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Research Article

FORMULATION DEVELOPMENT AND OPTIMIZATION OF EMPAGLIFLOZIN FILM COATED TABLET USING QUALITY-BY-DESIGN APPROACH

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ABSTRACT

Objective: Development of robust and effective oral solid immediate release film coated tablet of empagliflozin using Quality-by-Design (QbD) approach was the objective of present research work. This belongs to Sodium Glucose Co-Transporter-2 inhibitors-oral hypoglycemic class to treat Type-2 diabetes mellitus and associated cardiovascular comorbidities.

Methods: Assessment of risk factors (using Ishikawa fishbone diagram) was done by in-depth understanding of quality target product profile and critical quality attributes (CQAs) associated with material and process with justification. Randomized regular two levels full factorial design in addition with 5-center points was employed as Design of Experiment (DoE) tool. In this design, independent factors were concentrations of hydroxyl propyl cellulose (HPC SL) and croscarmellose sodium in mg. The responses selected for study were % drug release at 15-min *in vitro* dissolution time, disintegration time in sec, and hardness in Newton.

Results: ANOVA and lack-of-fit demonstrated that stipulated independent variables have significant impact on response variables and best correlation was seen in actual and predicted value. This optimization method confirmed that HPC SL (8 mg) and croscarmellose sodium (4 mg) were ideal concentrations of binder and disintegrant, respectively, to prepare said formulation with desired quality attributes and it was found to be better with respect to stability and effectiveness against marketed reference formulation.

Conclusion: QbD tools such as QTPP, CQAs, risk assessment, and DoE can be used in combination to optimize, screen, and understand the function of material and process parameters on quality characteristics of film-coated tablet.

Keywords: Empagliflozin, *In vitro* dissolution, Film coated tablet, Critical quality attributes.

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INTRODUCTION

In 2017, 6.28% of world's population were affected by Type-2 diabetes mellitus [1]. 0.33% of Type-2 diabetes patients are comorbid with cardiovascular problems, out of them 15% have heart failure and 20% have coronary heart disease [2]. Sodium Glucose Co-Transporter-2 (SGLT-2) inhibitors is novel class of oral hypoglycemic agents and proved beneficial to the any clinical stage of diabetic patient [3]. SGLT-2 inhibitors act by reducing blood glucose level, body weight, and blood pressure, through inducing glycosuria, natriuresis, and reduced intravascular volume. Their mechanism of action is independent of pancreatic beta cell function or insulin resistance [4].

Empagliflozin is SGLT-2 inhibitor that increases renal glucose excretion, decreases glycated hemoglobin level, and protects diabetic patient from cardiovascular risk [2]. This new chemical entity, having no pharmacopoeial status, was formulated into immediate release film-coated tablet that can develop therapeutic action and reach blood level quickly.

Quality-by-Design (QbD) is well structured scientific risk based technique in pharmaceutical evolution that initiate with determined objectives and understanding of controllable during the process as well as considering quality risk management. This is based on complete understanding product and process that can impact target product profile with an objective of improving pharmaceutical product quality in accordance with safety to achieve patient compliance [5]. This research work was carried out by considering two important elements of QbD, which are quality target product profile (QTTP), critical quality attributes (CQA), and risk assessment as well as implementation of QbD was done here using Design of Experiment (DoE) tool.

QTTP is necessary to find out the basis of drug product being developed. It includes dosage form design (route of administration, dosage form, and dosage strength), container-closure system, drug release parameters that affect pharmacokinetics, and drug product quality standards prior for marketing (purity and stability). CQAs of oral solid dosage form include details that affect the drug release profile, purity; strength; and stability which are further show their effect on product safety and efficacy. Quality risk management (ICH Q9 guideline) includes risk assessment that that gives proof to find out the material and process elements that show their effect on drug product CQAs. This can be based on earlier understandings and by referring initial drug product development data [6].

The objective of this research work was to develop robust and effective immediate release film coated tablet of empagliflozine for Type-2 diabetic patients using QbD approach.

MATERIALS AND METHODS

Materials

Emapagliflozin (Teva API India Pvt. Ltd.) was used as a model drug. Milled lactose monohydrate (Pharmatose®- DFE Pharma) and microcrystalline cellulose PH 102 (Avicel® PH 102- DuPont Nutrition) were used as diluents as the model drug has poor flow and low administered dose, hydroxyl propyl cellulose (HPC SL®- Nippon Soda Co. Ltd.), and croscarmellose sodium (Ac Di Sol®- DuPont Nutrition) were selected as binder and disintegrant, respectively. Lactose monohydrate (Shiefield SD fast flo®- Kerry Inc. Rothschild US) and microcrystalline cellulose PH 102 (Avicel® PH 112- DuPont Nutrition) are added to improve flow of granules. Colloidal silicon dioxide (Aerosil®- Evonik) and magnesium stearate

(Ligamed® MF 2 V- Azelis (India) Pvt. Ltd.) were applied to granules to prevent sticking. OPADRY® yellow (Colorcon Asia Pvt. Ltd.) was used as coating material to apply film coating to tablet. Jardiance® (Boehringer Ingelheim Pharmaceuticals, Germany) was selected as reference formulation for tablet evaluation test. All solvents used ere of analytical grade.

Methods

Determination of QTTP

QTTP for empagliflozin film coated tablet is shown in Table 1 with justification.

Identification of critical and non-CQAs

Critical and non-CQAs were determined and justified in Table 2.

Assessment of risk

Ishikawa (fishbone) diagram in Fig. 1 helps to identify the risk factors that showed potential effects on desired quality attributes.

Construction of DoE

As QTTP and CQA were determined, it enabled us to establish a design space considering risk factors. DoE was constructed using commercially

Table 1: Quality target product profile for empagliflozin film-coated tablet

Drug product quality attribute	Target	Justification
Route of Administration	Oral	Pharmaceutical equivalence requirement: Same route of administration.
Dosage form	Film Coated Tablet	Pharmaceutical equivalence requirement: Same dosage form and strength.
Dosage Strength	10 mg and 25 mg	
Dosage Design	Immediate release tablet	Immediate release design needed to meet label claims.
Container closure system	Suitable container closure system to achieve target shelf life and to ensure tablet integrity during shipping	PVC Aluminum perforated unit dose blister is selected based on similarity to reference product packaging.
Dissolution	Q=85% in 30 min	The drug release profile is important for achieving bioequivalence (BE); therefore, it is critical. A similar drug release profile to the reference product is targeted to ensure bioequivalence.
Stability study	Same or longer shelf life as reference product	Needed for ascertaining shelf life and ensuring patient safety and clinical effectiveness

Table 2: Critical and non-critical attributes (CQAs) for empagliflozin film coated tablet

Drug product quality attribute	Target	Is this critical?	Justification
Physical attribute			
Description	25 mg strength, oval, pale yellow, biconvex film-coated tablet	Yes	Tablet appearance is needed for patient compliance and acceptability. Compression/coating process can have an impact on this CQA, so it is assessed during development
Shape	Oval	No	Shape and size have a low impact on safety and efficacy, but are needed for comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens
Size	Length: 11.18 mm Width: 5.65 mm		
Uniformity of Mass (Weight)	The weights of not more than 2 of the tablets differ from the average weight by more than±7.5%	No	Even though formulation and process may have an impact on Uniformity of Mass. Uniformity of Mass of tablet will be monitored and controlled by in-process checks during batch manufacturing.
Disintegration Time	<30 min	Yes	Both formulation and process variables can affect disintegration. Failure to meet the disintegration specification could impact bioavailability, therefore efficacy and safety
Uniformity of Dosage unit (By Content Uniformity)	Acceptance value should be≤15.0	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process may impact the uniformity of blend thus may affect uniformity of dosage units.
Water content (by KF)	<1%	Yes	Water content may affect degradation and microbial growth in the product affecting safety and efficacy.
Assay	95–105% of label claim	Yes	Variability in assay will affect safety and efficacy; therefore, assay is critical.
Dissolution	Q=85% in 30 min	Yes	The drug release profile is important for achieving bioequivalence (BE); therefore, it is critical. Since *in vitro* drug release is a surrogate for *in vivo* performance, a similar drug release profile to the reference product is targeted to ensure bioequivalence.
Related substance	Known impurity: not more than 0.5% Maximum unknown impurity: Not more than 0.2% Total impurity: Not more than 1.0%	Yes	Formulation and process variables can impact the impurity profile. Therefore, they will be assessed during product and process development. The target for any unknown impurity will be set according to the ICH identification threshold for this drug product.

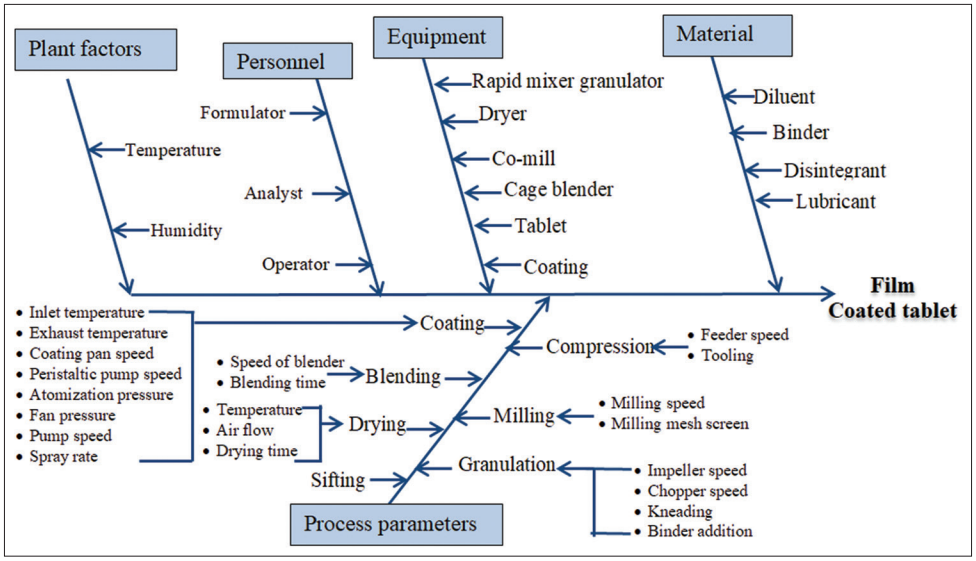

Fig. 1: Ishikawa fishbone diagram representing potential effect of factors on drug product CQAs during development of empagliflozin film-coated tablet

available Design Expert® software. A regular two level randomized full factorial design with 5-center points was employed to optimize the tablet formula. It consists of total nine runs of experiments. In this design, independent factors were concentrations of HPC and croscarmellose sodium in mg. The responses selected for study were CQAs of empagliflozin film coated tablet, such as % drug release at 15 min, disintegration time in sec, and hardness in Newton. The correlation of independent variable with responses was demonstrated by 3D surface model plot with the regions of maxima (red) and minima (blue). The coded values of design for empagliflozin film coated tablet are given in Table 3.

Table 3: Coded values of design

Name	Low (-1)	High (+1)
X1 (HPC SL)	4	8
X2 (Ac-di-sol)	0	4

Table 4: Composition of DoE batches

S. No.	Ingredients	Quantity in mg/tab								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Intragranular part										
1.	Empagliflozin	25	25	25	25	25	25	25	25	25
2.	Lactose monohydrate	60	64	60	60	60	60	60	60	56
3.	MCC PH 102	40	40	40	40	40	40	40	40	40
Binder solution										
4.	HPC SL	4	4	6	6	6	6	6	8	8
Extragranular part										
5.	Lactose SD Fast flo	53	53	53	53	53	53	53	53	53
6.	MCC PH 112	11	11	11	11	11	11	11	11	11
7.	Croscarmellose sodium	4	0	2	2	2	2	2	0	4
8.	Colloidal silicon dioxide	1	1	1	1	1	1	1	1	1
9.	Magnesium stearate	2	2	2	2	2	2	2	2	2
Coating solution										
10.	OPADRY yellow	6	6	6	6	6	6	6	6	6

Preparation of empagliflozin film coated tablet

Empagliflozin film-coated tablets are prepared using wet granulation technique [7].

Preparation of granules

All ingredients were accurately weighed on as shown in Table 4. Empagliflozin, lactose monohydrate, and microcrystalline cellulose were sifted through sieve no. 30. Binder solution was prepared by stirring the mixture of hydroxy propyl cellulose with 20% w/v purified water using mechanical stirrer (Remi Electrotechnik Ltd.) for 30 min. The sifted mass was put in rapid mixer granulator (Sams Techno Mesh Pvt. Ltd.) and mixed for 15 min at 100 rpm impeller speed. Addition of binder solution was carried out in next 5 min at same speed. Then, kneading was performed at 100 rpm impeller speed and 2100 rpm chopper speed for 5 min. These wet granules were subjected for drying in rapid dryer (Pharma Fab Engineers) till the moisture content in granules becomes 1%. The dried granules were passed through sieve no. 30. The retained hard granules are milled in Quadro® co-mill (Quadro engineering) to get uniform shaped granules passable through sieve no. 30. These uniform shaped granules were blended with extragranular part (previously passed through sieve no. 30) except mg stearate in Cage blender (Pharma Fab Engineers) for 30 min at 12 rpm. Then, the blended granules lubricated with magnesium stearate in blender at 12 rpm for 5 min.

Preparation of tablet

Lubricated granules were passed through hopper in die cavity and compacted using upper and lower punches using Tablet press® (Pharma Tools) to get core tablet. The coating solution was prepared by stirring the mixture of OPADRY yellow with purified water. This coating solution was sprayed on core tablets to get uniform coating using Gansons® automatic tablet coating machine.

Evaluation of lubricated granules [7]

Lubricated granules were evaluated for understanding their flow property.

Powder density analysis in gm/ml

Weighed 130±16 g (mass of untapped powder sample) of lubricated granules in 100 ml of measuring glass cylinder. Bulk density was measured by taking ratio of mass of untapped powder sample to its bulk volume. Tapped density was measured by taking ratio of mass of untapped powder sample to its tapped volume. Lubricated granules analysis was done by using Electrolab® tap density tester.

Compressibility index

Bulk density subtracted through tapped density and further divided by the same. This value was multiplied by 100 to get compressibility index in percentage.

Hausner ratio

It is ratio of tapped density to bulk density.

Evaluation of film coated tablet [7]

Uniformity of weight

Randomly selected 20 tablets were weighed using Contech® weighing balance and determined the average weight. If not more than two tablets deviate from the average weight by more than ±7.5%, then it passes the test.

Thickness

Five tablets were selected at random and measured their thickness using Mitutoyo® vernier caliper scale.

Hardness

Five tablets were selected at random and measured their hardness in Newton using Erweka tablet hardness tester (Labindia®)

Friability

Thirty-three tablets were selected randomly and subjected in drum of Roche tablet friability tester for 5 min at 25 rpm speed. % weight loss was calculated by taking initial and final weight.

Disintegration test

Six tablets were randomly selected and subjected in the tubes of disintegration test (Labindia®) USP apparatus A (media previously heated at 37±2°C) and tablet disintegration time in sec was noted.

In vitro dissolution study

As per [8], six tablets were randomly selected and subjected in cylindrical basket (USP dissolution Type 1 apparatus) at 100 rpm speed. This further put in dissolution glass vessel (already filled with preheated [at 37±2°C] 500 ml 0.1N hydrochloric acid as dissolution media). This Labindia® dissolution test apparatus started and the aliquot of solution (10ml) were withdrawn in glass test tubes at 5, 10, 15, 20, 30, 45, and 60 min time points. The withdrawn solution gets replenished by 10 ml dissolution media. Pipette out 3 ml of withdrawn aliquot of solution and diluted to 10 ml. This solution was analyzed using UV spectrophotometer (UV 1800 Shimadzu) and % drug release was calculated

Stability testing as per ICH guidelines

The optimized batch was loaded in Mack® stability chambers of long term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated storage conditions (40°C/75% RH) as per ICH Q1A (R2) guideline [9].

RESULTS AND DISCUSSION

Optimization of empagliflozin film coated tablet was done using regular two level randomized 2^2 full factorial design with 5-center points. The outline of data noted in Table 5.

Risk assessment and control strategy [10]

Ishikawa fishbone diagram (Fig. 1) represents different possible factors that can affect CQAs of empagliflozin film-coated tablet. Although practically, it was impossible to control all these risk factors, hence, it was need to select only those factors which known to be had significant effect on CQAs of empagliflozin film-coated tablet. Thus, qualitative risk measurement illustrated in Table 6. It includes the risk associated with process parameters and material attributes. From the initial formulation development study, it was proved that disintegrant concentration, drying and blending have high impact on CQAs and granulation, compression and binder concentration have medium impact.

Factors having low impact were eliminated from the study. Thus crucial factors showing high and medium impacts were chosen and considered during optimization to construct design space. This structural link was obtained between risk assessment and development of experimental plan.

Screening and selection of independent variables [10]

From the given Table 5, empagliflozine film-coated tablet formulation containing HPC SL (8 mg) and croscarmellose sodium (4 mg) gave foremost results with less disintegration time (15 s) and hardness (75.2 N). Highest concentration of disintegrant, that is, 4 mg of croscarmellose sodium reveals fastest disintegration and dissolution

Table 5: DoE design layout contains independent factors and noted responses

Experi-mental runs	Factor 1: hydroxy propyl cellulose	Factor 2: cros-carmellose sodium	Response 1: Dissolution at 15 min	Response 2: Tablet disintegration time	Response 3: Hardness
	mg	mg	% drug release	Sec	Newton
1	4	4	94.5±5.13	17	77.3
2	4	0	80.6±5.19	22	88.9
3	6	2	89.4±3.37	18	79.2
4	6	2	86±2.58	19	82.4
5	6	2	87.9±1.80	20	86.6
6	6	2	88.6±6.76	18	83.4
7	6	2	85.5±3.02	19	81.1
8	8	0	76.1±4.93	25	90
9	8	4	99±3.63	15	75.2

Table 6: Qualitative risk assessment associated with material and process parameters on CQAs of empagliflozin film-coated tablets

CQAs	Material attributes			Process parameters					
	Binder	Disintegrant	Lubricant	Granulation	Drying	Milling	Blending	Compression	Coating
Appearance	Low	Low	Low	Low	Medium	Low	Low	Medium	High
Disintegration time	Medium	High	Low	Medium	High	Low	Low	Medium	Low
Content uniformity	Low	Low	Low	Medium	Low	Low	High	Medium	Low
Hardness	Medium	Low	Low	Medium	High	Low	Low	High	Low
Assay	Low	Low	Low	Medium	Low	Low	High	Medium	Low
In-vitro drug release	Medium	High	Low	Medium	High	Low	Low	Medium	Low
Related substance	Low	Low	Low	Low	Medium	Low	Medium	Low	Low

Table 7: Evaluation of lubricated granules

Experimental runs	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner ratio	Inference on flow of granules
F1	0.518	0.658	21.311	1.271	Passable
F2	0.520	0.677	23.214	1.302	Passable
F3	0.546	0.696	21.538	1.275	Passable
F4	0.547	0.681	19.697	1.245	Fair
F5	0.563	0.664	15.152	1.179	Good
F6	0.543	0.708	23.28	1.304	Passable
F7	0.534	0.696	23.288	1.309	Passable
F8	0.517	0.676	23.611	1.309	Passable
F9	0.536	0.702	23.611	1.309	Passable

Table 8: *In vitro* dissolution profile of DoE batches

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	80.5±2.56	73.6±8.13	62.5±5.23	69.9±15.10	69.6±2.62	58.9±8.78	65.8±4.25	66.2±5.83	85.4±10.98
10	90.2±5.20	83.0±5.53	79.9±3.02	80.5±3.17	75.1±3.90	79.6±8.43	80.3±2.92	73.6±5.59	94.9±3.19
15	94.5±5.13	80.6±5.19	89.4±3.37	86±2.58	87.9±1.80	88.6±6.76	85.5±3.02	76.1±4.93	99±3.63
20	97.0±5.30	90.5±4.69	93.5±3.38	87±2.94	91.6±4.06	92.1±6.24	88.8±3.36	82.4±5.04	99.8±3.45
30	98.5±5.13	94.9±4.56	103.2±3.93	91.6±1.82	97.0±1.27	98.9±8.92	90.3±2.82	88.3±4.17	101.1±3.27
45	99.8±5.03	98.5±4.28	107.9±3.42	90.9±2.13	101.5±0.32	104.3±8.03	91.7±2.39	90.4±2.91	105.1±4.14
60	100.2±5.16	101.3±4.85	109.6±3.71	91.4±9.19	102.6±1.86	106.2±8.35	93.5±2.06	92.3±2.66	104.4±4.13

Table 9: Evaluation of empagliflozin film coated tablet of F9 optimized batch

S. No.	Evaluation parameters	Results
		Optimized batch (F9)
1	Appearance	Faint yellowish white
2	Average wt. (mg) (n=20)	202±3.12
3	Thickness (mm) (n=5)	3.91±0.03
4	Length (mm) (n=5)	11.04±0.02
5	Hardness (N) (n=5)	75.2±3.89
6	Friability (%)(n=33)	0.19±0.01
7	Disintegration time (sec.) (n=6)	15±0.7
8	*In-vitro* dissolution study (% drug release) (n=6)	
	5 min	85.4±10.98
	10 min	94.9±3.19
	15 min	99±3.63
	20 min	99.8±3.45
	30 min	101.1±3.27
	45 min	105.1±4.14
	60 min	104.4±4.13

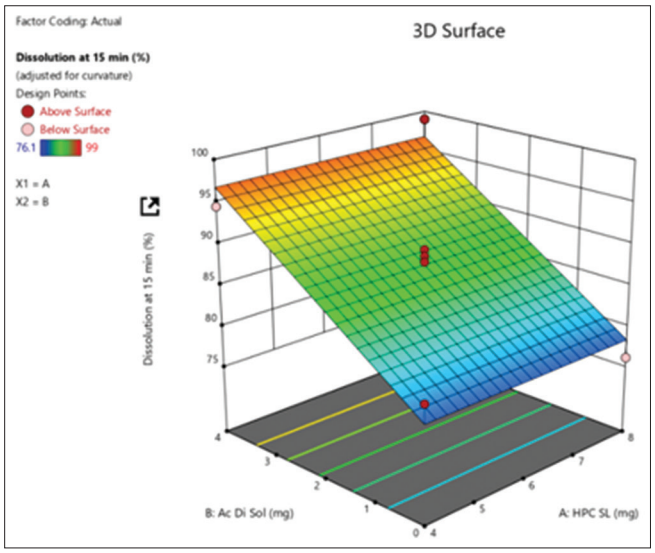

Fig. 2: 3D plot showing effect of independent variable on % drug release at dissolution time of 15 min

of tablet. 8 mg concentration of binder, that is, HPC SL benefitted in tablet friability and content uniformity to be in limit. Hence, these independent variables show significant effect on selected responses.

Flow properties of lubricated granules as per full factorial design experimental run

Calculated parameters to asses flow property of lubricated granules are given in Table 7. Good flow of granules was observed in lubricated granules of F5 batch run. Majority of runs show passable flow ability of lubricated granules, as it may show impact on blending, compression, and disintegration process parameters.

Effect of independent variables on *in vitro* % drug release

The Model F-value of 33.45 implies that the model is significant. p<0.0500 indicates that model terms are significant. The Lack of Fit F-value of 4.01 implies that the Lack of Fit is not significant relative to the pure error. Non-significant lack of fit is good and need model to fit. The Predicted R^2 of 0.6024 is not as close to the Adjusted R^2 of 0.8903 as one might normally expect; that is, the difference is more than 0.2. Adequate precision measures the signal to noise ratio. A ratio >4 is desirable. Your ratio of 14.167 indicates an adequate signal. This model can be used to navigate the design space. In Fig. 2, 3D plot represents the maximum (red) and minimum (blue) effect of independent variable on response. Overall both independent factors showed significant impact on % drug release at 15-min dissolution time.

Effect of independent variables on disintegration time

The Model F-value of 15.33 implies that the model is significant. p<0.0500 indicates that model terms are significant. The Lack of Fit F-value of 5.90 implies that there is a 6.41% chance that a Lack of Fit F-value this large could occur due to noise. Lack of fit is bad and need the model to fit. The Predicted R^2 of 0.2100 is not as close to the Adjusted R^2 of 0.7818 as one might normally expect; that is, the difference is more than 0.2. Adequate precision measures the signal to noise ratio. A ratio >4 is desirable. Your ratio of 10.208 indicates an adequate signal. This model can be used to navigate the design space. Fig. 3 represents middle point of each edge and center point of multi-dimensional cube (red color above the surface and pink color below the surface).

Table 10: Comparative evaluation study of optimized batch F9 with reference product

S. No	Parameter	Results		Inference
		F9	JARDIANCE®	
1.	Appearance	Faint yellowish-white	Faint yellowish-white	Complies
2.	Average wt. (mg) (n=20)	202±1.14	204±1.21	Complies
3.	Thickness (mm) (n=5)	3.91±0.02	3.88±0.02	Complies
4.	Length (mm) (n=5)	11.04±0.007	11.05±0.008	Complies
5.	Hardness (N) (n=5)	75.2±1.76	77.7±1.86	Complies
6.	Friability (%) (n=33)	0.19±0.01	0.21±0.02	Complies
7.	Disintegration time (sec.) (n=6)	15±4.24	21±2.14	Complies
8.	*In vitro* dissolution study (% drug release) (n=6)			
	5 min	85.4±10.98	78±1.74	Complies
	10 min	94.9±3.19	89±1.56	
	15 min	99±3.63	94±1.57	
	20 min	99.8±3.45	96±1.59	
	30 min	101.1±3.27	98±1.70	
	45 min	105.1±4.14	98±1.89	
	60 min	104.4±4.13	99±1.64	

Table 11: Evaluation of stability-loaded samples of optimized batch F9

S. No.	Parameters	Initial	25°C/60%RH	30°C/65%RH	40°C/75%RH	
			3 months	3 month	1 month	3 months
1.	Appearance	Faint yellowish white	Faint yellowish white	Faint yellowish white	Faint yellowish white	Faint yellowish white
2.	Average wt. (mg) (n=20)	202±1.58	200±1.56	201±1.48	199±2.00	198±1.68
3.	Thickness (mm) (n=5)	3.91±0.02	3.84±0.01	3.88±0.02	3.86±0.02	3.89±0.01
4.	Length (mm) (n=5)	11.04±0.01	11.05±0.015	11.06±0.01	11.03±0.01	11.02±0.02
5.	Hardness (N) (n=5)	75.2±1.40	71.8±1.31	72.4±1.36	74.4±1.41	73±1.35
6.	Friability (%) (n=33)	0.19±0.07	0.24±0.08	0.08±0.04	0.02±0.09	0.16±0.06
7.	Disintegration time (sec.) (n=6)	15±3.03	12±3.17	18±2.2	20±2.9	16±3.12
8.	*In vitro* dissolution study (% drug release) (n=6)					
	5 min	85.4±10.98	79±4.86	74±4.80	81±2.24	76±5.35
	10 min	94.9±3.19	89±4.05	85±3.67	92±2.02	89±3.79
	15 min	99±3.63	93±3.26	93±2.88	97±2.78	92±3.67
	20 min	99.8±3.45	95±2.89	96±2.74	101±3.19	94±3.67
	30 min	101.1±3.27	97±2.71	101±2.69	104±3.20	97±3.45
	45 min	105.1±4.14	101±2.84	104±2.87	107±1.37	99±2.72
	60 min	104.4±4.13	103±2.56	105±2.65	107±1.58	100±1.95

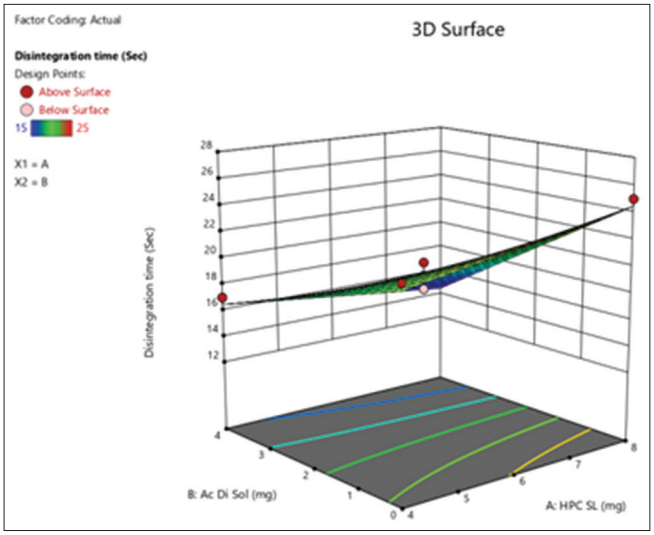

Fig. 3: 3D plot showing effect of independent variable on tablet disintegration time in sec

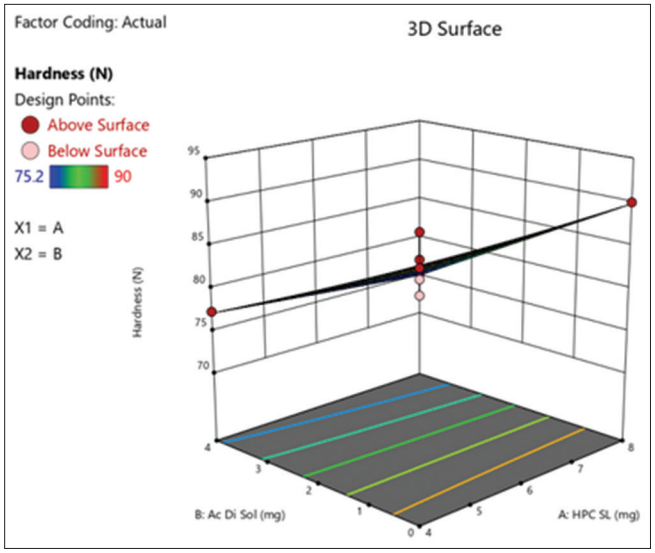

Fig. 4: 3D plot showing effect of independent variable on tablet hardness measured in Newton

Effect of independent variables on hardness

The Model F-value of 9.62 implies that the model is significant. p<0.0500 indicates that model terms are significant. The Lack of Fit F-value of 0.03 implies that the Lack of Fit is not significant relative to the pure error. There is an 87.52% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good

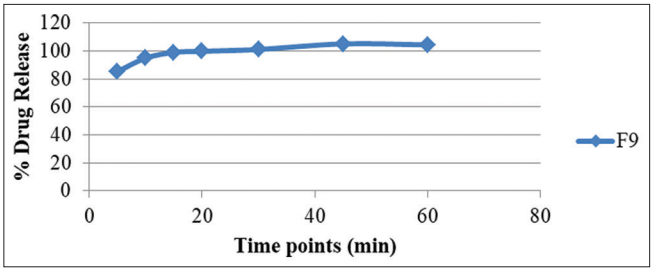

Fig. 5: *In vitro* dissolution profile of optimized batch F9 showing % drug release

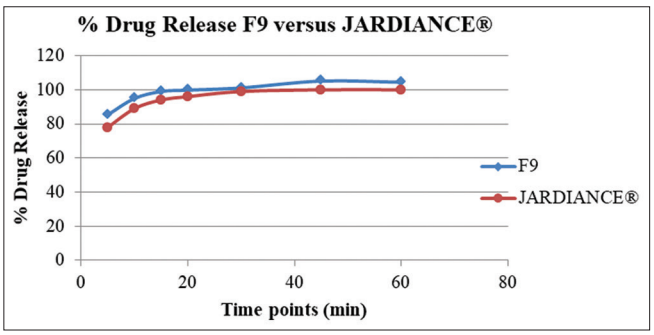

Fig. 6: Comparative *in vitro* dissolution profile of optimized batch F9 and reference product showing % drug release

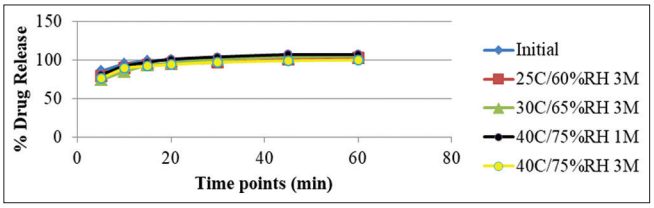

Fig. 7: *In vitro* dissolution profile of stability-loaded samples of optimized batch

and to the model to fit. The Predicted R^2 of 0.7842 is in reasonable agreement with the Adjusted R^2 of 0.7637; that is, the difference is <0.2. Adequate precision measures the signal to noise ratio. A ratio >4 is desirable. Your ratio of 8.961 indicates an adequate signal. This model can be used to navigate the design space. Fig. 4 represented 3D plot to see how response variable related to two predictor variables. This 3D plot is useful in investigating desirable response values and operating conditions.

Evaluation of optimized batch

By understanding Table 8 depicting overall *in vitro* dissolution profile; DoE run F9 (Table 9 and Fig. 5) said to be optimized batch because its tablet disintegrate in less time of 15±0.7 s, still having hardness of 75.2±3.89 N, it showed 99±3.63 % desirable drug release during *in vitro* dissolution study.

Comparison between *in vitro* drug release of optimized batch with reference product

F9 was said to be optimized batch and hence is compared with marketed formulation JARDIANCE®, as it complies all the parameters of marketed formulation given in Table 10 and Fig. 6. Further, this F9 batch formulation was studied for stability purpose.

Evaluation of stability samples

The loaded stability samples were unloaded after 3 months and they were evaluated as given in Table 11 and Fig. 7. The optimized batch F9 has shown no change after doing stability studies, it confirms that the formulation is stable as per ICH Guidelines.

CONCLUSION

The present research work represents the application of QbD approach for successful immediate release oral solid dosage form development that was Empagliflozin film-coated tablet. Design space was established after knowing QTTP and CQAs; assessing the risk factors, full factorial DoE was constructed. Based on 3D plots, it was observed that HPC SL and croscarmellose sodium were best suitable binder and disintegrant, respectively; and they showed significant effect on tablet hardness, disintegration, and *in vitro* dissolution. This significant impact was demonstrated using ANOVA and lack-of-fit. The magnificent fit was observed between actual and predicted values for all responses, this implies selected DoE tool was right. This optimization method confirmed that F9 formulation found to be better with respect to stability and effectiveness against marketed formulation. It indicates that HPC SL (8 mg) and croscarmellose sodium (4 mg) were ideal concentrations of binder and disintegrant, respectively, to prepare immediate release empagliflozin film-coated tablet with desired quality attributes. This formulation may prove beneficial to Type-2 diabetic patients and Type-2 diabetes mellitus patients with cardiovascular risk.

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AUTHOR'S CONTRIBUTION

Mr. Vardhaman Bafna and Mr. Mahesh Bhadgale were guided me in development and analysis of this formulation. Dr. Atul Phatak was guided me in interpretation of this research article.

CONFLICTS OF INTEREST

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REFERENCES

1. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 diabetes-global burden of disease and forecasted trends. J Epidemiol Glob Health 2020;10:107-11.
2. Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing Type 2 diabetes. Cleve Clin J Med 2021;88:47-59.
3. Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors : A review of their basic and clinical pharmacology. Diabetes Ther 2014;2:355-66.
4. Dalama B, Mesa J. New oral hypoglycemic agents and cardiovascular risk. Crossing the metabolic border. Rev Esp Cardiol (Engl Ed) 2016;69:1088-97.
5. Zhang L, Mao S. Application of quality by design in the current drug development. Asian J Pharm Sci 2017;12:1-8.
6. ICH. Q8(R2) Guideline Pharmaceutical Development, Current Step 4 Version. Switzerland: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2009.
7. Phatak A, Joshi D, Bhadgale M, Chaudhari P. Development and optimization of naproxen sodium controlled release tablets : QbD approach. Indian J Pharm Educ Res 2020;54(2s):s108-16.
8. FDA CDER Guidance for Industry. Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs Guidance for Industry Dissolution Testing and Specification Criteria for Immediate-Release. United States: Food and Drug Administration; 2015.
9. ICH. Q1A(R2) Guideline Stability Testing of New Drug Substances and Products, Current Step 4 Version. Switzerland: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2003.
10. Mishra SM, Rohera BD. An integrated, quality by design (QbD) approach for design, development and optimization of orally disintegrating tablet formulation of carbamazepine. Pharm Dev Technol 2017;22:889-903.