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Original Article

A DoE Study for Optimization of Control Quality Attributes and Critical Material Attributes in Development of Almotriptan Fast Dissolving Tablet for the Enhancement of Effective Surface Area

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ABSTRACT

Background: The primary goal of this study is to increase the effective surface area of Almotriptan and improve disintegration time and diffusion time of the tablet by using a direct compression technique for producing Fast-Dissolving Tablets (FDTs). **Materials and Methods:** As part of the Quality by Design (QbD) strategy, the Box Behnken Design (BBD) was used as the experimental design. Compression force (factor A), Polyplasdone XL 10 (factor B) and Explosol (factor C) are considered as key control variables. Response factors include Wetting Time (WT), Disintegration Time (DT) and Dissolution Release (%CDR), as well as the Target Product Quality Profile (TPQP). The response surface quadratic model was used to analyze the impact of the factors on three responses factors. **Results:** The two-way interactions of key control variables were found to have a significant impact on all three responses (at $p<0.05$). Graphical optimization was carried out using the desirability functions method to achieve low WT, low DT and maximum % CDR. The optimized ADFTs had times of 18.13 sec (WT), 47.84 sec (DT) and 99.2%CDR, respectively. Further optimized ADFT was subjected to *in vitro* diffusion and findings showed 98.2% diffusion. **Conclusion:** The increased in effective surface area witnessed through rate of diffusion by selecting optimized range of compression force (151.41MPa) as Critical Quality Attributes (CQAs) and Polyplasdone XL-10 (10 mg) and Explosol (20 mg) as Critical Material Attributes (CMAs).

Keywords: Almotriptan, Compression force, Fast dissolving tablets, Box Behnken design and Quality by design.

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INTRODUCTION

Qualities by Design (QbD) models are statistical and algebraic ensembles. It is extremely helpful in systematically developing dosage forms with higher quality and achieving the intended clinical action.[1,2] QbD will also aid in identifying and mitigating the risks involved with dosage form creation. Different models are accessible in QbD to create high-quality products based on the amount of dependent and independent variables Almotriptan is a sulfonamide triptan that acts as an extra cerebral and intracranial vasoconstrictor. Almotriptan preferentially binds and stimulates serotonin 5-HT 1B and 1D receptors in the CNS, producing extra cerebral and intracranial blood vessel constrictio.[3] This may result in vascular headache discomfort alleviation. Almotriptan may also alleviate vascular headaches by preventing the release of vasoactive neuropeptides from perivascular trigeminal axons during a migraine, lowering extravasation of plasma proteins and lowering the release of other inflammatory mediators from the trigeminal nerve.

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Almotriptan is has high water solubility and low Permeability as Class III drug under Bio pharmaceutics Classification System (BCS). This drug has a low Permeability and needs improvement. Orally administered Almotriptan is well taken and has a greater bioavailability than any other triptan.[4] several methods for improving the permeability characteristics of these compounds have been investigated and implemented. Traditional techniques such as prod rugs, permeation enhancers, ion-pairing and so on are included, as are more recent tactics such as micro and Nano encapsulation. Sizing at the micro and Nano levels.[5]

The particle size has an inverse relationship with the dissolution rate and permeability. As a consequence, reducing particulate size improves effective surface area, accelerates dissolution rate and permeation.[6] Compression force is significant in tablet formulations since it facilitates drug fractionation. Furthermore, the super disintegration agent encourages drug release fast. They accomplish this by increasing water flowing into the plug and promoting plug particle breakdown. The cause for this is that when a disintegrate breaks apart the plug, it does so by swelling and the disintegrate particles expansion pushes the adjacent particles apart. As a result, the drug's availability to permeate the cell membrane is considerable.[7]

These studies conclude that Almotriptan dissolution/permeability can be successfully improved by using compression force as a tool to increase effective surface area, Polyplasdone XL 10 and Explosol reduce the interfacial tension and promote deaggregation of the plug particles through direct compression techniques. However, no research has been published on the combined use of three variables for increasing the effective surface area and dissolution/permeability of Almotriptan. According to this critical evaluation of the literature, there is large scopes for utilizing the compression force and super disintegrates combination for increasing the effective surface area of drugs and reduce tension between drug and cell membrane. As a result, the current study sought to improve the effective surface area and permeability of Almotriptan by decrease of wetting time, disintegration time, increase of dissolution rate and diffusion rate.

The current project was developed using the quality by design method. Box Behnken design was chosen to design the experiments to increase the effective surface area by using optimized range of compression force[8] as Critical Quality Attributes (CQAs) and Polyplasdone XL-10 and Explosol as Critical Material Attributes (CMAs) for rapid wetting and disintegration time with increasing dissolution rate.

MATERIALS AND METHODS

Almotriptan was received from Arizest Pvt. Ltd., Bangalore, as a gift sample, Crospovidone purchased from Ozone international, Mumbai, Explosol, Magnesium Stearate were purchased from Himedia laboratories, Mumbai. Microcrystalline Cellulose (MCC), Polyplasdone XL 10, mannitol, were acquired as gift samples from Kemphasal pharmaceuticals. All other materials used belong to the analytical grade. The data were statistically analyzed using Design Expert statistical software version 8.0.6. (Stat-Ease, Inc., Minneapolis, MN). The coefficient of determination was used to assess the fit of the models (R2). The data were examined using Analysis of Variance (ANOVA) and the F test.

Preparation of Almotriptan Fast Dissolving Tablet (AFDT)

Almotriptan fast dissolving tablet were developed and optimized by employing QbD; below given were the QbD parameters for Almotriptan Fast Dissolving Tablet (AFDT).

Quality Target Product Profile (QTPP)

The AFDT are developed to increase effective surface area with the aim of improving wetting time, disintegration time and dissolution rate of Almotriptan.[9]

Critical Quality Attributes (CQAs)

These also go by the name of responses. Since compression force closely resembles the intended quality of the product, it was chosen as the crucial quality attribute.

Critical Material Attributes (CMAs)

The CMAs have a direct effect on product quality, so they must be chosen and adjusted to produce the desired standard of products. The concentration of super disintegrates such as Polyplasdone XL as factor B and Explosol as factor C (numeric factor; at three levels in the range of 10 mg to 20 mg of the AFDT) were chosen as the CMAs based on the literature and previous experience managing other products.

Experimental design

The Box-Behnken Design (BBD) was chosen to explore the impact of the factors on the chosen response due to the character and levels of the factors mentioned above. According to the BBD design, the potential combinations of the variables and their levels were displayed in Table 1. At each of these combinations, AFDT was formulated.

Formulation of fast-dissolving tablets of Almotriptan

The tablets were manufactured by using direct compression technology according to BBD by considering the control variables as compression force in the range of 77-231 Mpa (as factor A) and concentration of Polyplasdone XL-10 in the range of 10-20 mg (as factor B) and Explosol in the range of 10-20 mg (as factor C). Table 1 lists the variables and the combinations of their levels that BBD recommends for the formation of AFDTs. 6.25 mg of pure Almotriptan was mixed with the appropriate amount of super disintegrates for each formulation. The mixing was then resumed in the kneading technique with the addition of a small amount of

Table 1: Combinations of the variables and their levels recommended by BBD for developing AFDT, as well as the responses outcomes.

	Factor1	Factor 2	Factor 3	Response 1	Response2	Response3
Run	A:CF[8]	B:Polyplasdone XL-10(mg)	C:Explosol(mg)	WT (Sec)[15]	DT (Sec)[15]	%CDR
1	231	15	20	42±2.1	79±4.5	91.4±1.4
2	154	10	20	17.96±7	48.2±2.2	98.36±2.2
3	154	15	15	23±6.2	54±7.2	93±3.3
4	77	15	10	33±3	73.6±5.5	86.1±1.1
5	154	10	10	20.5±3.5	46.9±2.4	97.3±1
6	154	20	10	21.04±5	69.8±1.3	93.4±4
7	154	15	15	22.5±7	55±3.3	94.5±3.1
8	231	10	15	42.4±3.4	75.4±5.1	96±3
9	77	10	15	31.45±4	64.4±6	88.3±3.3
10	154	15	15	22.9±3.7	54.2±7.2	94±2
11	231	15	10	41.89±5	85.1±4.2	94.2±4
12	154	20	20	21.4±4	57.5±5.6	95±3.3
13	154	15	15	23.1±3	54±2	93.8±0.9
14	77	20	15	33.9±6	80.1±5.1	86.8±1.6
15	231	20	15	44.5±7	91.3±6.2	88.6±3.7
16	77	15	20	29±2	70±2.3	90.5±2
17	154	15	15	22.9±3	54±5	94±1.9

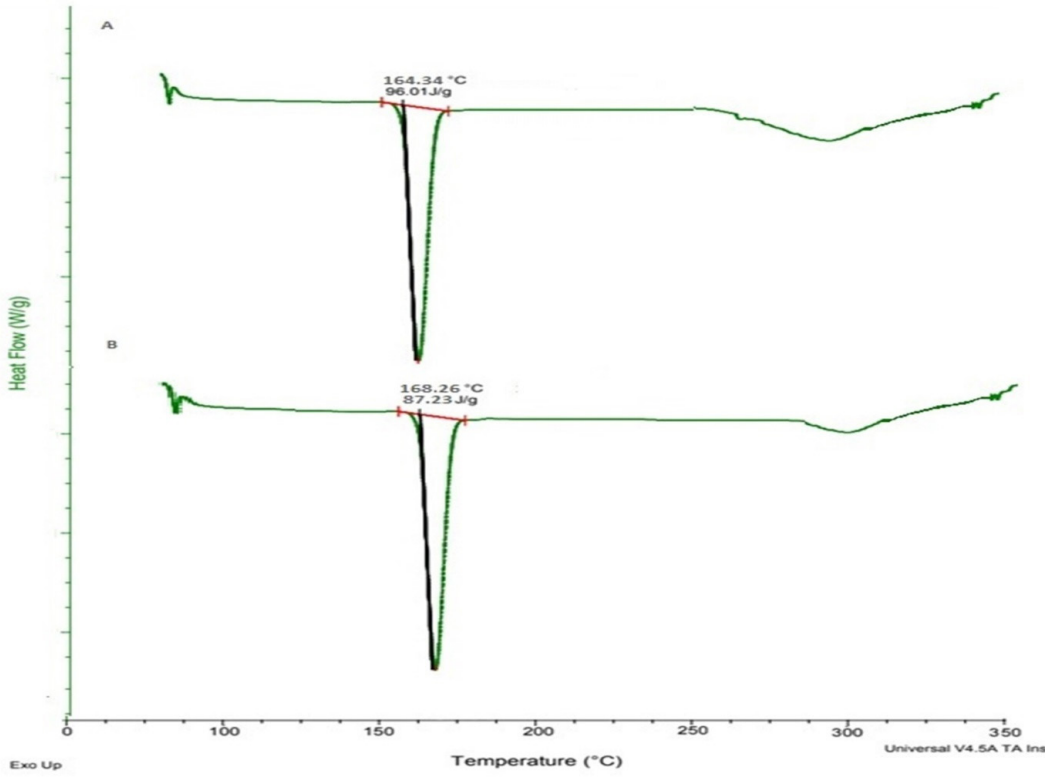

Figure 1: DSC thermogram of (a) Pure Almotriptan and (b) The AFDT.

water. This kneaded concoction was dried to remove moisture.[10] This mixture was then combined with the binder PVP-K30 2 mg, 2 mg of magnesium stearate, 2 mg of Aerosil and a sufficient quantity of MCC to yield a final tablet weight of 100 mg. Finally, the mixture was submitted to direct compression using a 12 mm punch Mini press-II rotary tablet compression machine to produce the tablets.

Physicochemical characterization of AFDT

Total drug content

Total drug content was determined by using the shake flask method. Briefly, a tablet is powdered and transferred to 50 mL volumetric flask. Then the volume was made up with, 0.1 N HCl and shaken or 25 min to ensure complete solubility of the drug. Then the solution was filtered. The sample solution absorbance was measured at 283 nm in UV-visible spectrophotometer.[11]

Differential Scanning Calorimetry (DSC)

DSC was executed for the pure Almotriptan and the prepared AFDT to know the nature of Almotriptan after blend. Briefly, 5 mg of the sample was dispensed and transferred into the flat aluminum pans with crimp-on lids.[12] The sample was scanned in the range of 50°C to 400°C at 10°C speed in the presence of nitrogen at a flow rate of 20 mL/min.

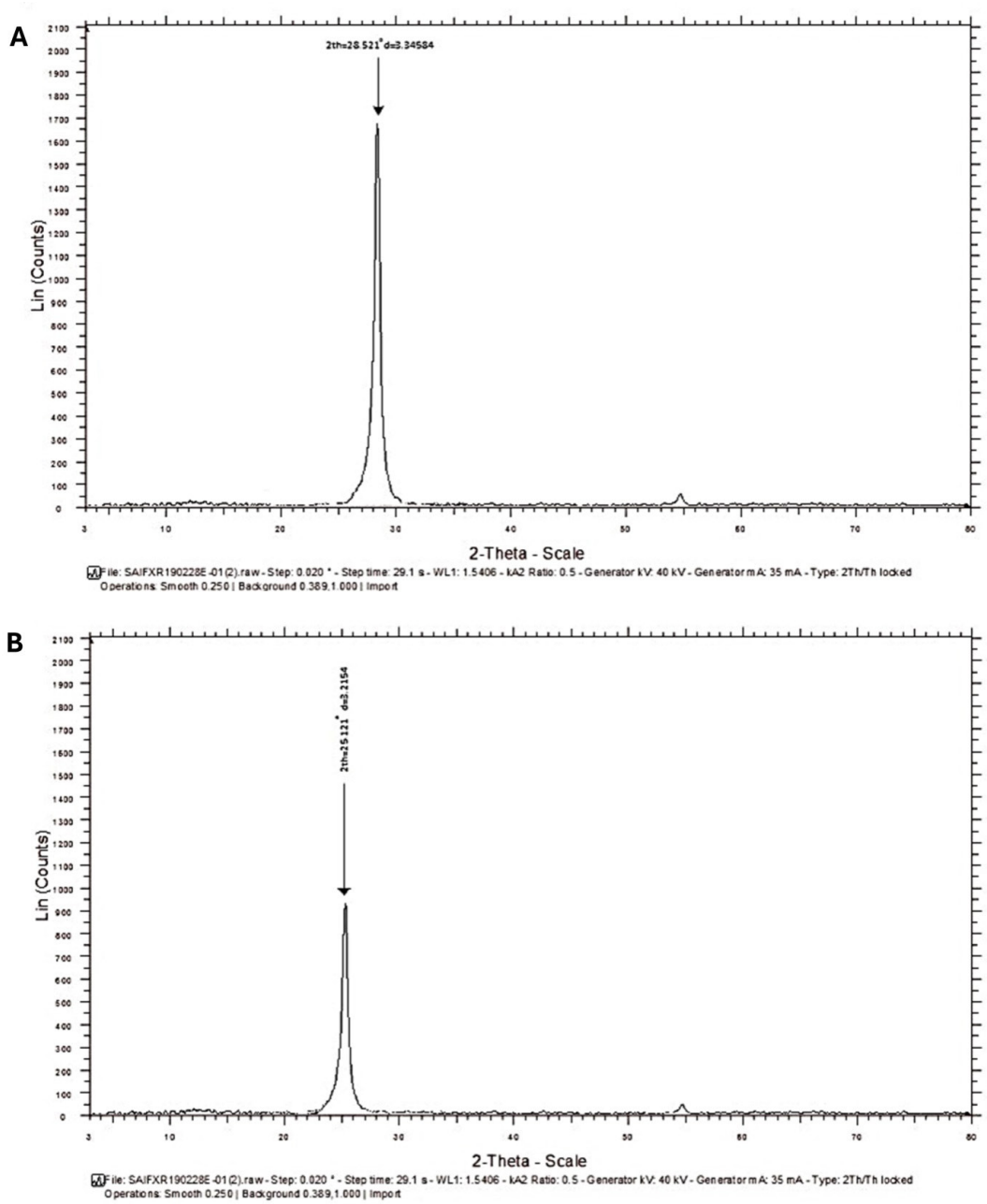

Figure 2: Powder Diffraction Studies of a) Pure Almotriptan and b) AFDT.

X-ray Diffraction (X-RD)

XRD studies help in finding the nature of the API before and after formulation with super disintegrants. In the present study, XRD was performed for pure drugs and prepared AFDT to know their crystalline nature before and after formulation. Usually, in the XRD graphs, the sharp, highly intense peaks intimate the presence of crystallinity, whereas the blunt or irregularly shaped, less intense peaks indicate the presence of an amorphous form.[13]

Characterization of fast-dissolving tablets

Weight variation, friability, disintegration: The prepared AFDTs of all the formulations studied for all these tests according to the procedure suggested in Indian pharmacopoeia. The Packing fraction (Pf) of tableting powder shows its ability to consolidate post-compression. It can be calculated using the equation.[14]

$$Pf=w/\pi r2t\rho$$

Where, w, r and t are the weight, radius and thickness of the tablet and ρ is the true density of the tableting powder.

Wetting time: This test was carried out in accordance with the general method described by Gupta B *et al.*[5,15]

All formulations' AFDTs underwent a dissolution test in accordance with USP-NF standards. Dissolution was carried out in 1000 mL of pH 1.2 buffers with a paddle device set to 50 rpm for 30 min. 5 mL samples were removed and replaced with new medium. The samples were analyzed spectrophotometrically at 283 nm to determine the % drug dissolved. The dissolution data was kinetically analyzed.

Design validation and optimization

StatEase Design Expert software was used for design confirmation and optimization. To determine the statistical model for analyzing the impact of the factors on solubility, the obtained response values for all factor combinations were analyzed using sequential model sum of squares. The fitness of the model and the effect of the factors on the responses were assessed using an ANOVA test and a comparison of the adjusted and predicted R^2 values (Table 3). The desirability functions method was used to perform additional graphical optimization for the input factors in order to produce the desired responses of the AFDTs. Later, the desirability functions method was used to optimize the factors for maximum solubility through least wetting time, fast disintegration and maximum dissolution.[16-18]

RESULTS

Physicochemical characterization of AFDT

The prepared AFDT were evaluated for their total drug content and solubility and also evaluated to find the physical interactions and changes in crystallinity using DSC and PXRD studies. The AFDT were also evaluated for the total drug content and the results were found to be in the range of 96.58% to 99.30%.

The ADFT was employed to check for any variations in crystallinity of Almotriptan before and after formulation. Figure

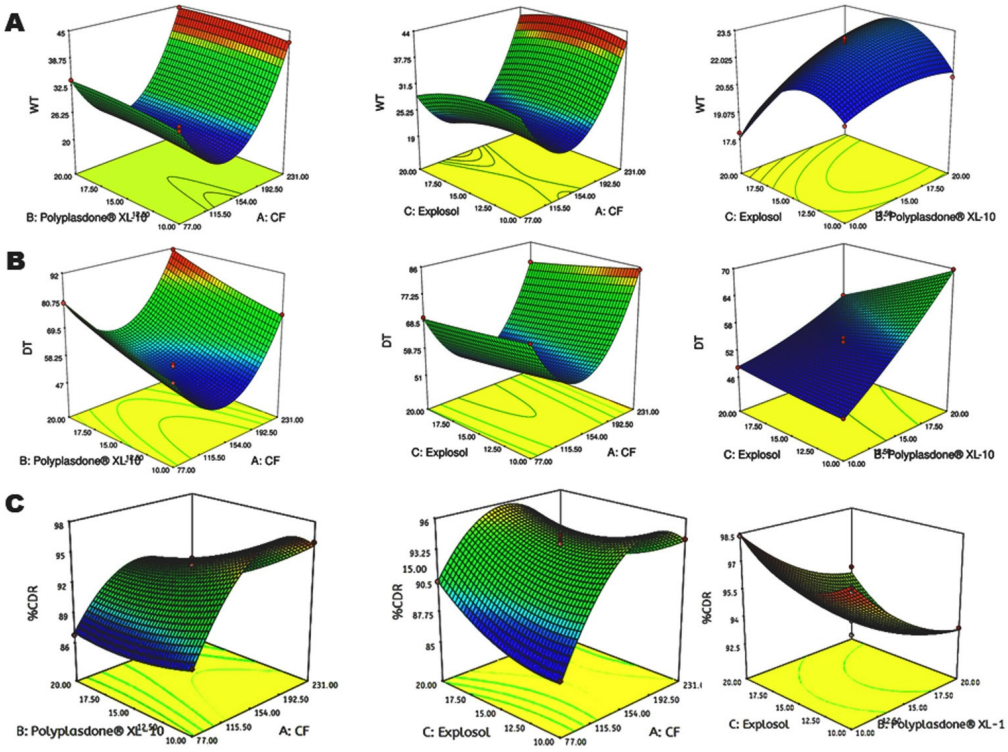

Figure 3: Response surface plots showing the simultaneous influence of independent variables on response parameter A-Wetting time,B-Disintegration Time, C-%CDR.

1 depicts the DSC thermogram of pure Almotriptan and the formulated ADFT. The thermogram of Almotriptan alone had a sharp endothermic peak at 164.34°C, showing the crystalline structure of Almotriptan. ADFT DSC spectrum almost has the same sharp point at 168.26°C as purified Almotriptan malate and no interaction between drug and super disintegrating agent was identified.[19]

The X-ray diffraction patterns of ALM and its AFDT are shown in Figure 2. Crystallinity can be found by comparing the peak heights of distinctive peaks in an ADFT sample's diffraction pattern to those of a standard. The crystallinity is calculated using the Relative Degree of Crystallinity (RDC). The characteristic peak 2 θ value in purified drug was discovered to be 28.521°. Similarly, the 2 θ value of prepared ADFT was observed to be 25.121° (Figure 2). However, when compared to the normal drug, the intensity of the peak in ADFT dropped significantly. The drop in peak intensity can be attributed to a decrease in crystallinity caused by the addition of amorphous excipients.[20]

DISCUSSION

Effect of Control Variable on Wetting Time (WT)

The *p*-value (<0.0001) indicates that main effect of factor A (compression force) and factor B (Polyplasdone XL-10), have a synergistic effect on wetting time as a response variable. The two-way interaction of AB shows has a greater antagonistic effect, where AC (compression force and Explosol) and BC shows has

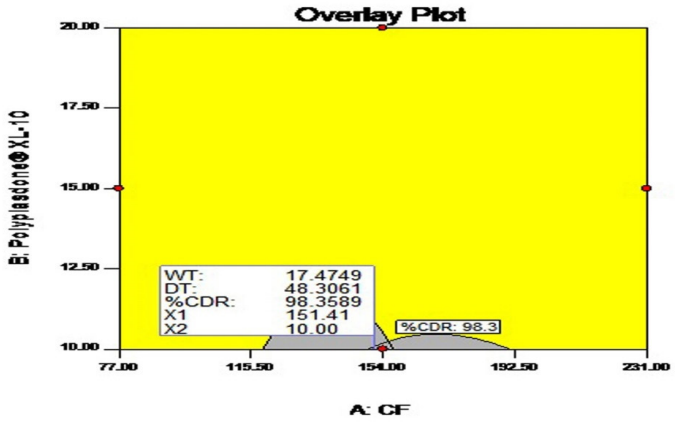

Figure 4: Overlay plot of Optimized AFDT.

Table 2: Physical characterization of Almotriptan FDTs.

Formulation	Packing fraction (Pf)	Porosity fraction (1-Pf)	Friability (%)	Drug content (%)	R1: WT [15]	R2: DT [15]
1	0.91±0.02	0.11±0.03	0.12±0.05	96.58±2.5	42±2.1	79±4.5
2	0.84±0.06	0.16±0.06	0.06±0.03	97.50±1.8	17.96±7	48.2±2.2
3	0.85±0.02	0.08±0.05	0.13±0.03	98.24±2.1	23±6.2	54±7.2
4	0.86±0.03	0.14±0.04	0.13±0.01	97.86±1.6	33±3	73.6±5.5
5	0.83±0.04	0.12±0.06	0.16±0.01	99.17±3.6	20.5±3.5	46.9±2.4
6	0.88±0.07	0.17±0.02	0.23±0.04	97.15±1.2	21.04±5	69.8±1.3
7	0.84±0.05	0.12±0.03	0.11±0.06	98.70±2.9	22.5±7	55±3.3
8	0.86±0.02	0.13±0.05	0.12±0.06	99.30±1.6	42.4±3.4	75.4±5.1
9	0.84±0.04	0.12±0.06	0.13±0.05	98.40±3.3	31.45±4	64.4±6
10	0.83±0.03	0.19±0.02	0.22±0.05	99.7±2.2	22.9±3.7	54.2±7.2
11	0.86±0.02	0.20±0.05	0.16±0.07	100.6±1.9	41.89±5	85.1±4.2
12	0.92±0.04	0.18±0.04	0.38±0.05	99.4±2.9	21.4±4	57.5±5.6
13	0.91±0.04	0.17±0.02	0.21±0.06	99.30±2.1	23.1±3	54±2
14	0.88±0.07	0.13±0.01	0.11± 0.03	100.3±2.7	33.9±6	80.1±5.1
15	0.83±0.02	0.13±0.05	0.16± 0.04	98.5±3.1	44.5±7	91.3±6.2
16	0.80±0.03	0.21±0.01	0.32±0.04	98.24±1.6	29±2	70±2.3
17	0.96±0.02	0.15±0.02	0.21±0.06	99.4±2.9	22.9±3	54±5

synergistic effect on WT. It is asserted by respective *p*-value and coded equation. In addition to that the coded factor claims that a synergistic effect was observed in binate amount of constrained independent variable A and B.

$$\text{Wetting time (WT)}=+22.88+5.34A+1.06B-0.76C-0.093AB+1.03AC+0.73BC+15.71A2-0.53B2-2.12C^2$$

The BC factor interaction lines are no longer parallel. There is a moderate interaction between the factors. The effect of Polyplasdone XL-10 (B) on wetting time is stronger when Factor C is at its high level than Factor C is at its low level. Where the factor C at low level goes increase in less slope compare to factor C at high level. Resulting a synergistic effect on wetting time (fast). When factor C at high level the wetting time increases as factor B increases, owing to Explosol (C) water intake in acidic medium is smaller than in alkaline medium and tangling of the polymer chains, which renders Polyplasdone XL-10 (B) water insoluble.[21]

In terms of AB (compression force and Polyplasdone XL-10) the two lines are essentially parallel curve. This means there is no interaction between the factors.so the effect of factor A and B on wetting time is additive fashion.In both level of factor B, wetting time increases as factor A increases.This isdue to availability of porosity in the tablet is decreases and leads in limited particle deformation,as factor A (compression force) increases (Figure 3A).[14]

Furthermore, the f-value of lack of fit (non-significant) indicates that the suggested model fit the experimental data and that the independent variables or parameters have a significant influence on the response factors.

Effect of Control Variable on Disintegration Time (DT)

In source A, B and C shows significant *p*-value (<0.0001) and in interaction effect BC shows *p*-value as significant compared to AB and AC. Shown in ANNOVA table.

$$DT=+54.24+5.34A+7.97B-2.59C+0.050AB-0.62AC-3.40BC+22.44A^2+1.12\ B2+0.24C^2$$

AB, AC and BC were verified for their effects on DT using the factor tool. The results of the study claim that two order interaction AB and AC show the curve in a additive fashion and parallel curve to one another. As a result, AB and AC have no interaction effect. However, BC (Polyplasdone XL-10 and Explosol) affect DT (response variable). Have no additive effect on DT (Figure 3B). As the DT time increases and prolong the disintegration process at low concentrations of factor C with higher slope as that of higher concentration of factor C, this may due to at high concentration of Explosol water absorption is great, with tridimensional expansion, making the tablets and granules disintegrate quickly.[22]

Effect of Control Variable on %CDR

The *p*-value (<0.0001) demonstrates that (A, B and C) individually and in combination, have a synergistic and antagonistic influence on %CDR as a response variable. The interaction was investigated using a quadratic model, as indicated by the design of expert. The model explicitly asserts that the lack of fit is non-significant (0.6649), implying that the input variable has a considerable effect on response factor

The two-way interaction of AB (compression force and Polyplasdone XL-10), AC (compression force and Explosol), had the strongest antagonistic effect on %CDR. A *p*-value and coded equation are used for assertion. Furthermore, the coded factor claims that a negative effect was observed in binate amounts of constrained independent variables A and positive effect on B and C.

$$\%CDR=+93.86+2.31A-2.02B+0.53C-1.47AB-1.80AC+0.13BC-4.70A2+0.77B^2+1.39C^2$$

According to the study's findings, two variable factors AB and BC exhibit the curve in an additive and parallel form. As a result, there is no interaction impact between AB and BC. However, AC (compression force and Explosol) have an impact on % CDR (response variable). At low concentrations of factor C, %CDR increases, as the factor A with increases (Figure 3C). This is owing to Explosol quick and broad swelling with minimal gelling at low concentrations. The average particle size of Explosol (38 nm-42 nm) is smaller than that of Polyplasdone XL-10. When exposed to an aqueous solution, Explosol expands up to 300 times its initial volume,[23,24] which is less than that of Polyplasdone XL-10, resulting in a translucent suspension in water. At high concentration of factor C (Explosol), shows greater swelling and the drug is controlled from escaping, as a result %CDR falls down.

Design validation for AFDT

To determine the significance of all factors on the response and to continue with optimization, the design was validated using sequential model sum of squares analysis followed by ANOVA.[25] The findings of the sequential sum of squares indicate that the linear model is appropriate for studying the effects of factors on the desired response. Following the application of ANOVA, it was observed that the chosen model was significant; all of the selected control variables were able to demonstrate an impact on the response factor such as wetting time, disintegration time and % CDR, which was significant at a *p*-value of< 0.05, as shown in Table 1. The adjusted and predicted R^2 values for the R1 (WT) were 0.9995 and 0.9989, for R2 (DT) were 0.9995 and 0.9990, respectively and for R3 (%CDR) were 0.9915 and 0. The adjusted R2 value has differed from the predicted R2 well below 0.2 in the case of all three responses. All of these design validation results showed that the used model was appropriate and that it could proceed to the optimization stage.

Table 3: ANOVA outcomes and statistical values of the QbD model for the response variables.

Parameters	Source	Sum of Squares	d_f	Mean Square	F Value	*p*-value	
WT	Model	170.09	9	18.9	128.37	<0.0001	significant
	A-PVP	24.15	1	24.15	164.06	<0.0001	
	B-Agitation Time	76.88	1	76.88	522.23	<0.0001	
	C-Polaxamer	65.55	1	65.55	445.28	<0.0001	
	AB	0.04	1	0.04	0.27	0.6183	
	AC	1.82	1	1.82	12.38	0.0097	
	BC	0.09	1	0.09	0.61	0.4599	
	A^2	0.16	1	0.16	1.12	0.3259	
	B^2	0.96	1	0.96	6.52	0.0379	
	C^2	0.51	1	0.51	3.45	0.1055	
	Residual	1.03	7	0.15			
	Lack of Fit	0.36	3	0.12	0.72	0.5885	not significant
	Pure Error	0.67	4	0.17			
	Cor Total	171.12	16				
Parameters	**Source**	**Sum of Squares**	**df**	**Mean Square**	**F Value**	***p*-value**	
DT	Model	4859.62	9	539.96	272.66	<0.0001	significant
	A-PVP	778.15	1	778.15	392.93	<0.0001	
	B-Agitation Time	144.5	1	144.5	72.97	<0.0001	
	C-Polaxamer	5.61	1	5.61	2.83	0.1362	
	AB	81	1	81	40.9	0.0004	
	AC	1200.62	1	1200.62	606.27	<0.0001	
	BC	100	1	100	50.5	0.0002	
	A^2	401.29	1	401.29	202.64	<0.0001	
	B^2	2044.85	1	2044.85	1032.57	<0.0001	
	C^2	6.45	1	6.45	3.26	0.1141	
	Residual	13.86	7	1.98			
	Lack of Fit	5.06	3	1.69	0.77	0.5692	not significant
	Pure Error	8.8	4	2.2			
	Cor Total	4873.48	16				
Parameters	**Source**	**Sum of Squares**	**d_f**	**Mean Square**	**F Value**	***p*-value**	
%CDR	Model	1.77	9	0.2	397.01	<0.0001	significant
	A-PVP	0.11	1	0.11	221.6	<0.0001	
	B-Agitation Time	0.015	1	0.015	31.27	0.0008	
	C-Polaxamer	0.21	1	0.21	424.59	<0.0001	
	AB	0.024	1	0.024	48.82	0.0002	
	AC	0.13	1	0.13	254.47	<0.0001	
	BC	0.19	1	0.19	384.72	<0.0001	
	A^2	0.59	1	0.59	1186.02	<0.0001	
	B^2	0.29	1	0.29	582.49	<0.0001	
	C^2	0.12	1	0.12	234.28	<0.0001	

Parameters	Source	Sum of Squares	d_f	Mean Square	F Value	*p*-value	
WT	Model	170.09	9	18.9	128.37	<0.0001	significant
	A-PVP	24.15	1	24.15	164.06	<0.0001	
	B-Agitation Time	76.88	1	76.88	522.23	<0.0001	
	C-Polaxamer	65.55	1	65.55	445.28	<0.0001	
	AB	0.04	1	0.04	0.27	0.6183	
	AC	1.82	1	1.82	12.38	0.0097	
	BC	0.09	1	0.09	0.61	0.4599	
	A^2	0.16	1	0.16	1.12	0.3259	
	B^2	0.96	1	0.96	6.52	0.0379	
	C^2	0.51	1	0.51	3.45	0.1055	
	Residual	1.03	7	0.15			
	Lack of Fit	0.36	3	0.12	0.72	0.5885	not significant
	Pure Error	0.67	4	0.17			
	Cor Total	171.12	16				
Parameters	**Source**	**Sum of Squares**	**df**	**Mean Square**	**F Value**	***p*-value**	
DT	Model	4859.62	9	539.96	272.66	<0.0001	significant
	A-PVP	778.15	1	778.15	392.93	<0.0001	
	B-Agitation Time	144.5	1	144.5	72.97	<0.0001	
	C-Polaxamer	5.61	1	5.61	2.83	0.1362	
	AB	81	1	81	40.9	0.0004	
	AC	1200.62	1	1200.62	606.27	<0.0001	
	BC	100	1	100	50.5	0.0002	
	A^2	401.29	1	401.29	202.64	<0.0001	
	B^2	2044.85	1	2044.85	1032.57	<0.0001	
	C^2	6.45	1	6.45	3.26	0.1141	
	Residual	13.86	7	1.98			
	Lack of Fit	5.06	3	1.69	0.77	0.5692	not significant
	Pure Error	8.8	4	2.2			
	Cor Total	4873.48	16				
Parameters	**Source**	**Sum of Squares**	d_f	**Mean Square**	**F Value**	***p*-value**	
	Residual	3.47E-03	7	4.95E-04			
	Lack of Fit	2.59E-03	3	8.62E-04	3.92	0.11	not significant
	Pure Error	8.80E-04	4	2.20E-04			
	Cor Total	1.77	16				

Graphical optimization

The desirability functions method was used to accomplish the graphical optimization. The desirability constraints were chosen to be within the range for all factors.[26] The desirability constraints for the responses were established in accordance with the intended quality of the FDTs, which should have a rapid wetting time, disintegration and dissolution. So the restriction for the R1 (WT) was set as a minimum with an upper limit of 18 sec, the constraint for the R2 (DT) was set as a minimum with an upper limit of 47 sec and the constraint for the R3 (%CDR) was set as a minimum with an upper limit of 86%. The results of the graphical optimization provided by the software as an overlay plot are displayed at (Figure 4) specified constraints. The yellow

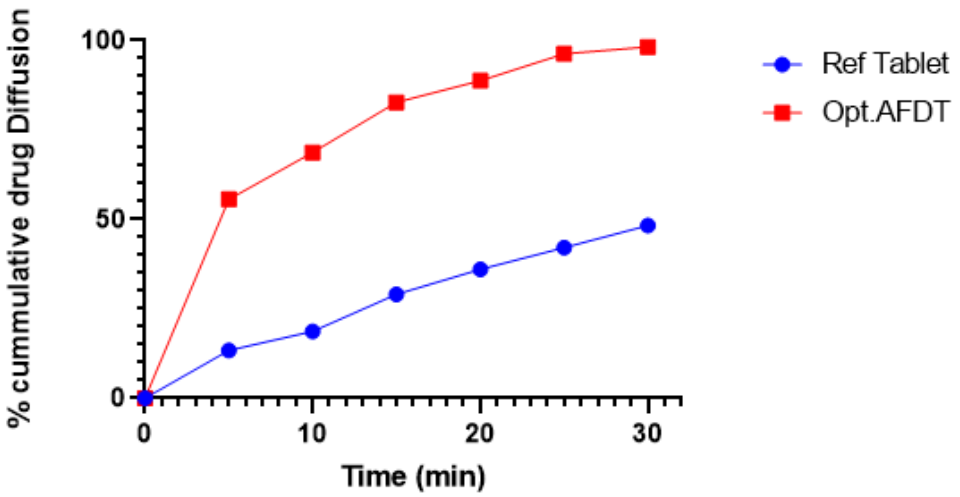

Figure 5: Comparative diffusion profile of reference tablet and the optimized ADFT.

colour region of the plot represents the design space, within which any combination of the variables will result in the desired quality of the FDTs, which should have the highest desirable response values. The software found one such best combination and the expected values of the responses at this combination are depicted in (Figure 4) overlay plot. A novel formulation of AFDTs was prepared using this combination of factors and tested for wetting time, disintegration time and %CDR. The experimental results for WT, DT and %CDR were 18.13 sec, 47.84 sec and 99.2%, respectively. These values were identified within the 95% confidence interval of the expected values. This result showed that the optimization was successful and the FDT formulation with wetting time, rapid disintegration and cumulative percentage drug release was deemed the optimised formulation.

Physical characterization studies of the AFDTs

The packing fraction, friability, disintegration time and drug concentration of the prepared AFDTs were determined and the findings are shown in Table 2. The packing fraction and porosity fraction show the compressibility of the powder combination and the strength of the compressed tablets while still allowing water to disperse and disintegrate the tablets. The packing fraction values of the produced FDTs ranged from 0.80 to 0.96, resulting in porosity fraction values ranging from 0.21 to 0.08. These findings indicated that the tablets were adequately hard while also having enough porosity to assist disintegration. Furthermore, the friability values, which were well below the upper limit of 1%, corroborate the physical robustness of the FDTs. The drug content values were found to be in the range of 96.58-100.6%, showing a uniform dispersion of the drug in the pre-compressed powder combination.

In vitro diffusion studies

Franz diffusion cells are typically used with dissected human or animal epidermis. When biological skin is unavailable, synthetic membranes are used. The synthetic membranes used in Franz cell drug diffusion experiments serve 2 purposes: modelling of the skin and quality control.[27] Polymethylsiloxane (PDMS) is an example of a synthetic membrane that is frequently used to mimic skin because it is hydrophobic and has rate-limiting characteristics similar to skin. The drug diffusion of Reference tablet and Opt-AFDT across synthetic membranes was studied using approved Franz cells and apparatus.[28] A spotless, dried receptor cell was filled with deaerated 0.1 N HCL and left to equilibrate for 15 min at 37°C in a hot magnetic block. The prehydrated membrane was inserted between the paired donor and receptor compartments and Opt-AFDT was placed on the donor compartment's membrane surface. At 200 rpm, the receptor chamber was agitated. Using a glass syringe, sample amounts (1-2 mL) were removed for UV assay (at 283 nm) and the receptor was replaced with new warmed substitute medium of the same volume. Air bubbles produced beneath the membrane were removed by gently tilting the Franz cells and allowing the air bubbles to exit through the sampling arm. The measurement intervals ranged from 5 to 30 min. For each membrane, the cumulative amount of diffusion of Opt-ADFT diffusion over 30 min (Figure 5) was measured. The steady-state slope of each plot was used to calculate the Opt-ADFT drug flux with minimum of 3 replicates.

CONCLUSION

The AFDT fast-dissolving tablets were designed to increase the effective surface area of Almotriptan by reducing wetting time, disintegration time and maximum %CDR using Qbd as a tool and Stat-Ease software to achieve the desired quality. The ADFT were

constructed using the experiments recommended by the BBD design and the design's significance was determined using sum of squares analysis followed by ANOVA. The formula was optimised to increase effective surface area; the software-suggested control variables include compression force (77-231Mpa), Polyplasdone XL-10 (10-20 mg) and Explosol (10-20 mg), The DoE analysis confirmed that the chosen design and statistical model were relevant, as all of the factors influenced the responses considerably. Further graphical optimization showed the optimised formulation of the FDTs, which includes 151.4MPa as a compression force, 10mg of Polyplasdone XL-10 and 20 mg of Explosol as a super disintegrant. The proposed mixture was developed and evaluated for wetting time, disintegration time and %CDR. The experimental findings for WT, DT and %CDR were 18.13 sec, 47.84 sec and 99.2%,respectively. The Opt.AFDT further studied for the permeability using the *in vitro* diffusion profile and the result found as 98.2% (Figure 5) at the end of 30 min, it was evident that the effective surface area increased. These findings showed that the work's objectives were met successfully owing to the statistically supported QbD approach.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AFDT: Almotriptan fast dissolving tablet; **ALM:** Almotriptan; **QbD:** Quality by design; **CMA:** Critical Material Attribute; **CPP:** Critical Processing Parameter; **TPQP:** Target product quality profile; **TPP:** Target product profile; **CF:** Compression force; **DSC:** Differential Scanning Calorimetry; **%CDR:** Percentage cumulative drug release; **DT:** Disintegration time; **WT:** Wetting time; **BBD:** Box-Bhenken deisgn; **Opt:** Optimized; **DoE:** Design of experiment.

SUMMARY

This DoE study meticulously optimize control quality attributes and critical material attributes for the development of Almotriptan fast-dissolving tablets, with a specific focus on enhancing effective surface area. Through systematic experimentation, the study identifies the Critical Quality Attributes (CQAs) of optimal compression force at 151.41 MPa, directly impacting the tablet's surface characteristics. Furthermore, the study designates Polyplasdone XL-10 (10mg) and Explosol (20 mg) as Critical Material Attributes (CMAs), underscoring their pivotal roles in achieving the desired increase in effective surface area. This strategic approach elucidates the interplay between compression force and material attributes in facilitating improved rates of diffusion for enhanced therapeutic outcomes.

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