CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Avalable online at: http://www.iajps.com *Research Article*

PROCESS OPTIMIZATION OF EMPAGLIFLOZIN, LINAGLIPTIN AND METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS USING DESIGN OF EXPERIMENTS

[1]Rajarao Chinta, [2]Rohini P

[1]Department of Pharmaceutics, University College of Pharmaceutical Sciences,
Acharya Nagarjuna University, Nagarjuna Nagar, Guntur-522510, Andhra Pradesh, India.

Article Received: November 2020 **Accepted:** December 2020 **Published:** January 2021

Abstract:

Triple fixed dose combination product Empagliflozin, Linagliptin and Metformin hydrochloride Extended-Release tablets consists two immediate release agents (Empagliflozin, Linagliptin) and one extended-release agent (Metformin hydrochloride) in a single tablet for the treatment of type 2 diabetes mellitus. The objective of the present study was to optimize process parameters of Empagliflozin, Linagliptin and Metformin hydrochloride Extended-Release tablets using design of experiments. Optimization studies were designed using statistical software (Design expert, stat ease) employing a face cantered central composite design to understand the impact of critical process parameters on responses/dependent variables. Impact of various process variables were assessed by using statistical interpretation such as ANOVA. The selected critical process parameters (fluid uptake and kneading time of high shear granulation process; atomization air pressure and spray rate of fluid bed granulation process) were studied to check the impact on responses/dependent variables (bulk density, %retains on #40 mesh, % passes of #60 mesh). From the obtained results, fluid uptake of 20% w/w, kneading time of 2 min (high shear granulation process); atomization air pressure of 0.9 kg/cm^2 and spray rate of 20 g/min (fluid bed granulation process) were selected as optimum process parameters to obtain pre-determined specifications.

Keywords: *Empagliflozin, Linagliptin, Metformin hydrochloride, Process variables, Design of Experiments, ANOVA.*

Corresponding author:

Rajarao Chinta

Ph. D. Scholar, Department of Pharmaceutics,
University College of Pharmaceutical Sciences, Acharya Nagarjuna University,
Nagarjuna Nagar, Guntur-522510, Andhra Pradesh, India.
E-mail: rajarao.ch114@gmail.com

QR code

Please cite this article in press Rajarao Chinta et al, ***Process Optimization Of Empagliflozin, Linagliptin And Metformin Hydrochloride Extended Release Tablets Using Design Of Experiments.,*** *Indo Am. J. P. Sci, 2021; 08(1).*

INTRODUCTION:

Empagliflozin, Linagliptin and Metformin hydrochloride extended-release tablets comprises immediate release Empagliflozin, Linagliptin and extended-release Metformin hydrochloride in a single dosage unit where ER part drug release should be extended over time and IR part Empagliflozin, Linagliptin should be disintegrated and dissolved immediately from the total tablet. To achieve these two different release patterns from single tablet, IR part and ER part blends were prepared individually and compressed into bi-layer tablets. Metformin hydrochloride (ER part) blend was prepared by wet granulation process in a high shear mixer granulator and fluid bed granulation process (top spray) was used to prepare Empagliflozin, Linagliptin part blend. [1-2] Formulation optimization of Empagliflozin, Linagliptin and Metformin hydrochloride extended-release tablets was covered in our earlier investigation.[3] The present investigation was aimed to optimize process parameters using statistical software (design expert, stat ease) employing face centered central composite design to understand the impact of critical process parameters on responses/ dependent variables.

MATERIALS AND METHODS:

Materials:

Empagliflozin, Linagliptin and Metformin hydrochloride were received as a gift sample from Aurobindo Pharma Ltd., Hyderabad. Sodium carboxymethyl cellulose 7HF PH (Ashland), HPMC K 100M CR (Dow chemicals), Microcrystalline cellulose Avicel PH112 (FMC), Mannitol Pearlitol SD 200 (Roquette), Hydroxypropyl cellulose SSL (Nippon soda), Colloidal silicon dioxide (Evonik), Magnesium Stearate (Peter greven), Meglumine (Merck), Crospovidone Polyplasdone XL 10 (Ashland) and Iron oxide yellow (Neelikon) were used as received.

Methods:

Preparation of Metformin hydrochloride part blend (ER part):

Dry mix material (Metformin hydrochloride and sodium CMC) was granulated using purified water as a granulating fluid in RMG at impeller slow speed and chopper slow speed. Wet mass was dried in a rapid dryer for 45 -60 min at the inlet temperature of 50 ± 5°C. Dried granules (LOD at 105°C: 0.5 to 1.5%w/w) were passed through ASTM mesh #20 and retains were milled using co-mill fitted with screen 1016 micron at slow to medium speed. Extra granular materials (HPMC K100M CR and aerosil) and milled granules were co-sifted through ASTM mesh #20 and blended in a low shear double cone blender for 10 minutes. Above blend was lubricated with magnesium stearate for 5 minutes in the blender.

Preparation of Empagliflozin, Linagliptin part blend (IR part):

Hydroxypropyl cellulose (SSL) and meglumine were dissolved in purified water under stirring till a clear solution was formed and Linagliptin was dispersed in it and stirred for another 30 min. Intragranular materials mannitol and microcrystalline cellulose were sifted together through ASTM mesh #40, loaded into a fluid bed processor (FBP, top spray), and pre-warmed with minimum effective fluidization for 10 min at inlet temperature of 35–40°C. Binder solution was sprayed onto intra-granular material in FBP at a product temperature of 27 to 30°C. After spraying, wet mass was dried for 30 min at product temperature of 35°C to 45°C and checked LOD at 105°C (Limit: NMT 2.5% w/w). Dried granules were sifted through ASTM mesh #30 and retains were milled using #40G screen in co-mill. Extra granular materials (Empagliflozin, microcrystalline cellulose, crospovidone, aerosil, Iron oxide yellow) were co-sifted with milled granules through ASTM mesh #30 and mixed in a low shear double cone blender for 20 minutes. Above blend was lubricated with magnesium stearate for 5 min in the blender.

Bi-layer tablets compression:

Empagliflozin, Linagliptin part and Metformin hydrochloride part blends were compressed into bi-layer tablets using Eliza Press compression machine at a hardness of 22 KP to 28 KP. Unit composition of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets is presented in Table 1.

Table 1: Unit composition of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets

S. No.	Ingredients	Quantity (mg/tablet)
I	**Layer 1: Empagliflozin, Linagliptin part**	
	Intragranular	
1	Mannitol (Pearlitol SD 200)	78.00
2	Microcrystalline cellulose (Avicel PH 112)	15.00
	Binder solution	
3	Hydroxypropyl cellulose (SSL)	15.40
4	Meglumine	12.00
5	Linagliptin	5.00
6	Purified water	Q.S.
	Extra granular	
7	Empagliflozin	25.00
8	Microcrystalline cellulose (Avicel PH 112)	32.40
9	Crospovidone (Polyplasdone XL 10)	33.00
10	Colloidal silicon dioxide (Aerosil 200 pharma)	2.00
11	Iron oxide yellow	0.20
12	Magnesium Stearate	2.00
Empagliflozin, Linagliptin part weight		**220.00**
II	**Layer 2: Metformin hydrochloride part**	
	Intragranular	
13	Metformin hydrochloride	1000.00
14	Sodium CMC (7HF PH)	65.00
	Binder	
15	Purified water	Q.S.
	Extra granular	
16	HPMC K 100M CR	221.00
17	Colloidal silicon dioxide (Aerosil 200 pharma)	7.50
18	Magnesium Stearate	6.50
Metformin hydrochloride part weight		**1300.00**
Total tablet weight (Bi-layer)		**1520.00**

Experimental design: [4-5]

The Face centered central composite design was used to evaluate the effect of critical process parameters on responses/dependent variables. A two factor, three level design (3^2) is used for discovering quadratic response surfaces and building second order polynomial models with design expert (stat-ease). After fitting the response data in experimental design, the experimental results were analysed by ANOVA. It demonstrated the various statistical parameters such as sum of squares, F values, P values of model terms and correlation coefficient (R^2) values. The suitability of model was authenticated by the predicted and adjusted R^2 values.

High shear granulation process optimization of metformin part using design of Experiments (DOE):

The process variables involved in the high shear granulation process (rapid mixer granulator) are batch size, fluid uptake, fluid addition rate, impeller speed, chopper speed, kneading time etc. Process parameters can be changed in a particular range without a critical effect on the high shear granulation process or on the granule's characteristics. In contrast, an alteration of a critical parameter would influence the high shear granulation process or the granules quality in a significant manner. Preliminary studies were conducted to freeze the process parameters which do not have any impact on product quality, such as batch size, fluid uptake, fluid addition rate, impeller speed, chopper speed, kneading time etc. However, fluid uptake and kneading time are found as critical process parameters. Optimization studies were designed using statistical software (Design expert, stat ease) employing face centered central composite design to understand the impact of critical process parameters [fluid uptake (X_1) and kneading time(X_2)] on responses/ dependent variables [Bulk density (Y_1), %retains on #40 mesh (Y_2) and % passes of #60 mesh (Y_3)]. After fitting the response data in experimental design as in Table 2, the experimental results were evaluated by ANOVA.

Table 2: Face centered central composite design for optimization of High shear granulation process

Factor	No. of levels	Actual (coded) values		
		Low (-1)	Medium (0)	High (+1)
Fluid uptake (%) (X_1)	3	15	20	25
Kneading time (min) (X_2)	3	1	2	3

Fluid bed granulation process optimization of Empagliflozin, Linagliptin part using Design of Experiments (DOE):

The process variables involved in fluid bed granulation process are batch size, spray nozzle diameter, filter bags, nature of the binder solution/suspension and quantity, inlet and product temperature, air volume, dew point, spray rate, atomization air pressure, drying time etc. Process parameters can be altered in a specific range without a major impact on the blend flow properties. In contrast, a deviation of a critical parameter would influence the blend flow properties in a significant manner. Preliminary studies were carried out to freeze the process parameters which do not have any impact on product quality, such as batch size, spray nozzle diameter, filter bags, dew point and drying time. However, atomization air pressure and spray rate are identified as critical process parameters. Optimization studies were designed using statistical software (design expert, stat ease) employing face centered central composite design to understand the impact of critical process parameters [atomization air pressure (X_1) and spray rate (X_2)] on responses/dependent variables [bulk density (Y_1), %retains on #40 mesh (Y_2) and %passess of #60 mesh (Y_3)] of Empagliflozin, Linagliptin part fluid bed granulation process. After fitting the response data in experimental design as in Table 3, the experimental results were evaluated by ANOVA.

Table 3: Face centered central composite design for optimization of Empagliflozin, Linagliptin part Fluid bed granulation Process.

Factor	No. of levels	Actual (coded) values		
		Low (-1)	Medium (0)	High (+1)
Spray rate (g/min) (X_1)	3	10	20	30
Atomization air pressure (kg/cm^2) (X_2)	3	0.7	0.9	1.1

Evaluation of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets Micromeritic properties:[6]

Bulk density (BD), tapped density (TD), Carr's compressibility index (CI) and Hausner ratio (HR) of lubricated blend was evaluated. BD and TD were tested by USP method I using a Tapped density tester.

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

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

Hausner ratio was calculated by following formulae

$$Hausner\ ratio = TD / BD$$

Compressibility index were calculated using below formulae

$$Compressibility\ index = \frac{TD-BD}{TD} X\ 100$$

Assay:

Assay of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets was performed using HPLC method. [7-8]

Dissolution:

Dissolution test was performed using USP Type-I (Basket), with the volume of 900 ml, at a stirring speed of 100 rpm and the temperature was maintained at 37°C ± 0.5°C. The study was carried out in pH 6.8 phosphate buffer separately for individual drugs at 1, 2, 4, 6, 8, 10 and 12 h for Metformin hydrochloride part and 10, 15, 20, 30, 45 and 60 min for Empagliflozin and Linagliptin part respectively. [9-10]

Drug release kinetics:

Optimized formulation of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets were evaluated using various mathematical equations. [11-12]

RESULTS AND DISCUSSION:

Data analysis and model validation:

High shear granulation process optimization of Metformin part:

Responses such as bulk density, %retains on #40 mesh and %passess of #60 mesh were used to assess the influence of the chosen factors i.e., fluid uptake and kneading time. Responses obtained from the experimental runs were represented in the Table 4. Flow properties (hausner ratio, carr's index) were evaluated for process optimization trials and data was presented in Table 5. Design expert® 11 software was employed for the statistical analysis and to carry out the interpretation of outcome of the process variables. The results of selected responses obtained from the experimental runs were evaluated to response surface regression analysis and results were presented in Table 6-8. Corresponding contour and three-dimensional surface plots were represented in Figure 1. Based on the obtained results, the predetermined specification for the responses i.e., bulk density (0.45 to 0.65 g/ml), %retains on #40 mesh (30 to 50%) % passes of #60 mesh (40 to 60%) were chosen. Corresponding overlay plot was presented in Figure 2. From the obtained results, fluid uptake 20% w/w and kneading time of 2 min were selected as optimum process parameters for high shear granulation process to obtain pre-determined specifications.

Table 4: Results of responses from experimental runs (high shear granulation, Metformin part)

Variable level (Actual values)		Dependent Variables/Responses		
X_1 (Fluid uptake)	X_2 (Kneading time)	Bulk density (g/ml) (Y_1)	Retains on #40 mesh (%), (Y_2)	Passess of #60 mesh (%), (Y_3)
20	3	0.58	48	42
15	1	0.43	24	68
15	2	0.45	28	64
20	2	0.55	41	50
20	2	0.54	42	49
15	3	0.47	30	61
25	1	0.58	55	31
25	3	0.64	62	23
25	2	0.61	58	27
20	2	0.55	40	51
20	1	0.51	34	56
20	3	0.57	49	39
15	1	0.44	25	66

Table 5: Blend characterization data of process optimization trials (high shear granulation, Metformin part)

Fluid uptake (%)	Kneading time (min)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's Index (%)
20	3	0.58	0.67	1.16	13.43
15	1	0.43	0.56	1.30	23.21
15	2	0.45	0.58	1.29	22.41
20	2	0.55	0.64	1.16	14.06
20	2	0.54	0.62	1.15	12.90
15	3	0.47	0.57	1.21	17.54
25	1	0.58	0.68	1.17	14.71
25	3	0.64	0.73	1.14	12.33
25	2	0.61	0.7	1.15	12.86
20	2	0.55	0.64	1.16	14.06
20	1	0.51	0.62	1.22	17.74
20	3	0.57	0.67	1.18	14.93
15	1	0.44	0.57	1.30	22.81

Table 6: Analysis of variance results for predicting bulk density (high shear granulation)

Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p value, prob > F
Y_1 (g/ml)						
Model	0.5460	0.0439	3	0.0146	337.81	< 0.0001
A	0.0800	0.0384	1	0.0384	886.15	< 0.0001
B	0.0283	0.0048	1	0.0048	111.15	< 0.0001
A^2	0.0160	0.0007	1	0.0007	16.11	0.0051
Residual		0.0003	7	0.0000		
Lack of Fit		0.0002	5	0.0000	1.42	0.4623
Pure Error		0.0001	2	0.0000		
Total		0.0442	10			
R^2=0.9931; adjusted R^2=0.9902; Predicted R^2= 0.9794 Regression equation of the fitted model[#]: Y_1=0.5460+0.0800*A+0.0283*B-0.0160*A^2						
A: Fluid uptake; B: Kneading time; df: Degrees of Freedom; *p<0.05 considered as significant. [#] Only the terms with statistical significance are included.						

Table 7: Analysis of variance results for predicting retains on #40 mesh (high shear granulation)

Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p value, prob > F
Y_2 (%)						
Model	29.00000	1563.00	2	781.50	201.68	< 0.0001
A	3.10000	1441.50	1	1441.50	372.00	< 0.0001
B	4.50000	121.50	1	121.50	31.35	0.0005
Residual		31.00	8	3.88		
Lack of Fit		29.00	6	4.83	4.83	0.1813
Pure Error		2.00	2	1.0000		
Total		1594.00	10			
R^2=0.9806; adjusted R^2=0.9757; Predicted R^2= 0.9598 Regression equation of the fitted model[#]: Y_2=-29.00000+3.10000*A+4.50000*B						
A: Fluid uptake; B: Kneading time; df: Degrees of Freedom; *p<0.05 considered as significant. [#] Only the terms with statistical significance are included.						

Table 8: Analysis of variance results for predicting passes of #60 mesh (High shear granulation)

Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p value, prob > F
Y_3 (%)						
Model	131.78788	2230.83	2	1115.42	148.99	< 0.0001
A	3.73333	2090.67	1	2090.67	279.25	< 0.0001
B	4.83333	140.17	1	140.17	18.72	0.0025
Residual		59.89	8	7.49		
Lack of Fit		57.89	6	9.65	9.65	0.0969
Pure Error		2.00	2	1.0000		
Total		2290.73	10			
R^2=0.9739; adjusted R^2=0.9673; Predicted R^2= 0.9495 Regression equation of the fitted model[#]: Y_3=131.78788-3.73333*A-4.83333*B						
A: Fluid uptake; B: Kneading time; df: Degrees of Freedom; *p<0.05 considered as significant. [#] Only the terms with statistical significance are included.						

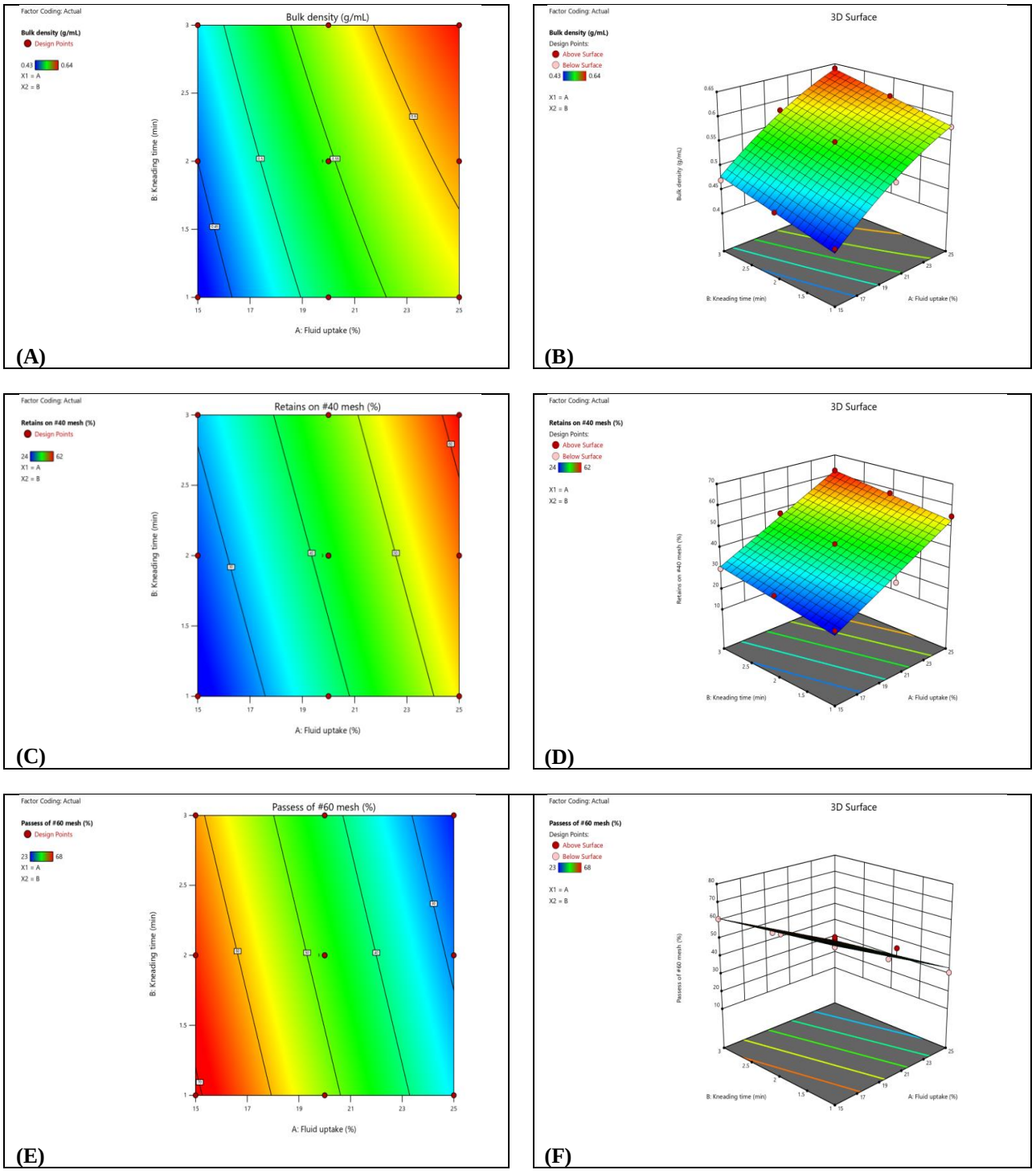


Figure 1: Contour plots (A, C and E) and response surface plots (B, D and F) showing the impact of factors (fluid uptake and kneading time) on responses (bulk density, %retains on #40 mesh and % passes of #60 mesh)-high shear granulation process

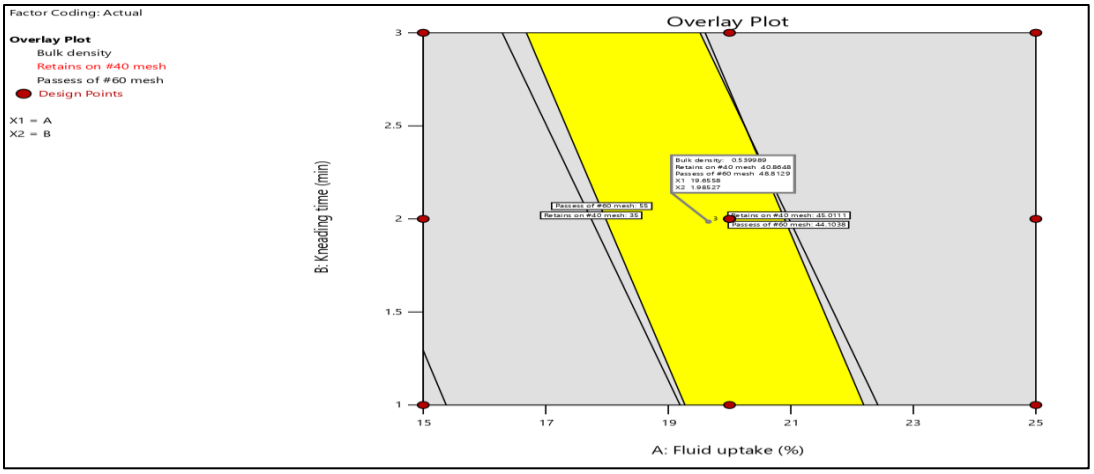


Figure 2: Overlaid contour plot of process variables, high shear granulation process

Fluid bed granulation process optimization of Empagliflozin, Linagliptin part using design of Experiments (DOE):

Responses such as bbulk density, %retains on #40 mesh and % passes of #60 mesh were used to study the effect of the chosen factors i.e. atomization air pressure and spray rate. Responses obtained from the experimental runs were presented in the Table 9. Flow properties (hausner ratio, carr's index) were evaluated for process optimization trials and data was presented in Table 10. Design expert® 11 software was employed for the statistical analysis and to carry out the interpretation of outcome of the process variables. The results of selected responses obtained from the experimental runs were evaluated to response surface regression analysis and results were represented in Table 11-13. Corresponding contour and three-dimensional surface plots were presented in Figure 3. Based on the obtained results, the predetermined specification for the responses i.e., bulk density (0.35 to 0.55 g/ml), %retains on #40 mesh (55 to 75%) % passes of #60 mesh (15 to 35%) were chosen. Corresponding overlay plot was presented in Figure 4. As per the obtained experimental results, atomization air pressure of 0.9 kg/cm^2 and spray rate of 20 g/min were selected as optimum process parameters for fluid bed granulation process to obtain pre-determined specifications.

Table 9: Results of responses from experimental runs (fluid bed granulation, Empagliflozin, Linagliptin part)

Independent Variables		Dependent Variables/Responses		
Spray rate (g/min) (A)	**Atomization air pressure (kg/cm^2) (B)**	**Bulk density (g/ml) (Y_1)**	**Retains on #40 mesh (%) (Y_2)**	**Passess of #60 mesh (%) (Y_3)**
30	0.9	0.50	73	16
20	0.9	0.45	66	26
10	1.1	0.34	49	44
20	1.1	0.43	58	36
20	0.9	0.45	65	25
20	0.9	0.46	63	28
10	0.9	0.36	53	39
20	0.7	0.47	69	21
30	0.7	0.52	77	12
10	0.7	0.38	56	35
20	0.9	0.45	66	26
20	0.9	0.45	64	28
30	1.1	0.48	69	19

Table 10: Blend characterization data of process optimization trials (fluid bed granulation, Empagliflozin, Linagliptin part)

Spray rate (g/min)	Atomization air pressure (kg/cm^2)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's Index (%)
30	0.9	0.5	0.58	1.16	13.79
20	0.9	0.45	0.49	1.09	8.16
10	1.1	0.34	0.42	1.24	19.05
20	1.1	0.43	0.49	1.14	12.24
20	0.9	0.45	0.5	1.11	10.00
20	0.9	0.46	0.5	1.09	8.00
10	0.9	0.36	0.44	1.22	18.18
20	0.7	0.47	0.54	1.15	12.96
30	0.7	0.52	0.6	1.15	13.33
10	0.7	0.38	0.46	1.21	17.39
20	0.9	0.45	0.49	1.09	8.16
20	0.9	0.45	0.5	1.11	10.00
30	1.1	0.48	0.55	1.15	12.73

Table 11: Analysis of variance results for predicting bulk density, fluid bed granulation

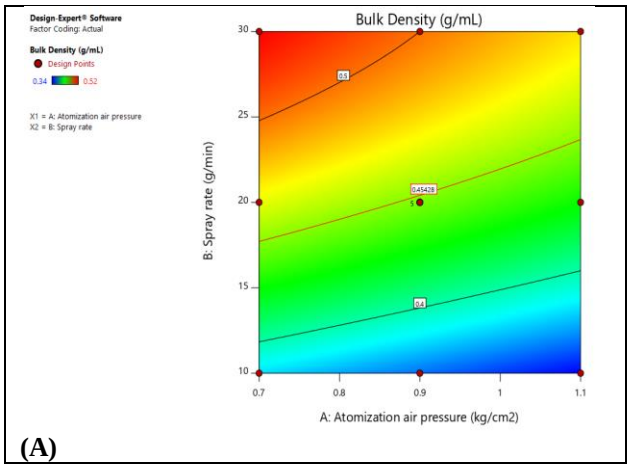
Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p-value, prob > F
Y_1 (g/ml)						
Model	0.315714	0.0333	3	0.0111	1164.92	< 0.0001
A	0.100000	0.0024	1	0.0024	252.00	< 0.0001
B	0.015571	0.0294	1	0.0294	3087.00	< 0.0001
B^2	0.000214	0.0015	1	0.0015	155.77	< 0.0001
Residual		0.0001	9	9.5238		
Lack of Fit		5.7142	5	1.1428	0.0571	0.9962
Pure Error		0.0001	4	0.0000		
Total		0.0334	12			
R^2=0.9974; adjusted R^2=0.9966; Predicted R^2= 0.9964 Regression equation of the fitted model[#]: Y_1 = 0.315714-0.100000*A+0.015571*B-0.000214*B^2						
A: Spray rate; B: Atomization air; df: Degrees of Freedom; p<0.05 considered as significant. [#] Only the terms with statistical significance are included.						

Table 12: Analysis of variance results for retains on #40 mesh, fluid bed granulation

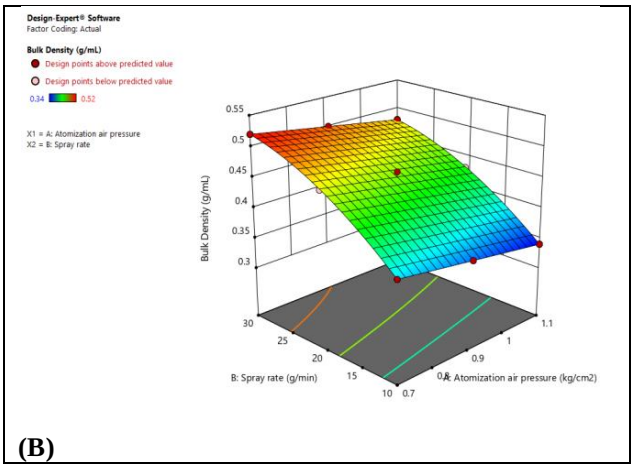
Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p-value prob > F
Y_2 (%)						
Model	62.85897	732.83	2	366.42	167.04	< 0.0001
A	21.66667	112.67	1	112.67	51.36	< 0.0001
B	1.01667	620.17	1	620.17	282.72	< 0.0001
Residual		21.94	10	2.19		
Lack of Fit		15.14	6	2.52	1.48	0.3660
Pure Error		6.80	4	1.70		
Total		754.77	12			
R^2=0.9709; adjusted R^2=0.9651; Predicted R^2= 0.9513 Regression equation of the fitted model[#]: Y_2 = 62.85897-21.66667*A+1.01667*B						
A: Spray rate; B: Atomization air pressure; df: Degrees of Freedom; p<0.05 considered as significant. # Only the terms with statistical significance are included.						

Table 13: Analysis of variance results for passes of #60 mesh, fluid bed granulation

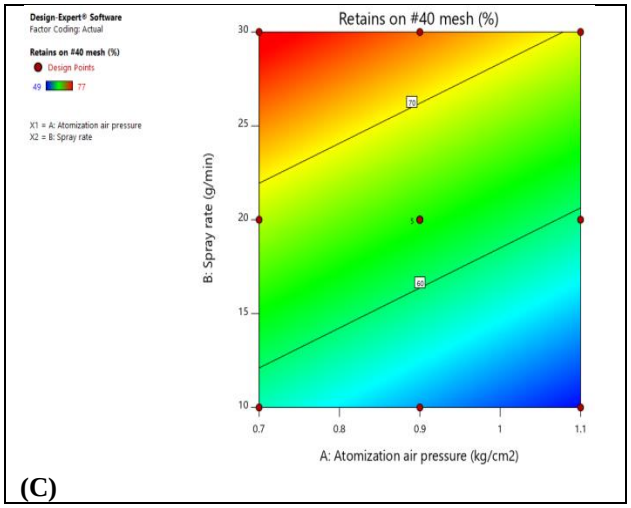
Source	b-coefficient	Sum of Squares	df	Mean Square	F-value	p-value prob > F
Y_3 (%)						
Model	27.72436	1000.33	2	500.17	164.33	< 0.0001
A	25.83333	160.17	1	160.17	52.62	< 0.0001
B	1.18333	840.17	1	840.17	276.04	< 0.0001
Residual		30.44	10	3.04		
Lack of Fit		23.24	6	3.87	2.15	0.2393
Pure Error		7.20	4	1.80		
Total		1030.77	12			
R^2=0.9705; adjusted R^2=0.9646; Predicted R^2= 0.9465 Regression equation of the fitted model[#]: Y_3 = 27.72436+25.83333*A-1.18333*B						
A: Spray rate; B: Atomization air; df: Degrees of Freedom; p<0.05 considered as significant. [#] Only the terms with statistical significance are included.						



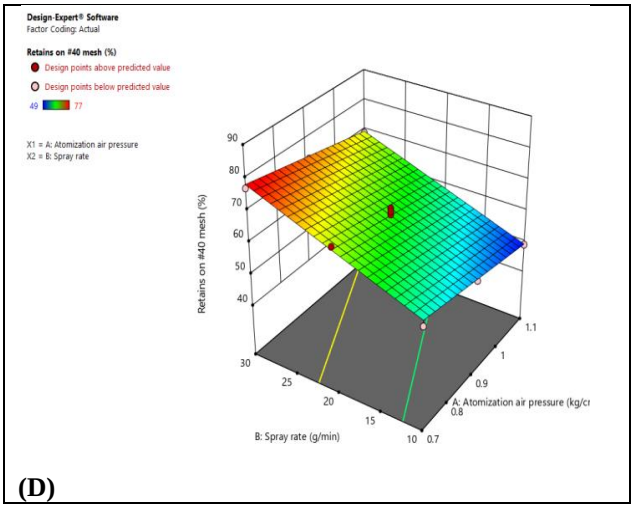
(A)



(B)



(C)



(D)

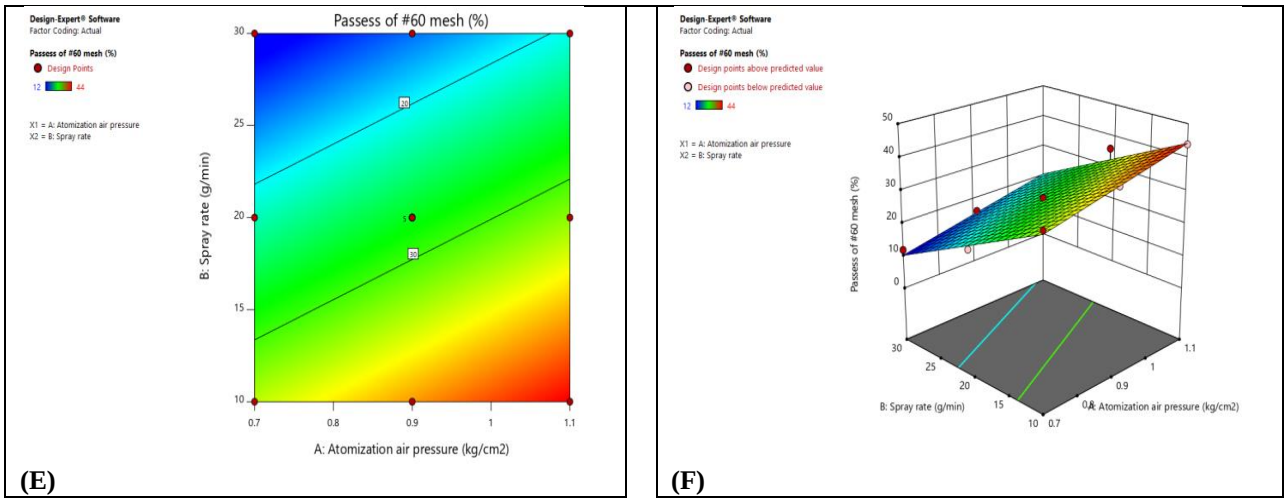


Figure 3: Contour plots (A, C and E) and response surface plots (B, D and F) showing the impact of factors (atomization air pressure and spray rate) on responses (bulk density, %retains on #40 mesh and % passess of #60 mesh)-fluid bed granulation process

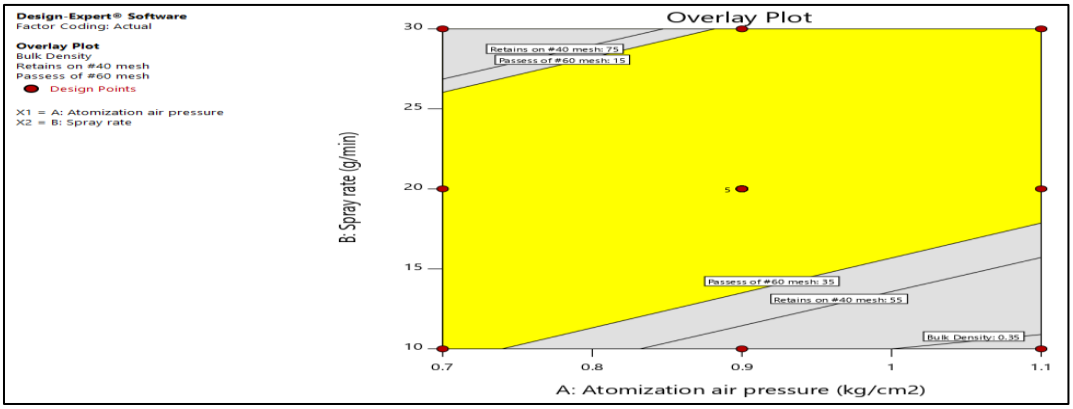


Figure 4: Overlay plot of fluid bed granulation process variables

Evaluation tablets:

Assay and dissolution:

The assay of the all formulations was tested, and results were found in the range of 99.1-102.0%, 98.9-100.5% and 100.3-101.4% for Empagliflozin, Linagliptin and Metformin hydrochloride respectively. Comparative dissolution profiles of individual marketed products and FDC test product are presented in Figure 5. Based on the observed data, assay results were meeting the specification limits and dissolution profiles of optimized FDC test product are comparable to individual marketed products.

Drug release kinetics:

The dissolution data of ER part was fitted into kinetic models and obtained results concluded that ER part drug release profiles followed the zero-order kinetics and the mechanism of drug release was non-fickian diffusion.

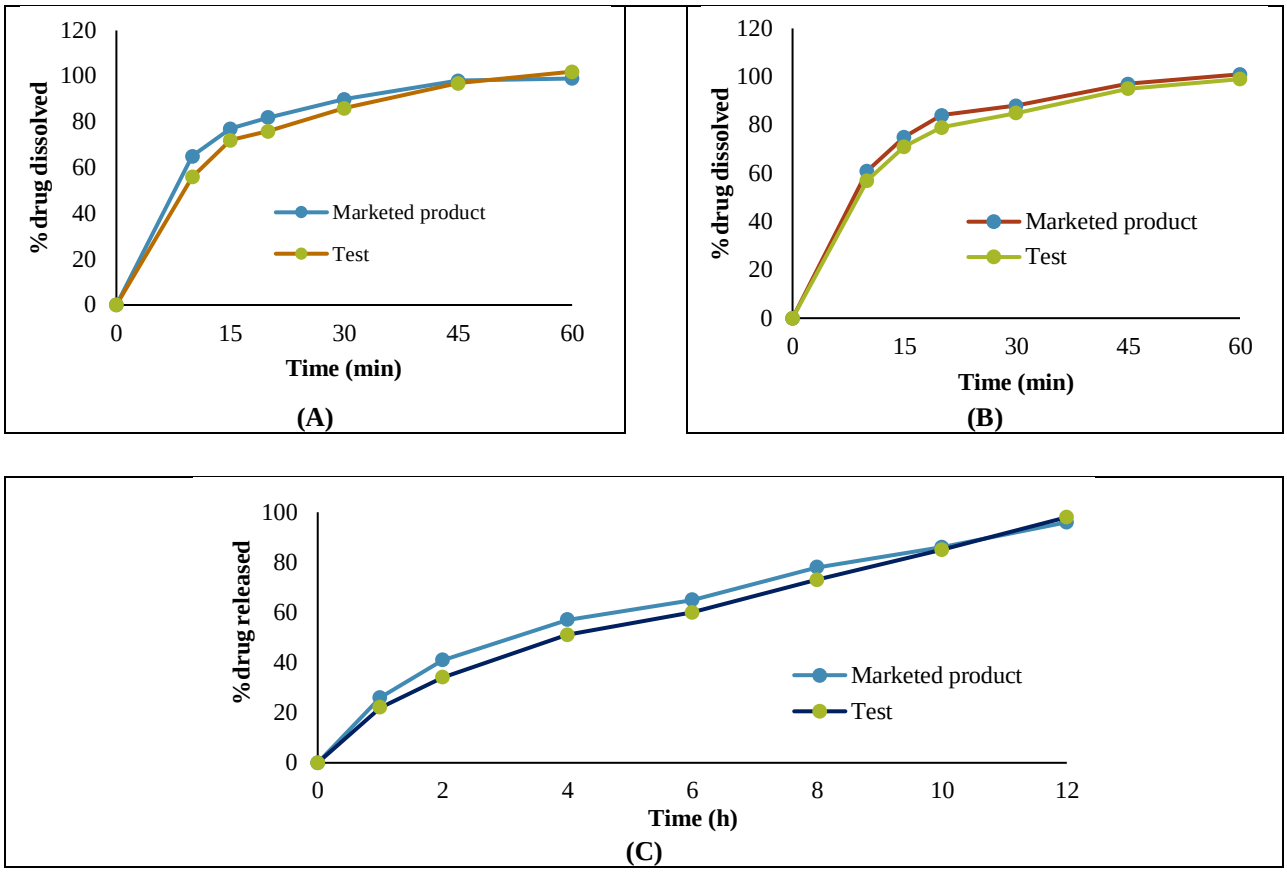


Figure 5: Comparative dissolution profiles of Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets.
(A): Empagliflozin part; (B): Linagliptin part; (C): Metformin hydrochloride part.

CONCLUSION:

Empagliflozin, Linagliptin and Metformin hydrochloride ER tablets were successfully developed by bi-layer tablets technology. Critical process parameters of high shear granulation and fluid bed granulation process were optimized using design expert software employing a face centered central composite design to evaluate the impact of process parameters on responses/dependent variables. From the obtained experimental results, fluid uptake of 20% w/w, kneading time of 2 min (high shear granulation process); atomization air pressure of 0.9 kg/cm^2 and spray rate of 20 g/min (fluid bed granulation process) were finalized. Optimized formulation was evaluated for assay and *in-vitro* dissolution studies. Dissolution profiles of optimized test formulation were comparable with individual marketed products.

REFERENCES:

1. Gilbert SB, Christopher TR. 2000. Modern Pharmaceutics. New York, USA: Marcel Dekker, Inc.
2. Sonali J, Aarti J, Ganesh D. Bilayer Tablet technology: A novel approach. Research J Pharm and Tech, 2013; 6(12):1443-51.
3. Chinta R, Pilli R. Formulation design of Empagliflozin and Metformin hydrochloride extended-release tablets: optimization of formulation using statistical experimental design. Int J Pharm Sci & Res, 2020; 11(12):6434-47.
4. Dilip MP. 2005. Handbook of Pharmaceutical Granulation Technology. New York, USA: Marcel Dekker, Inc.
5. Mohamed HF, Sayed IAR, Fars KA, Mahrous OA, Hesham MT, Ramadan IAS. High-Shear Granulation process: Influence of processing parameters on Critical Quality Attributes of Acetaminophen granules and tablets using Design Of Experiment approach. Acta Pol Pharm, 2017; 74(1):235-48.
6. Pharmacopoeia I. 2010. Indian Pharmacopoeia Commission. Ghaziabad, India:786.
7. Syed IA, Bharath RKP. Stability Indicating Simultaneous Estimation of Metformin and Empagliflozin in Pharmaceutical Tablet Dosage

form by RP-HPLC. Asian J Research Chem, 2017; 10(6):783-88.
8. Ravi K, Ramesh BB, Garima K, Rubina B. Optimization of a single HPLC-PDA method for quantifying Metformin, Gliclazide, Pioglitazone, Dapagliflozin, Empagliflozin, Saxagliptin, Linagliptin and Teneligliptin using central composite design. Bioorganic Chemistry, 2019; 91:103111.
9. Available at: https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm [Accessed on 26 June 2020].
10. Chinta R, Pilli R. Comparative hypoglycaemic activity of fixed dose combination anti-diabetic formulations versus respective monotherapies in diabetic rabbits. International Journal of Pharmaceutical Quality Assurance, 2020; 11(3):409-16.
11. Suvakanta D, Padala NM, Lilakanta Nath, Prasanta Chowdhury. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm, 2010; 67(3):217-23.
12. Moore JW, Flanner HH. Mathematical Comparison of Curves with an Emphasis on *invitro* dissolution profiles. Pharma Tech, 1998; 20(6):64-74.