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FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM COLON SPECIFIC TABLET BY APPLYING CCRD-RSM METHODOLOGY

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ABSTRACT

Diclofenac sodium is a Non-steroidal Anti-Inflammatory drug (NSAIDS). It useful for treatment of inflammatory bowel disorders (IBD). Diclofenac sodium colon specific tablet was fabricated by wet granulation technology by applying centre composite rotable design response surface model (CCRD-RSM). CCRD-RSM, independent variables such as guar gum (A), micro crystalline cellulose (MCC) (B) concentration were used. Optimised batch (8) had drug content was 99.95 ± 0.16(%) and % CDR (Y) 99.99 ± 0.21 (%) respectively. This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P value < 0.05 which is considered to be statistically significant. All concentrations of independent variables (A and B) shows significant effect on dependent variables (X and Y). The Prepared colon specific tablet evaluated In terms of bulk density (0.69 ± 0.02), tapped density (0.72 ± 0.05), Carr's Index (1.59 ± 0.21) angle of repose (24.23° ± 0.24) and *in vitro* study. The result associated in optimized batch (8) is good to Satisfactory and having a good free flowing property. *In vitro* release study is indicate that the prepared colon specific tablet (99.99 ± 0.21 %) shows maximum release as compared to marketed tablet (85.14 ± 0.25 %). It was found that the *in-vitro* drug release of colon specific tablet containing diclofenac sodium explained by First order model of Anomalous Non Fickian dissolution mechanism.

KEYWORDS

Diclofenac sodium, CCRD-RSM, RSM, Colon specific, *In vitro* release, ANOVA and First order.

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INTRODUCTION

In oral route of administration is most suitable route for drug administration in patients. Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAIDs) widely used clinically to reduce inflammation and pain in conditions. It is important to Inhibition of Cyclooxygenase (COX I, COX II) Enzyme is responsible for Inhibition of Prostaglandins Synthesis. It mainly useful for

treatment of various inflammatory bowel disorders (IBD). IBD is one of the colonic inflammatory disorder. IBD is disorder to cause cancer, if proper treatment was not taken patients was died. For oral delivery of diclofenac sodium arises problem presystolic metabolism, GI toxicity. To overcome this all drawbacks need to develop oral administration of drug is usually formulated as colon target sustained release tablets. Colon targeted delivery drug can administered orally it can directly targeted to colonic site for treatment of IBD. Colon specific tablet is formulate by wet granulation method in which drug complex with polymer such as guar gum and /micro crystalline cellulose. Guar gum is natural, non-toxic polymer is responsible for maximum drug loading efficiency as well as targeting efficiency. Guar gum is only degraded in colon due to the micro-flora. Guar gum is responsible for maximum drug release at colonic site for treatment of IBD. Centre composite rotable design response surface model (CCRD-RSM) was apply for development of colon targeting diclofenac sodium tablet. This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P value < 0.05 which is considered to be statistically significant. RSM methodology is important for determination of interaction pattern of independent and dependant response variables. The aim of present work to develop diclofenac sodium tablet by applying CCRD-RSM methodology for targeting colon to supply optimal concentration of drug for a longer time in local site[1-4].

MATERIAL AND METHODS

Materials

Diclofenac sodium was obtained from obtained from Loba Chemie Ltd. (Mumbai, India). Guar gum, Micro crystalline cellulose (MCC), Lactose, Talc and Magnesium stearate was obtained from obtained from Loba Chemie Ltd. (Mumbai, India). All other reagents used were of analytical grade.

Method

Experimental Design

To design the Diclofenac sodium colon specific tablet, Preliminary experiments revealed that the independent variables like Guar gum concentration (A) and Micro crystalline cellulose (MCC) concentration (B) during preparation, were the main factors that affected the dependent variables such as, Drug content and % Cumulative drug release (% CDR). CCRD-RSM (Design-Expert software, version 7, Stat-Ease, Inc., Minneapolis, Minnesota, USA) was applied to systemically investigate the influence of these two independent variables on two dependent variables of the tablet. All independent, coded and actual values of the variables of CCRD-RSM are given in Table No.1. This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P-value < 0.05 which is considered to be statistically significant[5-6].

Preparation of colon specific tablet

The Diclofenac sodium (100 mg), Guar gum (125 mg), MCC (6 mg), Lactose (Q.S.), Talc (Q.S.) and Magnesium stearate (Q.S.) were granulated by Isopropyl alcohol. Wet mass was passed through a mesh and granules were dried at 40ºC for 45 min. Diclofenac sodium granules was prepared by wet granulation technique. The Prepared Granules was compressed on the 9-staton tablet punching machine. Having a Hardness 9 - 12 Kg/cm^2.

Drug Content

Diclofenac sodium from tablet was extracted by dissolving in methanol. Diclofenac sodium content in the Methanolic extract was analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 276 nm.

Bulk density and tapped density

Amount of powder is weighed separately and transferred into 100 ml of measuring cylinder, initial volume of powder material is measured and calculated bulk density according to this formula, Bulk density: Mass / Volume. Tapped density is determined by placing a graduated cylinder containing a known mass of powder Undergoes Tapping manually (100 tapes) or mechanical

apparatus under powder bed volume has reached a minimum volume. The Tapped Density is calculated by this Formula, Tapped density: Weight of Powder/ tapped volume of Powder.

Compressibility Index or Carr's Index

Compressibility index is based on the tapped density (T. D) and bulk density (B. D). It is a ratio of tapped density and bulk Density i.e. Compressibility Index. The Following formula for determination of compressibility index (CI), CI: T. D. – B. D. / T. D. *100.

Angle of Repose

The angle of repose of granules was determined by the funnel method. In which the powder pour in funnel on a level, flat surface and measure the included angle. The Following Formula for determination of angle of repose, θ: Tan^{-1} (h/r) (θ = Angle of repose, h = Height of the powder cone, r =Radius of the powder cone).

***In vitro* release**

Dissolution of colon specific Tablet was determined by Paddle Type of Dissolution Apparatus. The tablet was added into cylindrical vessel containing 900 ml simulated gastric fluids pH 1.2 acidic media having 75 rpm for next two hours and tem.37±0.5°C. Dissolution media was changes tablet was added in to simulated gastric fluids pH 6.8 for next six hour. Particular time of interval sample was withdrawn and take absorbance by using U.V. spectroscopic technique and determine dissolution rate of tablet. In order to study drug release mechanism from diclofenac sodium colon specific tablet, the drug release data was fitted in Korsmeyer-Peppas equation. The logarithmic plot of cumulative percentage of drug released vs. log time gives the release exponent n value from the slope of the straight line and y intercept respectively $M_t / M_\infty = Kt^{n7-8}$.

RESULTS AND DISCUSSION

Experimental Design

Responses observed for thirteen formulations prepared were fitted to various models using Design-Expert® software 7.0.1. CCRD-RSM methodology offers to investigate a high number of variables at different levels with limited number of experiments. To fit the data, a linear second-order polynomial model was chosen as the best model. Polynomial Equation shows the relationship between independent variables and response variables such as Drug Content (X), % Cumulative drug release (% CDR) (Y) respectively. All values of R^2, SD and % coefficient of variation and ANOVA are depicted in Table No.2.

X= +99.95 + 0.77*A + 0.59*B.

Y=+98.99 + 0.73*A + 0.50*B.

Where, X= Drug Content (%), Y = % Cumulative drug release (% CDR), A =Guar gum concentration, B =Micro crystalline cellulose (MCC) concentration.

Response surface plots

Response surface plots was important three dimensional surface curves for studying the interaction patterns. Three dimensional response surface plots generated at different levels by the Design-Expert® software. Response surface plot showing effect of guar gumand MCC concentration on drug content (Figure No.1), response surface plot showing effect of guar gumand MCC concentration on % CDR (Figure No.2).

Drug content (%) and % Cumulative drug release (% CDR)

Drug content (%) and % CDR are reported in Table No.1. drug content in all thirteen formulations were found to be in the range of 96.62 % to 99.95 % and % CDR of the all thirteen formulations were found to be in the range of 97.32 % to 99.99 % respectively.

Effect of guar gum (A) and MCC (B) concentration on Drug content (%) and % CDR

In A concentration was increases to increases drug content and B concentration was increases to decreases drug content (Figure No.3-A). In A concentration was increases to increases % CDR and B concentration was increases to decreases% CDR (Figure No.3-B). Concentration of A and B shows significant effect on drug content (%) and % CDR.

Drug Content

Drug content of optimized batch (8) was found to 99.95 ± 0.16 for Diclofenac sodium colon specific tablet (mean ± SD, n=3).

Bulk, tapped density and Compressibility Index or Carr's Index

Bulk and tapped density of tablet (optimized batch 8) was found to be 0.69 ± 0.02 and 0.72 ± 0.05 (mean ± SD, n = 3) respectively. Compressibility Index or Carr's Index of tablet (optimized batch 8) was found to be 1.59 ± 0.21(mean ± SD, n = 3) respectively. Carr's Index is less than or equal to **<**10 indicates free flowing properties.

Angle of Repose

Angle of repose of optimized batch 8 was found to be 24.23° ± 0.24 (mean ± SD, n = 3). The Angle of repose is less than or equal to 40° indicates free flowing properties.

***In vitro* release**

The release profile of Diclofenac sodium from optimized batches 8 of colon specific tablet (99.99 ± 0.21) and marketed colon specific tablet (85.14 ± 0.25) through the USP type II dissolution apparatus (Figure No.4-A). The release pattern of optimized colon specific tablet appears to be fast release as compared to marketed tablet. The corresponding plot of (log cumulative percent drug release Vs log time) of the Korsmeyer-Peppa's equation release exponent (n) was found to be 0.84 (Figure No.4-B). It was found that the *in-vitro* drug release of tablet containing diclofenac sodium explained by First order model (R^2 = 0.9998) of Anomalous Non Fickian dissolution mechanism.

Table No.1: Independent variables along with their code, levels and respective drug content (%) and % CDR of different batches of Diclofenac sodium colon specific tablet (n = 3). These results are mean ± standard deviation

Batch	Guar gum (A)	MCC (B)	Drug content (X)	% CDR (Y)
1	125	1.757359	98.74	98.78
2	117.9289322	6	98.75	99.79
3	125	10.24264	99.82	99.85
4	125	6	99.91	99.95
5	130	3	96.62	97.32
6	132.0710678	6	96.75	97.51
7	125	6	99.93	99.95
8	125	6	99.95	99.99
9	125	6	99.85	99.89
10	125	6	99.92	99.94
11	120	9	99.86	99.89
12	130	9	98.85	99.87
13	120	3	98.92	99.93

A = guar gum concentration in mg (high level-130, low level-120); B = MCC concentration in mg (high level-9, low level-3)

Table No.2: Summary of results of regression analysis for responses X and Y and analysis of variance for drug content and % CDR

S.No	Parameter	DF	SS	MS	F	P value	R^2	SD	%CV
Drug Content (X)									
1	model	2	7.47	3.73	4.18	0.0480Significant	0.9998	0.95	0.95
2	Residual	10	8.94	0.89	-	-	-		
3	Total	12	16.40	-	-	-	-		
% CDR (Y)									
4	Model	2	6.31	3.15	6.95	0.0128Significant	0.9996	0.67	0.68
5	Residual	10	4.54	0.45	-	-	-		
6	Total	12	10.85	-	-	-			

DF, degrees of freedom; SS, sum of square; MS, mean sum of square; F, Fischer's ratio, p value, Probability value; SD, standard deviation; %CV, Coefficient of variation.

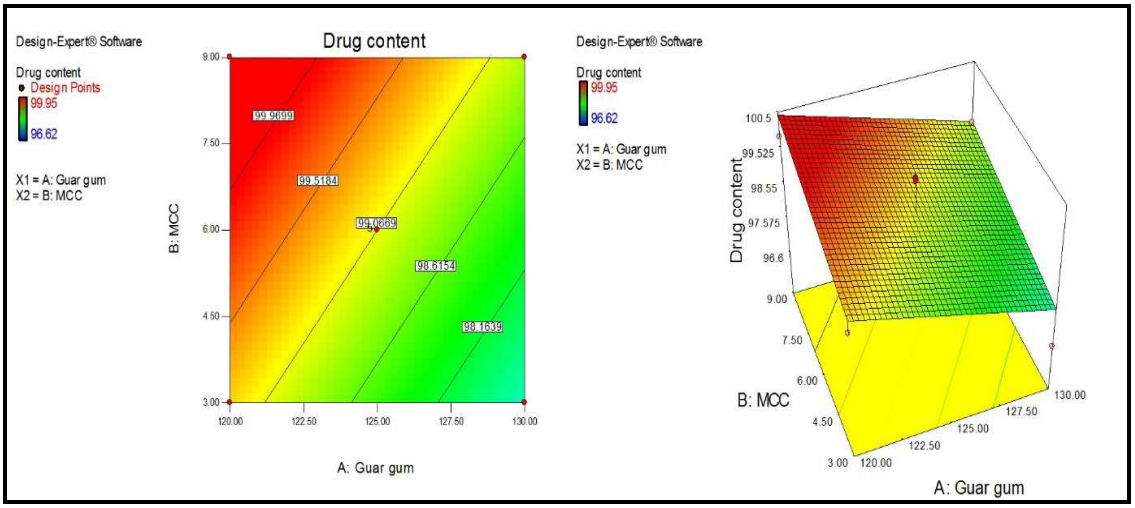

Figure No.1: Response surface plot showing effect of guar gum and MCC concentration on drug content

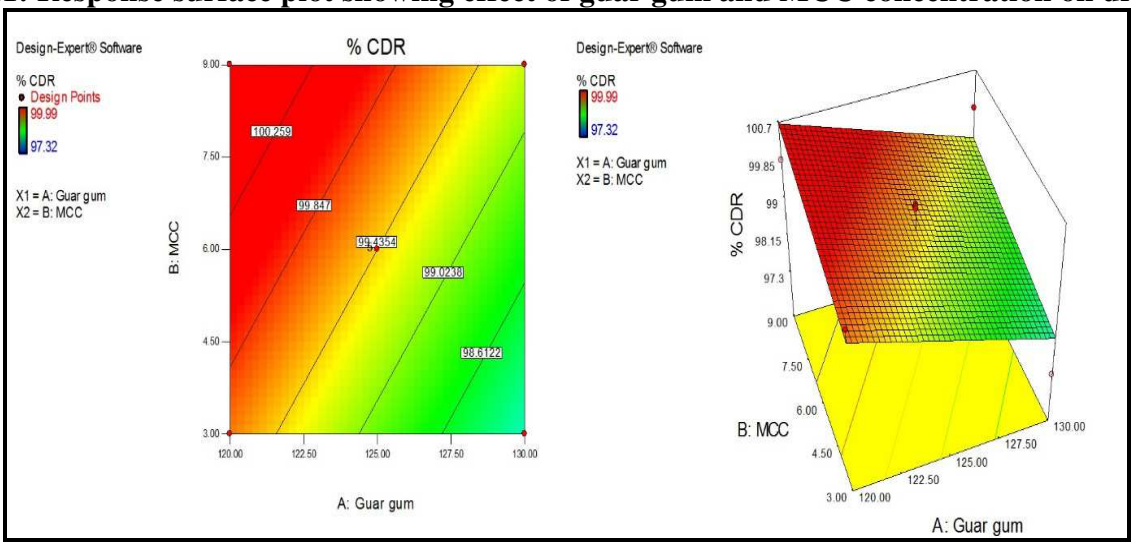

Figure No.2: Response surface plot showing effect of guar gum and MCC concentration on % CDR

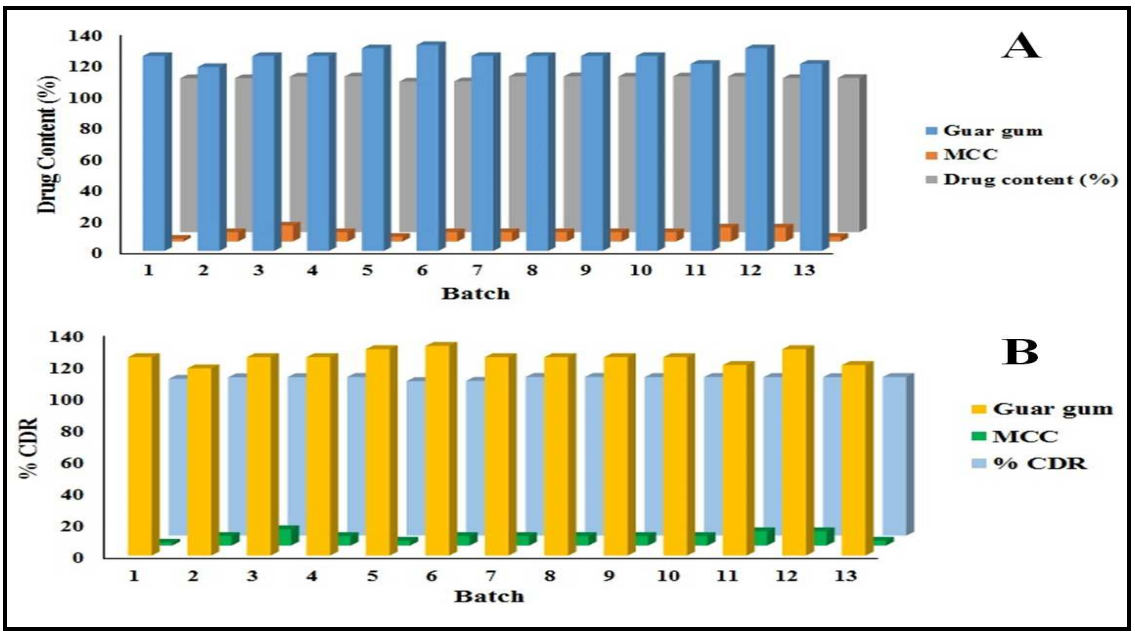

Figure No.3: Effect of guar gum and MCC concentration on Drug content (A), Effect of guar gum and MCC concentration on % CDR (B)

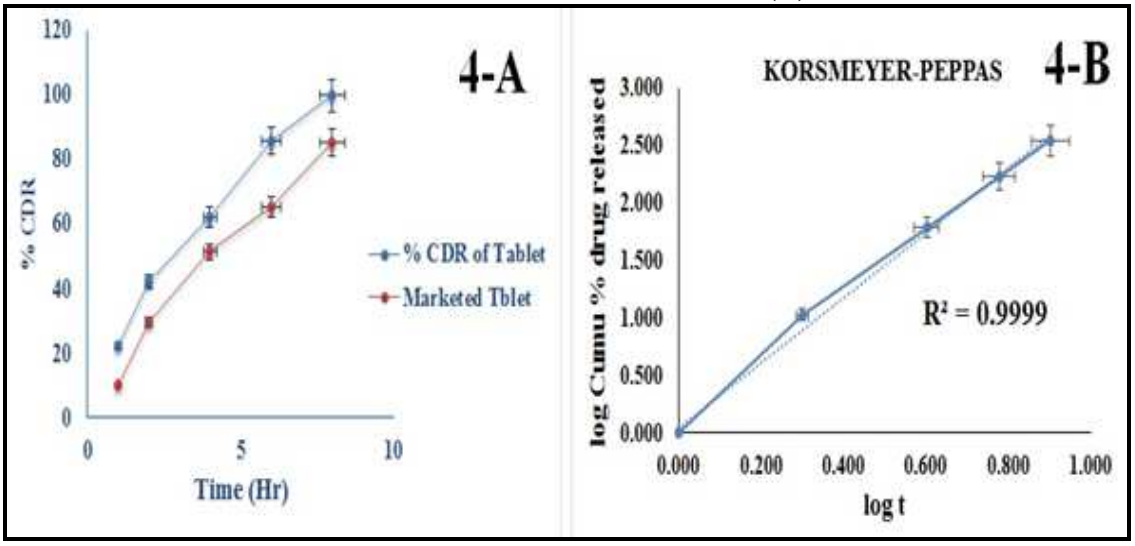

Figure No.4: % Cumulative Drug Release profile of colon specific tablet and marketed tablet (4-A), drug release mechanism of diclofenac sodium (4-B)

CONCLUSION

Diclofenac sodium colon specific tablet was developed and formulated by wet granulation technology using CCRD-RSM methodology. Aim of present work to develop colon targeting tablet for treatment of inflammatory bowel diseases. The result associated in Optimized batch (8) is good to Satisfactory and having a good free flowing property. Drug complex with guar gum is responsible for maximum drug targeting efficiency at colonic site and maximum drug release in tablet as compared to marketed colon specific tablet. Diclofenac sodium is mainly used for treatment of IBD, hence we develop diclofenac sodium colon specific tablet for treatment of various inflammatory colonic disorders.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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