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Sustained Release Matrix Tablets of Ketorolac Tromethamine: Formulation and Kinetic Modeling

Praveen Babu Choppala[1*]
[1*]Department of E.C.E, Andhra University, Visakhapatnam,530003, India
praveenchoppala@andhrauniversity.edu.in

Ramakrishna Gurajala[2]
[2]Department of E.C.E., AU-TDR-HUB, Andhra University, Visakhapatnam, 530003, India
ramagurajala@gmail.com

Mallela Harinagaraju[3]
[3]Department of CS&SE, WISTM, Andhra University, Visakhapatnam, 530003, India
mallelaharinagaraju@gmail.com

Mohammed Ashik[4]
[4]Department of E.C.E., WISTM, Andhra University, Visakhapatnam, 530003, India
ashikmd909@gmail.com

***Corresponding Author:** Praveen Babu Choppala
*Department of E.C.E, Andhra University, Visakhapatnam,530003,
praveenchoppala@andhrauniversity.edu.in

Abstract:

This study developed sustained-release matrix tablets of ketorolac tromethamine using natural (Hibiscus rosa-sinensis leaves mucilage) and synthetic (Hydroxy Propyl Methyl Cellulose) polymers at varying concentrations (20%, 40%, and 60%). Seven formulations were prepared, each maintaining 40 mg of ketorolac tromethamine while adjusting excipient levels. The tablets were evaluated for physical characteristics, including appearance, weight variation, thickness, hardness, and friability. Drug release was assessed through dissolution testing, with data analyzed using kinetic models. The combination of Hibiscus mucilage and HPMC achieved a 46% drug release over 10 hours, demonstrating the potential of using both natural and synthetic polymers to control drug release effectively. This study contributes to the development of sustained-release matrix tablets for ketorolac tromethamine.

Key words: Sustained release, Matrix tablets, Hibiscus rosa-sinensis leaves mucilage, Hydroxy Propyl Methyl Cellulose (HPMC), Ketorolac tromethamine.

I. INTRODUCTION

Oral drug delivery has stood the test of time as the most extensively utilized route for the systemic administration of pharmaceuticals. It serves as the foundation for a wide array of pharmaceutical products, encompassing immediate-release, sustained-release, and controlled-release systems. Regardless of the specific delivery mode or dosage form, the development of these products must be intricately aligned with the intrinsic characteristics of gastrointestinal (GI) physiology.

Immediate vs. Sustained Release: Oral drug formulations are carefully tailored to meet a

spectrum of release profiles. Immediate-release formulations are engineered for frequent dosing, often necessitating administration three to four times a day. On the other hand, sustained-release formulations are meticulously designed for once-daily dosing, with the primary aim of extending the therapeutic effect of the drug.

The Ideal Drug Delivery System: An ideal drug delivery system should fulfill two fundamental prerequisites. Firstly, it should offer a single-dose solution that covers the entire treatment duration, whether it's a short-term regimen for infections or a lifelong therapy for chronic conditions such as hypertension or diabetes. Secondly, the ideal system should ensure precise drug delivery to the intended site of action, effectively minimizing or eliminating undesirable side effects. This level of precision may require drug delivery to specific receptors, cellular targeting, or localized delivery within the body.

Sustained Release Systems: Sustained release systems encompass a broad category of drug delivery methods, characterized by the gradual release of the drug over an extended timeframe. If a sustained release system effectively maintains consistent drug levels in the bloodstream or the target tissue, it is categorized as a controlled release system. Even if it doesn't achieve constant drug levels but still extends the duration of action beyond what is achievable with conventional delivery methods, it falls into the category of prolonged release systems [1].

The distinction among various oral drug delivery systems plays a pivotal role in providing patients with effective and convenient treatment options, all while minimizing the potential for side effects. The diversity of oral pharmaceutical products contributes significantly to the richness and effectiveness of drug delivery in the field of medicine. Understanding and developing these delivery systems remains a cornerstone of pharmaceutical science and patient care [2]. This is illustrated in the following figure:

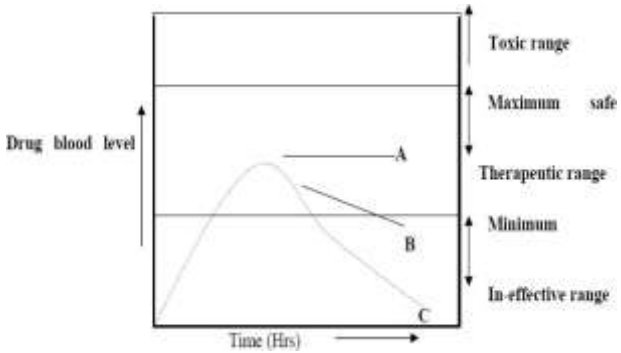

Fig. 1: Drug blood level verses time profile showing the relationship betweencontrolled release A. Prolonged Release, B. conventional Release

Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), is widely recognized for its effectiveness in treating inflammation and pain. Among NSAIDs, including Ibuprofen and naproxen, Ketorolac stands out as a particularly effective pain reliever for both inflammatory and non-inflammatory conditions. It is commonly utilized for the short-term management, typically up to five days, of moderately severe acute pain. Ketorolac tromethamine, an NSAID, is commonly employed to alleviate post-operative pain associated with surgical treatments for spine deformities and to address post-surgical pain. Its mechanism of action involves inhibiting prostaglandin synthesis. It's classified as a BCS class – I drug, indicating high solubility and permeability. However, conventional intake of Ketorolac can lead to gastric ulceration, bleeding, and other gastrointestinal complications [3, 4].

Rising Importance of Natural Gums and Mucilage: In contemporary pharmaceutical formulations, there's a growing emphasis on the use of natural gums and mucilage as vital medicinal components. These natural plant-based materials are prized for their cost-effectiveness, minimal side effects, biocompatibility, biodegradability, renewable sourcing, environmentally friendly processing, and enhanced patient compliance.

Hibiscus rosa-sinensis: Hibiscus rosa-sinensis L, a member of the Malvaceae family, is a common ornamental plant often used as a hedge or fence plant. Known by various names, including Chinese hibiscus, China rose, Hawaiian hibiscus, and shoeblack plant, it belongs to the tropical hibiscus species. This plant is native to East Asia and has found applications in pharmaceutical research.

Bioactive Components: Hibiscus rosa-sinensis has been explored for its various bioactive components. Different extracts of this plant have revealed the presence of alkaloids, glycosides, fatty materials, reducing sugars, resin, sterols, and the absence of tannins and saponins. Researchers have isolated compounds such as β-sitosterol, taraxeryl acetate, and four uncharacterized compounds, including an alkaloid and three sterols, from its leaves. Additionally, the leaves of this plant have been investigated for their fatty alcohol, fatty acids, and hydrocarbon content, identifying two cyclic acids, malvalic and sterculic.

Hibiscus rosa-sinensis Leaves Mucilage: Notably, Hibiscus rosa-sinensis leaves mucilage has been the subject of research, particularly in its role as a release retardant in sustained release *formulations. Matrix tablets incorporating this mucilage exhibited improvements in weight uniformity, hardness, friability, and drug content, with low variability. The swelling behavior, release rate characteristics, and in-vitro dissolution studies confirmed the suitability of dried Hibiscus rosa-sinensis leaves mucilage as a matrix-forming material for sustained release tablets. The kinetics of the chosen formulation adhered to zero-order, emphasizing the efficacy of Hibiscus rosa-sinensis leaves mucilage as an impressive matrix-forming polymer for retarding drug release.

The Experiment: In this particular experiment, the direct compression method was employed for matrix tablet formulation, a method known for its effectiveness. Ketorolac matrix tablet formulation involved the incorporation of a natural polymer, Hibiscus rosa-sinensis leaves mucilage, and the synthetic hydrophilic polymer, hydroxypropyl methylcellulose (HPMC), with varying concentrations. The primary objective of this study was to develop and evaluate Ketorolac sustained release matrix tablets using Hibiscus rosa-sinensis leaves mucilage and HPMC, contributing to the realm of pharmaceutical advancements.

II. MATERIAL AND METHODS

Pharmaceutical Materials: Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), was sourced from Dr. Reddy's Laboratories in Hyderabad. This served as the active pharmaceutical ingredient (API).

Hydroxypropyl Methylcellulose (HPMC), a synthetic polymer commonly used in pharmaceutical formulations, was obtained from Mylan Laboratories in Hyderabad.

Various excipients and chemicals, including Lactose Monohydrate, Magnesium Stearate, Talc, Microcrystalline Cellulose (Avicel), and Sodium Hydroxide, were procured from SD Fine Chemicals in Mumbai. These excipients are essential for the formulation of the sustained-release matrix tablets.

Purpose: The purpose of sourcing these materials is for the development and evaluation of sustained-release matrix tablets of Ketorolac, a potent NSAID. Hibiscus rosa-sinensis leaves were likely collected to extract natural mucilage, which can serve as a matrix-forming material to control the release of Ketorolac from the tablets. The HPMC and other excipients are essential components for tablet formulation, contributing to the tablet's physical properties and release characteristics. The study aimed to assess the effectiveness of these materials and formulations in achieving sustained drug release, which can be beneficial for managing acute pain and post-operative pain associated with surgical treatments.

Methodology

The study's methodology involved several essential steps in the development and evaluation of Ketorolac sustained-release matrix tablets using Hibiscus rosa-sinensis leaves mucilage and Hydroxypropyl Methylcellulose (HPMC). To begin, fresh leaves of Hibiscus rosa-sinensis were collected from a local area in Guntur. These leaves were carefully cleaned, washed, and dried to obtain the mucilage required for the formulations. Pharmaceutical materials, including Ketorolac, HPMC, and various excipients such as Lactose Monohydrate, Magnesium Stearate, Talc, Microcrystalline Cellulose, and Sodium Hydroxide, were sourced from reputable manufacturers in Hyderabad and Mumbai.

The formulation development phase was central to the study. Different sustained-release matrix tablet formulations were created using varying concentrations of Hibiscus rosa-sinensis leaves mucilage and HPMC. The objective was to keep the amount of Ketorolac consistent at 40 mg per tablet while altering the levels of these polymers [5, 6].

Tablet compression was carried out using the direct compression method, known for its efficiency in tablet manufacturing. The precise proportions of Ketorolac, Hibiscus mucilage, HPMC, and other excipients were blended thoroughly to ensure a uniform mix. This blend was then compressed into tablets using a tablet press machine, maintaining uniform tablet dimensions. The tablets were subjected to a series of physical tests to assess their quality and characteristics. These included visual inspection for appearance, weight measurement to ensure compliance with defined specifications, determination of tablet thickness using a calibrated instrument, assessment of tablet hardness to verify mechanical strength, evaluation of tablet friability to test resistance to abrasion during handling, and quantification of drug content using UV-visible spectrophotometry to check uniformity. The drug release profiles from the sustained-release tablets were studied through dissolution testing. A USP type II apparatus (paddle method) was employed, with tablets immersed in 900 ml of pH 7.4 phosphate buffer maintained at 37°C ± 0.5°C. At specific time intervals, 5 ml aliquots were withdrawn and replaced with an equal volume of freshly pre-warmed dissolution medium. Subsequently, the obtained dissolution data were analyzed by fitting them to various kinetic models, including zero-order, first-order, Higuchi, Hixon Crowell, and Korsmeyer-Peppas equations. These models were used to gain insights into the drug release mechanisms from each formulation. The results from physical characterization, drug release studies, and kinetic modeling were then analyzed to draw conclusions about the performance and effectiveness of the sustained-release matrix tablets. The findings were summarized, highlighting the potential of Hibiscus rosa-sinensis leaves mucilage and HPMC as effective matrix-forming materials for retarding drug release, with implications for pharmaceutical formulation and drug delivery discussed as well 7, 8].

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Angle of repose. The angle of repose is determined by the funnel method. The granules allowed to flow through the funnel freely on to the surface. The diameter of the granules cone is measured and angle of repose is calculated using the following equation [9].

tan h ¼ h=r or h ¼ tan —1ðh=rÞ (1)

where h = angle of repose, h = height of the cone, and r = radius of the cone base.
Bulk density. Bulk density (Db) is determined through measuring the volume (Vb) of known weighed quantity (W) of granules using bulk density apparatus [9].

Db ¼ W=Vb (2)

Tapped density: Tapped density (Dt) is calculated by measuring the volume (Vt) of known weighed quantity (W) of granules using bulk density apparatus and using the formula [9].

D_t ¼ $W=V_t$ (3)

Hausner's index*:* The Hausner's index is calculated by dividing the tapped density by the bulk density of the gran- ules [6].

Hausner's index ¼ Dt=Db (4)

where Dt = tapped density, Db = bulk density

Carr's index*:* The Carr's index that determines % of compressibility of the granules can be measured from the dif- ference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage [6].

Carr's Indexð%Þ¼ ðDt — DbÞ=Dt × 100 (5)

where Dt = tapped density Db = bulk density

Preparation of Ketorolac tromethamine sustained release matrix tablet

The preparation of sustained-release matrix tablets of Ketorolac tromethamine involved the direct compression method. In this method, various concentrations of natural and synthetic polymers, specifically 20%, 40%, and 60%, were utilized [10, 11]. A total of seven distinct formulations were developed while keeping the amount of Ketorolac tromethamine constant at 40 mg, with varying quantities of excipients. The primary polymers employed in these formulations were Hibiscus rosa-sinensis leaves mucilage, serving as the natural polymer, and Hydroxy Propyl Methyl Cellulose (HPMC), functioning as the synthetic polymer. These polymers, namely HPMC and Hibiscus rosa-sinensis leaves mucilage, were chosen as essential excipients for the sustained-release matrix tablet formulation (Table I). [12, 13]

Table I Formulation of sustained matrix tablets of ketorolac tromethamine

Ingredients(mg)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Ketorolac tromethamine	40	40	40	40	40	40	40
Hibiscus rosa-sinensis leaves mucilage	20	40	60	–	–	–	30
HPMC K100	–	–	–	20	40	60	30
Lactose	87	77	57	87	77	57	57
Avicel	47	37	37	47	37	37	37
Talc	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2
Total weight of each tablet	200	200	200	200	200	200	200

Phosphate Buffer Preparation: A phosphate buffer with a pH of 7.4 was prepared by

measuring 50 ml of 0.2M potassium dihydrogen phosphate and transferring it to a 200 ml volumetric flask. To this, 0.2M sodium hydroxide was added, and the volume was adjusted to 200 ml with distilled water. The pH of the buffer was adjusted to 7.4 using 0.2M sodium hydroxide.

Standard Calibration Curve for Ketorolac Tromethamine: A standard calibration curve for Ketorolac tromethamine was established using the prepared phosphate buffer with pH 7.4 as the solvent. Initially, 10 mg of Ketorolac tromethamine was dissolved in 100 ml of the buffer, creating a stock solution with a concentration of 100 µg/ml. This stock solution was used to prepare various aliquots with concentrations of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, and 25 µg/ml. The absorbance of these solutions was measured at 322 nm using a UV spectrophotometer with the phosphate buffer as the blank. The resulting absorbance-concentration data was used to construct a standard calibration curve for Ketorolac tromethamine, enabling the quantification of its concentration in subsequent sample analyses [14, 15].

III. RESULTS AND DISCUSSION

The study involved the formulation and evaluation of sustained-release matrix tablets containing Ketorolac Tromethamine, utilizing Hibiscus rosa-sinensis leaves mucilage and Hydroxy Propyl Methyl Cellulose (HPMC) as polymers. The key findings and results of the study are as follows:

Formulation Variability: Various formulations were developed, incorporating different concentrations (20%, 40%, and 60%) of natural Hibiscus mucilage and synthetic HPMC. These formulations aimed to investigate the impact of polymer concentration on sustained drug release [17].

Physical Characteristics: The physical evaluation of the formulated tablets encompassed parameters such as appearance, weight variation, thickness, hardness, and friability. These tests ensured the tablets' quality and integrity.

In-Vitro Drug Release: The drug release profiles of the formulated tablets were studied through dissolution testing. The tablets were subjected to a USP type II apparatus under specified conditions, resulting in sustained drug release [18].

Kinetic Modeling: The dissolution data was analyzed using various kinetic models, including zero-order, first-order, Higuchi, Hixon Crowell, and Korsmeyer-Peppas equations. This analysis provided insights into the drug release mechanisms.

Synergistic Polymer Combination: A notable finding was the synergy between Hibiscus mucilage and HPMC, which resulted in a sustained release of 46% over a 10-hour period. This indicates that the combination of natural and synthetic polymers effectively retards drug release, surpassing the performance of individual polymers.

These results underscore the potential of utilizing a combination of natural and synthetic polymers to achieve controlled and prolonged drug release in sustained-release matrix tablets for Ketorolac Tromethamine. This finding has significant implications for pharmaceutical formulation and drug delivery.

The pre-compression blend for matrix tablets was characterized with respect to Angle of repose, Bulk density, Tapped density, Carr’s index. Angle of repose was found to be27.42 to 30.70and carr’s index values were less than 18 for all batches which indicates good to fair flow ability and compressibility. Hausner’s ratio was less than 1.25 for all batches indicates good flow properties [19, 20].

Table.2: pre-compression parameters of different formulation

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Batch Code	Parameter				
	Bulk density (gm/ml)	Tappeddensity (gm/ml)	Carr's index (%)	Hausner'sratio	Angle ofrepose(θ)
F1	0.385	0.457	15.75	1.183	29.72
F2	0372	0.434	14.28	1.165	29.03
F3	0.356	0.404	11.87	1.130	24.25
F4	0.384	0.450	14.66	1.175	28.67
F5	0.388	0.454	14.53	1.170	30.70
F6	0.387	0.451	14.19	1.162	29.37
F7	0.382	0.454	15.85	1.188	28.05

In vitro drug release of ketorolac tromethamine SR tablet formulations:

Table. 3: Dissolution profile of F1- F7 formulations

Time (hrs)	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	7±0.23	7.23±0.9	5.54±0.12	11.98±0.56	9.76±0.72	7.32±0.56	5.53±0.74
1	13.08±0.19	11.34±0.78	9.12±0.17	17.45±0.57	14.64±0.56	11.76±0.78	7.78±1.65
2	20.12±0.98	15.56±0.16	14.23±0.54	24.07±0.38	19.81±0.34	16.44±1.56	11.98±0.67
3	24.17±0.67	22.19±0.87	18.76±0.23	27.23±0.75	24.61±0.87	21.26±0.87	15.17±0.34
4	32.78±0.08	28.76±0.17	22.54±0.54	34.90±0.89	29.05±0.45	26.21±4.78	21.12±0.73
5	39.12±0.12	34.18±0.34	27.12±0.31	41.76±1.90	35.08±0.39	30.65±0.76	25.45±0.68
6	45.87±0.433	40.12±0.65	33.76±0.78	46.67±0.69	40.26±1.34	36.18±0.73	29.15±0.73
7	51.23±0.56	44.07±0.14	39.06±0.17	51.06±0.18	46.92±0.45	42.81±0.23	33.06±0.91
8	55.80±0.67	50.89±0.45	44.14±0.65	56.73±0.53	51.75±1.34	47.50±0.34	37.98±0.55
9	59.12±0.12	55.12±0.12	47.76±0.98	62.46±0.76	57.11±2.56	52.96±0.56	42.13±0.63
10	64.56±0.54	60.34±0.76	53.76±0.19	66.13±0.56	62.83±0.98	56.72±0.12	47.12±1.09

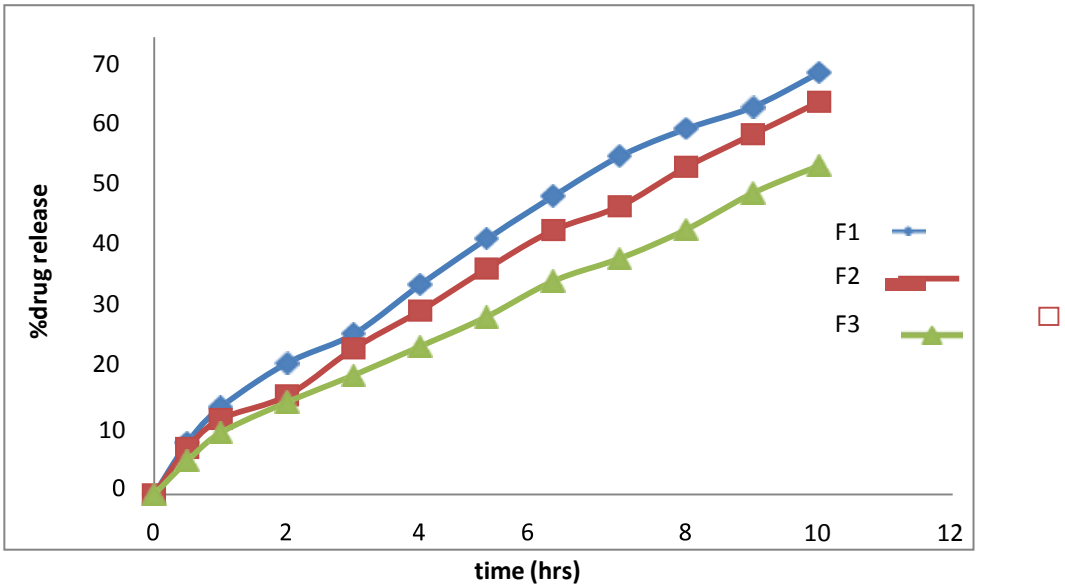

Fig. 1: *In vitro* dissolution plot of KT matrix containing hibiscus mucilage(F1-F3)

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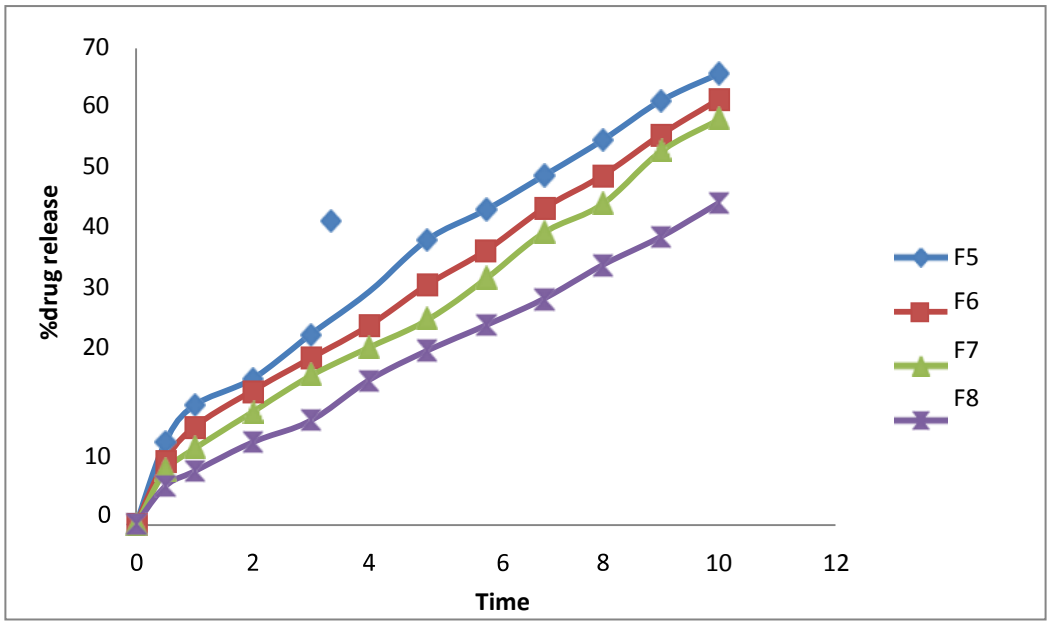

Fig. 2: *In vitro* dissolution plot of KT matrix containing hibiscus mucilage(F4-F7)

Table.4: *In vitro* release kinetics of ketorolac tromethamine sustained tabletsusing *Hibiscus rosa-sinensis* leaves mucilage (F1-F7)

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.984	0.971	0.994	0.994	0.703
F2	0.974	0.966	0.985	0.972	0.513
F3	0.962	0.964	0.974	0.994	0.599
F4	0.923	0.980	0.993	0.982	0.532
F5	0.956	0.971	0.981	0.987	0.750
F6	0.959	0.967	0.977	0.982	0.643
F7	0.869	0.934	0.954	0.966	0.551

IV CONCLUSION

This study provides crucial insights into the development of sustained-release tablets for Ketorolac Tromethamine, a promising avenue for achieving controlled and extended drug release. The successful use of a combination of natural Hibiscus mucilage and synthetic HPMC polymers demonstrates their effectiveness in this context. These findings hold significant implications for pharmaceutical formulation and drug delivery, potentially revolutionizing the creation of safe and efficient sustained-release medications. The synergy between these polymers enhances drug release control, promising improved patient outcomes and treatment adherence. This research marks a noteworthy contribution to the pharmaceutical field, offering a novel approach to drug delivery that can benefit a wide range of therapeutic applications. It highlights the potential of harnessing both natural and synthetic components to advance drug release science, promoting safer and more effective treatments.

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