WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 3, 1574-1588. Research Article ISSN 2277– 7105

DEVELOPMENT OF FENOFIBRIC ACID DRUG LOADED PELLETS BY EXTRUSION SPHERONIZATION: A STATISTICAL DESIGN FOR OPTIMIZATION OF PROCESS VARIABLES

Bala Vishnu Priya Mukkala[a]*, Gopala Krishna Murthy Talasila[b] and Prameela Rani Avula[c]

[a]Formulation Research and Development, RA Chem Pharma Ltd, Hyderabad, Telangana, India.

[b]Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla, Guntur, Andhra Pradesh, India.

[c]Department of Pharmaceutics, Acharya Nagajuna University, Guntur, Andhra Pradesh, India.

Article Received on
18 December 2017,

Revised on 08 Jan. 2018,
Accepted on 29 Jan. 2018

DOI: 10.20959/wjpr20183-10987

***Corresponding Author**
Bala Vishnu Priya Mukkala
Formulation Research and Development, RA Chem Pharma Ltd, Hyderabad, Telangana, India.

ABSTRACT

The objective of the present investigation was to develop a drug loaded pellets of Fenofibric acid employing Extrusion spheronization process. This study evaluates the impact of certain process variables of extrusion spheronization technique in the feasability of producing Fenofibric acid drug loaded pellets. Impact of various process variables were assessed by using statistical interpretation such as ANOVA. A 3^3 (three factor, three level) face centered central composite design was employed to study the effect of independent variables on dependent variables. The selected process variables such as % Fluid uptake, Spheronizer speed and Spheronization time were studied, as well as their influences on the properties of Bulk density, % fines and % retains were determined. Optimization was done by fitting experimental data to the software program (Design Expert). The design space for process variables and its influence on responses was developed. Low fluid uptake, Higher spheronization speed and time leads to fines generation as well as high fluid uptake, low spheronization speed and time results in agglomerates. Water content and spheronizer speed interaction influence the sphere density. Fabricated pellets were characterized for various physico-chemical parameters. The optimized formulation showed desired drug release profile. The information acquired in this

study recommends that the extrusion spheronization process can be effectively intended to develop drug loaded pellets of Fenofibric acid.

KEYWORDS: Fenofibric acid, Pellets, Extrusion, Spheronization, CCD.

1. INTRODUCTION

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Now a days, the multiparticulate drug delivery systems are notably relevant for attaining controlled or delayed release oral formulations with reduced risk of local irritation, low risk of dose dumping, increased bioavailability and less inter and intra subject variability.

Extrusion spheronization process is one of the most promising techniques for fabrication of pellets, as it provides the pellets of uniform particle size, narrow size distribution, good flowability, high strength and low friability. Extrusion- spheronization is a multiple-step compaction process. The main objective of extrusion spheronization is to provide pellets of uniform size with high drug loading capacity.[1-3]

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).[4]

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. 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. Central composite design is one type of RSM design enables, all factors to be varied simultaneously, allowing quantification of the effects caused by independent variables and interactions between them. Face centered central composite design contribute relatively high quality predictions over the entire design space and do not require using points outside the original factor range. Hence face centered central composite design was selected as design of experiment.[5]

Fenofibrate is a third-generation fibric acid derivative indicated for the treartment of primary hyper-lipidemia or mixed dyslipidemia. Choline fenofibrate is a newly developed choline salt

of fenofibric acid and is more hydrophilic than fenofibrate rapidly absorbed throughout the gastrointestinal tract.[6,7] The literature survey reveals that the pellets were prepared by fluid bed process and mini tablets of Fenofibric acid.[8,9] Hence, the present investigation aimed to fabricate a drug loaded pellets of Fenofibric acid by employing extrusion spheronization process. There are no reported studies available as present investigation. Preliminary studies were carried out to freeze the process parameters which do not have any impact on product quality, such as wet mixing time, extruder speed, extruder feed rate and drying time. However, % fluid uptake, spheronizer speed and spheronization time are found as critical process parameters.

2. MATERIALS AND METHODS

2.1 Materials

Choline fenofibrate was obtained from RA CHEM Pharma Ltd., Hyderabad as gift sample, Microcrystalline cellulose (MCC PH101) (FMC Biopolymer, Mumbai), 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.

2.2 Preparation of drug loaded pellets by Extrusion-spheronization process

2.2.1 Priliminary experimentation

Initial studies were conducted to establish viable ranges for experimental variables. Process variables examined included all controllable equipment parameters. For the extruder, the die orifice screen can be changed to produce extrudates of various diameters. Varying the speed of extruder feeder drive (which controlls the feed rate) and extruder drive (which forces material through the extruder screen) results in different extrusion pressure, and thus pellet densification. Spheronizer crosshatch plate groove size can be selected based on the target particle size. The shape of the pellets is influenced by spheronizer speed and residence time, hence these two process parameters were selected as an experimental variables.

Water is critical variable which acts as a binder during wet granulation, a lubricant during extrusion and a plasticizer during spheronization. From the preliminary trials, the effective water concentration was found to be a function of MCC concentration. High water levels with low MCC concentrations resulted in over wetted masses that could not be extruded or

spheronized. On the other hand, with high MCC and low water produced dry masses which could not be extruded. Hence, the impact of % fluid uptake was studied by varying the concentration between 17 to 23%w/w.

Throughout the study, the same composition (Table 1) was used, mainly consisting of Drug, MCC PH 101 and povidone. Water was used as granulating agent. Preparation of drug loaded pellets by extrusion and spheronization include sequence of multiple steps, as follows:

Wet granulation

Choline Fenofibrate, PVP K 30 and Microcrystalline cellulose PH 101 were sifted and allowed for dry mixing for 10 minutes in Rapid mixer granulator (RMG). Binder was added to the dry mix material and subjected for kneading. Wet mass was discharged from RMG.

Extrusion-spheronization

Wet mass was passed from 0.8mm die screen of extruder at an extruder speed of 30-40 rpm. Extrudes were transferred immediately to the spheronizer fitted with cross-hatched plate (groove size-1mm) with a spheronizer rotational speed of 500, 1000 and 1500 rpm. The residence time in the spheronizer varied between 1 to 5 minutes.

Drying and Sizing

Pellets were collected and subjected for drying at 40°C-50°C till attain LOD not more than 2.5%w/w. The dried spheroids were sized to separate the desired size.

2.2.2 Preparation of Fenofibric acid delayed release (DR) pellets

Fenofibric acid DR Pellets were prepared by employing bottom – spray fluid bed (Wurster) coating process (Glatt GPCG 1.1). The hydro alcoholic (IPA : Water 80:20) extended release (ER) coating solution was coated over the drug loaded pellets prepared by extrusion spheronization process, using 1.0 mm spray nozzle with a spray rate of 4-8 g/min, 1.0-1.2 Kg/cm^2 of atomization air pressure, 50-65 cfm of air volume and at a product temperature of 34-38°C. 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 2-6 g/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.

Table 1: Composition of the Fenofibric acid delayed release pellets.

S.No.	Ingredient	mg/capsule
	Drug loading	
1.	Choline fenofibrate	178.53
2.	Microcrystalline cellulose (MCC PH101)	143.03
3.	PVP K 30	13.97
4.	Purified water	QS
	Extended Release Coating	
5.	Ethylcellulose	7.45
6.	Polyethylene glycol 6000	1.49
7.	Hypromellose	0.74
8.	Isopropyl alcohol	Q.S
9.	Purified water	Q.S
	Enteric coating	
10.	Methacrylic acid copolymer (Eudragit L 30 D 55)	93.10
11.	Triethyl citrate	18.62
12.	Talc	9.31
13.	Purified Water	Q.S
	Capsule fill weight	**465.50**

2.2.3 Experimental design

Experimental design is applied to reduce the number of trials, and is needed to attain the maximum information on the product properties. The first step of experimental design is the selection of parameters and the choice of responses. The variables (i.e. factors) of drug loading process included the % fluid uptake, spheronizer speed and spheronization time. The bulk density, percentage fines and percentage retains were used separately as the responses in the mathematical modeling. This would help in the identification of the most significant factor influencing the properties. A mathematical model was generated between the factors and responses, for determining the levels of factors, which yield optimum responses.

The Face centered central composite design was used to evaluate the effect of critical process parameters on responses/dependent variables (Bulk density (Y_1), % Fines (Y_2), and % agglomerates (Y_3)) of Fenofibric acid drug loaded pellets. A three 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:

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_2X_3 + b_6X_3X_1 + b_7X_1^2 + b_8X_2^2 + b_9X_3^2$$

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 and X_3 are the coded levels of independent variables, X_1 X_2, X_2 X_3 and X_3 X_1 are the interaction terms and the polynomial terms (X_1^2, X_2^2 and X_3^2) are used to assess the non-linearity.

After fitting the response data in experimental design, 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.[10]

2.2.4 Optimization of Extrusion-sphronization process

The independent variables in extrusion-spheronization process were % fluid uptke, spheronizer speed and spheronization time. These process variables were studied at three levels (-1, 0, +1), the +1 and –1 levels were selected based on preliminary experiments and product characteristics. Percentage fluid uptake was selected based on process feasibility, spheronizer speed and spheronization time were adjusted based on the core size. Bulk density (Y_1), Percentage of fines (Y_2) and percentage of retains (Y_3) were selected as responses. The impact of each selected process parameter on responses were studied and optimized individually.

2.2.5 Characterization of Fenofibric acid DR Pellets

2.2.5.1 Evaluation of Fenofibric acid drug loaded pellets

2.2.5.1.1 Percentage of fines and percentage of retains were determined using following formulae

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

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

2.2.5.1.2 Bulk desnsity[11]

Bulk density of drug loaded pellets was determined using following formulae

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

2.2.5.2 Evaluation of Fenofibric acid DR pellets

2.5.2.1 Assay

Fenofibric acid DR 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 formula:

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

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

2.5.2.2 In vitro drug release studies[12]

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. 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, 240,360 and 480min. 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:

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

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

2.5.2.3 Drug release kinetics[13]

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.

3. RESULTS

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

Independent Variables			Dependent Variables/Responses		
Fluid uptake (%w/w) (A)	**Spheronizer speed (rpm) (B)**	**Spheronization time (minutes) (C)**	**Bulk density (g/mL) (Y_1)**	**Fines (%w/w) (Y_2)**	**Retains (%w/w) (Y_3)**
20	1500	1	0.64	7	4
17	1500	3	0.7	20	2.5
20	1000	3	0.66	2	3
23	1000	1	0.6	1.5	14
17	1000	1	0.72	19	7
20	1000	3	0.65	3	2
17	1000	5	0.69	21	1.5
20	500	1	0.64	2.5	7.5

17	500	3	0.71	18	2
20	1000	3	0.65	3	2
23	1500	3	0.62	1.9	13
20	500	5	0.64	3.1	6.2
23	1000	5	0.63	1.5	18
23	500	3	0.61	1	16

Table 3: ANOVA results for predicting process variables.

	DF	SS	MS	F	P	R^2
Bulk Density (g/mL) (Y_1)						
Model	9	0.018068	0.00201	109.505	0.00003	0.9949
Lack of Fit	3	0.000025	0.0000083	0.25	0.85757	
Fines %w/w (Y_2)						
Model	9	843.525	93.725	114.4617	0.00003	0.9952
Lack of Fit	3	3.4275	1.1425	3.4275	0.23401914	
Retains (%w/w) (Y_3)						
Model	9	450.587	50.065	81.3628	0.000069	0.9932
Lack of Fit	3	2.41	0.8033	2.41	0.30672603	

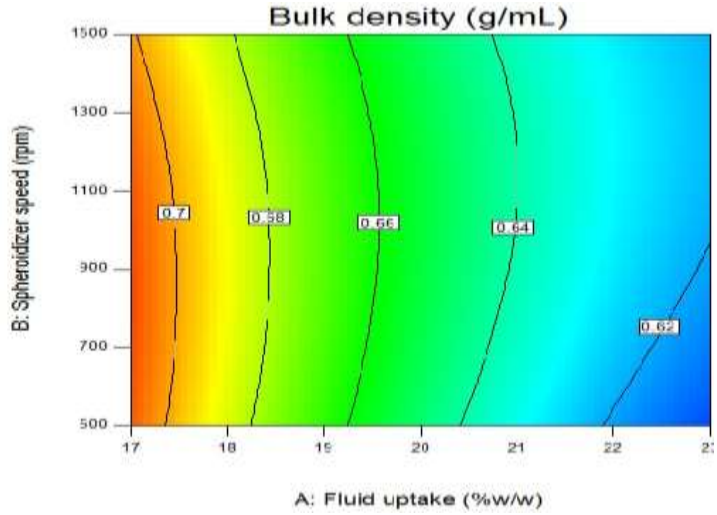
ANOVA: Analysis of variance; df: Degrees of Freedom; SS: Sum of squares; MS:Mean sum of squares; *p<0.05 considered as significant.

Table 4: The Criterion for Numerical Optimization.

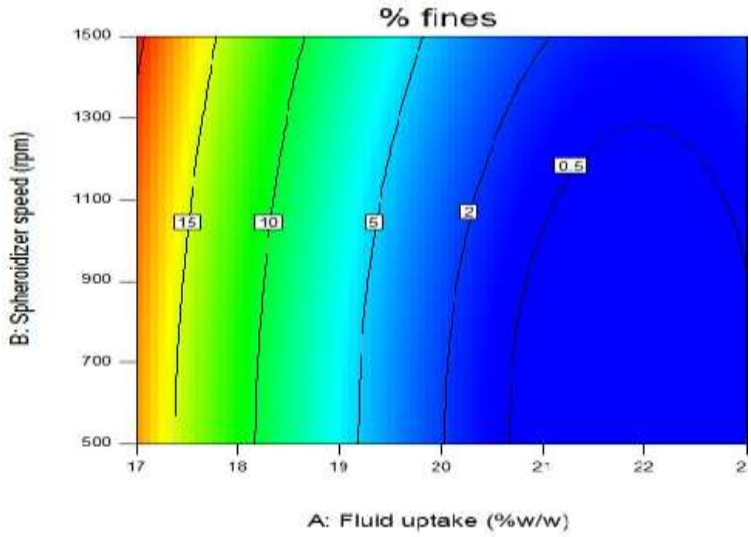
Parameters	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
Fluid uptake (%w/w) (A)	Is in range	17	23	1	1	1
Spheronizer speed (rpm) (B)	Is target = 1000	500	1500	1	1	1
Spheronization time (minutes) (C)	Is in range	1	5	1	1	1
Bulk Density (g/mL) (Y_1)	Maximize	0.60	0.67	1	1	1
Fines (%w/w) (Y_2)	Is in range	0	5	1	1	1
Retains (%w/w) (Y_3)	Is in range	0	5	1	1	1

Solutions						**Desirability**
Independent Variables				**Response Variables**		
Code	**A**	**B**	**C**	**Experimental values[a]**	**Predicted Values**	
Optimized formulation	20	1000	3	Y_1	0.653 ± 0.006	0.664	0.955
				Y_2	2.667 ± 0.577	5.0	
				Y_3	2.333 ± 0.577	1.260	

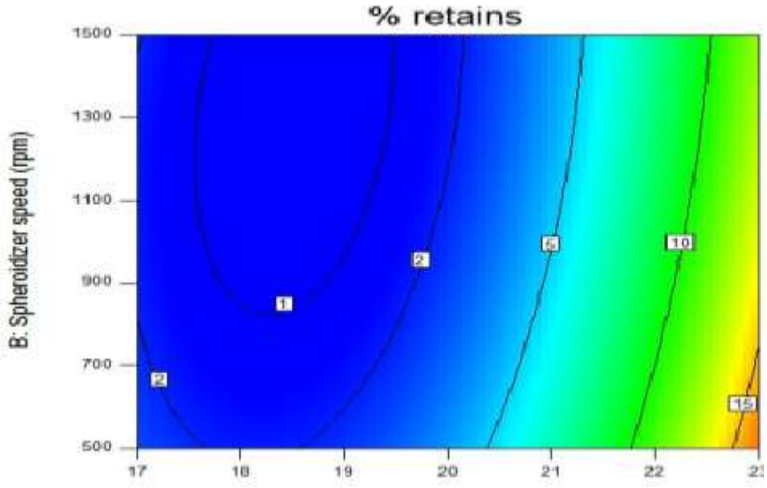
[a]Mean±SD, SD= Standard deviation;


Bulk density (g/mL)
B: Spheroidizer speed (rpm)
A: Fluid uptake (%w/w)
0.7
0.58
0.66
0.64
0.62

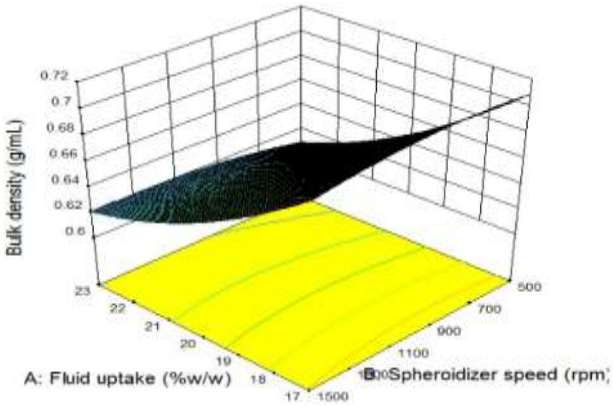
(A)


% fines
B: Spheroidizer speed (rpm)
A: Fluid uptake (%w/w)
15
10
5
2
0.5

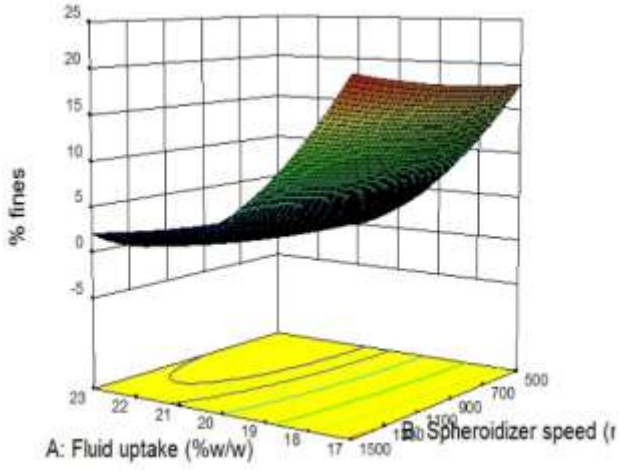
(B)


% retains
B: Spheroidizer speed (rpm)
1
2
5
10
15

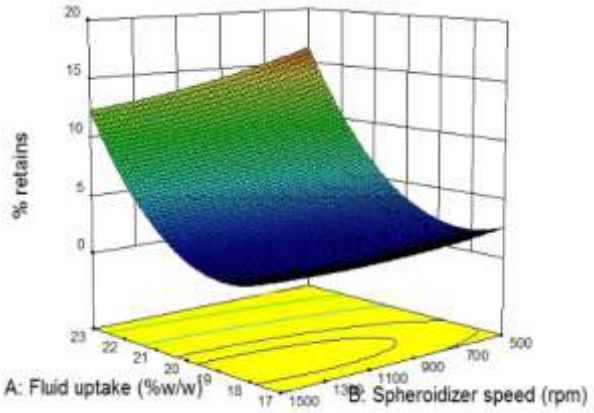
(C)



(D)



(E)



(F)

Fig 1: Contour plots (A,B,C) and response surface plots (D,E,F) showing the impact of factors (% Fluid uptake, Spheronizer speed & Spheronization rpm) on Bulk density, %Fines & % Retains.

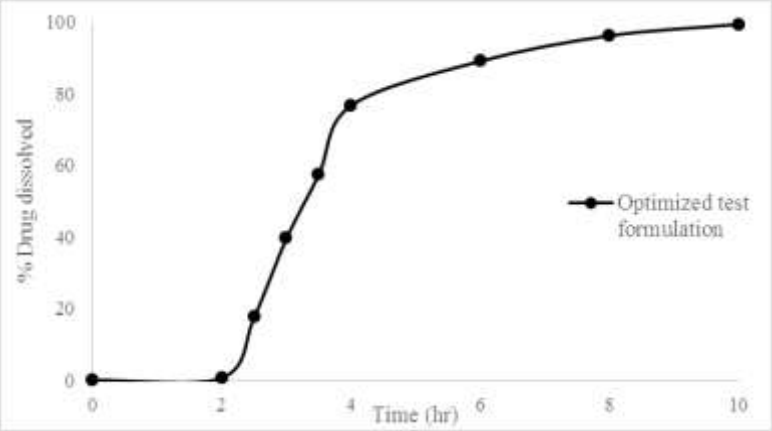


Fig 2: Dissolution profile of the optimized formulation.

4. DISCUSSION

4.1 Preparation of drug loaded pellets by Extrusion-spheronization process

Fenofibric acid drug loaded pellets were prepared by employing Extrusion-spheronization process. The impact of process variables on pellet quality such as bulk density, % fines and % retains evaluated in preliminary trials. From the obtained results, binder addition time (3 minutes), wet mixing time (3 minutes), extruder speed (30-40 rpm), extruder screen diameter (0.8mm), spheronizer friction plate groove size (1 mm) and drying time (until reaches the desired LOD) were selected.

% Fluid uptake (A), Spheronizer speed (B) and spheronization time (C) were identified as high risk variables have a potential impact on pellet quality (Bulk density, % Fines and % retains). Hence these factors were studied by a three factor, three level face centered central composite experimental design, individually.

4.2 Data analysis and model validation

4.2.1 Fitting of data to the model

Three factors with three levels face centered central composite experimental design require 14 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). The ANOVA results of each response were 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=1.6763-0.0795*A +0.0025*AC+0.00134*A^2

Y_2=363.727-33.478*A+0.00311*B+0.7727*A^2

Y_3= 229.262 -23.030*A+0.00478*B+0.3958*AC + 0.611* A^2+0.574* C^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 (Table 3), terms AC and A^2 have significant positive impact on Y_1.Terms B and A^2 shown a positive impact on Y_2. Terms B, AC, A^2 and C^2 shown a positive impact on Y_3, whereas term A shown significant negative impact on Y_1, Y2 and Y_3.

4.2.2 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 Figure 1, 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 curvi-linear relationship with responses Y_1, Y_2 and Y_3.

Among the studied range, the fluid uptake of 20 %w/w, spheronization speed of 1000 rpm and spheronization residence time of 3 minutes were selected as optimum process parameters for drug loading by Extrusion spheronization process.The results obtained from the formulation executed with optimized formulation and process variables were bulk density – 0.65g/mL, % fines – 2.6 %w/w and % retains -2.6 %w/w.Assay of the optimized formulation was observed as 99.7%w/w.

4.3 Characterization of Fenofibric acid DR pellets

4.3.1 Eavaluation of Fenofibric acid drug loaded pellets

4.3.1.1 Percentage fines and retains

Percentage fines and retains from all the batches ranges from 1.0 - 20%w/w and 1.5 – 18%w/w respectively.

4.3.1.2 Bulk density

The bulk density of the drug loaded pellets from all the batches ranges from 0.60 – 0.72 g/mL.

4.3.2 Eavaluation of Fenofibric acid DR pellets

4.3.2.1 Assay

The assay of the all formulations was tested and results were found in the range of 97.6 – 100.2%. Assay of the optimized formulation was observed as 99.7%w/w.

4.3.2.2 *In vitro* drug release studies and Drug release kinetics

The dissolution profile of optimized formulation represented in Figure 2. 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 (0.985) than zero order model (0.746). The n value is greater than 0.45 (0.584); hence the mechanism of drug release was non-fickian diffusion.

5. CONCLUSION

Fenofibric acid drug loaded pellets were successfully fabricated by extrusion spheronization technology. Impact of various process variables on drug loading by extrusion spheronization 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. Low fluid uptake, Higher spheronization speed and time leads to fines generation as well as high fluid uptake, low spheronization speed and time results in agglomerates. Water content and spheronizer speed interaction influence the sphere density. From the obtained results, 20%w/w as fluid uptake, spheronization speed of 1000 rpm and 3 minutes as spheronization residence time were selected as the operating ranges for robust process, desired yield and quality of the product. The fabricated delayed release pellets using fenofibric acid drug loaded pellets prepared by extrusion spheronization process shown desired drug release profile. The optimized batch showed 99.7%w/w of assay. Hence, the applicability of response surface methodology to optimize the process variables in the fabrication of Fenofibric acid drug loaded pellets by extrusion spheronization is apt enough.

6. ACKNOWLEDGEMENTS

Authors are thankful to RA Chem Pharma Ltd, Hyderabad for providing the gift sample of Choline fenofibrate, excipients and facilities to carry out the research work.

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