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DEVELOPMENT OF FENOFIBRIC ACID DELAYED RELEASE PELLETS: OPTIMIZATION OF PROCESS VARIABLES IN FLUID BED PROCESS

Bala Vishnu Priya Mukkala [1*], Gopala Krishna Murthy Talasila[2] and Prameela Rani Avula[3]

[1] Formulation research and development, RA Chem Pharma Ltd, Hyderabad, Telangana, India

[2] Department of pharmaceutics, Bapatla College of Pharmacy, Bapatla, Guntur, Andhra Pradesh, India

[3] Department of pharmaceutics, Acharya Nagajuna University, Guntur, Andhra Pradesh, India

Abstract:

The objective of the present study was to optimize the process of Fenofibric acid delayed release (DR) pellets. Wurster (Bottom spray fluid bed coating) process was employed to develop the Fenofibric acid DR pellets. This study assesses the impact of various process variables on drug layering by using statistical interpretation such as ANOVA. A face centered central composite design (CCD) was employed to study the effect of independent variables (product temperature, atomization air pressure, fluidization air volume and spray rate) on dependent variables (Fines, agglomerates, coating efficiency and assay). Fabricated pellets were characterized for various physico-chemical parameters and stability studies. Optimization was done by fitting experimental results to the software program (Design expert). The design space for process parameters and its influence on %fines, % agglomerates, coating efficiency and assay was developed. From the obtained results, 40°C ± 3°C as product temperature, 0.8 -1.2 kg/cm^2 as atomization air pressure, 50 -65 cfm as fluidization air volume and 2-6 g/min as spray rate were selected as the operating ranges for robust coating process, desired yield and quality of the product. The drug release from the optimized formulation followed first order kinetics and controlled by non fickian transport. There is no significant change observed during stability. It was concluded that the face centered central composite design facilitated the process optimization of Fenofibric acid DR pellets. The Fenofibric acid DR pellets were successfully developed by employing bottom spray fluid bed coating (Wurster) technique.

Key-Words: *Fenofibric acid, Pellets, Fluid bed process, Process parameters, CCD.*

Corresponding Author*:

Bala Vishnu Priya Mukkala,

Formulation research and development,
RA Chem Pharma Ltd,
Hyderabad, Telangana, India
E-mail: vishnupriya.mukkala@gmail.com

QR code

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INTRODUCTION:

Multiple-dose units have many kinetic and therapeutic advantages over single-dose sustained-release units, such as improved bioavailability, easy administration, reproducible gastric residence time, low risk of dose dumping, low intra and inter subject variability, flexibility of blending of different release profile and divided into various dose strengths without formulation changes [1]. The most commonly used pelletization techniques are Suspension/solution layering, extrusion spheronization and powder layering [2]. However, suspension/solution layering (Wurster) technique is most preferable in the pharmaceutical industry owing to its advantages like continuous process, less manual interruption and batch to batch reproducibility [3].

The process variables involved in the wurster process are batch size, air distribution plate, column height, spray nozzle diameter, filter bags, nature of the coating solution/suspension, inlet and product temperature, air volume, dew point, spray rate, atomization air pressure, drying/ curing time etc. Process parameters can be varied in a specific range without a critical effect on the fluid bed process or on the pellet quality. In contrast, a variation of a critical parameter would affect the fluid bed process or the pellet quality in a significant manner [4].

Quality by design (QbD) is a holistic and proactive approach to support the pharmaceutical development in a more scientific, risk based manner, by restricting the flexibility in the manufacturing process to ensure predetermined product specifications. It helps to assess the critical material attributes (CMAs) and critical process parameters (CPPs) that impacting the predefined critical quality attribute (CQAs). The design space (DS) concept is introduced as "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality." Using this approach, it is essential to define relationship between critical formulation/process parameters and critical quality attributes [5].

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation. Central composite design (CCD), three level factorial design, Box Behnken design and D-optimal design are the different types of RSM designs available for statistical optimization of the formulations. Face centered central composite design provide relatively high quality predictions over the entire design space and do not require using points outside the original factor range [6].

Parameters such as batch size, air distribution plate, column height, spray nozzle diameter, filter bags, nature of the coating solution/suspension, dew point, drying/ curing time, inlet/product temperature, spray rate, fluidization air volume and atomization air pressure were recognized as probable process parameters for fluid bed coating process.

Batch size should be kept within the recommended occupancy to obtain batch to batch uniformity. Working volume of batch at the initial and final stage should be in 20 – 100% and 40 – 80% for non-functional and functional coatings respectively. The air distribution plate was selected based on particle size and density of the material used. Appropriate air distribution plate has to be selected to get consistent fluidization at minimum attrition. 'C' plate was recommended for the pellet size in between 600 – 1800 micron. The height of the column changed on the basis of particle properties such as size, shape and density. Appropriate adjustment of the partition gap ensures proper substrate circulation through the spray zone and drying zone. When the gap is too small, fewer particles draw in the column and chances of material loss and chances of over wetting. When the gap is too more, leads to insufficient pressure differential created to draw the particles in column. The recommended gap for 6" wurster (Lab model) is 15 -25 mm. The droplet size would be controlled by the nozzle diameter used. Large droplets of coating suspension/solution do not distribute evenly over the core and also do not dry quickly as smaller droplets. Very small droplets may dry quickly which results in spray drying of the coating suspension/solution and irregular deposition over the surface of the core. Hence, it is necessary to select the proper nozzle diameter to get more consistent and uniform spray.

Filter bag is used to prevent loss of material and to allow the air to pass through. A filter bag is selected based on the particle size of the core. If the porosity of the filter bag is higher than optimal, the loss of material will be high and lower than optimal leads to clogging of the filter bag there by process interruption and product yield. Porosity of the filter bag is monitored by differential pressure. Coating solution or suspension should have enough solid content to easy spraying. If the viscosity of coating

liquid is more, it will affect the droplet size and leads to change in the pellet surface. Dew point indicates the amount moisture in the air. The change in dew point of air changes the evaporating efficiency of the air. Lower humidity in the inlet air will enhance the drying capacity of air even at low temperature but it will cause excessive static charge in the product. Too high absolute humidity will result in a depression in air temperature below dew point, which leads to condensation of water either on to machine or product surface. To eliminate static charge and process variability, required absolute humidity should be maintained. Drying process is a removal of water or volatile liquid from solution or suspension. In aqueous dispersion base coating, polymer particles come into contact with each other and form coalescence during drying. Drying/ curing time and temperature would be selected based on the selected based on solvent used and material to be coated. Usually the coating process is performed at sufficient high temperatures to assure the complete film formation and avoid further gradual coalescence.

Control of the inlet air temperature is important parameter as it affects the quality of coats formed. High temperature leads to spray drying and low temperature leads to agglomeration. The optimal temperature allows the evaporation of solvent at a sufficiently slow rate for adequate spreading of spray droplets and coalescence of polymer particles, and fast enough to avoid agglomeration and drug migration into the liquid layer. When the temperature of the air is too high, sprayed droplets dry quickly and do not coalescence when impinged on the core particles. This forms discontinuous coats which are rough and porous and will not impart desired controlled release properties of a functional coat. High temperatures may also leads to spray drying of atomized droplets before they reach the core, resulting in loss of coating material. Spray dried coating materials may also be embedded in the film coats and disrupting continuity of the film. On the other hand, when the temperature is too low, a longer time is required for drying and drug migration into moistened coat layers. If the temperature is lower than minimum film formation temperature, coalescing would not occur, leads to deformation and porous films.

Fluidization air volume is responsible for circulation and drying of substances during coating. Insufficient air flow may not provide sufficient drying air to circulate the substrates and remove the moisture from the deposited sprayed droplets during coating and consequently results in agglomeration. However, excessively high air flow rates can increase the attrition leads to friable cores or stress cracks on coats and augment the spray drying effect. Appropriate air volume is unique and which depends on product characteristics such as particle size, shape and density.

Spray rate depends on the size of the core particles as well as the solution properties. Spray rate has to be adjusted according to the drying efficiency and tackiness of the solution. To coat the smaller cores, the droplet size should be kept low either by increasing atomization air pressure or by reducing the spray rate. At the beginning of the coating process, the spray rate must be kept low to avoid solubilizing the core, seepage of the drug or coating polymer into other layer. Once the initial barrier formed, the spray rate can be increased up to optimum. High spray rates increase the propensity for agglomeration and results in non-uniform cores. Low spray rates also enable smaller spray droplets to be formed which would increase the coat uniformity, reduce agglomeration. However, too low spray rate leads to fast drying of droplets could prevent coalescence of polymer particles and leads to poor film formation.

Atomization air pressure controls the droplet size and thereby influences the spray pattern. High atomization air pressure result in smaller spray droplets and are required to prevent agglomeration. However, the atomization air pressure is too high, the spray droplets can be propelled away quickly and this does not promote droplet-core contact. High atomization air pressures also increases the attrition of cores and can produce more fines. On the other hand, low atomizing air pressure leads to formation of coarser droplets, which dry slowly and promotes the formation of liquid bridges between the cores, result in agglomeration [7].

The present investigation aimed to fabricate a Fenofbric acid delayed release (DR) pellets. Impact of the formulation variables were statistically interpreted and significant formulation variables were optimized employing fece centered central composite design in our earlier investigation [8]. Preliminary studies were carried out to freeze the process parameters which do not have any impact on product quality, such as batch size, air distribution plate, column height, spray nozzle diameter, filter bags, dew point and drying time. However, product temperature, atomization air pressure, fluidization air volume and spray rate are found as critical process parameters.

MATERIALS AND METHODS:

Materials:

Choline fenofibrate was obtained from RA CHEM Pharma Ltd., Hyderabad as gift sample, Sugar spheres (Arun pharma, Hyderabad), Povidone (BASF, Mumbai), Polyethylene glycol (Clariant, Hyderabad), Hypromellose (Dow chemical's, Mumbai), Ethocel 45 cps (Colorcon, Goa), Eudragit L 30 D55 (Evonik), Triethyl citrate (Merck, Mumbai), Talc (Luzenac, Mumbai), Isopropyl alcohol (Avantor, Hyderabad), Purified water and empty hard gelatin capsule shells size 0 (ACG, Hyderabad) were used as received.

Methods:

Preparation of Fenofibric acid Delayed Release (DR) Pellets by Wurster process

Fenofibric acid DR Pellets were prepared by employing bottom – spray fluid bed (Wuster) coating process (Glatt GPCG 1.1). The dosage form was designed to obtain the delayed extended release. Drug loaded pellets were prepared by spraying the aqueous drug dispersion over non pariel seeds (Sugar spheres (20#- 25# ASTM)) employing wurster process (Bottom spray fluid bed coating technology). The drug dispersion was coated on to sugar spheres using 1.0 mm of spray nozzle with a spray rate of 2-6 g/min, 0.8-1.2 Kg/cm^2 of atomization air pressure, 50-65 cfm of air volume and product temperature 37-43°C. The drug dispersion was sprayed until get desired weight gain. The drug loaded pellets were dried for 10 minutes at 37-43°C. Hydro alcoholic (IPA : Water 80:20) ER coating solution was coated over the drug loaded pellets using wurster process at a spray rate of 4-8g/min & 34-38°C as product temperature. The ER coated pellets were dried for 15 minutes at 34-38°C. Further, the aqueous enteric coating dispersion was coated on to the ER coated pellets at 28-32°C as product temperature and at a spray rate of 2-6g/min. Enteric coated pellets were subjected for drying at 35°C for 15 minutes. Final pellets were sifted through #14-#18 ASTM mesh to separate the fines and agglomerates and collect the desired portion. The composition of the optimized formula described in Table 1.

Table 1: Composition of the Fenofibric acid DR Pellets

S.No.	Composition	mg/Capsule
I	**Core**	
1	Sugar Spheres (#25-#30)	139.7
II	**Drug loading**	
2	Choline Fenofibrate	178.53
3	PVP K 30	13.97
4	Polyethylene glycol 6000	1.4
5	Purified water	Q.S
III	**Extended release coating**	
6	Ethylcellulose	8.38
7	Polyethylene glycol 6000	1.68
8	Hypromellose	0.83
9	Isopropyl alcohol	Q.S
10	Purified Water	Q.S
IV	**Enteric coating**	
11	Methacrylic acid copolymer (Eudragit L 30 D 55)	93.10
12	Triethyl citrate	18.62
13	Talc	9.31
14	Purified Water	Q.S
	Total	**465.50**

Experimental Design:
In preliminary trials, the process parameters were evaluated for their significance on pellet quality. Finally, Product temperature, atomization air pressure, fluidization air volume and spray rate are found as critical process parameters.

The Face centered central composite design was used to evaluate the effect of critical process parameters on responses/dependent variables (% Fines (Y_1), % Agglomerates (Y_2), Coating efficiency (Y_3) and Assay (Y_4)) of Fenofibric acid DR pellets drug loading pocess. A four factor, three level design is used for exploring quadratic response surfaces and constructing second order polynomial models with Design Expert (Stat-Ease).

Analysis of variance (ANOVA) is inevitably linked to experimental design, which was used to analyze significance of the model and each selected response. It was also generate polynomial equations. The response (Y_1) in each trial was estimated by carrying out a multiple factorial regression analysis using the generalized quadratic model:

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_1X_2 + b_6X_2X_3 + b_7X_3X_4 + b_8X_4X_1 + b_9X_1^2 + b_{10}X_2^2 + b_{11}X_3^2 + b_{12}X_4^2$$

Where Y_1 is the measured response associated with each factor level combination; b_0 is an intercept; b_1 and b_2 are regression coefficients computed from the observed experimental values of Y_1; and X_1, X_2, X_3 and X_4 are the coded levels of independent variables, X_1 X_2, X_2 X_3, X_3 X_4 and X_4 X_1 are the interaction terms and the polynomial terms (X_1^2, X_2^2, X_3^2 and X_4^2) are used to assess the non-linearity.

After fitting the response data in experimental design as in Table 2, the experimental results were analyzed by ANOVA. It demonstrated the various statistical parameters such as b coefficients, F values, p values of model terms and Correlation coefficient (R^2) values. The suitability of model was authenticated by the predicted and adjusted R^2 values [9].

Optimization of Drug loading process:
The independent variables in drug loading process were product temperature, atomization air pressure, fluidization air volume and spray rate. These process variables were studied at three levels (-1, 0, +1). Percentage of fines (Y_1), percentage of agglomerates (Y_2), coating efficiency (Y_3) and assay (Y_4) were selected as responses. The impact of each selected process parameter on responses were studied and optimized individually.

Evaluation of Fenofibric acid DR Pellets:
Percentage of fines and percentage of agglomerates were determined using following formulae

% Fines = (Weight of passes (g)/ Total weight of pellets (g)) X100

% Agglomerates = (Weight of retains (g)/ Total weight of pellets (g)) X100

Micromeritic properties:
Bulk density (BD), tapped density (TD) and Hausner ratio (HR) of pellets were determined [10]. BD and TD were determined by USP method I using a Tapped density tester.

Bulk density = Weight of the sample (g)/ Untapped volume (ml)

Tapped density = Weight of the sample (g)/ Tapped volume (ml)

Hausner ratio were calculated using following formulae

Hausner ratio = TD / BD

Where, TD and BD are tapped and bulk densities.

Assay:
Fenofibric acid drug loaded pellets equivalent to 135mg of Fenofibric acid were transferred into 100mL volumetric flask, added 70mL of methanolic NaOH and sonicated for 15minutes with intermittent shaking. Made up the volume with methanolic NaOH. The solution was filtered through 0.45µ nylon membrane filter. Transfer 5mL of this solution into a 50mL volumetric flask and made up the volume with diluent (Acetonitrile:pH 2.5 buffer = 700:300). The solution was filtered through 0.45µ nylon membrane filter.
The following chromatographic conditions were employed for analysis:
Column : Kromosil 100, C18, 250 x 4.6 rnm, 5 pm or equivalent.
Injection volume : 20µL
Flow rate : 1.0 mL/min.
Detector : UV, 286nm
Run time : 10 minutes

Calculations:
Assay of Fenofibric acid:

$$= \frac{A_T}{A_S} \times \frac{W_S}{25} \times \frac{5}{50} \times \frac{100}{W_T} \times \frac{50}{5} \times \frac{100}{LC} \times P \times 0.756$$

Where,
A_T = Peak area of Choline fenofibrate obtained from the Sample Solution.

A_S = Average Peak area of Choline fenofibrate obtained from the standard Solution
W_S = Weight of Choline fenofibrate working standard taken in mg
W_T = Weight of sample taken in mg
P= Potency of Choline fenofibrate working standard used (on as is basis)
LC = Label claim
0.756 = Mol. Wt of fenofibric acid/ Mol. Wt of Choline Fenofibrate

***In vitro* drug release studies:**
The Fenofibric acid DR pellets equivalent to 135mg Fenofibric acid were accurately filled into size 0 hard gelatin capsules and evaluated for in vitro drug release studies, which were performed using USP Type II dissolution test apparatus. The stirring speed of 50 rpm, and the temperature was maintained at 37°C±0.5°C [11]. These conditions were kept constant for all dissolution studies. The study was carried out in 500 mL of 0.05M sodium phosphate buffer pH 3.5 for 120min followed by 900 mL of 0.05M sodium phosphate buffer pH 6.8 at 30, 60, 90, 120, 240 and 360 min. 10ml of sample was withdrawn periodically and replaced with equal volume of fresh dissolution medium. The collected samples were filtered through 0.45µ nylon membrane filter and analyzed to assess the % drug dissolved by employing same chromatographic conditions as that of assay.
The % labeled amount of Choline fenofibrate dissolved at respective time intervals (Dn) was estimated from following formulae:

Acid stage:

$$= \frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{3}{100} \times \frac{500}{W_T} \times \frac{100}{LC} \times P \times 0.756$$

Buffer stage:

$$= \frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{3}{100} \times \frac{900}{W_T} \times \frac{25}{5} \times \frac{100}{LC} \times P \times 0.756$$

Where,
A_T = Peak area of Choline fenofibrate obtained from the Sample Solution.

A_S = Average Peak area of Choline fenofibrate obtained from the standard Solution
W_S = Weight of Choline fenofibrate working standard taken in mg
W_T = Weight of sample taken in mg
P = Potency of Choline fenofibrate working standard used (on as is basis)
LC = Label claim
0.756 = Mol. Wt of fenofibric acid/ Mol. Wt of Choline Fenofibrate

Drug release kinetics:
The drug release kinetics and mechanism from the formulations were studied by fitting the data obtained from the in vitro release study into several mathematical equations [12] .

RESULTS AND DISCUSSION:

Preparation of pellets:
Fenofibric acid DR pellets were prepared by employing wurster process. The impact of process variables on pellet quality such as % Fines, % Agglomerates, Coating efficiency and Assay in preliminary trials. From the obtained results, batch size (30% occupancy), air distibution plate ('C' Plate), spray nozzele diameter (1 mm) , filter bag (Bonnet bag 200µ), drying time (until reaches the product temperature) were selected.

Product temperature (A), atomization air pressure (B), fluidization air volume (C) and spray rate (D) were identified as high risk variables have a potential impact on pellet quality (% Fines, % agglomerates, coating efficiency and assay). Hence these factors were studied by a four factor, three level face centered central composite experimental design, individually.

Data analysis and model validation
Fitting of data to the model
Four factors with three levels face centered central composite experimental design require 19 experiments, the independent variables and responses for all experimental runs are given in table 2. Models of various responses were obtained using Design Expert (Stat-Ease).

Table 2: Observed responses in Face centered central composite design for Fenofibric acid DR pellets drug loading process.

Independent Variables				Dependent Variables/Responses			
Product temperature (°C) (A)	**Atomization air pressure (kg/cm^2) (B)**	**Fluidization air volume (CFM) (C)**	**Spray rate (g/min) (D)**	**Fines (%w/w) (Y_1)**	**Agglomerates (%w/w) (Y_2)**	**Coating efficiency (%w/w) (Y_3)**	**Assay (%w/w) (Y_4)**
40	1.0	60	6	1.2	3.5	97.7	97
50	0.8	80	6	6.6	0.3	90.5	91.5
40	0.8	60	4	1.6	2.5	95.5	96.4
30	0.8	40	2	0.5	0.5	88.2	89.1
30	0.8	80	2	0.3	0.2	88.9	89.3
40	1.0	60	4	1.1	1.4	97.4	98
50	1.0	60	4	2.7	0.6	95.2	96
40	1.0	60	2	0.3	0.4	92.9	93.3
30	1.2	80	6	2	6.9	89.3	90.1
40	1.2	60	4	2.2	3.4	96.7	97.5
30	1.0	60	4	1.6	4.9	93.5	94.4
40	1.0	60	4	1.3	1.4	97.8	98.7
40	1.0	60	4	1.5	1.1	98	98.5
40	1.0	80	4	2.6	0.5	95.2	96
50	0.8	40	6	2.5	2.9	92.3	92.7
50	1.2	40	2	2.1	0.3	91.7	92.4
30	1.2	40	6	1.2	7.2	86.9	87.3
40	1.0	40	4	0.3	1.3	93.5	94.5
50	1.2	80	2	7.5	0.2	92.9	93.4

The ANOVA result of each response was represented in table 3. Values of probability $p < 0.05$ represent significant model terms. The regression equations carry factors along with coefficients (positive/ negative) which quantify response values. A positive sign of coefficient indicates synergistic effects; whereas negative sign represents an antagonistic effect. After elimination of non significant ($p > 0.05$) coefficients from the obtained results, following correlations for response variables were obtained :

Y_1=36.65226-1.166646*A-0.316429878*C +4.439634146*D + 0.0055625*AC + 0.071875*BC-3.21875*BD + 0.0099268*A^2+ 18.56707317* B^2-0.101829268* D^2

Y_2=8.429695122-0.34019*A +4.993292683*D + 24.14634146* A^2 - 0.00271* C^2

Y_3=51.69193+ 5.75081*D + 1.36875*AB-0.024504065*A^2 - 0.0061260*C^2- 0.375101*D^2

Y_4 = 53.39293+ 6.86189*D+ 1.0875*AB-0.02212*A^2 - 0.005405* C^2- 0.56554878*D^2

All the responses observed for various formulations were fitted simultaneously to first order, second order and quadratic models using Design expert. All the responses were found to follow quadratic model. From the obtained ANOVA results, terms D, AC, BC, A^2 and B^2 have positive impact on Y_1,whereas C, BD and D^2 have a negative impact on Y_1. Terms D and A^2 shown a positive impact on Y_2, whereas A and C^2 have a negative impact on Y_2. D and AB shown a positive impact on Y_3, whereas A^2, C^2 and D^2 have a negative impact on Y_3. D and AB shown a positive impact on Y4, whereas A^2, C^2 and D^2 shown a negative impact on Y_4.

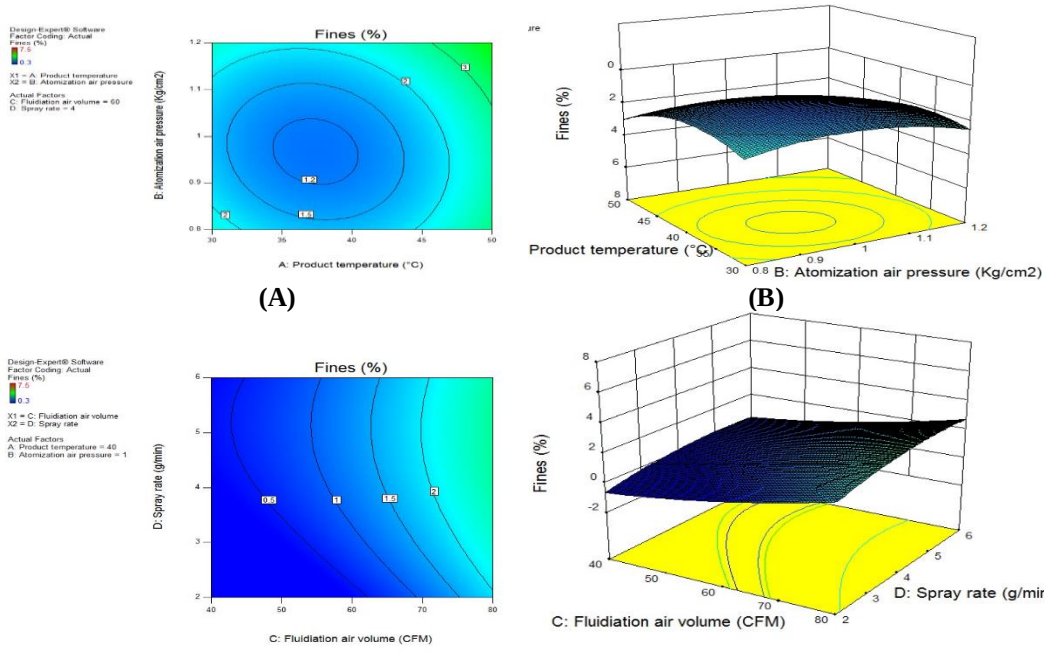
Table 3: Summary of ANOVA results - Fines, Agglomerates, Coating efficiency and Assay

	DF	SS	MS	F	P	R^2
Fines (Y_1 (%w/w))						
Model	14	66.42	4.74	129.43	0.00014	0.998
Lack of Fit	2	0.067	0.033	0.833		
Agglomerates (Y_2 (%w/w))						
Model	14	86.79	6.20	22.01	0.00437	0.987
Lack of Fit	2	1.066	0.533	17.773		
Coating efficiency (Y_3 (%w/w))						
Model	14	213.53	15.25	23.18	0.00395	0.988
Lack of Fit	2	2.445	1.222	13.097		
Assay (Y_4 (%w/w))						
Model	14	208.57	14.90	21.76	0.00446	0.987
Lack of Fit	2	2.479	1.239	9.533		

*ANOVA: Analysis of variance; df: Degrees of Freedom; SS: Sum of squares; MS:Mean sum of squares; *p<0.05 considered as significant.*

Contour and three dimensional response surface plot analysis

The design expert software (Stat-Ease) generated the contour and three dimensional surface plots are presented in Fig 1-4, which are very useful to study the interaction effects of the factors on responses. This type of the plot visualizes the effects of two factors on the response at a time. In all the cases, the factors exhibited a non linear relationship with responses Y_1, Y_2, Y_3 and Y_4.



(A) **(B)**

(C) **(D)**

Fig.1: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Product temperature, Atomization air pressure, Fluidization air volume and Spray rate) on percentage of fines.

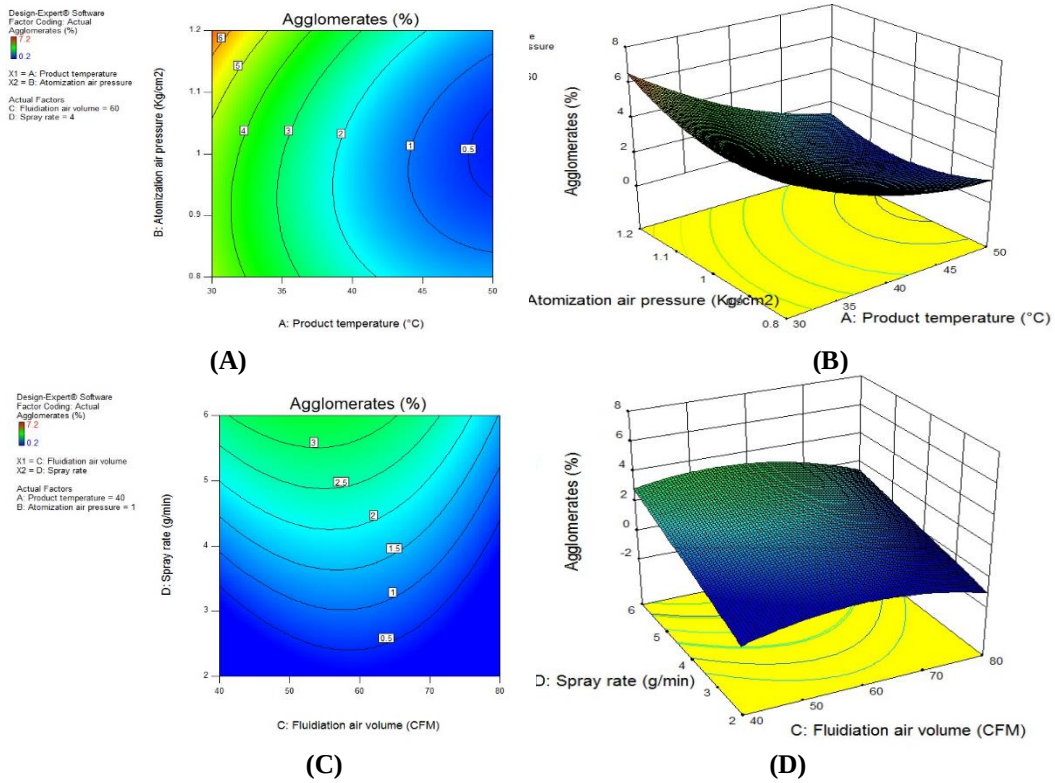


Fig.2: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Product temperature, Atomization air pressure, Fluidization air volume and Spray rate) on percentage of agglomerates.

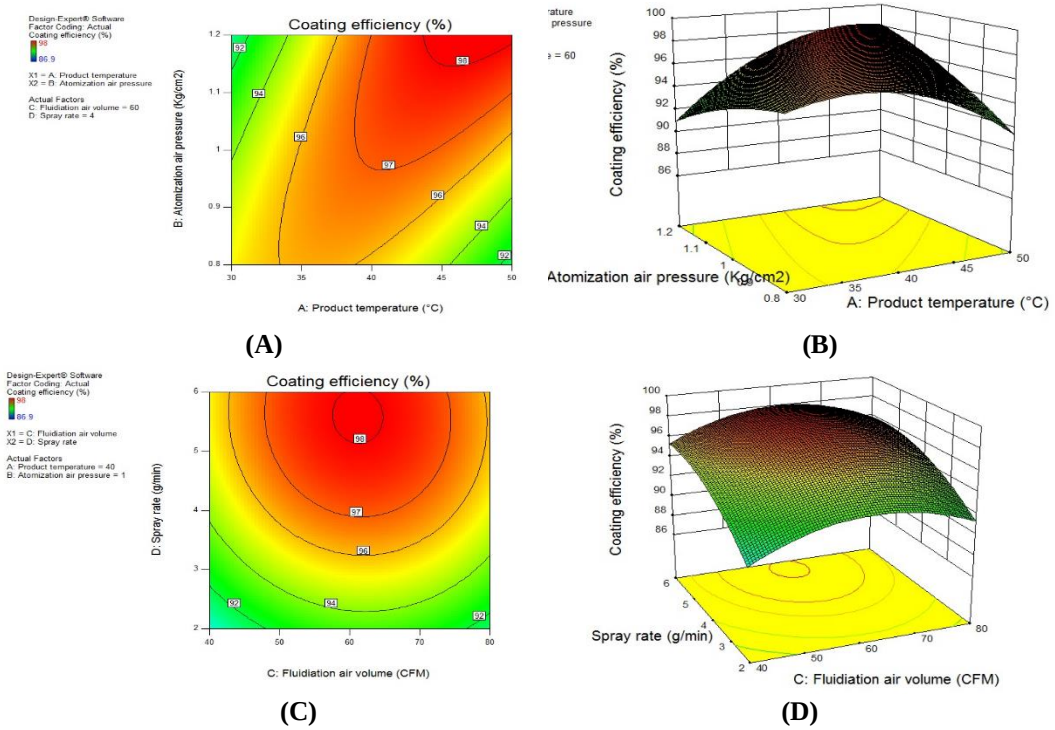


Fig.3: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Product temperature, Atomization air pressure, Fluidization air volume and Spray rate) on coating efficiency.

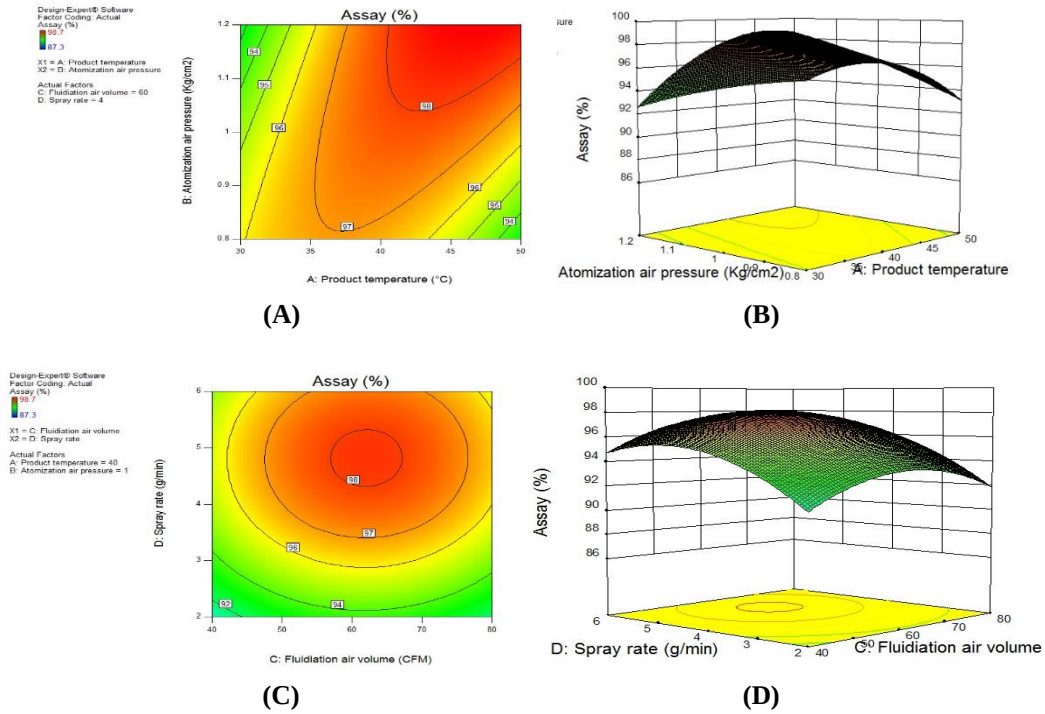


Fig. 4: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Product temperature, Atomization air pressure, Fluidization air volume and Spray rate) on assay.

The % fines, % agglomerates,Coatig efficiency and assay from all the batches ranges from 0.3-7.5%w/w, 0.2 – 7.2%w/w, 86.9 – 98.0%w/w and 87.3 – 98.7 %w/w respectively.

Among the studied range, the product temperature of 40°C ± 3°C, atomization air pressure of 0.8 -1.2 kg/cm^2, Fluidization air volume of 50 -65 cfm and spray rate of 2-6 g/min were selcted as optimum process parameters for drug loading process to obtain predetrmined specifications (Table 4).

Table 4: The Criterion for Numerical Optimization

Parameters	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
Product temperature (A)	is target = 40	37	43	1	1	3
Atomization air pressure (B)	is target = 1	0.8	1.2	1	1	3
Fluidiation air volume (C)	is in range	50	65	1	1	3
Spray rate (D)	is target = 4	2	6	1	1	3
Fines (Y_1)	minimize	0.3	5	1	1	3
Agglomerates (Y_2)	minimize	0.2	5	1	1	3
Coating efficiency (Y_3)	is in range	90	100	1	1	3
Assay (Y_4)	is in range	95	105	1	1	3

Solutions							**Desirability**
Independent Variables					**Response Variables**		
Code	**A**	**B**	**C**	**D**	**Experimental values[a]**	**Predicted Values**	
Optimized formulation	40	1	60	4	Y_1	1.30 ± 0.20	0.658	0.914
					Y_2	1.30 ± 0.17	1.690	
					Y_3	97.73 ± 0.31	96.29	
					Y_4	98.4 ± 0.36	96.99	

[a]Mean±SD, SD= Standard deviation;

Same process parameters were adopted for both Extended releasse (ER) coating and enteric coating process, except product temperature. 36°C ± 2°C and 30°C ± 2°C are selcted as product temperature for ER coating and enteric coating processes respectively, as recommended by excipient manufacturer.

Evaluation of pellets

Micromeretic properties

The bulk and tapped density of batches ranges from 0.64 – 0.69 g/cc & 0.67 -0.71 g/cc respectively. The Hausner's ratio values (1.03 -1.05) indicated good flow properties according to USP limits.

Assay

The assay of the all formulations was tested and results were found in the range of 87.3 – 98.7 %w/w. Assay of the optimized formulation was observed to be 98.7%.

***Invitro* drug release studies:**

Drug release from the optimized formulation was well within the predetermined specifications (Fig. 5).

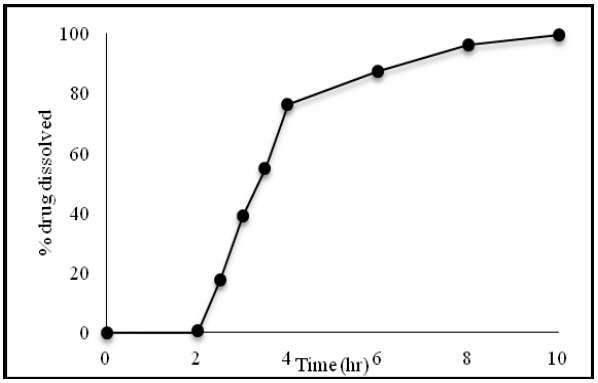


Fig. 5: Dissolution profile of the optimized formulation

Drug release kinetics

The dissolution data of optimized formulation fitted into kinetic models, the obtained results concluded that the drug release followed the first order kinetics as r^2 values were higher for first order model (0.954) than zero order model (0.847). The n value is greater than 0.45 (0.580); hence the mechanism of drug release was non-fickian diffusion.

CONCLUSION:

Fenofibric acid delayed release pellets were successfully fabricated by fluid bed coating technology. Impact of various process variables on drug layering process was assessed by using response surface methodology. This investigation revealed that independent variables had a significant impact on the measured responses. The quantitative effect of these factors at different levels on responses could be predicted by polynomial equations. Linearity observed between the actual and predicted values of the response variables indicated that analytical ability of the selected design. From the obtained results, 40°C ± 2°C as product temperature, 0.8-1.2 kg/cm^2 as atomization air pressure, 50-65 cfm as fluidization air volume and 2-6 g/min as spray rate were selected as the operating ranges for robust coating process, desired yield and quality of the product. The optimized batch showed 98.7% assay and drug release was well within the predetermined specifications (Similarity factor (F2) value - 71). Micromeritic properties of these pellets exhibited excellent flow properties, which are crucial to attain the uniformity of dosage units in capsule filling. The optimized formulation can be used as an alternative to the marketed formulation. Hence, the applicability of response surface methodology to optimize the process variables in the fabrication of Fenofibric acid DR pellets is apt enough.

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