UK Journal of Pharmaceutical and Biosciences
Available at www.ukjpb.com
ISSN: 2347-9442

Multi-particulate Drug Delivery Systems of Fenofibric Acid: Optimization of Formulation Using Statistical Experimental Design

Bala Vishnu Priya Mukkala[1*], Murthy T.E.G.K[2], Prameela Rani Avula[3]

[1]Formulation research and development, RA Chem Pharma Ltd, Hyderabad-500076, Telangana, India
[2]Department of pharmaceutics, Bapatla College of Pharmacy, Bapatla, Guntur-522101, Andhra Pradesh, India
[3]Department of pharmaceutics, Acharya Nagajuna University, Guntur-522510, Andhra Pradesh, India

Article Information
Received 02 November 2017
Received in revised form 28 Jan 2018
Accepted 1 February 2018

***Keywords*:**
Fenofibric acid,
Pellets,
Modified drug delivery systems,
Central composite design

Corresponding Author:
E-mail:
vishnupriya.mukkala@gmail.com
Mob.: xxxxxxxxxx

Abstract

The objective of the present research work was to develop a multi-particulate modified release system of Fenofibric acid using Wurster (Bottom spray fluid bed coating) process. Impact of various formulation variables was 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 (concentration of ER Polymer, plasticizer and pore former), on dependent variables (drug release at 2.5^{th} h & 6^{th} h). Optimization of the formulation variables was done by fitting experimental data to the software program (Design Expert). The design space for formulation variables was developed. Fabricated pellets were characterized for various physico-chemical parameters. *In vitro* release data of the optimized formulation was fitted into various kinetic equations. The optimized formulation showed a desired drug release at both 2.5^{th} h and 6^{th} h as 17.5 ± 2.28% & 87.1 ± 0.75% respectively. The drug release from the capsules followed first order kinetics and controlled by non fickian transport. The information acquired in this study recommends that the multi-particulates of Fenofibric acid can be effectively intended to give a delayed release of Fenofibric acid and thus enhanced bioavailability.

1 Introduction

Pharmaceutical research and development are increasingly focusing on advance drug delivery systems, which enhance desirable therapeutic intent 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.

Bottom spray fluid bed (Wurster) process is one of the most favourable techniques for fabrication of pellets, as it promotes uniform coating, which leads to an systematic and predictable drug release[1-3].

Quality by design (QbD) is a comprehensive 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 determine the critical material attributes (CMAs) and critical process parameters (CPPs) that influencing the predefined critical quality attribute (CQAs)[4].

Response surface methodology (RSM) is one of the desired methods in the development and optimization of drug delivery systems. Three level factorial design, Central composite design (CCD), D-optimal design and Box Behnken design are the various types of RSM designs available for statistical optimization of the formulations. Central composite design is one type of RSM design allows, 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 treatment of primary hyper-lipidemia or mixed dyslipidemia. Fenofibrate is a prodrug and requires enzymatic cleavage via first pass metabolism, hydrolysis at the ester bond to form fenofibric acid, which is the active metabolite. Insolubility of fenofibrate in water negatively impact the in vivo performance of the product. Hence, novel fenofibrate formulations were developed with different approaches to overcome the challenges with solubility, to prevent the recrystallization of drug in acidic pH and to improve bioavailability. Choline fenofibrate is a choline salt of fenofibric acid and is more hydrophilic than fenofibrate. It does not need first pass hepatic metabolism to become active, as it dissociates to free fenofibric acid within the gastrointestinal tract and rapidly absorbed throughout the gastrointestinal tract [6,7].

The present investigation aimed to fabricate a Fenofibric acid delayed release (DR) pellets. Preliminary trials were executed with various concentrations of binder (1 -3%w/w) and various types and concentration of extended release polymers (Eudragit RSPO, Eudragit RLPO and Ethocel) and delayed release coating polymers (Eudragit L30 D 55 & HPMC AS). Optimization of the Fenofibric acid DR pellets was done by employing face centered central composite design as optimization technique, with constraints on release of drug after 2.5thh (12-22%). The independent variables for the present study were concentration of release retardant polymer (Ethocel), plasticizer (Triethyl citrate) and pore former (HPMC E5). The dependent variables studied were drug release at 2.5thh (12-22%) and 6thh (Not less than 75%).

2 Materials and methods

2.1 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), Eudragit RSPO (Evonik, Mumbai), Eudragit RLPO (Evonik, Mumbai), Ethocel 45 cps (Colorcon, Goa), Eudragit L 30 D55 (Evonik), HPMC AS (Shin Etsu, Mumbai), 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 Methods

2.2.1 Drug-excepient compatibility studies

Choline fenofibrate and selected excipients were subjected for drug excipient compatibility study. The drug and individual excipients were intimately mixed in equal parts by weight and filled in glass vials stoppered with teflon plugs and sealed with aluminium seals. These samples were kept in incubators at 40°C/75%RH. Samples were analyzed for the solid state property of the drug in the blended mixtures was ascertained using differential scanning colorimeter (DSC) at initial and one month (40°C/75%RH).

2.2.2 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, 0.8-1.0 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 collects the desired portion.

2.2.3 Experimental design

In preliminary trials, the formulation variables in each step of the manufacturing process were evaluated for their significance by ANOVA. Finally, found that the type & concentrations of ER coating polymer, plasticizer concentration and pore former concentration had significant impact on drug release of prepared pellets.

The Face centered central composite design was used to evaluate the effect of independent variables (ER polymer, plasticizer & pore former concentration) on responses/dependent variables (Drug release at 2.5th h (Y_1) & 6th h (Y_2)) of Fenofibric acid DR 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:

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

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_1X_2, X_2X_3,X_3X_4 and X_4X_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, 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^2values[8].

2.2.4 Optimization of ER coating composition

The independent variables in extended release coating were concentration of ER polymer (Ethyl cellulose), plasticizer (Triethyl citrate) and pore former (HPMC E5). Three variables were studied at three levels (-1, 0, +1). Percentage of drug release at 2.5thh (Y_1) and percentage of drug release at 6th h (Y_2) were selected as responses. The impact of each selected ER polymer, plasticizer and pore former concentration on responses were studied and optimized individually.

2.2.5 Evaluation of Fenofibric acid DR pellets

2.2.5.1 Micromeritic properties[9]

Bulk density (BD), tapped density (TD) and Hausner ratio (HR) of pellets were determined. 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.

2.2.5.2 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:

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

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

2.2.5.3 In vitro drug release studies[10]

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 and 360min. 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:

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

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

2.2.5.4 Drug release kinetics[11]

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 and Discussions

3.1 Drug excepient compatibility studies

From the DSC thermograms, at the initial stage, the onset melting point of API and composite blend were observed at 215.15ºC& 178.17 ºC, respectively and peak melting point of API and composite blend were observed at 218.01 ºC and 186.66 ºC, respectively. The endothermic peaks after 4 weeks storage at 40 °C/75%RH, the onset melting point of API and composite blend were observed at 214.09 ºC &176.01 ºC, respectively and peak melting point of API and composite blend were observed at 216.43 ºC and 185.88 ºC, respectively (Fig 1). Hence, it was concluded that there was no interaction between the drug substance and the chosen excipients. Hence these excipients were considered for the use in the development of the formulation.

3.2 Preparation of pellets

Fenofibric acid DR pellets were prepared by employing wurster process. Drug loading stage (binder concentration) was optimized by evaluating assay of drug loaded pellets. The impact of formulation variables at each stage such as extended release coating (ER coating polymer type and concentration, plasticizer concentration and pore former concentration) & enteric coating (enteric coating polymer type and concentration, plasticizer concentration) on release rate constant were evaluated in preliminary trials, and results were interpreted by ANOVA. Process parameters were selected and established based on prior experience.

From the obtained results, 3% w/w Povidone as a binder in drug loading solution, 20% w/w Eudragit L 30 D 55 as enteric coating polymer with 20% w/w plasticizer concentration with respect to the polymer were found to be optimum. Among the studied ER coating polymers (Eudragit RLPO, RSPO and Ethyl cellulose), Ethylcellulose was opted as a release retardant. The concentration of selected ER polymer (Ethocel; 1.4, 1.8 & 2.2%w/w), plasticizer concentration (Triethyl citrate; 10, 20 & 30%w/w with respect to the polymer) and pore former concentration (HPMC E5; 0, 10 & 20%w/w) were identified as high risk variables have a potential impact on drug release. Hence these factors were studied at three levels employing face centered central composite design.

3.3 Data analysis and model validation

3.3.1 Fitting of data to the model

Three factors with three levels face centered central composite experimental design require 17 experiments, the independent variables and responses for all experimental runs are given in table 1. Models of various responses were obtained using Design Expert (Stat-Ease). The values of R^2 are shown in table 2, for each response along with their ANOVA results.

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:

$Y_1 = 17.32-5.81*A+0.36*B+2.34*C-3.8*A^2 +0.87*C^2$

$Y_2 = 85.50-9.03*A+3.74*C-3.60*B^2$

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 2), terms B, C and C^2 have positive impact on Y_1,whereas A and A^2 have a negative impact on Y_1.Term C has shown a positive impact on Y_2, whereas A and B^2 have a negative impact on Y_2.

3.3.2 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 Fig 2 and 3, 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. Fig 2 and 3 exhibited a

curvilinear relationship with Y_1 and non linear relationship with Y_2.

Table 1: Observed responses in face centered central composite design of Fenofibric acid delayed release pellets

Independent Variables			Dependent Variables/Responses	
Ethocel concentration (%w/w) (A)	**TEC concentration (%w/w) (B)**	**HPMC concentration (%w/w) (C)**	**Dissolution at 2.5th h (%) (Y_1)**	**Dissolution @ 6th h (%) (Y_2)**
1.8	20	20	21	88.4
1.8	20	10	17.5	87.2
1.8	30	10	17.3	81.2
2.2	20	10	7.8	73.1
2.2	30	0	7	68.7
1.4	10	0	17.9	83
2.2	10	0	5.7	66.9
1.4	30	20	22.5	93.4
1.8	20	10	17.1	86.5
1.4	10	20	22.1	91.2
2.2	30	20	11.2	74.3
1.8	10	10	16.4	80.1
1.8	20	0	15.1	77.3
1.4	30	0	18.3	84.1
1.4	20	10	19.6	91.7
1.8	20	10	17.9	87.8
2.2	10	20	10.6	70.1

Table 2: ANOVA results for predicting % drug release at 2.5th h and 6th h

	DF	SS	MS	F	P	R^2
% Drug release at 2.5th h (Y_1)						
Model	9	438.12	48.68	216.34	<0.0001	0.9964
Lack of Fit	5	1.26	0.25	1.57	0.4332	
% Drug release at 6th h (Y_2)						
Model	9	1114.06	123.78	30.38	<0.0001	0.9750
Lack of Fit	5	27.67	5.53	13.07	0.0726	

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

3.3.3 Optimization

A numerical optimization technique using the desirability function approach was employed to generate the optimum concentration of the independent variables. Suitable levels of constraints were choosen to achieve desired results of the formulation. It was found to satisfy the requisites of an optimum batch when the desirable ranges of responses were restricted % drug release at 2.5th h to 12 % – 22% and % drug release at 6th h to > 75% (75% - 100%). On analyzing various response variables and comprehensive evaluation of feasibility of exhaustive grid search, the following combination variable was

suggested by the software with desirability function of 0.805 as reported in Table 3,

Table 3: The criterion for numerical optimization

Parameters	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
Ethocel concentration (%w/w) (A)	Is in range	1.4	2.2	1	1	1
TEC concentration (%w/w) (B)	Is in range	10	30	1	1	1
HPMC concentration (%w/w) (C)	Is in range	0	20	1	1	1
Dissolution at 2.5th h (%) (Y_1)	Is in range	12	22	1	1	1
Dissolution at 6th h (%) (Y_2)	Maximize	75	100	1	1	1

Solutions

Independent Variables				Response Variables			Desirability
Code	**A**	**B**	**C**	**Experimental values[a]**	**Predicted Values**	**% Error[b]**	
Optimized formulation	1.8	20	10	Y_1 17.5 ± 2.28	17.317	1.06	0.805
				Y_2 87.17 ± 0.75	85.500	1.95	

[a]Mean±SD, SD= Standard deviation; [b] Percentage of error = [(actual value-predicted value)/predicted value)] x 100

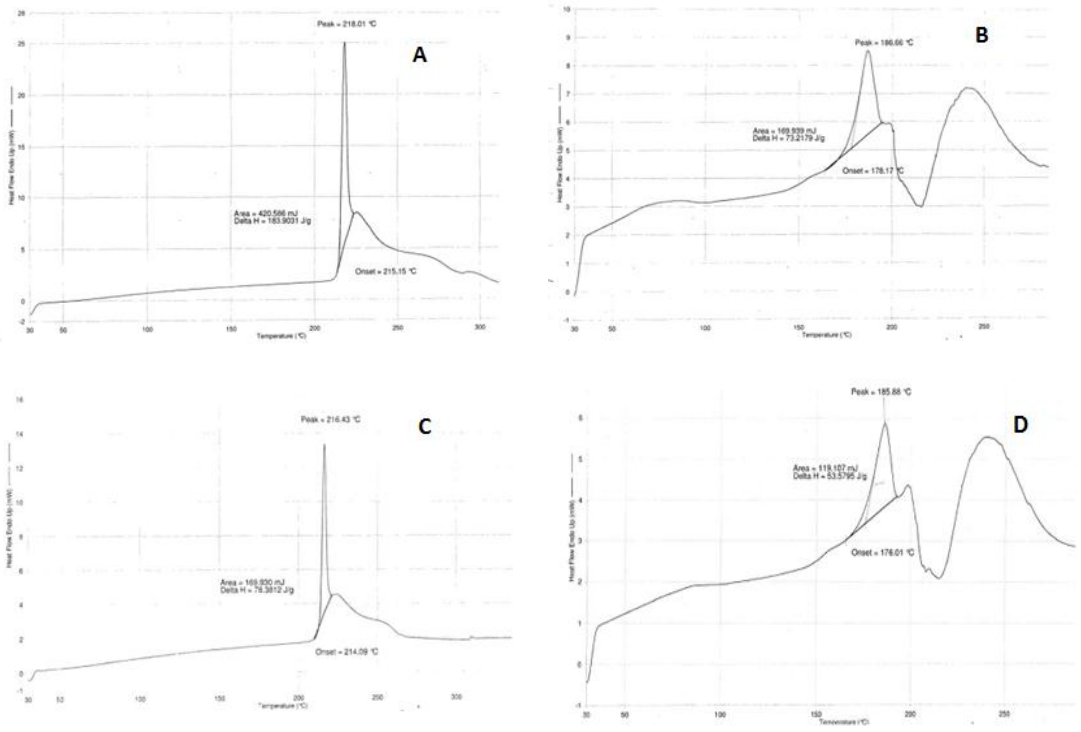

Fig 1: DSC thermograms A) Choline Fenofibrate API-Initial; B) Choline Fenofibrate composite blend- Initial; C) Choline Fenofibrate API - 4weeks@40°C/75%RH; D) Choline Fenofibrate composite blend-4weeks@40°C/75%RH

Ethocel concentration 1.8% w/w, TEC concentration 20% w/w (with respect to polymer) and HPMC concentration 10% w/w (with respect to polymer); the desirability function value (0.805) is closer to 1. The optimized formulation has shown a drug release at both 2.5th h and 6th h well within the predetermined specifications. The drug release profile of optimized formulation is presented in Fig 4. Hence, it was suggested that the generated models were well suited to optimization of the Fenofibric acid DR pellets.

3.4 Evaluation of pellets

3.4.1 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.

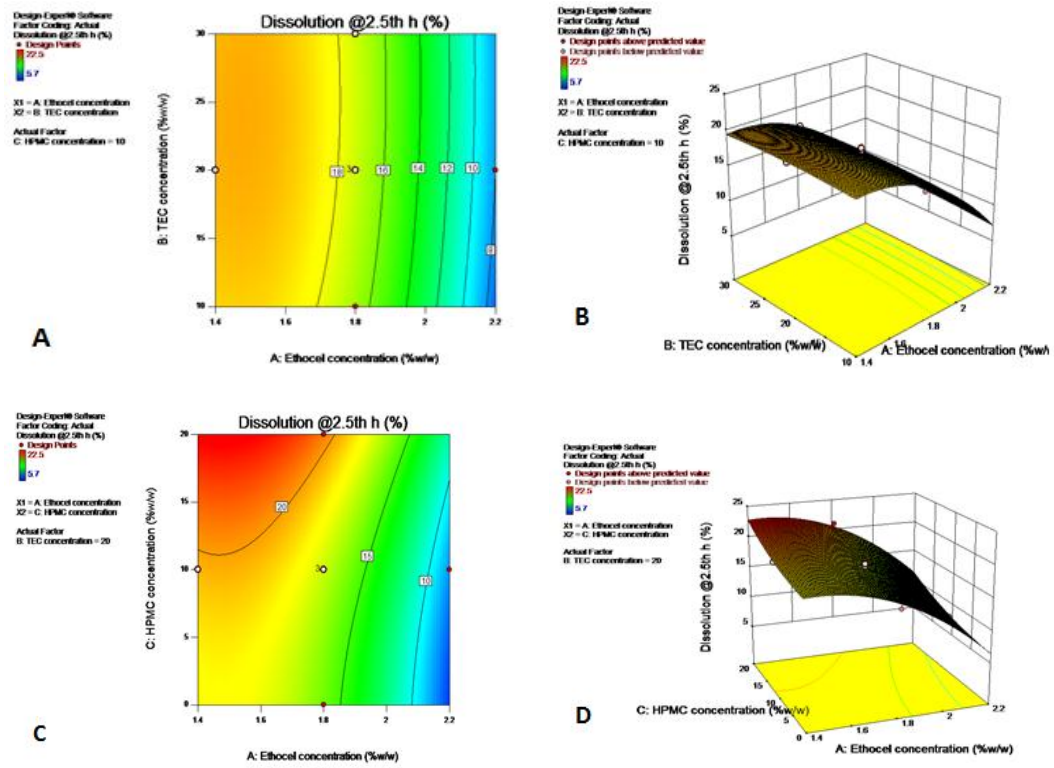

Fig 2: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Concentration of Ethocel, TEC& HPMC E5) on % drug release at 2.5thh.

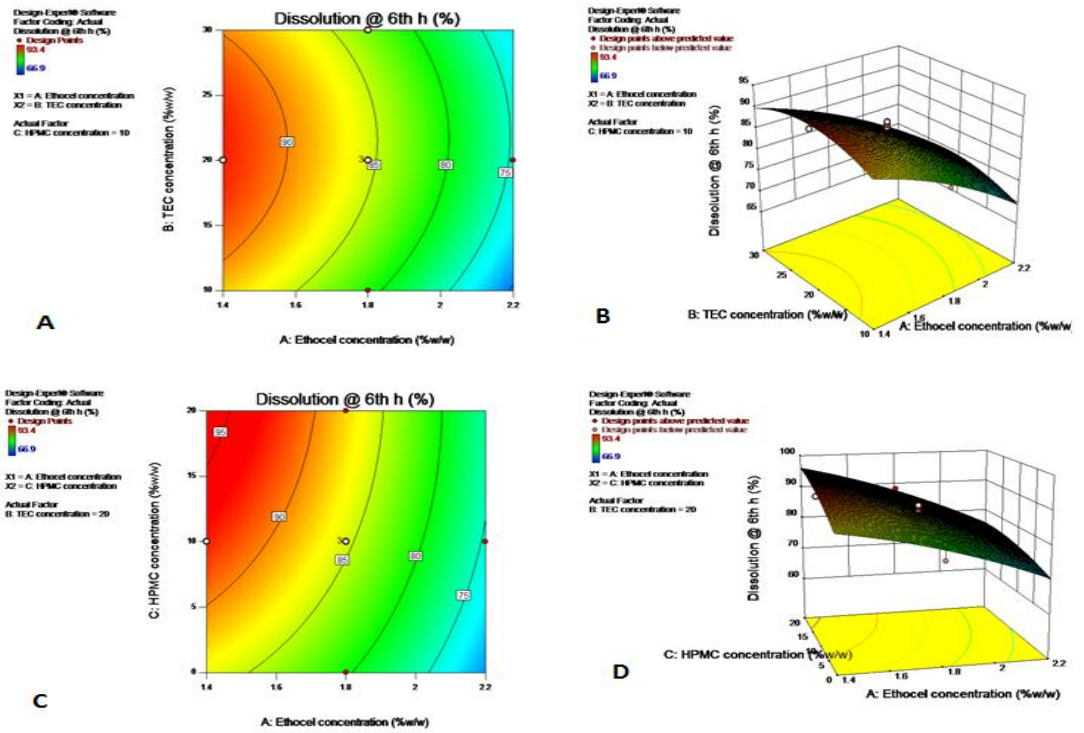

Fig 3: Contour plots (A,C) and response surface plots (B,D) showing the impact of factors (Concentration of Ethocel, TEC & HPMC E5) on % drug release at 6th h.

3.4.2 Assay

The assay of the all formulations was tested and results were found in the range of 98.9-101.1%. Assay of the optimized formulation was observed to be 100.1%.

3.4.3 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.

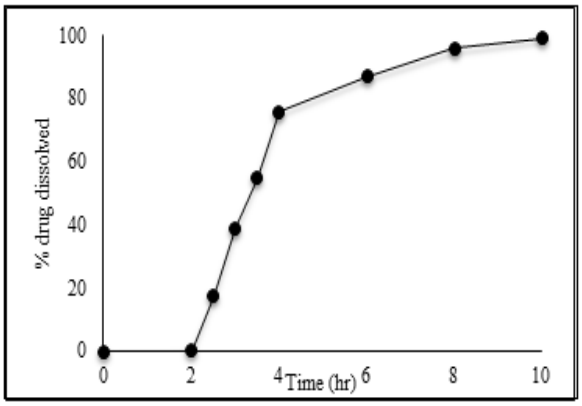

Fig 4: Dissolution profile of the optimized formulation

4 Conclusion

Fenofibric acid DR pellets were successfully fabricated by fluid bed coating technology. The effect of three independent variables (ER polymer concentration, plasticizer concentration & pore former concentration) on two responses was studied and optimized systematically 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 drug release 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. The optimized batch showed 100.1% assay and drug release was well within the predetermined specifications.

Micromeritic properties of these pellets exhibited excellent flow properties, which are crucial to attain the uniformity of dosage units in capsule filling. DSC studies evidenced that there was no interaction between drug and selected excipients. The optimized formulation can be used as an alternative to the marketed formulation. Hence, the applicability of response surface methodology to optimize the formulation variables in the fabrication of Fenofibric acid DR pellets is apt enough.

5 Acknowledgements

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

6 Conflict of Interest

Nil

7 Author's contributions

BVP carried out literature review, experimental studies, data analysis and manuscript preparation. GKM and APR participated in data analysis, editing and review of the manuscript.

8 References

1. Gehbre Sellasie I. Pellets: A general overview: Pharmaceutical pelletization technology. 1st ed. Newyork: Marcel Dekker. 1989; 101-43.
2. Hiren PP, Patel JK, Ravi RP, Manish PP. Pellets: A general overview. Int. J Pharm World Res. 2010; 1(2): 1-15
3. Shajahan A, Anil VC, Sunil BJ. A flexible technology for modified – release drugs: Multiple unit pellets system. J Control Release. 2010; 147(1): 2-16.
4. International Conference on harmonization (ICH). Guidance for industry: Q8 (R2) Pharmaceutical development, ICH harmonized tripartite guideline, 2009.
5. Dayal P, Pillay V, Babu RJ, Singh M. Box-Behnken experimental design in the development of a nasal drug delivery system of model drug hydroxyurea: characterization of viscosity, in vitro drug release, droplet size and dynamic surface tension, AAPS Pharm. Sci. Tech. 2005; 6 (4): E573–85.
6. Russell DC, Paterson JB, Yi G, Geoff G, Zhang Z, Long MA, Morris JB, Rosenberg J. Salts of fenofibric acid and pharmaceutical formulations thereof , US7259186, 2017.
7. Haralampos J Milionis. Management of dyslipidemias with fbrates,alone and in combination with statins: role of delayed-release fenofbric acid, Vasc Health Risk Manag. 2010; 6: 525–39.
8. Bolton S. Statistical applications in the pharmaceutical sciences, In: Lachman L, Lieberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy, 3rd ed. Bombay: Varghese Publishing House; 1987, 243-289
9. Pharmacopoeia I, Indian Pharmacopoeia Commission, Ghaziabad, India, 2010, 2: 786.

10. *https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm.*

11. Suvakanta D, Padala NM, Lilakanta N, Chowdhury P, Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems, Acta Pol. Pharm. 2010; 67 (3): 217-23.