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## Formulation development and Optimization of Diclofenac Sodium Extended release Matrix tablets as per USP standards.

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### Original Paper Artículo Original

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### ABSTRACT

**Aim:** To formulate Diclofenac sodium extended release tablets as per the standards given for extended release tablets of Diclofenac sodium in USP.

**Materials and Methods:** The extended release tablets of Diclofenac sodium was prepared by using different concentration of polymers such as hydroxyl propyl methyl cellulose sodium K4M (HPMC K4M) and hydroxyl propyl methyl cellulose sodium K15M (HPMC K15M). The drug polymer interactions were studied by using Fourier transform infrared (FT-IR) spectroscopy. The in vitro drug release and drug release kinetic studies of all the formulations were performed and compared with the marketed product Fenac SR. The optimization done by considering the factors such as drug release limit given as per USP standard, t50% and release exponent ('n' value as per Korsmeyer Peppas).

**Results and Conclusions:** The FT-IR spectroscopy studies revealed that there was no interaction between drug and excipients. The drug release observed that it depends on the concentration and nature of the rate controlling polymers used. The ANOVA studies revealed that the formulations show significant effect in drug release. The optimization studies proved that the formulation containing drug, polymer (HPMC K4M) ratio of 1:1.5 (Formulation M3) is the most satisfactory formulation. The stability studies proved that the formulation is stable.

**KEY WORDS:** Diclofenac sodium, Extended release matrix tablet, Optimization, Drug release kinetics.

### RESUMEN

**Objetivo:** Formular diclofenaco sódico extendido tabletas de liberación como por las normas dadas para las tabletas de liberación prolongada de diclofenaco sódico en USP.

**Materiales y métodos:** las tabletas de liberación prolongada de sodio diclofenaco fue preparado utilizando diferente concentración de polímeros como sódico de celulosa de metilo hidroxilo propilo K4M (HPMC K4M) y sodio de celulosa de hidroxilo propil metil K15M (HPMC K15M). Las interacciones de polímero de drogas se estudiaron utilizando espectroscopia de (FT-IR) infrarroja de transformada de Fourier. La liberación de drogas in vitro y drogas liberación estudios cinéticos de todas las formulaciones fueron realizadas y en comparación con el producto comercializado Sor Fenac La optimización hecha teniendo en cuenta factores tales como límite de liberación de drogas dado por exponente de t50 estándar, % y liberación USP ('n' valor como por Korsmeyer Peppas).

**Resultados y conclusiones:** FT-IR la espectroscopia estudios revelaron que no hubo ninguna interacción entre drogas y excipientes. La liberación de drogas señaló que depende de la concentración y naturaleza de la tasa de control de polímeros utilizados. Los ANOVA los estudios revelaron que las formulaciones muestran un efecto significativo en la liberación de drogas. Los estudios de optimización demostraron que la formulación que contiene drogas, proporción de polímero (HPMC K4M) de 1:1.5 (formulación M3) es la formulación más satisfactoria. Los estudios de estabilidad demostraron que la formulación es estable.

**PALABRAS CLAVE:** diclofenaco sódico, Extended versión matriz tableta, optimización, drogas versión cinética.

## INTRODUCTION

The oral route is the route, most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages<sup>1</sup>. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase the safety margin for high-potency drugs<sup>2</sup>.

Oral controlled release drug delivery system that provides continuous release of drugs with predictable and reproducible kinetics for a predetermined period, either throughout the course of GI transit or by targeting the delivery of a drug near/in a specific region within the GI tract for either a local or systemic action<sup>1</sup>.

In controlled release drug delivery systems, drug release is slower than the intrinsic absorption rate; therefore drug release from the system becomes the apparent rate of absorption. If absorption is slower than distribution, a two compartment model collapses in to a one-compartment model eliminating the pronounced peak obtained with two-compartment model<sup>3</sup>.

In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution<sup>4</sup>.

Diclofenac sodium is a most widely used non-steroidal anti inflammatory drug (NSAID) used for musculoskeletal complaints, especially arthritis (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis), gout attacks, and pain management in case of kidney stones and gallstones. Diclofenac sodium solubility is pH dependent and absorption occurs throughout the intestinal tract. Diclofenac sodium has biological half life of 2 h and it absorbs throughout the intestinal tract. The drug shows linear pharmacokinetics, is suitable for oral controlled release tablets and it would be advantageous to slow down its release in GI tract not only to prolong its therapeutic action but also minimize possible side effects of Diclofenac<sup>5</sup>.

### Materials and Methods

#### Materials:

Diclofenac sodium obtained as a gift sample from Modern pharmaceutical industries Pvt Ltd. Tirur, Hydroxy Propyl Methyl Cellulose K4M (HPMC K4M) & Hydroxy Propyl Methyl Cellulose K 15 M (HPMC K15M) obtained from Colorcon Asia Pvt Ltd. Goa, Magnesium stearate and talc

purchased from Karnataka Fine Chem.

#### Methods:

*Fourier transform infrared (FT-IR) spectroscopy:* Physical mixtures of drug and excipients were prepared to study the compatibility using FT-IR spectroscopy<sup>6</sup>.

*Powder flow properties:* The Angle of repose, Bulk density, Porosity, Carr's index of the drug excipient mixtures for all the formulations were determined officially<sup>7-9</sup>.

*Preparation of matrix tablet of Diclofenac sodium:* Matrix tablets were formulated by direct compression method using the formula as shown in the table 1. Diclofenac sodium, selected polymers were passed through #60 sieves separately and were blended in a mortar with a pestle for 10 min to obtain uniform mixing. This blended powder was lubricated with magnesium stearate and talc. The lubricated powder was compressed in to round tablets with 9 mm standard concave punch using rotary tablet punching machine<sup>10</sup>.

#### Evaluation of matrix tablets:

*Physicochemical parameters:* Diameter and thickness of the matrix tablets were determined by using screw gauge. Hardness and *Friability* were determined using Pfizer hardness tester and Roche Friabilator respectively<sup>7,9</sup>.

*Determination of drug content:* Five tablets were accurately weighed and powdered. A quantity of the powder equivalent to 100 mg of Diclofenac sodium was weighed accurately and extracted in 100 ml methanol by shaking for 20 min. After filtration through whatmann filter paper no.1 and sufficient dilution with methanol, samples were analyzed spectrophotometrically at 283 nm<sup>9,11</sup>.

*In vitro drug release studies:* Drug release studies were carried out using USP dissolution test apparatus (Apparatus I basket type). The dissolution medium was 900 ml of phosphate buffer pH 7.5. The release was performed at  $37 \pm 0.5$  °C, with a rotation speed of 100 rpm. 10 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 276.5 nm. The *in vitro* drug release profile was compared with the marketed product Fenac SR (Company: Ranbaxy, Batch number: 9735448)<sup>12</sup>.

#### Kinetics modeling of drug dissolution profiles

*Zero order release kinetic:* To study the zero order release kinetics the release data was fitted into the Following equation,

$$dQ/dt = K_0$$

Where, 'Q' is the amount of drug release, 'K<sub>0</sub>' is the zero

**Table 1: Master formula of Matrix tablet**

Ingredients/ 1 Tablet	M1(mg)	M2 (mg)	M3(mg)	M4(mg)	M5(mg)	M6(mg)	M7(mg)	M8(mg)
Diclofenac sodium	100							
HPMC K4M	50	100	150	200	-	-	-	-
HPMC K15 M	-	-	-	-	50	100	150	200
Magnesium stearate	2							
Talc	3							

order release rate constant and 't' is the release time<sup>13</sup>.

*First order release kinetic:* To study the first order release kinetics the release rate data are fitted into the following equation.

$$dQ/dt = K_1 Q$$

Where, 'Q' is the fraction of drug release, 'K<sub>1</sub>' is the first order release rate constant and 't' is the release time<sup>13</sup>.

*Higuchi release model:* To study the Higuchi release model the release rate data are fitted into the following equation:

$$Q = K_H t^{1/2}$$

Where, 'Q' is the fraction of drug release, 'K<sub>H</sub>' is the release rate constant and 't' is the release time<sup>13</sup>.

*Koresmeyer and Peppas kinetics:* To study the Koresmeyer and Peppas release kinetics the release rate data was fitted in to following equation:

$$Mt/M_\infty = K_{KP} t^n$$

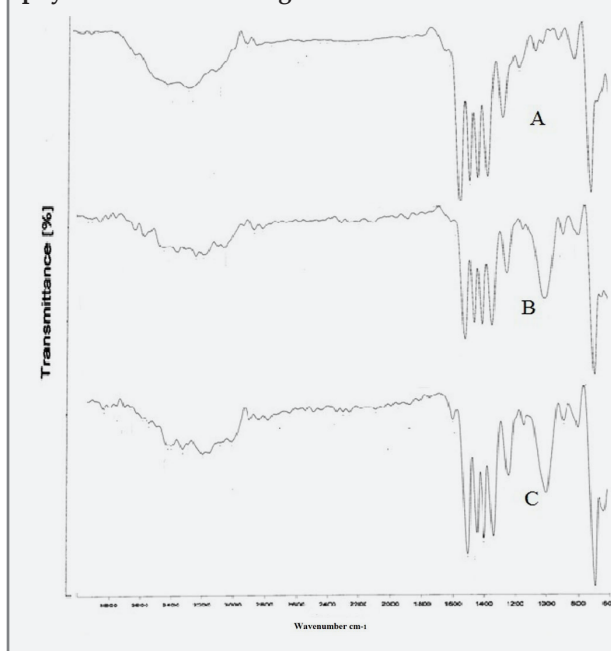
Where, Mt/M<sub>∞</sub> is the fraction of drug release, 'K<sub>KP</sub>' is the release rate constant and 't' is the release time and 'n' is the diffusion exponent related to mechanism of drug release<sup>13</sup>.

*Determination of ANOVA:* The One way ANOVA of the matrix tablets were determined using the Graph pad prism software by considered the *in vitro* drug release profile<sup>7</sup>.

*Optimization technique for Matrix tablets:* The optimized formula of the matrix tablets of Diclofenac sodium were found out by considered the drug release kinetics (Zero order, First order, Higuchi and Peppas), t<sub>50%</sub> and the standard drug release range given in USP for extended release tablets of Diclofenac sodium.

*Stability studies:* The optimized formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The formulation was sealed in an aluminum foil and stored at 30 ± 2 °C, 65 ± 5% RH and at 40 ± 2 °C, 75 ± 5% RH for 2 months. Tablets were periodically removed and evaluated for physical

**Figure 1. FT-IR Spectra of physical mixture of drug and excipientes. A) FT-IR spectra of pure drug diclofenac sodium. B) FT-IR spectra of physical mixture of drug and HPMC K4M. C) FT-IR spectra of physical mixture of drug and HPMC K15M.**



characteristics, *in vitro* drug release<sup>14</sup>.

## RESULTS AND DISCUSSION

*Drug - excipient compatibility studies:* The studies suggest that there is no incompatibility between drug and polymer. Spectra are shown in the figure 1.

*Powder flow properties:* The average values of Angle of Repose, Bulk Density, Tapped Density, Porosity and Compressibility of all the formulations were 28.39±0.31, 0.401±0.002, 0.473±0.004, 16.42±0.23 and 16.56±0.17 respectively. The flowability of the polymers was found to be good according to the flow properties.

*Physicochemical parameters:* The mean values of hardness, friability, thickness, weight and drug content of prepared matrix tablets are recorded in the table 2. The results were found to be within the pharmacopoeial limits.

**Table 2: Physicochemical parameters of developed matrix tablets**

Formulation code	Hardness <sup>a</sup> (kg/cm <sup>2</sup> )	Friability (%)	Thickness <sup>a</sup> (mm)	Weight <sup>a</sup> (mg)	Drug content <sup>a</sup> (%)
M1	7.320±0.1	0.180	3.019±0.03	155.4±1.25	98.93±0.38
M2	7.299±0.1	0.175	3.129±0.03	205.7±1.27	97.97±0.37
M3	7.47±0.09	0.103	4.034±0.02	250.5±1.35	99.85±0.76
M4	7.47±0.09	0.093	4.504±0.02	305.6±1.43	97.89±0.74
M5	7.48±0.091	0.143	3.08±0.02	155.2±1.59	98.92±0.36
M6	7.48±0.099	0.133	3.18±0.03	205.2±2.09	98.94±0.37
M7	7.73±0.096	0.076	4.22±0.04	255.8±1.42	99.45±0.61
M8	7.73±0.094	0.063	4.52±0.05	305.8±1.72	98.45±0.61

a: All values are the mean of three readings ± SD

*In vitro* dissolution studies: Release of drug from the matrix tablets varied according to the type and ratio of matrix-forming polymer. The formulation containing HPMC K4M shows more cumulative drug release rate than HPMC K15M. The results of *in vitro* studies indicated that the rate and extent of drug release decreased significantly ( $p < 0.05$ ) with an increase in polymer concentration, which may be attributed to increase in the density of polymer matrix followed by increasing diffusional path length for drug molecules. In comparison to HPMC K4 tablet, HPMC K15 tablets exhibited significant sustaining effect on drug release. This might be due to more viscosity and high molecular weight of HPMC K15 in addition to its slower rate of erosion and more swelling than HPMC K4. The formulation M1 have maximum cumulative drug release rate and M8 have least cumulative drug release rate in matrix tablets. Results are shown in the figure 2. The *in vitro* drug release from marketed product Fenac SR were compared and observed that the product is not following the USP standards for extended release tablets.

*Drug release kinetic studies:* The *in vitro* release data was fitted to various kinetic models like Higuchi, First order, Zero order and Korsmeyer Peppas. All the formulations

are follows Higuchi release. Results are given in the table 3. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, with regression value of 0.905; whereas the regression value for zero order equation was 0.972, which indicated that drug release from optimized formulation (M3) was independent of drug concentration. In matrix tablets the n value for Peppas model was found to be in between 0.45 and 0.89, indicates that the drug released from the formulation by anomalous (non-Fickians) mechanism.

*ANOVA:* One way ANOVA of matrix tablets the shows all the formulations was significant for response drug release. The sum square and mean square values were 7338 and 2446 respectively. The degree of freedom, F value and p value was 3, 6.492 and 0.0010 respectively. Values of p value less than 0.0500 indicate model terms are significant.

*Optimization:* In the numerical optimization techniques, the desirability approach was used to generate the optimum settings for the formulation. For the optimized formulation, the drug release at 2, 4, 8, 12 h,  $t_{50\%}$ , release exponent (n) were kept in target. The drug release target was kept according to the USP standards (Table 4),  $t_{50\%}$

**Table 3: Summary of drug release kinetics of formulations**

Kinetic profile of formulation	Korsmeyer Peppas		Zero order		First order		Higuchi	
	n	R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	K	R <sup>2</sup>	K <sub>H</sub>	R <sup>2</sup>
M1	0.518	0.980	7.769	0.903	-0.298	0.841	31.33	0.984
M2	0.558	0.985	7.556	0.960	-0.334	0.827	29.55	0.983
M3	0.575	0.982	7.094	0.972	-0.091	0.905	27.48	0.978
M4	0.524	0.992	5.352	0.947	-0.101	0.981	21.14	0.991
M5	0.565	0.993	7.228	0.953	-0.103	0.925	28.50	0.993
M6	0.572	0.992	6.490	0.964	-0.154	0.961	25.36	0.986
M7	0.591	0.983	5.905	0.970	-0.052	0.949	22.74	0.976
M8	0.514	0.938	3.731	0.964	-0.053	0.980	14.45	0.989

R<sup>2</sup>: Correlation coefficient of different models; n: drug release exponents, K<sub>0</sub>: zero order release rate constants, K: First order release rate constant.

**Table 4: Comparison of release profile of USP Diclofenac sodium extended release tablets with optimized formulation<sup>15</sup>.**

Time (h)	Release profile of Diclofenac sodium extended release tablets (USP tolerance limit) (%)	Release profile of optimized formulation M3 (%)
2	Between 22% and 42%	32.22
4	Between 34% and 61%	45.84
8	Between 52% and 82%	70.22
16	Not less than 73%	94.90 in 12 h

as 6h and release exponent (n) as maximum value. It was concluded that the formulation M3 is the most satisfactory formulation.

**Stability study:** During the 2 months storage of formulation M3, values of all parameters like hardness, diameter, thickness, % drug content, friability were checked and found to be almost similar to the initial values. The drug dissolution and diffusion profile were similar to the initial profile. There was not any significant change in any value and also no changes in the physical appearance. So it can be said that formulation is stable.

## CONCLUSIONS

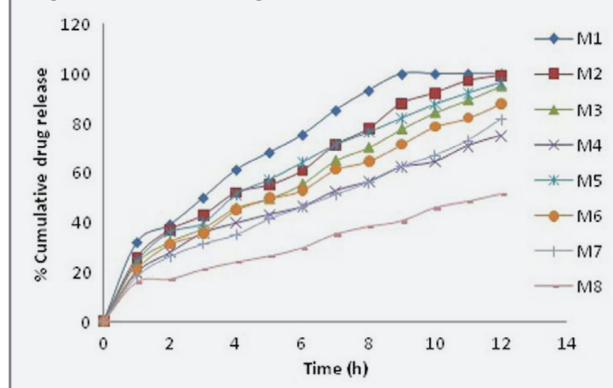
It was concluded that the optimized formulation M3 follows the USP standards for extended release (ER) tablets of Diclofenac sodium (DS) and also the formulation is stable and reproducible. So by manufacturing the ER tablets of DS using formula M3 can reduce the side effects of DS, improve patient compliance by avoiding the multiple dosing and also can improve the therapeutic efficacy of the formulation.

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**Figure 2. In vitro drug release profile of formulations**

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