was defined as the time required for the tablet to rise to the surface of the medium, while TFT represented the duration for which the tablet remained buoyant on the surface. These parameters were analyzed to evaluate the buoyancy performance of the formulation [23].

Swelling studies

To measure swelling also known as water absorption capacity petri dish equipment with a glass plate holding the tablet was utilized. The tablets were placed in a petri dish with 50 mL of dissolving medium at a temperature of 37±0.5°C. At regular intervals, the Petri dish was removed from the apparatus, blotted with absorbent tissue to remove any excess dissolution medium on the surface, and weighed [24]. The following equation was used to calculate the degree of swelling (% water uptake)

$$\text{Degree of swelling (\% water uptake)} = [(W_t - W_0)/W_0] \times 100$$

Where W_0 is the initial weight of the dry tablet, and Wt is the weight of the wet swollen tablet.

In vitro drug release studies

The *in vitro* drug release profile of ATZ gastric-floating tablets were assessed using a LABINDIA DS 8000 dissolution apparatus (Type-II, Paddle-DT-600). The study was carried out in 900 mL of 0.1N HCl used as the buffer, maintained at 37±0.5°C, and rotated at 50 rpm. Over 12 h, 5 mL of buffer was withdrawn at predetermined intervals (1, 2, 4, 6, 8, 10 h, and up to 12 h).

The collected samples were filtered through a 0.45 µm membrane filter, diluted appropriately with 0.1N HCl, and analyzed for drug content with a UV-visible spectrophotometer at a wavelength of 250 nm (ELICO Double Beam SL 210). This methodology enabled precise monitoring of drug release kinetics, simulating gastric conditions effectively [25].

Release kinetics of drug

Several mathematical models were used to better analyze the process and kinetics of releasing drugs from ATZ floating tablets. The drug release kinetics were analyzed using the Higuchi matrix model, zero-order model, Korsmeyer-Peppas model, Hixson-Crowell model, and first-order model.

Drug content uniformity (DCU)

The DCU was spectrophotometrically analyzed at 250 nm by a UV-spectrophotometer to confirm uniform drug distribution within the tablets. An equivalent mass of 200 mg of ATZ powder has been placed in a 100 mL measuring cylinder and then dissolved in 0.01N HCl. The resulting content was clarified later suitably diluted for analysis.

Statistical analysis

Statistical analysis of the data obtained was performed using ANOVA that compares the means of multiple groups to determine if there are

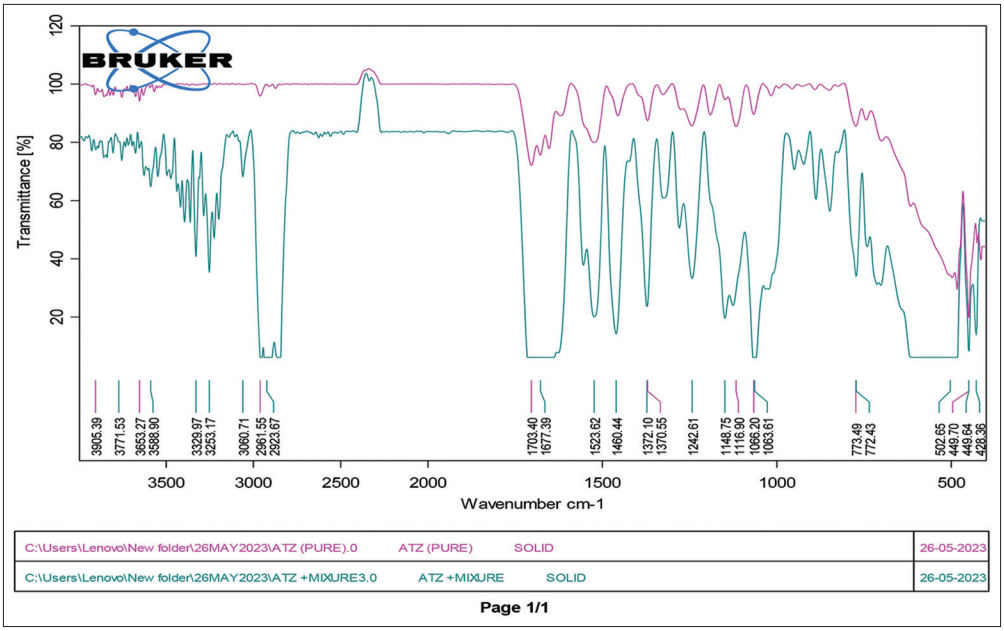

Fig. 2: Fourier transform infrared of pure drug (atazanavir) with a physical mixture

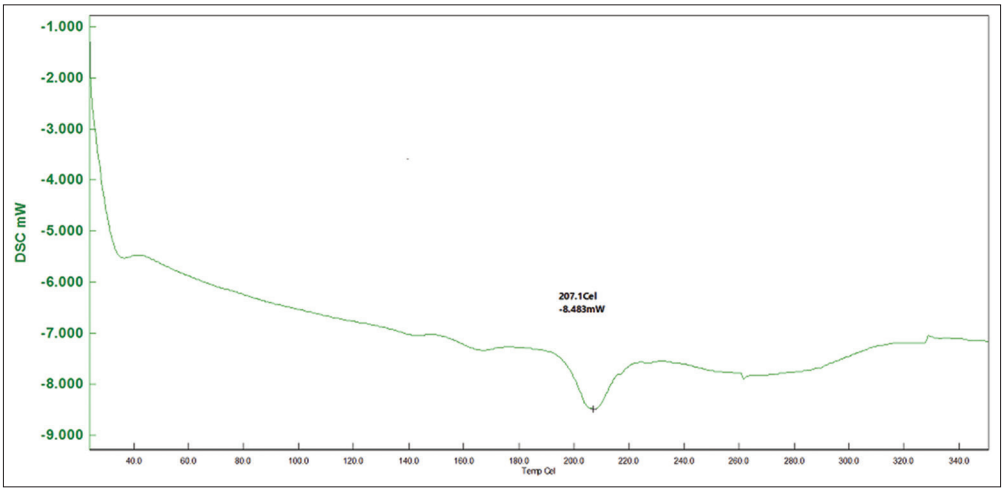

Fig. 3: Differential scanning calorimetry thermogram of pure atazanavir sulfate

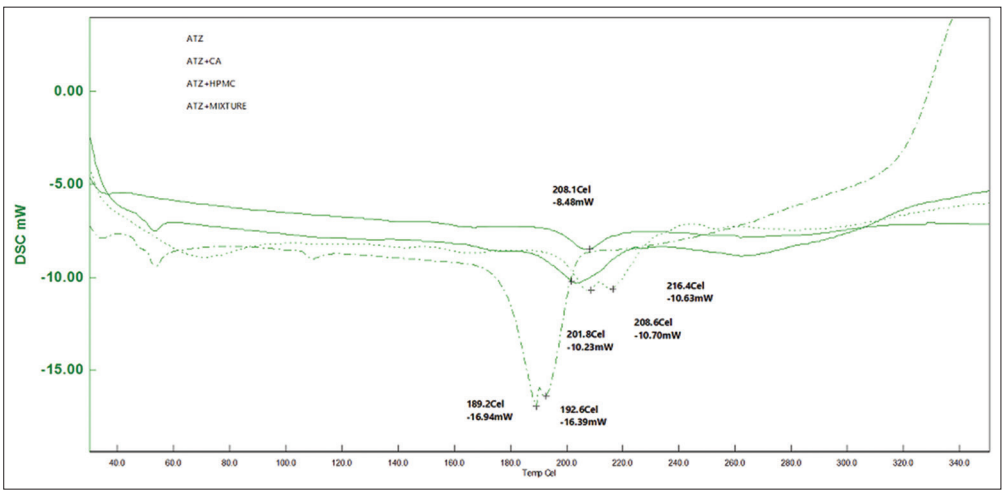

Fig. 4: Differential scanning calorimetry thermogram of atazanavir with mixture overlay plot

significant differences between them. The level of statistical significance was chosen as $p<0.05$.

RESULTS AND DISCUSSION

Analytical method of ATZ

The spectrophotometric method was determined using 0.1N Hydrochloric acid at 250 nm for the estimation of ATZ. The standard calibration curve was developed to show that the drug samples were linear for 0.009×+0.016 and had a high R^2 value of about 0.998 over their concentration ranging from 10 to 70 ug/mL.

Drug excipient compatibility studies

The FTIR analysis spectrum of ATZ showed characteristic peaks observed at 773 cm^{-1} (-NH) 1066cm-1(-C-C stretching) and 111.90 cm^{-1} (-C=C stretching) and 1243.67 cm^{-1} (-N-H bending) and 1703 cm^{-1} (-C=C stretching) and 2961 cm^{-1} (-CH stretching) 3653 cm^{-1}(-OH stretching) follows confirming ATZ pure drug structure. The spectrum peaks of the physical were similar to that of the pure ATZ, clearly indicating that there is no change in characteristics with no drug and excipient interaction. FTIR of pure ATZ and pure ATZ with physical mixture were depicts in Figures 1 and 2.

The DSC thermogram of ATZ revealed a sharp endothermic peak at 201.7°C which corresponds to a pure ATZ melting point (193°C–209°C). The DSC thermogram (Fig. 3) of ATZ mixture (1:1) with methocel K100, ethyl cellulose, cetyl alcohol, and sodium bicarbonate also showed endothermic peaks in the range of (193.2°C–215.6°C) indicating no changes in melting point of ATZ-Mixture. The DSC observation indicates no interaction between the drug and the excipients used shown in figure 4.

The SEM image of pure ATZ (Fig. 5) revealed a needle-shaped, rectangular crystalline structure. In contrast, the SEM image of the solid solution (Fig. 6) demonstrated notable changes in surface morphology and the transformation of the drug into an amorphous form. These observations indicated that the drug diffused into the polymer and was uniformly distributed within the carrier matrix.

XRD studies demonstrated the crystalline nature of ATZ, which transformed into an amorphous state in the final formulation (Figures 7 and 8).

Results of post-compression parameters

Hardness

The tablet exhibits a hardness from 4 to 5.5 kg/cm^2. It can be attributed to the cohesive properties imparted by these excipients. This harness was found to be good enough to withstand while handling. Data are provided below in Table 4. These tablets have better hardness compared to the tablets formulated by Dias *et al*., (3.6±0.547–4.2±0.447) [26].

Friability

As per USP the recommended friability range for the tablet dosage forms is Not More Than (NMT 1.0 %). Each formulation was tested 3 times for friability and data are presented below in Table no 4: The friability data 0.42±0.06–0.86±0.06 revealed that the prepared tablets have good mechanical strength during manufacturing, packing, and shipping. These tablets have higher friability compared to the tablets formulated by Shankar *et al*., (0.29±0.005–0.82±0.015) [27]

Weight variation

The weight variation ranged from 492±5 to 505±3.5 mg/tab. The results meet the official pharmacopoeial standards shown in the following Table 4.

In vitro buoyancy studies

The FLT of several tablets remained within the stated range of 20±0.9 s–45±0.3 s. Furthermore, the floating time varies among various floating tabs, ranging from 2 to >12 h. These results show that the tablets floated satisfactorily and could stay buoyant over an extended amount of time; outcomes are illustrated in Table 4.

DCU

The content uniformity of ATZ floating tablets ranged from 96.01±1.34 to 99.76±0.75 g/tab. The results obtained from this method are shown in the following Table 4. These tablets have higher DUC compared to the tab formulated by Rajkumar *et al*., (95.9± 1.5–98.56±2.0) [28].

Swelling index

The tablet exhibits an SI ranging from 40.32±6 to 51.34±4%, the validated optimized (VO) formula having a swelling index of 66.52±3%, results are represented in Table 4**.** Swelling enables buoyancy and medication dissolution, notably in floating tablets, because polymer molecules make a gel layer as they come into contact with water, influencing drug release. As the quantity of methocelK100M in the formulation increased, it increased the water intake capacity. The water content of the tablet has a significant effect on drug diffusion. The quantity of water in the system may have a significant impact on this due to the flexibility of the polymer chain. The rise in volume is used to soften the high-water-content polymer chain, which successfully promotes network expansion. Higher moisture content may also suggest additional gastric fluid penetration into the tab, which would lower the FLT by accelerating the release of carbon dioxide gas. Faster

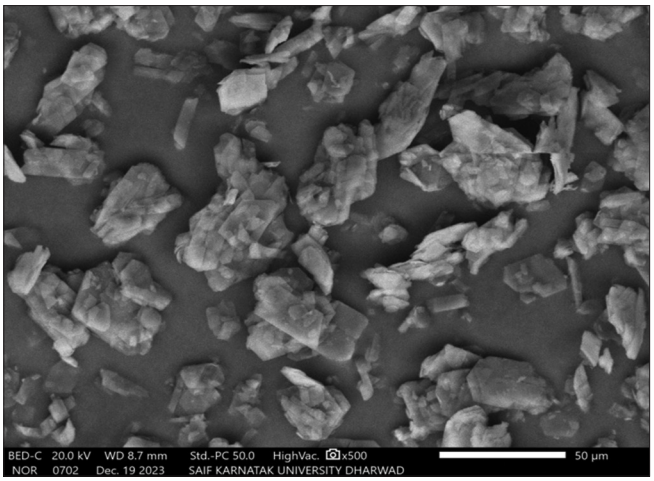

Fig. 5: Scanning electron microscopy of pure atazanavir

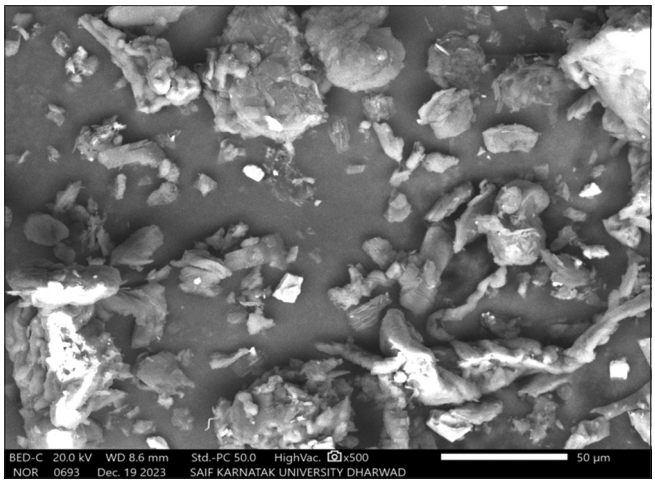

Fig. 6: Scanning electron microscopy of optimized formula

Table 4: Post-compression measurements of atazanavir floating tablet from F1 to F17

S.No.	Formulation	Weight variation (mg/tab)	Friability (%)	Hardness (Kg/cm^2)	Total floating time (h's)	Drug content
1	F1	500±10	0.56±0.03	5.8±0.45	>12	96.23±0.96
2	F2	505±3.5	0.64±0.01	4.2±0.78	>12	98.26±1.05
3	F3	495±6.5	0.42±0.06	5.6±0.95	>12	99.12±1.81
4	F4	510±2.5	0.50±0.07	6±0.56	>12	99.16±0.87
5	F5	492±5	0.84±0.03	4.8±0.42	>12	97.45±0.76
6	F6	498±8.2	0.75±0.04	4.5±0.47	>12	97.83±1.03
7	F7	502±3	0.64±0.03	5.2±0.54	>12	96.01±1.34
8	F8	494±3.5	0.78±0.06	5±0.72	>12	98.13±1.35
9	F9	500±1.5	0.86±0.04	4.4±0.47	>12	99.15±0.95
10	F10	495±5	0.72±0.05	4.2±0.37	>12	98.16±0.89
11	F11	505±2.5	0.66±0.06	4±0.45	>12	97.19±0.76
12	F12	500±3.5	0.59±0.03	5±0.57	>12	98.16±1.05
13	F13	500±3.5	0.59±0.05	5±0.81	>12	97.19±1.03
14	F14	500±3.5	0.59±0.06	5±0.36	>12	99.15±1.04
15	F15	500±3.5	0.59±0.07	5±0.44	>12	99.58±0.94
16	F16	510±4.5	0.82±0.06	4.8±0.41	>12	97.23±0.93
17	F17	498±5.4	0.76±0.08	4.6±0.58	>12	98.42±0.85
18	VO	500±1.2	0.62±0.07	5.4±0.61	>12	99.76±0.75

*n=3, Mean±standard deviation

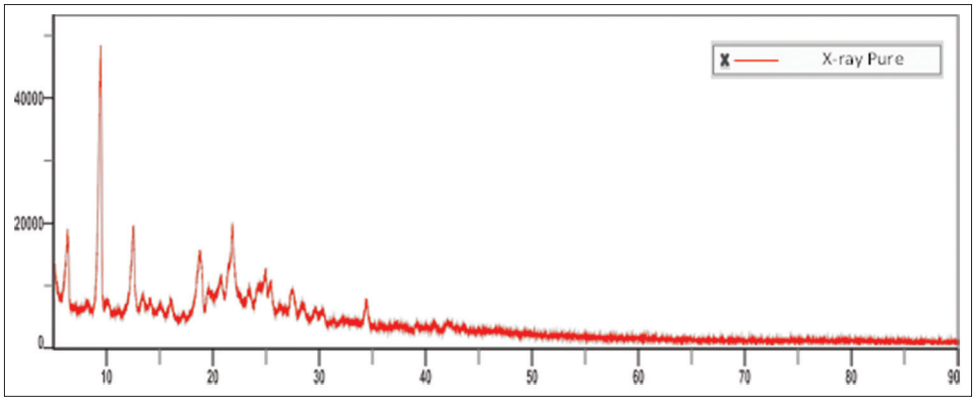

Fig. 7: X-ray image for pure atazanavir

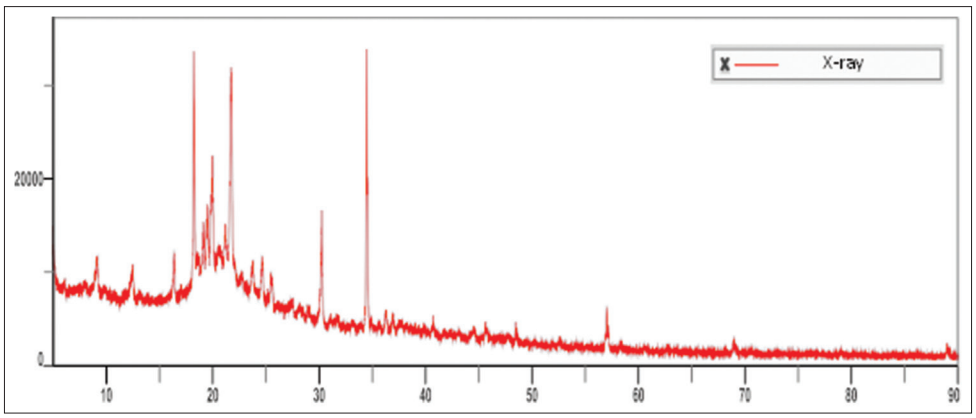

Fig. 8: X-ray image for atazanavir and physical mixture

and larger tab swelling thus caused tab dimensions to increase, which, in turn, caused an expanding diffusion channel and, ultimately, a reduction in the diffusion rate. As a result, Rahamathulla *et al*. reported initially significant drug release followed by gradually decreased drug release (Figure 9) [29].

In vitro drug release

Figs. 10 and 11 illustrate the *in vitro* release profiles of ATZ floating tablets over time. The amount of drug released from the matrix tablets were determined by the nature of the polymers included in the formula. An increase in polymer content resulted in a viscous swelling layer, which decreased the *in vitro* dissolution of ATZ from composition (F1) [30]. Contrastingly the lower proportion of ethyl cellulose and methocel K100 influences higher drug release 90.30±0.420% for 12 h (F8), due to faster-FLT and a greater degree of swelling and erosion of the hydrophilic polymer. The increasing order of drug dissolution of various floating formulations is shown in below F8>F13>F2>F10>F1 4>F16>F17>F12>F7>F15>F3>F6>F1>F4>F11>F5. These tablets are

having highest *in vitro* drug release compared to the tab formulated by Komati *et al*., (67% of drug release after 12 h) [31].

Drug release kinetics

The *in vitro* drug release studies were analyzed using various kinetic studies models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The results, as summarized in Table 5, indicated that the zero-order model provided the best fit for the data, with formulation F8 demonstrating the highest R^2 value. Furthermore, the release exponent values (n) for formulations F1, F2, F3, F4, F5, F7, F9, F10, F11, F12, F13, F14, F15, F16, and F17 suggested a non-Fickian diffusion mechanism, implying that the drug release from these formulations was followed by both diffusion and erosion processes [32].

Table 5: Kinetics of tablet dissolution profiles (r and n values)

Formulae	Correlation Co-efficient (r)			n value for tablets	
	Zero-order	First-order	Higuchi	Peppas	"n" (diffusion exponent)
AF1	0.98801	0.7863	0.9932	0.9317	0.6567
AF2	0.9914	0.7997	0.9866	0.9402	0.8190
AF3	0.9870	0.7809	0.9900	0.9298	0.6681
AF4	0.9857	0.7923	0.9844	0.9331	0.8560
AF5	0.9842	0.7666	0.9942	0.9180	0.6227
AF6	0.9948	0.8170	0.9848	0.9524	0.7659
AF7	0.9966	0.7414	0.9973	0.9020	0.5137
AF8	0.9952	0.7720	0.9920	0.9214	0.7909
AF9	0.9871	0.7685	0.9835	0.9150	0.7326
AF10	0.9725	0.7346	0.9978	0.9009	0.5639
AF11	0.9786	0.7714	0.9945	0.9256	0.5056
AF12	0.9842	0.7666	0.9942	0.9180	0.6227
AF13	0.9842	0.7666	0.9942	0.9180	0.6227
AF14	0.9842	0.7666	0.9942	0.9180	0.6227
AF15	0.9842	0.7666	0.9942	0.9180	0.6227
AF16	0.9948	0.8170	0.9848	0.9524	0.7659
AF17	0.9809	0.7616	0.9958	0.9178	0.5962
optimized	0.9652	0.7923	0.9844	0.9331	0.8560

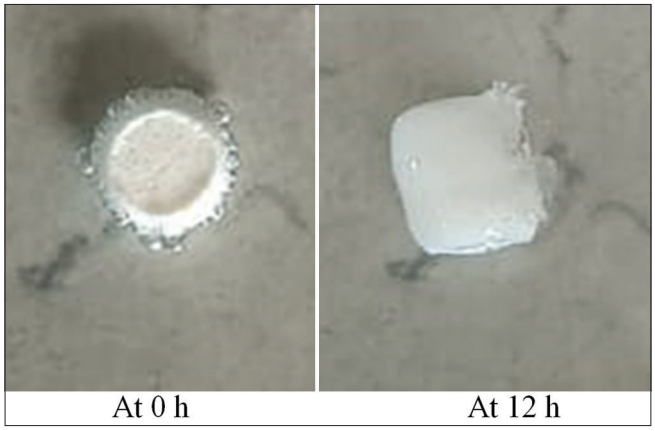

Fig. 9: Swelling index of validated optimized formulation

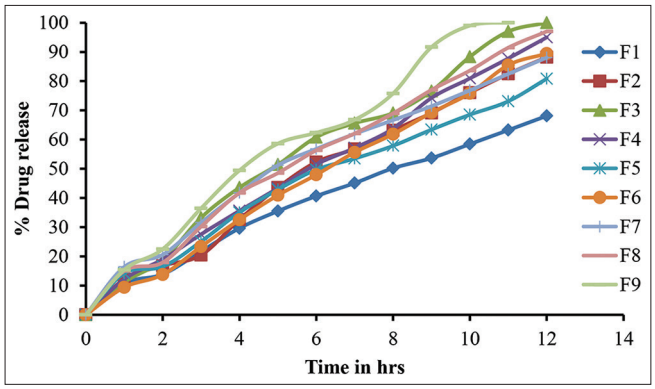

Fig 10: *In vitro* drug release profiles of atazanavir floating tables F1–F9

Comparative studies

Comparative studies were conducted with marketed tablets (Laurus: AT200), F8, and the VO formulation. The commercial tablets released their entire contents within 1 h. F8 achieved drug release at 90.30±0.420% in 12 h, and the VO formulation shows 100% of drug release in 12 h. The dissolution profile of marketed F8 and VO formulation are presented in Fig. 12.

Experimental design

A mathematical polynomial equation was formulated using Design Expert software to quantitatively evaluate the impact of independent variables Y1, Y2, and Y3 at various combinations and levels on dependent responses. The analysis was carried out by utilizing the coded values of the independent factors.

FLT (sec) Y1; A model with F-value 103.10 implies the statistically significant result. Table 6 explains the model equation for FLT. The FLT R^2 value of 0.9925 indicates a significant connection among both dependent and independent variables.

$FLT\ (Y1)=+33+1.50A-5B-2.50C-2.50AB+2.50AC-0.500BC+1.25A^2+2.25B^2-6.75C^2$

In equation (Y1) the main effect A, and their quadratic terms A, B, and interaction effect AC had positive regression coefficient. Interaction terms (AB, BC) and main effect B and quadratic term C had negative

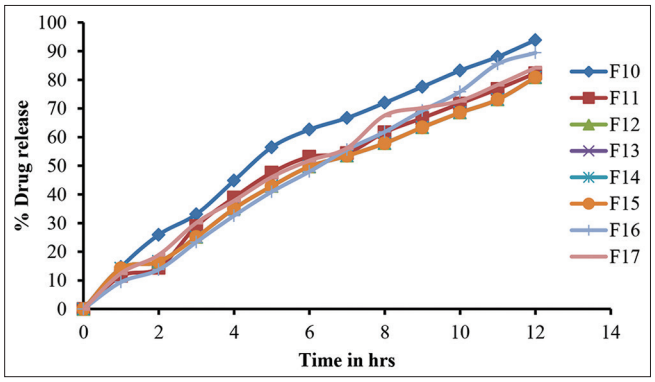

Fig 11: *In vitro* drug release profiles of atazanavir floating tables F10–F17

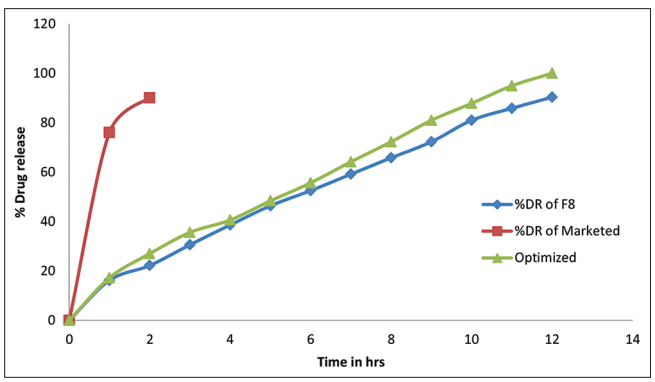

Fig. 12: *In vitro* drug release profiles of marketed atazanavir, F8, validated optimized floating tables

regression coefficients. The model equation indicates that a rise in sodium bicarbonate content results in a decline in FLT. This effect can be attributed to the enhanced generation of effervescence at higher sodium bicarbonate concentrations, which accelerates the formation of pores and, in turn, promotes the rapid hydration of the sustained-release layer of the tablets. The significance of each coefficient was assessed using p-values, as shown in Table 6. The main effects of all the selected independent variables were found to be highly significant, as demonstrated by their corresponding p-values. The combinatorial effects of AB, BC, and AC were also significant based on their p-values. These results suggest that the amount of the A, and the combined effect of AC and quadratic effect A and B have a direct relationship for achieving a formulation that releases 90.30±0.420 % of the drug in 12 h with minimal FLT. Figs. 13-15 depict the effects of response 3D contour

Table 6: Summary of regression findings with outputs Y1, Y2, and Y3 after fitting into a quadratic equation

Analysis	Predicted mean	Adjusted R^2	Predicted R^2	Standard deviation	% coefficient of variation	p-value	F value
Floating lag time	20.2076	0.9829	0.8802	0.7406	2.40	0.0500	103.10
Swelling index	50.4747	0.9683	0.8486	0.4804	1.06	0.0500	55.39
Cumulative drug release	81.1693	0.9736	0.8149	0.7985	0.9880	0.0500	66.47

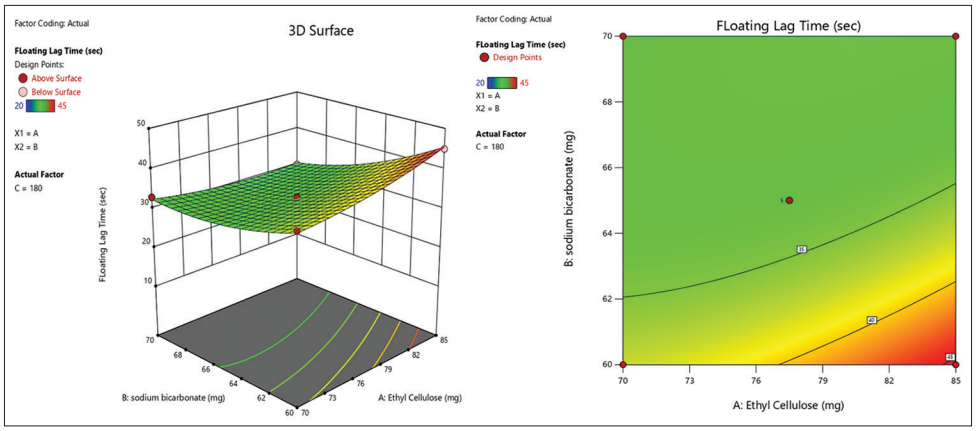

Fig. 13: Explains 3D RSM and contour plot (effect from ethyl cellulose and sodium bicarbonate) on floating lag time

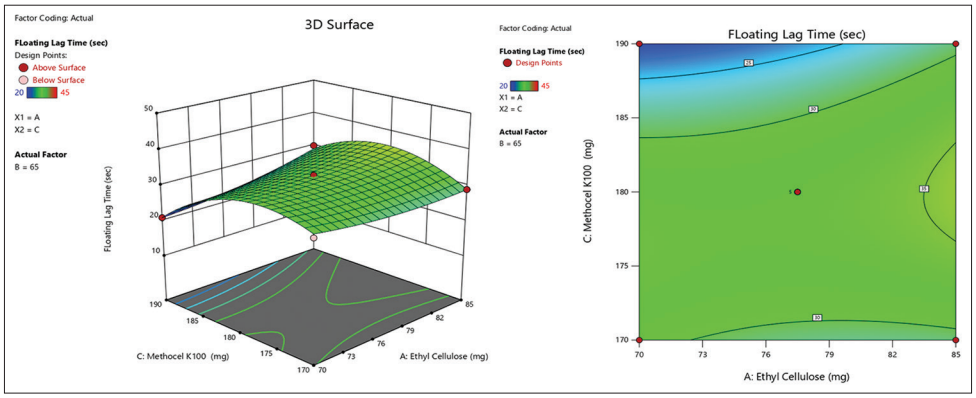

Fig. 14: Explains 3D RSM and contour plot (effect from ethylcellulose and Methocel K100M) on floating lag time

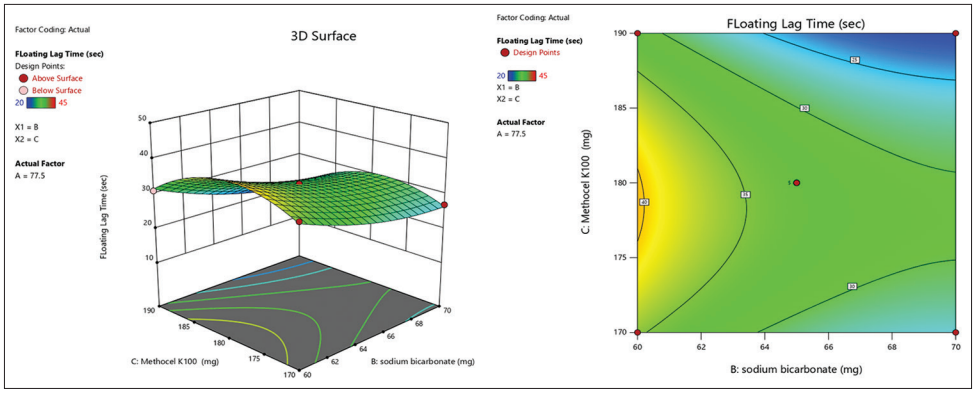

Fig. 15: Explains 3D RSM and contour plot (effect from sodium bicarbonate and methocel K100M) on floating lag time

plots and surface plots, illustrating the influence between interaction terms on FLT.

Swelling index Y2: An estimated F-value of 55.39 demonstrates that the fit of the model is significant in statistical terms. p-values lower than 0.0500 indicate that the corresponding parameters of the model are significant. The Swelling Index R-squared score of 0.9862 indicates a good association between each of the dependent and independent variables.

Swelling index=+44.42−1.48A−1.49B+ 0.8325C−1.94AB−3.49AC −0.730BC+ 0.4775A^2+0.3325B^2 +1.23C^2

The main effect of A, B, and the interaction effect of AB, AC, and BC shows a negative effect on the swelling index. The main effect of C and quadratic terms of A, B, and C shows a positive effect. As the concentration of A increases swelling index also increases, as the concentration of C increases swelling index decreases due to the hydrophobic nature of the polymer, so a medium level of Methocel K100M and a low level of EC shows 100% of drug release with 50% swelling index. Figs. 16-18 depict the effects of response 3D contour plots and surface plots, illustrating the influence between interaction terms on swelling index.

% Drug release (Y3): The estimated F-value of 66.47 demonstrates that the model is statistically significant, with only a 0.01% probability of such a large F-value occurring due to random noise. The % drug release R-squared value of 0.9884. There is an excellent correlation among the variables that are both independent and dependent.

% Drug release (Y3)=+85.20−5.08A−0.4375B−2.96C+ 0.1875AB+2.4 0AC+1.19BC− 4.45A^2−0.78 8B^2−0.503C^2

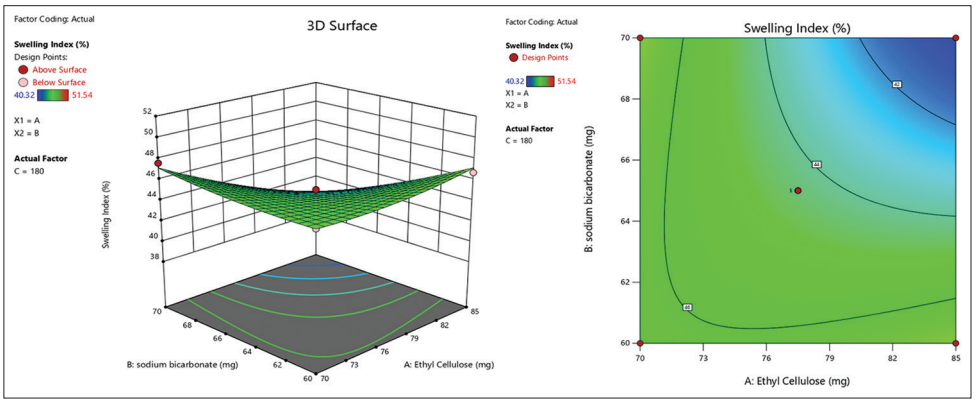

Fig. 16: Explains 3D RSM and contour plot (effect from ethyl cellulose and sodium bicarbonate) on swelling index

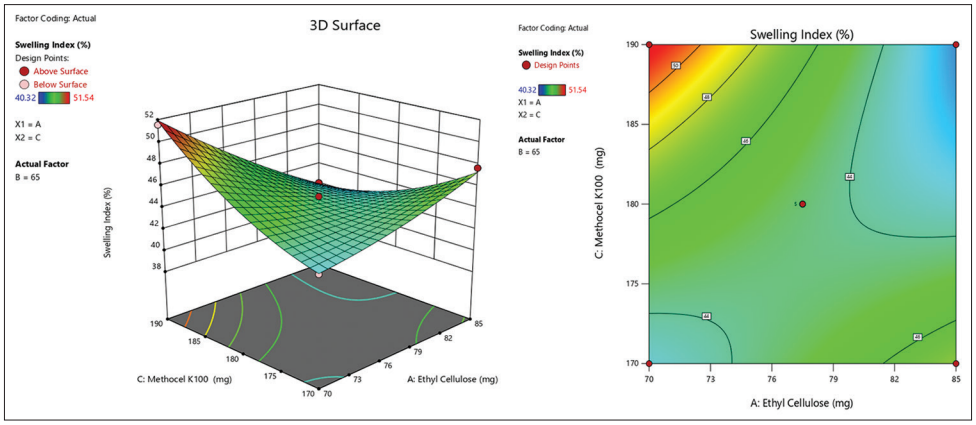

Fig. 17: Explains 3D RSM and contour plot (effect from ethyl cellulose and Methocel K100M) on swelling index

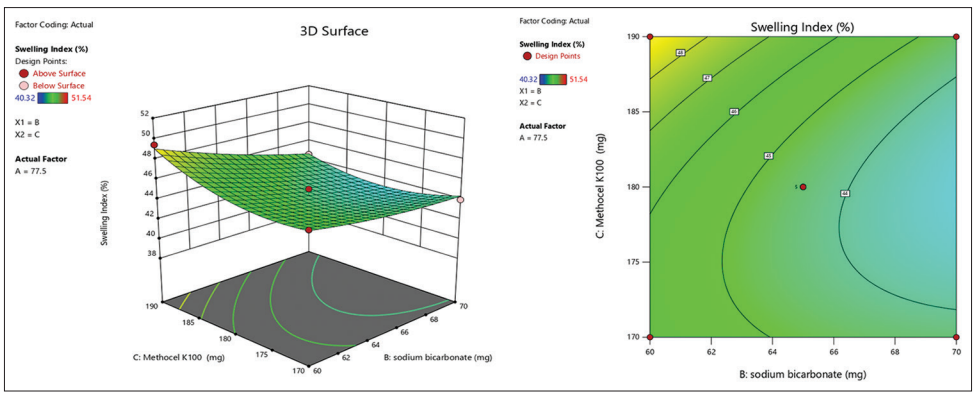

Fig. 18: Explains 3D RSM and contour plot (effect from sodium bicarbonate and methocelK100M) on swelling index

In equation (Y3), the main effects (A, B, and C,) and their quadratic terms had negative regression coefficients. Interaction terms (AB, AC, and BC) had a positive effect. The contour and RSM plots depict the maximum drug release observed at methocelK100M 170–182 mg, ethyl cellulose 70–80 mg, and sodium bicarbonate 65–68 mg. Figs. 19-21 depict the effects of response 3D contour plots and surface plots, illustrating the influence between interaction terms on percent drug release.

As the concentration of A (MethocelK100M) increases, a denser gel network is formed, which can also slow down drug release. While the concentration of EC increases shows reduced diffusion resistance, as the concentration of B increases, it shows unstable floating of the tablet due to rapid gas escape.

To maintain the medication's release for a maximum of 12 h, methocelK100M and EC need to be carefully optimized by considering the polymer ratio. From the design matrix formula, F8 shows a maximum percent release of 90.30±0.420 Methocel $K_{100}M$ 190mg, EC was 71.55 mg, Sodium bicarbonate was 67.3mg shown in Fig. 22.

Validation and optimization

The statistical regression equation originated by BBD was used for optimizing the ATZ floating tablet. The responses were examined, and a single checkpoint formulation was created. Table 6 displays the experimental and projected response values for the validation batch. The validated batch contained Methocel K100M 190 mg,

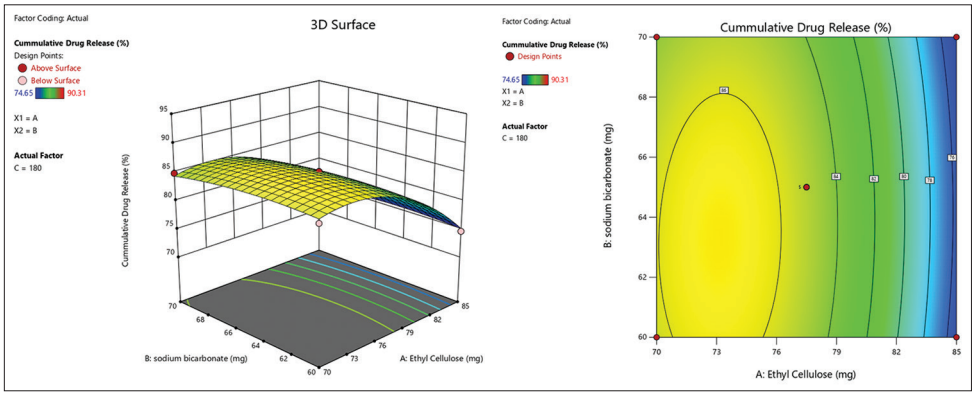

Fig. 19: Explains 3D RSM and contour plot (effect from Ethylcellulose and sodium bicarbonate) on percentage drug release

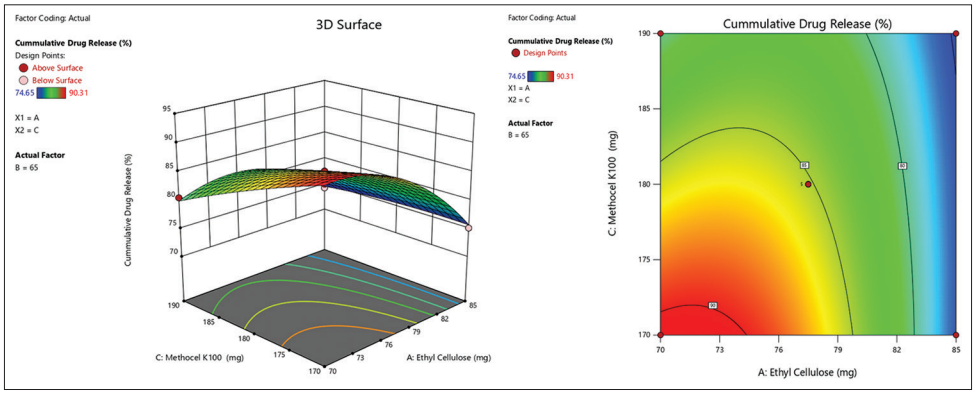

Fig. 20: Explains 3D RSM plot and contour plot (effect from Ethylcellulose and MethocelK100M) on percentage drug release

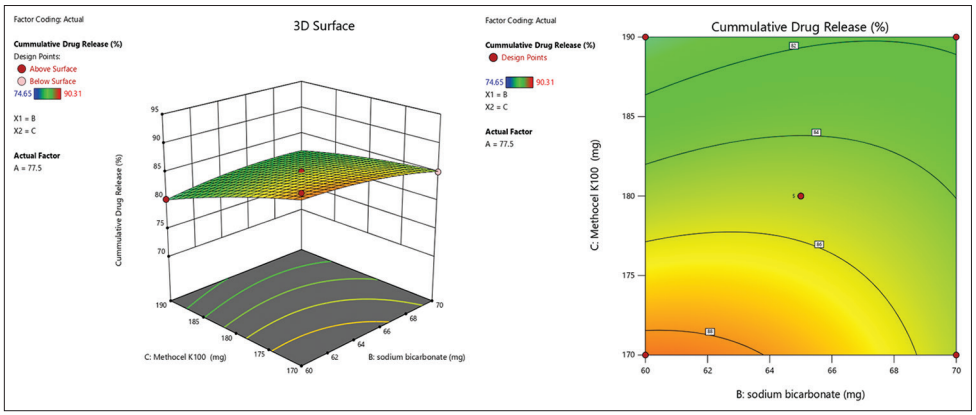

Fig. 21: Explains 3D RSM and contour plot (effect from sodium bicarbonate and methocelK100M) percentage drug release

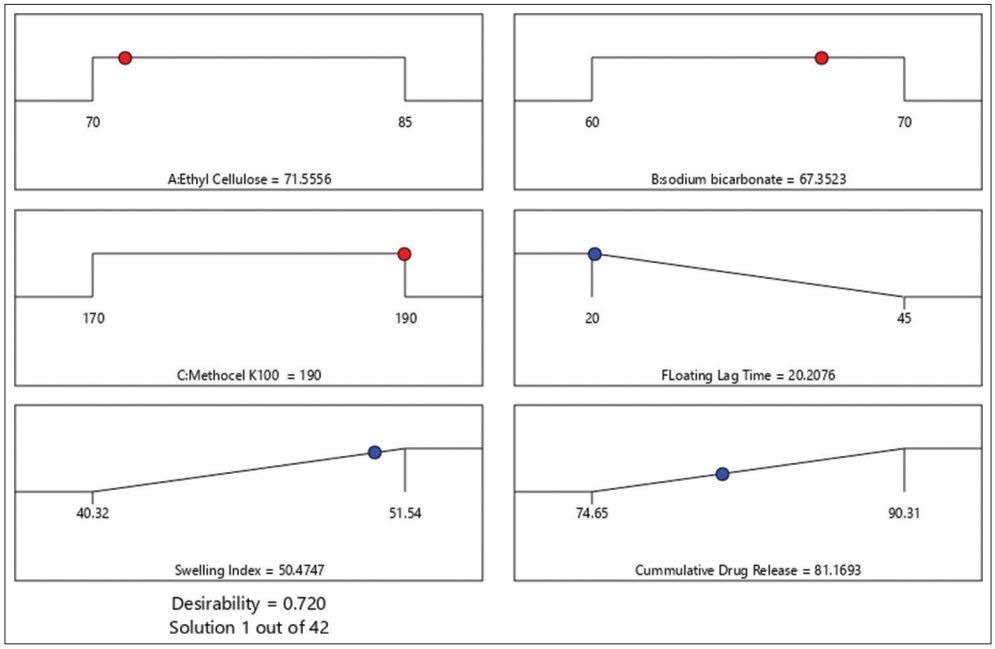

Fig. 22: Ramps plots explains about the optimized batch independent variable values

EC was 71.55 mg, and sodium bicarbonate was 67.3 mg shown in Figure 22. Validation formulation shows 100% or drug release after 12 h.

CONCLUSION

The present study successfully employed BBD to design and develop an ATZ floating tablets. The quality control parameters of the prepared tablets met the official IP tablet specifications. Among the formulations, F8, which contained Methocel K100 (170 mg), sodium bicarbonate (65 mg), EC (70 mg), and cetyl alcohol 50 mg demonstrated notably 90.30±0.420% of drug release in 12 h. A comparative dissolution study revealed distinct differences between the F8 formulation and marketed tablets. In the marketed ATZ 200 capsule, 100% drug release occurred within 30 min, whereas the F8 formulation released 90% of the drug within 12 h, and the VO formulation released 100% of the drug over 12 h and followed non-Fickian diffusion mechanism and followed zero-order kinetics. The optimized formulation was further subjected to statistical optimization to guarantee that it had met key dissolution, therefore supporting the mathematical prediction that ATZ sulfate floating tablets contain sodium bicarbonate and methocelK100, ethyl cellulose. The QBD technique determined the best combination of A, B, and C in the formula to produce the ATZ floating tab that has the desired characters, and BBD is the most promising model for making the ATZ floating tablets which have the intended characters.

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AUTHORS CONTRIBUTIONS

Balijepalli Murali Krishna, method selection, compilation of data, and writing the original draft. Chandra Sekhar Patro, CH. Taraka Ramarao, Review, compilation of data, editing, and supervision. All the authors have contributed equally

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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