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Design and Assessment of Fixed Dose Combination Containing Fenofibrate and Pravastatin Sodium in Tablet Formulation: A Bioinformatics Approach

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Abstract

The aim of this is study is to formulate and evaluate fixed dose combination of Fenofibrate and Pravastatin sodium in tablet dosage for the treatment of Dyslipidemia. For the formulation and optimization of fenofibrate layer, two factor three level factorial design was used as experimental design for optimization with a minimum of nine run. All the nine trial (F1–F9) has been formulated according to the experimental design by wet granulation method. The independent variable studied were amount of HPMC (X1) and amount of crospovidone (X2). Drug release at 45 minutes (Y1) and disintegration time (Y2) was chosen as dependent variable. For the formulation and optimization of Pravastatin sodium layer, Trial and error method was employed. Total three trial (P1-P3) has been formulated. Trial P1 was formulated by direct compression, the results of this trial indicates that it has extremely poor flow property and lower hardness and high %friability. So it is concluded that direct compression is not feasible. So trial P2 is formulated using wet granulation all the post compression parameter was within the acceptable range but trial P2 show poor flow property. Hence trial P3 was formulated as like trial P2 but with increased quantity of cellulose microcrystalline in extragranular material. The observed precompression parameter of trial P3 shows it has good flow property and weight variation, hardness, friability and assay where within the limit. The disintegration time of Trial P3 was found to be optimum. Hence it was concluded that, bilayer tablet show no significant advantage over monolithic tablet on the basis of drug release and stability. So monolithic prototype formulation is chosen for the scale up process of fixed dose combination of Fenofibrate and Pravastatin sodium tablet.

Keywords: Formulation, Evaluation, Fixed Dose Combination, Fenofibrate, Pravastatin Sodium In

INTRODUCTION

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Fixed dose combinations (FDCs) are defined as a combination of two or more active ingredients within a single form of pharmaceutical administration [1–6]. They have been shown to appreciably reduce the risk of medication non-adherence, which is particularly important in patients with chronic diseases [7]. However, their rationality for use should be based on sound medical principles as there have been concerns with their irrationality and utility in several countries [1, 2, 4, 5, 8]. Concerns with FDCs include potentially altering the optimal dosing of one or more of the components due to differences in pharmacokinetic profiles and half-lives of the various constituents [1]. FDCs may also increase the chances of adverse

drug reactions or drug: drug interactions due to the different profiles of the medicines in the FDC as well as not fully recognizing the differences that can occur in the pharmacogenetic profiles of patients during the development of FDCs [1, 6, 9, 10]. Pharmacogenetic concerns are particularly important in FDCs when the components are either an essential part of the primary pathway for eliminating the medicines of interest or a critical step in their onset of action [6]. The pharmacokinetic profiles of the constituents in FDCs are also important in patients with infectious diseases as there can be concerns with resistance development due to the combination [11, 12]. Additionally, pharmacokinetic and pharmaco dynamic considerations of the constituents are important in the elderly where safety profiles may be altered [13]. Evidence has also shown that inappropriately manufactured FDCs can result in their reduced effectiveness or enhanced toxicity in routine clinical care as well as peak effectiveness at different times along side concerns with their shelf life [14].

To formulate and evaluate fixed dose combination of Fenofibrate and Pravastatin sodium in tablet dosage form.

MATERIALS AND METHODS

Methodology

Preformulation Studies

Chemical Compatibility study by FT-IR:

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture there by we can study incompatibility with two compounds. Compatibility in between two pure drug and compatibility in between both drug and excipient has been investigated by FTIR. The IR spectra of the test samples were obtained by pressed pellet technique using Potassium bromide as seen in Table 1.

Table 1. List of materials and their applications in formulation.

S.N.	Name of the material	Manufacture/supplier	Use in formulation
1.	Fenofibrate	Omshri Labs Pvt. Ltd., India	Active Ingredient
2.	Pravastatin Sodium	Biocon Limited, India	Active Ingredient
3.	Sodium Lauryl Sulfate	Basf, Germany	Wetting Agent
4.	Docusulate Sodium	CYTEC Industries, United State	Wetting Agent
5.	Lactose Monohydrate	DMV-Fonterra, Germany	Diluent
6.	Microcrystalline Cellulose	DU Point, Ireland	Diluent

CALIBRATION CURVE

For Fenofibrate

25 mg of Fenofibrate was weighed and transferred to a 100 ml volumetric flask and made up to volume using methanol. From the resulting solution 1, 2, 3, 4 and 5 ml were pipetted out into separate 50 ml volumetric flasks and made up to volume using methanol to represent 5, 10, 15, 20 and 25 μg/ml of the drug.

The absorbance of the solutions was measured at 287 nm taking methanol as blank using UV-Visible spectrophotometer. The calibration curve was then plotted taking concentration (μg/ml) along X-axis and absorbance along Y-axis.

For Pravastatin Sodium

25 mg of Pravastatin sodium was weighed and transferred to a 100 mL volumetric flask and made up to volume using methanol. From the resulting solution 1, 2, 3, 4 and 5 ml were pipetted out into separate 50 ml volumetric flasks and made upto volume using methanol to represent 5, 10, 15, 20 and 25 μg/ml of the drug.

The absorbance of the solutions was measured at 237 nm taking methanol as blank using UV-Visible spectrophotometer. The calibration curve was then plotted taking concentration (μg/ml) along X-axis and absorbance along Y-axis.

FORMULATION OF FENOFIBRATE TABLET

Fenofibrate tablet was prepared by wet granulation and using Design of experiment, optimization was carried out. Final optimized blend is used to compress monolithic and bilayer fixed dose combination tablet.

- The weighed quantities of intra granular material (Fenofibrate, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate) were sifted through #30 mesh.
- Sifted intra granular materials were subjected to dry mixed for 3 minutes.
- Water was chosen as solvent for binder solution. The quantity of the water was fixed based on 20% weight of intragranular material.
- Weighed quantities of hypermellose, sodum lauryl sulfate, was passed through #30 mesh along with docusate sodium all three material was mixed in water to make binder solution.
- The binder solution was poured over dry mix and granulated. The granules were then kept for drying at 55ºC in Hot air oven. Drying was continued till LOD reaches NMT 2.5%.
- Dried granules were passed through #20 mesh, and transferred to polyethylene bag.
- The extragranular materials consists of croscarmellose sodium and microcrystalline cellulose were passed through #30 mesh and magnesium stearate through #60 mesh.
- Extragranular material (except magnesium stearate) was added to the dried granules and blended for 10 minutes.
- Finally sifted magnesium stearate transferred into the above prelubricated material and blended for 3 minutes.
- The tablets were compressed by 8 station tablet compression machine using 15.42 × 7.48 mm caplet punch.

Design of Experiment (DOE)

A two factor and three-level factorial design was used as the experimental design. The independent variables studied were amount of HPMC (X1) and amount of Crospovidone (X2). Drug release at 45 minutes (Y1) and Disintegration time (Y2) were considered as dependent variable.

Experimental Design

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses. Experimental runs were designed by Design Expert 11.0.1 [Stat Ease. Inc.] software following full factorial method. 3^2 full factorial design was applied for examining two variables (factors) at three levels with a minimum of 9 runs. Totally nine Fenofibrate tablet formulations were prepared employing selected combinations of the two factors as per 3^2 Factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired immediate release Fenofibrate tablet as seen in Table 2.

Table 2. Factors and factor levels investigated in factorial experimental design.

Factors: Formulation Variables	**Levels (mg/tablet)**		
	-1	0	+1
HPMC	10.5	14	17.5
Crospovidone	10.5	21	31.5
Response	*Goal*		
Drug release at 45 min	Maximize		
Disintegration time	Minimize		

Optimisation

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables optimization was carried out using established statistical tools.

Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 11). In a full factorial design, all the factors are studied in all the possible combinations. Hence, 3^2 factorial designs were chosen for the current formulation optimization study as seen in Table 3.

Table 3. Formulation batches of fenofibrate tablets.

Ingredients (mg\tablet)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Dry mix									
Fenofibrate	160.00	160.00	160.00	160.00	160.00	160.00	160.00	160.00	160.00
Crospovidone	15.70	10.50	15.70	5.20	15.70	5.20	10.50	10.50	5.20
Microcrystalline cellulose	17.60	22.80	19.30	28.10	15.80	26.30	21.00	24.50	29.80
Lactose monohydrate	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00	99.00
Binder									
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC	14.00	14.00	10.50	14.00	17.50	17.50	17.50	10.50	10.50
Sodium Lauryl Sulfate	5.20	5.20	5.20	5.20	5.20	5.20	5.20	5.20	5.20
Docusate sodium	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Extragranular material									
Microcrystalline cellulose	17.60	22.80	19.30	28.10	15.80	26.30	21.00	24.50	29.80
Crospovidone	15.70	10.50	15.70	5.20	15.70	5.20	10.50	10.50	5.20
Lubricant									

FORMULATION OF PRAVASTATIN SODIUM TABLET:

Formulation was carried out by trial and error method for Pravastatin sodium tablet. Total three formulation, of which one by direct compression and remaining by wet granulation was done. Final optimized blend is used to compress monolithic and bilayer fixed dose combination tablet.

Direct compression process steps for Pravastatin sodium tablet:

- Pravastatin sodium, croscarmellose sodium, microcrystalline cellulose, dibasic sodium phosphate, magnesium oxide were shifted through #16 mesh and transferred into the polyethylene bag and they were blended for 10 minutes.
- Iron oxide brown with one part of microcrystalline cellulose was passed through #60 mesh and mixed for 5 minutes with the above blend.
- Colloidal anhydrous silica was passed through #30 mesh and mixed for 2 minutes with the above blend.
- Magnesium stearate was passed through #60 mesh mixed for 2 minutes with the above blend.
- The tablets were compressed by 8 station tablet compression machine using 13 × 6 mm oblong punch as seen in Table 4.

Wet granulation process for Pravastatin sodium tablet:

- The weighed quantities of intra granular material (Pravastatin sodium, croscarmellose sodium, microcrystalline cellulose, dibasic sodium phosphate, magnesium oxide, sodium lauryl sulfate, povidone, lactose monohydrate) were sifted through #16 mesh.
- Sifted intra granular materials are dry mixed for 10 minutes.
- Ethanol was chosen as binder solution. The quantity of the ethanol was fixed based on 5.5% weight of intragranular material.

Table 4. Formulation batches of pravastatin sodium tablets by direct compression.

Ingredient	P1 (mg)
Pravastatin sodium	40.00
Microcrystalline cellulose	179.30
Dibasic sodium phosphate	33.60
Croscarmellose sodium	10.08
Magnesium Oxide	14.00
Iron Oxide brown	0.21
Colloidal anhydrous silica	1.40
Magnesium stearate	1.40

Table 5. Formulation batches of pravastatin sodium tablets by wet granulation.

Ingredient	P2 (mg)	P3 (mg)
Intragranular material		
Pravastatin sodium	40.00	40.00
Cellulose microcrystalline	14.00	20.00
Lactose	14.00	20.00
Dibasic sodium phosphate	33.60	48.00
Croscaramellose sodium	5.04	7.20
Sodium Lauryl Sulfate	1.40	2.00
Povidone	8.40	12.00
Magnesium Oxide	14.00	20.00
Binder		
Ethanol	Q.S	Q.S
Extragranular material		
Cellulose microcrystalline	141.40	219.30
Iron Oxide brown	0.21	0.30
Croscaramellose sodium	5.04	7.20
Lubricant		
Collidal Anhydrous silica	1.40	20.00
Magnesium stearate	1.40	20.00
Core Tablet weight	280.00	400.00

- The binder solution was poured over dry mix and was mixed together. The granules were then kept for drying at 55ºC in Hot air oven. Drying was continued till LOD reaches NMT 2.5%.
- Dried granules were passed through #20 mesh, and transferred to polyethylene bag.
- The extragranular materials consists of iron oxide brown and one part of microcrystalline cellulose were passed through #60 mesh colloidal anhydrous silica passed through #30 mesh and magnesium stearate passed through #40 mesh.
- Extragranular material (except magnesium stearate) was loaded into the polyethylene bag containing dried granules and blended for 10 minutes.
- Finally sifted magnesium stearate transferred into the above granules and blended for 2 minutes.
- The tablets were compressed by 8 station tablet compression machine using 14 × 7 mm oval punch as seen in Table 5.

FORMULATION OF BILAYER TABLETS OF FENOFIBRATE AND PRAVASTATIN SODIUM

Based on the formulation development and optimization, the optimized blend of Fenofibrate and Pravastatin sodium was used for bilayer tablet.

Weighed quantity of Pravastatin sodium blend and Fenofibrate blend was placed in separate hopper. First Pravastatin sodium blend were filled in die cavity and slight compression is applied then Fenofibrate blend was filled over the Pravastatin sodium layer and final compression is given to form bilayer tablet by 8 station tablet compression machine using 18.97×8.79 mm caplet punch.

FORMULATION OF MONOLITHIC TABLETS OF FENOFIBRATE AND PRAVSTATIN SODIUM

Based on the formulation development and optimization, the optimized blend of Fenofibrate and Pravastatin sodium was used for monolithic tablet.

Optimized blend of Pravastatin sodium and optimized blend of Fenofibrate is mixed for the period of 5 minutes. The resulted blend is compressed into a monolithic tablet by 8 station tablet compression machine using 18.97×8.79 mm caplet punch.

RESULTS AND DISCUSSION

Chemical Compatibility Study by FTIR

The drug-drug interaction and drugs-excipients interaction was studied by FTIR spectroscopy as seen in Table 6.

Table 6. IR spectral interpretation of fenofibrate and pravastatin sodium.

S.N.	Wavenumber cm^{-1}	Interpretation
1	977.03	C-O-C ring stretching
2	1179.48, 846.41	CH bending
3	1246.53,1286.21, 1589.62	C-O ester
4	1408.23	C-O-C ring stretching
5	1457.72	CH_3 bending
6	1725.52, 1649.54	CH_3 bending
7	2971.63	C=O stretching

Inference

The FTIR peak of Spectra for final monolithic formulation showed no shift and no disappearance of the characteristic peaks suggesting that there is no interaction between the two drugs and also with the excipients in the final formulation as seen in Table 7

Table 7. Data for calibration curve of fenofibrate in methanol

Concentration (µg/mL)	Absorbance at 287 nm
5	0.227
10	0.451
15	0.686
20	0.915
25	1.149

Calibration Curve

Fenofibrate

It was found that the solution of Fenofibrate in methanol show linearity ($R^2 = 0.9999$) in absorbance at concentrations of 5–25 (µg/mL) and obey Beer Lambert Law as seen in Figure 1.

= Pravastatin sodium:

It was found that the solution of Pravastatin sodium in methanol show linearity ($R^2 = 0.9987$) in absorbance at concentrations of 5–25 (µg/mL) and obey Beer Lambert Law as seen in Table 8.

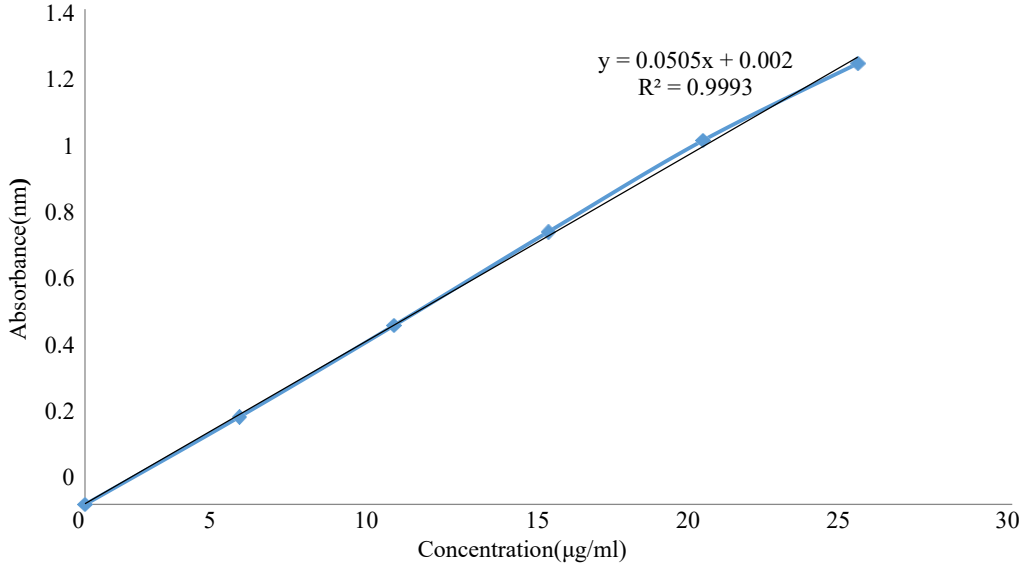

Figure 1. Calibration curve of fenofibrate in methanol.

Table 8. Data for calibration curve of pravastatin sodium in methanol.

Concentration (µg/mL)	Absorbance at 237 nm
5	0.248
10	0.506
15	0.771
20	01.029
25	1.246

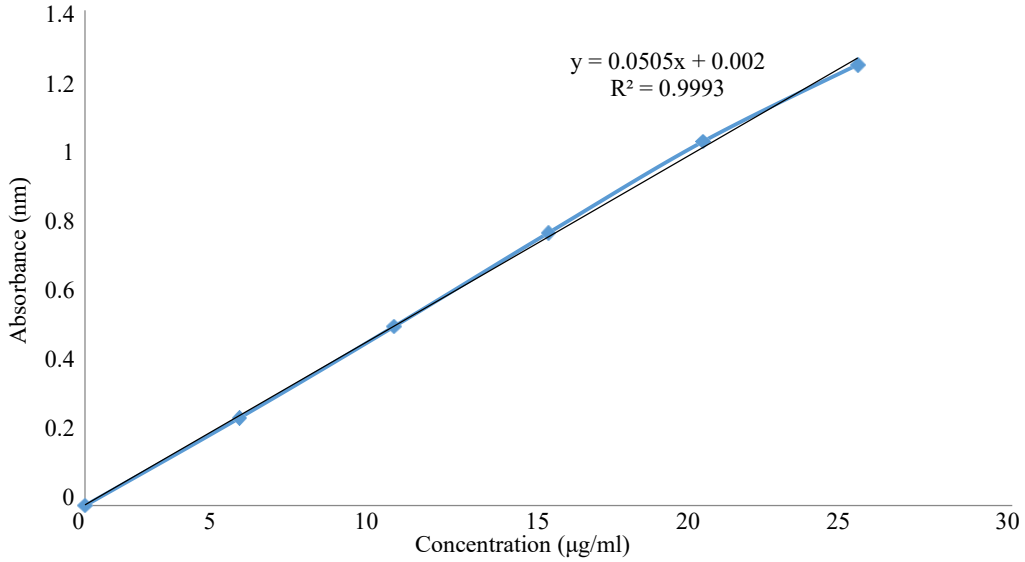

Figure 2. Calibration curve of pravastatin sodium in methanol.

For Fenofibrate Tablet

Precompression Study

The formulated blends of Fenofibrate were evaluated for precompression parameters.

The results are given in Table 9.

Table 9. Precompression study of fenofibrate blend.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.488±0.10	0.605±0.11	19.39±0.89	1.17±0.01	30.4±1.40
F2	0.479±0.13	0.604±0.13	20.60±1.12	1.25±0.01	31.7±1.23
F3	0.491±0.12	0.617±0.12	20.89±1.45	1.26±0.03	31.8±0.95
F4	0.487±0.11	0.612±0.12	20.41±1.23	1.25±0.01	31.8±0.89
F5	0.490±0.13	0.599±0.11	18.19±1.16	1.09±0.02	26.2±1.15
F6	0.479±0.11	0.605±0.13	20.82±1.31	1.25±0.01	29.9±1.63
F7	0.486±0.11	0.609±0.11	20.32±0.93	1.25±0.02	29.4±1.34
F8	0.477±0.14	0.600±0.14	20.51±0.96	1.25±0.02	30.3±0.90
F9	0.482±0.13	0.605±0.13	20.33±0.94	1.25+0.02	29.5±0.87

The bulk density of the Fenofibrate blend ranged from 0.477 g/ml to 0.490 g/ml and the tapped density ranged from 0.599 g/ml to 0.617 g/ml. The compressibility index of the blend ranged from 18.19% to 20.89% and Hausner's ratio ranged from 1.17 to 1.26. The angle of repose is ranged from 26.2 to 31.8. Hence the entire formulations blend was found to be good, passable flow property as seen in Figure 2.

Post Compression Study

The formulated Fenofibrate tablets were evaluated for post compression parameters.

Table 10. Post compression study of fenofibrate tablet.

Trial	Weight Variation (%)	Thickness (mm)	Hardness (N)	Friability (%)	Assay (%w/w)	Disintegration time (second)
F1	350±0.38	4.20±0.01	76±4	0.032	98.3±0.13	92±5
F2	351±0.12	4.21±0.01	78±3	0.063	99.7±0.28	165±6
F3	350±0.45	4.20±0.02	81±2	0.051	98.8±0.42	85±8
F4	350±1.02	4.21±0.01	75±6	0.045	98.5±0.31	185±3
F5	350±0.55	4.20±0.01	87±1	0.036	101.5±0.09	157±8
F6	350±0.81	4.20±0.01	84±6	0.052	99.1±0.37	199±5
F7	350±1.11	4.19±0.01	89±4	0.063	99.4±0.18	168±6
F8	350±0.75	4.21±0.01	69±1	0.069	98.2±0.16	161±5
F9	350±0.34	4.21±0.02	76±2	0.056	99.7±0.56	214±4

Weight Variation

The percentage weight variations for all formulations were tabulated in Table 19. The formulated batches passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits.

Thickness

The measured thickness of tablets of each batch ranged between 4.19 to 4.21 mm. The value shows that formulated tablets have uniform thickness. The parameters were reported in Table 10.

Hardness

The measured hardness of tablets of each batch ranged between 69 to 89 N. This ensures good handling characteristics of all batches. The results were shown in Table 10.

Friability

The values of friability test were tabulated in Table 19. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Assay

The assay of the formulations ranged between 98.2 to 101.5%w/w. The values are within the pharmacopoeial limits. The results were shown in Table 10.

Disintegration time:

The disintegration time of all the batches were found between 85 to 214 second and results were shown in Table 10. The effects of independent variables on disintegration time were investigated as per optimized response parameters

In-vitro Dissolution

The *in-vitro* dissolution of all the Fenofibrate tablet are given in table 11

Table 11. In vitro Dissolution study of Fenofibrate tablet

Time (minutes)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	19.23±0.28	16.43±1.33	25.78±0.25	14.11±1.17	15.52±1.12	11.43±0.21	13.12±2.33	15.34±0.24	16.53±0.39
20	34.43±1.52	29.47±0.12	43.54±.31	26.52±0.29	24.06±0.31	19.42±2.37	22.35±1.17	31.34±1.32	28.83±0.26
30	51.67±2.15	44.54±0.25	67.76±1.12	43.89±2.14	48.37±0.34	38.25±0.51	44.72±.014	53.52±0.56	49.75±1.33
40	75.34±1.13	71.21±2.31	78.42±0.23	69.63±0.32	64.84±1.18	57.61±1.64	66.43±0.31	71.64±0.12	68.64±0.67
45	86.57±0.34	84.84±0.11	89.75±0.21	81.33±0.25	74.47±1.26	69.36±0.36	71.57±1.22	82.45±1.25	79.22±0.15

The dissolution profiles of Fenofibrate studied in 0.05 M sodium lauryl sulfate in water.

The drug release of the formulations were determined as shown in table 12.

The cumulative drug releases for formulations were found within the range of 74.47–89.75%. The effects of independent variables on cumulative drug release were investigated as per optimized response parameters.

Optimization by 3^2 Factorial Design

On the basis of defined constraints for each independent variable, the Design Expert® Software version 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained.

Table 12. Results of independent variable and corresponding dependent variable according to 3^2 factorial design.

Run	Factor 1	Factor 2	Response 1	Response 2
	HPMC	***Crospovidone***	***Drug release at 45 minutes***	***Disintegration time***
	mg/tablet	*mg/tablet*	*%*	*Seconds*
F1	14	31.5	86	92
F2	14.	21	84	165
F3	10.5	31.5	89	85
F4	14	10.5	81	185
F5	17.5	31.5	74	157
F6	17.5	10.5	69	199
F7	17.5	21	71	168
F8	10.5	21	82	161
F9	10.5	10.5	79	214

Drug Release at 45 Minutes

The Figure 3 illustrates, when the amount of HPMC increase there is decrease in drug release and when the amount of Crospovidone increase there is increase in drug release.

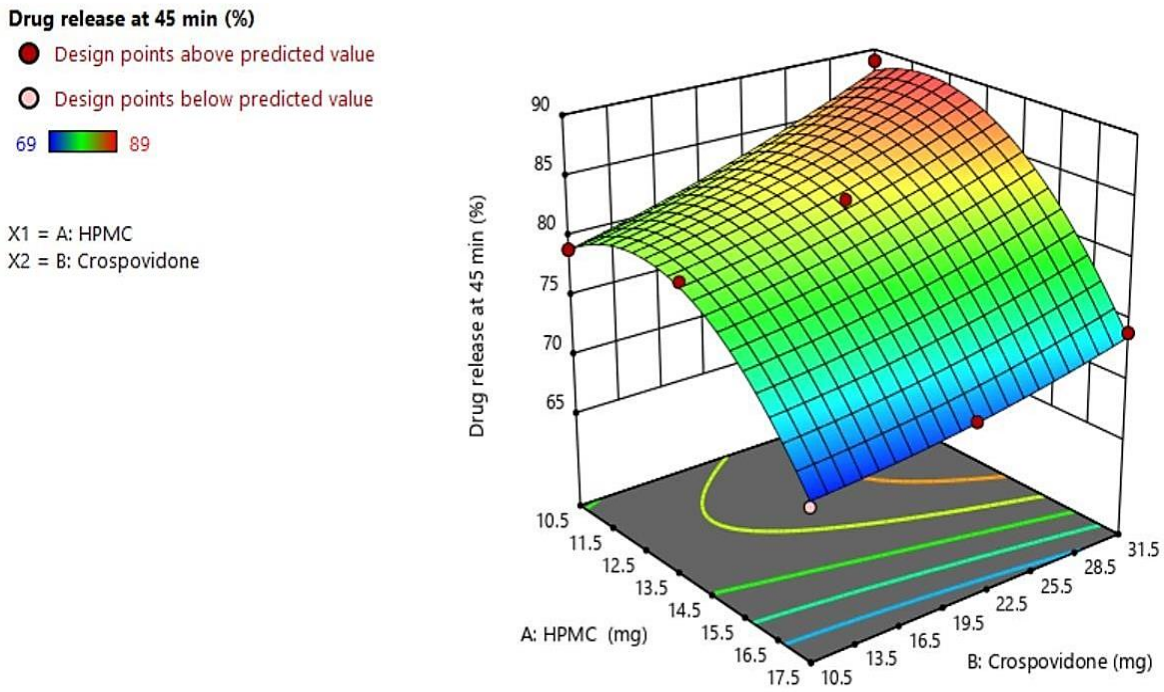

Figure 3. Effect of HPMC and crospovidone on drug release presented by response surface plots.

Disintegration Time

The Figure 4 illustrates, when the amount of HPMC increase there is increase in disintegration time and when the amount of crospovidone increase it shows decrease in disintegration time.

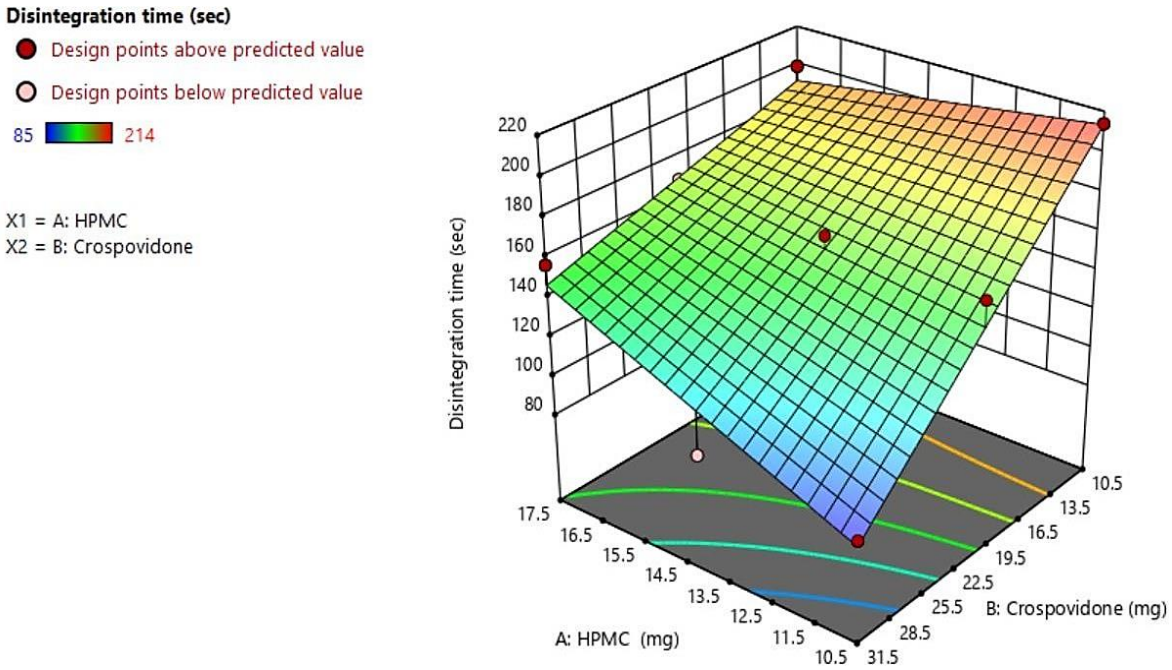

Figure 4. Effect of HPMC and Crospovidone on Disintegration time presented by response surface plots.

ANOVA

Table 22 represents the statistical parameters such as adjusted R2, predicted R2, model P values, adequate precision and %CV. Based on Table xx the responses drug release, disintegration time was well fitted to the linear model with P value of <0.0500. Table xx shows adjusted R2 for Y1 and Y2 which is in reasonable agreement with the predicted R2. Adequate precision measures the signal-to-noise ratio.

A ratio greater than 4 is desirable ratio indicating an adequate signal. This model can be used to navigate the design space. The results show that 90% of response variations in drug release, disintegration time could be described by Factorial design as a function of main composition. So it can be concluded that quadratic model was suitable model for analysis and could show very good interaction between drug release and disintegration time of Fenofibrate tablets.

Table 13. Response model and statistical parameters obtained from ANOVA for 3^2 factorial design.

Responses	Adjusted R2	Predicted R2	Model P-value	Adequate precision	%CV
Drug release at 45 minutes	0.9701	0.8806	0.0040	19.3346	1.49
Disintegration time	0.8755	0.7554	0.0033	12.7468	9.77

Point Prediction

The Fenofibrate tablets were formulated and responses were measured. The software generated the optimized formulation and predict the response based on the constraint. Then batch was formulated based on the suggested formulation and response were observed as shown in table 13. The observed values of responses were compared to the predicted values of the response and %error was calculated to validate the method. The observed value of Y1 and Y2 were in a close agreement to the predicted one. By this the validity of optimization procedure was proven. The point prediction has been shown in Table 14.

Desirability of optimum formulation was 0.992. When desirability value is between 0.8 and 1, the formulation quality is regarded to be acceptable and excellent. When this value is <0.63, the formulation quality is regarded as poor as seen in Table 15.

Table 14. Optimum formulation derived by factorial design.

Factor	HPMC	Crospovidone	Desirability
Optimum formulation	14.51	31.50	0.990

Table 15. Point Prediction for fenofibrate tablets.

Point Prediction	Drug release at 45 minutes (%)	Disintegration time (seconds)
Predicted	88.5	85
Observed	89.6	90
%error	0.7	5.88

% error = (observed value-predicted value)/predicted value x 100

Post Compression Study of Optimized Formulation

The Optimized formulation of Fenofibrate tablets were evaluated for post compression parameters. The results of weight variation, thickness, hardness, friability, assay, disintegration time as seen in Table 16.

All the post compression parameter of the above optimized trials are within the acceptable limit. So it was concluded that blend of the above trial is used for formulating fixed dose combination of monolithic and bilayer tablets as seen in Table 17 and Figure 5. For Pravastatin sodium tablet

Table 16. Post compression report of optimized fenofibrate tablets.

Trial	Weight Variation (%)	Thickness (mm)	Hardness (N)	Friability (%)	Assay (%w/w)	Disintegration time
Optimi-zed Formu-lation (Op)	350±0.38	4.20±0.21	80±4	0.063	98.34±0.31	90±5

Table 17. *In-vitro* dissolution study of fenofibrate optimized formulation.

Time(minutes)	Optimized Formulation
10	24.62±0.28
20	44.36±1.52
30	63.21±0.15
40	79.74±0.13
45	89.67±0.34

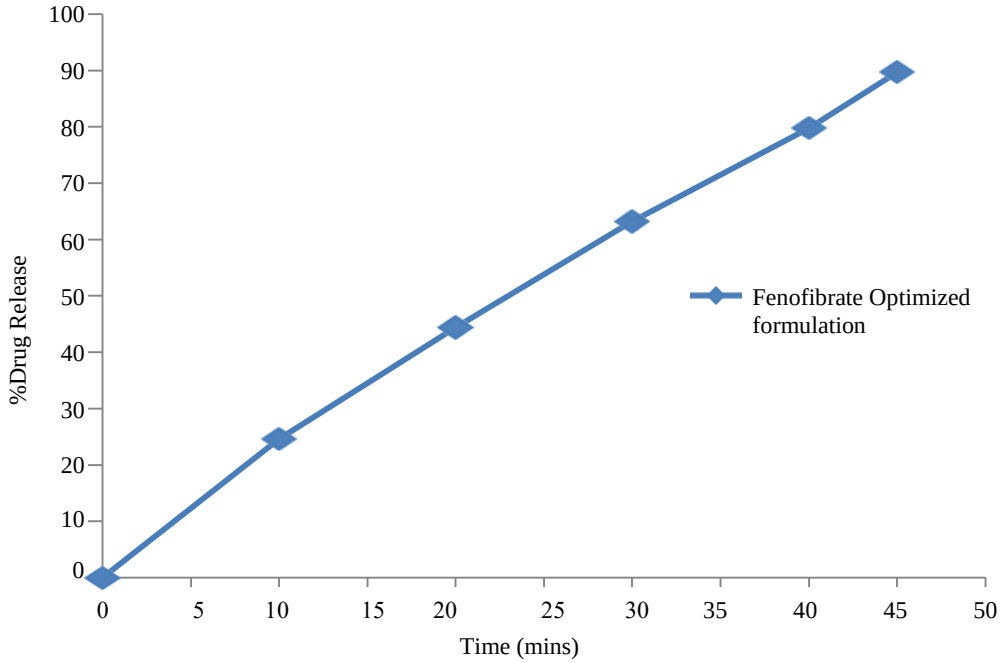

Figure 5. In vitro dissolution study of fenofibrate optimized formulation.

Precompression Study

The formulated blends of Pravastatin sodium were evaluated for precompression parameters.

Table 27. Precompression study of Pravastatin sodium blend

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
P1	0.440±0.12	0.737±0.11	40.2±0.52	1.67±0.01	43.4±1.20
P2	0.470±0.13	0.690±0.12	31.4±1.22	1.46±0.01	37.7±1.33
P3	0.488±0.12	0.621±0.12	21.7±0.43	1.22±0.02	28.5±1.45

Trial P1 precompression parameters indicates that it has extremely poor flow property, trial P2 show poor flow property but comparatively better flow property than trial P1. The trial P3 had shown fair flow property.

Post Compression Study

The formulated Pravastatin sodium tablets were evaluated for post compression parameters. The results of weight variation, thickness, hardness, friability, assay, disintegration time are given in Table 18.

Table 18. Post compression study of pravastatin sodium tablets.

Trial	Weight Variation (%)	Thickness (mm)	Hardness (N)	Friability (%)	Assay (%w/w)	Disintegration time
P1	280±0.72	3.37±0.01	35±3	0.95	98.9±0.24	30±5
P2	280±0.22	3.24±0.02	80±5	0.43	99.5±0.39	28±6
P3	400±0.21	4.35±0.01	110±3	0.31	99.7±0.19	32±4

Weight variation

The percentage weight variations for all formulations were tabulated in Table 18. All the formulated batch passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits.

Thickness

The measured thickness of tablets of each batch have uniform thickness. The parameters were reported in Table 18.

Hardness

The measured hardness of tablets of each batch ranged between 35–110 N. The results were shown in Table 18.

Friability

The values of friability test were tabulated in Table 18. The %friability of each batch was ranged between 0.3–0.9.

Assay

The assay of the formulations ranged between 98.2–99.8%w/w. The values are within the limits. The results were shown in Table 18.

Disintegration Time

The disintegration time of all the batches were found between 28 to 32 seconds and results were shown in Table 18.

***In-vitro* Dissolution**

The *in-vitro* dissolution of all the Pravastatin sodium tablet are given in Table 29 and Figure 8.

The dissolution profiles of Pravastatin sodium tablet were studied in 0.05 M sodium lauryl sulphate in water. The cumulative drug releases for formulations were found within the range of 91.7–96.3%.

Table 19. *In-vitro* dissolution study of pravastatin sodium tablet.

Time (minutes)	F1	F2	F3
10	62.73±0.13	58.65±0.33	55.61±0.35
20	89.26±1.34	84.81±0.22	86.36±0.81
30	93.41±0.15	91.32±1.15	90.72±0.12
40	95.87±0.45	93.73±0.31	91.28±0.25
45	96.33±0.31	94.58±0.16	91.74±0.19

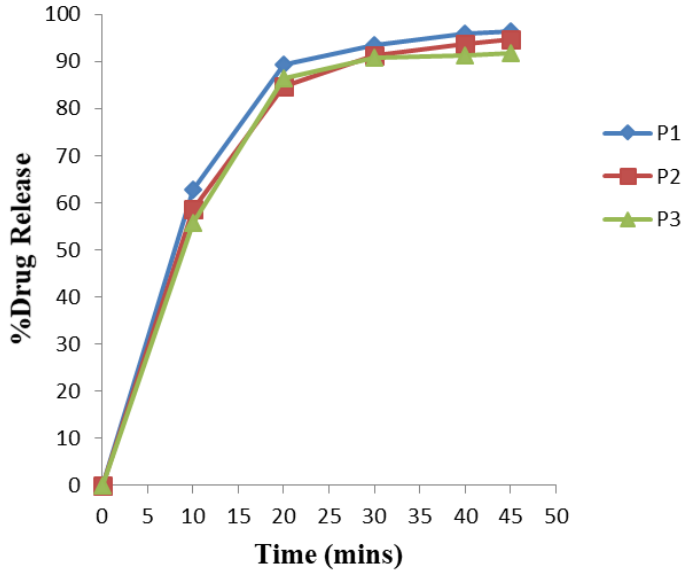

Figure 6. In vitro Dissolution study of Pravastatin sodium tablet (P1 – P3).

From the above observation it has been clear that trial P1 shows extremely poor flow property (compressibility index 40.2), lower hardness with higher %friability, hence it is concluded that direct compression is not feasible. So trial P2 was formulated using wet granulation method all the post compression parameter was within the acceptable range but trial P2 show poor flow property but comparatively better flow property (compressibility index 31.4) than trial P1 as seen in fig 6.

Hence trial P3 was formulated as like trial P2 but with increased quantity of microcrystalline cellulose in extragranular material. The observed pre and post compression parameter of trial P3 (compressibility index 21.7) was within the acceptable limit. Hence trial P3 was chosen as optimized formulation. Thus for the further formulation of Fixed dose combination of bilayer and monolithic tablet, the blend of trial P3 was finalized as seen in table 19.

POST COMPRESSION STUDY OF BILAYER TABLETS

The compressed bilayer tablets were evaluated for following parameters such as post compression parameters. The results of weight variation, thickness, hardness, friability, assay, disintegration time as seen in Table 20.

Table 20. Post compression study of bilayer tablets.

Parameter	Result
Weight variation (mg)	750±0.54
Thickness (mm)	6.23±0.01
Hardness (N)	108±4
Friability (%)	0.12
Disintegration time (seconds)	94±4
Assay (Simultaneous Estimation Method) i. Fenofibrate (%) ii. Pravastatin sodium (%)	 98.34±0.15 98.79±0.27

Bilayer tablets passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits. The measured hardness of bilayer tablet is 108 N it clearly explain that it has sufficient mechanical strength to resist the transportation. The % friability was less than 1% ensuring that the tablets were mechanically stable. The measured thickness of tablets were uniform. The disintegration time were found to be 94 seconds. The percentage of drug content for Fenofibrate was

found to be 98.34% w/w and 98.79%w/w for Pravastatin sodium, it complies with official specifications as seen in Table 21.

Table 21. *In-Vitro* dissolution of bilayer tablet

Time (minutes)	Fenofibrate	Pravstatin sodium
10	21.45±0.23	53.64±0.35
20	37.75±0.42	81.75±0.13
30	53.83±0.15	85.41±0.17
40	79.58±0.12	86.94±0.15
45	88.48±0.36	90.72±0.29

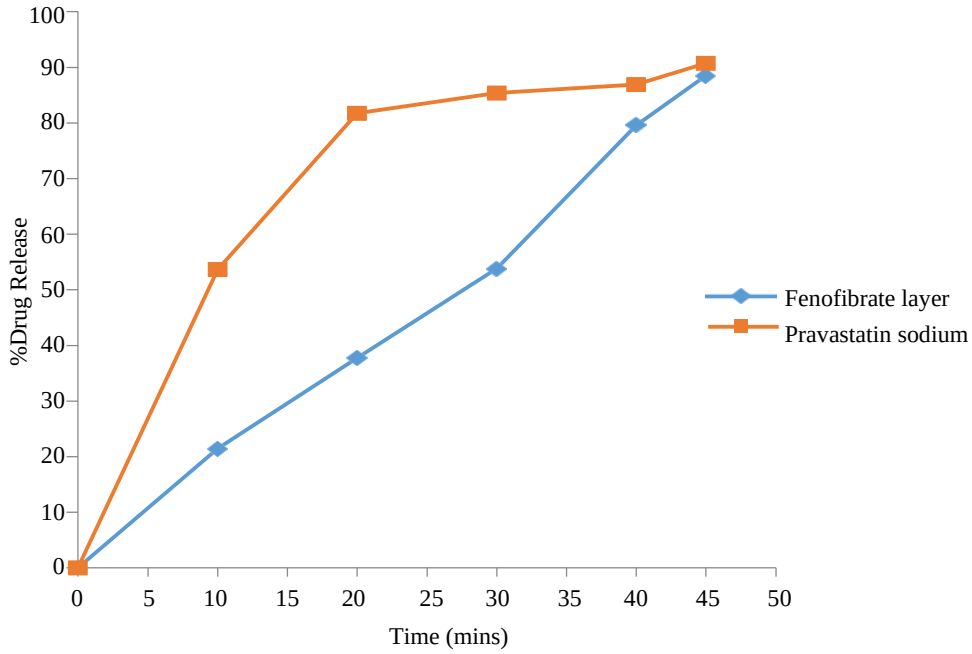

Figure 7. In vitro dissolution study of bilayer tablet.

The bilayer tablets showed release of 88.48% of Fenofibrate in 45 minutes and 90.72% of Pravastatin sodium in 45 minutes. The drug release of the bilayer formulation was within the Pharmacopoeial limits as seen in fig 7.

POST COMPRESSION STUDY OF MONOLITHC TABLETS

The compressed monolithic tablets were evaluated for following parameters such as post compression parameters as seen in Table 22.

Table 22. Post Compression Study of monolithic tablets

Parameter	Result
Uniformity of weight (mg)	750±0.28
Thickness (mm)	6.23±0.01
Hardness (N)	95±4
Friability (%)	0.17
Disintegration time (seconds)	73±4
Assay (Simultaneous Estimation Method) i. Fenofibrate (%)	98.62±0.12

ii. Pravastatin sodium (%)	99.75±0.24

Table 23. *In-Vitro* dissolution of monolithic tablet

Time (minutes)	Fenofibrate	Pravstatin sodium
10	19.37±0.23	55.62±0.25
20	35.46±0.42	82.89±0.33
30	55.34±0.15	86.21±0.47
40	77.52±0.12	88.94±0.25
45	86.74±0.28	90.68±0.19

Monolithic tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits. The measured hardness of monolithic tablet is 95±4 N it clearly explain that it has sufficient mechanical strength to resist the transportation. The % friability was less than 1% ensuring that the tablets were mechanically stable. The measured thickness of tablets were uniform. The disintegration time were found to be 73±4 seconds. The percentage of drug content for was found to be 98.62% for Fenofibrate and 99.75% for Pravastatin sodium, it complies with official specifications as seen in Table 23.

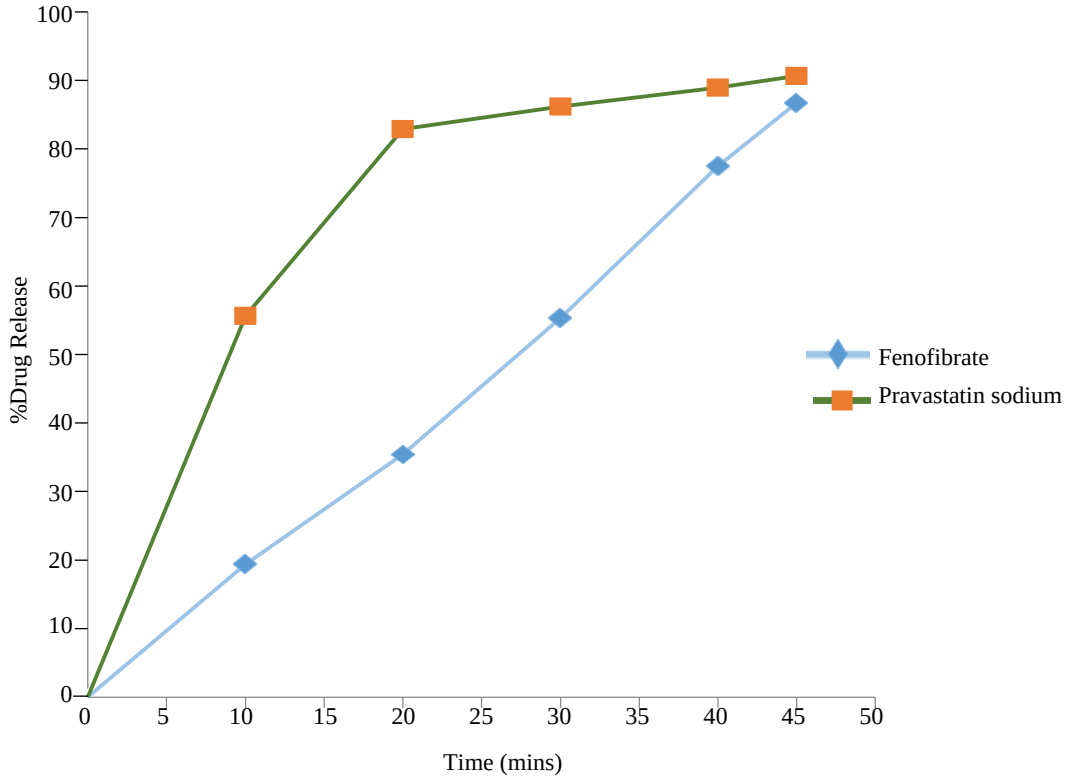

Figure 8. In vitro dissolution study of monolithic tablet.

The monolithic tablets showed release of 86.74% of Fenofibrate in 45 minutes and 90.68% of Pravastatin sodium in 45 minutes. The drug release of the monolithic formulation was within the pharmacopoeial limits as seen in Figure 8.

Similarity Factor and Differential Factor

The dissolution profiles of bilayer and monolithic tablet were compared by calculating similarity factor (f2) and dissimilarity factor (f1). The f2 and f1 was found to be 83 and 4 for the comparison of dissolution profiles of Fenofibrate layer in the bilayer and monolithic tablet. The f2 and f1 was found

to be 88 and 2 for the comparison of dissolution profiles of Pravastatin sodium layer in the bilayer and monolithic tablet. It was anticipated that due to the difference in BCS class (Fenofibrate is a BCS class 2 drug and Pravastatin sodium is a BCS class 3 drug), the dissolution behavior of the both drugs may differ, where one drug may alter the dissolution behaviour of another drug.

But as per the experimental result there is no considerable differences between the drug release from monolithic and bilayer tablet as seen in Table 24.

For Fenofibrate Layer

For Pravastatin Sodium Layer

Table 24. Similarity factor and differential factor of fenofibrate layer.

Differential Factor-f1 (Acceptable criteria: 0–15)	4
Similarity Factor–f2 (Acceptable criteria: 50–100)	84

Table 25. Similarity factor and differential factor of pravastatin sodium layer.

Differential Factor-f1 (Acceptable criteria: 0–15)	2
Similarity Factor–f2 (Acceptable criteria: 50–100)	88

Hence it was concluded that, bilayer tablet show no significant advantage over monolithic tablet on the basis of drug release. So only based on stability studies of both the prototype formulation, monolithic or bilayer tablet dosage form will be chosen for scale up process as seen in Table 25.

Stability Studies

Stability studies were carried out of the optimized formulation at 40ºC ± 2ºC & 75% ± 5% RH for 30 days as per ICH guidelines. At various time intervals (initial, 15 days & 30 days), samples were evaluated for appearance, weight variation, thickness, hardness, friability, disintegration time and *In-vitro* dissolution.

There was no major change in the evaluation parameters. The results were shown below, So it was concluded that monolithic prototype formulation is chosen for the scale up process of fixed dose combination of Fenofibrate and Pravastatin sodium tablet as seen in table 26, 27, 28,29.

For Bilayer Tablet

For Monolithic Tablet

Table 26. Stability study of bilayer formulation.

Parameters	**Storage condition 40°C ± 2°C & 75% ± 5% RH**		
	Intial	***15 days***	***30 days***
Appearance	*No change*	*No change*	*No change*
Weight variation (mg)	750	750	750
Thickness (mm)	6.23	6.23	6.23
Hardness (N)	108	106	105
Friability (%)	0.12	0.12	0.13
Disintegration time (seconds)	94	91	95

Table 27. Assay and dissolution profile of bilayer tablets.

Parameters		Storage condition 40°C ± 2°C & 75% ± 5% RH		
		Intial	***15 days***	***30 days***
Assay (%)	Fenofibrate	98.34	98.21	98.15
	Pravastatin sodium	98.79	98.69	98.79
% drug release	Fenofibrate	88.48	87.79	88.62
	Pravastatin sodium	90.72	90.68	91.12

Table 28: Stability study of monolithic formulation.

Parameters	Storage condition 40°C ± 2°C & 75% ± 5% RH		
	Intial	***15 days***	***30 days***
Appearance	*No change*	*No change*	*No change*
Weight variation (mg)	750	750	750
Thickness (mm)	6.23	6.23	6.23
Hardness (N)	95	96	93
Friability (%)	0.17	0.17	0.18
Disintegration time (seconds)	73	70	71

Table 29. Assay and Dissolution profile of monolithic tablets

Parameters		Storage condition 40°C ± 2°C & 75% ± 5% RH		
		Intial	***15 days***	***30 days***
Assay	Fenofibrate	98.62	98.54	98.33
	Pravastatin sodium	99.75	99.68	99.52
% drug release	Fenofibrate	86.74	85.24	87.12

SUMMARY AND CONCLUSION:

The aim of this is study is to formulate and evaluate fixed dose combination of Fenofibrate and Pravastatin sodium in tablet dosage for the treatment of Dyslipidemia. Monolithic and Bilayer tablets prototype formulation were investigated because there is a compatibility in between Fenofibrate and Pravastatin sodium based on Infrared spectroscopy studies, So a monolithic tablet is possible. But Fenofibrate is a BCS class 2 drug and Pravastatin sodium is a BCS class 3 drug. Due to the difference in BCS class, the dissolution behavior of the both drugs may differs, where one drug may alter the dissolution behaviour of another drug, so a bilayer approach is also chosen. Based on dissolution studies and stability studies of both the prototype formulation, monolithic or bilayer tablet dosage form will be chosen for scale up process.

So, experiment was breaked into three part

Part 1: Fenofibrate part is formulated and optimized.

Part 2: Pravastatin sodium part is formulated and optimized.

Part 3: Based on above formulaion and optimization, Optmized blend of both Fenofibrate and Pravastatin sodium is used for formulating fixed dose combination of monolithic and bilayer tablet.

By comparing the dissolution and stability data of the monolithic and bilayer tablet. Appropriate tablet dosage form (i.e., monolithic or bilayer tablet) will be chosen for scale up process as a Fixed dose combination tablet.

Fenofibrate Layer

For the formulation and optimization of fenofibrate layer, two factor three level factorial design was used as experimental design for optimization with a minimum of nine run. All the nine trial (F1 – F9) has been formulated according to the experimental design by wet granulation method. The independent variable studied were amount of HPMC (X1) and amount of crospovidone (X2). Drug release at 45 minutes (Y1) and disintegration time (Y2) was chosen as dependent variable. The software generated the optimized formulation and predict the response based on the constraint and the response of the dependent variable of the nine trial. Then batch was formulated based on the suggested formulation and response were obsereved. The observed pre and post compression parameter of the suggested trial was within the acceptable limit. Hence it has chosen as optimized formulation and used for formulating fixed dose combination of bilayer and monolithic tablets.

Pravastatin Sodium Layer

For the formulation and optimization of Pravastatin sodium layer, Trial and error method was employed. Total three trial (P1-P3) has been formulated. Trial P1 was formulated by direct compression, the results of this trial indicates that it has extremely poor flow property and lower hardness and high %friability. So it is concluded that direct compression is not feasible. So trial P2 is formulated using wet granulation all the post compression parameter was within the acceptable range but trial P2 show poor flow property. Hence trial P3 was formulated as like trial P2 but with increased quantity of cellulose microcrystalline in extragranular material. The observed precompression parameter of trial P3 shows it has good flow property and weight variation, hardness, friability and assay where within the limit. The disintegration time of Trial P3 was found to be optimum. The *In-vitro* drug dissolution of the Trial P3 was 91.74%

Hence trial P3 was chosen as optimized formulation. Thus for the further formulation of Fixed dose combination of bilayer and monolithic tablet, the blend of trial P3 was used.

Monolithic and Bilayer Tablet

The optimized blend of Fenofibrate and Pravastatin sodium is used for preparing both monolithic and bilayer tablets. The post compression parameter for monolithic and bilayer tablet are within the acceptable limit. But the experimental result clearly explains that there is no considerable differences between monolithic and bilayer tablet in terms of drug release and stability studies.

Hence it was concluded that, bilayer tablet show no significant advantage over monolithic tablet on the basis of drug release and stability. So monolithic prototype formulation is chosen for the scale up process of fixed dose combination of Fenofibrate and Pravastatin sodium tablet.

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