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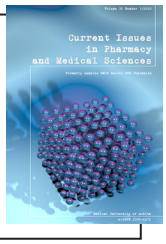

Optimized Rapid Disintegrating Tablets produced through Central Composite Design

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ABSTRACT

The work is aimed at producing fast disintegrating diclofenac potassium tablets to relieve pain and tenderness by applying a quality-by-design approach. Diclofenac potassium (DP) is of BCS class II and has issues of minimal oral bioavailability. This can be overcome by complexing DP with β-cyclodextrin (β-CD) and sodium starch glycolate (SSG). The attempt was to optimize DP tablets by applying central composite design (CCD). Nine different DP tablet formulations were created and assessed for physicochemical constraints, disintegration time and drug dissolution at the end of 30 min. The separate and mutual consequences of β-CD and SSG on the disintegration time of DP tablets are highly significant (P<0.01). The DP tablets made with β-CD in 150 mg disintegrated rapidly within 39±2 sec, and gave very rapid drug dissolution (96.35±2.36%) at the end of 30 min. These DP tablets (F-8) contain β-CD (150 mg) and SSG at 32.07 mg. The intermittent levels of β-CD and higher levels of SSG gave good dissolution of DP tablets. The polynomial equation linking the response, i.e. disintegration time in sec (Y_1) and the levels of β-CD (A) and SSG (B) based on the pragmatic results, is Y_1=45-3.14277A-2.46599B-1.25AB+1.75A2-0.5B^2. In contrast, the DP release at the end of 30 min was expressed as $Y_2 = 88.57 + 4.09333A + 3.27837B + 1.2525AB - 2A^2 + 0.8875B^2$. The study concludes that SSG decreases the disintegration time with its concentration and β-CD concentration ingresses the drug release from the formulation.

INTRODUCTION

Diclofenac potassium (DP) is a BCS class II NSAID administered for systematic body/joint pains and inflammation. Its effective formulation [1] and design [2] is a challenge for the industrial Pharmacist. For resolving issues related to the poor aqueous solubility of DP (a common trait held by all BCS class II drugs), numerous tactics have been employed, among them, creating complexes with β-cyclodextrin (β-CD)[3] and Sodium starch glycolate (SSG) [4] in the form of tablet dosages [5].

In this study, nine different DP complexes with β-CD and the addition of SSG were created so as to lessen disintegration time (DT) and >95% dissolution in 30 min. Herein, β-CD and SSG quantities were optimized by central composite design (CCD), using Design Expert software (V.11 trial). Optimization of pharmaceutical strictures like picking and merging excipients were found to generate certain definite crucial prerequisites. The utilization of plan optimization methods is generally new to the act of pharmacy. Overall, the system embraces setting up an evolution of provisions, hence shifting the groupings of the describe activity in some effectual way. In this, the authors adopted a central composite design for optimization [6,7].

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AIM

The work is aimed to prepare fast disintegrating DP tablets by applying a quality by design approach. DP tablets were then appraised for other attributes such as uniformity in size/shape, hardness, friability and dissolution.

MATERIALS

Diclofenac potassium was gifted from Waksman Selman pharmaceuticals Ltd, Anantapur AP, India. β-cyclodextrin, SSG, colloidal silicon dioxide and talc were purchased from Qualigens. The rest of the materials were of AR grade.

METHODS

Estimation of Drug

A UV Spectrophotometric method by measuring absorbance at 282 nm in 0.1 N HCl was utilized for establishing a DP complex recipe that was validated for linearity, accuracy, precision and interference. The process applies pragmatic Beer's law at 1-10 µg/ml [8,9].

Formulation of Tablets

For DP tablet optimization as per CCD, factor A (β-CD) was incorporated at 100 mg and 200 mg and factor B (SSG) at 20 mg and 30 mg. Nine DP tablets formulated by varying the aforementioned quantities were made by applying the direct compression method (Table 1). The required quantities of DP, β-CD and SSG were first blended thoroughly in a closed polythene bag. Colloidal silicon dioxide and Talc were then included by passing through mesh #80 and blended, after which the tablet form was created by compressing by way of a karnavati 16 station machine.

Table 1. Formulae of DP Tablets as per central composite design

Contents (mg)	Formulations								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Diclofenac potassium	50	50	50	50	50	50	50	50	50
β-Cyclodextrin	100	200	100	200	79.29	220.7	150	150	150
Sodium Starch Glycolate	20	20	30	30	25	25	17.93	32.07	25
Micro Crystalline Cellulose	170	70	160	60	185.71	44.3	122.07	107.93	115
Colloidal silicon dioxide	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Wt. of the tablet	350	350	350	350	350	350	350	350	350

Evaluation of Tablets

All the diverse DP tablet recipes made were appraised for drug content, hardness, friability, DT and DR, as described [10-13].

Hardness and Friability

The hardness of the created DP tablets was established by employing a Pfizer hardness tester, and the interpretation was attained as kg/cm^2. Five tablets of each formulation were tested. The friability of the tablets was measured in a Roche friabilator using the formula:

$$\text{Friability (\%)} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad (1).$$

Drug Content

Ten tablets of each individual formulation were powdered and ≡50 mg of DP was placed into a 100 ml volumetric flask, dissolved in 0.1 N HCl, with the solution subsequently filtered through Whatman filter paper no.41. The filtrate was gathered and suitably diluted with 0.1 N HCl and assayed for DP at 282 nm [14].

Disintegration time (DT)

The DT of the tablets was assessed by means of utilizing a single unit disintegration test apparatus (Electronics India-2901) with water as the test fluid.

Drug release study

The DR of the individual created DP tablet fomulations was studied in 0.1N HCl (900 ml) by means of employing a six-station dissolution apparatus (Electrolab-ED-2L) at 37±0.5°C, using a paddle maintained at 50 rpm. During this activity, 5 ml of sample was withdrawn at altered time intervals and assayed for DP at 282 nm (sink conditions were maintained for every sample) [15].

Analysis of Data

The Design-Expert programme was used to examine the DT and dissolution data (11.0.5.0, Stat-Ease Inc.,). The essential interface and quadratic possessions of independent variables on dependent variables with CCD were the design's primary objectives [16,17].

RESULTS AND DISCUSSIONS

Using specific combinations of the two parameters as per CCD, nine DP tablet formulations were created. The tablets were produced using the direct compression method (Table 1), and their uniformity of size and shape, hardness, friability, and DT and DR characteristics were all assessed. To determine the significance of the individual and combined effects of the two components involved in the DR, the DT and dissolution in 30 min were examined using CCD's ANOVA. Table 2 lists the physical characteristics of the DP tablets. The weight loss in the friability test was <1 in every case, and the tablets had a hardness of >4.0 kg/cm^2. The DT was between 39 and 53 sec. DP tablets (F-8) that were made with 150 mg of β-CD and 32.07 mg of SSG quickly dissolved in 39 sec. All other tablets fell apart after 53 sec, although slowly. The DT was decreased by incorporating intermittent amounts of β-CD, whereas the physical characteristics were deemed to be affected by an increase in SSG. All of the DP tablets, however, met the formal and informal standards for size/shape, hardness, friability, DT, and dissolving for an uncoated tablet (Figure 1).

Both the individual and combined effects of the two components, β-CD and SSG, in influencing the DR of DP tablets are highly significant (P 0.01) according to the fit summary provided for linear with P-value 0.01 (Table 2) and the ANOVA for the DT (Table 3). The model is significant, according to the its 10.87 Model F-value.

Table 2. Fit Summary for the responses

Fit Summary for response 1 i.e., disintegration time (R_1)			
Source	Sequential p-value	Adjusted R^2	Predicted R^2
Linear	**0.0101**	**0.7117**	**0.4792**
2FI	0.3466	0.7154	0.4633
Quadratic	0.1274	0.8799	
Cubic	0.5222	0.9018	
Fit Summary for response 2 i.e., DP release at the end 30 min (R_2)			
Linear	**0.0055**	**0.7651**	**0.5728**
2FI	0.4205	0.7557	0.5705
Quadratic	**0.0611**	**0.9369**	
Cubic	0.7031	0.9064	

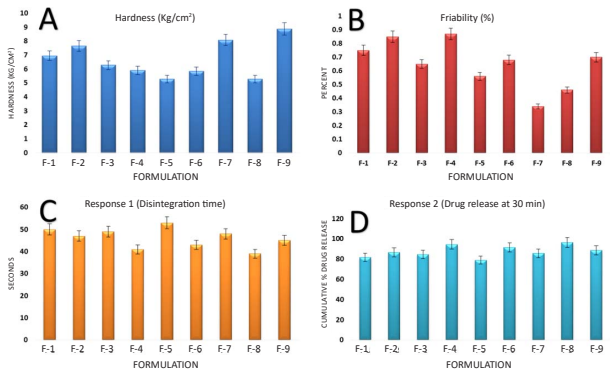

Figure 1. Graphical representation of hardness, friability, disintegration and drug release

The **Model F-value** of 24.75 denotes the model is significant. There is only a 1.21% chance that the enhanced F-value is due to noise.

Table 3. ANOVA for the responses

ANOVA for response 1 i.e., Disintegration time (R_1)			
Source	Sum of Squares	F-value	p-value
Model	127.66	10.87	0.0101
A-β-CD	79.02	13.46	0.0105
B-SSG	48.65	8.29	0.0281
ANOVA for response 2 i.e., DP release at the end of 30 min (R_2)			
Model	260.75	24.75	0.0121
A-β-CD	134.04	63.61	0.0041
B-SSG	85.98	40.80	0.0078

Diagnostic plots were used to examine the DT and measure the goodness of fit (Figure 2A-D). The normal likelihood plot of the externally studentized residuals showed that the normal probability line was where the highest number of coloured spots illustrating the DT could be found. Given that the residuals are positioned close to the straight line [18],

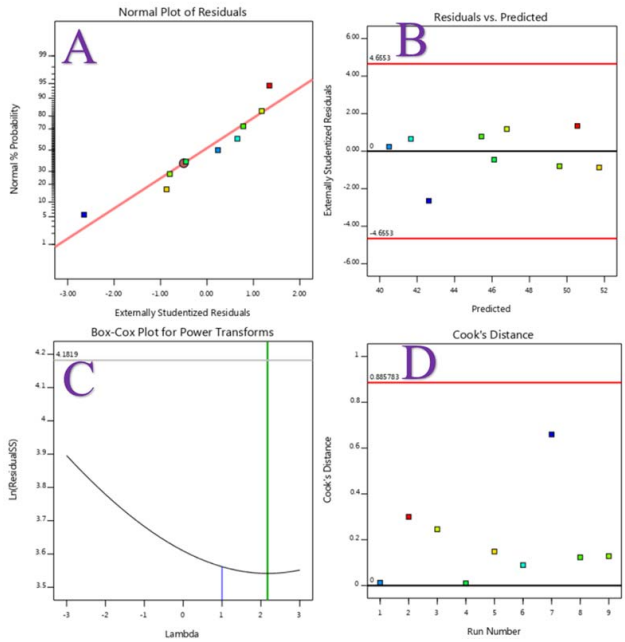

Figure 2. Plots showing the interaction impact of β-CD and SSG on disintegration time

the typical residuals graphic was acceptable (Figure 2A). The residuals *vs.* anticipated tenets plot, which appears to be studentized, indicates that the coloured spots of DT were given priority above the limits (Figure 2B). Using the Box-cox plot, a linear relationship was revealed for power (Figure 2C). The red line shows DT was very close to the projected values and the Cook's distance was maintained; no points were crossed (Figure 2D).

The normal plots, residual plots, Box-cox plots and cooks distance for DT and DR at 30 min are shown in Figure 3. The 3D surface plots for DT and DR at 30 min are shown in Figure 4.

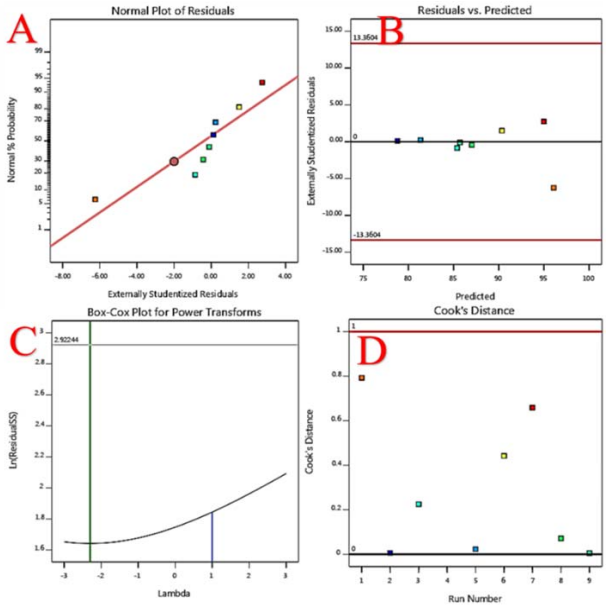

Figure 3. Plots showing the impact of β-CD and SSG on the responses

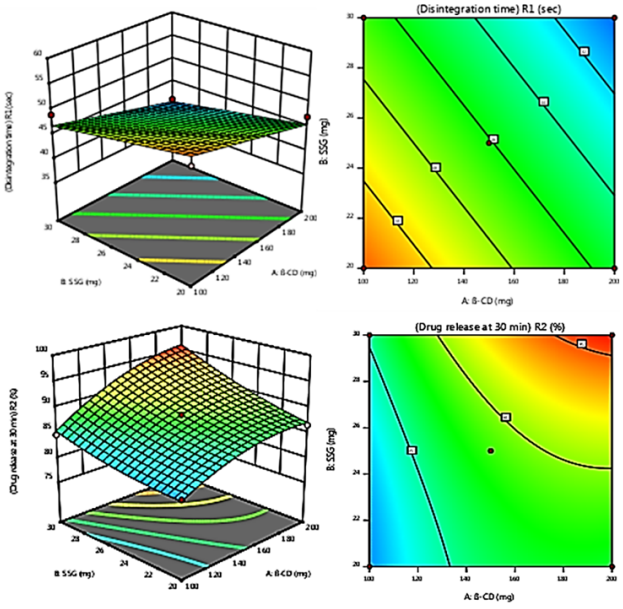

Figure 4. Contour plot and 3D response plot for the responses

The DT was completed much more quickly using DP tablets (F-8) prepared with β-CD (150 mg) and SSG at 32.07 than with other methods. After 30 min, these tablets (F-8) provided 96.35% disintegration. DP pills were well

dissolved when β-CD levels fluctuated and SSG levels were greater. The decreasing order of DT was F-8> F-1> F-6> F-9> F-2> F-7> F-3> F-1> F-5. The multinomial equation narrating the interconnection allying the response (Y_1) and the variables A and B, based on the perceived data, was found to be Y_1= 45-3.14277A-2.46599B-1.25 AB+1.75A^2-0.5B^2 (for DT) and Y_2=88.57+4.09333A+3.27837B +1.2525AB-2A^2+0.8875B^2 (for drug dissolution at the end of 30 min).

CONCLUSIONS

1. Both the individual and combined effects of sodium starch glycolate and beta-cyclodextrin on the diclofenac discharge are highly significant (P<0.01).
2. The lowest disintegration time of the tablets was brought about by β-CD levels that were intermittently allied with higher amounts of SSG.
3. The multinomial equation relating the correlation linking the response i.e. disintegration time in sec (Y_1) and the levels of β-CD (A) and SSG (B), based on the detected results, were Y_1=45-3.14277A-2.46599B-1.25 AB+1.75A^2-0.5B^2. The multinomial equation unfolding the linking the response i.e. drug dissolved in 30 min (Y_2) and the levels of β-CD (A) and SSG (B) based on the perceived results was Y_2=88.57+4.09333A+3.27837 B+1.2525AB-2A^2+0.8875B^2.
4. Based on the above polynomial equation, the optimized DP tablet with >95% dissolution in 30 min could be formulated employing β-CD at 150 mg and SSG at 30 mg. The optimized DP tablets gave 96.35% dissolution in 30 min, thus satisfying the target dissolution set. Hence, the tablets with >95% dissolution in 30 min could be optimized by central composite design.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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