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Development of *in-vitro in-vivo* correlation of optimized fenofibrate tartaric acid co-crystal tablet

Ashwini Madgulkar[1*], Mangesh Bhalekar[1], Anil Battase[2], Pravin Waghchaure[2], Sumedh Pradhan[1], Dhananjay Pagare[1]
[1] Pharmaceutics, ISSMS College of Pharmacy, Kennedy, Pune, Maharashtra, India
[2] Pharmaceutics, Govindrao Nikam College of Pharmacy Sawarde, Ratnagiri, Maharashtra, India

Abstract
Fenofibrate an antilipidemic drug belonging to BCS class II, has very low oral bioavailability. Many approaches have been reported in literature and we selected a simple approach of formulating co-crystals to enhance the dissolution and subsequently bioavailability of fenofibrate. After reporting conformer screening, preparation and *in-vitro* evaluation of tartaric acid fenofibrate co-crystals as separate research work, formulation and *in-vivo* studies were undertaken in this work and an attempt to develop *in-vitro in-vivo* correlation was made using deconvolution and time scaling approach.

Keywords: feno fibrate-tartaric acid co-crystal tablet, design expert, IVIVC (*in-vitro in-vivo* correlation)

Introduction

Fenofibrate is a drug of the fibrate class which has the ability to reduce lipids level in the blood through decreasing plasma fibrinogen level, decreasing uric acid level and decreasing plasma level of both inflammatory markers, C - reactive protein and interleukin which may play a significant role in prevention and treatment of hyperlipidemia associated diseases.

Fenofibrate belongs to class-II compounds of the Biopharmaceutics Classification System (BCS) with low aqueous solubility and high permeability (log P 5.3) [1] that result in low oral bioavailability of Fenofibrate (~30%).

Several techniques have been developed to improve the dissolution rate and enhance bioavailability of Fenofibrate as liposomes [2], microemulsions [3], micronization, silica based formulations, nanosuspensions [4], nanoemulsions [5], solid lipid nanoparticles [6] and co-crystal which is considered as successful strategies used to improve the dissolution rate and hence bioavailability of poorly water soluble drugs.

Co-crystals are defined as "solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds (co-former) generally in a stoichiometric ratio which are neither solvates nor simple salts". These offer a relatively simple strategy for improvement of dissolution and compression properties of compounds [7]. Co-crystals of fenofibrate with tartaric acid as conformer have been formulated with scientific conformer screening using molecular docking and evaluated by us which shows improved dissolution rate and flow properties [8]. The aim of present study was to formulate these co-crystals into tablets, optimize the formula and establish an *In-vitro In-vivo* correlation using *In-vivo* data obtained from study in rats (IVIVC) [9].

Materials and Methods

Materials

Fenofibrate was provided by Medley pharmaceutical Ltd. All required solvents and excipients were provided by LOBA CHEMIE PVT LTD.

Molecular docking was performed on Schrodinger suit version 9.0 software. Experimental design was performed using design expert version 12.0 software.

Method

Molecular Docking

The co-formers were initially selected based upon supramolecular synthon approach that depicts possibility of hydrogen bond formation with fenofibrate [10]. Co-former structures were prepared by LigPrep 2.3 module of Schrodinger suite [11]. The structure of fenofibrate was prepared using protein preparation wizard of Maestro [12]. The protein structure was optimized and minimized using OPLS-2005 force field. Molecular docking was performed using Glide docking program [13]. The results were run on the basis of glide score.

Preparation of fenofibrate-tartaric acid co-crystal:

Antisolvent addition method

Fenofibrate and co-former weigh in 1:1 molar ratio were dissolved in 25 ml ethanol using moderate stirring. The solution was then filtered through a Whatman filter paper to remove any undissolved material. Distilled water was then added dropwise to the above solution with constant stirring to induce co-crystal precipitation. The co-crystals were allowed to dry overnight in desiccators [10, 14].

Preparation of tablets

Fenofibrate-tartaric acid co-crystal, lactose, MCC (Microcrystalline cellulose), were blended and the powder was moistened using Povidone k30 solution in water was used as a binder. Dough was passed through sieve no 10 dried in oven at 45℃. The dried mass was mixed with cross povidone, magnesium stearate and SLS (Sodium Lauryl Sulphate). Compressed using 6 mm punch using B tooling on Rimek MINI PRESS-II MT.

Micromeritic properties of fenofibrate and fenofibrate-tartaric acid co-crystal

The various powder flow properties were evaluated of drug like angle of repose, Hausner's ratio and carr's index were determined as described in literature [15, 16].

Experimental Design

A 3^2 full factorial design was used to evaluate two variables at 3 levels *viz*. concentration of cross povidone (3.5, 2, 5 mg) and PVP k30 (3, 1, 5 mg) in order to determine their effect on three responses *viz* disintegration time (min), % drug release and hardness of tablet. The layout of experimental design is shown in table 1. Two factors were evaluated each at three levels & experimental trials were performed at all possible nine combinations as shown in table 2.

Table 1: 3^2 full factorial design layout for optimization of fenofibrate-tartaric acid co-crystal tablet

Sr. No.	Factors				Responses
1	cross povidone	-1	0	+1	Disintegration time (min)
2	PVP k30	-1	0	+1	% drug release (%)
3					Hardness (kg/cm^2)

Table 2: Composition of fenofibrate-tartaric acid co-crystal tablet (All quantities in mg)

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Fenofibrate co-crystals	40	40	40	40	40	40	40	40	40
2	Lactose	44.25	42.75	44.75	43.75	47.75	42.25	46.25	40.75	45.75
3	MCC	5	5	5	5	5	5	5	5	5
4	Cross povidone	3.5	5	5	2	2	3.5	3.5	5	2
5	SLS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
6	PVP K 30	3	3	1	5	1	5	1	5	3
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
	Total	100	100	100	100	100	100	100	100	100

Evaluation of optimized batch

Hardness, disintegration test and friability test was carried out as per methods described in literature [15, 17].

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester (Nevtex).

Friability is the measure of tablet strength. Roche friabilator (Veego, Mumbai) was used for testing the friability. Friability test was performed as described in IP the tablets were weighed and the percentage loss in tablet weight was determined.

$$\%\ loss = \frac{Initial\ weight\ of\ tablets - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablets} \times 100$$

Determination of drug content

The quantity of powder equivalent to 10mg of fenofibrate was taken and dissolved in 10 ml of methanol, sufficient amount methanol was added to produce 100 ml and filtered.

The Absorbance was measured spectrophotometrically at 286 nm after suitable dilution

***In vitro* dissolution test**

Drug release studies (n=3) were conducted for the optimized formulation using dissolution test apparatus (DA-6D USP Standard), phosphate buffer pH 7.4 containing 0.5% SLS (900 ml) was taken as the release medium at 100 rpm and 37±1ºC employing USP II paddle method (Apparatus 1)[8]. Aliquots of 10 ml were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 286 nm. The release studies were conducted in triplicate (6 tablets in each set) and the mean values were plotted versus time.

Additionally *in vitro* dissolution of optimized batch was performed in different medium like 0.1N HCl, pH7.4 buffer.

Optimization and validation model

The response from the release data was fed to the design expert software 11.0 and the equations were generated. The numerical optimization was done using desirability function and predicted formula were prepared analysed to test whether the result matches to the optimized release data by DOE.

***In-vivo* pharmacokinetic study**

The pharmacokinetic studies were conducted to determine the C_{max}, T_{max}, AUC, K_{el} and total AUC in order to predict the behavior of tablet in the animal model. The *In-vivo* study was performed on wistar rats with weight of 200-250 gm. Three groups containing 6 rats each were created. The animals were housed individually under environment conditions (25^0, 12 h light and dark cycle).

The rats were fasted overnight and allowed free accesses to water only. The fenofibrate and fenofibrate-tartaric acid co-crystal tablet respectively was selected for *in-vivo* studies For group fenofibrate-tartaric acid co-crystal tablet 6.7 mg was dispersed in 5 ml of distilled water and administered orally to the rats. Blood samples of 0.5 ml were withdrawn at first hour and then after every hour interval till 8th hour and 24th hour for all groups.

Blood sample collected by retro-orbital method from the rat. Blood sample was collected in screw capped EDTA tubes at predetermined time intervals. After collection, blood samples were immediately centrifuged for 10 minutes 4000 rpm and separated plasma was stored in screw capped polypropylene tubes at -5 °C till analysis. To each tube was added 5 ml of ethyl acetate as a liquid-liquid extracting solvent. The contents of the tube were vortex mixed for 3 minutes and then centrifuged for 3 minutes at 3000 rpm. The organic layer was collected in the glass tubes and evaporated to dryness on water bath at 40^0C under a nitrogen stream. The contents of the tubes were then reconstituted with 50 µL of methanol and 20 µL of each was injected into HPLC system.

a. **Column:** Agilent C18 column (250 x 4.6 mm, 5 µ) protected with guard column
b. **Mobile phase:** Methanol : Water (80:20 v/v)
c. **Wavelength:** 286 nm
d. **Elution:** Isocratic
e. **Flow rate:** 1 ml/minute
f. **Temperature:** Ambient
g. **Injection volume:** 20 µL

***In vitro in-vivo* modelling**

The *in-vivo* absorption or dissolution time course was estimated using an appropriate deconvolution technique for each formulation. The fenofibrate plasma levels were converted to the % fenofibrate absorbed by the use of modified Wagner-Nelson method. This IVIVC comprised suitable time scaling for linearity profile [18]. Then to establish IVIVC, the % fenofibrate dissolved *in vitro* was plotted against the % fenofibrate absorbed *In-vivo*.

Results and Discussion

Micrometric flow properties of fenofibrate-tartaric acid co-crystal

Tablets were formulated by wet granulation method and the granules containing co-crystals were evaluated for micrometric flow properties. fenofibrate-tartaric acid co-crystal shows improved flow properties than fenofibrate as shown in (Table 3).

Table 3: Micrometric flow properties of fenofibrate and fenofibrate-tartaric acid co-crystal. Mean± SD (n=3)

System	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's index
Fenofibrate	39.65± 2.41	0.145±0.12	0.168±0.26	1.15±0.66	13.26±4.45
Fenofibrate Tartaric acid co-crystal	30.96±3.12	0.159±0.25	0.170±0.23	1.06±0.2	6.47±3.5

Experimental Design

For formulation of tablets as per 3^2 full factorial design the concentrations of PVP K-30, cross povidone were considered as the two independent factors. Design comprised of 9 experimental runs to evaluate the significance of individual and combined effects of the PVP K-30 and cross povidone on hardness, disintegration time and percent drug release. The values of examined responses obtained for all trial formulations were fitted in the 3^2 factorial design (Table 4) to get model equations for responses analysed. Quantitative effect of independent variable in the obtained equation are mean results obtained by changing one factor from its low to high value keeping another factor constant. Response surface methodology is a most practiced approach in the development and optimization of formulation variables. The results were visualized with the help of 3D response Surface Graphs.

Table 4: Experimental run & responses for optimization of co-crystal tablet using 3^2 full factorial design.

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Run	A:Cross povidone	B:PVP K30	Disintegration time	% drug release	Hardness
	%	%	Min	%	Kg/cm^2
1	3.5	3	3.6	89	4.1
2	5	3	3	94	3.3
3	5	1	3	98	3.1
4	2	5	5	85	5.2
5	2	1	3.5	92	2.9
6	3.5	5	4.2	85	5.1
7	3.5	1	3	91	3.6
8	5	5	4	89	3.8
9	2	3	3.5	90	4.1

Optimization Data Analysis:

The formulations prepared as per the experimental design were evaluated and the analysis of experimental results was done by using Stat-Ease Design Expert. The ANOVA, P-value and Model F-value for disintegration time, % drug release and hardness were obtained (Table 5).

Table 5: ANOVA output for optimization of fenofibrate tartaric acid co-crystal tablet

Sr. No.	Outcomes	Disintegration time	% Drug release	Hardness
1	Models	Quadratic	Quadratic	Quadratic
2	R^2 VALUE	0.9452	0.9877	0.9941
3	F – VALUE	10.35	48.36	101.79
4	P – VALUE	0.0415	0.0046	0.0015
5	ADEQUATE PRECISION	9.1208	21.63	27.66

F value for both models was found to be high which indicated that the models were significant.

P value less than 0.05 indicated that the model terms were significant.

Adequate precision indicates signal to noise ratio, its value higher than 4 indicates minimum noise.

Higher R^2 value indicated good agreement between formulation variables and response parameters. Thus both models can be used to predict the values of the response parameters at selected values of formulation variables within the design space**.**

The statistical model generated for Disintegration time is represented by Equation 1

Disintegration time=+3.32-0.3333A+0.6167B-0.1250AB+0. 0667A^2+0.4167^2.. Equation 1

Concentration of cross povidone (A) is having dominant effect on disintegration time whereas concentration of PVP k-30 (B) having significantly less effect on the disintegration time. As the concentration of cross povidone i.e. disintegrating agent increases the disintegration time decreases on other hand concentration of PVP k-30 increases the disintegration time increases (Figure 1).

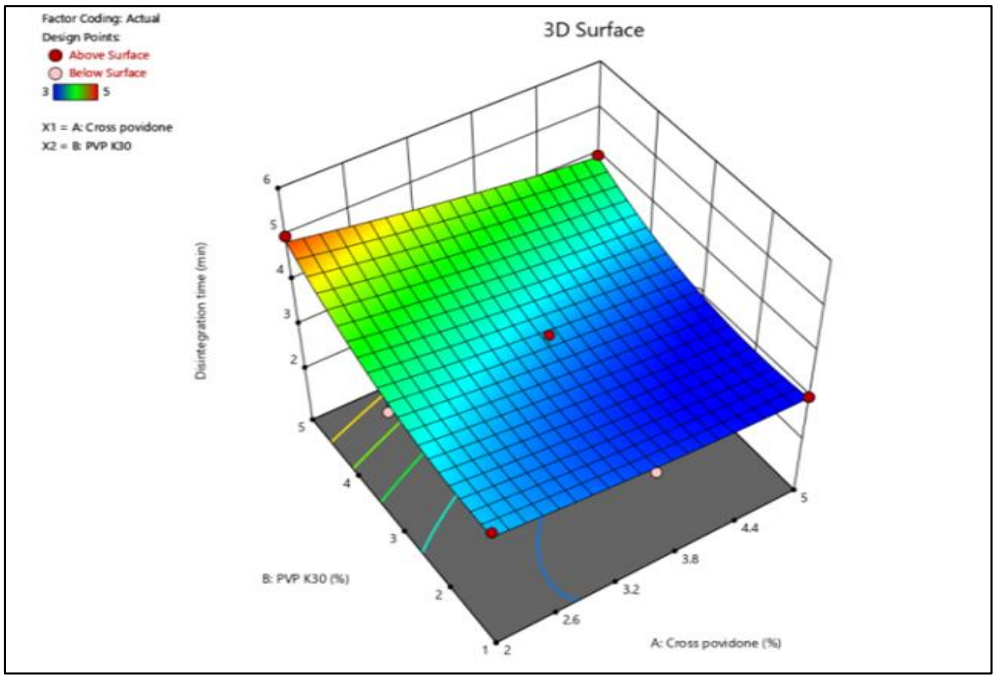

Fig 1: Response surface plot (3D) showing the effect of Cross povidone & PVP K30 on disintegration time.

Equation for % drug release

% drug release = +89.00+2.33 A-3.67B-0.5000 AB+3.00 A^2-1.00 B^2.....Equation 2

The model indicates that as the negative sign of coefficient B that is factor code for PVP k-30 binder indicates that concentration ofB has dominant influence on % drug release as compared to A that is factor code for cross povidone disintegrating agent.

As the concentration of B increases the % drug release decreases and concentration of increases the % drug release increases (Figure2).

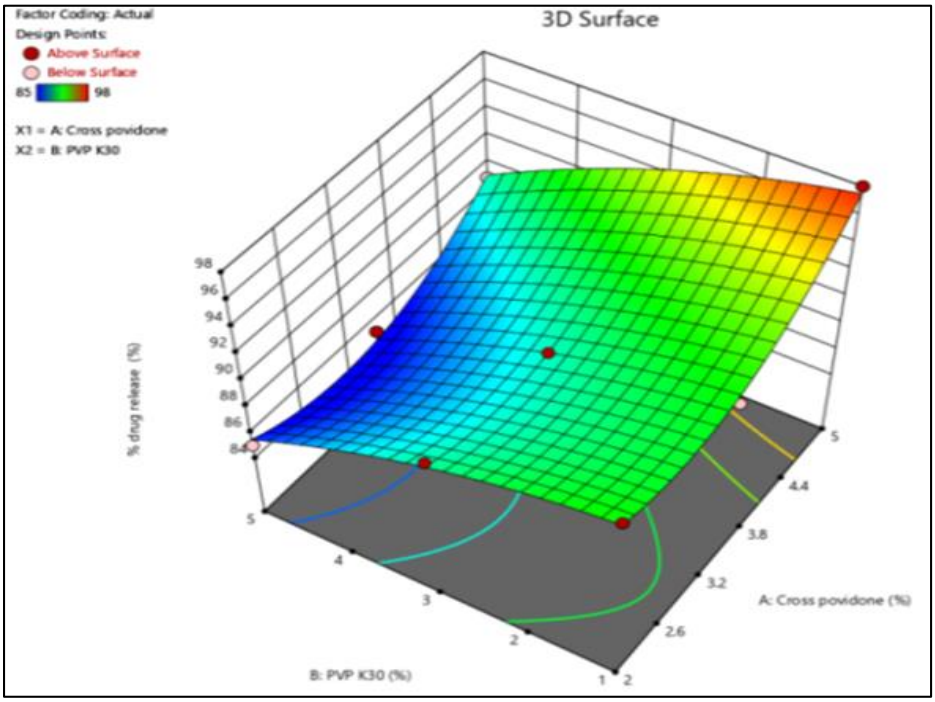

Fig 2: Response surface plot (3D) showing the effect of Cross Povidone & PVP K30 on % drug release.

Response 3: Hardness

Hardness =+4.19 -0.3333 A +0.7500 B -0.4000 AB-0.5333 A^2+0.1167 B^2…… Response 3

The model indicates that as the hardness of tablet goes on increasing as the concentration of binder PVP k-30 increases. the negative sign of coefficient A that is factor code for cross povidone disintegrating agent indicates that concentration of A has dominant influence on hardness as compared to B that is factor code for binder PVP k-30(Figure 3).

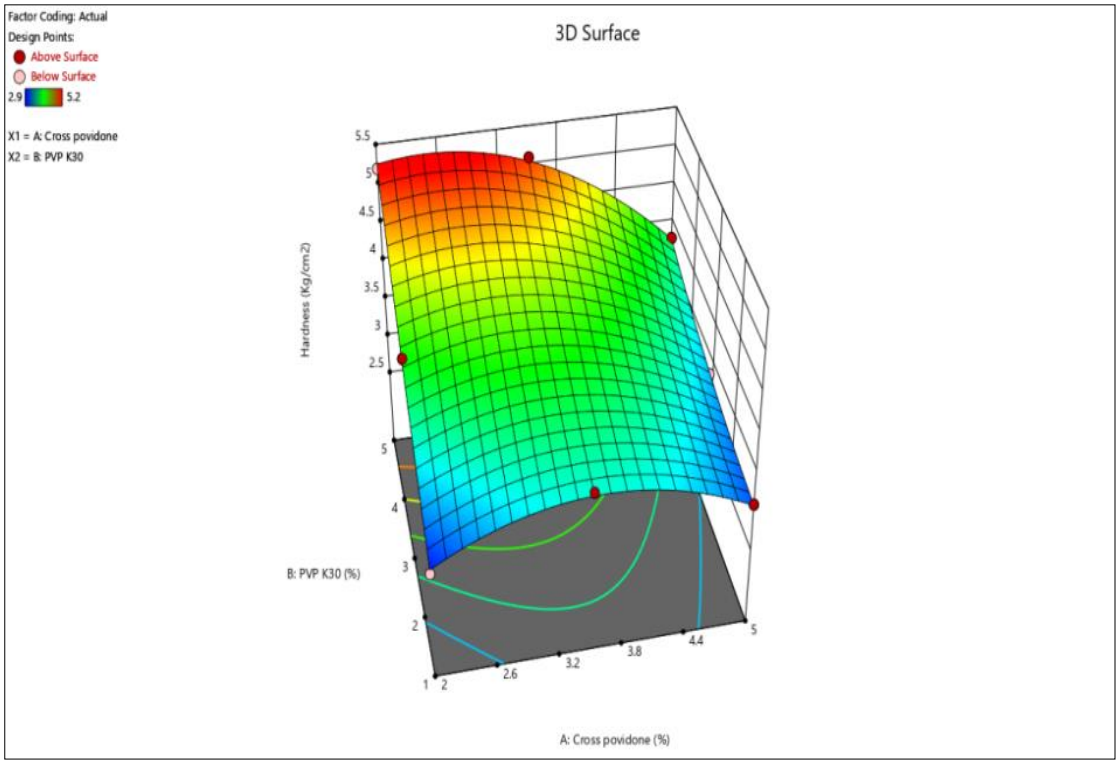

Fig 3: Response surface plot (3D) showing the effect of Cross Povidone & PVP K30 on hardness.

Validation of the Response Surface Methodology (RSM)

Thus, the formulation batch giving minimum disintegration time and maximum hardness and % drug release was chosen as the optimized batch based on desirability function.

Thus, the optimized batch consisted of concentration of disintegrating agent that is cross povidone is (5%) and binder PVP k-30 is (1%). To evaluate the findings of the RSM, verification run was carried out and no significant difference was found between the theoretical and the actual values of disintegration time, hardness and % drug release is given in (Table 6).

Thus the model is seen to have good prognostic ability.

Table 6: Validation of Optimized batch

Formulation Code	Composition of optimized formulation		Response	Predicted Value	Actual Value	% Error
	X1	X2				
Optimized batch	5%	1%	Y1	2.981min	3.01min	0.96%
			Y2	97.500%	96.89%	0.62%
			Y3	3.089kg/cm^2	3.098 kg/cm^2	0.29%

Evaluation of post compression parameters of optimized formulation:

The bulk density and tap density values of the powder ranged from 0.50 ± 3.2gm/ml to 0.62 ± 3.1 gm/ml and 0.56 ± 3.1 gm/ml to 0.65 ± 2.9gm/ml. Angle of repose ranged from 27.14±1.8 to 32.03 ± 1.5 and Hausner's ratio below 1.15 which indicates that all the flow properties are good.(Table 7)

Table 7: Evaluation of post compression parameters of optimized formulation.

Sr. no.	Post compression parameters	Result	Inference
1	Hardness	3.189	Within range
2	Disintegration time	2.991	Within range
3	Thickness	3.5mm	Complies with IP
4	Friability	0.15 %	Complies with IP
6	Drug content	96.86%±4.1	Complies with IP

***In-Vitro* Drug release**

The *in vitro* dissolution profiles of the co-crystal tablet were compared with that of fenofibrate (figure 3). The *in vitro* dissolution rate of co-crystal tablet was increased compared to the fenofibrate. fenofibrate shows 42.55% drug release after 60 min, whereas co-crystals show 96.89%. The high dissolution rate of prepared co-crystal can be attributed to change in crystallinity of fenofibrate due to possible hydrogen bond interaction with co-former[8]. This implies that the fenofibrate-tartaric acid tablet shows similar drug release as powder co-crystal.

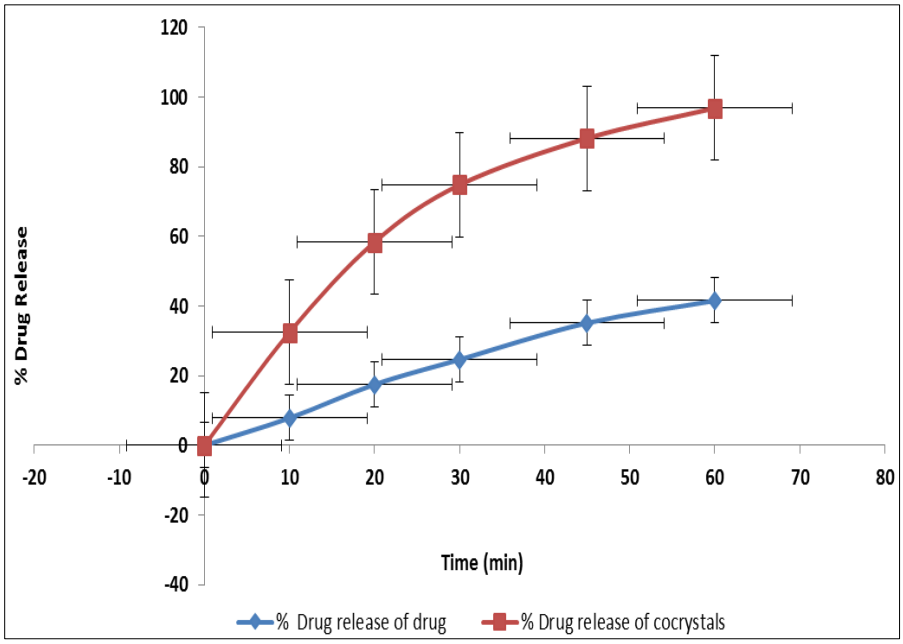

Fig 4: *In vitro* drug release from fenofibrate tablet and fenofibrate-tartaric acid co-crystal tablet.

***In vitro in-vivo* modelling**

FDA guidance describes four levels of correlation (level A, B, C and multiple level C) [19]. Level A correlation of these levels, representing point to point correlation between the *in vitro* input rate (e.g. dissolution rate) and the *in-vivo* input rate. Hence for IVIVC level A was selected. To obtain a good correlation,

Calibration curve in spiked plasma samples

Linearity was performed on plasma samples spiked with fenofibrate in the range 2 to 10 µg/ml. Each sample was analysed in three replicates and peak areas were recorded. The response factors (peak area) were plotted against the corresponding concentrations to obtain the calibration curve the equation obtained y = 10565x - 12672with R^2 (regression coefficient) 0.992.

Phamacokinetic parameters

The *in-vivo* plasma concentration profiles of fenofibrate and co-crystal tablet is presented in Figure 5. t_{max} of fenofibrate tablet was achieved in 3 h whereas that of fenofibrate-tartaric acid co-crystal tablet was attained in 2 h

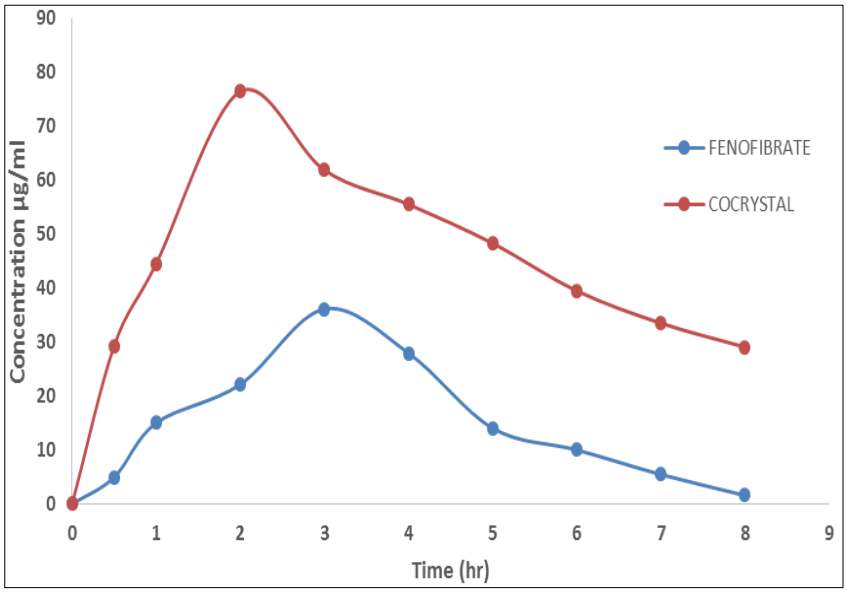

Fig 5: *In-vivo* release profile of fenofibrate and fenofibrate-tartaric acid co-crystal tablet.

The C_{max} of co-crystal tablet (60.02 µg/ml) was also increased over fenofibrate tablet (36.12 µg/ml). The AUC for co-crystal tablet (549.67 µg,h/ml) was greater than fenofibrate tablet (132.48 µg,h/ml). The increased AUC may be due to greater permeation enhancing effect or due to increased dissolution of fenofibrate-tartaric acid co-crystal tablet[8].

Table 8: Pharmacokinetic parameters of fenofibrate and fenofibrate-tartaric acid co-crystal tablet.

Parameter	Fenofibrate tablet	Co-crystal tablet
C_{max} (µg/ml)	36.12	60.02
T_{max} (h)	3	2
K_{ele} (h)	0.716	0.169
AUC $_{0\rightarrow t}$ (h µg/ml)	130.28	377.66
AUC $_{t\rightarrow\infty}$ (h µg/ml)	2.206	172.01
$AUC_{0\rightarrow\infty}$ (h µg/ml)	132.48	549.67

***In-vitro* dissolution**

in vitro dissolution was performed in different medium like pH 7.4 buffer show 91.8% drug release in 60 min, 0.1N HCl which show 96.86% drug release in 60 min, and pH 7.0 buffer containing 0.5% SLS show 96.86% drug release in 60 min.

Table 9: *In-vitro* dissolution at different pH

pH 7.0 buffer contain 5% SLS			0.1 N HCL			pH 7.4 Phosphate buffer		
Time(min)	% Release of drug	% Release of cocrystals	Time(min)	% Release of drug	% Release of cocrystals	Time(min)	% Release of drug	% Release of cocrystals
0	0	0	0	0	0	0	0	0
10	7.852	32.5	10	6.52	21.1	10	8.12	30.2
20	17.475	58.4	20	13.45	43.2	20	17.475	51.4
30	24.65	74.8	30	22.41	67.3	30	28.52	73.8
45	35.15	88.2	45	32.17	78.2	45	37.45	82.6
60	41.55	96.86	60	38.15	96.86	60	42.55	91.8

IVIVC model development & validation

Its most standard IVIVC model are described as a simple linear equation between the in-vivo absorption and dissolved in-vitro drug.

Y (in-vivo drug absorbed) = m X (in-vitro drug dissolved) + C

In the above equation the relationship slope is m, and the intercept is C. Generally, m=1 and C=0, which indicate a linear relation. The equation may be applied to most formulations with a comparable in-vitro and in-vivo release duration, in-vitro release may not exceed the same in-vivo release time scale. In order to model such data, the time-shifting and time-scaling parameters must therefore be incorporated within the model. This particular data is always expected in the development of dosage forms.

The *in vitro* release points are scaled by time scaling formula (Time × 3/60) formula. All three dissolution profiles yielded a simple linear equation between the *in-vivo* absorption and dissolved *in-vitro* drug. The % release of drug in *in vitro* 10, 20, and 60 min is correlated to % *in-vivo* absorption at 0.5, 1, and 3 h. The drug release in pH 7.4 Phosphate buffer (Figure 7) showed highest slope 0.9992. On the basis of linearity equation was developed y = 1.0493x+0.017 and R^2 = 0.9992.

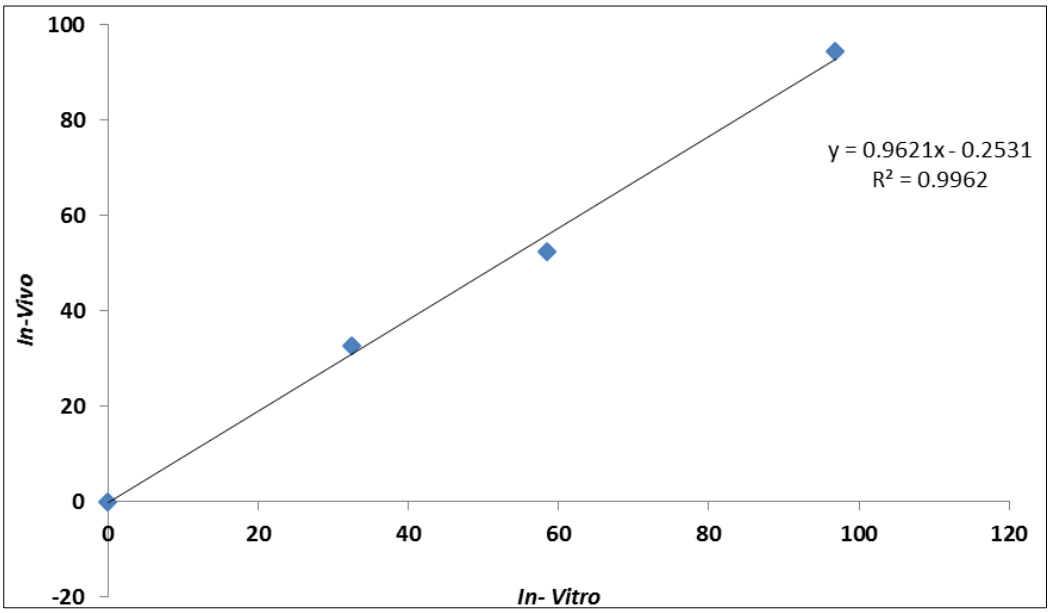

Fig 6: pH 7.0 buffer containing 5% SLS

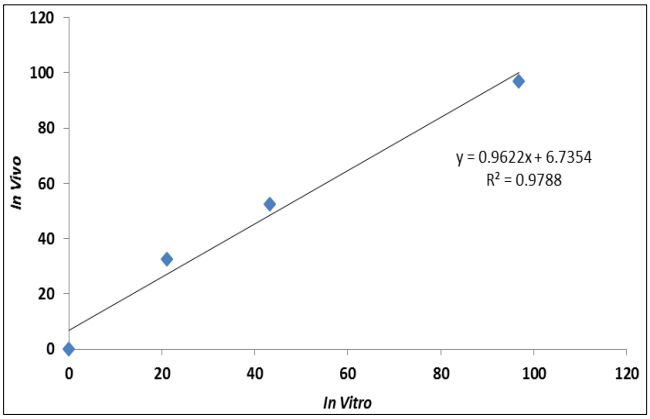

Fig 7: 0.1 N HCL

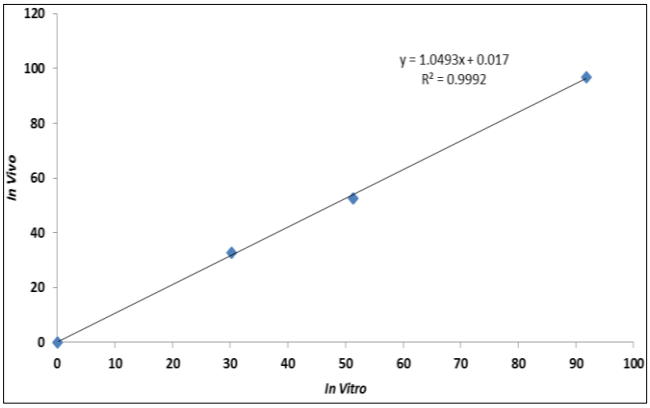

Fig 8: pH 7.4 Phosphate buffer

Conclusion

Fenofibrate-tartaric acid co-crystal tablet was formulated to form suitable oral dosage form. The formula for dosage form was optimized using Design Expert Software. The optimized tablet batch show 96.89% drug release in 60 min. The IVIVC was developed by modified Wagner-Nelson method. From the results of current study level A IVIVC was developed.

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