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Research Article

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Development of Novel Etodolac Matrix Tablet and their Pharmaceutical Characterization

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ABSTRACT

The current work poses a difficulty in producing etodolac oral controlled release tablets using five of the most well-known hydrophilic release rate retardant polymers, including non-toxic materials like HPMC K4M, Carbopol 974, and Eudragit RS100. The batches were created using the wet granulation process. According to the prescribed methods, the pre- and post-compression properties were evaluated. To identify the likely drug release mechanism, the formulations were tested for their capacity to release the drug in the simulated gastric medium. The results were then fitted into several kinetic model(s). The investigation of short-term stability was also carried out. The bulk and tapped densities, which are in the range of 0.85 to 0.86 g/cm^3 and 0.95 to 0.98 g/cm^3, respectively, show an excellent pre-compression feature. The drug concentration was discovered to be between 98.26%-100.15%. The formulation F3 (102.95%) had the maximum *in vitro* drug release because it had the ideal concentration of polymer combination, which delayed the drug release and used the diffusion cum erosion process (s). When matrix formulations are carefully fabricated, the frequency of medication administration may be reduced to twice daily while also reducing blood level variations, which ultimately improves patient compliance and therapy regimens.

Keywords: Etodolac, Formulation Matrix, Tablet, Release, Characterization

INTRODUCTION

Etodolac (ETO) is a non-steroidal anti-inflammatory (NSAID) medication that belongs to the biopharmaceutics classification system (BCS) Class-II and is primarily used to treat arthritic pain. Peripheral prostaglandins, which play a role in modulating inflammation, are produced in less quantity when ETO is present. Arachidonic acid, the enzyme's substrate, cannot enter the active site of the cyclooxygenase (COX) enzyme because of its binding to the top part of the active site. It is significantly more effective in controlling arthritis-related pain because it is 5–50 times more selective for COX-2 than COX-1. The medication exhibits >99% protein binding, mostly to albumin, and has a half-life of 6.4 hours. The drug's average apparent volume of distribution is 390 mL/kg, which indicates that the liver is heavily involved in the metabolism of ETO. Etodolac and its metabolites were still mostly eliminated by the kidneys (72%). Urine metabolites include unmodified ETO (1%), ETO glucuronide (13%), hydroxylated metabolites (6-OH, 7-OH, and 8-OH; 5%), hydroxylated metabolite glucuronides (20%), and unidentified metabolites (33%), with percentages of the dosage delivered for each. 16% of its removal is due to fecal excretion. Although it is unknown if ETO is excreted in human milk, its physical-chemical characteristics indicate that it is likely to be excreted in breast milk[1].

Several anti-inflammatory medications are being used in the therapy of arthritis. However, in order to ensure that patients receive the necessary care, the therapeutic regimen must be achieved by keeping the drug's intended systemic concentration at a consistent level during the treatment period. However, for the patient group, affordability remained a key concern for committing to a lengthy course of therapy. The management of the patient's condition likely lasted the entirety of their life, which ultimately put a financial strain on them. Therefore, this might be the first attempt to create an ETO formulation based on a generic that satisfies the requirements of providing equivalent bioequivalency, holding a high similarity index, and showing relatively comparable *in vitro* drug release patterns [2].

The goal of the current study is to formulate ETO sustained release matrix tablets using hydrophilic release rate retardant polymers like HPMC K4M, Carbopol 974, and Eudragit

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RS100; to ascertain the role of rate controlling agents in the formulation through *in vitro* dissolution studies; to ascertain the pattern of drug release from the matrix formulations using a variety of release models; and to investigate the stability of the produced batch under short-term acceleration. In order to create sustained release tablet formulations with potential for generic medication, research was conducted.

MATERIALS AND METHODS

Materials

The drug, polymers, analytical grade reagents, and HPLC-grade solvents were obtained from HiMedia Chemicals Ltd., Mumbai, India.

Preparation of ETO matrix tablet

The active component ETO, polymers, and diluents were processed through sieve #44 to create formulations. The matrix tablets containing 500 mg of ETO were made using the wet granulation technique by combining all of the aforementioned materials (excluding lubricants) in a mortar, adding the granulating fluid propyl alcohol, and uniformly granulating the dry mixture until it produced homogeneous granules. Through sieve #22, the dry granules were filtered. The moist granules from the previous stage were placed in a quick air dryer. The wet mass was then dried at a temperature of 50°C, with a loss on drying (LOD) of no more than 3% for the dried granules. Magnesium stearate was added to dried granules after drying to enhance their flow characteristics. A tablet punching machine was used to compress the produced mix into tablets using a 17 mm punch [3] (**Table 1**).

Table 1: Formulation details

Ingredients	F1	F2	F3
Etodolac	500	500	500
HPMC K4M	10	-	-
Carbopol 974	-	10	-
Eudragit RS 100	-	-	10
Lactose	75	75	75
Talc	10	10	10
Magnesium stearate	5	5	5
Propyl alcohol	q.s.	q.s.	q.s.

Drug-Interaction Studies

In order to determine the compatibility and inherent stability of the formulation, Fourier transformed infrared (FT-IR) spectroscopy was used to monitor any potential interactions between the medicine (ETO) and the polymers used, HPMC K4M, Carbopol 974, and Eudragit RS100. There were documented physical changes in the medication and polymer combination that may be construed as interactions[4].

Evaluation of granule properties

Physical properties such bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index were used to describe the final granule mix. The produced granules were first properly assessed for their distinctive properties, including angle of repose (by funnel technique), bulk density, and tapped density (by cylinder method). The pharmacopoeia formula was used to get the Hausner's ratio[5].

Evaluation of tablet characteristics

The manufactured ETO tablets were appropriately assessed for the desired characteristics of thickness (using Vernier Calipers), weight variation, hardness (using a Pfizer hardness tester), friability (using Roche friability testing apparatus), and content uniformity (by crushing 20 tablets and weighed powder equivalent to 100 mg of ETO and measuring absorbance at 273 nm with the help of UV spectrophotometer)[6].

In-vitro dissolution studies

The generated batches' *in vitro* drug release tests were carried out in 900 mL of simulated gastric fluid (dissolution medium with pH 1.2) for 2 hrs at first utilizing USP 33 (Type-II) equipment, which was kept at a temperature of 37°C±0.5°C and a speed of 100 rpm. Phosphate buffered saline medium (pH 7.4) was substituted for the dissolution after three hours and continued for an additional ten hours. Throughout the 12 hrs period, 5 mL of the sample were taken out every 1 hour with a calibrated pipette. To keep the sink conditions constant, an equivalent volume of new dissolving media was supplied every time. Utilizing a UV-visible spectrophotometer at 273 nm, the drug content was ascertained[7]. The release studies were carried out three times.

Kinetic modeling of drug release

The dissolution profiles of all batches were fitted to a variety of models, including zero-order, first-order, Higuchi, Hixon-Crowell, and Korsmeyer and Peppas (drug release until the polymer chains reassert themselves). Higuchi describes the release of a drug from an insoluble matrix as the square root of a time-dependent process. The best model was decided upon using the goodness-of-fit test [8].

Accelerated stability study

For 90 days, the optimized batch (F3) was exposed to accelerated stability conditions (40°C±2°C and 75%±5% RH). The pill was kept inside a PVC bottle and wrapped in aluminum foil. Following the study's conclusion, pharmacopoeia rules were used to establish factors such hardness, friability, weight fluctuation, content uniformity, and thickness [9].

Statistical Analysis

One-way analysis of variance was used in the statistical analysis, with least significant difference multiple comparison methods, and a statistical probability (P) value of < 0.05 being used to define a significant difference.

RESULTS AND DISCUSSION

Appearance

Biconcave flat punches with dimensions of 10 mm were used to create the tablets. The manufactured tablets were found to be defect-free, meaning they had no chipping, capping, or picking.

Drug-Interaction Studies

For the purpose of identifying potential interactions, the FTIR spectra of the drug (ETO), polymers (HPMC K4M, Carbopol 974, and Eudragit RS100), and drug-polymer blends (ETO-HPMC K4M, ETO-Carbopol 974, and ETO-Eudragit RS100. The drug primarily showed distinctive peaks, however no overlapping peaks were seen in the physical combination with the polymer, indicating no drug-polymer interactions.

Pre-compression parameters

The assessed granules were found to be within acceptable bounds. The bulk and tapped densities, which range from 0.853 to 0.874 g/cm^3 and 0.946 to 0.959 g/cm^3, respectively, show good granule packing. For the batches, the angle of repose was observed to be between 29° and 31°, indicating flow characteristics that were generally adequate. The computed Hausner's ratio and Carr's index were in the range of 1.11–1.15; this indicates that packing ability is rather excellent. In essence, the tablet blend showed reasonable micromeritic qualities necessary for demonstrating sustained release properties (**Table 2**).

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

Formulation	Angle of repose (°)	Bulk density (in g/mL)	Tapped density (in g/mL)	Compressibility Index (in %)	Hausner ratio
F1	30.28±0.53	0.853±0.026	0.959±0.085	11.31±1.81	1.15±0.025
F2	31.19±0.55	0.867±0.043	0.976±0.073	10.67±1.37	1.12±0.017
F3	29.13±0.49	0.874±0.024	0.946±0.054	9.76±1.68	1.11±0.019

Post-compression parameters

The assessment criteria showed that the batches of manufactured matrix tablets have the necessary characteristics. The needed hardness of more than 5 kg/cm^2 and a friability value of less than 1% were both present in every batch that was manufactured, demonstrating the essential strength and resistibility of the matrix compositions. Compared to HPMC, it was discovered that the combination of Eudragit RS100 and anhydrous lactose had a significant impact in the formulation's ability to impart hardness. The addition of Carbopol 974 and anhydrous lactose gave the formulations similar properties. It was determined that the drug content was between 98.26-100.19%. The manufactured batches showed a weight difference of less than 1%, indicating nearly consistent drug content in all ETO formulations (**Table 3**).

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

Formulation	Thickness (in mm)	Friability (%)	Hardness (kg/cm^2)	Drug content (%)
F1	6.2±0.33	0.68±0.13	5.3±0.37	99.17±1.06
F2	6.3±0.47	0.76±0.19	5.2±0.27	98.26±1.21
F3	6.1±0.61	0.73±0.11	5.5±0.23	100.19±1.15

In-vitro dissolution

Compared to traditional dose forms, the majority of formulations employing release regulating agents showed a constantly sustained release characteristic. Drug solubilization, drug dissolution, diffusion, and erosion mechanisms interact intricately to release the drug from the hydrophilic matrix (s). Due to the concentration of the polymer (HPMC K4M), Formulation F1 demonstrated the maximal drug release within 4 hrs. Due to the high polymer content of Carbopol 974, Formulation F2 showed a minimal drug release for up to 12 hrs. Eudragit RS100, a suitable polymer concentration, is a component of Formulation F3, which delays the release of 90.22 mg of medication over the course of 12 hrs. The medication is thought to dissolve quickly because it diffuses out of the matrix, creating holes through which the solvent molecules may enter. According to the hypothetical pre-formulation hypothesis of formulation creation based on *in vivo* and *in vitro* data

of innovator drug, the batch did not stand up in sustaining a sustained release attribute and was eliminated for future research. The formulation F3 (102.95%) had the greatest *in vitro* drug release because it had the right amount of polymers to effectively delay drug release. The degree of HPMC hydration in the matrix—which finally encourages drug diffusion—was responsible for the phenomena of water penetration, swelling of polymer and gel formation, concomitant activities of drug diffusion and matrix erosion from the formulation. Looking at the dissolving chart, it was discovered that the formulation F3 had a burst phenomena in which more than twice the amount of medicine was released from the manufactured product during the third and fourth hours. It can be determined from the theoretical release profile of F3 that drug release continues until the polymer chains have achieved their equilibrium state.

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

Time (hr)	Medium	F1	F2	F3
1	pH 1.2	33.39±0.36	10.84±0.59	9.76±0.63
2	pH 1.2	38.47±0.84	13.17±0.86	12.38±0.28
3	pH 7.4	65.94±0.67	26.43±0.73	37.65±0.98
4	pH 7.4	66.93±0.86	67.88±0.66	44.73±0.14
5	pH 7.4	71.84±0.34	89.92±0.27	61.97± 0.55
6	pH 7.4	76.83±0.42	93.82±0.12	75.52±0.16
7	pH 7.4	78.82±0.64	94.17±0.44	87.81±0.58
8	pH 7.4	83.78±0.86	95.61±0.57	89.46±0.43
9	pH 7.4	83.84±0.99	96.47±0.38	92.26±0.76
10	pH 7.4	85.62±0.48	98.98±0.29	95.18±0.45
11	pH 7.4	88.25±0.74	99.52±0.21	97.33±0.38
12	pH 7.4	91.33±0.81	100.73±0.11	102.95±0.51
	pH 7.4			
	pH 7.4			

Release characteristics

Finding the most likely drug release mechanism from the matrix formulations was made easier by fitting the *in vitro* drug release data into zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. It was discovered that all of the formulations followed the Korsmeyer-Peppas model by applying the release models to the formulas. It was discovered that the release exponent (n) was greater than 0.5 and had strong linearity, indicating that non-Fickian diffusion was involved in the drug release, which closely matched the swelling erosion investigation (**Table 5**). Drug release was found to be controlled by a number of processes, and it may be described as an anomalous diffusion in which both the diffusion and erosion mechanisms operate, according to the release exponent (n).

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

Batch	Zero order	Hixon-Crowell	Higuchi plot
F1	0.8827	0.8789	0.9842
F2	0.8953	0.9768	0.9356
F3	0.9697	0.9218	0.9735

Accelerated stability study

The improved formulation's physical characteristics, hardness, thickness, and *in vitro* drug release profile showed no discernible change throughout the stability investigation conducted under accelerated conditions of temperature and humidity. Despite the fact that a change in drug content (0.49%) was discovered after 90 days, this is still regarded to be within the permitted range. It can be infer that the produced tablet remained stable under expedited circumstances.

CONCLUSION

The current research poses a challenge for the formulation of etodolac oral controlled release tablets using well-known hydrophilic release rate retardant polymers, such as HPMC K4M, Carbopol 974, and Eudragit RS100, which are non-toxic, affordable, and widely accessible. When the matrix formulations are carefully fabricated, it is possible to reduce the frequency of medication administration to twice daily while also reducing blood level variations, which ultimately improves patient compliance and therapy regimens. From the investigation, it was concluded that the type(s) and content of the polymer affect the drug release pattern, the achievement of steady state, and the biopharmacokinetic profile of the formulation to demonstrate sustained release(s). The maximum drug release was seen in formulation F3, at 102.95%, which is remarkably close to that of commercial formulations. The study's findings provided encouragement and fresh directions for formulating twice-daily "generic medicines" with sustained release. The effort also has the potential to translate the created formulation from the lab to the commercial level after passing regulatory inspections.

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CONFLICT OF INTEREST

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