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Development and Characterization of Controlled Release Tablets of Tizanidine

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Abstract
Tizanidine hydrochloride is a centrally act as skeletal muscle relaxant and is used to manage spasticity in neurological disorders such as multiple sclerosis and spinal cord injury. The current study aimed to develop and evaluate controlled-release (CR) matrix tablets of Tizanidine hydrochloride to achieve sustained drug release and improved therapeutic performance. Control Release tablets were prepared using polymers including Hydroxypropyl Methylcellulose (HPMC K100M), Ethylcellulose (Ethocel 10FP), and Kollidon SR in varying concentrations through direct compression. The formulations were evaluated for hardness, friability, weight variation, drug content, and in-vitro dissolution for 12 hours. Release kinetics was analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Results indicated that polymer type and concentration significantly affected drug release, with HPMC-based formulations showing sustained diffusion-controlled release, while Ethocel and Kollidon SR provided slower or balanced profiles. The optimized formulation sustained drug release for up to 12 hours, following near zero-order kinetics. All formulations exhibited acceptable physical and chemical properties. However, further in-vivo studies and long-term stability assessments are required to establish pharmacokinetic correlation and clinical efficacy.

Keywords: Tizanidine Hydrochloride, Controlled-Release Tablets, Sustained Drug Delivery, Polymer Optimization

Introduction

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant used in the management of spasticity associated with multiple sclerosis, as well as other neurological conditions such as spinal cord injury (ZENGİN, 2024). Tizanidine has a short half-life, approximately 2.5 hours, and undergoes high first-pass metabolism, which results in ~ 34-40% oral bioavailability, making substantial clinical use is a challenge (Silva et al., 2024). It is necessary to take the drug multiple times a day in order to achieve the desired plasma level, therefore, it is taken 3 times a day (Zhu et al., 2024). This elevates the patient burden in long-term therapy and, in turn, has implications for patient compliance (Gobetti et al., 2020). Control release tablets are intended to provide a constant therapeutic plasma concentration of the API for an extended time frame and release the API uniformly and continually, which, in turn, reduces the dosing frequency a patient must adhere to. This is achieved through the use of hydrophilic or hydrophobic polymers, which control the release of a drug through a combination of erosion, diffusion, or osmotic action. The most relevant

include the type of polymer, polymer viscosity, drug-polymer weight ratio, and matrix integrity (Atre & Rizvi, 2025). Controlled-release (CR) and extended-release formulations are designed to sustain plasma concentration, allowing Tizanidine and other similar medications to operate effectively for extended periods (Andrade, 2015).

Current research on controlled-release formulations of Tizanidine remains fragmented, with most studies focusing on single-polymer systems or limited in-vitro evaluations without comprehensive comparative analysis. Moreover, data on polymer combinations such as HPMC K100M, Ethocel 10FP, and Kollidon SR—each with distinct gel-forming and diffusion-controlling properties—are scarce. Therefore, a systematic formulation and evaluation of polymer-based controlled-release tablets of Tizanidine is warranted to achieve sustained drug delivery, reduce dosing frequency, and enhance therapeutic consistency in chronic spasticity management.

Materials and Methods

The chemicals and excipients used in this study are pharmaceutical-grade chemicals and were used in the preparation of controlled-release tablets of Tizanidine and were used as received without any further purification. Different laboratory instruments and analytical equipments i.e. Single punch tablet compression machine, HPLC, Dissolution apparatus, Ultrasonic sonicator, Tablet friabilator and Hardness tester were employed during formulation development and characterization All equipment were calibrated and maintained according to Good Laboratory Practice (GLP) standards.

Preparation of Controlled-Release Tablets of Tizanidine:

All excipients and the drug were weighed accurately, passed through a 40-mesh sieve, and blended thoroughly using the tumble mixing method inside a polybag for 8 to 10 minutes. The mixed powders were pressed between two pieces of a single-punch tablet press which was manually operated but had a round and convex shaped punch. The tablets were 96 mg to 126 mg based on the formulation composition.

Three core formulations of Tizanidine controlled-release tablets were prepared using varying drug-to-polymer ratios, as presented in the table below:

S. No.	Formulation Code	Drug-to-Polymer Ratio	Drug (mg)	Polymer (mg)
1	F1	10:1	30 mg	3 mg
2	F2	10:1.5	30 mg	4.5 mg
3	F3	10:2	30 mg	6 mg

Quality control Evaluation of Tizanidine Tablets

All the formulations were evaluated for standard pharmaceutical quality control parameters including:

- Dose uniformity was measured by weight variation by the use of a calibrated digital analytical balance. Weight was measured on individual units and deviations of weight of mean weight were calculated. This test guarantees conformity of dosage and also adherence to pharmacopeial standards since consistent weight is one measure of consistent distribution of drug in solid dosage forms (Bendicho-Lavilla et al., 2024).
- The tablet hardness tester was used to determine the mechanical strength of the formulations by measuring hardness. This test identifies the capability of the tablet to survive the handling, packaging, and transportation without compromising the structure of the tablet and satisfying proper functioning (Zhao et al., 2022)
- A vernier caliper was used to measure the thickness to ensure that the tablets were physically consistent. Regular thickness indicates the same die fill and compression in the

process of manufacturing and is a part of the total quality and dose uniformity (Sultan et al., 2022).

- Friability was determined by use of friabilator to determine resistance to abrasion of the tablet during handling and transportation. The pre-weighed sample of tablets was rotated under standard conditions, and it was followed by re weighing the tablets and calculating the percentage weight loss. An acceptable pharmacopeial range in friability value denotes that the formulation was sufficiently strong mechanically (Pardhi et al., 2024).
- The disintegration time was established by a USP tablet disintegration apparatus which was used to measure the time needed to disintegrate tablets into small fragments in standardized conditions. Even though disintegration is not a major parameter of performance in a controlled-release system, the test was carried out to ensure quality assurance that the tablet integrity was acceptable and that the test satisfied the pharmacopeial standards (Pace et al., 2023) .

Dissolution test

In-vitro dissolution test was performed to compare the profile of drug release of each Tizanidine formulation. The method was based on the USP dissolution technique with the Apparatus II (paddle method) at 50-100 rpm, in 900ml of the dissolution medium kept at 37ºC. To replicate the intestinal conditions, the medium used was selected (i.e., phosphate buffer, pH 6.8) (Sinha et al., 2022). To determine the pattern of drug release of the formulation, the analysis of the release kinetics was done. The in vitro dissolution data were modeled to a zero-order and first-order kinetic model. The percentage of drug released was plotted against time on a cumulative basis on the zero-order model, whereas the logarithm of the rest of the drug was plotted against the time under the first-order model. The model with the highest linearity, according to the regression coefficient (R^2) was taken to explain the release behaviour of the formulation (Askarizadeh et al., 2023).

Results and Discussion

Quality control Evaluation of Tizanidine Tablets

Each of the formulations was assessed based on the standard tablet criteria of weight variation, hardness, thickness, friability, and disintegration time (for reference). These results are summarized in Table 1.

The weights of the tablets fell within the 125 mg to 136 mg range establishing the weights within the 5% mean range per USP specifications. Hardness ranged from 5.2 to 7.5 kg/cm² with the higher values being ascribed to the formulations with more polymer (specifically HPMC K100M). All formulations showed a Friability of less than 0.8% which is an indication of good mechanical strength. The thickness of all formulations was consistent with a range of 3.1mm to 3.8mm. While all formulations were able to have disintegration times of more than 30 minutes which confirmed the formulations were of controlled-release. This reinforces the RTC physical robustness and justifies the need for further evaluation of swelling and dissolution.

Table 1: Post-Compression Evaluation of Tizanidine Tablets

Formulation Code	Avg. Tablet Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disinteg-ration Time (min)	Remarks
F1 (10:1)	98.5 ± 1.2	3.2 ± 0.1	5.3 ± 0.2	0.61	>30	Acceptable
F2 (10:1.5)	112.6 ± 1.4	3.5 ± 0.1	6.4 ± 0.3	0.52	>30	Acceptable
F3 (10:2)	125.4 ± 1.6	3.8 ± 0.2	7.5 ± 0.4	0.48	>30	Acceptable

F1 (Ethocel)	101.3 ± 1.1	3.1 ± 0.1	5.6 ± 0.2	0.67	>30	Acceptable
F2 (Kollidon SR)	116.2 ± 1.5	3.6 ± 0.1	6.1 ± 0.3	0.55	>30	Acceptable
F3 (HPMC K100M)	124.7 ± 1.3	3.8 ± 0.2	7.2 ± 0.3	0.49	>30	Acceptable

In-vitro Drug Release Studies

Drug release from the tablets was assessed over a 12-hour period, and the cumulative release (%) was plotted against time for each formulation. The data are presented in Table 2 and Figures 1.

- Formulation F1 (10:1) released approximately 85% of the drug within 6 hours, indicating faster release due to lower polymer content.
- Formulation F2 (10:1.5) exhibited a more gradual release, with 75% release by 8 hours and extended release up to 12 hours.
- Formulation F3 (10:2) showed sustained release of 90% over 12 hours, particularly in HPMC K100M and Kollidon SR systems.

Ethocel-based formulations demonstrated slower, diffusion-limited release profiles, with only 60–70% release by 12 hours, due to reduced water uptake and limited pore formation. In contrast, HPMC-based formulations released the drug through hydration, swelling, and erosion mechanisms, allowing for a controlled but higher overall release.

These findings confirmed that polymer type and concentration significantly influenced the release profile of Tizanidine from matrix tablets.

Table 2: Cumulative Drug Release (%) at Specific Time Intervals

Time (Hr.)	F1-HPMC K100M	F1-Ethocel 10FP	F1-Kollidon SR	F2-HPMC K100M	F2-Ethocel 10FP	F2-Kollidon SR	F3-HPMC K100M	F3-Ethocel 10FP	F3-Kollidon SR
0	0	0	0	0	0	0	0	0	0
1	25	15	20	20	10	18	18	8	15
2	40	25	35	35	22	30	32	19	28
4	65	38	58	55	34	52	50	31	49
6	82	55	75	70	47	68	68	45	66
8	90	68	86	85	60	82	84	59	80

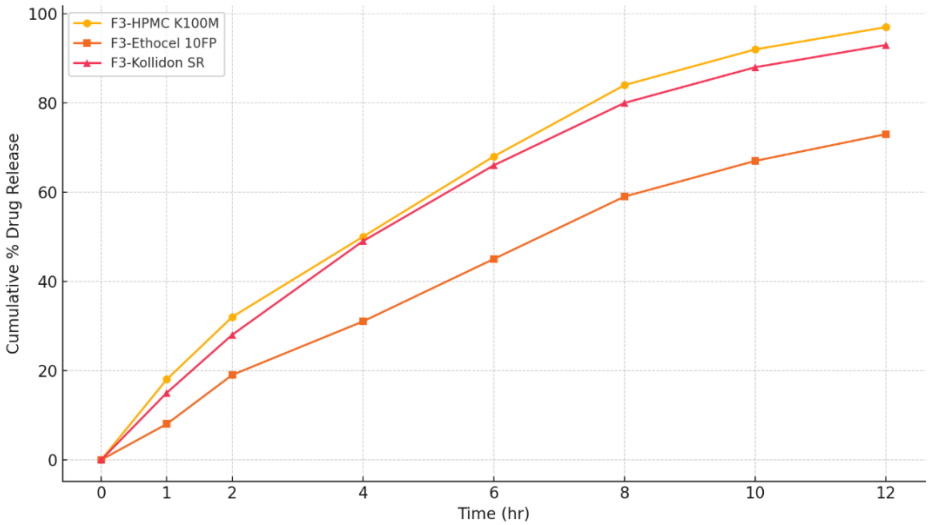

Figure 1: Cumulative Drug Release (%) at Specific Time Intervals

Table 2 and Figure1 show cumulative drug release data for Tizanidine hydrochloride from controlled release matrix tablets incorporating different polymers. For the formulations F1, F2, or F3 (as drug-to-polymer ratios increase these formulations use respectively, more, or less polymer: HPMC K100M, Ethocel 10FP, Kollidon SR). These results illustrate how the type and the amount of polymer affect drug release and diffusion for the controlled release (12 hours).

Drug Release Kinetics and Mechanism

To characterize the mechanism of drug release, the dissolution data were fitted into various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas. The regression coefficients (R^2 values) are summarized in Table 3.

- Most HPMC K100M and Kollidon SR formulations followed Zero-order kinetics ($R^2 > 0.98$), indicating constant drug release independent of concentration.
- Ethocel formulations exhibited Higuchi-type release ($R^2 \sim 0.95–0.97$), supporting a diffusion-dominated release mechanism.
- The Korsmeyer–Peppas model showed release exponent (n) values ranging from 0.45 to 0.89, suggesting that drug release occurred via non-Fickian (anomalous) transport in most hydrophilic formulations and Fickian diffusion in hydrophobic matrices.

Table 3: Kinetic Modeling Parameters for Tizanidine CR Formulations

Formulation Code	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	n-value	Release Mechanism
F1-HPMC K100M	0.976	0.951	0.982	0.988	0.63	Anomalous (non-Fickian) diffusion
F1-Ethocel 10FP	0.891	0.947	0.968	0.971	0.45	Fickian diffusion
F1-Kollidon SR	0.963	0.938	0.979	0.982	0.58	Anomalous diffusion
F2-HPMC K100M	0.987	0.954	0.975	0.991	0.68	Anomalous (non-Fickian) diffusion
F2-Ethocel 10FP	0.902	0.933	0.962	0.963	0.43	Fickian diffusion
F2-Kollidon SR	0.975	0.942	0.980	0.986	0.61	Anomalous diffusion
F3-HPMC K100M	0.991	0.960	0.978	0.994	0.71	Anomalous (non-Fickian) diffusion
F3-Ethocel 10FP	0.905	0.940	0.958	0.968	0.44	Fickian diffusion
F3-Kollidon SR	0.984	0.950	0.981	0.989	0.66	Anomalous diffusion

To better understand the mechanism and rate of drug release from the formulated controlled-release (CR) matrix tablets, the in-vitro dissolution data were subjected to kinetic modeling using various mathematical models: Zero-order, First-order, Higuchi, and Korsmeyer–Peppas equations. Table 3 also presents the correlation coefficients (R^2 values) for each model and the diffusion exponent (n) from the Peppas model, which helps classify the drug release mechanism.

Effect of Polymer Concentration (F1–F3)

A consistent trend across all formulations was that increasing the polymer concentration (from F1 to F3) resulted in:

- Higher R^2 values for Zero-order and Korsmeyer–Peppas models
- Increased n-values, shifting toward non-Fickian mechanisms

This is expected, as greater polymer content enhances matrix integrity, prolongs water penetration time, and strengthens the gel barrier or diffusion path, thereby slowing drug release and improving control. HPMC showed the most prominent shift in kinetics with increasing concentration, highlighting its suitability for dose titration via polymer adjustment.

The kinetic modeling results confirmed that:

- HPMC K100M systems follow Zero-order and anomalous diffusion, ideal for consistent plasma levels.
- Ethocel 10FP exhibits Fickian diffusion with limited swelling and slower release.
- Kollidon SR shows a balanced release mechanism involving both diffusion and erosion.

Conclusion and Recommendations

The current research study investigates the design and assessment of controlled-release matrix tablets of Tizanidine hydrochloride using the different polymers HPMC K100M, Ethocel 10FP, and Kollidon® SR, with varying drug-to-polymer ratios of 10:1, 10:1.5, and 10:2. The main aim was to address the challenges posed by the immediate-release formulations regarding short half-life, inconsistent plasma levels, and poor patient compliance due to frequent dosing. All of the formulations also for post compression evaluation completed the necessary requirements and standards for the tablets in terms of hardness and friability, as well as weight uniformity, thickness and the friability. The tablets that were HPMC based also showed primary strength above the rest of the tablets and thus lower friability made them more compact for sustained periods of transit in the GI. Over a 12-hour period, the in-vitro dissolution studies showed that the type and the amount of the polymer used do affect drug release. HPMC HAD the longest and most complete release profiles, CI. Zero-order release. Breathe easy, HPMC works. Balancing releases formulated with Kollidon, Ethocel, had decreased, slower, diffusion-based release and did not complete drug release by 12 hours. Kinetic modeling corroborated the previously described results… Ethocel-based formulations were best described by Fickian diffusion, fitting the Higuchi. HPMC and Kollidon tablets SR used were anomaly guided drift, combination of swelling and drift diffusion as well as some form of erosion with scaffolding and gas binding to the polymer while Ethocel was best described and aligned to the Fick Model. R^2 and the Peppas n values also showed that swelling dominance of the polymer and the cohesion of the matrix is the controlling factor. Higher grade/preferred HPMC matrices (K100M, esp in F3) resulted in the most complete release, Tizanidine had the best release kinetics, mechanical props, and predictable kinetics. Region de. Release Kollidon SR, Release Ethocel proficiency decreases with complete diffusion release. Ethocel works best with mobile co-polymers and improved retarding features and may have to be used with Ethocel especially for applications with slow release.

Based on the findings of this study, the following future directions are recommended:

1. In-vivo pharmacokinetic and bioavailability studies should be conducted to establish an in-vitro/in-vivo correlation (IVIVC), particularly for the HPMC and Kollidon SR-based formulations.
2. Further research may include patient-centric assessments, such as acceptability, adherence, and therapeutic outcomes, in clinical settings.
3. Investigations into advanced drug delivery systems, such as multi-layered tablets, microspheres, or lipid-based carriers, may offer even more tailored release profiles.
4. Stability studies under ICH conditions should be extended to confirm long-term shelf life, especially for commercial development.

5. Exploration of abuse-deterrent or night-time release technologies may expand the therapeutic application of Tizanidine in spasticity management.

Conflict of interest

We have no conflict of interest.

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