ORIGINAL ARTICLE

RESPONSE SURFACE METHODOLOGY FOR OPTIMIZATION OF DICLOFENAC SODIUM ORODISPERSIBLE TABLETS (ODTs)

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Abstract

The aim of this study was to optimize 25 mg diclofenac sodium orodispersible tablets. For this it was used a Box - Behnken experimental design to establish the relation between independent variables, such as, concentration of Pharmaburst™ 500 (X_1), Avicel PH 102 (X_2) and compression force (X_3), and dependent variables: friability (Y_1), disintegration time (Y_2), wetting time (Y_3) and hardness (Y_4) in order to obtain the optimal formula of the technological process using Response Surface Methodology (RSM). To calculate the coefficients for the response equation we used Design Expert Trial version 7.0.0 software (Stat - Ease Inc. Minneapolis). ANOVA test was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant, if the p - value is less than 0.05. The estimation error values proved the validity of the used mathematical method. After generating the polynomial equations that relate the dependent and independent variables, the process was optimized for all four responses. The optimum formulation was selected based on the constraints set on independent variables: Y_1 (0 - 1%), Y_2 (0 - 180 s), Y_3 (55 - 75 s) and Y_4 (63 - 123 N). The optimum formulation for diclofenac sodium 25 mg ODTs was: 71.4% (X_1), 9.65% (X_2) at 10 kN (X_3) compression force, providing good tablet properties (friability, disintegration time, wetting time and hardness).

Rezumat

Scopul acestui studiu a fost de a optimiza formularea comprimatelor orodispersabile conținând diclofenac sodic 25 mg. În acest sens a fost utilizat programul de design experimental Box - Behnken, pentru a stabili relația dintre variabilele independente: concentrația de Pharmaburst™ 500 (X_1), Avicel PH 102 (X_2) și forța de comprimare (X_3) și variabilele dependente: friabilitate (Y_1), timp de dezintegrare (Y_2), timp de umectare (Y_3) și rezistență mecanică (Y_4), cu scopul de a obține formula optimă a procesului tehnologic, pe baza Metodologiei de Răspuns a Suprafeței (MRS). Pentru a calcula coeficienții din ecuațiile generate am folosit softul Design Expert Trial versiunea 7.0.0 (Stat - Ease Inc. Minneapolis). Am efectuat analiza ANOVA pentru a determina impactul modelului. Modelul este concludent la un nivel de 5% al factorului de impact, dacă valoarea p este mai mică de 0,05. Valoarea erorilor estimate dovedește validitatea metodei matematice folosite. După generarea ecuațiilor polinomiale ce inter-relaționează variabilele dependente și cele independente, procesul a fost optimizat pentru toate cele patru răspunsuri. Formula optimă a fost selectată pe baza cerințelor impuse de variabilele independente: Y_1 (0 - 1%), Y_2 (0 - 180 s), Y_3 (55 - 75 s) and Y_4 (63 - 123 N). Formula optimă a comprimatelor orodispersabile cu diclofenac sodic 25 mg este: 71,4% (X_1), 9,65% (X_2), forța de comprimare de 10 kN (X_3) asigurând proprietățile adecvate: rezistență mecanică, friabilitate, timp de umectare și dezintegrare.

Keywords: diclofenac sodium, orodispersible tablets (ODTs), Response Surface Methodology (RSM), Pharmaburst™ 500, optimization, Box - Behnken experimental design

Introduction

The development and implementation of rapidly disintegrating tablets in the buccal cavity will widen the possibilities of pharmacotherapy, particularly the need to use medicines in emergencies and drugs that are extensively metabolized in the liver.

Orally administered dosage forms e.g. tablets, capsules are convenient for many drugs –but they are challenging to formulate if the active substances have poor dissolution or low bioavailability. The rapidly disintegrating tablets, in the mouth, (orodispersible tablets) overcome all the above problems and thus offer an alternative form of oral medication, which provide patients with a more convenient mean of taking their medications. Addition of super disintegrating agents in the formulation is one of the approaches to formulate orodispersible tablets [1]. Orally disintegrating tablets contain a wide variety of pharmaceutical active ingredients covering many therapeutic

categories. The European Pharmacopoeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth, before swallowing.

Orally disintegrating tablets are characterized by high porosity, low density and low hardness, when administered, an *in-situ* suspension is obtained in the oral cavity as the tablet disintegrates and is subsequently swallowed.

A large majority of the new chemical entities and many new existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products, so lastly the purpose of this study was to increase diclofenac sodium dissolution using fast dissolving tablets [8].

Sodium diclofenac - 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid monosodium salt is a non-steroidal anti-inflammatory drug (NSAID) administered in order to reduce inflammation and as an analgesic reducing pain in certain conditions. It is a faintly yellowish white to light beige, virtually odourless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in water and practically insoluble in chloroform and in diluted acid [5, 9]. Regarding Biopharmaceutics Classification System (BCS), high permeability and low solubility drugs are grouped in class II. In this case, the dissolution profile must be quite definite and highly reproducible. Drugs dissolution of this class is the limiting step for drug absorption. Although it has excellent bioavailability (99%), its poor aqueous solubility makes absorption and dissolution rate-limited, thus delaying the onset of action [7, 8].

Response Surface Methodology (RSM) represents a set of statistical and mathematical methods used for analysing the relation between one or more measured answers (dependent variables) and a number of independent variables, in order to obtain an optimal formula. We applied RSM in order to obtain the optimal formula of the experimental conditions, which minimize or maximize a response of the system and the modifications of response surface in the domain of independent variables [6, 10].

Materials and Methods

Diclofenac sodium (Amoli Organics Pvt. Ltd. India), Pharmaburst^{TM} 500 (SPI Pharma USA), Avicel PH 102 (JRS Pharma Germany) and Magnesium stearate (Union Derivan Spain) were kindly provided by Magistra C&C. For ODTs development we used the direct compression method at 10 and 20 kN compression forces and different excipients for four formulations (Avicel PH 102, magnesium stearate) and co-processed excipient Pharmaburst^{TM} 500 in two concentrations (70 % and 80 % w/w).

Co-processed Pharmaburst^{TM} 500 excipient improves the internal porosity of the platform's constituent particles, which allows a more rapid liquid penetration into the tablet matrix, reduces disintegration time and compressibility of the material. Additionally, the excipient system was developed in a manner which makes it amenable to direct compression tableting methodologies at normal conditions of temperature and humidity that is devoid of product adherence to punch faces. It contains manitol, crosspovidone, sorbitol, precipitated silicon dioxide [11].

All the formulations should offer an acceptable disintegration time less than 3 minutes and at the same time and finally to increase dissolution rate, possess sufficient mechanical strength so that they will withstand the course of manufacturer and subsequent packaging [1, 4]. From Pharmaburst^{TM} 500 composition mannitol was used as diluent to impart multidimensional benefits such as good aqueous solubility and good wetting properties, that facilitates tablet breakdown as well as negative heats of solution and crospovidone, used as superdisintegrant leading to a rapid breakdown and fast drug dissolution [3, 7].

A randomized full factorial design was adopted to optimize the variables. In this design, 3 factors were evaluated, and experimental trials were performed in 15 possible combinations. The amounts of Pharmaburst^{TM} 500 (A), Avicel PH 102 (B), and compression force (C) were selected as independent variables.

The independent variables and the selected interval for these are shown in Table I. The friability (Y_1), disintegration time (Y_2), wetting time (Y_3) and hardness (Y_4) were selected as dependent variables.

Table I

Variables and intervals selected to perform Box-Behnken experimental design

Variables	Minimum	Medium	Maximum
Pharmaburst^{TM} 500 (X_1)	98	105	112
Avicel PH 102 (X_2)	1.60	8.60	15.60
Compression force (X_3)	10	15	20
Transformed values	-1	0	1

The actual formulation design of oral disintegrating tablets of diclofenac sodium according to factorial design layout is shown in Table II. The data was interpreted using Response Surface Methodology (Design Expert Trial version 7.0.0 software (Stat - Ease Inc. Minneapolis).Regression polynomials for the individual dependant variables (friability, disintegration time, wetting time and hardness) were calculated with

Design Expert trial version 7.0.0 software and applied to approximate the response surface and contour plots. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. Formulation of desired characteristics can be obtained by factorial design application [10]. ANOVA test was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant if the p - value is less than 0.05.

Table II

Design of diclofenac sodium ODT formulations and their responses according to the factorial design

Batch	Independent variable			Dependent variable			
	Pharmaburst^{TM} 500 (X_1)	Avicel PH 102 (X_2)	Compression force (X_3)	Friability (Y_1)	Disintegration time (Y_2)	Wetting time (Y_3)	Hardness (Y_4)
F1	112	15.60	15.00	2.38	197	59	103
F2	105	8.60	15.00	1.69	172	62	92
F3	98	8.60	10.00	0.4	140	55	112
F4	98	8.60	20.00	1.48	125	67	84
F5	112	8.60	10.00	1.77	190	65	111
F6	112	1.60	10.00	1.65	162	70	100
F7	105	15.60	20.00	2.3	178	63	84
F8	105	8.60	15.00	1.69	172	68	92
F9	112	8.60	20.00	3.34	233	63	64
F10	105	8.60	15.00	1.69	172	65	92
F11	105	1.60	20.00	2.3	178	75	63
F12	105	1.60	10.00	1.09	165	71	100
F13	98	1.60	15.00	1.01	147	66	82
F14	98	15.60	10.00	0.74	170	60	123
F15	105	15.60	10.00	1.09	165	63	122

Results and Discussion

Optimization of formulation using response surface quadratic model

As seen in Table III, the Model F-value of 74.73 implies that it is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case, X_1, X_3, X_1X_3 are significant model terms.

Final Equation in Terms of Actual Factors:

Friability = $8.81185 - 0.22435 \cdot X_1 + 0.16358 \cdot X_2 - 0.33883 \cdot X_3 - 1.42857 \cdot 10^{-3} \cdot X_1X_2 + 4.59524 \cdot 10^{3} \cdot X1X3 - 1.09524 \cdot 10^{-3} \cdot X_2 X_3 + 1.30102 \cdot 10^{-3} \cdot X_1^2 + 2.29592 \cdot 10^{-4} \cdot X_2^2 - 2.50000 \cdot 10^{-4} \cdot X_3^2$

The tablets showed a high friability >1%, which refers to an inadequate resistance against abrasion, except formula I (0.74). The surface response plot revealed (Figure 1) that a corresponding increase in the friability (%w/w) was observed with the increased in concentration of Pharmaburst^{TM} 500. This may be due to linearity in formation of interstitial pores/ channels with increased concentration of super-disintegrant, thereby leading to moderately tender solid state characteristics of the tablet.

Response 1 - Friability (%w/w): Analysis of variance (ANOVA) for Response Surface Quadratic Model

Table III

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of square	df	Mean square	F Value	p-value Prob > F
Model	7.65	9	0.85	74.73	< 0.0001
X_1-Pharmaburst^{TM} 500	3.74	1	3.74	328.75	< 0.0001
X_2-Avicel PH 102	$4.07 \cdot 10^{-4}$	1	$4.07 \cdot 10^{-4}$	0.036	0.8573
X_3-Compression force	3.21	1	3.21	282.42	< 0.0001
X_1X_2	0.012	1	0.012	1.01	0.3608
X_1X_3	0.12	1	0.12	10.91	0.0214
$^3X_2 X_3$	$7.05 \cdot 10^{-3}$	1	$7.05 \cdot 10^{-3}$	0.62	0.4667
X_1^2	0.014	1	0.014	1.19	0.3256
X_2^2	$4.21 \cdot 10^{-4}$	1	$4.21 \cdot 10^{-4}$	0.037	0.8551
X_3^2	$7.89E \cdot 10^{-5}$	1	$7.89E \cdot 10^{-5}$	$6.93 \cdot 10^{-3}$	0.9369
Residual	0.057	5	0.011		
Lack of Fit	0.057	3	0.019		
Pure Error	0	2	0		
Cor Total	7.71	14			

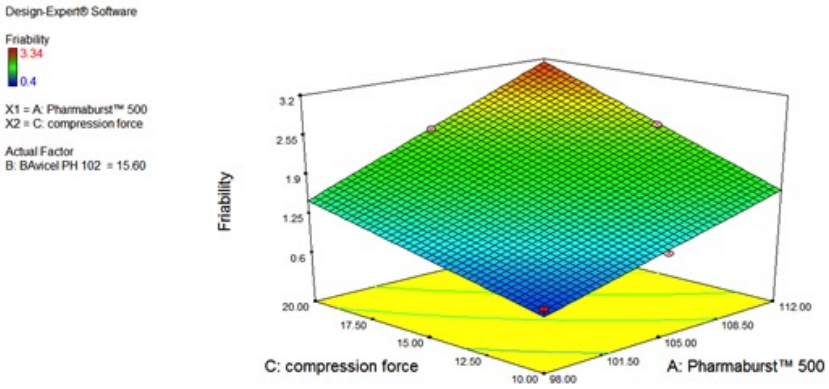

Figure 1.
Surface response plot for Friability (% w/w)

Response 2 - Disintegration time (s): Analysis of variance (ANOVA) for Response Surface 2FI Model

Moreover, it is also observed from Table IV, the Model F-value of 13.83 implies the model is significant. There is only a 0.08% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case X_1, X_1X_3 are significant model terms as seen from Figure 2.

Since the values of R^2 are quite high for the two responses, i.e., 0.9926 and 0.9121, the polynomial equations form excellent fits to the experimental data and are highly statistically valid.

The surface response plot revealed that a corresponding increase in the disintegration time (seconds) was observed with an increase in the concentration of Pharmaburst^{TM} 500.

The Pharmaburst^{TM} 500 (70%) co-processed excipient and Avicel PH 102 filler (11.1%) collaborate to the good results showed in the experimental tests, unless for the disintegration test.

Final Equation in Terms of Actual Factors:

Disintegration time = $531.01185 - 3.79358 \cdot X_1 + 2.94743 \cdot X_2 - 55.481 \cdot X_3 - 6.69886 \cdot 10^3 \cdot X_1X_2 + 0.55238 \cdot X_1X_3 - 0.13810 \cdot X_2X_3$

Table IV
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of squares	df	Mean square	F	p-value Prob > F
Model	8016.05	6	1336.01	13.83	0.0008
X_1-Pharmaburst™ 500	6607.44	1	6607.44	68.39	< 0.0001
X_2-Avicel PH 102	10.01	1	10.01	0.1	0.7558
X_3-Compression force	386.96	1	386.96	4.01	0.0803
X_1X_2	0.39	1	0.39	$4.00 \cdot 10^{-4}$	0.9511
X_1X_3	1794.13	1	1794.13	18.57	0.0026
X_2X_3	112.13	1	112.13	1.16	0.3127
Residual	772.89	8	96.61		
Lack of Fit	772.89	6	128.81		
Pure Error	0	2	0		
Cor Total	8788.93	14			

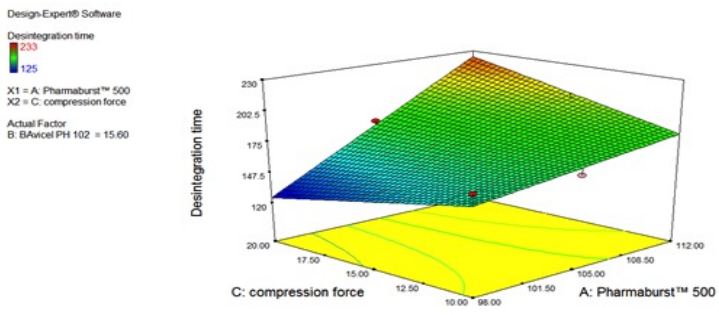

Figure 2.
Surface response plot for the disintegration time (seconds)

Response 3 - Wetting time (s): Analysis of variance (ANOVA) for Response Surface Linear Model

The Model F-value of 4.70 implies the model is significant. There is only a 2.39% chance that a "Model F-value" this large could occur due to noise (Table V).

Table V

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of squares	df	Mean square	F value	p-value Prob > F
Model	200.25	3	66.75	4.7	0.0239
X_1-Pharmaburst™ 500	10.12	1	10.12	0.71	0.4164
X_2-Avicel PH 102	171.13	1	171.13	12.06	0.0052
X_3-Compression force	19	1	19	1.34	0.2718
Residual	156.15	11	14.2		

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case, X_2 is a significant model term.

The surface response plot (Figure 3) revealed that the modified ratio of excipients Pharmaburst™ 500 (80%) and Avicel PH 102 (1.14%) didn't improve the quality parameters for fast dissolving tablets: friability, disintegration, wetting time.

Final Equation in Terms of Actual Factors:

Wetting time = +49.60166 + $0.16071 \cdot X_1$ - $0.66071 \cdot X_2 + 0.27945 \cdot X_3$

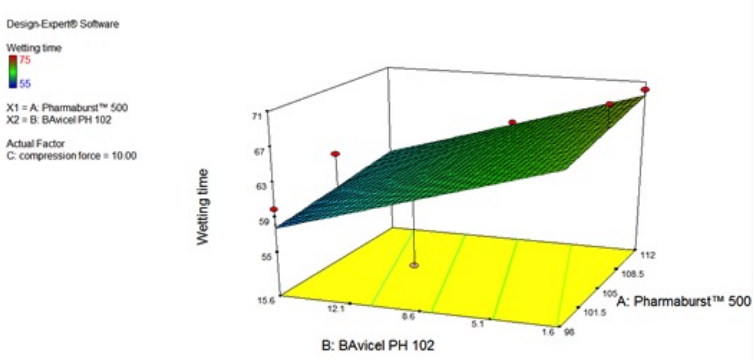

Figure 3.

Surface response plot for the wetting time (seconds)

Response 4 - Hardness (N): Analysis of variance (ANOVA) for Response Surface Quadratic Model

The F-value Model of 94.62 implies the model is significant. There is only a 0.01% chance that a "F-value Model" this large could occur due to noise.

In this case A, B, C and AC are significant model terms (Table VI).

Table VI

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of squares	df	Mean square	F value	p-value Prob > F
Model	4546.83	9	505.2	94.62	< 0.0001
A-Pharmaburst™ 500	106.4	1	106.4	19.93	0.0066
B-Avicel PH 102	1005.31	1	1005.31	188.29	< 0.0001
C-compression force	2812.24	1	2812.24	526.72	< 0.0001
AB	$9.37E10^{-3}$	1	$9.37 \cdot 10^{-3}$	$1.76 \cdot 10^{-3}$	0.9682
AC	113.98	1	113.98	21.35	0.0057
BC	0.027	1	0.027	$5.09 \cdot 10^{-3}$	0.9459
A^2	$1.47E10^{-3}$	1	$1.47 \cdot 10^{-3}$	$2.76 \cdot 10^{-4}$	0.9874
B^2	0.024	1	0.024	$4.41 \cdot 10^{-3}$	0.9496
C^2	0.014	1	0.014	$2.68 \cdot 10^{-3}$	0.9607
Residual	26.7	5	5.34		
Lack of Fit	26.7	3	8.9		
Pure Error	0	2	0		
Cor Total	4573.53	14			

Final Equation in Terms of Actual Factors:

Hardness = -19.68259 + 1.42444·X_1 + 1.65619·X_2 + 10.78661·X_3 + 1.28912·10^{-3} ·X_1X_2 - 0.13923·X_1X_3 - 2.15·10^{-3} ·X_2 X_3 + 4.29422·10^{-4} ·X_1^2 - 1.71854·10^{-3} ·X_2^2 + 3.36833·10^{-3} ·X_3^2

R^2 is 0.9943 and the "Pred R-Squared" of 0.9681 is in reasonable agreement with the "Adj R-Squared" of 0.9900.

"Adeq Precision" measures the signal to noise ratio. Our model ratio of 49.790 indicates an adequate signal and that the model can be used to navigate the design space.

The 10 kN compression force and Pharmaburst™ 500 70% (F1) decreased the disintegration time in optimum correlation to friability, hardness, and wetting time (Figure 4).

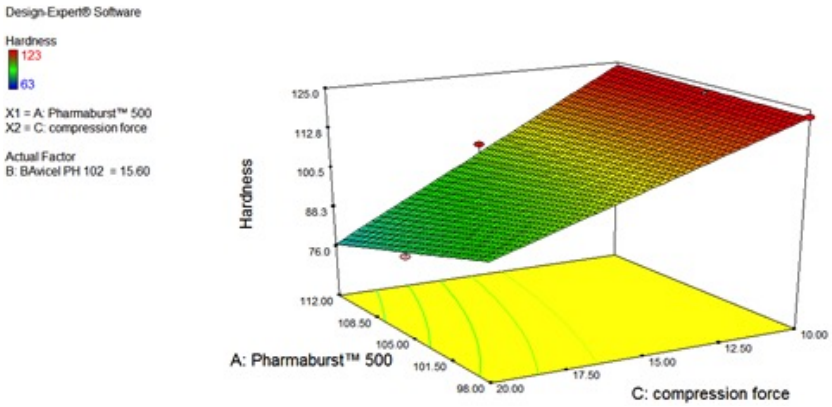

Figure 4.
Surface response plot for tablet hardness (N)

Optimization

After generating the model polynomial equations to relate the dependent and independent variables, the process was optimized for all four responses.

The optimum formulation was selected based on the constraints set on independent variables: Y_1 (0 - 1%), Y_2 (125 - 180 seconds), Y_3 (55 - 75 seconds) and Y_4 (63 - 123 N) (Figure 5).

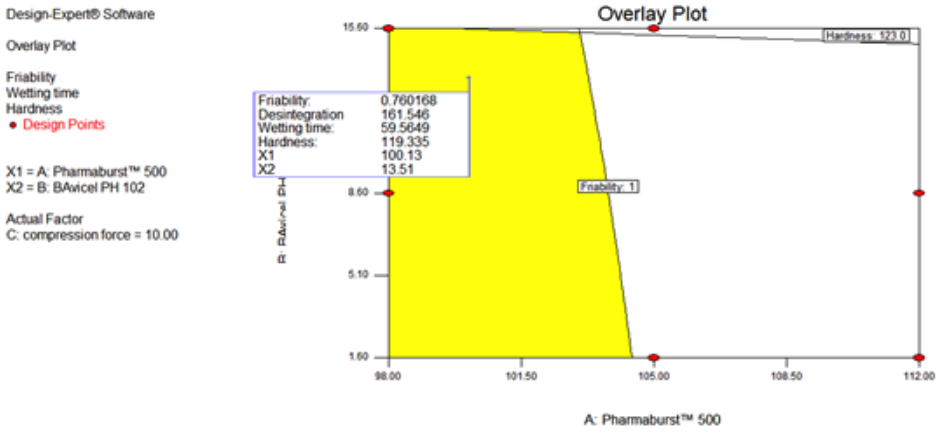

Figure 5.
Optimum formulation for 25 mg sodium diclofenac ODTs

Conclusions

Based on the obtained results from the optimization step, the proposed optimum formula for 25 mg diclofenac sodium OTDs obtained by direct compression is: diclofenac sodium 25 mg, 71.4% Pharmaburst™ 500, 9.65% Avicel PH 102, 1% magnesium stearate at a 10 kN compression force, providing good tablet properties: friability (0.76%), disintegration time (161.5 sec.), wetting time (59.56 sec.) and hardness (119.33 N).

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