



OPTIMIZATION OF DICLOFENAC SR TABLET FOR MULATION BY FACTORIAL DESIGN

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ABSTRACT

The objective of the study is to design diclofenac SR tablets employing a combination of HPMC K 100 M (hydrophilic polymer) and ethyl cellulose (lipophilic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized by 2^2 - factorial design. Diclofenac SR tablets were formulated employing the selected combinations of HPMC (Factor A) and EC (Factor B) as per 2^2 - factorial study and prepared by wet granulation method. The SR tablets were evaluated for drug release kinetics and mechanism. For optimization, time for 50 % release (T_{50}) was taken as response (Y) and the percent of HPMC as X_1 and percent of EC as X_2 . The polynomial equation describing the relationship between the response Y and the variables X_1 and X_2 based on the observed data was worked out.

Diclofenac release from the matrix tablets prepared employing HPMC K 100 M (Factor A) and EC (Factor B) as per 2^2 factorial design was slow and spread over longer period of time up to 12 h. The release depended on the composition of the matrix tablet. Diclofenac release from formulations (F_a , F_b , and F_{ab}) was slow and spread over 10-12 h. Drug release from these tablets was diffusion controlled. Non fickian diffusion was the drug release mechanism. ANOVA indicated that the individual main and combined effects of the two factors involved (HPMC and EC) in influencing the drug release rates are highly significant ($P < 0.01$).

The polynomial equation describing the relationship between the response Y (T_{50}) and the variables X_1 (% HPMC) and X_2 (% EC) based on the observed data was found to be $Y = 2.95 + 1.05 X_1 - 0.25 X_2 - 1.75 (X_1 X_2)$. Based on the above polynomial equation the optimized diclofenac SR tablets with a T_{50} of 4 hours could be formulated employing 50 % HPMC and 5.5 % ethyl cellulose as release retarding polymers. The optimized SR formulation prepared gave slow release of diclofenac over 12 h with a T_{50} of 4 h indicating validity of the optimisation technique employed. Diclofenac release from the optimized SR formulation was diffusion controlled and release was by non-fickian (anomalous) diffusion mechanism. Based on pharmacokinetics, diclofenac SR tablets for b.i.d administration should contain a total dose of 100 mg of diclofenac and the desired release rate (K_0) is 8.66 mg/h. The drug release rate of optimised SR tablets formulated was found to be 8.54 mg/h, which is very close to the theoretical desired release rate. Hence the optimised formulation is considered as the best diclofenac SR formulation developed.

Keywords: Optimization, Factorial Design, Diclofenac, Sustained Release.

INTRODUCTION

Controlled release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue.

Drug release from these systems should be at a desired rate, predictable and reproducible^{1,2}.

Polymers which are used as release-retarding materials in the design of Controlled release drug delivery systems play a vital role in controlling the delivery of drug from the systems. The success of Controlled drug delivery systems depends on how well the polymer regulates the release of drug from the system. A wide range of polymers and other release retarding polymers are available.

Formulation and manufacture of SR matrix tablets is a least complicated approach widely used in industry for obtaining oral controlled release. Matrix tablet formulation needs an

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efficient release retarding material which plays a critical role in regulating drug release from matrix tablets. The objective of the study is to design diclofenac SR tablets employing a combination of HPMC K 100 M (hydrophilic polymer) and ethyl cellulose (lipophilic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized³ by 2^2 -factorial design.

Diclofenac sodium is a widely used non-steroidal anti-inflammatory analgesic and antipyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half life⁴ of 2.0 h. The drug also causes⁵ gastro intestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

EXPERIMENTAL

Materials:

Diclofenac sodium was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. HPMC K100M, ethyl cellulose (500 cps), talc, magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods:

Estimation of Diclofenac:

An UV spectrophotometric method based on the measurement of absorbance at 276 nm in phosphate buffer of pH 7.2 was used for the estimation of diclofenac. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. Low RSD values (less than 1.96 %) ensured reproducibility of the method. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85 % and 1.45 % respectively. No interference by excipients used in the study was observed.

Formulation of Diclofenac SR Tablets:

Diclofenac SR tablet formulation was optimized by 2^2 – factorial design. In the 2^2 – factorial design the two levels of HPMC are 5 % and 50 % and the two levels of ethyl cellulose are 1 % and 10 %. Diclofenac SR tablets were formulated employing the selected combinations of HPMC and EC as per 2^2 – factorial study.

Preparation of Diclofenac SR Tablets:

The SR tablets were prepared by wet granulation method as per the formulae given in Table 1. The required quantities of diclofenac, HPMC K100M and ethyl cellulose were thoroughly mixed in a dry mortar by following geometric dilution technique. The blend of ingredients were granulated with a solvent blend of alcohol-water (1:1) to form a dough mass. The wet mass was pressed through mesh no 12 to obtain wet granules. The wet granules were dried at 70°C for 1 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants talc and magnesium stearate were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 8-station tablet punching machine (Karnavathi RimekMinipress II) to a hardness of 8-9 Kg/cm².

Evaluation of Tablets:

Diclofenac tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. The hardness of prepared tablets were determined by using Monsanto hardness tester and measured in terms of kg/cm². The friability of the tablets were measured in a Roche friabilator using the formula,

$$\text{Friability} = \frac{[(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100}{}$$

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid

Drug Content:

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of diclofenac sodium was taken into 100 ml volumetric flask, dissolved in phosphate buffer

of pH 7.2 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 7.2 and assayed for diclofenac at 276 nm.

Dissolution Rate Study:

Dissolution rate of diclofenac SR tablets prepared was studied in phosphate buffer of pH 7.2 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for diclofenac sodium at 276 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn. Each dissolution experiment was run in triplicate (n=3).

Analysis of Release Data

Drug release data were analysed as per zero order, first order, Higuchi⁶ and Korsmeyer-Peppas⁷ equation kinetic models to assess the release kinetics and mechanism. Release rates were subjected to ANOVA of 2^2 factorial design to find out the significance of the effects of the two factors involved i.e., HPMC K 100 M (Factor A) and ethyl cellulose (Factor B).

RESULTS AND DISCUSSION

Formulation and manufacture of SR matrix tablets is a least complicated approach widely used in industry for obtaining oral controlled release. Matrix tablet formulation needs an efficient release retarding material which plays a critical role in regulating drug release from matrix tablets. The objective of the study is to design diclofenac SR tablets employing a combination of HPMC K 100 M (hydrophilic polymer) and ethyl cellulose (lipophilic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized by 2^2 – factorial design

Optimization of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain

prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis.

The application of formulation optimization techniques is relatively new to the practice of pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

For optimizing diclofenac SR tablet formulation employing HPMC and EC, a 2^2 factorial design was used. In the 2^2 -factorial design the two levels of HPMC are 5 % and 50 % and the two levels of ethyl cellulose are 1 % and 10 %. Diclofenac SR tablets were formulated employing the selected combinations of HPMC and EC as per 2^2 -factorial study. The SR tablets were prepared by wet granulation method as per the formulae given in Table.1 and were evaluated for drug release kinetics and mechanism.

The hardness of the matrix tablets prepared was in the range of 8-9 kg/cm². Friability of the tablets was less than 0.95% in all the case. Drug content was within 100±3% of the labelled claim. The tablets were non disintegrating in 0.1N HCl and phosphate buffer of pH 7.2 and as such suitable for oral sustained release. Diclofenac release for the matrix tablets prepared as per 2^2 was studied in phosphate buffer of pH 7.2. The drug release profiles are shown in Figs 1.

Diclofenac release from all the matrix tablets was slow and spread over longer period of time up to 12 h. The release depended on the composition of the matrix tablet. Release data were analyzed as per Zero order, First order, Higuchi and Korsmeyer-Peppas equation model to assess the release kinetics and mechanism.

Diclofenac release from the formulation F_1 was very rapid and completed in 2 h. Drug release from formulation F_1 obeyed first order kinetics. The release exponent 'n' in Korsmeyer-Peppas equation was 0.16 for this formulation indicating Fickian diffusion as the release mechanism. Diclofenac release from formulations (F_a , F_b , and F_{ab}) was slow and spread over 10-12 h. Release data of these formulations obeyed Higuchi, Korsmeyer-Peppas equation models.

Linear Higuchi plots indicated diffusion controlled drug release from all the SR tablets prepared. Release exponent 'n' was above 0.45 with these formulations indicating non Fickian diffusion as the drug release mechanism. Release rates (K_1) were subjected to ANOVA to find out the significance of the individual and combined effects of the two factors (HPMC and EC) on the drug release rates of matrix tablets. Results of ANOVA (Table 2) indicated that the individual main and combined effects of the factors involved in influencing the drug release rates are highly significant ($P < 0.01$).

Optimization of Diclofenac SR Tablet Formulation

For optimization, time for 50 % release (T_{50}) was taken as response (Y) and the percent of HPMC as X_1 and percent of EC as X_2 . The polynomial equation describing the relationship between the response Y and the variables X_1 and X_2 based on the observed data was found to be

$$Y = 2.95 + 1.05 X_1 - 0.25 X_2 - 1.75 (X_1 X_2)$$

Based on the above polynomial equation the optimized diclofenac SR tablets with a T_{50} of 4 hours could be formulated employing 50 % HPMC and 5.5 % ethyl cellulose as release retarding polymers. To verify, diclofenac SR tablets were formulated employing the optimized concentrations of HPMC and EC. The formula of optimised SR tablets was given in Table 1. The optimised formulation was also prepared by wet granulation method.

The optimized SR formulation prepared gave slow release of diclofenac over 12 h (Fig 5) with a T_{50} of 4 h indicating validity of the optimisation technique employed.

Diclofenac release from the optimized SR formulation was diffusion controlled and release was by non-Fickian (anomalous) diffusion mechanism.

Determination of Desired Release Rate (K_0) for the Design of Diclofenac SR Tablets.:

The initial and maintenance doses and desired drug release rate (K_0) for the design of diclofenac SR tablets were estimated based on its pharmacokinetic parameters as follows.

The pharmacokinetic parameters of diclofenac:

Conventional Dose: 25 mg

$t_{1/2} = 2$ h

t_p (time to reach peak concentration) = 1.4 h

$K_{el} = 0.693/2 = 0.3465 \text{ h}^{-1}$

$K_0 = C_{ss} \times V_d \times K_{el} \times 1/F$

Dose = $C_{ss} \times V_d \times 1/F = 25$ mg

$K_0 = \text{Dose} \times K_{el} = 25 \times 0.3465 = 8.66 \text{ mg/h}$

Maintenance Dose = $8.66 \times (12-2) = 86.6$ for b.i.d administration

Corrected Initial Dose = Dose - ($K_0 \times t_p$) = $25 - (8.66 \times 1.4) = 12.876 \text{ mg}$

Total Dose = $12.876 + 86.6 = 99.476 = 100 \text{ mg}$

Hence diclofenac SR tablets for b.i.d administration contain a total dose of 100 mg of diclofenac. The desired release rate (K_0) is 8.66 mg/h.

In the present study diclofenac SR tablets were formulated to contain 100 mg of diclofenac per tablet. The drug release rate of optimised SR tablets formulated was found to be 8.54 mg/h, which is very close to the theoretical desired release rate. Hence the optimised formulation is considered as the best diclofenac SR formulation.

Table 1: Formulae of Diclofenac SR Tablets Prepared as per 2² Factorial Study

S. No	Ingredient (mg / tablet)	Formulation				
		F_1	F_a	F_b	F_{ab}	F_{op}
1	Diclofenac Sodium	100	100	100	100	100
2	HPMC K 100 M	5.0	50	5.0	50	50
3	Ethyl Cellulose	1.0	1.0	10	10	5.50
4	Talc	2.0	2.0	2.0	2.0	2.25
5	Magnesium Stearate	2.0	2.0	2.0	2.0	2.25
	Total weight (mg)	110	155	119	164	160

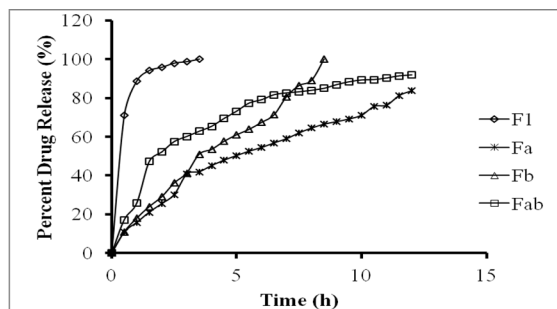


Fig.1: Dissolution Profiles of Diclofenac SR Tablets prepared as per 2^2 Factorial Study

Table 2: ANOVA of Release Rates (K_1) of Diclofenac SR Matrix Tablets prepared as per 2^2 Factorial Design

Source of Variance	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Sum of Squares (MSS)	F- Ratio
Total	11	3.27087	0.297352	
Treatment	3	3.249622	1.083207	407.834
Error	8	0.021248	0.002656	
F a	1	1.261008	1.261008	474.7772
F b	1	0.922965	0.922965	347.502
Fab	1	1.065648	1.065648	401.2229

$F_{0.05}(3, 8) = 4.07$; $F_{0.05}(1, 8) = 5.32$; $F_{0.01}(3, 8) = 7.59$; $F_{0.01}(1, 8) = 11.3$

Table 3: Release Parameters of Diclofenac SR Tablets prepared as per 2^2 Factorial Study

S. No	Formulation	T_{50} (h)	T_{90} (h)	K_0 (mg/hr)	K_1 (hr^{-1})	Release Exponent (n)
1	F ₁	0.4	1.2	51.05	1.591	0.16
2	F _a	6.0	> 12	7.82	0.133	0.63
3	F _b	3.4	8	11.83	0.221	0.76
4	F _{ab}	2.0	11	10.05	0.227	0.47
5	Optimised	4.0	>12	8.54	0.126	0.57

CONCLUSIONS

1. Diclofenac release from the matrix tablets prepared employing HPMC K 100 M (Factor A) and EC (Factor B) as per 2^2 factorial design was slow and spread over longer period of time up to 12 h. The release depended on the composition of the matrix tablet.
2. Diclofenac release from formulations (F_a, F_b, and F_{ab}) was slow and spread over 10-12 h. Drug release from these tablets was diffusion controlled. Non

fickian diffusion was the drug release mechanism.

3. ANOVA indicated that the individual main and combined effects of the two factors involved (HPMC and EC) in influencing the drug release rates are highly significant ($P < 0.01$).
4. The polynomial equation describing the relationship between the response Y (T_{50}) and the variables X_1 (% HPMC) and X_2 (% EC) based on the observed data was found to be
5. $Y = 2.95 + 1.05 X_1 - 0.25 X_2 - 1.75 (X_1 X_2)$
6. Based on the above polynomial equation the optimized diclofenac SR tablets with a T_{50} of 4 hours could be formulated employing 50 % HPMC and 5.5 % ethyl cellulose as release retarding polymers.
7. The optimized SR formulation prepared gave slow release of diclofenac over 12 h with a T_{50} of 4 h indicating validity of the optimisation technique employed.
8. Diclofenac release from the optimized SR formulation was diffusion controlled and release was by non-fickian (anomalous) diffusion mechanism.
9. Based on pharmacokinetics, diclofenac SR tablets for b.i.d administration should contain a total dose of 100 mg of diclofenac and the desired release rate (K_0) is 8.66 mg/h.
10. The drug release rate of optimised SR tablets formulated was found to be 8.54 mg/h, which is very close to the theoretical desired release rate.
11. Hence the optimised formulation is considered as the best diclofenac SR formulation developed.

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