doi.org/10.36721/PJPS.2021.34.4.SUP.1519-1525.1

Optimization of empagliflozin immediate release tablets (10 mg) using central composite rotatable design with response surface methodology

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Abstract: Empagliflozin is a selective inhibitor of sodium glucose co-transporter II, given as mono therapy or an add-on treatment to reduce the glycated hemoglobin levels in type 2 diabetes. This work deals with designing, formulating and optimizing empagliflozin (10mg) immediate release (IR) tablets by direct compression technique using different excipients. Through central composite rotatable design (CCRD), total nine formulations (EF1-EF9) were generated by changing the composition of binder avicel PH 102® (X1) and superdisintegrant acdisol® (X2). Formulation runs with in suitable weight range and powder properties were subjected to compression. The influence of interaction of excipients on friability (Y1), hardness (Y2) and disintegration (Y3) were analyzed by fitting the polynomial quadratic model with response surface methodology (RSM). Trials EF2, EF7, EF8 and EF9 exhibited acceptable tablet attributes upon physico-chemical testing. Different dissolution models were applied to observe the in vitro drug release pattern in phosphate buffer of pH 6.8. The cumulative drug release of IR tablet batches followed the Weibull kinetics with regression coefficient (r^2) values of 0.983-0.992. Empagliflozin trials were exposed to accelerated storage conditions (40±2°C/ 75±5% RH) for stability testing. Shelf life period of exposed formulations were computed in range of 22 to 25 months. Keeping in view of the results, it is concluded that the employed technique of preparation and optimization are observed to be excellent for developing immediate release empagliflozin (10mg) tablets.

Keywords: Empagliflozin, optimization, direct compression, response surface methodology, central composite rotatable design

INTRODUCTION

Empagliflozin, BCS Class III drug (Grube *et al*., 2019) acts as a selective sodium-glucose co-transporter-2 SGLT2 inhibitor (Nair and Wilding, 2019). It is among one of the novel anti-diabetic moieties, offering a new option for management of type II diabetes mellitus (T2DM) targeting the kidney to remove glucose from the body (Hedrington and Davis, 2015). Several FDA-approved pharmacotherapies are available for T2DM but many patients are unable to achieve desirable hypoglycemic effects owing to various side effects, associated with the therapy. Hypoglycemia, fluid retention, weight gain, gastrointestinal complications and metabolic effects are well documented (Acharya and Deedwania 2019; Chaudhury *et al*., 2017; Rodbard *et al.*, 2007). Empagliflozin has gained popularity globally due to effective glycemic control and safety. It is well absorbed orally in recommended dose of 10mg once daily either with or without food taken in the morning. The drug reaches to its maximum concentration within 2 hrs with an elimination half-life ($t_{1/2}$) of 13 hours. It can be utilized as a first line monotherapy however; other hypoglycemic agents may co-administered to intensify the hypoglycemic actions at any level of DM (Levine 2017; Hedrington and Davis, 2015; Frampton, 2018).

Oral drug deliveries are advantageous in different aspects offering higher patients' acceptance all over the world (Viswanathan *et al.,* 2017). Direct compression method for tablet manufacturing is considered to be one of the preferred methods of tableting in pharmaceutical industries. It is reported to be the simplest, time saving and cost-effective technique as compared to the wet and dry granulation procedures (Asif *et al.*, 2016). The choice of pharmaceutical excipients is a critical step in direct compression formulation (Thoorens *et al.,* 2015). A variety of pharmaceutical excipients are commercially available for the development of formulation. Avicel is microcrystalline cellulose (MCC) utilized as directly compressible binder/filler and forms strong and cohesive compacts even at low compression pressure (Thoorens *et al.,* 2015). Croscarmellose sodium (acdisol) is a superdisintegrant used in a concentration range of 0.5-3% for the facilitation of rapid disintegration leading to an acceleration of the dissolution process for directly compressed tablets (Kaur and Mehara, 2016; Mor *et al*., 2016).

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Scientists have immensely utilized the statistical design tools for the formulation development and optimization of a variety of pharmaceutical dosage forms (Zafar *et al*., 2018; Madgulkar et *al*., 2009). These mathematical experimental designs are systematic and powerful tool for the determination correlation of independent variables to the dependent variable. Henceforth, helps to draw statistically significant interpretation using less number of experiments for the design space estimation (Zhang and Mao *et al.*, 2016; Bushra *et al.*, 2018). The central composite design is one of the efficient mathematical models with response surface methodology (RSM) applied for the development of optimized formulations by assessing the interaction among dependent and independent variables. It also reduces number of trials and provides adequacy of the proposed model through ANOVA with construction of 3D response/ contour plots (Awotwe-Otoo *et al.*, 2012).

The objective of the current study was to develop and optimize immediate release empagliflozin (10 mg) tablet formulations by direct compression utilizing central composite design.The effect of the two independent factors avicel and acdisol at five different levels were determined on responses including tablet friability, hardness and disintegration time. Pre and post-compression quality attributes of all formulations are assessed for formulation optimization. Moreover; response surface methodology (RSM) was applied to construct the plots for excipients' interaction, influencing the quality attributes of experimental tablet batches.

MATERIALS AND METHODS

Chemicals/reagents

Empagliflozin (API) was courteously provided by Sami Pharma (Pvt.) Ltd. Pakistan. Croscarmellose Sodium (*acidisol*®), microcrystalline cellulose (avicel® PH 102), silicon dioxide (aerosil®) and magnesium stearate were of BDH supplier. Potassium dihydrogen phosphate (KH_2PO_4), hydrochloric acid (HCl) and sodium hydroxide (NaOH) were of suitable analytical (Merck KGaA Darmstadt 6427 Germany) grade used for drug dissolution and assay of trial formulations.

Methodology

Designing of formulations and optimization

Different immediate release (IR) tablet formulation trials of empagliflozin were attained by Design Expert® (Version 7.0, Stat-Ease Inc., MN) using central composite rotatable design (CCRD). 2K factorial model was applied by changing the amount of two selected formulation variables: X1 avicel ® PH 102 (45-212mg) and X2 acdisol® (0.75-9.24mg). Total nine formulation combinations (EF1-EF9) including four factorial, four axial and one centre point were generated at five different levels -1, -α, 0, +1, +α (α=1.414). Empagliflozin (API) and other formulation ingredients (aerosil and magnesium stearate were kept constant (table 1). Optimization of designed formulation was made by assessing the selected response variables includingfriability (Y1), hardness (Y2) and disintegration (Y3). Response surface methodology was applied to investigate the excipient's effect on the physico-chemical properties of compressed tablet batches. Polynomial quadratic analysis was made to study the interaction of independent and dependent variables on responses. Model summary of *p* value, r^2 value and F value computed through the RSM of same software Design Expert® version 7.0 (Stat-Ease Inc.).

Pre-Compressional testing

Pharmacopeial methods were applied for determining the micromeritic properties of powder blends. Equations 1-3 were used to calculate Hausner's ratio, angle of repose and compressibility index, respectively (USP, 2012).

$$Hausner\ ratio = \left(\rho_{tapped} / \rho_{bulk}\right) \quad (1)$$

$$tan(\theta) = height/0.5\ base \quad (2)$$

$$Compressibility\ Index = 100\ x \left[\left(\rho_{tapped} - \rho_{bulk}\right)/\rho_{tapped}\right] \quad (3)$$

Where, ρ_{tapped} and ρ_{bulk} are the tapped and the bulk densities, respectively.

Empagliflozin immediate release tablet preparation

All formulation ingredients were sieved through mesh 40 for uniformity in size. Powder was weighed using electronic balance (AUW-220, UNI Blog, Shimadzu, Corp, Japan) accurately and then mixed manually by tumbling action in a clean empty jar with capacity double the batch weight. Powder blends with good micromeritic properties and compressible weight were then directly compressed using double punch compression machine (D type 16-station D3B, Manesty, England) and evaluated for tablet quality attributes.

Tablet Characterization

Physical test including weight variation (electronic balance), thickness (measuring gauge; CD-6, CSX, Mitutoyo, Japan), diameter (measuring gauge; CD-6, CSX, Mitutoyo, Japan), friability (double drum friabilator; EF-2, Electro Lab, India), hardness (hardness tester; Fujiwara Seisakusho, Ogawa Seiko Co Ltd, Tokyo, Japan) and disintegration (USP Basket-rack assembly, Model: DA 6D, Veego) were performed by randomly taken empagliflozin compressed trial formulations. Single point drug dissolution (n=6) was performed for 30 min in phosphate buffer of pH 6.8 using USP dissolution apparatus II (PT-DT70, Pharma Test, Germany). Drug assay (n=10) was estimated by high performance liquid chromatography (HPLC) technique using mobile phase containing orthophosphoric acid and acetonitrile (70:30) with a flow rate of 1mL/min. Sample was prepared by taking content equivalent to 10mg of API, filtered, diluted, sonicated and analyzed thrice at wavelength of

Table 1: Formulation Design of various Empagliflozin (10mg) immediate release tablets by Central Composite Rotatable Technique

Batch Code	Rotation Points	Coded Levels of variables		Amount of formulation Ingredients (mg)				Amount per tablet (mg)
		Avicel (PH 102)	Acdisol	Avicel (PH 102)	Acdisol	Magnesium Stearate/ Aerosil	Empagliflozin	
EF1	Axial Formulation Run Points	-1.414	0	45	5	1.5/1	10	62.5
EF2		+1.414	0	212.44	5			229.94
EF3		0	-1.414	129	0.76			142.26
EF4		0	+1.414	129	9.24			150.74
EF5	Factorial Formulation Run Points	-1	1	70	8			90.5
EF6		-1	-1	70	2			84.5
EF7		1	-1	188	2			202.5
EF8		1	1	188	8			208.5
EF9	Central Formulation Run Point	0	0	129	5			146.5

Table 2: Powder blend properties and Quality Comparison of directly compressible Empagliflozin tablet trials (IR)

Batch Code	Angle of Repose (n=3)	Hausner's Ratio (n=3)	Carr's Index (n=3)	USP Remarks	Weight Variation (mg) Mean ± SD (n=20)	Thickness (mm) Mean ± SD (n=20)	Hardness (Kg) Mean ± SD (n=20)	Friability (%)	Disintegration time (Sec)	Drug Release (%) Mean ± SD (n=6)	Assay (Mean ± SD (n=3)
EF2	33.13±0.350	1.156±0.012	13.732±0.773	Good	227.4±3.574	3.090±0.216	10.79±1.379	0.32	219	99.36±1.125	100.33±0.472
EF4	41.55±0.585	1.313±0.055	21.245±0.784	Passable	145.53±5.676	2.90±0.047	7.50±1.142	0.89	47	84.566±2.316	89.666±1.527
EF7	32.33±0.514	1.15±0.04	14.305±0.636	Good	199.12±4.582	3.041±0.055	9.81±1.421	0.43	232	95.617±1.587	99.166±1.040
EF8	33.75±0.665	1.16±0.0088	14.013±0.877	Good	202.87±4.192	3.081±0.052	9.78±1.403	0.44	88	93.445±1.025	98.60±1.630
EF9	34.166±0.503	1.221±0.0182	17.49±1.105	Fair	141.75±4.124	2.87±0.054	9.27±1.229	0.51	165	94.70±1.048	97.233±1.365a

233nm using HPLC (LC 20A, Shimadzu Corp., Kyoto, Japan) (Shyamala *et al.,* 2016).

Selection of optimized trials

Optimized empagliflozin IR trials were selected on the basis of acceptable/excellent physico-chemical responses as mentioned.

In vitro release kinetic study of optimized empagliflozin immediate release tablets

In vitro release profile of empagliflozin formulations was performed on six replicates using USP <711> dissolution apparatus II at 75rpm. Preparations were tested in 900mLphosphate buffer (6.8) maintained at 37±0.5°C. Samples were taken at 5, 10, 15, 20 and 30 min, filtered and diluted with the respective buffer and analyzed through HPLC. Model dependent analysis was performed using DD-Solver as Add-Ins program to Microsoft Excel for fitting of dissolution data in to following equations of first order, Hixson-Crowell and Weibull kinetics (4-6) models.

$$LogQ_t = LogQ_0 - \frac{kt}{2.303} \quad (4)$$

Where the drug released at time t is represented by Q_t and Q_o indicates initial amount of drug present in dosage form and k is the first order rate constant (Varles *et al.,* 1995).

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t \quad (5)$$

k_{HC} is Hixson-Crowell rate constant (Hixson and Crowell, 1931).

$$Log[-ln(1-m)] = bLog(t-T_i) - log \propto \quad (6)$$

Where T_i is the lag time, α is the time process and β is the shape parameter (Langenbucher, 1972).

Stability testing

Stability testing under accelerated condition (40±2°C/ 75±5% RH) was performed on optimized sets of empagliflozin formulations as per stability protocol recommended by International Council of Harmonization (ICH, 2003) for 6 months. The samples were drawn at specific time intervals and assessed for the various physico-chemical factors including physical appearance (colour, odour, and surface quality), hardness, dissolution and assay.

STATISTICAL ANALYSIS

Tablet characters were expressed in mean ±SD, calculated by Microsoft Excel program version 2016. R-Gui version 3.3.1 (stab) package [Copyright © 2016, The R-Gui Foundation for Statistical Computing] was used to calculate the shelf life of optimized trial formulations.

RESULTS

Overall, nine formulation runs of immediate release empagliflozin tablets were generated by the software

Table 3: Statistical model summary of response variables

Analysis	Polynomial Quadratic Model		
Variables / Parameters	Friability (Y1)	Hardness (Y2)	Disintegration (Y3)
R-Square	0.9407	0.9707	0.9986
Standard Deviation	0.11	1.15	4.40
Adequate Precision	8.437	12.615	63.33
Mean Residual	0.016	1.32	19.32
% CV	18.32	16.84	3.22
p-Value	0.041	0.0166	0.0002
F-value	9.52	19.90	436.66
Remarks	Significant interaction of Excipients		

Table 4: *In-vitro* dissolution modeling of immediate release empagliflozin tablet batches

CODE	First Order				Hixson-Crowell				Weibull				
	r^2	K (hr^{-1})	AIC	MSC	r^2	K_{HC} ($hr^{-1/3}$)	AIC	MSC	r^2	α	β	AIC	MSC
EF2	0.957	0.116	33.903	2.491	0.967	0.027	32.317	2.756	0.983	20.539	1.285	31.568	2.714
EF7	0.9809	0.0980	29.768	3.289	0.983	0.025	29.051	3.408	0.994	30.591	1.355	29.010	3.619
EF8	0.976	0.0104	30.602	3.063	0.981	0.025	29.154	3.204	0.992	23.591	1.290	28.742	3.373
EF9	0.944	0.096	34.063	2.227	0.951	0.023	33.508	2.350	0.964	12.884	1.078	33.028	2.463

design expert. Five formulations having acceptable excipients' weight were exposed to direct compression. Table 2 presents the preformulation characters of the powder blend. Three blends of trials (EF2, EF7 and Ef8) showed angle of repose, Hausner's ratio and Carr's index in good range while EF4 exhibited passable flowability and compressibility. Tablet attributes of empagliflozin trials were listed in table 3. Formulation EF4 showed higher friability and lower drug dissolution and assay. Henceforth, this formulation was not proceeding for further quality studies such as *in vitro* drug release kinetics and stability testing. Excipients interaction and optimization were evaluated by RSM. The polynomial quadratic analysis was applied to study the effect of variables on quality of tablets. Model fit summary is given in table 3. RSM plots of interaction affecting drug friability, hardness and disintegration are shown in fig. 1. Dissolution models (table 4) including first order, Hixson-Crowell and Weibull were applied on selected immediate release empagliflozin formulations (EF2, EF7, EF8 and EF9) using dissolution medium phosphate buffer of pH 6.8. All formulation trials followed Weibull kinetic mechanism for drug release with regression of coefficient of (0.983-0.992). Shelf lives of immediate release trials were estimated by R-Gui software, computed to be 25, 24, 24.7 and 22months respectively for EF2, EF7, EF8 and EF9.

DISCUSSION

Excipients although inert in nature, but play a significant role in formulation development of pharmaceutical products. Quality of pharmaceutical dosage forms are primarily relies on the selection and the appropriate levels of formulation additives or excipients. Tablets are still one of the most utilizing products among other available dosages owing to benefits to the consumers. Empagliflozin is widely prescribed to control the blood glucose level in early stages of diabetes mellitus type II effectively. It is also administered in combination with other hypoglycemic agents (metformin and linagliptin) in fixed dose combination to enhance the treatment outcomes (Lingvay *et al.,* 2020; Hu *et al.,* 2016).

In the present study, empagliflozin immediate release tablet formulation was designed using central composite rotatable design with two independent factors (filler/binder and disintegrant). It is one of the reliable statistical tools with RSM to observe the influence of formulation variables (independent) on the product quality (dependent). It offers second order, polynomial quadratic analysis that even may applied on two factorial designs. Quantity of avicel PH 102 (binder/filler) and acdisol (superdisintegrant) are formulation variables, titled to be X1 and X2 respectively. Overall, nine formulations were produced by rotating the excipients on factorial, axial and center points. Sets of center, axial and factorial points are basically generated by rotating the variables below (-1.414) and above (+1.414) the median of two factor levels. EF1 to EF4 trials were on axial points, EF5 to EF8 trials were factorial and EF9 was center point formulation. These formulations contained five different levels of excipients including -1.414, -1, 0, +1 and 1.414. On the basis of acceptable weight of ingredients five formulations (two factorial, two axial and one center point) were selected for tablet compression. The powder blend features of the formulations were fall within the acceptable limits as recommended by United

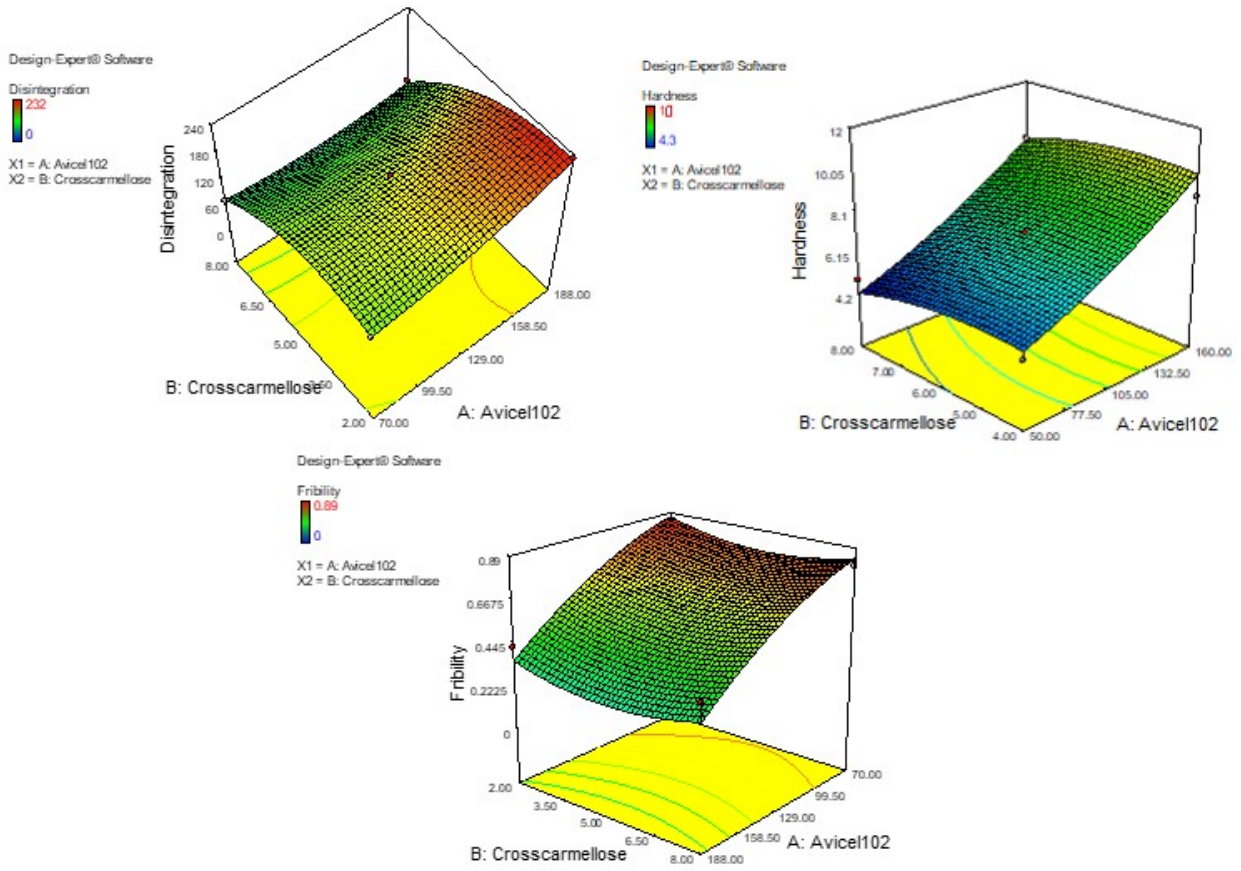

Fig. 1: Influence of excipients on friability, hardness and disintegration of various empagliflozin (10mg) immediate release trials.

State Pharmacopeia. Combination of magnesium stearate and silicon dioxide were incorporated for uniform flowability and easy ejection of units after compression. Angle of repose was found to be in good to fair range except for EF4. The angle was higher in EF4 probably due to the decrease level of avicel PH 102. Moreover, increased amount of superdisintegrant may also induce the softening of particles result in compromised flowability. Avicel PH 102 is granular in appearance providing largest particle size than other available grades of avicel including PH 101, PH 103, PH 105, PH 301 and others. Avicel possessed lower the coefficient of friction hence aiding the flow property to the blends. It is one the recommended diluent and binder for direct compression due to excellent binding and flow aiding properties (Thoorens *et al.,* 2015). Patro and Sahu had developed cetirizine hydrochloride oral disintegrating tablets by central composite design (CCD) by varying the quantity of natural and synthetic disintegrants. Effects were observed on the tablet friability, disintegration and % drug release. The design was found to be valid as least differences were observed between the predicted and estimated values of the model (Patro and Sahu, 2017). Similarly in another study authors reported CCD as an appropriate statistical approach to optimize semi liquid fenofibrate tablet batches (Patel *et al.,* 2014).

Direct compression was applied on the various combinations of powder blends as offers many benefits over other techniques of tableting like dry and wet granulation. It avoids water addition and heat exposure for drying; henceforth considered to be the best technique for thermolabile drugs. Cost effectiveness with quality is one of the major advantages of direct compression as mentioned in past studies (Chen *et al.,* 2019; Bushra *et al.,* 2018; Chattoraj *et al.,* 2017). Presently, empagliflozin immediate release tablet batches (EF2, EF4, EF7, EF8 and EF9) were prepared by simplest and economical way of direct compression. Tablets were examined visually for physical defects. Physico-chemical characterization was done as recommended by compendial and non-compendial test. All formulation trials exhibited good quality features including friability, hardness, drug release and assay except EF4. Least hardness and higher friability was observed in batch EF4. This might be due to the softening effect of acdisol on tablets, as EF4 contained increased content of acdisol (6.13%). The hardness of the trials were found higher in EF2 due to the increased content of binder. Avicel deforms plastically, providing the maximum area of interparticle bonding, consequently compacts of higher strength were produced. Microcrystalline cellulose (MCC) is considered to be the gold standard binder and filler for directly compressible

tablets. It even may facilitate the disintegration to some extent, but the need of true disintegrant still remains in the formulation. It is recommended to be used with superdisintegrant like crospovidone, croscarmellose and sodium starch glycolate (Bala *et al.,* 2013; Mostafa *et al.,* 2013). In the current study acdisol as superdisintegrant was incorporated in the formulations. Rapid disintegration was observed in EF4 (47 sec) owing to higher level of acdisol. Formulation trial EF2 disintegrated comparatively slow due to increase content of the binder. On the whole, trials EF2, EF7, EF8 and EF9 exhibited good quality parameters and were selected for further studies. Past studies dealing with formulation development of immediate release tablets also documented the efficiency of acdisol in drug deaggregation and disintegration (Yousaf *et al.,* 2019; Hanif *et al.,* 2011). Excipient interaction was studied using response surface methodology. The interaction of the excipients are presented by response surface plots in the form of basic, contour and perspective plots. Such plots showed the rotation and interference of excipients (2 factors) against the response variables of friability, hardness and disintegration. Different lines and shadings reflect the interaction of excipients and their effect on responses. Quadratic equations (4-6) for dependent variables friability (Y1), hardness (Y2) and disintegration time (Y3) are given below in coded Terms;

Friability= 0.6-0.24983*A -.01061*B 0.005*A*B - 0.006938*A^2 0.073125*B^2 (Eq 7)
Hardness= 9.15+3.373681*A – 1.72996*B+0.425*A*B-0.55*A^2- 2.075*B^2 (Eq 8)
Disintegration=165+23.30483*A-.52.7147*B-19.25*A*B-12.8125*A^2-44.6875*B^2 (Eq 9)

Selected trials of empagliflozin immediate release tablets were also subjected to multi point dissolution testing to estimate the in vitro kinetic behavior. All immediate release trials exhibited Weibull kinetics with higher regression coefficient values. The Akaike Information Criterion (AIC), and the Model Selection Criterion (MSC) are also recommended for data model fitting. AIC is typically depends on the magnitude with respect to time points while MSC being the reciprocal of the AIC could not be rely on time scaling. Higher values of MSC and lower values of AIC support the goodness of fit for any specific dissolution model (Bushra *et al.,* 2018; Zhang *et al.,* 2010). Stability studies were conducted for six months at accelerated conditions as mentioned in experimental section. Units were inspected for product quality in terms of physical defects along with drug dissolution and assay. Tablets of trials EF2, EF7, EF8, and EF9 were found to be devoid of any physical defect within the specified time period. Shelf life was computed by fitting data of assay obtained during six months of stability. Highest stability was exhibited by EF2 (25 months) while least was shown by formulation EF9 (22 months). On the basis of physico-chemical parameters and stability data results, trials EF2, EF7 and EF8 were selected as optimized immediate release empagliflozin tablet formulations.

CONCLUSION

Immediate release empagliflozin (10mg) tablets were successfully developed by direct compressing the formulation run trials generated through central composite rotatable design. Polynomial quadratic analysis and 3D-response plots were found to be appropriate to observe the interaction of independent variables on dependent variables (r^2>0.94). Regression coefficient, AIC and MSC values confirmed the fitting of Weibull model for immediate release empagliflozin trials. Formulations EF2, EF7 and EF9 were found to be optimized immediate release trials due to good tablet attributes and stability.

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