Research Article

Influence of Diluents on Diclofenac Sodium Release from Gum Kondagogu Based Matrix Tablets.

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ABSTRACT

The purpose of the study was to investigate the influence of formulation variables on the release profile of diclofenac sodium from gum kondagogu matrix tablets. Experimental design was applied to evaluate the influence of concentration of the gum and type of diluent with the final goal of drug release behavior optimization. Two independent variables considered were concentration of the gum (X1) and type of diluents (X2). The considered responses were the percentage drug released at three determined times (Q4, Q7, Q10), zero order rate constant and the time to release 50% of drug. Matrix tablets were prepared by wet granulation method. Physical properties and drug release studies were carried out for the prepared tablets. The physical properties indicated good handling properties of the prepared matrix tablets. Polynomial equations and response surface plots were generated for all dependent variables. The present study indicates that both the factors have a significant effect on drug release profile. The dissolution studies indicate the release behavior of all the formulations was super case II transport mechanism with zero order kinetics. The results demonstrate the reliability of the model in the preparation of matrix tablets of diclofenac sodium for sustained release using gum kondagogu with the selected diluents.

Keywords: Diluents, experimental design, gum kondagogu, matrix tablet, response surface methodology.

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INTRODUCTION

Diclofenac sodium is one of the potential NSAIDS which is commonly used as an anti inflammatory, analgesic and anti pyretic. It is used for the long term symptomatic treatment of several alignments such as osteoporosis, rheumatoid arthritis, ankylosing spondolitis. Diclofenac is rapidly and completely absorbed after oral administration and peak plasma concentration is reached within 2-3 hr. It undergoes extensive first pass metabolism; hence only 50% of Diclofenac is available systemically. Its half life in plasma is 1-2 hr. It is also used for acute musculo skeletal injury, acute painful shoulder post operative pain; dysmenorrheal [1]. From several investigations, it was found that Diclofenac sodium was feasible for the development of sustained release formulation.

The advances in drug delivery urged the discovery of novel excipients which are safe and fulfill specific functions, directly or indirectly influence the rate and extent of release and absorption. Many plant derived natural materials are studied for use in novel drug delivery systems, out of which polysaccharides, resins and tannins are most extensively studied and used [2]. Gum kondagogu (GKG) is a naturally occurring polysaccharide derived as an exudate from the tree *Cochlospermum gossypium,* belongs to Cochlospermum spp. and family Bixaceae. It is a polymer of arabinose, rhamnose, mannose, fructose, galactose,galacturonic acid, b-D-galactopyranose, glucuronic acid, a-

Dglucose and b-D-glucose. It is used as a food additive and for sustained drug delivery [3,4]. A few works were reported on GK as mucoadhesive polymer, polymer in gastro retentive systems and also proved that it can be used as food additive as it is non toxic [5-7].

MATERIALS AND METHODS

Diclofenac is obtained as a gift sample from Hetero Drugs, Hyderabad. Gum Kondagogu (GK) is procured from Girijan co-operastive corporation, Vizag. All other ingredients are of analytical grade.

Preparation of matrix tablets

Diclofenac sodium matrix tablets were prepared by wet granulation method. Diclofenac sodium (100 mg) was blended with appropriate quantities of GK (5 %, 10 % and 15 %) and diluents (lactose, starch and MCC). This Premix blend was wet granulated with 3 % w/v solution of PVP K-90. The wet mass was passed through No.10 sieve. The wet granules were air dried at for one hour and the dried granules were sieved through No.16 sieve. Granules were evaluated for angle of repose, bulk density (BD) and tapped density (TD). Carr's index (CI) and Hausner ratio were calculated using following equations [8]. After evaluation these granules were blended with lubricating agents (1% w/w magnesium stearate and 1% w/w talc) and compressed using 16 station rotary punching machine, equipped with flat-faced, round punches of 8-mm diameter. The composition of matrix tablets and pre compression parameters of the granules were given in (**Table 1 and 2**) respectively.

$$Hausner\ ratio = \frac{TD}{BD}$$

$$\%\ CI = \frac{TD - BD}{TD}\ X\ 100$$

Table 1: Composition of matrix tablets for experimental design.

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Diclofenac sodium	100	100	100	100	100	100	100	100	100
GK	10	20	30	10	20	30	10	20	30
Lactose	80	70	60	-	-	-	-	-	-
Starch	-	-	-	80	70	60	-	-	-
MCC	-	-	-	-	-	-	80	70	60
PVP	6	6	6	6	6	6	6	6	6
MS	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight.	200	200	200	200	200	200	200	200	200

All the ingredients mentioned were in mg/tablet.

Table 2: Pre compression parameters of formulation blends (mean ± S.D; n=3).

Formulation code	Angle of repose (°)	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index (%)	Hausner ratio
F_1	27.70±0.88	0.508±0.004	0.570±0.004	10.9±0.010	1.12±0.000
F_2	26.30±1.37	0.499±0.007	0.531±0.008	5.89±0.005	1.06±0.000
F_3	25.11±1.52	0.437±0.007	0.471±0.009	7.14±0.183	1.07±0.002
F_4	27.56±0.92	0.433±0.006	0.472±0.007	8.32±0.192	1.14±0.096
F_5	28.73±1.72	0.507± 0.007	0.530±0.008	4.39 ±0.026	1.04±0 .00

F_6	28.95±1.41	0.399±0.002	0.428±0.002	6.76±0.046	1.07±0.000
F_7	28.53±0.69	0.502±0.004	0.533±0.004	5.86±0.057	1.06±0.002
F_8	27.49±1.39	0.481± 0.004	0.560± 0.005	13.98±0.108	1.16±0.001
F_9	27.63±1.34	0.402±0.004	0.442±0.005	8.96±0.160	1.09±0.002

Evaluation of formulated matrix tablets

The prepared matrix tablets were evaluated for hardness, friability, thickness, uniformity of the weight and content uniformity. Hardness was determined by using Pfizer hardness tester. Friability was determined using Roche friability testing apparatus. Thickness was measured using vernier calipers. Uniformity of the weight and content uniformity were performed according to the I.P method [9, 10].The results were reported in (**Table 3**).

Table 3: Physical characteristics and drug content of the matrix tablets (mean ± S.D; n=3).

Formulation code	Hardness (Kg/cm²)	Friability (%)	Drug content (%)	Tensile strength	Average weight (mg)
F_1	6.80 ± 0.00	0.35	101.47±0.90	18.02±0.00	198±0.001
F_2	7.26 ± 0.11	0.35	100.88±0.92	19.61±0.53	202±0.001
F_3	7.60 ± 0.20	0.45	102.64±0.72	20.14±0.53	199±0.001
F_4	6.80 ± 0.20	0.35	99.41±1.475	18.02±0.53	198±0.001
F_5	7.40 ± 0.20	0.35	99.11±1.045	19.61±0.53	200±0.001
F_6	6.80 ± 0.20	0.51	97.35±0.836	18.02±0.53	201±0.001
F_7	6.73 ± 0.11	0.45	99.7±0.830	17.84±0.30	199±0.001
F_8	7.06 ± 0.11	0.43	97.94±1.020	18.72±0.305	198±0.001
F_9	6.93 ± 0.11	0.42	102.05±0.975	18.73±0.30	199±0.001

Drug release studies

The *in vitro* drug release studies were assessed by USP type II dissolution apparatus at 50 rpm in 900 ml of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 10 hours, maintained at 37°C ± 0.5°C.An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 276 nm. The dissolution studies were carried out in triplicate. The amount of drug present in the sample was calculated with the help of appropriate calibration curve constructed from reference standards. Dissolution profiles for various formulations were depicted in (**Fig 1A, 1B and 1C**).

Release Kinetics

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, first order and Highuchi equation [11]. the dissolution data was also fitted to the well known experimental equation (Koresmeyer's Peppas equation), which is often used to describe the drug release behavior from polymer systems [12].

$$\log\left(\frac{Mt}{Mf}\right) = logK + nlogt$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time; K is a release rate constant incorporating structural and geometrical characteristics of the tablet and n is the differential exponent indicative of the mechanism of drug release.

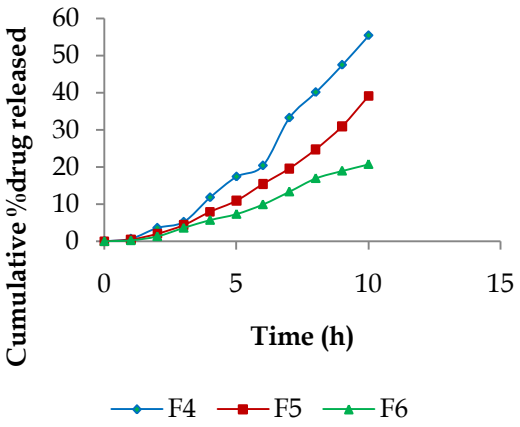

Figure 1B: In vitro release profile of matrix tablets containing starch as diluent

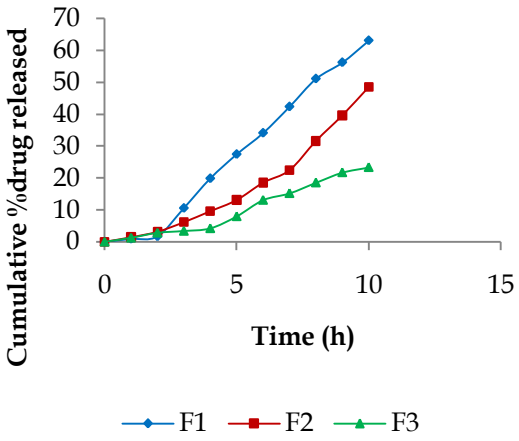

Figure 1A: In vitro release profile of matrix tablets

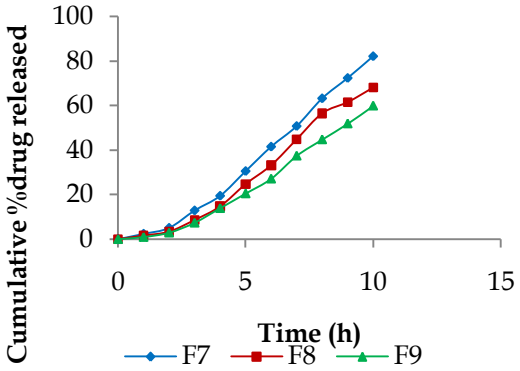

Figure 1C: In vitro release profile of matrix tablets containing MCC as diluent

To clarify the release exponent for the different batches of matrix tablets, the log value of %drug was plotted against log time. A value of n=0.45 indicates Fickian (case I) release; >0.45 but <0.85 for non Fickian (anomalous) release; > 0.89 indicates super case II type of release. Case II gradually refers to the erosion of the polymeric chain and anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled drug release [13]. Mean dissolution time (MDI) was calculated for dissolution data using the following equation [14].

$$MDI = \left(\frac{n}{n+1}\right) \times K^{-1/n}$$

Where n= release exponent and K= release rate constant.

Experimental design and data analysis

A 3^2 factorial design was employed to study the effect of the gum and their concentration on the release rate of diclofenac sodium matrix tablets. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the factorial design. The percent of drug release in 4thh (Q_4), 7thh (Q_7), 10thh (Q_{10}), time to release 50% drug ($t_{50\%}$) and zero order rate constant (K_0) were taken as response variables. The factors, levels and the experimental runs with their factors combination were given

in (**Table 5 and 6**) respectively. The response surface graphs and mathematical models were obtained from DOE software.

The effect of formulation variables on the response variables were statically evaluated using a commercially available software package design of Experiments® 8.0 (design expert). The fitting of an empirical polynomial equation to the experimental results facilitates the evaluation of the responses. The general polynomial equation is as follows:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response on nine runs and b_1 is the estimated coefficient for factor X_1. The main effects (X_1, X_2) represent the average values of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are changed simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

Table 4: Mathematical modeling of the dissolution data.

Code	Zero order		First order		Higuchi		Korse-meyerPeppas			$T_{50\%}$ (h)
	K_0(mg/h)	r	$K_1(h^{-1})$	r	$K_h(h^{-0.5})$	R	$K_p(h^{-n})$	r	n	
F_1	7.83	0.981	0.085	0.954	15.11	0.857	1.177	0.975	1.98	6.37
F_2	5.33	0.979	0.048	0.921	9.67	0.801	1.177	0.995	1.55	9.36
F_3	2.42	0.948	0.025	0.96	5.48	0.839	1.013	0.978	1.33	20.6
F_4	4.71	0.949	0.062	0.923	1.75	0.809	1.306	0.995	1.88	10.61
F_5	3.12	0.946	0.036	0.933	7.77	0.804	1.967	0.998	1.88	16.02
F_6	1.92	0.97	0.023	0.97	4.84	0.843	2.992	0.991	1.88	26.04
F_7	7.45	0.971	0.126	0.908	18.78	0.844	2.074	0.995	1.62	6.71
F_8	6.27	0.962	0.092	0.929	15.75	0.83	1.339	0.993	1.74	7.97
F_9	5.29	0.963	0.071	0.936	13.25	0.828	1.061	0.997	1.85	9.45

Table 5: Factors and levels of the experimental design

Factor/ Level	-1	0	+1
X_1 (Concentration of the gum)	5%	10%	15%
X_2 (type of diluent)	Lactose	Starch	MCC

Table 6: Dissolution characteristics of formulations in a 3^2 full factorial design

Trail no	Formulation code	Coded factor levels		Percentage drug released			Zero order rate constant	$T_{50\%}$
		X_1	X_2	Q_4	Q_7	Q_9		
1	F_1	-1	-1	19.87	42.37	63.11	7.837	6.37
2	F_2	0	-1	9.6	22.47	48.6	5.337	9.36
3	F_3	1	-1	4.23	15.24	23.4	2.427	20.6
4	F_4	-1	0	11.8	33.24	55.42	4.71	10.61
5	F_5	0	0	7.94	19.61	39.15	3.12	16.02
6	F_6	1	0	5.71	13.36	20.75	1.92	26.04
7	F_7	-1	1	19.48	50.87	82.32	7.45	6.71
8	F_8	0	1	14.73	44.87	68.1	6.27	7.97
9	F_9	1	1	13.91	37.47	59.92	5.29	9.45

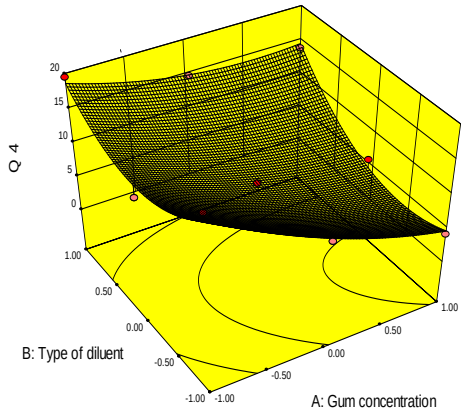

Figure 2A: Response surface plot of tablet formulations after 4 hours dissolution

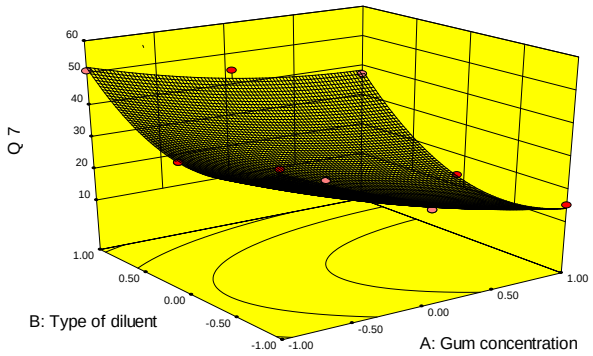

Figure 2B: Response surface plot of tablet formulations after 7 hours dissolution

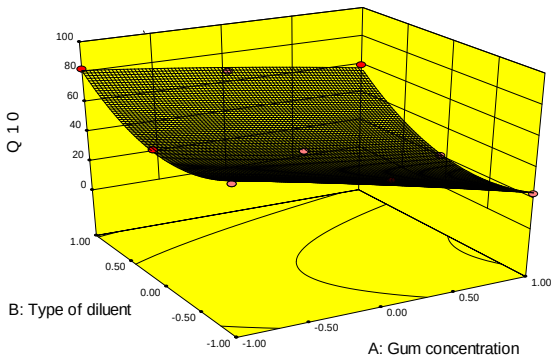

Figure 2C: Response surface plot of tablet formulations after 10 hours dissolution

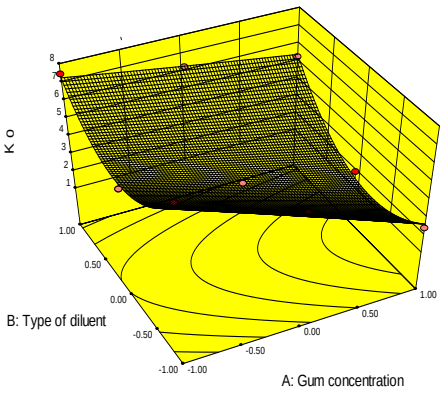

Figure 2D: Response surface plot of tablet formulations showing the effect of polymer on zero order rate

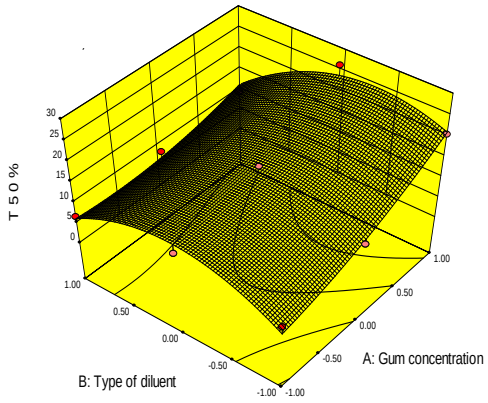

Figure 2E: Response surface plot of tablet formulations showing the effect of polymer on $T_{50\%}$

Table 7: Summary of the regression output of significant factors for the measured responses

Parameters	Coefficients of regression parameters						
	b0	b1	b2	b12	b11	b22	R^2
Q_4	7.32	-4.55	2.40	2.52	1.74	5.15	0.9692
Q_7	20.00	-10.07	8.8	3.43	3.11	13.48	0.9889
Q_{10}	39.19	-16.13	12.54	4.33	-1.13	19.13	0.9917
K_0	3.23	-1.73	0.57	0.81	0.03	2.52	0.9891
$T_{50\%}$	16.10	5.40	-2.03	-2.87	2.18	-7.48	0.9429

Table 8: Analysis of variance for dependent variables in factorial design

For Q_4				
Regression	SS	DF	MS	F value
Treatment	354.18	5	70.84	9.90
Residual	21.47	3	7.16	
Total	375.64	8		
For Q_7				
Treatment	35.15	5	7.03	54.33
Residual	0.39	3	0.13	
Total	35.54	8		
For Q_{10}				
Treatment	3314.08	5	662.82	71.82
Residual	27.68	3	9.23	
Total	3341.76	8		
K_0				
Treatment	1508.48	5	301.70	53.60
Residual	16.88	3	5.63	
Total	1525.36	8		
T_{50}				
Treatment	243.41	5	48.68	18.88
Residual	7.74	3	2.58	
Total	251.15	8		

RESULTS AND DISCUSSION

The granules of diclofenac sodium matrix tablets were prepared by wet granulation method according to the formula given in (**Table 1**). The formulation blends were characterized with respect to angle of repose, BD and TD. The angle of repose was less than 29° indicates satisfactory flow behavior. Physical characteristics of the prepared granules were given in (Table 2).

The matrix tablets were evaluated for hardness, friability, content uniformity, uniformity of weight, tensile strength and *in vitro* drug release studies. The hardness of the tablets in all the batches was found to be in the range of 6.73 – 7.60 Kg/cm^2. The friability of all the formulations was less than 1%. The drug content was found to be uniform for all the batches of tablets prepared and was found to be within 99±2% of labeled claim. The tensile strength of the tablet ranges from 17.84 - 20.14. Evaluation data of the matrix tablets were given in (Table 3). The hardness and friability values indicated good handling properties of the prepared matrix tablets. The prepared matrix tablets were also studied to *in vitro* drug release studies. (Table 4) indicates the data analysis of release profiles according to different kinetic models. Drug release from the matrix tablets was found inversely proportional to the concentration the gum and depends on type of diluent. . The drug release fitted zero order kinetics and mechanism of release is by diffusion. The dissolution profile of matrix tablets was depicted in (**Fig. 1 A-C**).

In vitro release data obtained from formulations prepared were fitted to multiple linear regression analysis. Mathematical relationships generated using multiple linear regression analysis (MLRA) for the studied response variables are expressed as equations and were represented below.

The factors selected are concentration of the gum (5%, 10% and 15%) and type of diluents (lactose, starch and MCC). The responses selected are drug release at 4th (Q_4), 7thh (Q_7), 10th h (Q_{10}), $t_{50\%}$ and K_0. The fitted polynomial equations are given below and the regression coefficients are given in (**Table 7**).

$Q_4 = +7.32-4.55\ X_1 +2.40\ X_2 +2.52\ X_1X_2 +1.74\ X_1^2 +5.15\ X_2^2$

$Q_7 = +20.00-10.07\ X_1 +8.8\ X_2 +3.43\ X_1X_2 +3.11\ X_1^2 +13.48\ X_2^2$

$Q_{10} = +39.19-16.13\ X_1 +12.54\ X_2 +4.33\ X_1X_2 -1.13\ X_1^2 +19.13\ X_2^2$

$K_0 = +3.23-1.73\ X_1 +0.57\ X_2 +0.81X_1X_2 +0.030\ X_1^2 +2.52\ X_2^2$

$T_{50\%} = +16.10+5.40\ X_1 -2.03\ X_2 -2.87\ X_1X_2 +2.18\ X_1^2 -7.48\ X_2^2$

The high levels of correlation coefficients for the dependent variables indicate a good fit i.e., good agreement between the dependent and independent variables. The polynomial equation can be used to draw a conclusion after considering the magnitude of the coefficient and the mathematical sign it carries (positive or negative). Positive sign before a factor in polynomial equations represents that the response increases with the factor, while a negative sign means the response and factors have reciprocal relation.

From the equations it was quite clear that the release of drug from matrix tablets had negative effect on the concentration of gum(X_1) and positive effect on the type of diluent (X_2). The results indicated that the release of drug in 4h 7h, 10h, $t_{50\%}$ and K_0 depends mainly upon the X_1 compared to X_2. It is indicating that the release of the drug from the dosage form idepends upon concentration of gum compared to type of diluent.

The quadratic models generated by regression analysis were used to construct 3D response surface plots in which response parameter was generated by a curvature surface as a function of independent variable. (**Figure 2 A-E**) show the effect of the two factors on the drug release at 3h, 7h and 10h, $t_{50\%}$ and K_0. **Fig 13** depicts a curvilinear relationship for the repsonses. This can be attributed to the potential occurrence of interaction between the two independent variables at the corresponding factor levels, construing that each independent variable is tending to modify the effect of another towards the release of diclofenac sodium.

Concentration of gum has synergestic effect on Q_4, Q_7 , Q_{10}, K_0 and antagonistic effect on $t_{50\%}$ where as type of diluent has antagonistic effect on the Q_4, Q_7 , Q_{10}, K_0

with decrease in the drug release and synergestic effect on $t_{50\%}$. The rate diclofenac sodium release was related inversely to the concentration of the gum in all the studied responses suggesting that the concentration of the gum was the most effective factor in controlling the drug release.

ANOVA table data of the dependent variables was given in (**Table 8).** Multiple regression analysis for all the dependent variables showed that both factors had significant effect ($p<0.05$).

CONCLUSION

In our study, to evaluate the effect of formulation variables on drug release profile, sustained release formulation of diclofenac sodium tablets were developed with polymer gum kondagogu and diluents lactose, starch and MCC. It has been revealed that diluents such as lactose, starch and MCC with gum kondagogu can be used with wet granulation method. Response surface methodology was an important tool for understanding the change of responses and effect of formulation variables. Study indicated that increase in amount of the gum in the tablets resulted in a reduction in the release rate. The calculated release exponents (n values) and rate constants (K values) indicated the release behavior of all the formulations was super case II transport mechanism with zero order kinetics. It was concluded that GK with the three diluents were able to produce desired effects.

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Abbreviations

CRDDS = Controlled drug delivery system. NSAID = Non-steroidal anti inflammatory drug. GK= Gum Kondagogu. MCC = Micro crystalline cellulose. BD = Bulk density. TD = Tapped density. CI = Carr's index.

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