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Design development and optimization of immediate release tablet of valsartan

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ABSTRACT

The objective of the present study was to prepare immediate release tablets (IRTs) of valsartan by direct compression method. Two types of superdisintegrants i.e. sodium starch glycolate (SSG) and Ac-Di-sol were used in the formulation of tablets. Twelve preliminary trial batches were prepared by varying the concentration of superdisintegrants. It was found that formulation containing Ac-Di-Sol disintegrated in less time as compared to formulation containing sodium starch glycolate. Values of friability was found to be more in case of formulation containing Ac-Di-Sol. Attempts were also made to prepare the tablets containing superdisintegrants in combination and these resulted in the formulation with improved values of disintegration time and friability. On the basis of preliminary studies optimization of IRT was done employing 3^2 full factorial design using design expert 7. The optimized batch of IRTs showed friability and disintegration time values of 0.82 ± 0.07 and 29 ± 1 respectively. The percent release was also found to be 94.73 ± 4.97% in 5 min.

Keywords: Immediate release tablets, Valsartan, Hypertension, Sodium starch glycolate, Ac-Di-Sol, 3^2 full factorial design

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INTRODUCTION

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. In present study IRTs were formulated that disintegrate in less time delivering fine suspension of particles of drug with large surface area, resulting in increased rate of dissolution[1].

In the present study, Valsartan was selected as the model drug. Valsartan blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure. The drug binds to angiotensin type I receptors (AT1), working as an antagonist. This mechanism of action is different than the ACE inhibitor drugs, which block the conversion of angiotensin I to angiotensin II. Since valsartan acts at the receptor, it can provide more complete angiotensin II antagonism since angiotensin II is generated by other enzymes as well as ACE. Also, valsartan does not affect the metabolism of bradykinin like ACE inhibitors do.[2]

In the formulation of immediate release tablets basic approach is to use superdisintegrants. In the present study two types of superdisintegrants (sodium starch glycolate and Ac-Di-Sol) were used. Concentration of both superdisintegrants was optimized by employing 3^2 full factorial design.

MATERIALS AND METHOD

Materials

Valsartan and Avicel pH101 was obtained from Zydus Cadilla, Ahmedabad. Sodium starch glycolate, talc and magnesium stearate were obtained from Nice Chemicals Pvt. Ltd. Kerala, India. Ac-Di-Sol was obtained from Optica Pharmaceuticals, Haryana, India.

Methods

Preparation of immediate release tablets

The complete set of ingredients (Table no. 1) including the drug and excipients were passed through sieve no 20. Valsartan, sodium starch glycolate, Ac-Di-Sol and Avicel PH-101 were blended using a mortar and pestle. Into this the measured quantity of talc and magnesium stearate were added. This blend was compressed using a 6.0-mm tooling punch on a single punch tablet machine.

Table 1: Composition of preliminary trial batches of immediate release tablets

Ingredients (mg)	Formulation Code											
	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9	CT10	CT11	CT12
Valsartan	80	80	80	80	80	80	80	80	80	80	80	80
Ac-di-sol	2	4	6	8	-	-	-	-	2	4	6	8
Sodium starch glycolate	-	-	-	-	2	4	6	8	2	4	6	8
Avicel PH 101	64	62	60	58	64	62	60	58	62	58	54	50
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2

Evaluation

The prepared immediate release tablets were evaluated for weight variation and thickness. Using micrometer thickness was determined for twenty tablets[3]. Weight variation of prepared tablets was determined as per USP[4] by taking twenty tablets and comparing average weight with the individual weight of tablets. Hardness of ten tablets[5] from each batch was determined using pfizer hardness tester and Friability of all batches of IRT was determined as per USP[6] using Roche friabilator. Sample of whole tablets corresponding to about 6.5 g was placed in the friabilator and were subjected to 100 revolutions.

The prepared IRTs were subjected to assessment of *in-vitro* disintegration time using USP-27/NF-22 disintegration test apparatus[7]. Drug content of prepared IRTs were carried out by crushing ten tablets in a glass mortar and transferred quantitatively with methanol in a stoppered conical flask. The flask was placed in a sonicator for 30 min. The mixture was filtered and an aliquot, following suitable dilution, was analyzed at 248 nm using a UV spectrophotometer[8].

In vitro release study

The dissolution studies of prepared IRTs were carried out using USP type II dissolution test apparatus[9].The paddle rotation speed and temperature were set to 100 rpm and 37±0.5°C respectively. The dissolution medium was 900 ml of the 0.1N HCl of pH 1.2. At particular time intervals 5 ml sample was withdrawn and analysed in UV spectrophotometer at 248 nm. Samples were collected periodically at different time intervals (1,2,3,4 and 5min) and replaced with fresh dissolution medium. The absorbance was determined spectrophotometrically at 248 nm. Dissolution profiles were constructed as shown in Fig 1. Concentrations were calculated using calibration curves developed in respective media.

Experimental design

To know the actual amount of polymers for the desirable property of tablets a 3^2 randomized full factorial design was used. Combination of these trials is represented in table 2. Nine formulations (Table 3) were prepared according to experimental design. In this design 2 factors are evaluated, each at 3 levels and experimental trials are performed at all 9 possible combinations. The amount of Ac-di-sol (X_1) and the amount of Sodium starch glycolate (X_2) was selected as independent variables. The amount of polymers was varied from 2,4 and 6mg. The friability and disintegration time were selected as dependent variables.

Table 2: Experimental plan of 3^2 full factorial design

F. Code	SSG Concentration (X_1)	Ac-Di-Sol Concentration (X_2)
ECT1	-1	-1
ECT2	0	-1
ECT3	+1	-1
ECT4	-1	0
ECT5	0	0
ECT6	+1	0
ECT7	-1	+1
ECT8	0	+1
ECT9	+1	+1

Table 3: Formulation of experimental batches of Immediate release tablets

Ingredients (mg)	Formulation Code								
	ECT1	**ECT2**	**ECT3**	**ECT4**	**ECT5**	**ECT6**	**ECT7**	**ECT8**	**ECT9**
Valsartan	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Ac-di-sol	**4**	**6**	**4**	**2**	**4**	**6**	**2**	**6**	**2**
Sodium starch glycolate	**4**	**2**	**6**	**6**	**2**	**4**	**2**	**6**	**4**
Avicel PH 101	**58**	**58**	**56**	**58**	**60**	**56**	**62**	**54**	**60**
Magnesium Stearate	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Talc	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity. [10]

Optimization of IRT

After application of full factorial design and with help of polynomial terms the optimized tablet (FRC1) was produced. Tablets were prepared as per composition given in table 4. This batch targeted to the friability of less then 1% and disintegration time of 30 s. The observed response for friability and disintegration time were 0.82 ± 0.07 and 29±1 respectively.

Table 4: Composition of optimum batch (FRC1) of immediate release tablet

Ingredients	FRC1
Valsartan	80
Acdisol	4.32
Sodium starch glycolate	4.36
Avicel PH 101	67.32
Magnesium Stearate	2
Talc	2

Stability studies

To assess the stability of formulation, the optimum IRTs were packed in an amber colored air tight vial and stored at (40 ± 2 °C and 75 ± 5% RH) for a period of 6 months. The tablets were withdrawn after a particular period of time, analyzed for physical appearance, weight, hardness, friability, disintegration time, drug content, and % drug release. At this point, the data was statistically analyzed using ANOVA to test the significance of difference at the level of significance.

RESULTS AND DISCUSSION

Evaluation of preliminary FDT batches and experimental batches

Preliminary batches of IRT of valsartan were prepared by direct compression method employing sodium starch glycolate and Ac-Di-Sol as superdisintegrants. Directly compressible Avicel PH 101, was used as diluent. A total of twelve formulations were designed, in formulation CT1-CT4 and CT5-CT8 varying concentration of Ac-Di-Sol and sodium starch glycolate were incorporated respectively. CT9-CT12 formulations were prepared, containing both sodium starch glycolate and Ac-Di-Sol in different concentrations. Low Hausner's ratio (≤ 1.25), compressibility index (≤ 11.122) and angle of repose (≤ 28.33) values indicated a fairly good flow ability of powder mixture. All the formulations exhibited uniform weight, as per USP[5] with low standard deviation values, indicating the uniformity of the tablets prepared by direct compression method. Average tablet thickness was found to be within limits (± 5%) (Banker et al. 1987[11] and Beringer et al. 2005[12]). The % friability of all the formulations was found to be 0.445–1.253. Results of preliminary batch are shown in Table 5.

Table 5: Characterization of preliminary batch of compressed immediate release tablets

Parameters	Thickness (mm)	Weight (mg)	Hardness (kg/cm2)	Friability (%)	Disintegration test	Drug content (%)
CT1	3.5604±0.004	150.65 ± 2.796	3.33±0.15	0.48±0.047	98.667±3.055	100±0.25
CT2	3.5603±0.004	150.95 ± 3.649	3.13±0.25	0.776±0.012	91.667±4.163	100±0.47
CT3	3.2073±0.002	150.95 ± 4.11	3.27±0.06	0.843±0.038	78±4	99±0.32
CT4	3.728±0.124	150.9 ± 4.376	3.2±0.1	0.934±0.041	67±2	101±0.11
CT5	3.3258±0.004	150.3 ± 4.473	3.57±0.15	0.445±0.021	126.333±2.517	100±0.23
CT6	3.454±0.002	150.7 ± 3.496	3.8±0.1	0.574±0.021	116.333±1.528	99±0.45
CT7	3.6631±0.11	151.45 ± 3.441	3.3±0.2	0.681±0.017	109±2	100±0.13
CT8	3.2165±0.002	150.45 ± 3.17	3.37±0.21	0.853±0.03	104.333±2.082	101±0.28
CT9	3.3568±0.004	148.45 ± 5.853	2.9±0.2	0.659±0.018	57.333±2.082	99±0.18
CT10	3.1603±0.014	151.6 ± 3.068	3.33±0.06	0.894±0.009	35.667±1.528	100±0.13
CT11	3.4073±0.022	150.05 ± 2.911	3.33±0.25	0.981±0.006	22±1	102±0.29
CT12	3.5208±0.014	147.95 ± 5.558	3±0.36	1.253±0.041	10±1	100±0.36

On the basis of preliminary studies it was found that with increase in concentration of SSG and Ac-Di-Sol tablets disintegrated in less time and value of friability increased. Disintegration time of tablets containing SSG was more as compared to tablets containing Ac-Di-Sol, whereas friability value was more in case of tablets containing Ac-Di-Sol. Thus based on this study both SSG and Ac-Di-Sol were used together for further studies. Drug content of randomly selected ten tablets were determined and it was found that obtained values were within the limits as per USP. Obtained data for experimental batch was found to be between 99.18-102.29%.

Statistical and response surface analysis of models

Statistical analysis

It was found there was a wide variation in the values of disintegration time and friability with change in concentration of two factors. Table 6 describes the effect of SSG concentrations (2, 4, and 6mg) and Ac-Di-Sol concentrations (2,4 and 6mg) on the characteristics of IRT. Results showed that with increase in concentration of SSG and Ac-Di-Sol disintegration time decreased. The formulation (ECT1-ECT9) showed disintegration time ranging from 22 to 57.

Table 6: Effect of superdisintegrant concentration on the characteristics of the prepared immediate release tablet formulations of experimental batch

Formulation	Acdisol (X1)	SSG (X2)	Disintegration time (sec)	Friability (%)
ECT 1	0.00	0.00	35	0.894
ECT 2	1.00	-1.00	27	0.934
ECT 3	0.00	1.00	31	0.921
ECT 4	-1.00	1.00	47	0.834
ECT 5	0.00	-1.00	38	0.872
ECT 6	1.00	0.00	24	0.954
ECT 7	-1.00	-1.00	57	0.659
ECT 8	1.00	1.00	22	0.981
ECT 9	-1.00	0.00	52	0.721

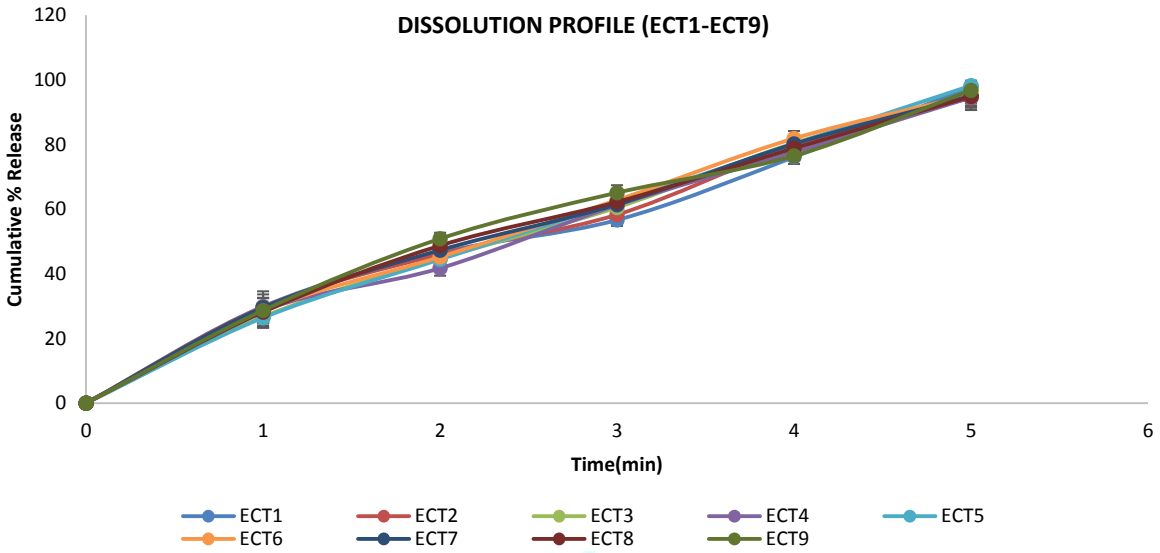

Figure 1: Percent released of Valsartan from compressed immediate release tablets.

In case of friability it was found that with increase in concentration of SSG and Ac-Di-Sol friability value of IRTs also increased.

The *in vitro* drug release data of prepared IRTs is depicted graphically in fig.1. According to the dissolution profile it was found that all batches released drug within 5 min. Percentage of drug released from all the formulation varied between 94.471-98.08% within 5 min.

Optimization

Optimization was done employing a 3^2 FFD. The dependent and independent variables were related using quadratic equations obtained with the Design Expert software (Version 7). ANOVA was performed to identify insignificant factors. Model selection was based on lower p values than assigned significance level, high F value, absence of lack of fit, highest level of adjusted R2 and predicted R2, low standard deviation and lower press value. All values are represented in Table 7. F-value of 49.464 in case of friability and 646.01 in case of disintegration time, implies the model is significant. High values of R2 for all dependent variables were obtained, which indicate a good fit. Adj-R2 and Pred-R2 values for all responses were in reasonable agreement, signifying good model fit. Further, the adequate precision value greater than four indicated adequate model discrimination. Values of p less than 0.05 indicated that model terms are significant.

Table 7: ANOVA results of full and reduced model for immediate release tablets

	Std. Dev.	R-Squared	Sum of squares	Mean of squares	F Value	p-value Prob > F
DT	0.624404478	0.998763166	1259.340476	251.8680952	646.0128244	< 0.0001
FRIABILITY	0.0194194	0.984084042	0.093267648	0.01865353	49.46401957	0.0011

Response surface analysis

Response surface plots were generated for each response to study the behavior of the system. Response surface plot for friability in (Fig. 2) shows that with the increase in the concentration of SSG and Ac-Di-Sol the friability value of the tablet also increases in a linear manner. In case of disintegration time Response surface plot (Fig. 3) shows that with the increase in the concentration of SSG and Ac-Di-Sol the disintegration time decreased in a linear manner.

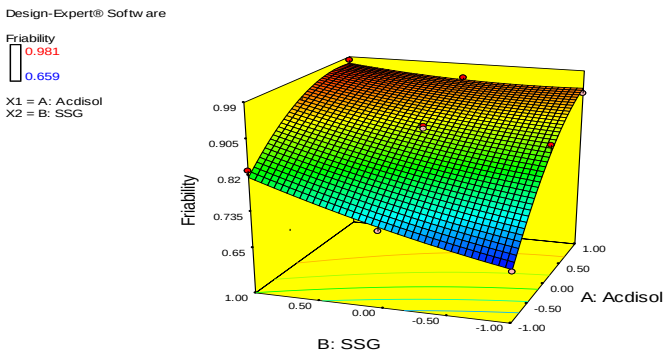

Figure 2: Response surface graph showing the influence of X_1 and X_2 on the friability of immediate release tablets of Valsartan

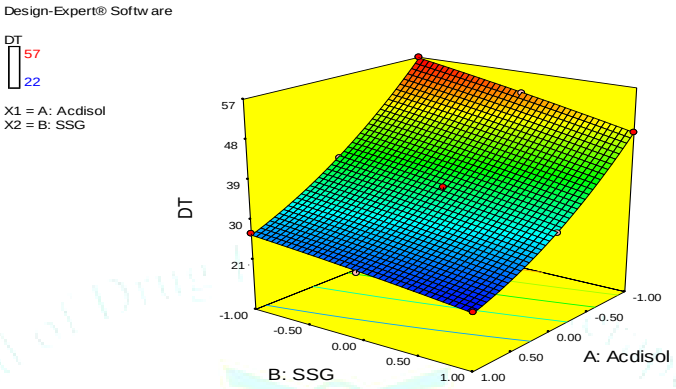

Figure 3: Response surface graph showing the influence of X_1 and X_2 on the disintegration time of immediate release tablet of Valsartan

Stability studies

Accelerated stability studies on the optimized promising formulation were carried out by storing the tablet at 40 ± 2 °C and 75 ± 5% RH for 6 months. At regular intervals, the formulation was characterized for weight, hardness, disintegration time, friability and drug content. It is found that there was no change in physical appearance, and other tablet characteristics during the study period and at the end of the 6 months. Also, no significant change was shown in the percent drug release. Thus, results imply good stability of the formulation on 6-month storage.

CONCLUSION

It can be concluded from the present study that using appropriate concentration of Superdisintegrants SSG and Ac-Di-Sol IRT can be formulated with acceptable values of disintegration time and friability. Addition of super disintegrating agent resulted in development of a formulation with lesser disintegration time. It was also found that above 90% of drug was released within 5 min. due to quick disintegration of the tablet. Thus, the present investigation concluded that it is possible to formulate IRT with acceptable physical characteristics having less disintegration time and could be used to provide immediate relief in hypertension.

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Conflict of interest: All authors declare that they have no conflict of interest.

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