JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

RESEARCH ARTICLE

Development and *In Vitro* Characterization of Sustained-Release Tranexamic Acid Matrix Tablets Using Chitosan and HPMC K15M

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Publication history: Received on 26th July 2025; Revised on 6th September 2025; Accepted on 10th September 2025

Article DOI: 10.69613/124zse95

Abstract: Tranexamic acid (TXA), an antifibrinolytic agent, has a short biological half-life, which needs frequent administration and can lead to non-adherence. This investigation focused on the design and *in vitro* assessment of sustained-release (SR) matrix tablets for TXA to provide a 12-hour dosing interval. Two different polymeric carriers, the natural polysaccharide Chitosan and the synthetic cellulose derivative Hydroxypropyl Methylcellulose (HPMC K15M), were evaluated for their release-retarding capabilities. Ten formulations (CF1-CF5 with Chitosan; HF1-HF5 with HPMC K15M) were prepared by the direct compression method, varying the polymer concentration. Fourier Transform Infrared (FT-IR) spectroscopy confirmed the absence of chemical interactions between TXA and the excipients. All prepared formulations exhibited satisfactory pre-compression flow characteristics and post-compression parameters (weight variation, hardness, thickness, friability, and drug content) that complied with official pharmacopeial specifications. *In vitro* dissolution studies conducted in 0.1 N HCl for 12 hours revealed that drug release was inversely proportional to the polymer concentration. The optimized formulations, CF5 (20 mg Chitosan) and HF5 (20 mg HPMC K15M), indicated the most effective release modulation, with cumulative drug release of 94.9% ± 0.30 and 94.5% ± 1.24, respectively. Kinetic modeling of the release data indicated that both CF5 and HF5 formulations closely followed a zero-order release pattern, suggesting a constant rate of drug liberation. The results indicate that both Chitosan and HPMC K15M can be effectively employed to formulate SR matrix tablets of Tranexamic acid, with the Chitosan-based system (CF5) providing a marginally superior and highly consistent release profile suitable for twice-daily dosing.

Keywords: Tranexamic Acid; Sustained Release; Matrix Tablets; Chitosan; HPMC K15M

1. Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent, a synthetic analogue of the amino acid lysine [1]. It functions by competitively and reversibly inhibiting the activation of plasminogen to plasmin, a key enzyme responsible for fibrin degradation. By preventing the breakdown of fibrin, TXA effectively stabilizes blood clots [2]. This mechanism of action makes it a cornerstone therapy in the management and prevention of hemorrhage associated with diverse clinical scenarios, including major trauma, surgery (such as cardiac and orthopedic procedures), postpartum bleeding, and heavy menstrual bleeding (menorrhagia) [3, 4].

Despite its established efficacy, the therapeutic utility of orally administered TXA is constrained by its pharmacokinetic profile. It is rapidly absorbed but exhibits a short biological half-life, typically reported to be between 2 and 3 hours [5]. This brevity in duration necessitates a frequent and high-dose dosing regimen, often requiring 1-1.5 g to be administered three to four times daily to maintain plasma concentrations within the therapeutic window [6]. Such frequent dosing schedules are a significant cause of poor patient adherence, which can lead to fluctuating plasma drug levels and sub-optimal therapeutic outcomes.

The development of an oral sustained-release (SR) dosage form for tranexamic acid presents a logical and viable strategy to overcome these limitations. An effective SR system can prolong the *in vivo* drug release, maintain stable therapeutic concentrations over an extended period, and reduce the dosing frequency to once or twice daily. This approach is expected to significantly enhance patient compliance and improve the overall consistency of the antifibrinolytic effect [7].

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Among the various technologies for achieving sustained release, the hydrophilic polymer matrix tablet is a frequently employed platform. This approach is favored due to its formulation simplicity, cost-effectiveness, robust manufacturing scalability, and reproducible release kinetics [8]. In these systems, the drug is uniformly dispersed within a polymer matrix. Upon ingestion and contact with gastrointestinal fluids, the polymer hydrates to form a viscous gel layer on the tablet's surface. Drug liberation is then meticulously controlled by a combination of diffusion through this hydrated gel matrix and/or the progressive erosion of the matrix itself [9].

The choice of the rate-controlling polymer is a critical determinant of the formulation's success. Hydroxypropyl Methylcellulose (HPMC) is a semi-synthetic, non-ionic cellulose ether that is extensively used for this purpose. Its popularity stems from its non-toxic nature, excellent compressibility, pH-independent release, and the ability to form a strong, viscous gel layer upon hydration. HPMC K15M, a high-viscosity grade, is particularly well-suited for extending the release of highly water-soluble drugs like TXA [10].

In parallel, natural polymers have gained significant interest for pharmaceutical applications. Chitosan, a cationic polysaccharide derived from the deacetylation of chitin, is notable for its inherent biocompatibility, biodegradability, low toxicity, and well-documented mucoadhesive properties [11]. In acidic environments, such as the stomach, the amino groups of chitosan become protonated, rendering the polymer soluble and allowing it to swell. This swelling process forms a matrix structure that can effectively control the release of an entrapped drug [12].

This research work was therefore carried out to formulate and evaluate sustained-release matrix tablets of Tranexamic acid. The study comparatively assesses the efficacy of Chitosan and HPMC K15M as the primary release-retarding polymers. The tablets were prepared using the direct compression method, and the objective was to identify an optimized formulation capable of providing a 12-hour *in vitro* drug release profile that adheres to a zero-order kinetic model.

2. Materials and Methods

2.1. Materials

Tranexamic acid, Hydroxypropyl methylcellulose (HPMC K15M), and Chitosan were procured from Yarrow Chemical Products (Mumbai, India). Microcrystalline cellulose was provided by Generics – Research & Development (Tehsil Nalagarh, India), and Magnesium stearate was obtained from Alembic Limited (Vadodara, India). All other solvents and reagents used in the study were of analytical grade.

2.2. Methods

2.2.1. Analytical Method Development

A primary stock solution of tranexamic acid (1000 µg/ml) was prepared by accurately weighing 50 mg of the drug, dissolving it in a minimal volume of methanol, sonicating for five minutes, and subsequently adjusting the final volume to 50 ml using 0.1 N HCl buffer. From this stock, serial dilutions were prepared to obtain working standards of various concentrations. The absorbance of these solutions was measured using a UV-Visible spectrophotometer at the pre-determined λmax of 209 nm. A standard calibration curve was then constructed by plotting absorbance values versus their corresponding concentrations.

2.2.2. Drug-Excipient Compatibility Study via FT-IR

Fourier Transform Infrared (FT-IR) spectroscopy was employed to assess potential chemical interactions between tranexamic acid and the selected polymers. The FT-IR spectra of pure tranexamic acid, pure Chitosan, pure HPMC K15M, and physical mixtures of the drug with each polymer were recorded. The samples were prepared using the KBr (potassium bromide) pellet technique. A small amount of the sample (~2% w/w) was triturated with dry KBr and compressed into a transparent pellet under high pressure (approx. 10,000 psi). Each pellet was scanned over a wavenumber range of 4000–400 cm^{-1} with a resolution of 2 cm^{-1}.

2.2.3. Pre-formulation Studies of Powder Blends

To ensure suitability for the direct compression process, the flow characteristics of the powder blends for all formulations were evaluated. Standard pre-compression parameters were determined, including bulk density and tapped density. From these two values, the Compressibility Index (Carr's Index) and the Hausner's ratio were calculated to objectively predict the blend's flowability and compressibility. The angle of repose was also measured as an indicator of inter-particulate friction.

2.2.4. Formulation of Sustained-Release Tablets

A series of ten distinct formulations of tranexamic acid SR tablets were developed. Five formulations (CF1–CF5) utilized Chitosan, and five (HF1–HF5) utilized HPMC K15M as the release-retarding polymer. The tablets were manufactured using the direct compression technique. The precise quantities of the active drug, polymer, microcrystalline cellulose (as a diluent/filler), and magnesium stearate (as a lubricant) for each formulation are detailed in Table 1. For each batch, all ingredients were accurately weighed, passed through a 24-mesh sieve to ensure uniformity and break any aggregates, and blended thoroughly in a mortar and pestle. The final homogeneous blend was then compressed into tablets using a single-punch tablet compression machine, maintaining consistent compression force.

Table 1. Formulation compositions of Tranexamic acid SR tablets (CF1-CF5 and HF1-HF5)

Ingredients	F1	F2	F3	F4	F5
Tranexamic acid	250	250	250	250	250
Chitosan/ HPMCK15M	50	40	30	24	20
Microcrystalline cellulose	157	167	177	183	187
Magnesium stearate	3	3	3	3	3
Total	460	460	460	460	460

2.2.5. Post-Compression Evaluation of Tablets

The prepared tablets from all ten formulations were subjected to a battery of pharmacopeial quality control tests to assess their physical properties.

- **Weight Variation:** Twenty tablets were randomly selected from each batch and weighed individually using an electronic analytical balance. The mean weight, standard deviation, and percentage deviation were calculated to assess compliance with Indian Pharmacopoeia (IP) standards for dosage uniformity.
- **Hardness:** The crushing strength (hardness) of ten tablets from each batch was measured using a Monsanto hardness tester. The force required to break the tablet diametrically was recorded, and the average hardness was expressed in kg/cm^2.
- **Thickness:** The thickness of ten randomly selected tablets from each batch was measured using a digital Vernier caliper. The mean thickness and standard deviation were calculated.
- **Friability:** Twenty tablets from each batch were accurately weighed (designated as W_1) and placed in a Roche friabilator. The apparatus was operated at 25 rpm for 4 minutes (100 revolutions). After rotation, the tablets were carefully removed, de-dusted, and re-weighed (designated as W_2). The percentage friability was calculated, with a value of less than 1% being considered acceptable.
- **Drug Content (Assay):** One tablet from each batch was accurately weighed and crushed into a fine powder. An amount of this powder equivalent to the average tablet weight was transferred to a volumetric flask, dissolved in 0.1 N HCl, and sonicated to ensure complete extraction of the drug. The solution was then filtered, diluted appropriately, and the tranexamic acid content was determined spectrophotometrically at 209 nm against a blank.

2.2.6. In Vitro Dissolution Study

The *in vitro* drug release characteristics of the formulated tablets were assessed using a USP Dissolution Apparatus II (paddle method). The study was conducted in 900 ml of 0.1 N HCl, which served as the dissolution medium, simulating gastric fluid. The medium was maintained at a constant temperature of 37 ± 0.5 °C, and the paddles were rotated at a speed of 50 rpm. At predetermined time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours), 5 ml aliquots of the dissolution medium were withdrawn. To maintain sink conditions and constant volume, each aliquot was immediately replaced with 5 ml of fresh, pre-warmed dissolution medium. The collected samples were filtered through a 0.45 µm filter, diluted as necessary, and analyzed spectrophotometrically at 209 nm to determine the cumulative percentage of tranexamic acid released.

Drug Release Kinetics and Mechanism

To characterize the drug release profile and understand the underlying mechanism of release from the matrix, the *in vitro* dissolution data of the most promising formulations were fitted to several established kinetic models:

- **Zero-order model:** (Cumulative % Release vs. Time)
- **First-order model:** (Log Cumulative % Remaining vs. Time)
- **Higuchi model:** (Cumulative % Release vs. Square Root of Time)

- **Korsmeyer-Peppas model:** (Log Cumulative % Release vs. Log Time)

The coefficient of determination (R^2) was calculated for each model. The model that yielded the highest R^2 value was considered the best fit for describing the drug release kinetics

3. Results and Discussion

3.1. Analytical Method

The UV spectrophotometric method was validated for the quantification of tranexamic acid. The standard calibration curve, generated by plotting absorbance against known concentrations in 0.1 N HCl, is presented in Figure 1. The plot showed excellent linearity over the tested concentration range. The regression analysis yielded an equation of y = 0.0005x + 0.0098, with a high coefficient of determination (R^2) of 0.9975. This strong linear relationship confirms that the analytical method is precise, accurate, and suitable for quantifying tranexamic acid in the subsequent drug content and *in vitro* dissolution studies.

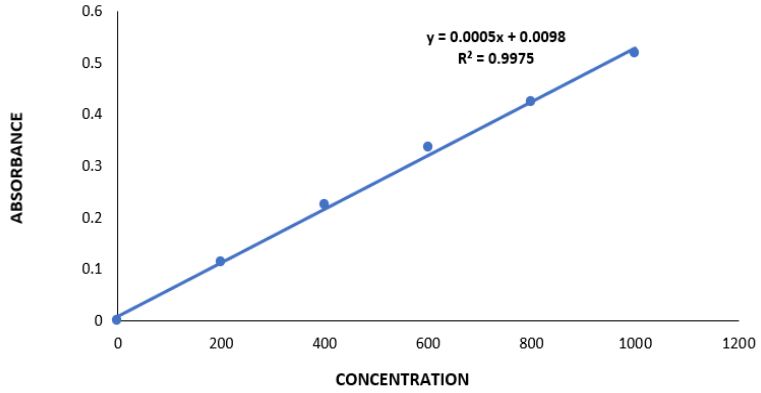

Figure 1. Standard calibration curve of tranexamic acid in 0.1 N HCl

3.2. Drug-Excipient Compatibility (FT-IR)

The FT-IR spectra were analyzed to confirm the chemical compatibility and integrity of tranexamic acid within the formulations. Figure 2a displays the spectrum of pure tranexamic acid, which shows its characteristic functional group peaks. The spectra for the physical mixtures (drug + excipients) are presented in Figure 2b.

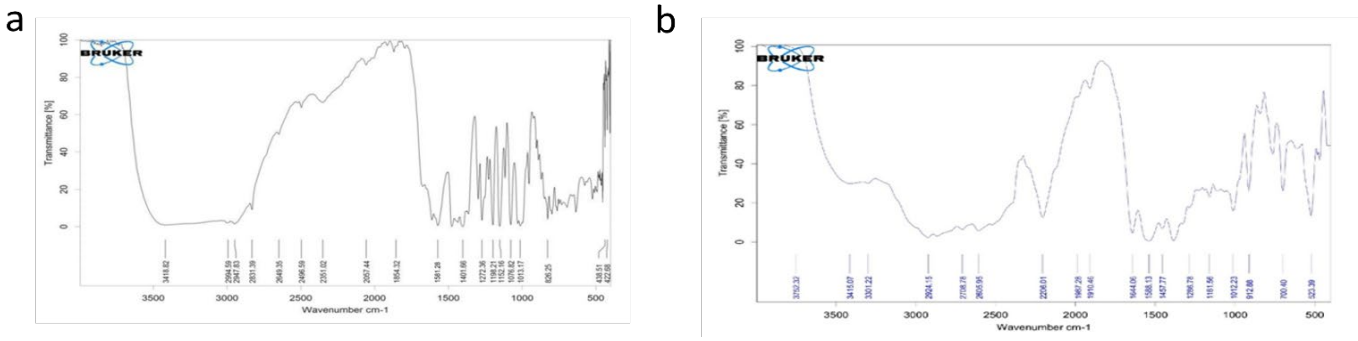

Figure 2. FTIR spectrum of a. pure Tranexamic acid and b. Pure drug + Excipients

A comparison of the spectra reveals that the principal peaks characteristic of tranexamic acid were retained in all physical mixtures and final formulations. There was no significant shifting, disappearance of existing peaks, or appearance of new peaks, which would have indicated a chemical interaction. This spectral evidence confirms the absence of any significant chemical incompatibility between tranexamic acid and the polymers (Chitosan, HPMC K15M) or other excipients during the formulation process.

3.3. Pre-compression Parameters of Powder Blends

The flow properties of the powder blends are a critical factor in direct compression, as they dictate the uniformity of die-fill and, consequently, the consistency of tablet weight and content. The results for bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio for all ten formulations are summarized in Table 2.

Table 2. Pre-formulation flow properties of powder blends (Mean ± SD)

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
CF1	0.46±0.01	0.57±0.00	28.0±1.34	19.29±1.20	1.24±0.03
CF2	0.48±0.02	0.58±0.01	28.9±1.54	17.24±1.05	1.20±0.04
CF3	0.45±0.04	0.55±0.00	29.3±1.32	18.18±1.09	1.22±0.02
CF4	0.47±0.03	0.56±0.01	29.5±1.01	16.07±1.20	1.19±0.01
CF5	0.44±0.02	0.53±0.01	28.7±1.65	16.98±1.26	1.20±0.02
HF1	0.47±0.02	0.58±0.01	27.5±1.54	18.96±1.26	1.23±0.02
HF2	0.45±0.04	0.57±0.01	28.2±1.61	21.05±1.02	1.26±0.03
HF3	0.46±0.01	0.56±0.00	26.9±1.08	17.86±1.05	1.22±0.02
HF4	0.44±0.04	0.55±0.00	29.1±1.17	20.00±1.60	1.25±0.02
HF5	0.45±0.01	0.50±0.01	27.0±1.34	19.64±1.20	1.24±0.03

All formulations showed acceptable to good flow characteristics, as indicated by the values falling within the pharmacopeial-specified ranges. For the Chitosan-based formulations, CF4 exhibited particularly favorable flow properties, with a Carr's index of 16.07%, a Hausner's ratio of 1.19, and an angle of repose of 29.5°. Among the HPMC-based formulations, HF3 showed superior flow, with a Carr's index of 17.86%, a Hausner's ratio of 1.22, and an angle of repose of 26.9°. These results affirm that all the prepared powder blends were suitable for the direct compression manufacturing process, minimizing potential issues like "rat-holing" or "arching" in the hopper.

3.4. Post-compression Evaluation of Tablets

The physical characteristics of the compressed tablets for all ten formulations are presented in Table 3. All batches of tablets met the required pharmacopeial standards for quality.

Table 3. Physical characterization of formulated Tranexamic acid tablets (Mean ± SD)

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
CF1	464±1.65	5.2±0.35	2.6±0.05	0.40±0.02	97.01±1.5
CF2	463±1.40	5.4±0.57	2.2±0.08	0.42±0.05	98.45±1.6
CF3	450±1.84	5.3±0.24	2.8±0.02	0.39±0.02	95.34±1.2
CF4	462±1.15	5.1±0.34	2.3±0.04	0.38±0.01	97.02±1.4
CF5	470±1.32	5.5±0.21	2.4±0.06	0.45±0.02	98.15±1.3
HF1	498±1.43	5.2±0.21	2.4±0.01	0.38±0.02	98.03±1.2
HF2	464±1.58	5.0±0.32	2.6±0.08	0.42±0.01	98.49±1.5
HF3	452±1.74	5.3±0.25	2.2±0.02	0.36±0.02	99.47±1.3
HF4	463±1.82	5.1±0.24	2.8±0.06	0.39±0.03	98.21±1.4
HF5	450±1.08	5.4±0.32	2.1±0.05	0.41±0.02	97.02±1.2

The weight variation for all batches was within the acceptable ±5% limit, indicating high uniformity in die-fill during compression. Tablet hardness for all formulations was found to be in the range of 5.0 to 5.5 kg/cm^2, which signifies adequate mechanical strength to withstand the rigors of handling, packaging, and transportation. This mechanical robustness was further corroborated by the friability test, where all formulations exhibited a weight loss of well below the 1% threshold (ranging from 0.36% to 0.45%). The thickness of the tablets was consistent within each batch, and the drug content (assay) for all formulations was found to be within the acceptable USP/IP range of 95% to 105% (specifically, 95.34% to 99.47%). These data collectively confirm the production of high-quality, uniform, and robust tablets.

3.5. *In Vitro* Drug Release Studies

3.5.1. Chitosan-Based Formulations (CF1-CF5)

The cumulative drug release profiles for the five Chitosan-based formulations are presented in Table 4. A clear polymer concentration-dependent effect on drug release was observed. As the concentration of Chitosan in the matrix increased (from 20 mg in CF5 to 50 mg in CF1), the rate and extent of drug release progressively decreased.

Table 4. *In vitro* drug release profiles for Chitosan formulations (CF1-CF5) (Mean ± SD)

TIME (hours)	Percentage of Tranexamic Acid Released				
	CF1	CF2	CF3	CF4	CF5
1	4.3±1.21	3.2±1.19	5.1±1.18	6.3±1.22	9.5±1.12
2	13.6±1.31	11.3±1.20	12.1±1.14	13.3±1.25	15.5±1.15
3	19.5±1.24	17.2±1.22	18.4±1.12	19.5±1.22	20.4±1.19
4	25.1±1.25	24.3±1.35	27.1±1.17	23.3±1.24	25.6±1.21
5	35.6±1.26	33.3±0.29	39.2±1.21	34.4±1.26	36.3±1.22
6	38.4±1.36	40.4±1.33	42.2±1.36	40.1±1.29	45.6±1.28
7	45.5±1.21	52.8±1.12	49.9±1.25	45.6±1.31	52.3±1.29
8	56.6±1.24	65.1±1.37	55.6±1.26	56.9±1.33	64.1±1.10
9	63.2±1.31	71.9±1.19	64.2±1.28	64.8±1.35	72.8±1.35
10	73.4±1.25	78.6±1.35	72.3±0.33	75.4±1.34	79.9±1.36
11	79.9±1.26	80.4±1.20	76.6±1.14	84.6±0.33	85.4±1.32
12	82.1±1.25	85.9±1.12	86.9±1.36	91.5±1.25	94.9±0.30

This behavior is attributed to the fact that in the acidic dissolution medium (0.1 N HCl), the Chitosan polymer hydrates and swells, forming a viscous gel matrix. A higher concentration of Chitosan results in a more robust and denser gel layer, which increases the tortuosity of the diffusion path for the water-soluble drug, thereby slowing its release. Formulation CF1 (50 mg Chitosan) showed the slowest release, with only 82.1% ± 1.25% of the drug liberated after 12 hours. In contrast, formulation CF5 (20 mg Chitosan) provided the most complete and controlled release, achieving 94.9% ± 0.30% over the 12-hour study period.

3.5.2. HPMC K15M-Based Formulations (HF1-HF5)

A similar and predictable trend was observed for the HPMC K15M-based tablets, with release data detailed in Table 5. The release-retarding effect was directly proportional to the concentration of HPMC K15M.

Table 5. *In vitro* drug release profiles for HPMC K15M formulations (HF1-HF5) (Mean ± SD)

TIME (hours)	Percentage of Tranexamic Acid Released				
	HF1	HF2	HF3	HF4	HF5
1	6.4±1.38	8.2±1.21	5.1±1.15	4.6±1.21	3.4±1.19
2	12.5±1.35	15.2±1.24	11.3±1.14	14.5±1.22	15.7±1.18
3	23.4±1.36	26.1±1.15	22.2±1.18	27.6±1.24	26.5±1.17
4	34.5±1.33	38.3±1.25	32.3±1.11	30.7±1.33	35.1±1.20
5	39.2±1.30	40.5±1.36	37.3±1.25	36.7±1.25	40.3±1.21
6	40.5±1.31	45.4±1.25	39.1±1.36	40.2±1.26	41.6±1.25
7	46.6±1.29	56.2±1.34	41.5±1.25	45.5±1.36	56.6±1.26
8	55.6±1.27	62.4±1.28	51.1±1.35	53.6±1.35	64.8±1.29
9	63.9±1.24	70.5±1.39	59.6±1.26	66.4±1.24	75.4±1.28
10	72.1±1.25	76.9±1.14	68.8±1.14	74.5±1.25	80.6±1.19
11	80.3±1.23	82.4±1.25	76.5±1.28	80.4±1.18	85.4±1.12
12	82.4±1.22	85.2±0.33	84.5±1.25	91.5±1.17	94.5±1.24

Upon contact with the aqueous medium, the high-viscosity HPMC K15M hydrates rapidly to form a strong, cohesive gel layer. This layer acts as a diffusion barrier, controlling the release of the highly water-soluble tranexamic acid from the matrix. Formulation HF1, containing the highest polymer load (50 mg HPMC), exhibited the most pronounced sustained effect, releasing only 82.4% ± 1.22% at 12 hours. Conversely, formulation HF5, with the lowest polymer load (20 mg HPMC), showed the highest cumulative release, liberating 94.5% ± 1.24% at 12 hours.

3.5.3. Comparison of Optimized Formulations

Both polymers proved to be effective carriers for sustaining the release of tranexamic acid over a 12-hour period. The optimized formulations from each series, CF5 (20 mg Chitosan) and HF5 (20 mg HPMC K15M), were identified as the most successful, as they allowed for a near-complete (over 94%) drug release within the desired timeframe.

When compared, CF5 (Chitosan) released 94.9% ± 0.30% of the drug, while HF5 (HPMC K15M) released 94.5% ± 1.24%. While both formulations are highly effective and show statistically similar total release, the Chitosan-based formulation (CF5) exhibited a slightly more consistent release profile, as indicated by its remarkably low standard deviation at the 12-hour mark.

4. 3.6 Drug Release Kinetics

To elucidate the mechanism of drug release, the dissolution data from the two optimized formulations (CF5 and HF5) were fitted to various kinetic models. The regression coefficients (R^2) derived from this analysis are presented in Figures 3 and 4.

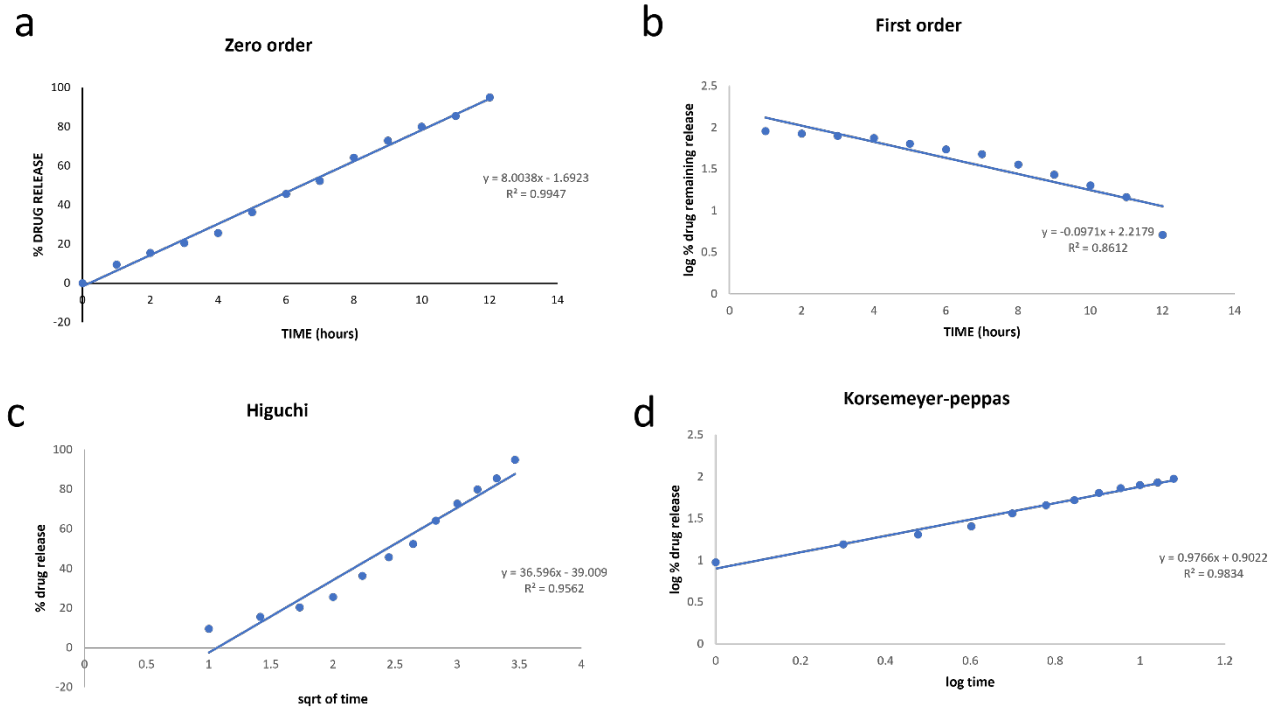

Figure 3. Release rate kinetics plots for formulation CF5

For both formulations, the kinetic model that provided the best fit was the zero-order model, as evidenced by its high R^2 value. This finding is highly desirable for a sustained-release system. It indicates that the drug release rate from the matrix was nearly constant over the 12-hour period and was independent of the remaining drug concentration within the dosage form. This zero-order release profile is the ideal kinetic behavior, as it theoretically ensures a stable and predictable therapeutic plasma concentration of tranexamic acid throughout the entire dosing interval.

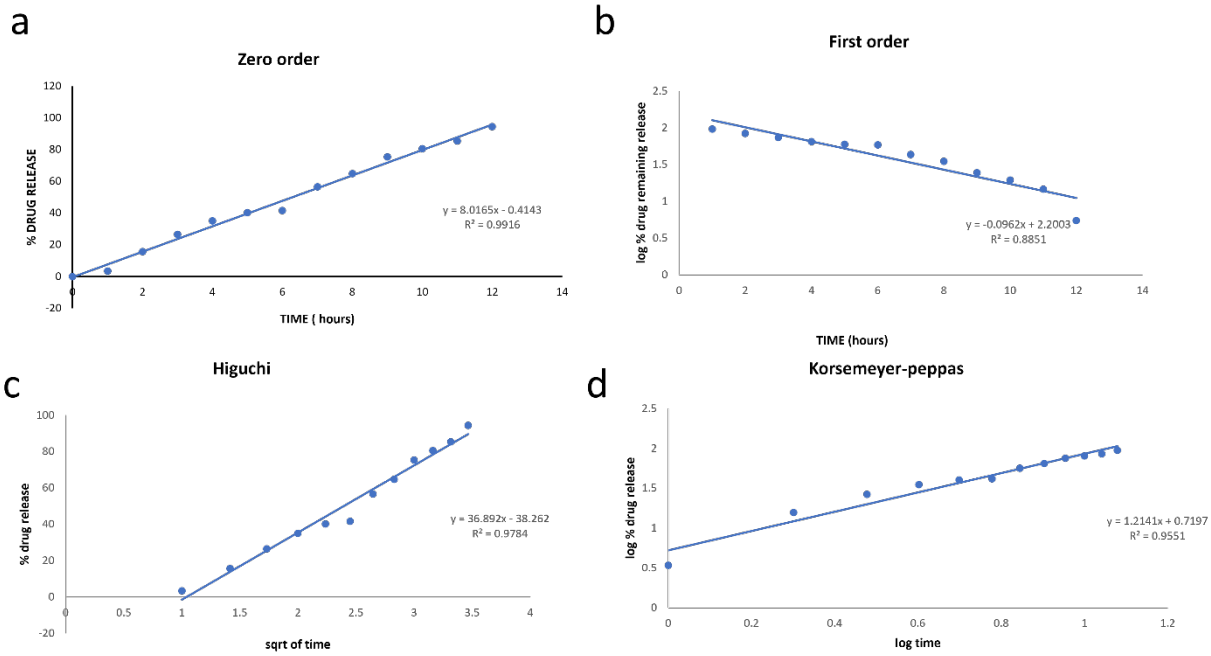

Figure 4. Release rate kinetics plots for formulation HF5

5. Conclusion

This work successfully showed the feasibility of formulating 12-hour sustained-release matrix tablets of tranexamic acid using either Chitosan or HPMC K15M as the primary release-controlling polymer. The direct compression method was employed to produce tablets with satisfactory pre-compression flow properties and post-compression physical characteristics, all of which complied with official pharmacopeial standards. FT-IR analysis confirmed the absence of any significant chemical incompatibilities between the drug and the selected excipients. The *in vitro* dissolution studies revealed that both polymers effectively retarded drug release over a 12-hour period, with the release rate being inversely proportional to the polymer concentration. The optimized formulations from each series, CF5 (containing 20 mg Chitosan) and HF5 (containing 20 mg HPMC K15M), exhibited a near-complete drug release (94.9% and 94.5%, respectively) that closely adhered to a zero-order kinetic model. This release pattern is ideal for maintaining consistent plasma drug levels and reducing dosing frequency. Between the two optimized formulations, the Chitosan-based tablet (CF5) showed a marginally superior and more consistent release profile. These results indicate that a Chitosan-based matrix tablet is a highly promising and viable platform for developing a twice-daily oral dosage form of tranexamic acid, which could significantly improve patient adherence and therapeutic efficacy in the long-term management of bleeding disorders.

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