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RESEARCH ARTICLE

Formulation Design and Evaluation of Fixed Dose Combination of Diclofenac sodium [sustained release] and Rabeprazole sodium [enteric coated].

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ABSTRACT

The fixed dose combination of diclofenac sodium-sustained release [DIC-SR] and rabeprazole sodium-enteric coated [RAB-EC] was developed. DIC-SR matrix was formulated with xanthan gum using as release retardant to release drug over 24hrs. The concentrations of xanthan gum evaluated at levels of 30%, 40% and 50%. The DIC-SR formulation was optimized by 3^2 factorial design. RAB-EC was developed with enteric coating polymer Eudragit-S100 at levels of 5%, 10% and 15% weight gain. Instacoat universal®, HPMC based coating material was utilized for primary coating of RAB and secondary coat is given with Eudragit-S100. The optimum batches of DIC-SR and RAB-EC were combined to obtain fixed dose combination and evaluated.

Keywords: Diclofenac, Rabeprazole, Sustained release, Enteric coated, Fixed dose combination..

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs [NSAID] are frequently prescribed in orthopedic diseases for their anti-inflammatory, antithrombotic, antipyretic and analgesic effects. Despite of their indisputable efficacy and wide use it poses dilemma in physicians mind due to their possible gastrointestinal complications. The relative risk of gastrointestinal complications is three times greater in case of NSAID user than non users [1,2]. NSAID's are proposed to exert their deleterious action on small as well as large bowel through both local and systemic action. Being weak acids, they cause topical mucosal irritation. They alter the hydrophobic function of the mucus gel layers on the surface of the gastric mucosa [3], disrupt permeability and enter the epithelial tissue. Then it become ionized and subsequently damage the cells and capillaries.

Diclofenac sodium [DIC] is NSAID drug commonly used for treatment of orthopedic diseases. DIC act through inhibition of prostaglandin synthesis. But, it has well known potential to generate gastritis and peptic ulcers. Rabeprazole sodium [RAB] is benzimidazole derivative which act as a proton pump inhibitor [PPI]. It is used for the prophylaxis and treatment of peptic ulcers. It acts by inhibition of H^+/K^+ ATP'ase pump which is involved in secretion of gastric acid. Since, proton pump inhibitor possess ability to raise intra-gastric pH above 4 for a substantial proportion of 24-hours period, these drugs are effective as healing agents for NSAID-associated ulcer. The RAB was found to be effective than ranitidine [H_2 receptor antagonist] in controlling gastric acidity and gastric as well as duodenal ulcers [4]. RAB is emerged as treatment of choice over other drugs for acid related diseases. The RAB is evolved as more potent and rapid inhibitor of H^+/K^+ ATP'ase inhibitor than omeprazole [5]. PPI's are well tolerated option for control of NSAID induced ulcers. The RAB has daily dose of 20 mg per day. Hence, RAB an acid suppressing agent is selected as drug candidate for embodiment with DIC to reduce its gastroirritant effects.

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Long acting DIC preparation were reported as rapid release component and sustained release [SR] component with eudragit derivatives and ethyl cellulose polymer coatings [6,7]. The matrix formulations of DIC are also reported using methyl-hydroxy propyl cellulose, Natrosol™ as SR polymer [8]. There is no reported fixed dose combination of diclofenac sodium and rabeprazole sodium.

The objective of present study was to formulate combined formulation of DIC [sustained release-SR] and RAB [enteric coated-EC]. The DIC [SR] was desired to sustain its drug release over 24 hours. The RAB requires enteric coating since it is degraded in stomach by gastric acid [9].

2. MATERIALS AND METHODS:

Diclofenac sodium [Glenmark Ltd., Nasik], Rabeprazole sodium [Wockhardt Ltd., Aurangabad], Xanthan Gum [Shreya Biotech Ltd., Aurangabad], Eudragit S100 [Evonik Degussa Ltd., Mumbai], Instacoat Universal [Instacoat Ltd., Mumbai], MCC PH101 [Mapple syrups Ltd., Pune], PVP K30 [ICPA Ltd., Ankaleshwar], Magnesium stearate [Concept Pharm. Ltd., Aurangabad] were obtained as generous gift sample. All other chemical were of reagent grade.

2.1. Formulation of DIC SR Mini-tablets:

Experimental Design:

The formulations were fabricated using 3^2 factorial experimental designs. The independent formulation variables were-A- Xanthan gum [levels-30%, 40%, 50%] and B- PVP K30 [levels-3%, 5%, 7%]. The dependent variables were Q1, Q5, Q10, Q16 and Q24 which were percent drug release at the end of 1 hr, 5 hrs, 16 hrs and 24 hrs respectively.

Preparation of Diclofenac sodium SR mini tablets:

Dose of DIC was calculated for SR formulation extending drug release over 24 hrs [10]. The DIC SR granules were prepared by wet granulation method. All the ingredients were passed through the sieve no. 100. The DIC and MCC PH 101 were mixed thoroughly in mortar and pestle for 5 min. The 50% of xanthan gum in each batch was mixed with above blend thoroughly.

PVP-K30 was dissolved in IPA used as binder for each batch. It was further used as granulating solution for granulation of the prepared blend. The prepared damp mass was passed through the sieve no. 22 to prepare granules. The granules were dried at 60˚C for 1 hour. The granules were mixed with remaining 50% xanthan gum. The blend of these granules and xanthan gum was lubricated with aerosil and magnesium stearate. The two tablets of weight 150 mg for each formula [total wt. 300 mg] were compressed using 6 mm flat faced punches at Labpress rotary tablet compression machine. Formula for each batch is in reported table 1.

2.2. Formulation of Rabeprazole sodium Enteric coated Minitablets:

The RAB min-tablets were prepared by direct compression method. All ingredients as reported in formula [table 2] were passed through sieve number 100 separately. All ingredients except the RAB, aerosil and magnesium stearate were mixed thoroughly for 5 min. in beaker wrapped with aluminum foil. Then RAB was mixed with the above blend and mixed thoroughly. Then dry blend was lubricated with magnesium stearate and aerosil. The die fill weight was adjusted to 150 mg. The dry blend was compressed at rotary tablet compression machine with 6 mm concave punches. The sodium carbonate was used as alkalizing agent, lactose and MCC PH101 were used as diluents. PVP K30 was used as binder. Magnesium stearate and aerosil were used as lubricants.

Seal Coating:

The RAB min-tablets were seal coated with HPMC-E5 and titanium dioxide based coating material Instacoat universal® for the reason mentioned above. The coating material [5% w/v] was dispersed in Dichloromethane: IPA mixture [35:60]. Carminosine dye was used in required quantity as colorant. The coating was applied to tablets with using R & D pan coater. The inlet temperature was 35 ˚C and speed of pan was 30 rpm. The tablets were coated to 2% weight gain.

Enteric Coating:

The enteric coating of seal coated RAB mini-tablets was carried out by Eudragit S100. The enteric polymer [6% w/v] was dissolved in IPA. The solution was plasticized with propylene glycol [2% v/v] and lubricated with talc [2% w/v]. The volume was made upto 100% with IPA. The coating was applied with R&D pan coater to achieve 5%, 10% and 15% wt gain. The pan speed was 30 rpm and inlet temperature was 35˚C.

2.3. Evaluation of DIC SR minitablets

Hardness and Friability:

Hardness was determined with Monsanto hardness tester [n=3]. Friability was tested with Roche friabilator [V-scientific] with preweighed sample.

Uniformity of weight:

Uniformity of weight test was carried out on randomly selected 20 tablets from each batch [11].

Drug Content:

Randomly selected 6 DIC [SR] mini-tablets were crushed and powder equivalent to 120 mg of DIC was dissolved in 100 ml of alkaline borate buffer I.P. [pH 8] in triplicate. Solutions were filtered through Whatmann filter paper No. 42 and concentration of DIC in filtrate was analyzed at 276 nm by using U.V. spectrophotometer [Shimadzu Pharm Spec 100].

Randomly selected 3 RAB [EC] tablets were crushed and powder equivalent 20 mg of RAB was dissolved in 50 ml of alkaline borate buffer in a centrifuge tube wrapped with aluminum foil. 20 ml of 0.5M NaOH was added to it and centrifuged at 10°C with 3500 rpm for 10 min. The supernatant solution was filtered from Whattman's filter paper No. 42 and solutions were analyzed at 284 nm by using U.V. spectrophotometer.

Drug Release Studies:

Drug release study was carried out using USP dissolution app. type I. The study for DIC SR tablets was performed using 900 ml alkaline borate buffer I.P. of pH 8 at 100 rpm at 37±0.5°C for 24 hrs intrpilicate. Aliquots [5 ml] of dissolution medium were withdrawn at an interval of 1 hr, 2hrs, 3hrs, 4 hrs, 5 hrs, 8hrs, 10hrs, 12hrs, 16hrs and 24hrs. The withdrawn samples were replaced with fresh dissolution medium to maintain sink. The samples were filtered through Whatmann filter paper No. 42 and concentration of DIC in each sample was analyzed at 276 nm. The study was carried in triplicate. The drug release was calculated by PCP Disso® software.

The study for RAB [EC] was performed using 900 ml 0.1 N HCL for 2 hrs followed by 900 ml alkaline borate buffer I.P. of pH 8 at 100 rpm. The temperature of medium was maintained at 37±0.5°C. The tablets were removed at interval of 2 hr and drug content was determined by same way given above in drug content study. Aliquots [5 ml] of dissolution medium were withdrawn from another set of tablets at intervals of 2 and 3 hrs interval and filtered through Whatmann filter paper No. 42. Filtrate was analyzed by U.V. spectrophotometer at 284 nm. The study was carried in triplicate.

2.4. Preparation of Combined Dosage Form of DIC [SR] and RAB [EC] its Drug Release Study

The optimum batches were selected from developed formulation of DIC [SR] and RAB [EC]. The two mini-tablets from batch EF4 of DIC [SR] and one mini-tablet of RAB [EC] were filled in a capsule shell [Size 0] to form caplet. The drug release of DIC and RAB was performed in alkaline borate buffer [pH 8]. The bowels of dissolution apparatus were wrapped with aluminum foil to protect the drug released in media from light. 5 ml of aliquots of drug samples were removed at intervals of 1 hr, 2hr, 5 hrs, 10 hrs, 16 hrs and 24 hrs. The samples were filtered through Whattman filter paper no.42 in amber colored vials. The aliquot samples were analyzed by RP-HPLC with previously reported method [12]. Another set of caplet was subjected drug release in 0.1 N HCl to confirm there is no release or negligible release of RAB in acid stage for two hours.

The drug release of caplets was also studied separately in 0.1 N HCl for 2 hrs to confirm no or acceptable drug release in acid stage. The tablets from the acid medium were removed at the end of 2 hrs and the drug content of tablets was determined to confirm no or acceptable level [10%] of drug release in 0.1 N HCl.

3. RESULT AND DISCUSSION

Ingredients	EX1	EX2	EX3	EX4	EX5	EX6	EX7	EX8	EX9
DIC	120	120	120	120	120	120	120	120	120
Xanthan gum	90	90	90	120	120	120	150	150	150
PVP K30	9	15	21	9	15	21	9	15	21
MCC PH101	72	66	60	42	36	30	12	6	---
Aerosil	6	6	6	6	6	6	6	6	6
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total Wt.	300	300	300	300	300	300	300	300	300

TABLE 1. Formulae for DIC SR Mini-Tablets

The hardness of DIC [SR] tablets was 6.33 to 7.5 Kg/Cm^2 while that of RAB [EC] tablets was within limits of 3.33 to 4.0 Kg/Cm^2. Friability of both tablets was less than 0.5%. The hardness and friability of tablets was sufficient for handling and transportation. The percent weight variation of all tablets was less than 7.5% which complies with weight variation test I.P. The drug content of tablets was controlled within 90 to110% of stated drug content indicating drug content uniformity.

Ingredients	Quantity
Rabeprazole sodium	20 mg
Sodium carbonate	20 mg
Lactose	37.5 mg
MCC PH 101	60.5 mg
PVP K30	7.5 mg
Magnesium stearate	1.5 mg
Aerosil	3.0 mg
Total Weight	150 mg

TABLE 2. Formula of rabeprazole mini-tablets

The drug release profiles of all batches of DIC [SR] mini-tablets were of obtained from calculations by PCP Disso® software and reported in graphical representation below

PVP K30 was used as binder in the formulations, it was found to increase the drug release 24 hrs at 30% concentration of xanthan gum with increasing concentrations of PVP K30. This increasing drug release with increasing concentration of PVP K30 may be attributed to its hydrophilic nature. The increasing concentrations of soluble polymer i.e. PVP K30 may

increase the drug release by its dissolution in the matrix. dissolution media by forming pores or capillaries in the

Batch/ Model	Zero Order	First Order	Matrix	Korsmeyer Peppas	Hixon Crowell	N	K
EF1	**0.9988**	-0.9758	-0.9758	0.9971	-0.0547	0.7188	17.7636
EF2	**0.9976**	-0.979	0.9903	0.9961	-0.9907	0.6751	19.3811
EF3	0.9846	-0.9965	**0.9973**	0.9962	-0.9936	0.6809	21.066
EF4	0.9906	-0.9866	0.9883	**0.9931**	-0.9905	0.6448	16.9496
EF5	**0.9966**	-0.9763	0.9831	0.9938	-0.9848	0.8299	12.5378
EF6	**0.9976**	-0.9641	0.9862	0.9955	-0.9801	0.8427	11.5056
EF7	0.9983	-0.9921	0.9942	**0.999**	-0.9975	0.696	16.4738
EF8	0.9941	-0.9929	0.9917	**0.9961**	-0.9959	0.7101	15.361
EF9	**0.9996**	-0.9893	0.9914	0.9982	-0.996	0.7254	15.5423

Table 3. Drug release kinetics of factorial batches

Time Point	Equation for % drug release	r^2
01 hr	Q_{1hr}=14.34-1.60A+0.14B-0.69AB+3.45A^2+-0.048B^2	0.9904
05 hrs	Q_{5hrs} = 44.45-4.17A-0.43B-1.00AB+7.89 A^2+1.50 B^2	0.8860
10 hrs	$Q_{10\ hrs}$ = 84.12-3.44A+2.66B-1.22AB+4.72 A^2+1.88 B^2	0.5712
16 hrs	$Q_{16\ hrs}$ = 95.04-1.81A+ 0.17B- 1.03AB+ 6.51 A^2 + 0.057 B^2	0.9722
24 hrs	$Q_{24\ hrs}$ = 99.78-2.00A + 1.08B - 1.78AB + 3.72A^2 + 1.63B^2	0.9937

Table 4. Equations for percent drug release from DIC SR tablets

Time [hrs]	DIC Release from caplets [EF4]	DIC Release from tablets [EF4]	Required % drug release as per USP
1	14.60 ± 3.43	14.51 ± 3.65	15-35%
2	17.78 ±10.71	25.47 ± 4.77	Not specified
5	57.59 ± 7.24	49.213±7.08	45-65%
10	85.71 ± 11.60	81.287 ± 8.15	65-85%
16	94.77 ± 4.29	94.879 ± 4.80	75-95%
24	101.72 ± 5.61	100.368 ± 6.63	Not less than 80%

Table 5. Comparative release of DIC tablets and caplets

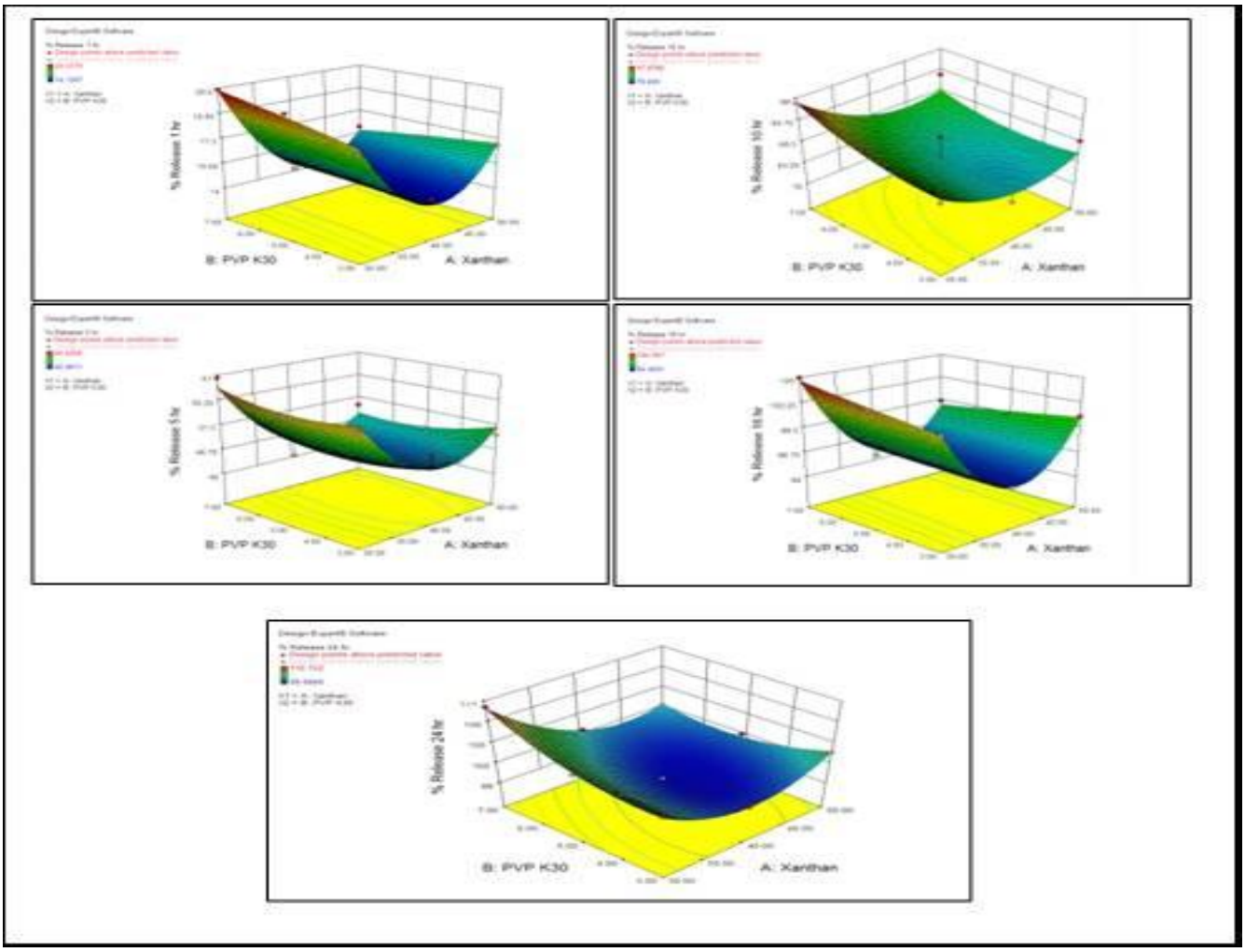

Figure 1: Response surface plots of diclofenac sodium release at 1, 5 10, 16 and 24 hours.

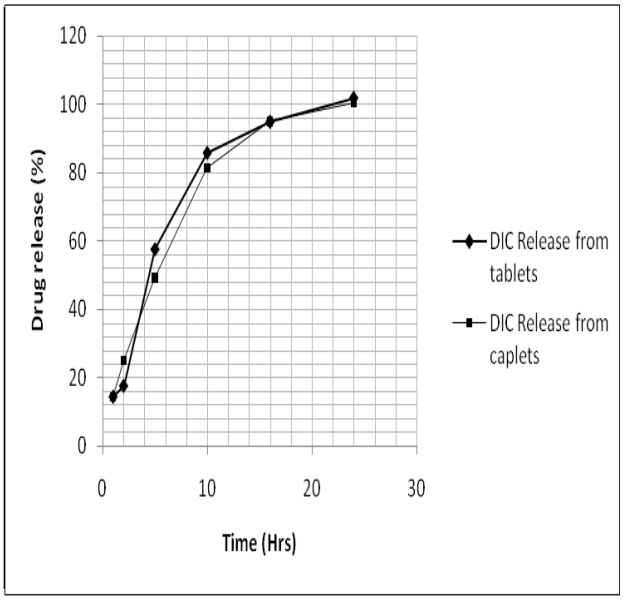

Figure 2: Drug release of DIC from batch EF4 tablets and caplets

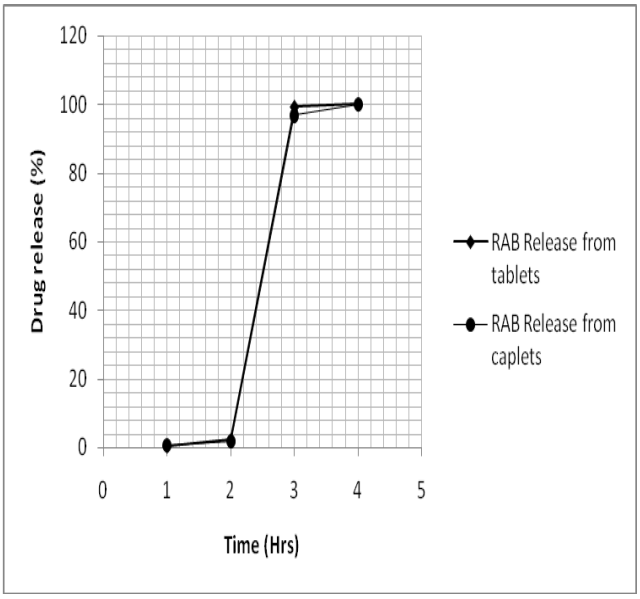

Figure 3: Drug release of RAB from batch F1 tablets and caplets

The drug release in batches with 30% and 50% concentrations of xanthan gum shows the comparable

drug release at 24 hrs. The drug release was found decrease further at 40% concentration of xanthan gum. Increasing further the concentration of xanthan gum to 50% does not retard the drug the drug release further at 24 hrs but, increases the drug release. There was no significant difference in the drug release at the end of 24 hrs in batches EF4 to EF9. The U-shaped response surface plots were observed for drug release pattern at each time point. There was no significant difference in the drug release in batches with same concentration of xanthan gum. But variation in the release pattern was observed with variation in the xanthan gum concentration. The variations observed only at lower concentration i.e. 30% concentration of xanthan gum with variation in PVP K30 concentration but, not at 40% and 50% concentrations of xanthan gum. Hence, it was concluded that PVP K30 does not contribute significantly to the drug release from the matrix at higher concentrations of xanthan gum, but it has significant effect at 30% xanthan gum level.

The drug release kinetic data showed that the batches EF1, EF2, EF5, EF6 and EF9 follows the zero order drug release kinetics, batches EF4, EF7 and EF8 follows Korsmeyer Peppa's model while batch EF3 follows matrix drug release model [Table 4]. The drug release rate is rapid initially followed by progressively slow drug release through the matrix. The initial rapid drug release may be attributed to slower hydration of xanthan gum in a matrix that would result in thicker hydrated layers owing to greater penetration of dissolution medium. This layer will remain intact once the swelling of dissolution medium occurs. Due to gelation of xanthan with time, it would affect to extend the diffusional path length in a matrix. The drug release takes place by the initial diffusion followed by erosion, for the drugs with low solubility which is dominant mechanism in the zero order drug release.

The experimental design methodology systemically exploited for optimization of excipients for desired drug release pattern from matrix. A 3^2 full factorial design was used for the study and the 2 factors were evaluated at 3 levels. Xanthan gum [A] and binder PVP K30 [B] in DIC [SR] tablets, with aim identifying most significant factor in drug release and their best level are established for optimizing considered experimental responses. The swelling property of xanthan gum retards the drug release rate of DIC from matrix.

The responses under study were percent drug release at 1hr [Q1], 5 hrs [Q5], 10 hrs [Q10], 16 hrs [Q16] and 24 hrs [Q24]. The response data was analyzed by using Stat Ease Design Expert 7.1.4 software. The software gives statistical analysis of data with general equation-

$$Y=b_0+b_1A+b_2B+b_{12}AB+b_{11}A^2+b_{22}B^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i [b_1,b_2,,b_{12},b_{11} and b_{22}] is the estimated coefficient for corresponding factor X_i [A, B, AB, A^2, and B^2] which represents the average results of changing one factor at a time from its low to high value. The interaction term [AB] depicts the changes in the response when two factors are simultaneously changed. The polynomial terms [A^2 and B^2] are included to investigate nonlinearity.

The final equations in terms of coded values of factors and actual values of factor obtained from software Design Expert® were given below in table 5 by which effects of variables can study. The regression coefficient values indicate validation of the model fitting. The regression coefficient was high indicating the adequate fitting of the quadratic model for response $Q_{1hr,}$ $Q_{5hrs,}$ Q_{10hrs}, Q_{16hrs} and Q_{24hrs}. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and mathematical sign it carries; i.e. positive or negative. If the terms in the equation are positive it contribute positively to the response similarly if the terms is negative it contribute negatively to the response.

The negative coefficient of independent factor xanthan gum shows that it has negative effect on drug release i.e. retardation of the drug release at all response points and it is a significant variable in the drug release. However, the positive coefficient of PVP K30 in equations of Q_{1hr}, Q_{16hrs} and Q_{24hrs} and negative coefficient of PVP K30 in equations of $Q_{5hrs,}$ Q_{10hrs} indicates insignificance of independent variable.

The analysis of variance study of the data also showed same results revealing the xanthan gum as significant variable [P value <0.5] at all response points except response point 10 hrs, while the PVP K30 was insignificant variable at all response point except response point of 24hrs. It again indicates the significance of xanthan gum in the drug release from the developed matrix formulation of DIC.

The 3-D surface plots were constructed from quadratic model obtained from the regression analysis through Design Expert® in which the responses were represented by curvature surface as a function of independent variables as shown in figure 1. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots used to observe the response's dependence on the input variables to predict this response over the whole of the domain, and possibly also at its periphery [13]. The relationship between the response and the independent variables is shown by graphical 3D plots which aid in visual analysis of the data. The information

which is interpreted from equations was also obtained from graphical 3D plots.

Enteric coated tablets were of RAB were evaluated for different evaluation parameters of tablets. The enteric coated tablets were off pink in color, circular and concave faced with rough surface texture.

The seal coating of RAB tablets was carried out by using Instacoat Universal®, HPMC and titanium dioxide based coating material. The seal coating was applied to the tablets to achieve 2% wt. gain. The polymer used for enteric coating was Eudragit S100.The enteric coating was applied to achieve 5%, 10% and 15% weight gain.

The weight variation test of enteric coated tablets showed that weight of individual tablet was within limits specified in I.P. There was no tablet outside the ±7.5% weight variation. The drug content RAB [EC] tablet showed that the drug was stable during the compression and coating process.

The drug release study of enteric coated tablets was carried out by using 0.1N HCl for 2 hrs and alkaline borate buffer [pH 8] was used for further study. The alkaline borate buffer [pH 8] and 0.5N NaOH were used for drug release study as RAB shown stability at pH 8 and its stability further improved with addition of 0.5N NaOH solution.

The drug release of RAB in acid stage was not more than 2%. The batch F1 showed rapid release in pH 8. The batch F2 and F3 requires more 3 hours for drug release. The drug release was not complete in 4 hrs from batch F3. Hence, the batch F1 was selected as optimum batch. The drug release of DIC [SR] and RAB [EC] from optimum batches was comparable from tablets and caplets. DIC and RAB from combined dosage form [caplet] showed the optimum profile drug release. The drug release pattern of DIC and RAB from caplets matches with optimum batches EF4 of DIC [SR] tablet and F1 of RAB [EC] tablet. The drug release from DIC SR minitablet and DIC SR caplets complies to specification for Diclofenac sodium extended release tablet USP as shown in table 5. The drug release of DIC and RAB from the caplets was matches with release patterns in previous studies reported as above for individual minitablets [figures 2 and 3]. The bowels of dissolution apparatus were wrapped with aluminum foil and amber color vial were used for sample collection because RAB is light sensitive drug that degrades on exposure of light. The RP-HPLC enabled the simultaneous analysis of drug release from the caplets. The matching drug release profile of DIC and RAB from minitablets and caplets showed success of novel and simple caplet, a combined dosage form with potential of its commercial extrapolation.

4. CONCLUSION

The batch EF4 of DIC [SR] containing 40% of xanthan gum and 3% PVP K30 was selected as optimum batch as its drug release pattern complies with USP release profile. The enteric coated batches of RAB showed optimal drug release in the buffer stage. The batch F1 with 5% weight gain of enteric coating was selected as optimum batch which gives required drug release in buffer stage and not more than 2% drug release in acid stage. The formulations of RAB [EC] and DIC [SR] and minitablets can be assembled in caplet to overcome side effects of later.

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Conflict of Interest: None Declared

