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Research Article

Design, development and optimization of immediate release tablet of deflazacort

Raina Binu ^{1*}, Shrivastava Birendra ², Bhargava Anurag ¹, Sharma Shailesh ³, Sharma Abhimanyu Rai ¹, Bajwa Prabhjot Singh ¹¹ Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India² School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India,³ Department of Pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India

ABSTRACT

The objective of the present study was to prepare immediate release tablets (IRTs) of deflazacort 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 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 3² full factorial design using design expert 7. The optimized batch of IRTs showed friability and disintegration time values of 0.598 and 64.17±3.50 respectively. It was also found that 96.26±1.82% of drug was released within 5 min.

Keywords: Immediate release tablets, deflazacort, Rheumatoid arthritis, Sodium starch glycolate, Ac-Di-Sol, 3² full factorial design**Article Info:** Received 31 Jan 2019; Review Completed 04 March 2019; Accepted 09 March 2019; Available online 15 March 2019

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*Address for Correspondence:

Binu Raina, Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India E-mail: binuraina407@gmail.com

INTRODUCTION

Oral route is the preferred route of administration for administering therapeutic agents. Rate of absorption of drug is controlled by rate of dissolution. Rate of dissolution can be increased by various methods. 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 dissolution¹. Deflazacort was chosen as the model drug. Solubility of deflazacort is low thus making its dissolution controlled by disintegration.

Deflazacort is a corticosteroid which is an oxazoline derivative of prednisolone, characterized by a high binding affinity to tissue glucocorticoid receptors and exert anti-inflammatory and immunosuppressive effects. Deflazacort significantly inhibits both the proliferation of mononuclear cells derived from human peripheral blood, and the release of inflammatory cytokines by these cells. Thus deflazacort is rapidly effective in symptoms and objective indices of disease activity in rheumatoid arthritis². RA is a chronic disorder in which, the body's own immune system starts to attack body tissues, reasons of which are unknown. This disorder is accompanied with swelling, stiffness and pain. In

this disorder the attack is not only directed at the joint but to many other parts of the body. In RA, the joint lining and cartilage gets more damaged which eventually results in erosion of two opposing bones. Based on the studies, it has been reported that deflazacort could be used in treatment of RA. It is as efficacious as prednisolone with less adverse effects as compared to other corticosteroids³.

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 3² full factorial design.

MATERIALS AND METHOD

Materials

Deflazacort and Avicel pH101 was obtained from Oscar Remedies Pvt. Ltd. Haryana, India. Sodium starch glycolate, talc and magnesium stearate was obtained from Nice Chemicals Pvt. Ltd. Kerala, India. Ac-Di-Sol was obtained from Optica Pharmaceuticals, Haryana, India.

Methods

Preparation of immediate release tablets

Based on composition of deflazacort IRT tablets with deflazacort IRT tablet depicted in table 1 6mg deflazacort and excipients (except the lubricant; magnesium stearate and glidant ; talc) were physically mixed by geometric

mixing. Powdered mixture was passed through 60 # sieve and blended properly using a mortar and pestle. The resultant blend was lubricated with the addition of lubricant and glidant and finally compressed into tablets (30 mg) using 3 mm round flat punches. Machine settings were adjusted to get the desired hardness value, which gave an intact tablet.

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

Ingredients (mg)	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Deflazacort	6	6	6	6	6	6	6	6	6	6	6	6
SSG	0.6	1.201	1.802	2.403	-	-	-	-	0.6	0.6	1.802	2.40
Ac-Di-Sol	-	-	-	-	0.6	1.201	1.802	2.403	0.6	1.802	0.6	2.40
Talc	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Mag. stearate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Avicel pH101	22.5	21.99	21.39	20.79	22.5	21.89	21.29	20.697	21.9	20.69	20.69	18.29

Evaluation

The prepared immediate release tablets were evaluated for weight variation and thickness. Using micrometer thickness was determined for twenty tablets⁴. Weight variation of prepared tablets was determined as per USP⁵ by taking twenty tablets and comparing average weight with the individual weight of tablets. Hardness of ten tablets⁶ from each batch was determined using pfizer hardness tester and Friability of all batches of IRT was determined as per USP⁷ 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 apparatus⁸. 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 242 nm using a UV spectrophotometer⁹.

In vitro release study

The dissolution studies of prepared IRTs were carried out using USP type II dissolution test apparatus¹⁰. The tablets

were placed in dissolution vessel containing 900 ml of phosphate buffer pH 6.8 maintained at 37°C ± 0.5 and stirred at 75 rpm. Samples (6 ml) were collected periodically at different time intervals (1, 2, 4, 6, 8, 10, 15, 20, 25, 30 min) and replaced with fresh dissolution medium. The absorbance was determined spectrophotometrically at 242 nm. Dissolution profiles were constructed as shown in Fig. 1 Concentrations were calculated using calibration curves developed in respective media.

Experimental design

A two factor, three level (3²) FFD was used in the optimization of IRTs of deflazacort. The study design involved the investigation of the effect of independent variables i.e. concentration of Sodium starch glycolate (X₁) and concentration of Ac Di Sol (X₂) on the dependent variables such as disintegration time, and friability. The levels of the factors study was selected on the basis of preliminary studies. Concentration of sodium starch glycolate (2, 4, 6%) and Ac-Di-Sol (6, 7, 8%) were selected as independent factors X₁ and X₂ respectively. Combination of these trials is represented in table 2. Nine formulations (Table 3) were prepared according to experimental design.

Table 2: Experimental plan of 3² full factorial design

F. Code	SSG Concentration (X ₁)	Ac Di SolConcentration (X ₂)
CT1	-1	-1
CT2	0	-1
CT3	+1	-1
CT4	-1	0
CT5	0	0
CT6	+1	0
CT7	-1	+1
CT8	0	+1
CT9	+1	+1

Table 3: Formulation of experimental batches of Immediate release tablets

Ingredients (mg)	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9
Deflazacort	6	6	6	6	6	6	6	6	6
SSG	0.6	1.2	1.8	0.6	1.2	1.8	0.6	1.2	1.8
Ac-Di-Sol	1.8	1.8	1.8	2.1	2.1	2.1	2.4	2.4	2.4
Talc	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium stearate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Avicel PH101	20.7	20.1	19.5	20.4	19.8	19.2	20.1	19.5	18.9

Optimization of IRT

The optimization process was used to obtain a model equation ($Y = B_0 + B_1X_1 + B_2X_2 + B_3X_1X_2 + B_4X_1^2 + B_5X_2^2$) that provides a means of evaluating changes in response due to changes in the independent variable levels. After application of full factorial design and with help of

polynomial terms the optimized tablet (C1) was produced. Tablets were prepared as per composition given in table 4. This batch targeted to the friability 0.566 and disintegration time of 63.773 s. The observed response for friability and disintegration time were 0.598 and 64.167±3.502 respectively.

Table 4: Composition of optimum batch (C1) of immediate release tablet

Batch	Deflazacort	SSG	Ac-Di-Sol	Talc	Magnesium stearate	Avicel pH101
C1	6	1.8	1.974	0.6	0.3	19.36

Stability studies

To assess the stability of formulation, the optimum IRTs were packed in an amber colored air tight vial and stored at ($40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ 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 0.05.

RESULTS AND DISCUSSION

Evaluation of preliminary FDT batches and experimental batches

Preliminary batches of IRT of deflazacort 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 F1-F4 and F5-F8 varying concentration of sodium starch glycolate and Ac-Di-Sol were incorporated respectively. F9-F12 formulations were prepared, containing both sodium starch

glycolate and Ac-Di-Sol in different concentrations. Low Hausner's ratio (≤ 1.32), compressibility index (≤ 24.68) and angle of repose (≤ 18.13) values indicated a fairly good flow ability of powder mixture as per Setty et al. 2008¹¹. All the formulations exhibited uniform weight, as per USP⁵ 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 ($\pm 5\%$) (Banker et al. 1987¹² and Beringer et al. 2005¹³). The % friability of all the formulations was found to be 0.372–0.898. Results of preliminary batch are shown in Table 5.

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 97.34–103.17%.

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

F. Code	Weight variation (mg) (Mean±SD)***	Thickness (mm) (Mean±SD)***	Hardness (Kg/cm ²)****	Drug content	Friability (%)*****	Disintegration time (sec)*****
F1	30.25±2.50	3.3449±0.089	3.166±0.057	99.83	0.372	621.000±3.605
F2	29.6±2.258	3.5576±0.086	3.067±0.173	99.76	0.402	234.667±4.163
F3	31.15±1.579	3.6953±0.112	2.867±0.100	99.74	0.442	227.333±3.177
F4	31.4±2.627	3.8069±0.128	2.633±0.208	99.69	0.575	183.667±5.507
F5	28.15±2.998	3.4608±0.074	2.935±0.058	99.87	0.398	147.667±2.516
F6	30.75±1.762	3.6313±0.097	2.8±0.153	99.82	0.447	114.000±4.582
F7	30.25±2.417	3.48±0.103	2.667±0.142	101.2	0.533	70.000±3.605
F8	29.6±2.208	3.520±0.154	2.433±0.153	98.51	0.617	56.667±3.512
F9	31.15±2.852	3.510±0.099	2.867±0.208	102.21	0.425	129.667±4.509
F10	30.4±2.577	3.59±0.087	2.767±0.058	97.71	0.614	60.000±3.605
F11	28.15±2.998	3.46±0.117	2.905±0.100	98.13	0.579	114.000±4.582
F12	32.75±1.162	2.70±0.094	2.533±0.153	101.82	0.898	49.000±4.358

*** Each value is average of twenty independent determinations; **** Each value is average of ten independent determinations,

***** Each value is average of 216 tablets, ***** Each value is average of six independent determinations.

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 6%) and Ac-Di-Sol concentrations (6, 7 and 8%) on the characteristics of IRT. Results showed that with increase in concentration of SSG

and Ac-Di-Sol disintegration time decreased (Patel et al, 2015)¹⁴. The formulation (CT1-CT4) showed unaccepted increase in disintegration time (106, 92, 78 and 87 s respectively), that exceeded the limits specified for IRTs, which is less than 75 s (Dobetti 2012)¹⁵

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 the entire batches released drug within 10 min.

Percentage of drug released from all the formulation varied between 95.48-98.86% within 10 min.

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

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

F. Code	Sodium starch glycolate (% w/w)	Ac-Di-Sol (% w/w)	Hardness(Kg/cm ²)****	Disintegration Time (s)*****	Friability***** (%)
CT1	2	6	2.8±0.1	106±0.058	0.436
CT2	4	6	3.01±0.1	92±1.53	0.484
CT3	6	6	3.1±0.15	78±1.15	0.502
CT4	2	7	2.67±0.05	87±1	0.492
CT5	4	7	2.82±0.05	69±1.15	0.574
CT6	6	7	2.8±0.1	53±0.58	0.592
CT7	2	8	2.57±0.15	65±1.53	0.586
CT8	4	8	2.5±0.1	52±1	0.613
CT9	6	8	2.43±0.05	39±0.58	0.798

**** Each value is average of ten independent determinations; *****Each value is average of two hundred sixteen tablets;***** Each value is average of six independent determinations

Optimization

Optimization was done employing a 3² FFD. The dependent and independent variables were related using quadratic equations obtained with the Design Expert software (Version 7). For each dependent variable, a summarizing equation was generated as shown in Table 7. ANOVA was performed to identify insignificant factors. Model selection was based on lower p values than assigned significance level, high F value i.e. 9.68 and 132.42, 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 8. F-value of 9.68 in case of friability and 132.42 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: The quadratic equations relating friability and disintegration time with independent variables in IRTs tablets.

Response	Experimental Parameters					
	β_0	β_1	β_2	β_3	β_4	β_5
Friability	0.55	0.063	0.096	0.037	0.011	0.07
Disintegration Time	69.44	-14.67	-20.00	0.50	0.33	2.33

Table 8: ANOVA results of full and reduced model for core tablets

Measured Response	SS	DF	MS	F-Value	Prob > F	SD	R ²
Friability	0.085	5	0.017013	9.68	0.0454	0.042	0.9416
Disintegration time	3702.78	5	740.56	132.42	0.0010	2.36	0.9955

DF-Degree of freedom; MS-Mean of squares; SS-Sum of squares

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 deflazacort

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

Stability studies

Accelerated stability studies on the optimized promising formulation were carried out by storing the tablet at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 3 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 3 months. Also, no significant change was shown in the percent drug release. From the statistical analysis, it was found that there was no significant difference between before and after storage ($P < 0.05$). The similarity factor f_2 was calculated to compare the dissolution profiles of optimized formulation before and after storage and it was found to be 84 which is more than 50 indicating similarity between the dissolution profile before and after storage.

Thus, results imply good stability of the formulation on 3-month storage.

CONCLUSION

It can be concluded from the present study that using appropriate concentration of superdisintegrant SSG and Ac-Di-Sol IRT can be formulated with acceptable values of disintegration time and friability. Addition of superdisintegrating 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 from the pain and stiffness that occurs in RA.

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

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