

Original Article

## RATIONAL DESIGNING OF SUSTAINED RELEASE MATRIX FORMULATION OF ETODOLAC EMPLOYING HYPROMELLOSE, CARBOMER, EUDRAGIT AND POVIDONE

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### ABSTRACT

**Objective:** The existing investigation represents a challenge in formulating etodolac oral controlled-release tablets employing five most prominent hydrophilic release rate retardant polymers like hydroxypropyl methylcellulose (HPMC) grades K100M, K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90 which are non-toxic substances, cost-effective, and easily available.

**Methods:** Utilizing the wet granulation method, employing talc, anhydrous lactose, and magnesium stearate, the batches were formulated. The pre-compression and post-compression characteristics were assessed according to the specified protocols. The formulations were accessed for their ability to release the drug in the simulated gastric media and the obtained results were fitted into various kinetic models to determine the probable drug release mechanism(s). A short-term stability study (for 90 d duration) was also performed.

**Results:** The densities (bulk and tapped) lie in the range of 0.74-0.75 g/cm<sup>3</sup> and 0.84-0.87 g/cm<sup>3</sup>, respectively, representing an excellent pre-compression characteristic. The drug content was found in the range 97.61-99.04%. The most proper *in vitro* drug release was observed for the formulation F6 (101.84%) due to the optimum concentration of carbomer, hypromellose, and povidone combination which retarded the drug release; following the diffusion cum erosion mechanism(s) (called anomalous diffusion) and also illustrated comparable drug release with marketed formulation (Etogesic®-ER 600 mg). The batches did not show any significant changes under accelerated conditions.

**Conclusion:** The judiciously planned fabrication of the matrix formulations possess the ability to decrease the frequency of drug administration to twice-daily along with minimizing the blood level fluctuations, which ultimately leads to enhanced patient compliance and better therapeutic regimens.

**Keywords:** Etodolac, Matrix, Release Mechanism, Sustained, Stability, Tablet

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### INTRODUCTION

Etodolac (ETO) is a biopharmaceutics classification system (BCS) Class-II drug used primarily as non-steroidal anti-inflammatory (NSAID) drugs for treating pain related to arthritis. ETO decreases the synthesis of peripheral prostaglandins which are involved in mediating inflammation. It binds to the upper portion of the cyclooxygenase (COX) enzyme active site and prevents its substrate, arachidonic acid, from entering the active site. It is 5-50 times more selective for COX-2 than COX-1, which makes it therapeutically more efficient in managing arthritis-related pain [1-2]. The drug is having a half-life of 6.4 h and exhibit >99% protein binding, primarily to albumin. The mean apparent volume of distribution of the drug is 390 ml/kg, which represents ETO is extensively metabolized in the liver. Renal elimination remained the chief excretion route for both etodolac and its metabolites (72%). Metabolites found in urine (with percents of the administered dose) includes; unchanged ETO (1%), ETO glucuronide (13%), hydroxylated metabolites (6-, 7-, and 8-OH; 5%), hydroxylated metabolite glucuronides (20%), and unidentified metabolites (33%). Fecal excretion accounts for 16% of its elimination. It is not known whether ETO is excreted in human milk; however, based on its physical-chemical properties, excretion into breast milk is expected [3-4].

At present, several anti-inflammatory drugs for arthritis are currently employed in the management. Yet, it is essential to achieve the therapeutic regimen by maintaining the constant desired systemic concentration of the drug during the treatment period to meet required patient fulfilment. On the other hand, the cost remained a critical factor among the patient population to sustain a long duration of therapy. Probably, the treatment or rather the management involved the entire tenure of patient's life, ultimately causing a financial burden. Therefore, this might be a maiden attempt to design a Generic based development of ETO formulation

which may meet the patient demand by fulfilling the key features of delivering identical bioequivalency, holding high similarity index, and demonstrate quite comparable *in vitro* drug release profiles.

The objectives of the present study includes (1) formulating ETO sustained release matrix tablets using five hydrophilic release rate retardant polymers such as HPMC K100M, HPMC K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90; (2) determining the role of rate controlling agents in the formulation by *in vitro* dissolution studies and determining the pattern of drug release from the matrix formulations using diverse release models; and (3) studying the stability of the fabricated batch under short-term accelerated conditions. This research was done with an intention to fabricate sustained release tablet formulations which will have perspectives of generic medicine.

### MATERIALS AND METHODS

#### Materials

ETO was obtained as a generous gift from Emcure Pharmaceuticals Ltd., Mumbai, India. HPMC K4M and HPMC K100M were obtained from Virgo Pharmaceutical Ltd., Goa, India. Eudragit RS100 was procured from Glenmark Pharmaceutical, Ltd. Nasik, India. Polyvinylpyrrolidone K90, carbopol 934P, lactose, talc, magnesium stearate, potassium dihydrogen phosphate, and isopropyl alcohol were purchased from Molychem Ltd., Mumbai, India. All other procured chemicals were of analytical grade. Etogesic® ER 600 mg (Cadila Pharmaceuticals Ltd.) was purchased from the local pharmacy store located in Nagpur, Maharashtra, India.

#### Instruments

Double-beam Shimadzu® ultraviolet-visible spectrophotometer (Model UV-1800, Kyoto, Japan) was used for the spectroscopic

analysis. The system comprised of a pair of 10 mm path length matched quartz cells and a beam delivering unit of the spectral bandwidth of 1 nm with a wavelength accuracy of  $\pm 0.3$  nm, connected with a computer. Shimadzu® electronic balance (Model AUW220D, Kyoto, Japan) was employed for the weighing of chemicals. Shimadzu® IRAffinity-1S instrument was employed for carrying out the FT-IR analysis. Vernier caliper (Indian caliper, Ambala, India), Pfizer hardness tester (Pfizer, Spacelabs, India), Dissolution test apparatus (Electrolab, India), and Roche friabilator (Electrolab, India) were employed for the evaluation of prepared tablets. Stability chamber (Bio-Technics, India) was used for conducting the accelerated stability studies.

#### Preparation of ETO matrix tablet

For the preparation of formulations, the active ingredient ETO,

polymers and diluents were sifted through sieve #44. Using the wet granulation method, the matrix tablets containing 600 mg of ETO were prepared by mixing all the above ingredients (except lubricants) in a mortar, then add granulating fluid, i.e. isopropyl alcohol and the dry mixture were granulated and uniform was done till it forms uniform granules.

The dried granules were sifted through sieve #22. The wet granules of above step were taken into a rapid air-dryer. Then the wet mass was dried at an inlet temperature of 50 °C and loss on drying (LOD) of the dried granules should not more than 3%. After drying, magnesium stearate was added to dried granules to improve its flow property. The prepared blend was compressed into tablets by using 17 mm punch using 10-station tablet punching machine. Table 1 portrays the complete formulation chart.

**Table 1: Formulation of etodolac matrix tablet**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	600	600	600	600	600	600	600	600	600
HPMC K100M	15	22.5	37.5	15	30	22.5	-	-	-
HPMC K4M	30	45	18.75	-	-	-	-	-	-
Carbopol 974	-	-	-	7.5	10	8.75	-	-	-
Eudragit RS 100	-	-	-	-	-	-	7.5	15	11.25
Polyvinyl pyrrolidone K 90	1.5	7.5	7.5	1.5	3.75	3.75	-	-	-
Anhydrous lactose	53.5	27	38.25	76	58.25	67	92.5	87	90.25
Talc	45	45	45	45	45	45	45	45	45
Magnesium stearate	5	3	3	5	3	5	5	3	3
Isopropyl alcohol	q. s.								

The ingredients are expressed in mg. The average weight of tablet is 750 mg.

#### Drug-interaction studies

The possibility of any such interaction between the drug (ETO) and the five utilized polymers; HPMC K100M, HPMC K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90 was monitored by Fourier transformed infrared (FT-IR) spectroscopy to observe the compatibility and inherent stability of the formulation. Any change in the physical mixture of drug and polymer was reported, which may be interpreted as an interaction [5].

#### Evaluation of granule properties

The final granule blend was characterized by the physical parameters such as bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index. The prepared granules were initially evaluated suitably for their characteristic parameters such as angle of repose (by funnel method), bulk density and tapped density (by cylinder method). The Hausner's ratio was determined by the pharmacopoeia formula [6].

#### Evaluation of tablet characteristics

The fabricated ETO tablets were properly evaluated in terms of their desired attributes of thickness (using Vernier Calipers), weight variation (according to the IP guidelines), hardness (employing Pfizer hardness tester), friability (Roche friability testing apparatus), and content uniformity (by crushing 20 tablets and weighed powder equivalent to 100 mg of ETO and dissolving in 100 ml of alcohol, stirred and filtered; termed as 'Solution A'. 5 ml of the Solution A was further diluted with 10 ml alcohol; termed as 'Solution B'. 1 ml of the Solution B was again diluted with 10 ml alcohol and the absorbance was recorded at 273 nm with the help of UV spectrophotometer) [7].

#### In vitro dissolution studies

The *in vitro* drug release studies for the prepared batches were performed in 900 ml of simulated gastric fluid (dissolution medium having pH 1.2) for 2 h initially using USP 33 (Type II) apparatus, maintained at  $37 \pm 0.5$  °C temperature at a speed of 100 rpm. After 3 h, the dissolution was replaced by phosphate buffer saline media (pH 7.4) and continued for additional 10 h. After every 1 hr, 5 ml of

the sample was withdrawn using a calibrated pipette for the 12 h duration. Consistently, an equivalent amount of fresh dissolution medium was added to maintain the sink conditions. The drug content was determined using UV-visible spectrophotometer at 273 nm [8]. The release studies were executed in triplicate manner. The obtained results were compared with the marketed formulation Etogesic®-ER 600 mg (Cadila Pharmaceuticals Ltd.).

#### Kinetic modelling of drug release

The dissolution profiles of all the batches were fitted to various models such as zero-order (drug release rate is independent of its concentration), first-order (drug release rate is concentration dependent), Higuchi (release of drug from an insoluble matrix as square root of time dependent process), Hixon-Crowell (drug release from systems due to change in the surface area and the diameter of particle), and Korsmeyer and Peppas (drug release till the polymer chains rearrange to equilibrium state) in order to determine the mechanism of drug release from the formulation [9]. Based on the goodness-or fittest, the most appropriate model was selected.

#### Short-term stability study

The optimized batch (F6) was subjected to accelerated stability conditions ( $40 \pm 2$  °C and  $75 \pm 5\%$  RH) for the duration of 90 d. The tablet was packed in an aluminium foil and kept inside a PVC bottle. After the completion of the study, the parameters such as hardness, friability, weight variation, content uniformity, and thickness were determined using pharmacopoeia guidelines [10].

#### Statistical analysis

The statistical analysis applied was a one-way analysis of variance (ANOVA) with least significant difference (LSD) multiple comparison procedures, keeping the statistical probability (P) value of  $< 0.05$  as a significant difference.

#### RESULTS AND DISCUSSION

The tablet fabrication was done employing the biconcave flat punch having a dimension of 17 mm. The produced tablets were detected to be free from any problems like capping, picking, and chipping.

The FTIR spectra for the drug (ETO), polymers (HPMC K100M, HPMC K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90), and drug-polymer blends (ETO-HPMC K100M, ETO-HPMC K4M, ETO-carbopol 934P, ETO-eudragit RS100, and ETO-polyvinyl pyrrolidone K90) were recorded to determine the possible interactions. Predominantly, the drug displayed characteristic peaks at 3583, 3022, 2966, 1740, 1260, 1141  $\text{cm}^{-1}$ , respectively. In the physical mixture with the polymer, no such overlapping peaks were noticed, which confirmed no such drug-polymer interactions. The evaluated granules were observed to be

acceptable as per the limits. The densities (both bulk and tapped) lie in the range of 0.74-0.75  $\text{g}/\text{cm}^3$  and 0.84-0.87  $\text{g}/\text{cm}^3$ , respectively, which represented an excellent packing of the granules. The angle of repose was observed to be  $26^\circ$ - $30^\circ$  for the batches which indicated reasonably satisfactory flow property. The calculated Hausner's ratio and Carr's index were in the order of 1.08-1.14, which may be interpreted as relatively good packing ability. In short, the tablet blend demonstrated fairly good micromeritic attributes essential for exhibiting sustained release characteristics. The pre-compression parameters are shown in table 2.

**Table 2: Evaluation of pre-compression parameters for extended release etodolac matrix tablets**

Formulation	Angle of repose <sup>#</sup> (°)	Bulk density <sup>#</sup> (in g/ml)	Tapped density <sup>#</sup> (in g/ml)	Compressibility <sup>#</sup> Index (in %)	Hausner <sup>#</sup> ratio
F1	29.17±0.52	0.742±0.013	0.848±0.00745	12.42±1.94	1.14±0.025
F2	30.08±0.53	0.76±0.0098	0.862±0.0022	11.7±1.24	1.13±0.017
F3	28.02±0.48	0.763±0.013	0.838±0.0065	8.87±1.75	1.10±0.019
F4	29.15±0.15	0.756±0.014	0.856±0.0051	11.97±0.99	1.13±0.022
F5	26.66±0.53	0.772±0.0074	0.858±0.0056	11.06±1.13	1.11±0.017
F6	27.39±0.34	0.77±0.0062	0.862±0.0058	10.67±0.82	1.12±0.012
F7	30.74±0.47	0.784±0.0037	0.878±0.0036	10.77±0.73	1.12±0.011
F8	28.19±0.30	0.784±0.0031	0.849±0.0045	7.77±0.61	1.08±0.004
F9	29.14±0.65	0.781±0.0055	0.877±0.0065	11.23±1.09	1.12±0.008

# n = 6 (The number of samples are 6)

The evaluation parameters revealed that the prepared matrix tablet batches presented the essential attributes. All the fabricated batches displayed the necessary hardness of more than 5  $\text{kg}/\text{cm}^2$  along with friability value of less than 1%, ultimately representing the required strength and resistibility of the matrix formulations. The Eudragit RS100 and anhydrous lactose combination were found to exhibit a profound role in imparting hardness to the formulation as compared

to HPMC. Similar characteristics were imparted with carbopol 974 and anhydrous lactose combination to the formulations. The drug content was identified to be in the range of 97.61-99.04%.

A weight variation of <1% was observed for the prepared batches, indicating almost uniform drug content in all the ETO formulations. The post-compression parameters are described in table 3.

**Table 3: Evaluation of post-compression parameters for extended release etodolac matrix tablets**

Formulation	Thickness <sup>#</sup> (in mm)	Friability <sup>#</sup> (%)	Hardness <sup>#</sup> ( $\text{kg}/\text{cm}^2$ )	Drug content <sup>#</sup> (%)
F1	5.04±0.11	0.59±0.03	5.2±0.19	98.09±0.51
F2	5.1±0.10	0.64±0.07	5.3±0.08	97.14±0.87
F3	5.06±0.18	0.62±0.06	5.4±0.12	99.04±0.66
F4	5.06±0.11	0.67±0.03	5.7±0.17	96.19±0.92
F5	5.1±0.16	0.54±0.04	5.6±0.11	99.52±0.49
F6	5.02±0.13	0.68±0.08	5.4±0.09	99.04±0.83
F7	5.02±0.18	0.52±0.06	5.3±0.10	96.66±0.76
F8	5.14±0.15	0.63±0.09	5.7±0.07	98.57±0.58
F9	5.12±0.16	0.69±0.06	5.9±0.13	97.61±0.94

# n = 6 (The number of samples are 6)

The majority of the release controlling agent containing formulations displayed a steadily sustained release attribute as compared to conventional dosage forms. The release of drug from the hydrophilic matrix involves a complex interaction between drug dissolution, solubilization, diffusion, and erosion mechanism(s). Formulation F1 showed the maximum drug release within 4 h due to lowest polymer concentration. Formulation F2 demonstrated a low drug release up to 12 h due to the high polymer concentration of HPMC K4M. Formulation F3 consists of a proper ratio of polymers such as HPMC K4M and HPMC K100M which retard the drug release of 90.22% in the duration of 12 h.

Formulation F4 exhibited the cumulative drug release of 102.45% within 5 h. The reason may be the absence of HPMC K4M and low polymeric concentration of povidone (1.5 g). It may be believed that the drug diffuses out of the matrix forming pores from which the solvent molecules entered that leads to a fast dissolution of the drug. From the hypothetical pre-formulation assumption of formulation development based on *in vitro* dissolution and *in vivo* data of innovator drug, the batch does not hold good in maintaining a sustained release attribute and was discarded for further studies.

Formulation F5 presented a similar drug release profile with that of formulation F3, where a low drug release was exhibited up to 12 h due to high polymer concentration (HPMC K100M). The polymer HPMC K100M on contact with aqueous media forms an intense and viscous gel which results in controlled delivery of the drug. The most proper *in vitro* drug release was observed in the formulation F6 (101.84%) due to the optimum concentration of carbomer, hypromellose, and povidone combination which retarded the drug release (fig. 1). The phenomenon of aqueous penetration, swelling of polymer and gel formation, and concurrent actions of drug diffusion and matrix erosion from the formulation were governed by the level of HPMC hydration in the matrix that eventually promotes drug diffusion. On viewing the dissolution chart, it was observed that a burst phenomenon was prevailed in case of formulation F6, in the duration of 3<sup>rd</sup> to 4<sup>th</sup> hr where more than twice the drug was released from the fabricated product. Based on the theoretical release profile of F6, it may be ascertained that the drug release gets released till the polymer chains rearrange to the equilibrium state.

Formulation F7, having the lowest polymer concentration, represented a fast drug release within 5 h, quite similar to that of

formulations F1 and F4. The formulation contained only 7.5 g of eudragit RS100. Formulation F8 offered one of the lowest drug releases up to 12 h. Due to the twice the concentration of polymer eudragit RS100, the drug release was hindered in the intended 12 h duration. The formulation F9 signified analogous release profile with that of formulation F6. The optimized concentration of polymer eudragit RS100 leads to maximum drug release observed by 100.97% within 12 h, owing to rate retardant attributes. Although, it is well known that in any anomalous overlapping phenomenon of diffusion, erosion, and solubilization, all three components are closely associated. It may be an insight that the diffusion and erosion mechanism(s) were dominant in case of formulation F3, F6, and F9 as compared to solubilization.

The marketed formulation Etogesic® ER 600 mg (Cadila Pharmaceuticals Ltd.) demonstrated excellent cumulative drug release profile of 108.44% within 12 h period. The formulations F3, F6, and F9 showed a comparable drug release profile with that of the marketed preparation. The formulation F6 displayed analogous release with that of the marketed product. On the basis of *in vitro* drug release data and also from the similarity factor by considering the bio-waiver conditions, it might be predicted that the batch may exhibit bioequivalent result and may hold the perspective of utility as a Generic product in future. However, based on the available data of *in vitro* dissolution testing, in relation to the innovator drug, an IVIVC might be predicted for the optimized formulation F6 which may be used as a bio-equivalent product. Although, the human volunteer-based study is foremost essential and necessary to

establish such profiles in reality. Table 4 highlights the *in vitro* drug release profile of the fabricated matrix tablet batches and marketed formulation.

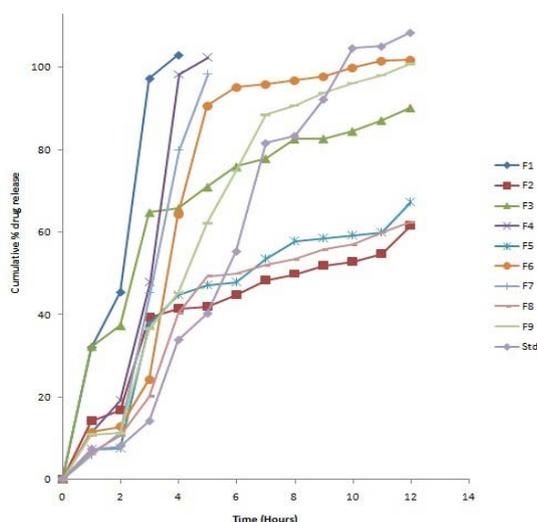
The combination of hydroxypropyl methylcellulose (HPMC) grades K100M, K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90 demonstrated that the release is dependent exclusively on the type and amount. In some formulations, F1, F3, and F7 where at 5 h complete drug release is observed. The optimized formulation F6 comprising of HPMC K100M (22.5 mg), carbopol 974 (8.75 mg), and polyvinylpyrrolidone K 90 (3.75 mg) displayed the highest release of 101.84%. In comparison with the previously reported literature a remarkable difference in the drug release and the pattern was noticed. The ETO tablets fabricated by drug release retardant polymer Kollidon®SR showed 71.67% after 12 h [11]. ETO tablet fabricated with hydroxyl propyl methyl cellulose E-15, E-50, xanthan gum, and guar gum presented 70.81% drug release after 12 h [12]. The ETO matrix tablet containing HPMC K100 LVCR and polyox WSR 303 expressed 81.57% release after 12 h in basic media [13].

Similarly, the formulation prepared by the combination of tamarind xyloglucan, gellan gum, sodium CMC, and xanthan gum exhibited drug release of 84.51% for 12 h [14]. Therefore, while designing twice daily formulation, the fabricated formulation from hydroxypropyl methylcellulose (HPMC) grades K100M, K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90 revealed the best results which is quite comparable with the innovator product brand (108.44%).

**Table 4: *In vitro* drug release profiles of the fabricated batches and comparison with marketed formulation**

Time (h)	Cumulative drug release (%) #										
	Medium	F1	F2	F3	F4	F5	F6	F7	F8	F9	MP
1	pH 1.2	31.99±0.12	14.15±0.51	32.23±0.24	11.43±0.27	7.25±0.18	11.51±0.42	5.94±0.28	6.68±0.09	11.02±0.71	7.35±0.48
2	pH 1.2	45.43±0.33	16.82±0.69	37.33±0.98	19.10±0.40	7.68±0.62	12.75±0.91	11.33±0.70	10.57±0.37	11.27±0.16	8.15±0.88
3	pH 7.4	97.29±0.47	39.22±0.76	64.8±0.56	47.97±0.81	37.68±0.92	24.31±0.68	45.23±0.20	20.21±0.89	36.54±0.86	14.15±0.39
4	pH 7.4	102.98±0.21	41.43±0.60	65.84±0.79	98.30±0.08	44.76±0.26	64.33±0.75	79.83±0.66	40.3±0.26	45.23±0.07	33.86±0.64
5	pH 7.4	-	41.94±0.74	70.98±0.24	102.45±0.23	47.25±0.42	90.64±0.37	98.35±0.50	49.3±0.62	62.3±0.46	40.26±0.57
6	pH 7.4	-	44.89±0.63	75.94±0.34	-	47.99±0.58	95.23±0.06	-	49.98±0.46	74.97±0.14	55.32±0.80
7	pH 7.4	-	48.40±0.15	77.9±0.53	-	53.58±0.49	95.97±0.31	-	52.02±0.82	88.55±0.77	81.59±0.22
8	pH 7.4	-	49.88±0.44	82.67±0.71	-	57.86±0.95	96.95±0.41	-	53.44±0.72	90.82±0.59	83.34±0.25
9	pH 7.4	-	51.92±0.38	82.73±0.87	-	58.54±0.23	97.87±0.45	-	55.82±0.38	93.88±0.67	92.24±0.54
10	pH 7.4	-	52.88±0.17	84.51±0.36	-	59.27±0.88	99.87±0.73	-	56.95±0.22	96.26±0.52	104.65±0.35
11	pH 7.4	-	54.64±0.30	87.14±0.65	-	60.05±0.78	101.66±0.10	-	59.9±0.43	98.22±0.29	105.08±0.32
12	pH 7.4	-	61.61±0.27	90.22±0.72	-	67.38±0.83	101.84±0.19	-	62.45±0.55	100.97±0.61	108.44±0.49

# n = 6 (The number of samples are 6); MP = Marketed Product, Etogesic® ER 600 mg (Cadila Pharmaceuticals Ltd.)



**Fig. 1: Dissolution profile of prepared matrix formulations**

# n = 6 (The number of samples are 6); Std. = Standard Drug, Etogesic® ER 600 mg (Cadila Pharmaceuticals Ltd.); Formulation F9 described the highest and comparable drug release as compared to the marketed formulation.

Fitting the *in vitro* drug release data into zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models helped in determining the probable drug release mechanism from the matrix formulations.

Table 5 explains the values of release exponent (n) of the formulations with the probable release mechanism(s). By applying

the release models for the formulations F3, F6, and F9, it was found that all the formulations followed the Korsmeyer-Peppas model.

The release exponent (n) was found to be more than 0.5 with good linearity which indicated that drug release involved non-Fickian diffusion which closely overlaps with the swelling erosion study.

It was also observed from the release exponent (n) that drug release was governed by multiple processes and can be defined as an anomalous diffusion, where both diffusion and erosion mechanism works.

**Table 5: Kinetic profile of drug release (release exponent, n) for selected formulations**

Batch	Zero-order	Hixson-Crowell	Higuchi plot
F3	0.8827	0.7666	0.9731
F6	0.8953	0.8659	0.9245
F9	0.9595	0.9107	0.9624

The stability study under accelerated conditions of temperature and humidity expressed no as such noticeable alteration in terms of physical appearance, hardness, thickness, drug content, and *in vitro* drug release profile of the optimized formulation. Although change

in drug content (0.28%) was detected after the duration of 90 d, that can be considered within the prescribed limits. It may be concluded that the prepared tablet was stable under accelerated conditions. Table 6 depicts the changes before and after the stability study.

**Table 6: Short-term stability study of optimized formulation (F6)**

Parameter	Controlled sample#	Stability sample#
Appearance	White, circular, uncoated tablet	No change observed
Thickness (mm)	5.02±0.01	5.02±0.02
Hardness (kg/cm <sup>2</sup> )	5.4±0.04	5.3±0.08
Friability (%)	0.68±0.07	0.66±0.03
Drug content (%)	99.04±0.12	98.76±0.18
<i>In vitro</i> drug release % (at 12 h)	101.84±0.43	100.29±0.27

# n = 6 (The number of samples are 6)

## CONCLUSION

The existing investigation represents a challenge in formulating etodolac oral controlled-release tablets employing five most prominent hydrophilic release rate retardant polymers like HPMC K100M, HPMC K4M, carbopol 934P, eudragit RS100, and polyvinylpyrrolidone K90 which are non-toxic substances, cost-effective, and easily available. The judiciously planned fabrication of the matrix formulations possesses the ability to decrease the frequency of drug administration to twice-daily along with minimizing the blood level fluctuations, which ultimately leads to enhanced patient compliance and better therapeutic regimens. From the study, it was perceived that the drug release pattern, the attainment of steady state, and the bio pharmacokinetic profile of the formulation to exhibit sustained release is a function of the type(s) and the content of the polymer(s). The formulation F9 displayed the highest drug release of 100.97%, which is quite comparable with that of marketed formulation. The research outcomes encouraged and opened new avenues for developing sustained release formulations capable of providing twice-daily attribute as "generic medicine". The work additionally bears the perspective in translating the fabricated formulation from lab to commercial level after some regulatory checks.

## AUTHORS CONTRIBUTION

**Nilesh N. Mahajan**, has provided the design, intellectual content, innovations, and protocol for conducting the experiment along with mentorship.

**Pooja Wadhavane**, has majorly performed the experiment in the laboratory.

**Debarshi Kar Mahapatra**, has a minor role in the conducting the experiment in the laboratory, analysis of obtained data, and sincerely authored the article.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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