RESEARCH ARTICLE

Experimental Design Statistically by Design Expert Software: A Model Poorly Soluble Drug with Dissolution Enhancement and Optimization

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ABSTRACT

The experimental factorial design was performed design expert software to the formulation of rapid orally disintegrating tablets of a poorly soluble model drug to investigate by using superdisintegrant, β-Cyclodextrin (βCD) and surfactant (SLS) on the onset of the anti-hypertensive action of poorly soluble irbesartan. The three independent factors, %, βCD (X1) its concentration (1:1 and 1:5), superdisintegrant (crosspovidone) concentration (2% and 30) (X2) and SLS (0, 2%) (X3) were studied for their main effects on three independent variables on dependent variables, percent dissolved 15 minutes (PD 15%), dissolution efficiency 30 minutes (DE 30), time for 50% dissolved (Q 50%) and disintegration time (DT). Statistical analysis of obtained data and optimization of formulation variables were carried out using Design-Expert trail version software exhibit counter plots and ANOVA studies are significant. The combination maximized desirability over the indicated region to 0.973193. The drug-excipients interaction studies by differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FT-IR) indicate no interaction. The accelerated stability study at 40°C and 75% relative humidity (RH) for 6 months and *in-vitro* evaluation against conventional market tablets are significantly identical on dissolution.

Keywords: ANOVA, Dependent variable, Independent variable, Irbesartan.

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INTRODUCTION

Irbesartan is 2-butyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl] phenyl]methyl]-1,3 diazaspiro[4.4]non-1-en-4-one as shown in Figure 1a, a widely prescribed anti-hypertensive drug belongs to class II under breast conserving surgery (BCS) classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. In the earlier reported[1] many variations were observed in the dissolution rate and dissolution efficiency of etoricoxib tablets formulated employing selected combinations of binder, disintegrant and β-CD as per 2^3 factorial design (Figure 1b). The oral route is preferred its better patient compliance. Many of the drugs are specific absorption in the gastrointestinal (GI) tract and various factors depending on solubility, stability, ionization various polymers on the drug in different portions of the GI tract influence delayed absorption.[2,3] The optimized formulation with NLT 85% dissolution in 10 minutes could be developed employing 2^3 factorial designs.[4] The tablet dosage form is one of the most preferred formulations because it is economical, accurate dosing, good stability, and administration when compared to other pharmaceutical dosage forms.[5] The surfactants on the dissolution of poorly soluble drugs were compared to identify the most suitable surfactant, sodium lauryl sulfate (SLS) as an anionic surfactant, and polysorbate 80 as a non-ionic surfactant were used successfully developed reported.[6] The incorporation of superdisintegrants in solid dispersion tablets containing a high drug load can strongly enhance the dissolution rate of the highly lipophilic drug fenofibrate, the dissolution rate was more increased when the superdisintegrant was incorporated in the drug-containing solid dispersions than when it was physically

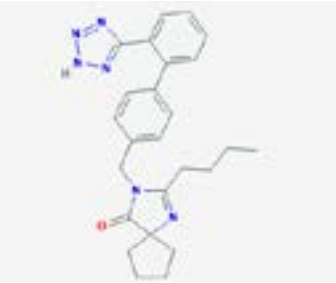

Figure 1a: Chemical structure of irbesartan.

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mixed with the solid dispersions was reported.[7] For the tablets prepared from naproxen-disintegrant agglomerates, having a dissolution time below 30 minutes, a linear relationship existed between disintegration time and DRi and AUC.[8] The binary inclusion complexes of itraconazole with two commonly used cyclodextrin derivatives and a recently introduced cyclodextrin derivative were prepared.[9] The objective of the present study was to characterize the prepared Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) as well as dissolution studies were performed. A 2^3 factorial design was used to study the effect of formulation variables on the performance of these tablets.

The drug-loaded solid dispersion composed of valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75 improves the drug solubility by about 43-fold.[10] *in-vitro* dissolution of crystalline and amorphous form of both the drugs, crystalline and amorphous physical mixtures and co-amorphous systems were conducted at a non-sink condition in dissolution media with 0.5% SLS.[11] The rapid dissolved tablets were prepared by using either crospovidone or sodium starch glycolate (SSG) as superdisintegrants and commonly available excipients.[12] More than 94% of itraconazole was dissolved out of the β-CD 1/3 physical mixture after 60 min.[13] The excipient variability of superdisintegrants (SSG–viscosity type) and lubricants (MgSt) on the dissolution of a highly and poorly soluble drug from immediate release formulations was assessed in a biopharmaceutical perspective.[14] The formulation development by various formulations, including drug release and statistically evaluated factorial design, were reported *in-vitro* and *in-vivo*.[15-19]

MATERIALS AND METHODS

Materials

Irbesartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Crospovidone, SLS and β-CD were gift samples from M/s. Eisai Pharma Technology Ltd, Visakhapatnam. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Experimental Design

Design expert software and used to generate the study design and the response surface plots. The best fitting model was selected based on statistical comparison parameters, including the coefficient of variation (CV), coefficient of determination (R^2) and adjusted coefficient of determination (adjusted R^2), predicted coefficient of determination (Pred. R^2), adeq precision, optimization and desirability provided by design expert software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F test and *p*-values were also calculated using the software. Three factors three level factorial design was used to optimize irbesartan tablets, namely β-CD (X_1) and crospovidone (X_2) and SLS (X_3) concentrations with Statistical models. To find interaction terms were derived to evaluate the effect of the three factors on the percentage dissolved in 15 minutes (PD 15%) (Y_1), DE_{30} (dissolution efficiency 30 minutes),[20] (Y_2), Q 50% (time for 50% dissolved) (Y_3), disintegration time (min/sec) (Y_4) on the prepared tablets as per factorial design model. The statistical model incorporating interactive and polynomial terms was used to evaluate the responses

Table 1: Independent variable and dependent variables
(Independence variables on 2^3 factorial designs)

Independent variables	*Low(-1)*	*High(+)*
X_1: β-Cyclodextrin	1:1	1:5
X_2 :Crosspovidone	2%	30%
X_3 :Sodium dodecyl Sulphate(SLS)	0%	2%

Dependent variable, Response
Y1: PD 15 (%) Percent dissolved 15 min
Y2: DE_{30} (Dissolution Efficiency 30 min)
Y3:Q 50% (Time for 50% dissolved)
Y4: Disintegration Time (min/sec)

Table 2: Factorial design for irbesartan tablet formulations

Formulation	*X1 (β Cyclodextrin)*	*X2(Crosspovidone) (%)*	*X3(SLS) (%)*
F1	1:1	2	0
F2	1:5	2	0
F3	1:1	30	0
F4	1:5	30	0
F5	1:1	2	2
F6	1:5	2	2
F7	1:1	30	2
F8	1:5	30	2

$$Y= \beta 0 + \beta_1 X_1 + \beta_2 X_2) + \beta_{12} (X_1 X_2) + \beta_3 (X_3) + \beta_{13} (X_1 X_3) + \beta_{2,3} (X_2 X_3) - \beta_{123} (X_1 X_2 X_3).$$

Where Y are the dependent variables, namely, percentage dissolved in 15 min (PD 15%) (Y_1), DE30 (dissolution efficiency 30 min), (Y_2), Q 50% (time for 50% dissolved), Y_3, Disintegration Time (min/sec) Y_4, here β0 is the arithmetic mean response of the 8 runs; and β_1, β_2 and β_3 are the estimated coefficients for the factors X_1, X_2 and X_3, respectively. The interaction term (X_1X_2, X_1X_3 and X_2X_3) shows the response.

Preparation of Tablets

Each tablet was prepared by direct compression method as per the factorial design given in Table 1 and 2. The required quantities of drug and independent variables as per the formula in a mortar and triturate well in each case were blended thoroughly in a closed polythene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then compressed directly into tablets using a single punch tablet punching machine employing 9 mm or 12 mm round and flat punches.

Estimation of Irbesartan

A UV spectrophotometric method based on the measurement of absorbance at 244 nm in 0.1N hydrochloric acid was used for the estimation of Irbesartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0–10 µg/mL.

Evaluation of Tablets

All the irbesartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows:

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2. 5 tablets of each formula with a known weight. The average hardness and standard deviation were calculated.

Friability

Tablet friability was determined according to IP. In this, twenty tablets were weighed (initial weight) and placed into the friabilator (LABINDIA) that was rotated at 25 rpm for 4 minutes. The tablets then were re-weighed after removal of fine particles (final weight). The friability of the tablets was measured using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content

An accurately weighed quantity of powder equivalent to 20 mg of irbesartan was taken into 100 mL volumetric flask, dissolved in 0.1N Hydrochloric acid and the solution was filtered through Whatman filter paper no. 41. The filtrate was collected and suitably diluted with 0.1N hydrochloric acid and assayed for irbesartan at 244 nm.

Disintegration Time

The method was done following the procedure outlined in the IP (2006). Six tablets were separately placed into a disintegration test apparatus (LABINDIA) The basket rack assembly of the apparatus was immersed into 900 mL distilled water maintained at 37 ± 1°C. The time was recorded when the tablet had fully disintegrated.

In-vitro Dissolution Rate

The study was conducted (LABINDIA, DS 8000) in 0.1N hydrochloric acid (900 mL) as a dissolution medium with paddle speed of 50 rpm at a temperature of 37 ± 0.5°C. Aliquots of dissolution medium (5 mL) were withdrawn at specified intervals 5, 10,15, 20, 30, 40, 50 and 60 minutes and replaced with an equal volume of fresh medium. Dissolution studies were performed in replicates of four (n=4). The concentration of drug in samples was analyzed using UV spectrophotometer (ELICO SL100) at 244 nm.

FT-IR Spectral Studies

FT-IR Spectra of drug and its mixtures (1:1) with βCD, Crospovidone and SLS in each case were recorded on a Perkin Elmer IR spectrophotometer using KBr disk. The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC thermograms of drug and its mixtures (1:1) with βCD, Crospovidone and SLS in each case were recorded on DSC Q20 V24.11 build 124. Samples (2.1 mg) were sealed into aluminum pans and scanned at a heating rate of 10°C min^{-1} over a temperature range of 30–300°C under a nitrogen gas stream.

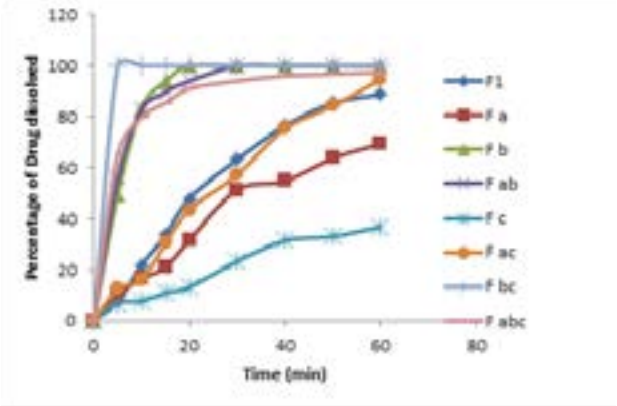

Figure 1b: Dissolution profiles of tablets prepared employing as per factorial design

Statistically Comparison

The difference factor (f1) and similarity factor (f2) is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by the following equation

where n is the number of withdrawal points, Rt is the percentage dissolved of reference at the time point t, and Tt is the percentage dissolved of test at the time point t. A value of

$$f1\,(\text{Difference factor}) = \sum_{t=1}^{t=n}(Rt - Tt)/Rt \times 100$$

$$f_2\,(\text{similarity factor}) = 50 \log \{[1+1/n\sum_{t=1}^{t=n}(Rt - Tt)^2]^{-0.5} \times 100\}$$

100% for the similarity factor (*f*2) suggests that the test and reference profiles are identical. The values between 50 and 100 indicate that the dissolution profiles are similar, whereas smaller values imply an increase in dissimilarity between release profiles. The Difference factor (f1) and similarity factor (f2) were compared with optimized formulation with marketed tablets (Irovel) IROVEL-150 (uncoated tablets each containing 150 mg of Irbesartan manufactured by Sun Pharma Ltd, B.No.BSMO761).

Stability Studies

Stability of the optimized tablets of irbesartan formulations tested according to ICH guidelines of accelerated stability testing. A storage condition of 40°C ± 2°C and 75 ± 5% RH for 6 months was used for short term accelerated stability testing. A temperature of 40°C ± 2°C and a humidity of 75 ± 5% RH were maintained in a humidity chamber (Make: Paramount). The tablets were taken in screw-capped HDPE bottles and were stored at 40°C ± 2°C and 75% RH for 6 months in humidity chamber. After the storage period, the products were evaluated for dissolution rate.

RESULTS AND DISCUSSION

Evaluation of Tablets

The physical parameters of the irbesartan tablets prepared are given in Table 3. The hardness of the tablets was in the range 4.5–5.0 kg/cm^2. Weight loss in the friability test was less than 0.92% in all the cases acceptable limits less than 1%. The drug content of the tablets prepared was within 100 ± 3%.

Table 3: Physical characteristics of irbesartan tablets prepared employing as per 2^3 factorial design

Formulation	*Hardness (Kg/cm²)*	*Friability (% Wt loss)*	*Disintegration Time (min-sec)*	*Drug Content (mg/tablet)*
F_1	4.5	0.85	8-50	98.6
F_2	4.5	0.92	6-55	99.5
F_3	5.0	0.75	1-00	99.4
F_4	4.5	0.85	3-20	98.2
F_5	5.0	0.80	8-05	98.4
F_6	5.0	0.91	2-10	99.5
F_7	5.0	0.75	1-15	99.3
F8	4.5	0.80	1-10	98.5

The disintegration times were in the range 1 min to 8 min 50 sec. The tablet formulations (F_3, F_6, and F_8) disintegrated rapidly with in 1-minute. All other tablets disintegrated rather slowly in about 2–9 minutes. However, all the prepared irbesartan tablets fulfilled the official (USP 2008) requirements regarding drug content, hardness, friability and dissolution profile shown in Figure 1b.

Dependent variable Y1 - PD 15 (%)

The formulations contain Independent variable X_1 from 1:1 to 1:5, X_2 contain 2 to 30% and X_3 level 0 to 2%. The percent drug dissolve in 15 min varied from 10.94 to 100%. The influence independent variables on F_3, F_4, F_7 and F_8 incorporated led to an increase in the PD 15 (%). The individual and combined effect of high level of X_1, X_2 and X_3. Based on the polynomial equation described below.

PD 15= +26.43091+2.46812* Cros-PVP

The effects of both individually and combine effect X_1, X_2 and X_3, ANOVA of PD 15% statistically significant ($p > 0.05$) shown in Table 4. Each variable effect on Y_1 is the concentration of the other variable shown in plots in Figure 2.

Dependent variable Y_2- DE_{30} (Dissolution Efficiency, 30 min)

The percent dissolution efficiency of various formulations were found to be *f*1- 29.23, f^2- 17.7, f^3-80.05, f^4-78.24, f^5-11.44, F-6,30.30, F-7, 91.29, F-8, 76.89. Based on the polynomial equation described below.

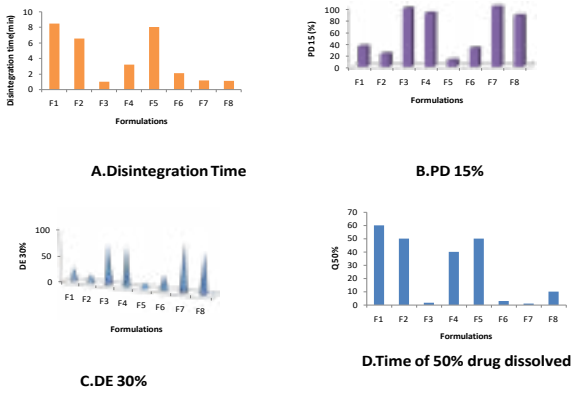

Figure 2 (A): Disintegration Time (B). PD 15% (C). DE 30% (D). Time of 50% drug dissolved Prepared employing as per Factorial Design

DE30= +23.80117+2.12277* Cros-PVP

The effects of both individually and combined effect X_1, X_2 and X_3, ANOVA of DE30% statistically significant ($p > 0.05$) shown in Table 4. Each variable effect on Y_3 is the concentration of the other variable shown in Figure 2.

Dependent variable Y_3 - Q50% (Time for 50% dissolved)

The time for 50% dissolution influence independent variables varies from 1-minute to 60 minutes. The low levels of all independent variable gave low dissolution. The X_1, X_2 and X_3 significantly influence but X_2 alone and combined more significant, X_1 combined with X_2 and X_3 gave significant shown in Figure 2. The polynomial equation describes below Q50%= +61.18182 - 0.033304* βCD-2.51562*- Cros-PVP-1.61161*- SLS + 4.30804E-003* -0.036562 Beta CD * Cros-PVP* Beta CD * SLS

Dependent variable Y_4 - Disintegration Time (DT)

The effect of disintegrant concentration vary from all formulations from 2–30% significantly influence. The formulations contain Independent variable X_1 from 1:1 to 1:5, X_2 containing 2 to 30% and X_3 level 0 to 2%. The *in-vitro* disintegration from 1.30 to 8.50 (min. sec). The influence independent variables of F_3, F_4, F_6, F_7 and F_8 incorporated led to a pronounced decrease in the disintegration time of the tablets from 1.30 to 8.50 (min. sec), respectively. The individual and combined effect of high levels of X_1, X_2 and X_3 (F_3, F_4, F_6, F_7 and F_8). Based on the polynomial equation described below DT= +9.05076- 6.86964E-003*βCD - 0.31589* Cros-PVP + 0.41000* SLS + 4.66071E-004* β CD * Cros-PVP - 4.30000E - 003* βCD * SLS

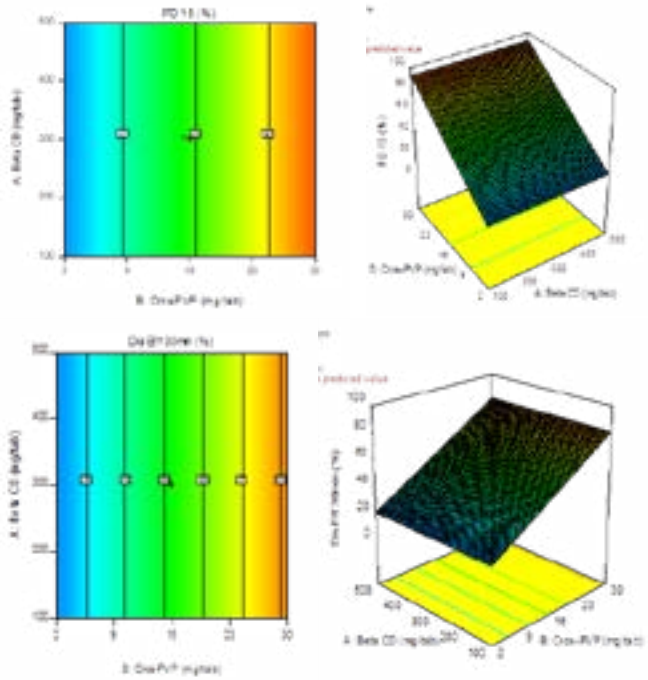

Figure 3: Counter and 3D Surface plots for the PD 15% (Y1) and DE 30% (Y2) A, B, C, D.

Table 4: Analysis of variance table of different dependent variables Y1, Y2, Y3, Y4

Source	*Sum of squares*	*df*	*Mean square*	*f-value*	*p-value* *Prob > F*	*Remarks*
PD 15						
Model	9551.69	1	9551.69	171.53	< 0.0001	Significant
B-Cros-PVP	9551.69	1	9551.69	171.53	< 0.0001	
Curvature	1594.23	1	1594.23	28.63	0.0007	
Residual	445.47	8	55.68			
Lack of Fit	445.47	6	74.25			
Pure Error	0.000	2	0.000			
Cor Total	11591.39	10				
DE 30						
Model	7065.63	1	7065.63	148.60	< 0.0001	Significant
B-Cros-PVP	7065.63	1	7065.63	148.60	< 0.0001	
Curvature	1009.60	1	1009.60	21.23	0.0017	
Residual	380.38	8	47.55			
Lack of Fit	380.38	6	63.40			
Pure Error	0.000	2	0.000			
Cor Total	8455.61	10				
Q50						
Model	4180.19	6	696.70	66883.00	< 0.0001	Significant
A-Beta CD	0.28	1	0.28	27.00	0.0138	
B-Cros-PVP	1755.28	1	1755.28	1.685E+005	< 0.0001	
C-SLS	790.03	1	790.03	75843.00	< 0.0001	
AB	1164.03	1	1164.03	1.117E+005	< 0.0001	
AC	427.78	1	427.78	41067.00	< 0.0001	
BC	42.78	1	42.78	4107.00	< 0.0001	
Curvature	1147.92	1	1147.92	1.102E+005	< 0.0001	
Residual	0.031	3	0.010			
Lack of Fit	0.031	1	0.031			
Pure Error	0.000	2	0.000			
Cor Total	5328.14	10				
DT						
Model	78.76	5	15.75	34.50	0.0022	Significant
A-Beta CD	4.41	1	4.41	9.66	0.0359	
B-Cros-PVP	48.61	1	48.61	106.45	0.0005	
C-SLS	6.20	1	6.20	13.57	0.0211	
AB	13.62	1	13.62	29.84	0.0055	
AC	5.92	1	5.92	12.96	0.0228	
Curvature	21.68	1	21.68	47.49	0.0023	
Residual	1.83	4	0.46			
Lack of Fit	1.83	2	0.91			
Pure Error	0.000	2	0.000			
Cor Total	102.27	10				

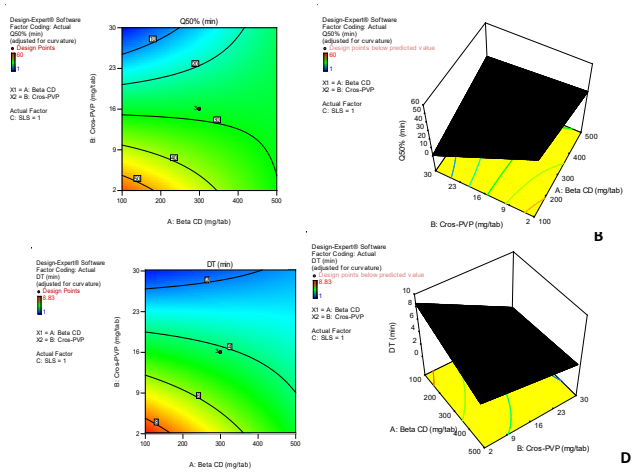

Figure 4: Counter and 3D Surface plots for the Q50 (Y3) and DT (Y4) A, B, C, D

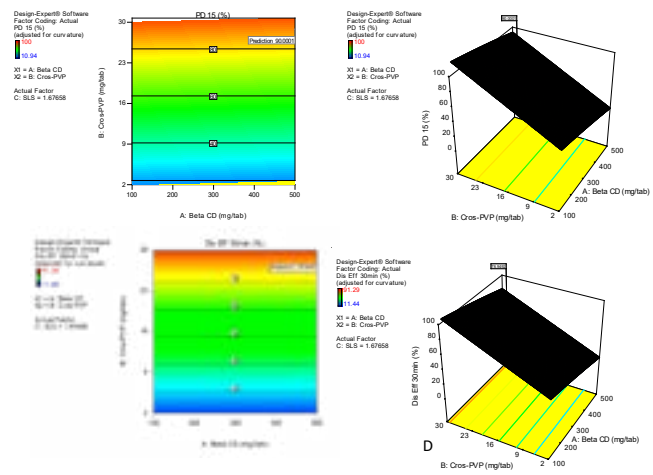

Figure 5: Optimized Prediction formulation Counter and 3D Surface plots for the PD15, DE30 A, B, C, D

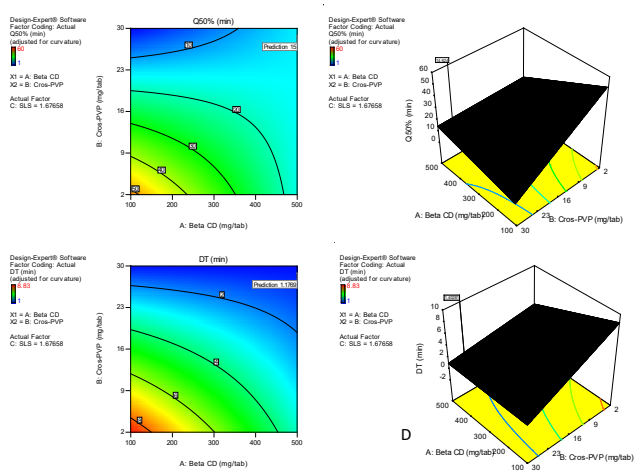

Figure 6: Optimized Prediction formulation Counter and 3D Surface plots for the Q50, DT A, B, C, D

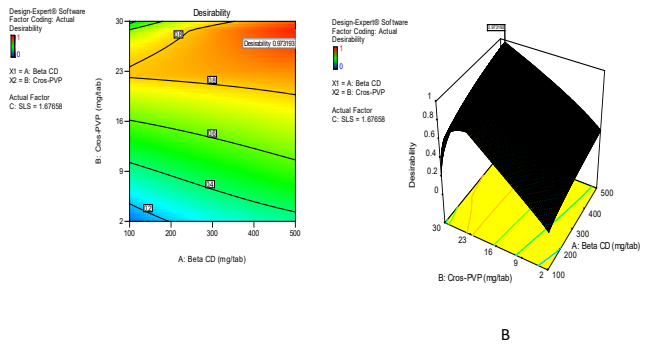

Figure 7: Desirability counter and 3D surface plots- A, B.

Table 5: Statistical parameters

Parameter	*PD15*	*DE 30*	*Q50*	*DT*
Std. Dev.	7.46	6.90	0.10	0.68
Mean	65.92	57.77	21.68	3.29
C.V. %	11.32	11.94	0.47	20.52
PRESS	791.95	676.23	2.00	29.22
-2 Log Likelihood	71.93	70.19	-33.28	11.47
R-Squared	0.9554	0.9489	1.0000	0.9773
Adj R-Squared	0.9499	0.9425	1.0000	0.9490
Pred R-Squared	0.9208	0.9092	0.9995	0.6373
Adeq Precision	17.734	16.506	677.858	15.165
BIC	76.73	74.99	-16.50	25.85
AICc	77.43	75.69	18.05	44.47

However, the effects of both individually and combined effect X_1, X_2 and X_3, ANOVA of tablet disintegration are statistically significant ($p > 0.05$) shown in Table 4.

Statistical Interpretation- Responses (Dependent Variables)

The *f*-value for were found to be 171.53, 148.60, 66883.00, 34.50, indicating that the models are significant. The values of Prob >F were found to be <0.0001 for all responses indicating that the model was statistically significant. The PD 15 R-Squared 0.9554, Adj R-Squared 0.9499, Pred. R2 0.9208, DE 30 R-Squared 0.9489, Adj R-Squared 0.9425, Pred. R^2 0.9092, Q50 R-Squared 1.0000, Adj R-Squared 1.0000, Pred. R^2 0.9995, DT R-Squared 0.9773, Adj R-Squared 0.9490, Pred. R^2 0.6373, respectively. It indicates good correlation between independent and dependent variables. The term with ($p < 0.01$) were considered significant are shown in Table 4 and 5. The Adeq precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable; ratio of 17.734, 16.506, 677.858, and 15.165 indicates an adequate signal. This model can be used to navigate the design space. The contour and response surface plots for all responses of all formulation factors are shown in Figure 3 and 4 and Optimized formulation in Figure 5 and 6. The contour and response plots of the response surface as a function of three factors at a time are more helpful in understanding the factors' main and interaction effects.

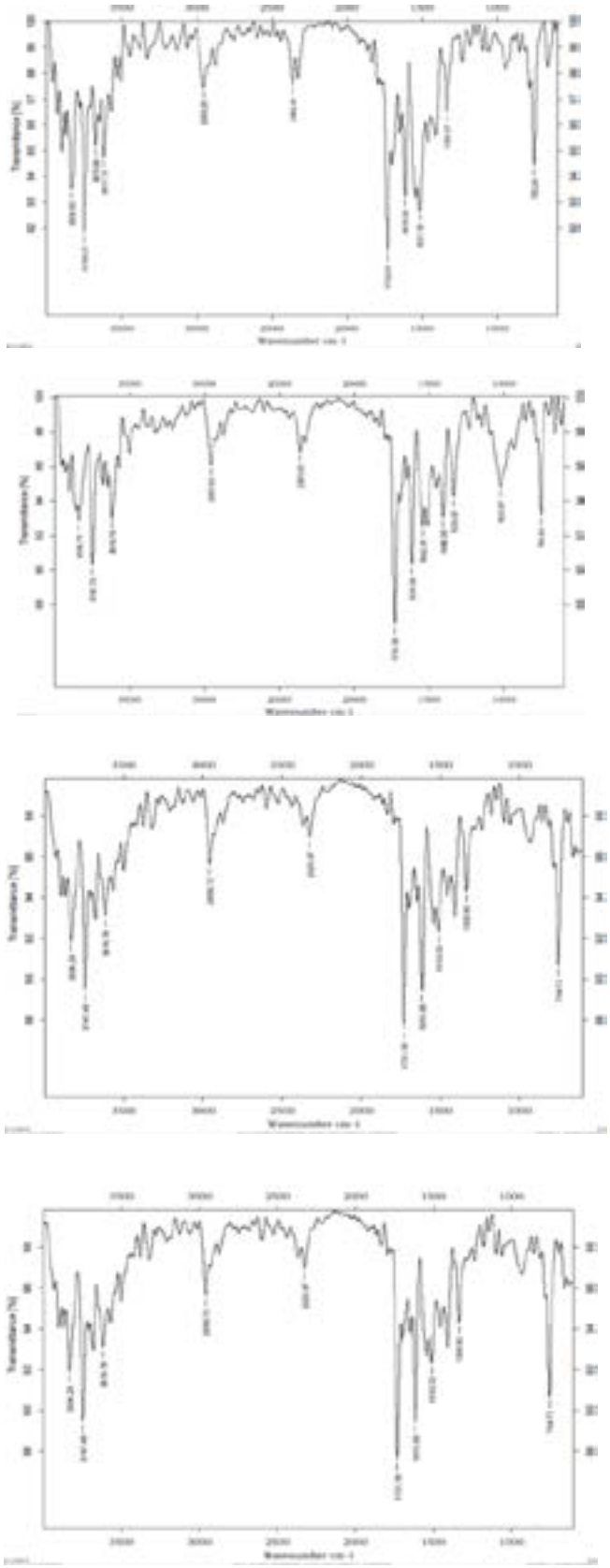

Figure 8: FT-IR of Irbesartan with various Excipients (A) Irbesartan (B) βCD (C) Crospovidone (D)SLS.

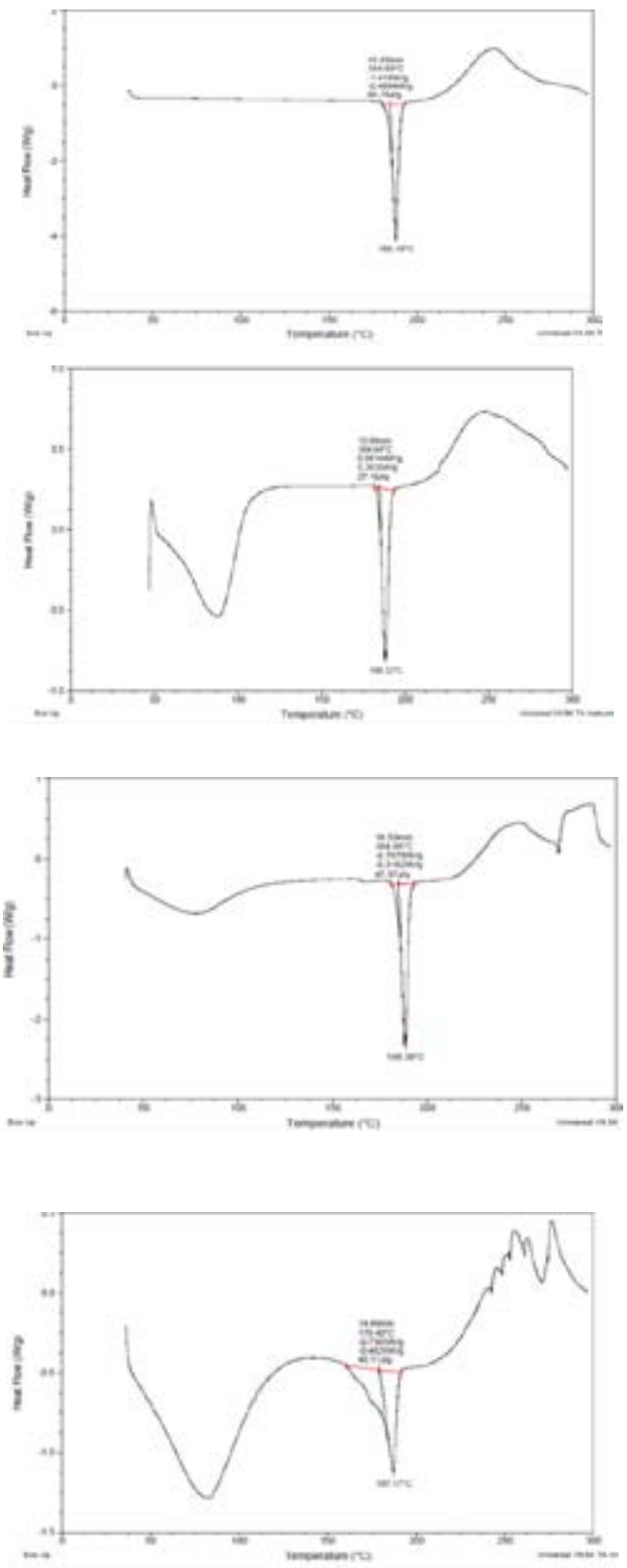

Figure 9: DSC Thermogram of (A) Irbesartan Pure drug (B) Drug-βCD (C) Drug-Crospovidone (D) Drug-SLS.

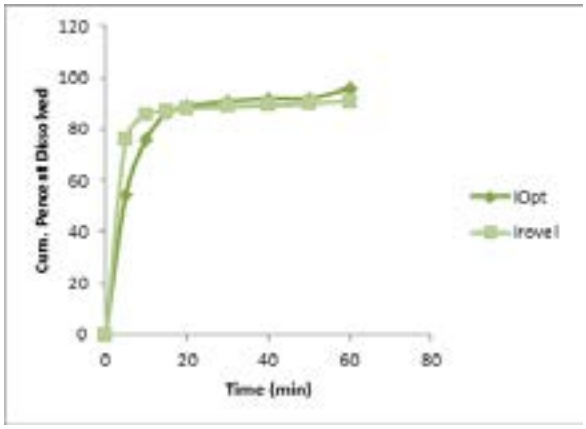

Figure 10: Dissolution profiles of optimized tablets with marketed product (Irovel)

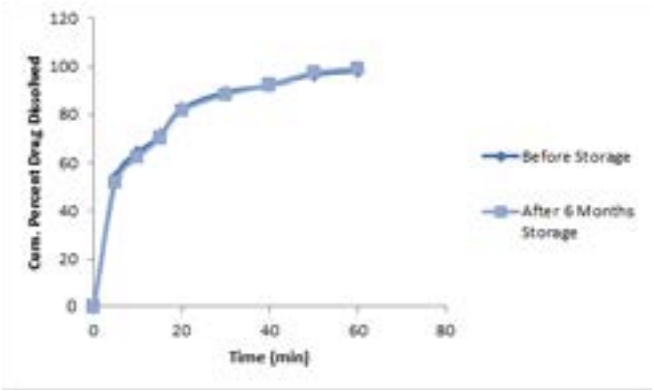

Figure 11: Stability studies-dissolution curves of optimized formulation.

The PD 15 prediction value 90.00, DE 30 prediction values 78.94, Q50 prediction value 15 and DT prediction value 1.17 was find design expert. Its indicate validity with the experiment. The combination maximized desirability over the indicated region to 0.973193. The feasibility provided that the optimum formulations and the desired function of surface and response plots are shown in Figure 7. Optimized formulation had good physicochemical properties and was found to fulfill the requirement of an optimum. The predicted release profile given by the software was found to be quite close to the profile obtained experimentally, indicating the developed model's validity.

FT-IR

The FT-IR spectra of pure drug showed the following characteristic absorption peaks at 3617 cm^{-1} (due to N-H stretching) 2955 cm^{-1} (due to C-H stretching) 1732 cm^{-1} (due to C=O stretching) 1517 cm^{-1} (due to C=C stretching) 1615 cm^{-1} (due to N-H bending). These IR spectral observations indicated no chemical interaction between irbesartan and the excipients used. It's shown in Figure 8.

DSC

The DSC thermogram of irbesartan showed a single sharp endothermic peak at 188.16°C, corresponding to its melting point (180-188°C). The DSC thermograms of irbesartan mixtures with βCD, crospovidone and SLS also showed endothermic peaks in the range 187.17 to 188.43°C indicating no change in the melting point of irbesartan-excipient mixtures. These DSC observations indicated no interaction between irbesartan and the excipients used. It's shown in Figure 9.

Statistically Comparsaion

The difference factor (f1) and similarity factor (f2) were compared with optimized formulation with marketed tablets (Irovel) were found 2.88 and 52.82, respectively. Its indicate identical dissolution profile with market product. It's shown in Figure 10

Stability studies:

No visible changes were noticed in the optimized tablets formulated using βCD, cross povidone and SLS after storage for 6 months at 40°C ± 2°C and 75 ± 5% RH. The dissolution character of all the tablets stored remained unchanged after 6 months of storage. The fast dissolution characteristics of the formulations tested remained unchanged during the storage period. The dissolution curves of the products are similar before and after storage shown in Figure 11.

CONCLUSION

The present investigation showed the Crosspovidone, βCD and SLS as a formulation the preparation of irbesartan tablets. As compatibility studies both FT-IR and DSC, exhibit an explanation of better dissolution rate. The significant effects of the interaction and polynomial variables on the investigated dissolve tablets were verified using^{23} factorial designs. The suitability with the experimental optimized preparation stability and marketed tablets (Irovel) identical dissolution profile.

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