EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 11
271-284
Year: 2023

FORMULATION AND EVALUATION OF FIXED DOSE COMBINATION OF FENOFIBRATE AND PRAVASTATIN SODIUM IN TABLET DOSAGE FORM

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Article Received on 20/09/2023 **Article Revised on 10/10/2023** **Article Accepted on 30/10/2023**

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. 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. For the formulation and optimization of fenofibrate layer, two factor three levelfactorial 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 amountof crospovidone (X2). Drug release at 45 minutes (Y1) and disintegration time (Y2) was chosenas 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. 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 formulatedby direct compression, the results of this trial indicates that it has extremely poor flow propertyand 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 theTrial 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.

KEYWORDS: Formulation, Evaluation, Fixed Dose Combination, Fenofibrate And Pravastatin Sodium, Tablet Dosage Form.

INTRODUCTION
For the last few decades, the pharmaceutical industry has been researching the potential of improving the currently available medicinal products, including increasing the safety and effectiveness of their use or reducing the side effects of therapy. The work carried out in this direction also aims to increase patients' access to modern therapies and facilitate patients' compliance with their doctor's instructions. In particular, new drug applications (forms, administration routes) and more cost-effective and improved technologies for their production are being developed. Despite the growing popularity of FDC-type drugs and a significant increase in the formulations available on the market for various disease entities, FDC-type drugs have drawbacks that limit their use or raise some controversies related to the risk for the patient.[1,2]

However, as with any innovative solution, special attention should be paid to whether the advantages outweigh the disadvantages, which we see in the case of FDCs. The observed benefit in favor of their use is confirmed by the increasing number of formulations on the market and the frequency of their use in patients, particularly in chronic diseases requiring multi-drug therapy. Developed in the 19th century, the two-piece hard capsule is still a popular dosage form in the pharmaceutical industry; moreover, it is a suitable dosage form for delivering fixed-dose combinations drugs (FDCs). The first patent for producing capsules and their capsules was issued in France in 1834. These were hard gelatin capsules. Their production technology was to solidify hot liquid gelatin on a cold brass rod. The capsules quickly gained popularity in France and abroad.

In 1835, France alone used 3.5 tons of gelatin.[3] There are two main types of capsules used as dosage forms in the pharmaceutical industry: gelatin and hydroxypropyl methylcellulose (HPMC) capsules.[4] Combodart/Jalyn was the first FDC designed to treat moderate to severe benign prostatic hyperplasia (BPH) and reduce the risk of acute urinary retention in BPH-related surgery.[5] The product consists of dutasteride, an alpha-reductase inhibitor, and an alpha-blocker, tamsulosin hydrochloride. Dutasteride delays the progression of BPH by inhibiting the production of dihydrotestosterone, the hormone that stimulates the growth of the male prostate, while tamsulosin provides quick symptom relief by reducing smooth muscle tone in the prostate and bladder neck. A polypill is a drug product in a pill (i.e., capsule or tablet) that combines multiple active pharmaceutical ingredients. The prefix "poly" means "many", referring to many different drugs in a given "pill". An occasional synonym is combopil. It is commonly manufactured as a fixed-dose medicinal product (FDC) to treat or prevent chronic disease. The term "polypill" was first used to prevent cardiovascular disease.[6,7,8] but has since gained wider acceptance, including combinatorial drugs that existed before the term was used.

The first combination drugs for hypertension that appeared in the 1950s included hydralazine or reserpine. In the 1960s, drugs containing a combination of methyldopa and a diuretic, and reserpine and a diuretic, were introduced.[9] They demonstrated high antihypertensive efficacy and, at that time, constituted a valuable supplement to the treatment of arterial hypertension. However, they were withdrawn due to frequent and severe side effects. We had to wait several years for other combination drugs to follow.

Over the past decade, tremendous efforts have been made to develop a variety of cardiovascular polypills in response to the global rise in cardiovascular disease. In 2001, experts from the World Health Organization and the Wellcome Trust discussed interventions in noncommunicable diseases and noted that taking one pill can encourage patient compliance and seriously reduce drug costs.[10] In 2002, the annual report of the World Health Organization identified a significant potential impact on public health and cost-effectiveness of increasing access to combined cardiovascular treatment.[11] The choice of drugs to be included in the combined pill is a multi-step process. A Lancet article outlined that a four-component combination pill would reduce cardiovascular risk by about 75% among people with vascular disease.[12] Wald and Law, in 2003, suggested a pill consisting of six different compounds to maximize the potential benefits. They presented a statistical model that suggested how widespread use of such a polypill could reduce mortality from heart disease and stroke by up to 80%, while using drugs whose interactions are already relatively well known and understood due to many years of prescribing them together.[6,7]

The Fuster-CNIC-Ferrer CV Polypill as a multi-layered formulation, housed in a capsule, was developed using a technology patented by Ferrer.[13]

The development of FDCs is becoming increasingly high, either to improve compliance and/or to benefit from the added effects of the two or more active drugs given together. In terms of commercial perspective, opportunities to maximize the value of single drug products, to sustain their product's life, and ultimately to extend market exclusivity with a resultant increasein sales and profits.

Dyslipidemia is recognized as a prominent risk factor for cardiovascular disease pharmacological regulation of lipid metabolism in patients with dyslipidaemia is undeniably associated with significant reductions in risk of cardiovascular morbidity and mortality. Where, Statins and fibrates are two classes of drug that have demonstrated significantly reduced cardiovascular event rates in prospective, placebo-controlled clinical trials. However, monotherapy with either of these drugs does not always achieve lipid goals in the dyslipidaemic patient. Furthermore, even in those patients who do achieve lipid goals with monotherapy there often remains a high residual risk of cardiovascular events, warranting even further therapy. An effective therapeutic approach for many of these patients is combination therapy with statins and fibrates. Particularly Fenofibrate and Pravastatin as combination therapy shown to be more effective than pravastatin alone in reducing non-HDL-cholesterol levels. Non-HDL- cholesterol levels were reduced on average by around 14% in patients taking Pravastatin and Fenofibrate as combination therapy compared with 6% in patients taking pravastatin alone.

Hence an attempt was made to develop Fixed Dose Combination of Fenofibrate and Pravastatin sodium for the treatment of dyslipidemia in tablet dosage form.

So, Monolithic and Bilayer tablets prototype formulation were investigated. Since there is a compatibility in between Fenofibrate and Pravastatin sodium based on Infrared spectroscopy studies, a monolithic tablet is feasible in terms of manufacturing point of view.

Since Fenofibrate is a BCS class II drug and Pravastatin sodium is a BCS class III drug. Due to the difference in BCS class, the dissolution behavior of the both drugs differs, where one drug may alter the dissolution behavior 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.

Fenofibrate activates peroxisome proliferator activated receptor alpha (PPARα), increasing lipolysis, activating

lipoprotein lipase, and reducing apoprotein C-III. PPARα is a nuclear receptor and its activation alters lipid, glucose, and amino acid homeostasis. Activation of PPARα activates transcription of gene transcription and translation that generates peroxisomes filled with hydrogen peroxide, reactive oxygen species, and hydroxyl radicals thatalso participate in lipolysis. This mechanism of increased lipid metabolism is also associated with increased oxidative stress on the liver. In rare cases this stress can lead to cirrhosis and chronic active hepatitis.

The aim of the work is to formulate and evaluate fixed dose combination of Fenofibrate and Pravastatin sodium in tablet dosage form.

MATERIALS AND INSTRUMENTATION

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

S.No	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, Unitedstate	Wetting agent
5.	Lactose Monohydrate	DMV-Fonterra, Germany	Diluent
6.	Microcrystalline Cellulose	Du point, Ireland	Diluent

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.

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 bilayerfixed 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 bindersolution.
- 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 granulesand 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 parametersand 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.

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.

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
Microcrystallinecellulose	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 LaurylSulfate	5.20	5.20	5.20	5.20	5.20	5.20	5.20	5.20	5.20
Docusatesodium	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Extragranular material									
Microcrystallinecellulose	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									
Magnesium stearate	1.70	1.70	1.70	1.70	1.70	1.70	1.70	1.70	1.70

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 sodiumphosphate, 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 withthe above blend.
- Magnesium stearate was passed through #60 mesh mixed for 2 minutes with the aboveblend.
- The tablets were compressed by 8 station tablet compression machine using 13 × 6 mm oblong punch.

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
Core tablet weight	280.00

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 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 for2 minutes.
- The tablets were compressed by 8 station tablet compression machine using 14 × 7 mmoval punch.

FORMULATION OF BILAYER TABLETS OF FENOFIBRATE ANDPRAVASTATIN 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 compressionis 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 ANDPRAVSTATIN 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 forthe 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. The results are given in the Figures below.

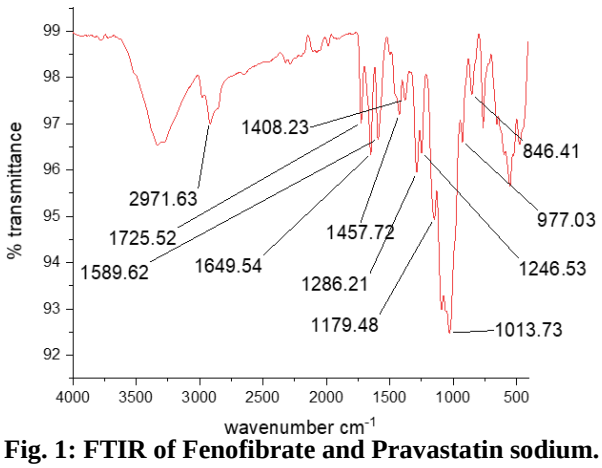

Fig. 1: FTIR of Fenofibrate and Pravastatin sodium.

Table 6: IR Spectral Interpretation of Fenofibrate and Pravastatin sodium.

S.No	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.

For Fenofibrate Tablet

Precompression Study

The formulated blends of Fenofibrate were evaluated for precompression parameters.

The results are given in Table 7.

Table 7: Precompression study of Fenofibrate blend.

Formulation	Bulk density (gm/ml)	Tapped densitygm/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.

Post Compression Study

The formulated Fenofibrate tablets were evaluated for post compression parameters. The results of weight variation, thickness, hardness, friability, assay, disintegrationtime are given in Table 8.

Table 8: Postcompression 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 8. The formulated batches passed weight variation test as the Percentage weight variation was withinthe 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 8.

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 8.

Friability

The values of friability test were tabulated in Table 8. The % friability was less than1% 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 8.

Disintegration time

The disintegration time of all the batches were found between 85 to 214 second and results were shown in Table 8.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.

Table 9: 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± 0.31	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 0.05M sodium lauryl sulfate in water.

The drug release of the formulations were determined.

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 asper 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 10: 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 Fig. 2 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.

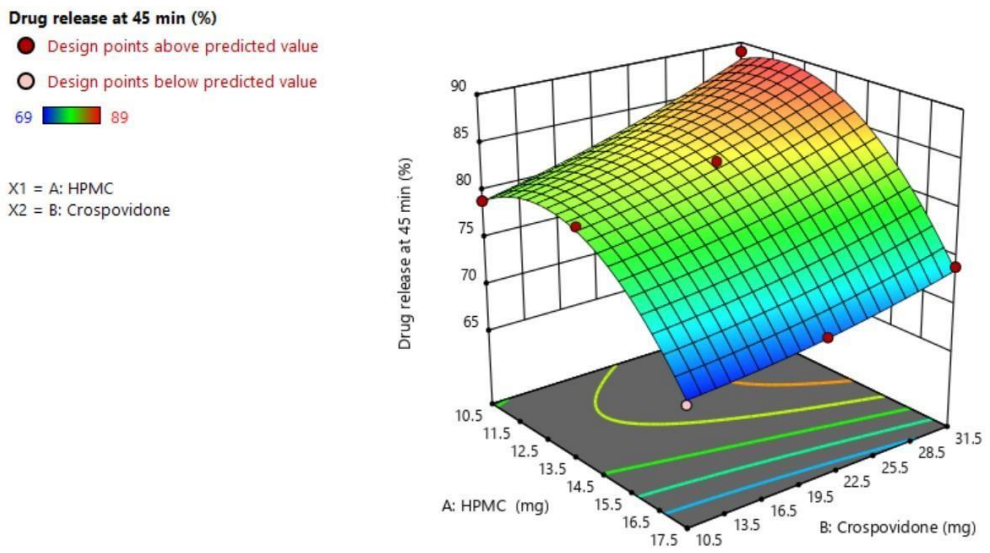

Fig. 2: Effect of HPMC and Crospovidone on Drug release presented by response surfaceplots.

Disintegration time

The Fig.3 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.

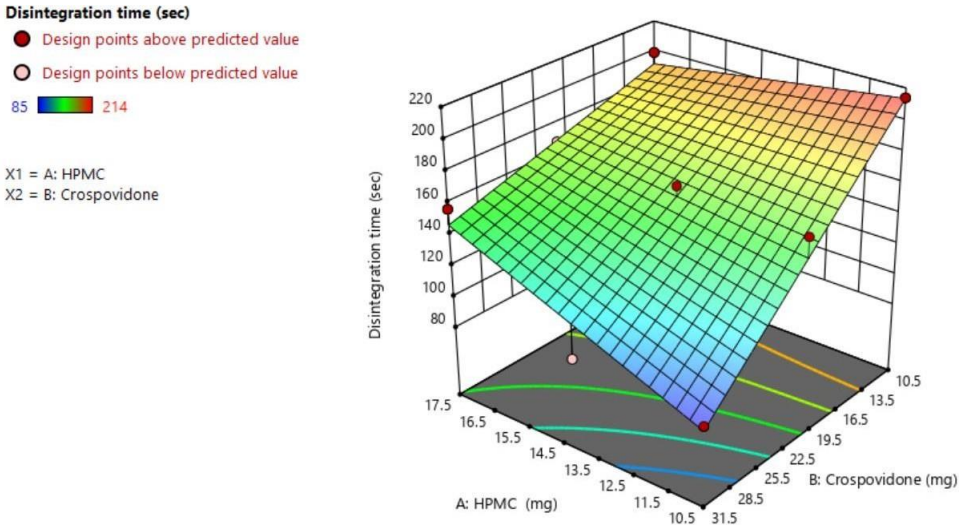

Fig. 3: Effect of HPMC and Crospovidone on Disintegration time presented by response surface plots.

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 Fenofibratetablets.

Table 12: Response Model And Statistical Parameters Obtained from ANOVA for 3^2 Factorial Design.

Responses	Adjusted R2	PredictedR2	Model Pvalue	Adequateprecision	%CV
Drug releaseat 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 obsereved. The observed values of responses were compared to the predicted values of the response and %errorwas 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 13.

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.

Table 13: Optimum formulation derived by Factorial design.

Factor	HPMC	Crospovidone	Desirability
Optimum formulation	14.51	31.50	0.990

Table 14: 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 compressionparameters. The results of weight variation, thickness, hardness, friability, assay, disintegration time and *In - vitro* dissolution study are given in table 15 & 16.

Table 15: 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 16: *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

All the post compression parameter of the above optimized trials are within theacceptable limit. So it was concluded that blend of the above trial is used for formulating fixed dose combination of monolithic and bilayer tablets.

For Pravastatin sodium tablet

Precompression Study

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

The results are given in Table 17.

Table 17: Precompression study of Pravastatin sodium blend.

Formulation	Bulk density (gm/ml)	Tappeddensity (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle ofrepose (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 trialP3 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, disintegrationtime 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 Table18. All the formulated batch passed weight variation test as the Percentage weight variation was withinthe 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 resultswere shown in Table 18.

Friability

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

Assay

The assay of the formulations ranged between 98.2 - 99.8%w/w. The values are withinthe 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 dissolution profiles of Pravastatin sodium tablet were studied in 0.05M sodium lauryl sulphate in water. The cumulative drug releases for formulations were found within therange 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

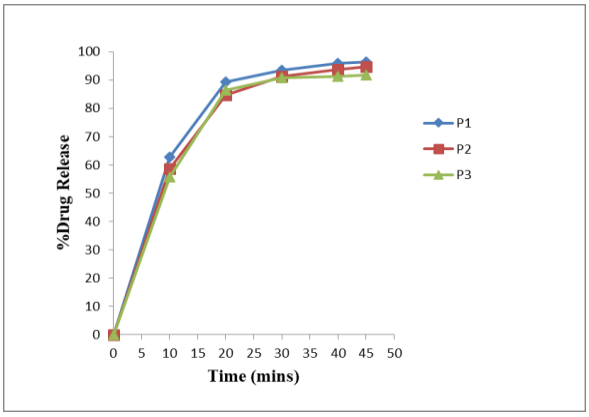

Fig. 4: In vitro Dissolution study of Pravastatin sodium tablet (P1 – P3).

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 index31.4) than trial P1.

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.

POST COMPRESSION STUDY OF BILAYER TABLETS

The compressed bilayer tablets were evaluated for following parameters such as post compression parameters.

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.

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

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.

POST COMPRESSION STUDY OF MONOLITHC TABLETS

The compressed monolithic tablets were evaluated for following parameters such as post compression parameters.

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 (%) ii) Pravastatin sodium (%)	 98.62±0.12 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.

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.

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 alterthe dissolution behaviour of another drug.

But as per the experimental result there is no considerable differences between the drugrelease from monolithic and bilayer tablet.

For fenofibrate 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

For Pravastatin sodium layer

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.

Stability studies

Stability studies were carried out of the optimized formulation at 40°C ± 2°C & 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 scaleup process of fixed dose combination of Fenofibrate and Pravastatin sodium tablet.

For Bilayer Tablet

Table 26: Stability study of bilayer formulation.

Parameters	Storage condition 40^{O}C ± 2^{O}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^{0}C ± 2^{0}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

For Monolithic Tablet

Table 28: Stability Study of Monolithic Formulation.

Parameters	Storage condition 40^{O}C ± 2^{O}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^{O}C ± 2^{O}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
	Pravastatin sodium	90.68	90.81	89.76

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 Pravastatinsodium 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 upprocess.

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 ofmonolithic 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 propertyand 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 theTrial 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 andstability 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.

REFERENCE

1. Auwal F., Dahiru M., Abdu-Aguye S. Availability and Rationality of Fixed Dose Combinations Available in Kaduna, Nigeria. *Pharm. Pract.*, 2019; 17: 1470. doi: 10.18549/PharmPract.2019.2.1470. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Dalal K., Ganguly B., Gor A. Assessment of Rationality of Fixed Dose Combinations Approved in CDSCO List. *J. Clin. Diagn. Res.*, 2016; 10: FC05–FC08. doi: 10.7860/JCDR/2016/17856.7691. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. Podczeck F., Jones B.E. *Pharmaceutical Capsules*. Pharmaceutical Press; London, UK., 2004. [Google Scholar]
4. El-Malah Y., Nazzal S., Bottom C.B. Hard Gelatin and Hypromellose (HPMC) Capsules: Estimation of Rupture Time by Real-Time Dissolution Spectroscopy. *Drug Dev. Ind. Pharm.*, 2007; 33: 27–34. doi: 10.1080/03639040600685183. [PubMed] [CrossRef] [Google Scholar]
5. Combodart 0.5 Mg/0.4 Mg Hard Capsules—Summary of Product Characteristics (SmPC)—(Emc) [(accessed on 18 March 2022)]. Available online: https://www.medicines.org.uk/emc/product/507/smpc#gref
6. Wald N.J., Wald D.S. The Polypill Concept. *Heart.*, 2010; 86: 257–260. doi: 10.1136/hrt.2009.186429. [PubMed] [CrossRef] [Google Scholar]
7. Wald N.J., Law M.R. A Strategy to Reduce Cardiovascular Disease by More than 80% *BMJ.*, 2003; 326: 1419. doi: 10.1136/bmj.326.7404.1419. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Polypill. The Free Dictionary. polypill. (n.d.) Abused, Confused, & Misused Words. (2007, 2013) [(accessed on 19 January 2022)]. Available online: https://www.thefreedictionary.com/polypill
9. Broncel M., Wójcik K., Jabłonowska E. Expanding role of single tablets regimens in selected therapeutic areas. *Med. Rodz.*, 2015; 2: 79–88. [Google Scholar]
10. WHO Secondary Prevention of Noncommunicable Diseases in Low- and Middle-Income Countries through Community-Based and Health Service Interventions; Proceedings of the World Health Organization-Wellcome Trust Meeting of Experts; Cambridge, UK. 1–3 August 2001; Geneva, Switzerland: World Health Organization, 2002. [Google Scholar]
11. World Health Report: Reducing Risks, Promoting Healthy Life., 2002. [(accessed on 19 January 2022)]. Available online: https://www.who.int/publications-detail-redirect/9241562072
12. Yusuf S. Two Decades of Progress in Preventing Vascular Disease. *Lancet.*, 2002; 360: 2–3. doi: 10.1016/S0140-6736(02)09358-3. [PubMed] [CrossRef] [Google Scholar]
13. Tamargo J., Castellano J.M., Fuster V. The Fuster-CNIC-Ferrer Cardiovascular Polypill: A Polypill for

Secondary Cardiovascular Prevention. *Int. J. Cardiol*, 2015; 201(1): S15–S22. doi: 10.1016/S0167-5273(15)31028-7. [PubMed] [CrossRef] [Google Scholar]