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INFLUENCE OF FORMULATION VARIABLES ON THE *IN VITRO* DISSOLUTION OF GUM DAMAR BASED MATRIX TABLETS

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ABSTRACT

The objective of the study was to examine the influence of two variables, concentration of the matrixing agent and diluent on the release of diclofenac sodium from hydrophobic matrix tablets. A 32 full factorial design was employed to optimize drug release profile. Concentration of the hydrophobic matrixing agent (X1) and type of diluent (X2) were taken as independent variables. The dependent variables selected were percentage drug release at 3h, 6h, 9h, time required for 50% drug release and zero order rate constant. Matrix tablets were evaluated for hardness, friability, weight variation and in vitro drug release. Polynomial equations and response surface plots were generated for all dependent variables. It was observed that all the factors had significant contribution on all dependent variables.

INTRODUCTION: Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes [1]. In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process, level of reproducibility, stability of the raw materials and dosage forms as well as ease of up operation and also resistant to dose dumping. These systems improve patient compliance and decreased adverse drug reactions [2].

Natural gums are promising biodegradable polymeric materials. The fact for increase in importance of natural plant based material is that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw materials [3]. Many natural polymeric materials have been successfully used in sustained-release tablets.

Gum damar is a hard resin collected by tapping trees from *Shorea spp.* (including *S. javanica, S. lamellata, S. retinodes*), Dipterocarpaceae from South-East Asia, including Malay & Indonesian archipelagos. Damar gum is a triterpenoids resin, containing a large number of triterpenes and their oxidation products. Many of them are low molecular weight compounds (Dammarane, Dammarenolic acid, Oleanane, Oleanonic acid, etc), but dammar also contains a polymeric fraction, composed of polycadinene.

Their main use is in the manufacture of paper or wood varnishes and lacquers, particularly as a varnish for the fine art, and some paints.

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It is a water- resistant coating, sometimes also used for its glazing functionality, and found in the indigenous system of medicine [4]. A few works were reported on gum dammar using it as a matrixing agent for sustained release [5, 6].

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 [7-9]. From several investigations, it was found that diclofenac sodium was feasible for the development of sustained release formulation.

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

METHODS:

Preparation of Matrix Tablets: Diclofenac sodium matrix tablets were prepared by wet granulation method. Diclofenac sodium (100mg) was blended with appropriate quantities of GD (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 1 hour and the dried granules were sieved through No. 16 sieve.

The granules were dried and passed through mesh no: 16. Granules were evaluated for angle of repose bulk density (BD) and tapped density (TD). Carr's index (CI) and Hausner's ratio were calculated using following equations [10] 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.

Composition of the matrix tablets and the pre compression parameters of the granules were given in the **Table 1 and 2** respectively.

$$\text{Hausner's Ratio} = \frac{TD}{BD}$$

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

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
GD	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 in the formulations are mentioned in mg/tablet

TABLE 2: PRE COMPRESSION PARAMETERS OF PREPARED GRANULES (MEAN ± S.D; N=3)

Formulation code	Angle of repose (°)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio
F_1	25.13±2.0	0.520±0.004	0.573±0.005	9.13±0.017	1.10±0.000
F_2	28.73±1.72	0.507±0.007	0.530±0.008	4.39±0.026	1.04±0.002
F_3	26.04±1.41	0.430±0.003	0.442±0.003	2.71±0.017	1.02±0.000
F_4	28.73±1.72	0.507± 0.007	0.530±0.008	4.39 ±0.026	1.04±0 .00
F_5	27.63±1.34	0.402±0.004	0.442±0.005	8.96±0.160	1.09±0.002
F_6	28.53±0.69	0.502±0.004	0.533±0.004	5.86±0.057	1.06±0.002
F_7	27.70±0.88	0.508± 0.004	0.570±0.004	10.9± 0.01	1.12± 0.00
F_8	28.95±1.41	0.399±0.002	0.428±0.002	6.76±0.046	1.07±0.000
F_9	27.49±1.39	0.481± 0.004	0.560± 0.005	13.98±0.108	1.16±0.001

Experimental Design: 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 3rd h (Q_3), 6th h (Q_6), 9th h (Q_9), 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 3 and 4** respectively. The response surface graphs and mathematical models were obtained from DOE software.

Determination of Hardness, Friability and Drug Content: 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 [11, 12] (**see table 5**).

TABLE 3: 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 4: 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	T50
		X1	X2	Q3	Q6	Q9		
1	F_1	-1	-1	14.53	47.8	73.35	5.974	8.36
2	F_2	0	-1	9.66	30.6	51.66	3.881	12.88
3	F_3	1	-1	3.73	13.52	22.95	2.177	22.96
4	F_4	-1	0	21.51	68.41	96.65	10.84	4.61
5	F_5	0	0	7.35	59.47	81.52	8.89	5.62
6	F_6	1	0	5.05	40.71	72.59	7.17	6.97
7	F_7	-1	1	29.06	79.25	99.47	11.75	4.25
8	F_8	0	1	19.48	75.7	92.91	10.52	4.75
9	F_9	1	1	11.44	40.82	69.88	7.14	7

TABLE 5: PHYSICAL CHARACTERISTICS AND DRUG CONTENT OF THE MATRIX TABLETS (MEAN ± S.D; N=3)

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Tensile strength	Weight variation
F_1	6.46 ± 0.11	0.41	97.640±0.76	17.13±0.30	198±0.001
F_2	6.80 ± 0.20	0.35	99.410±1.47	18.02±0.53	202±0.001
F_3	7.33 ± 0.11	0.47	98.760±1.00	19.43±0.30	199±0.001
F_4	6.40±0.20	0.35	99.41±1.475	18.02±0.53	198±0.001
F_5	6.93±0.11	0.42	101.05±0.975	18.73±0.30	200±0.001
F_6	7.26 ± 0.11	0.35	100.88±0.92	19.61±0.53	201±0.001
F_7	6.80±0.20	0.51	97.35±0.836	18.02±0.53	199±0.001
F_8	7.06±0.11	0.81	101.17±1.372	19.25±0.30	198±0.001
F_9	6.86 ± 0.11	0.51	98.520±0.84	18.19±0.30	199±0.001

Drug Release Studies: The *in vitro* drug release studies were assessed by USP type II dissolution apparatus (paddle method) 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 (37°C ± 0.5°C) 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.

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 Higuchi equation [13]. 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 [14].

$$\log(M_t/M_f) = \log k + n \log t$$

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.

To clarify the release exponent for the different batches of matrix tablets, the log value of %drug was plotted against log time for each batch according to the equation 4. 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 [15]. Mean dissolution time (MDI) was calculated for dissolution data using the following equation [16].

$$MDI = \binom{n}{n+1} \times K^{-1/n}$$

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

TABLE 6: MATHEMATICAL MODELLING OF MATRIX TABLETS

Code	Zero order		First order		Higuchi		Koresmeyer's Peppas			$T_{50\%}$ (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	5.97	0.977	0.135	0.923	19.87	0.866	1.156	0.981	1.98	8.36
F_2	3.88	0.942	0.073	0.956	13.61	0.859	1.006	0.983	1.86	12.8
F_3	2.17	0.965	0.027	0.939	6.060	0.81	2.471	0.991	1.89	22.9
F_4	10.84	0.983	0.26	0.892	27.28	0.893	2.728	0.986	1.74	4.61
F_5	8.89	0.961	0.186	0.890	22.41	0.837	1.183	0.974	2.17	5.62
F_6	7.17	0.953	0.119	0.888	17.89	0.816	1.599	0.981	2.19	6.97
F_7	11.75	0.998	0.214	0.848	29.31	0.913	5.559	0.985	1.40	4.25
F_8	10.52	0.975	0.28	0.908	27.03	0.886	4.092	0.988	1.47	4.75
F_9	7.14	0.976	0.115	0.921	18.04	0.853	2.182	0.997	1.58	7.00

Experimental Design Data Analysis: 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.

RESULTS AND DISCUSSIONS: 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 weigh, 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 6.46 – 7.33 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 17.13 – 19.43. Evaluation data of the matrix tablets were given in **Table 5**. 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 6** 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 **Figures 1 (A- C)**.

In vitro release data obtained from formulations prepared were fitted to multiple linear regression analysis. The factors selected are concentration the gum (5%, 10% and 15%) and type of diluent (lactose, starch and MCC). The responses selected are drug release at 3^{rd} h (Q_3), 6^{th}h (Q_6), 9^{th} h (Q_9), $t_{50\%}$ and K_0. Mathematical relationships generated using multiple linear regression analysis (MLRA) for the studied response variables are expressed as Equations and were given below. The regression coefficients are given in **Table 7**.

$$Q_3 = +9.93 - 7.48X_1 + 5.3\,X_2 - 1.70\,X_1X_2 + 2.06X_1^2 + 3.35X_2^2$$

$$Q_6 = +60.76 - 16.74X_1 + 17.31X_2 - 1.04X_1X_2 - 6.84X_1^2 - 8.25X_2^2$$

$$Q_9 = +85.51 - 17.34X_1 + 19.05X_2 + 5.20X_1X_2 - 2.88X_1^2 - 15.22X_2^2$$

$$K_0 = +9.14 - 2.01X_1 + 2.90X_2 - 0.20X_1X_2 - 0.26\,X_1^2 - 2.06X_2^2$$

$$T_{50\%} = +4.88 + 3.29X_1 - 4.70X_2 - 2.96X_1X_2 + 1.28\,X_1^2 + 4.30\,X_2^2$$

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 the gum (X_1) and positive effect on the type of diluent (X_2). The results indicated that Q_3 is mainly based upon the X_1 compared to X_2. The release of drug in 6h, 9h and $t_{50\%}$ mainly based upon the X_2 compared to X_1 and zero order rate constant depends on the both independent variables. It is indicating that the release of the drug from the dosage form initially depends upon concentration of gum and finally on type of diluent.

The quadratic models generated by regression analysis were used to construct 3D response surface plots in which rsponse 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, 6h and 9h, $t_{50\%}$ and K_0. **Fig. 2** depicts a curvilinear relationship for the responses. 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 the gum has synergistic effect on Q_3, Q_6, Q_9, K_0 and antagonistic effect on $t_{50\%}$ whereas type of diluent has antagonistic effect on the Q_3, Q_6, Q_9, and K_0 with decrease in the drug release and synergistic 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 along with the type of diluent 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 ($p<0.05$).

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_3	9.93	-7.48	5.3	-1.70	2.06	3.35	0.9696
Q_6	60.76	-16.74	17.31	-1.04	-6.84	-8.25	0.9709
Q_9	85.51	-17.34	19.05	5.20	-2.88	-15.22	0.9728
K_0	9.14	-2.01	2.90	-0.20	-0.26	-2.06	0.9909
$T_{50\%}$	4.88	3.29	-4.70	-2.96	1.28	4.30	0.9455

TABLE 8: ANALYSIS OF VARIANCE FOR DEPENDENT VARIABLES IN FACTORIAL DESIGN

		For Q_3		
Regression	SS	DF	MS	F value
Treatment	549.50	5	109.90	19.11
Residual	17.25	3	5.75	
Total	566.75	8		
		For Q_6		
Treatment	3711.73	5	742.35	20.04
Residual	111.11	3	37.04	
Total	3822.85	8		
		For Q_9		
Treatment	4569.78	5	913.96	21.44
Residual	127.86	3	42.62	
Total	4697.64	8		
		K_0		
Treatment	83.42	5	16.68	65.08
Residual	0.77	3	0.26	
Total	84.19	8		
		$T_{50\%}$		
Treatment	272.62	5	54.52	10.40
Residual	15.72	3	5.24	
Total	288.35	8		

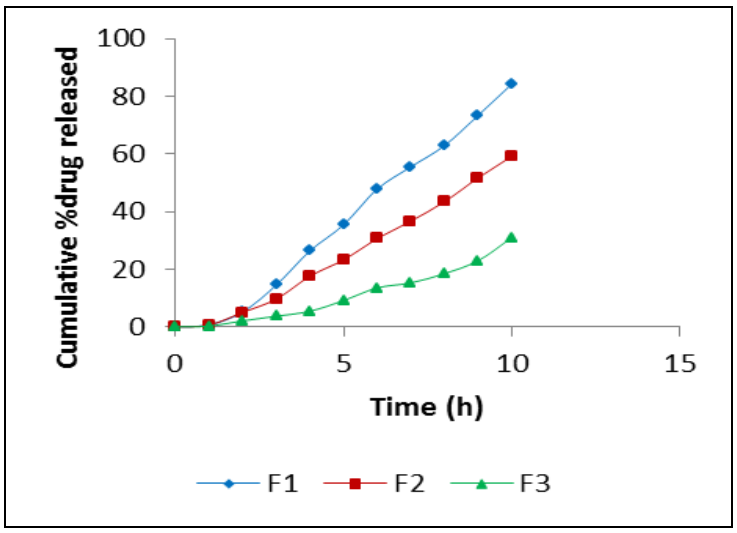

FIGURE 1A: *IN VITRO* RELEASE PROFILE OF MATRIX TABLETS CONTAINING LACTOSE AS DILUENT

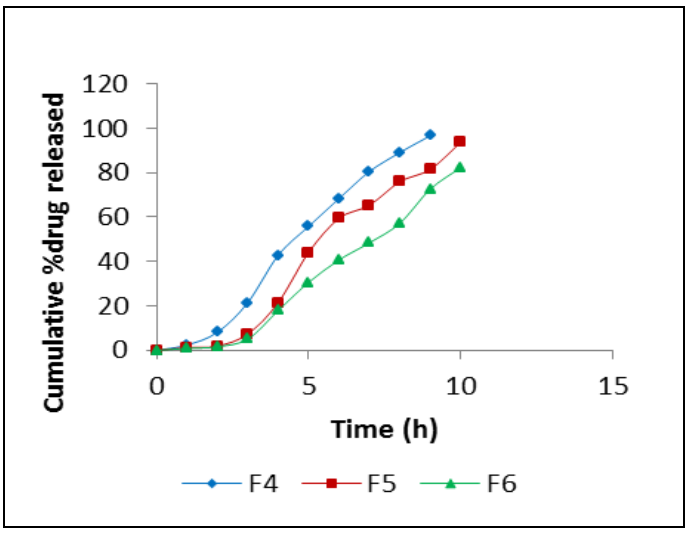

FIGURE 1B: IN VITRO RELEASE PROFILE OF MATRIX TABLETS CONTAINING STARCH AS DILUENT

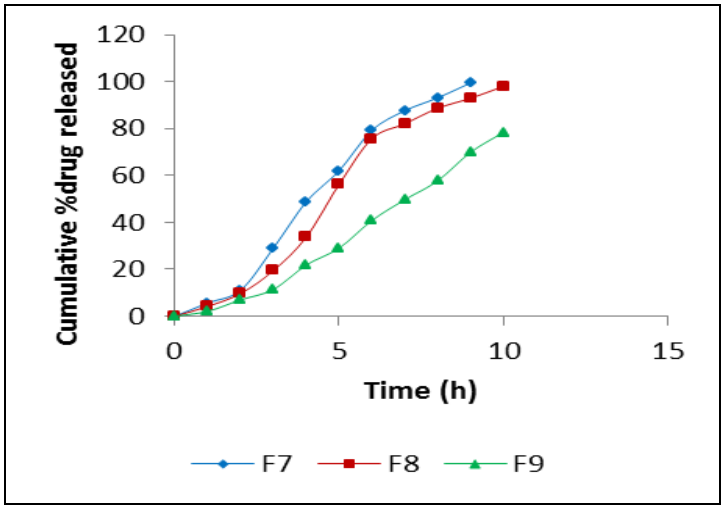

FIGURE 1C: *IN VITRO* RELEASE PROFILE OF MATRIX TABLETS CONTAINING MCC AS DILUENT

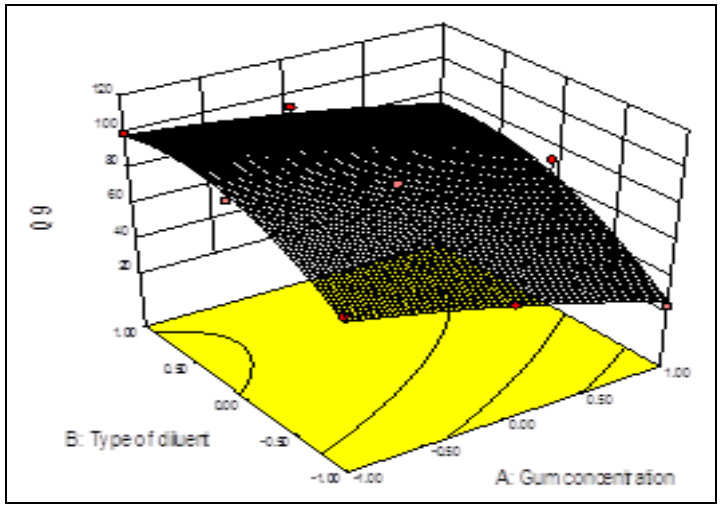

FIGURE 2C: RESPONSE SURFACE PLOT OF TABLET FORMULATIONS AFTER 9 HOURS DISSOLUTION

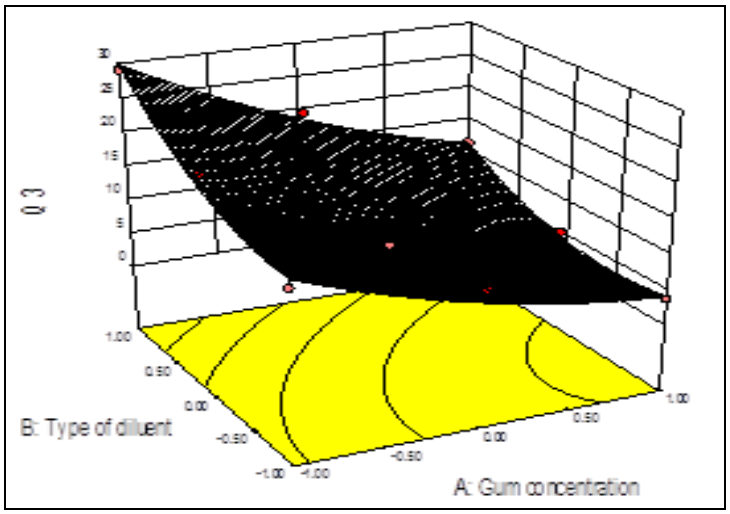

FIGURE 2A: RESPONSE SURFACE PLOT OF TABLET FORMULATIONS AFTER 3 HOURS DISSOLUTION

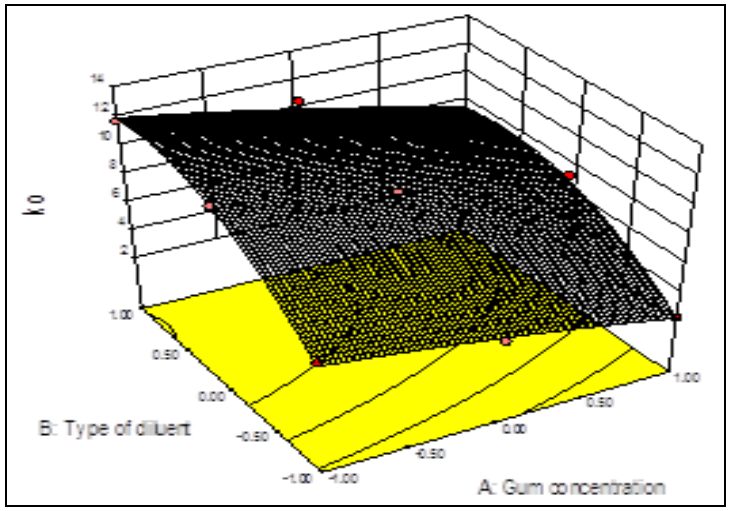

FIGURE 2D: RESPONSE SURFACE PLOT OF FORMULATIONS SHOWING THE EFFECT OF POLYMER ON ZERO ORDER RATE CONSTANT

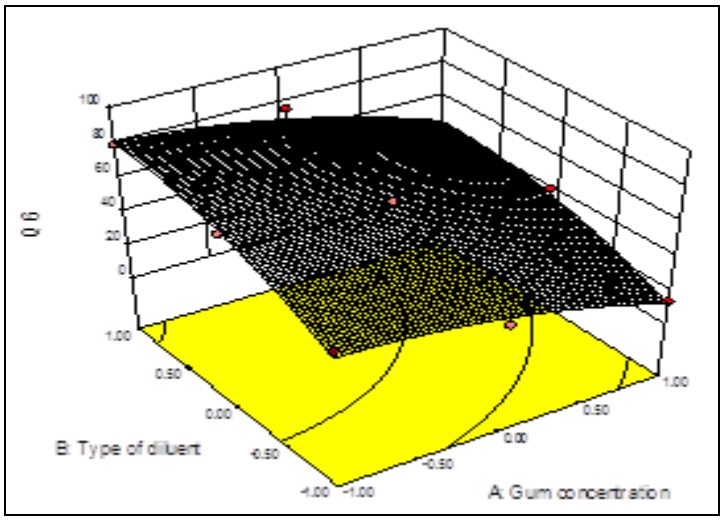

FIGURE 2B: RESPONSE SURFACE PLOT OF TABLET FORMULATIONS AFTER 6HOURS DISSOLUTION

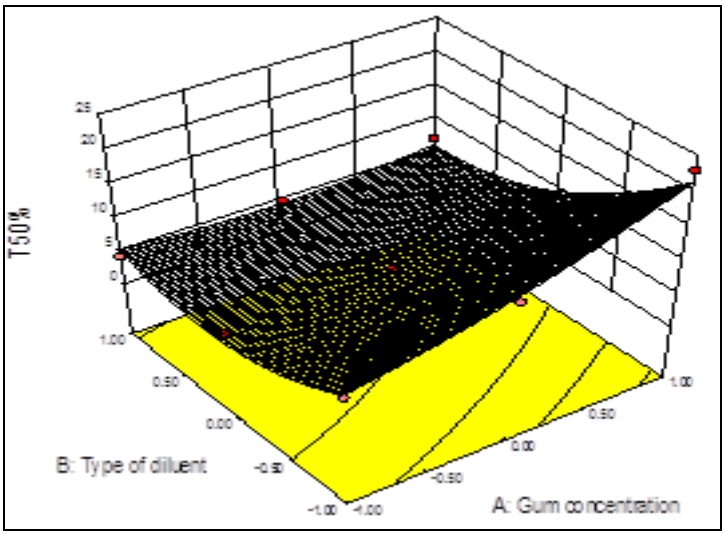

FIGURE 2E: RESPONSE SURFACE PLOT OF TABLET FORMULATIONS SHOWING THE EFFECT OF POLYMER ON $T_{50\%}$

CONCLUSION: Study indicates that release of diclofenac sodium from gum dammar based matrix tablets highly depends on type of diluent along with the concentration of the gum. However, in developing SR formulations with gum damar containing DS, it has been shown that higher release rates are observed with matrix tablets containing MCC as diluent whereas lactose with gum damar provides a better result. In addition, better results have been seen with higher concentrations of gum with starch and MCC. 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. Response surface methodology was an important tool for understanding the change of responses and effect of formulation variables.

ABBREVIATIONS:

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

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