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TIME-TAILORED TREATMENT: OPTIMIZING CARDIAC ARREST MANAGEMENT WITH CHRONOMODULATED DELIVERY OF TORSEMIDE USING CELLULOSE ACETATE PHTHALATE POLYMER

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ABSTRACT

Background: The objective of this study was to design and assess Chronomodulated matrix tablets containing Torsemide. **Methodology**: The Chronomodulated matrix tablets of Torsemide were formulated via the wet granulation method. Different concentrations of cellulose acetate phthalate and hydroxypropyl methylcellulose K4M were employed to assess their effects on drug release kinetics. For prolonged drug release, an enteric coating polymer, cellulose acetate phthalate, was integrated. Under alkaline conditions, cellulose acetate phthalate dissolves, thereby facilitating drug liberation. **Results**: The formulated tablets underwent pre-compression and post-compression evaluations, yielding results compliant with the standards outlined in the Indian Pharmacopoeia. The optimized formulation demonstrated a 2-hour lag period and achieved an 87.67% drug release over 10 hours, characterized by a non-Fickian mechanism and zero-order release kinetics. Furthermore, the formulation exhibited physical stability throughout short-term stability studies. These Torsemide matrix tablets present a promising strategy for achieving prolonged and sustained drug release. **Conclusion**: Chronomodulated drug delivery of Torsemide demonstrates promising potential in offering effective treatment for patients at risk of cardiac arrest by releasing the drug in synchrony with the circadian rhythm, thereby targeting the times when symptoms are most likely to manifest.

INTRODUCTION:

Chrono-therapeutics represents a strategic approach to synchronizing medication administration with the body's innate biological rhythms, aimed at mitigating adverse effects while maximizing therapeutic efficacy. This methodology employs chrono-modulated dosage forms that release medication in a concentrated burst following a predetermined delay, thereby optimizing absorption dynamics and achieving an ideal plasma concentration profile over time. Many chronic diseases, such as asthma, arthritis, ischemic heart disease, and hypertension, exhibit pronounced circadian variations in Symptom severity, necessitating precise temporal drug delivery for optimal treatment outcomes. These conditions often manifest exacerbations during early morning or late-night periods, rendering conventional immediate-release formulations less effective. In contrast, controlled or sustained-release systems engineered for zero-order release kinetics maintain steady drug levels throughout the day. This consistency in drug concentration offers superior management of symptoms such as cardiac events, morning stiffness associated with arthritis, and nocturnal exacerbations of asthma. By aligning drug delivery with the

body's natural oscillations, chrono-therapeutic approaches hold promise for enhancing treatment efficacy and patient outcomes in chronobiologically influenced diseases. [1,2] Torsemide, a loop diuretic renowned for its effectiveness in treating fluid overload associated with conditions such as hypertension, heart failure, kidney disease, and liver disease, has garnered attention for its potential role in cardiac arrest scenarios. By targeting the thick ascending limb of the loop of Henle, Torsemide facilitates the rapid excretion of water, chloride, and sodium ions, thereby aiding in fluid management critical during cardiac arrest management. Orally administered, Torsemide demonstrates rapid absorption, achieving peak plasma concentrations within an hour. Its oral bioavailability, notably around 80% in healthy individuals and potentially higher in patients with edema, underscores its reliable uptake profile. With an average half-life of 3.5 hours, Torsemide is efficiently metabolized hepatically and eliminated via urinary excretion, ensuring swift clearance from the circulatory system. These pharmacokinetic properties position Torsemide as a promising candidate warranting further exploration in cardiac arrest management strategies. [3] Matrix systems are frequently utilized in the formulation of controlled-release dosage forms. These systems entail the compression of a blend comprising the drug, a retardant material, and additives into a tablet matrix. This matrix serves as a reservoir for the drug, and its release is governed by hydrophobic polymers, which impede liquid ingress and promote drug release via diffusion mechanisms. In contrast, hydrophilic polymers provide versatility in achieving specific drug release profiles owing to their substantial gelling capacity, thereby regulating the kinetics of drug release. [4,5] Formulating Chronomodulated Torsemide tablets for the management of hypertension represents a significant advancement in therapeutic strategy. These specialized tablets are engineered to release Torsemide in a time-dependent manner that aligns with the body's circadian rhythm, thereby optimizing treatment efficacy during critical periods of symptom exacerbation. The formulation process employed a rigorous optimization strategy based on a 3^2 factorial design, ensuring precise control over drug release kinetics and therapeutic effectiveness throughout the day. Such chrono-modulated formulations not only enhance drug efficacy but also aim to improve patient compliance and overall treatment outcomes. They represent a promising avenue in cardiovascular medicine, offering the potential to stabilize patients at risk of cardiac arrest through targeted and temporally optimized drug delivery strategies.

MATERIALS AND METHODS

2.1 Materials: Torsemide was generously provided as a gift sample by Alkem Laboratories Ltd., Mumbai, India. CAP was procured from Yarrowchem Products, Mumbai. HPMC K4M, Guar Gum, Lactose, and Magnesium Stearate were sourced from Himedia Pvt. Ltd., Mumbai. Talc was obtained from Ozone International Pvt. Ltd., while Starch was acquired from Loba Chemie Laboratory Reagents, Mumbai

2.2 Methods

2.2.1 Fourier Transform Infrared Spectroscopy (FTIR): The Fourier-transform infrared (FTIR) spectra of both the pure Active Pharmaceutical Ingredient (API) and its respective excipients were acquired using a Shimadzu FTIR spectrometer. Pellets containing the drug were formulated with potassium bromide (KBr) and subjected to scanning over the spectral range of 400 to 4000 cm^{-1}. The obtained spectra were meticulously analyzed to discern and characterize functional groups present within the formulation. [6, 7]

2.2.2 Differential Scanning Calorimetry (DSC): Shimadzu model DSC-60 thermal analysis system was employed to acquire differential scanning calorimetry (DSC) thermograms. Physical mixtures comprising the drug and excipients were precisely weighed and encapsulated in aluminum crucibles equipped with lids. The experiments were conducted under a nitrogen atmosphere at a controlled heating rate of 10°C per minute,

spanning a temperature gradient from 30°C to 350°C. [8]

2.2.3 Preparation of Torsemide Matrix Tablets: Chronomodulated matrix tablets of Torsemide were formulated via the wet-granulation method. Table 1 provides a comprehensive breakdown of the tablet's components. Prior to granulation, all ingredients, excluding magnesium stearate and talc, underwent sieving through a #20 mesh. Subsequently, a starch paste granulating solution was meticulously integrated into the dry blend and blended for 10-15 minutes. The resultant dough mass was further processed through a #12 mesh screen and subjected to a 30-minute drying period at 50°C. Following partial drying, the granules were double-screened through a #22 mesh followed by a #44 mesh to ensure uniform particle size. To finalize the formulation, precise quantities of talc and magnesium stearate were thoroughly incorporated into the granules. Compression was achieved using an 8mm flat-faced punch on a tablet punching machine (Rimek Mini Press-I), yielding individual tablets weighing 200 mg each. The flow diagram depicting the aforementioned process is illustrated in Figure 1. [9,10]

Figure 1: Preparation of Torsemide matrix tablets.

2.2.4 Experimental Design: To develop a matrix tablet formulation, a comprehensive 3^2 full factorial design approach was employed to determine the optimal polymer type and quantity essential for achieving targeted hardness and drug release characteristics. This experimental design involved the selection of nine distinct formulations based on systematic variations of two independent variables: X1, representing Cellulose Acetate Phthalate (CAP) content, and X2, representing Hydroxypropyl Methylcellulose (HPMC K4M) content. The dependent variables assessed were Y1, indicating the percentage of drug release at the 10th hour, and Y2, reflecting the hardness of the tablets. Statistical analysis of the experimental outcomes was conducted using Design Expert version 13.0.11.0 software to determine the significant effects of the independent variables on the responses. The analytical process included the generation of contour plots and 3D response surface plots to visualize and interpret the influence of CAP and HPMC K4M on drug release and tablet hardness. These plots provided crucial insights into the interplay between formulation components and their impact on the desired pharmaceutical attributes. The formulation table, derived through the application of Design Expert software, is presented in Table 1. This table encapsulates the comprehensive formulation parameters and their respective levels, meticulously optimized to achieve the desired pharmaceutical characteristics. [11]

Table 1: Formulation table derived through Design Expert software

2.2.5 Pre-compression evaluations [12]

Flow Properties Assessment of Granules from Various Batches (F1-F9): The flow properties of granules from batches F1 to F9 were comprehensively evaluated through the determination of bulk densities, tapped densities, angles of repose, Carr's compressibility indices, and Hausner's ratios. These parameters are crucial indicators of the physical characteristics and flow behaviour of pharmaceutical granules.

Bulk Density and Tapped Density Measurement: Bulk density and tapped density measurements were conducted using a tapped density instrument (Electro Lab, India) equipped with a graduated cylinder. The procedure involved weighing the granules and transferring them into a measuring cylinder to record the bulk volume. Subsequently, the same instrument was used to determine the tapped density. Both densities were calculated in grams per millilitre (g/mL) using the following formulas:

$$\text{Bulk Density (g/mL)} = \frac{\text{Mass of the Powder}}{\text{Bulk Volume}}$$

$$\text{Tapped Density (g/mL)} = \frac{\text{Mass of the Powder}}{\text{Tapped Volume}}$$

These measurements provide insights into the packing characteristics and particle arrangement within the granules, essential for understanding their flow properties and

potential implications for manufacturing processes and dosage form performance. This detailed assessment allows for a comprehensive comparison across different batches (F1-F9), aiding in the optimization of formulation parameters and ensuring consistent product quality and performance in pharmaceutical applications

Compressibility Index (Carr's Index):

Carr's index serves as a crucial metric in assessing the flow properties of granules or powders, essential in pharmaceutical and powder technology. It is computed using the formula:

$$\text{Carr's Index } (\%) = \frac{VT - VL}{VT} * 100$$

Where VT represents the total volume occupied by the sample, and VL denotes the volume after tapping, an essential step to simulate bulk density post-handling.

This index quantifies the powder's compressibility: lower values indicate better flow properties, implying minimal volume change upon tapping and better suitability for manufacturing processes such as tableting and encapsulation. Conversely, higher values signify poor flowability, necessitating modifications in formulation or processing to enhance handling efficiency and dosage uniformity. In conclusion, Carr's index serves as a pivotal tool in the pharmaceutical industry, aiding in the optimization of powder flow characteristics critical for product quality and manufacturing efficiency.

Hausner's Ratio: Hausner's Ratio (HR), a critical parameter in pharmaceutical formulation, assesses the flow properties of granules, influencing their manufacturability and efficacy. It is calculated using the formula:

$$\text{Hausner's Ratio (HR)} = \frac{Tapped\ density}{Bulk\ density}$$

Where the tapped density represents the density of a powder or granule after it has been tapped or compacted to minimize void spaces, and the bulk density denotes the density of the powder in its loose, unpacked state. A lower Hausner's Ratio indicates better flow properties, suggesting that the granules can flow more easily during processing, facilitating uniform compression into tablets. Conversely, a higher ratio indicates poorer flow properties, which may lead to issues such as uneven distribution of active pharmaceutical ingredients (APIs) or inconsistent tablet weights.

Therefore, Hausner's Ratio serves as a crucial indicator during formulation development, aiding in optimizing granule characteristics to ensure robust manufacturing processes and reliable pharmaceutical products.

Angle of Repose:

The angle of repose refers to the maximum angle observed between the surface of a horizontal plane and the slope formed by a pile of granular material poured onto it from a fixed height. This measurement is crucial in understanding the flow properties of granular substances. To determine the angle of repose, the funnel method was employed. Initially, a pre-measured quantity of granules was introduced into a funnel secured on a stand, with its outlet sealed. Upon releasing the granules, they naturally accumulated into a conical heap on the surface below. The diameter of this heap was carefully recorded once the apex of the heap touched the tip of the funnel. The angle of repose (θ) was subsequently computed using the formula:

$$\text{Angle of repose} = \frac{h}{r}$$

Where:

- h represents the height of the cone (heap) formed,
- r denotes the radius of the base of the cone (heap).

This method allows for precise measurement and characterization of the flow behavior of granular materials, essential for applications in pharmaceutical manufacturing

2.2.6 Physical evaluation of matrix tablets [13]

Weight Variation: Twenty tablets were randomly sampled from each batch, and their individual weights were measured. The average weight of these tablets was

subsequently computed to establish a batch-specific mean. The percentage deviation from this mean weight was then calculated for each tablet to quantify the extent of weight variation within the batch. This method enabled the assessment of uniformity in tablet weight across different batches.

Thickness: To evaluate tablet thickness consistency within each batch, five tablets were randomly chosen and measured using a Vernier calliper. The resulting measurements were used to compute the standard deviation, providing insight into the variability of tablet thickness. This approach facilitated a thorough examination of the uniformity in tablet dimensions across the sampled batches.

Hardness: Tablet hardness refers to the force required to break a tablet in diametric compression. For this study, five tablets were randomly selected from each batch and assessed using a Monsanto hardness tester. The obtained hardness values were used to calculate the standard deviation, providing a measure of the uniformity of tablet hardness within the batch.

Friability: Friability testing involved placing twenty pre-weighed tablets into a friabilator and subjecting them to a specified number of rotations. Post-testing, the tablets were cleaned to remove any debris and re-weighed. The percentage friability was then determined using the formula: % Friability = (Initial Weight - Final Weight) / Initial Weight * 100.
This test serves to evaluate the tablets' resistance to mechanical stress during handling and transportation.

Drug Content: The drug content of the tablets was determined by randomly selecting five tablets from each batch, crushing them, and extracting a portion equivalent to 40 mg of Torsemide. This extract was dissolved in a suitable buffer solution, and its absorbance was measured using a UV spectrophotometer. Triplicate measurements were taken for each tablet, and the average value was calculated. The standard deviation of these measurements provided an assessment of the consistency of drug content across the batch.

In-Vitro Dissolution Study: The dissolution study employed USP dissolution apparatus type II, with tablets immersed in varying pH solutions. Samples were periodically withdrawn, and their absorbance was quantified. This investigation aims to characterize the dissolution behaviour of the tablets across different time intervals and environmental conditions.

Release Kinetics: Software analysis was utilized to fit dissolution data to several kinetic models, including the Peppas model, Higuchi matrix, zero-order, and first-order models. This approach facilitated the elucidation of the release mechanism and kinetics governing drug liberation from the tablets. [14]

Short-Term Stability Studies: Stability assessments were conducted under accelerated conditions to evaluate the tablets' performance over time. Exposure to controlled temperature and humidity settings preceded evaluations for hardness, friability, drug content uniformity, and in-vitro drug release profiles. These studies provide critical insights into the tablets' stability under simulated storage conditions. [15]

Comparison of Dissolution Profile with Marketed Product: A comparison of the dissolution profile between the optimized batch and a commercially marketed product was conducted to assess performance. The optimized batch was selected for its superior drug delivery characteristics relative to other formulations, as determined through comprehensive plotting and analysis.

1. RESULTS AND DISCUSSION

3.1 Fourier transform infrared spectroscopy

Fourier Transform Infrared Spectroscopy (FT-IR) is a pivotal analytical technique employed for elucidating the chemical composition of substances through the measurement of infrared light absorption. This method is particularly valuable in pharmaceutical studies, where it facilitates the characterization of Active Pharmaceutical Ingredients (APIs) and their formulations. In the present investigation, FT-IR spectra were meticulously acquired for both the pure API and a composite comprising the drug integrated with polymers. These

spectra were meticulously scrutinized to identify characteristic functional peaks, which signify specific chemical bonds and functional groups within the molecular structure. [18]

The preservation of these functional peaks at anticipated wavelengths, devoid of substantial alterations, serves as a robust indicator that the chemical integrity of the drug remains uncompromised. Such integrity is imperative as it underscores the drug's efficacy and safety profile. Illustratively, Figure 2a and 2b present the FT-IR spectra of the pure API and the drug-polymer amalgam, respectively. Notably, these spectra manifest negligible deviations in their functional peaks, reinforcing the inference that the chemical structure of the drug has sustained its original form throughout the mixing process. This finding substantiates the pivotal role of FT-IR spectroscopy in ensuring the fidelity of pharmaceutical formulations, thereby safeguarding therapeutic efficacy and patient safety.

Figure 2a: FT-IR Spectra of Torsemide

Figure 2b: FT-IR Spectra of physical mixture

3.2 Differential scanning calorimetry

The DSC thermograph of pure Torsemide prominently manifested a singular endothermic peak at 167°C, distinctly signifying its melting point. Notably, this observed peak aligns meticulously within the stipulated range specified by the IP monograph, validating the thermal integrity of the substance. Equally significant, the DSC thermograph of Torsemide in conjunction with polymers exhibited a comparably sharp endothermic peak, indicative of harmonious compatibility between the drug and the polymer matrix.[18]

The demonstrated compatibility between Torsemide and the polymers holds profound implications for the formulation process, ensuring the robust stability and therapeutic efficacy of the drug within complex pharmaceutical matrices. This finding underscores the critical role of DSC in elucidating thermal behaviour crucial for optimizing drug formulation strategies and ensuring product efficacy and safety. The DSC thermogram of pure torsemide and physical mixture is illustrated in Figure 3 and Figure 4

Fig. 3: DSC thermogram of pure Torsemide

Fig. 4: DSC thermogram of physical Mixture

3.3 Determination of flow characters of APIs and blend of batches (F1 – F9)

Determining the flow characteristics of Active Pharmaceutical Ingredients (APIs) and blends of batches (F1 – F9) is important for tablet compression processes. The flow characteristics of powders impact how well they can be compressed into tablets, affecting the accuracy of analysis and the distribution of the drug within the tablet. Poor flow characteristics can lead to uneven drug distribution and may affect the performance of the final product. Therefore, understanding and optimizing the flow characteristics of APIs and blends are crucial steps in pharmaceutical manufacturing.

Based on the findings from the compressibility index (%) and Hausner's ratio, it was observed that the granules exhibited favourable flow characteristics. Detailed micromeritic properties are presented in Table 2.

Table 2: Micromeritic Properties of API Blend of all formulations

3.4 Evaluation of Matrix Tablets:

The assessment of matrix tablets involved a comprehensive analysis of various parameters, including average weight, thickness, friability, hardness, drug content, and in-vitro dissolution profiles. The results, as detailed in Table 3, encompassed a range of measurements across different formulations (F1 to F9).

Table 3: Physical evaluation of matrix tablet

3.4.1 Weight of the tablets [17]

Regarding average weight, the tablets exhibited a range from 194.9± 0.24mg to 199.4 ± 0.10 mg, all falling within acceptable limits.

Impact on Dissolution Rate: The weight of a tablet is a critical determinant of its surface area, which directly influences the dissolution rate of the active pharmaceutical ingredient (API). Heavier tablets typically contain more bulk material, potentially decelerating the dissolution process. This delay can affect the drug's bioavailability and therapeutic efficacy, as the release of the API into the bloodstream may be slower than intended.

Patient Compliance: Larger, heavier tablets can present difficulties in swallowing, especially for paediatric and geriatric populations. This issue can negatively impact patient compliance, as the discomfort associated with swallowing large tablets may deter adherence to prescribed medication regimens.

3.4.2 Thickness [17]

Thickness measurements varied from 3.8 ± 0.065mm to 4 ± 0.08mm.

Influence on Disintegration: The thickness of a tablet can markedly influence its disintegration time. Thicker tablets may require more time to break down in the gastrointestinal tract, potentially delaying the release and subsequent absorption of the API. This delay can affect the onset of the drug's therapeutic action.

Mechanical Strength: Tablet thickness contributes significantly to the structural integrity of the dosage form. While thicker tablets are generally more resistant to physical damage, such as breaking or crumbling, it is essential that they still disintegrate efficiently upon ingestion. Ensuring a balance between mechanical strength and disintegration is critical for optimal therapeutic efficacy.

Manufacturing Considerations: Consistency in tablet thickness within a production batch is crucial for maintaining uniform dosage and performance. Variations in thickness can lead to dose inaccuracies, compromising the reliability of therapeutic outcomes. Strict quality control measures must be implemented to ensure uniformity in tablet thickness during manufacturing.

3.4.3 Hardness [17] Hardness ranged between 4 ± 0.08 - 5.5 ± 0.04 Kg/cm^2

Impact on Disintegration and Dissolution: Tablet hardness is a pivotal parameter that influences both disintegration and dissolution rates. Excessively hard tablets may not disintegrate properly, resulting in delayed drug release. Conversely, tablets that are too soft may crumble easily, leading to dose inaccuracies and potential loss of therapeutic effectiveness.

Mechanical Stability: Optimal hardness is essential to ensure that tablets can withstand mechanical stresses encountered during handling, packaging, and transportation. Maintaining the tablet's integrity until it reaches the patient is vital for ensuring the correct dosage and therapeutic efficacy.

Patient Experience: For chewable or orally disintegrating tablets, hardness affects the mouthfeel and ease of administration. Achieving the right balance of hardness is crucial for ensuring patient acceptance and adherence to the medication regimen. Tablets that are too hard may be uncomfortable to chew, while those that are too soft may not provide the intended sensory experience.

3.4.4 Friability [17]

Friability percentages were observed between 0.48 ± 0.007% to 0.51 ± 0.008%.

Handling and Packaging: Friability, or the tendency of a tablet to crumble, has a direct impact on handling and packaging characteristics. Tablets with low friability are less likely to break or crumble during manufacturing, transportation, and storage, ensuring that they remain intact until administration.

Dosage Accuracy: Low friability is essential for maintaining accurate dosing. Tablets that crumble easily can result in the loss of material, leading to inaccurate dosing and potentially compromising therapeutic efficacy. Ensuring low friability is crucial for the reliability of the dosage form.

Manufacturing Efficiency: The friability of tablets also affects production efficiency. Tablets with high friability can lead to increased waste and necessitate more stringent quality control measures, impacting overall manufacturing costs. Ensuring optimal friability enhances manufacturing efficiency and product quality.

3.4.5 Drug content [17] Drug content percentage spanned from 80.44 ± 0.65% to 87.89 ± 0.21%.

Uniformity and Consistency: Uniform drug content within tablets is paramount for ensuring that each dosage unit delivers the intended amount of API. Variations in drug

content can result in inconsistent therapeutic outcomes and pose potential safety risks. Ensuring uniformity in drug content is a fundamental aspect of quality control in tablet manufacturing.

Therapeutic Efficacy: Accurate drug content is critical for achieving the desired therapeutic effect. Each tablet must contain the precise amount of API to ensure consistent and effective treatment. Deviations from the intended drug content can compromise the medication's efficacy and safety.

Regulatory Compliance: Adherence to regulatory standards for drug content uniformity is essential for product approval and market acceptance. Regulatory agencies require stringent quality control measures to ensure that each tablet meets specified criteria for drug content. Compliance with these standards is crucial for the successful commercialization of pharmaceutical products.

3.4.6 *In-vitro* dissolution studies [17]

The results of the in-vitro drug dissolution study for formulations F1, F2, and F3 revealed substantial drug release percentages of 99.24%, 96.325%, and 93.25%, respectively, at the 6-hour mark (Figure 5). These formulations were evaluated under simulated gastric conditions with a pH of 1.2 using 0.1N hydrochloric acid (HCl), where drug release occurred effectively due to the absence of the enteric coating polymer cellulose acetate phthalate (CAP).

Fig. 5: In-vitro cumulative percent drug release of F1-F9

In contrast, batches F4, F5, F6, F7, F8, and F9 exhibited drug release percentages of 87.67%, 85.86%, 83.71%, 79.70%, 77.84%, and 75.86%, respectively, observed at the 10-hour mark (see Figure 5). These formulations experienced an initial 2-hour delay before drug release initiation, attributed to the presence of an enteric coating polymer designed to resist dissolution in acidic environments. Following this initial lag, sustained drug release patterns were observed in a pH 6.8 medium, facilitated by the incorporation of HPMC K4M as detailed in Table 4.

Table 4: *In-vitro* dissolution data of Torsemide matrix tablets formulation (F1-F9).

These findings underscore the influence of formulation components on drug release kinetics, with formulations lacking an enteric coating showing rapid and complete drug release in acidic conditions, while those with an enteric coating demonstrated delayed release followed by prolonged release in a less acidic environment. The use of CAP in formulations F4 to F9 effectively targeted drug release to the intestinal region by preventing premature release in the acidic stomach environment. This delayed release mechanism ensures that the drug is delivered to the desired site of action, minimizing potential side effects and optimizing therapeutic efficacy. The incorporation of HPMC K4M further facilitated sustained drug release, offering controlled and prolonged drug delivery suitable for various therapeutic applications.

These findings highlight the critical role of enteric coating polymers like CAP and viscosity-modifying agents such as HPMC K4M in tailoring drug release kinetics for enhanced therapeutic outcomes, emphasizing their potential in the development of effective oral drug delivery systems.

3.4.7 Release kinetics [16, 17]

The experimental results revealed distinct release patterns for the various formulations. Specifically, formulations F1, F2, and F3 exhibited release rates consistent with a first-order release pattern, which conforms to the principles of Fickian diffusion as described by Peppas. The correlation coefficients (R values) for these formulations were impressively high, ranging from 0.9174 to 0.9273, indicating a strong fit to the first-order kinetic model. The release exponent "n" values calculated from the Korsmeyer-Peppas equation fell within the narrow range of 0.44 to 0.47. These values are characteristic of a controlled release mechanism predominantly governed by diffusion processes, where the rate of drug release is proportional to the concentration gradient. In contrast, formulations F4 through F9 demonstrated release kinetics that adhered

to a zero-order release pattern. This pattern is indicative of a non-Fickian diffusion mechanism, wherein the drug release rate remains constant over time, independent of its concentration. The correlation coefficients (R values) for these formulations ranged from 0.9375 to 0.9283, suggesting a robust fit to the zero-order kinetic model. More interestingly, the release exponent "n" values derived from the Korsmeyer-Peppas equation for these formulations were significantly higher, ranging from 1.5 to 1.72, as illustrated in Table 5. Such elevated "n" values imply a more complex release mechanism that likely involves additional factors beyond simple diffusion.

Table 5: Drug Release Kinetics of Formulation (F1- F9)

These high "n" values could be attributed to mechanisms such as the swelling of the polymer matrix or the erosion of the drug delivery system, which facilitate a more sustained and controlled release of the drug. Swelling occurs when the polymer matrix absorbs fluid and expands, allowing for a more gradual and controlled release of the drug as the matrix gradually disintegrates. Erosion, on the other hand, involves the gradual breakdown of the polymer matrix, which also contributes to a sustained release profile.

The release profiles of the formulations studied exhibit distinct kinetic behaviors. Formulations F1, F2, and F3 align with a Fickian diffusion mechanism, characterized by first-order kinetics and moderate "n" values. Meanwhile, formulations F4 through F9 demonstrate a more complex release mechanism, characterized by zero-order kinetics and significantly higher "n" values, suggesting the involvement of additional factors such as matrix swelling or erosion.

3.4.8 Comparison of dissolution profile of optimized formulation with marketed product: A comparative assessment between the optimized formulation (F4) and a marketed product highlighted distinct release profiles. While the marketed product exhibited an initial burst release with 98.87% drug release by the 5th hour, the optimized formulation demonstrated a delayed release followed by a burst effect, culminating in an 87.67% drug release by the 10th hour (Figure 6).

Fig. 6: Comparison of In-Vitro drug release profile of optimized formulation(F4) and marketed formulation.

3.4.9 Optimization results [16] The findings from the full factorial study are comprehensively detailed in the following sections:

Response – 1: *In-Vitro* Dissolution (%) The assessment of in-vitro dissolution percentage involves quantifying the amount of drug substance that dissolves within a specified period under simulated physiological conditions, replicating those encountered outside a living organism.

Analysis of Variance (ANOVA) Table 6 summarizes the ANOVA results for the selected factorial model. The computed F-value of 53.91 indicates a statistically significant effect of the model. This underscores that the factors and their interactions investigated in the study exert a substantial influence on the in-vitro dissolution percentage.

Table 6: ANOVA for Response-1 factorial model.

Significance of Model Terms: The significance of each term within the model is determined using Prob>F values. Notably, all Prob>F values are below the conventional threshold of 0.05. This robustly signifies that both the main effects and interactions incorporated in the factorial design are statistically significant in explaining the observed variations in in-vitro dissolution percentage. This statistical confidence underscores the reliability of the model in predicting and optimizing dissolution characteristics crucial for drug delivery systems.

Response surface analysis: Response surface analysis entails investigating the interdependency between multiple variables and a desired response. In this study, the utilization of 3D response surface plots and 2D counter plot analyses elucidates the substantial impact of HPMC K4M and cellulose acetate phthalate concentrations on the rate of in-vitro

dissolution. Notably, escalating concentrations of these polymers correlate with extended drug release durations under simulated in-vitro conditions.

Figure 7 illustrates the three-dimensional response surface plot, providing a visual representation of how changes in both polymer concentrations affect the dissolution rate. Meanwhile, Figure 9 presents the corresponding two-dimensional counter plot, offering a detailed contour map that further elucidates the interaction between these variables and their impact on drug release dynamics.

Fig. 7: Contour plot and response surface plot showing the effect of concentration of CAP (X1) and HPMC K4M (X2) on In-Vitro drug release (Y1)

Response –2 Hardness

The analysis of variance (ANOVA) results for the factorial model selected are summarized in Table 7. The obtained F-value of 7.32 indicates the overall significance of the model in explaining the variation observed in tablet hardness. Importantly, all Prob>F values are below 0.05, underscoring the statistical significance of each term included in the model.

Table 7: ANOVA for response 2 Factorial model

Response Surface Analysis: Moving to response surface analysis, this study utilized both 3D response surface plots and 2D contour plots to explore the relationship between tablet hardness and the concentrations of HPMC K4M and cellulose acetate phthalate. These analyses revealed a substantial and statistically significant impact of polymer concentrations on tablet hardness. Specifically, increasing concentrations of HPMC K4M and cellulose acetate phthalate led to a pronounced elevation in tablet hardness, as illustrated in detail in Figures 8 and 9.

In Figure 8, the 3D response surface plot vividly depicts how varying concentrations of HPMC K4M and cellulose acetate phthalate interact to influence tablet hardness. The plot demonstrates that higher concentrations of both polymers generally result in increased tablet hardness, suggesting a synergistic effect. Additionally, Figure 9 provides corresponding 2D contour plots, offering a more detailed view of the relationship between the two variables and tablet hardness.

Figure 8: Contour plot and response surface plot showing the effect of concentration of CAP (X1) and HPMC K4M (X2) on hardness (Y2)

Figure 9: Optimization of matrix tablet of Torsemide (a) Desirability, (b) Overlay plot

3.4.10 Stability studies

Stability studies were meticulously executed to rigorously assess the durability and performance consistency of the optimized matrix tablet formulation over a defined short-term period. The comprehensive findings, meticulously recorded in Table 8, unveil a reassuring picture of the formulation's resilience. Throughout the study, there were no significant deviations observed in crucial parameters such as drug content uniformity, tablet hardness, and dissolution profiles. These results underscore the formulation's robust stability profile, affirming its capacity to sustain structural integrity and therapeutic efficacy under the specified experimental conditions.

Table 8: Stability data of optimized formulation

CONCLUSION

The present study utilized HPMC K4M and cellulose acetate phthalate polymers to develop chronomodulated matrix tablets for Torsemide, employing a 3^2 factorial design. Analysis of the data demonstrated a negative relationship between polymer concentration and drug release, underscoring the beneficial role of these polymers in achieving sustained release profiles. The optimized formulation exhibited zero-order release kinetics and followed a non-Fickian diffusion mechanism. Therefore, chronomodulated delivery of Torsemide shows potential for effectively treating patients vulnerable to cardiac arrest by synchronizing drug release with circadian rhythms, thereby targeting peak symptomatology periods.

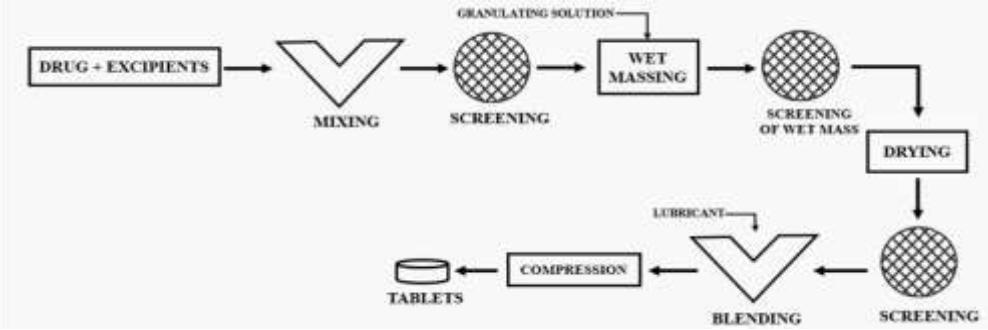

Figure 1: Preparation of Torsemide matrix tablets.

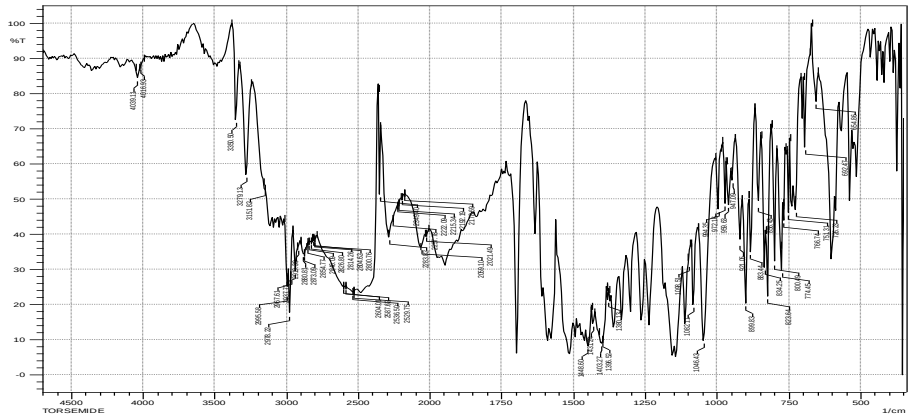

Figure 2a: FT-IR Spectra of Torsemide

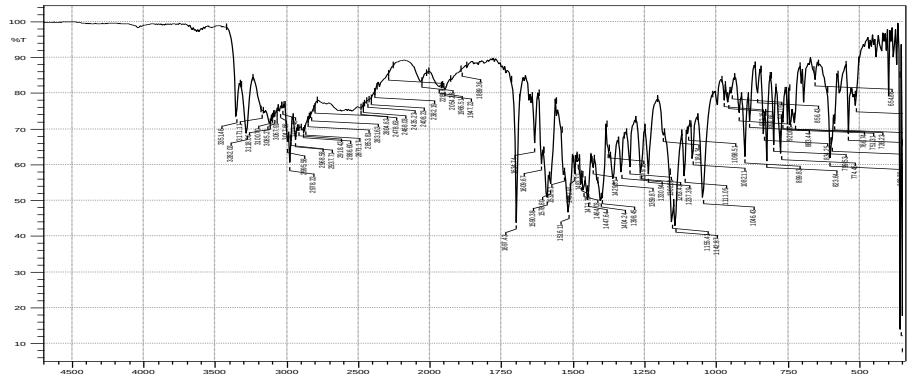

Figure 2b: FT-IR Spectra of physical mixture.

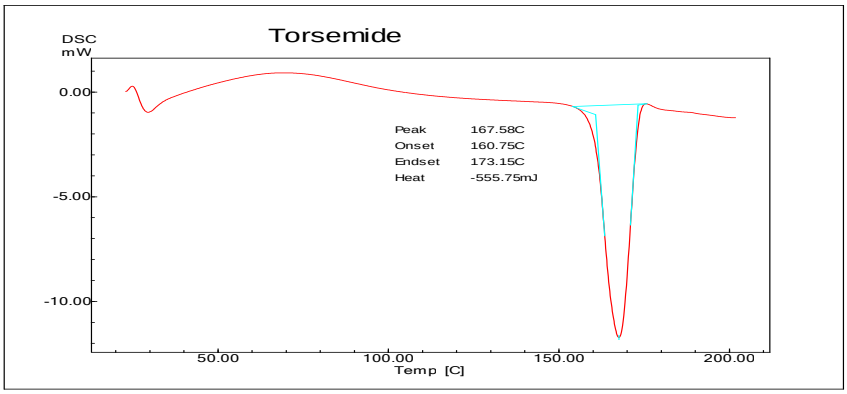

Figure 3: DSC thermogram of Pure Torsemide

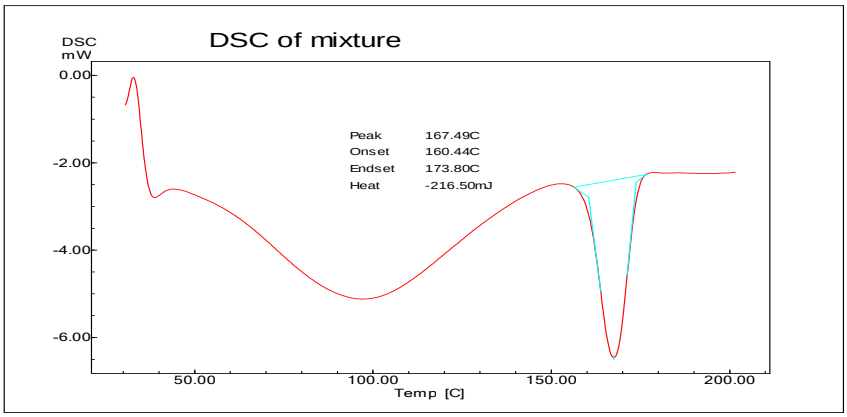

Figure 4: DSC thermogram of physical Mixture

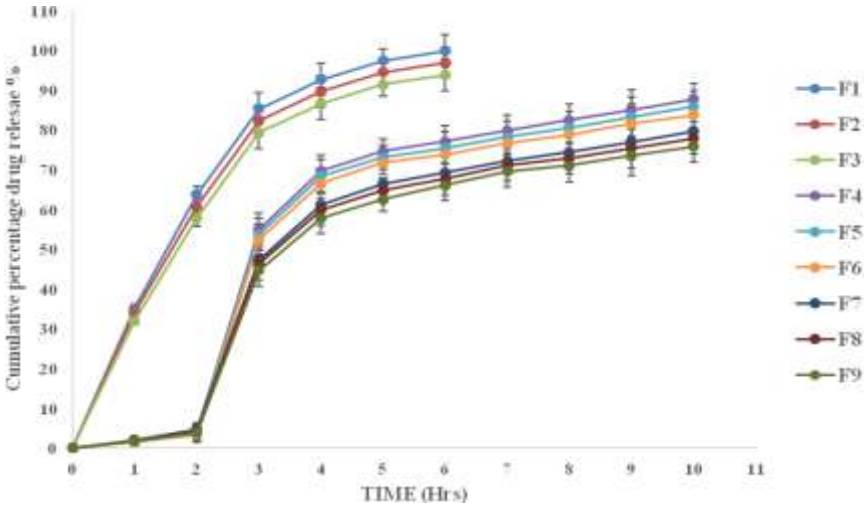

Figure 5: *In-vitro* cumulative percent drug release of F1-F9

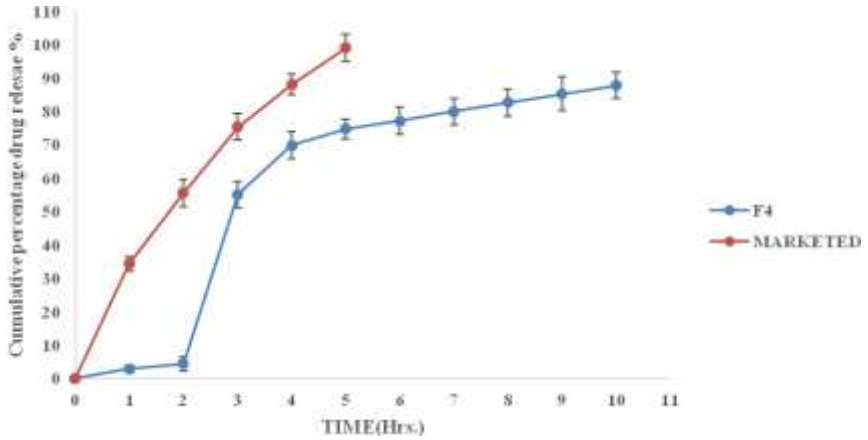

Figure 6: Comparison of *In-Vitro* drug release profile of optimized formulation (F4) and marketed formulation.

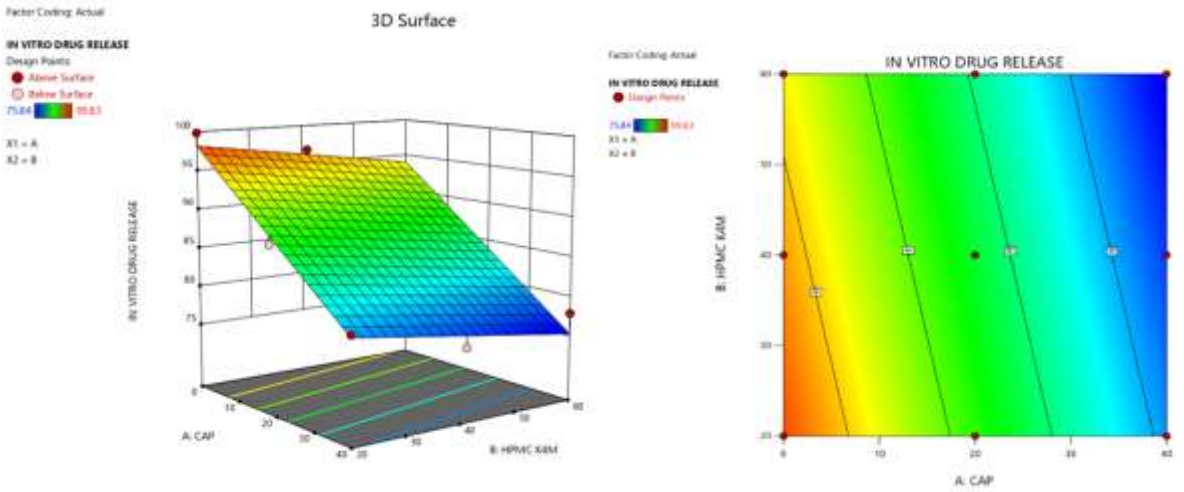

Fig. 7: Contour plot and response surface plot showing the effect of concentration of CAP (X1) and HPMC K4M (X2) on In-Vitro drug release (Y1)

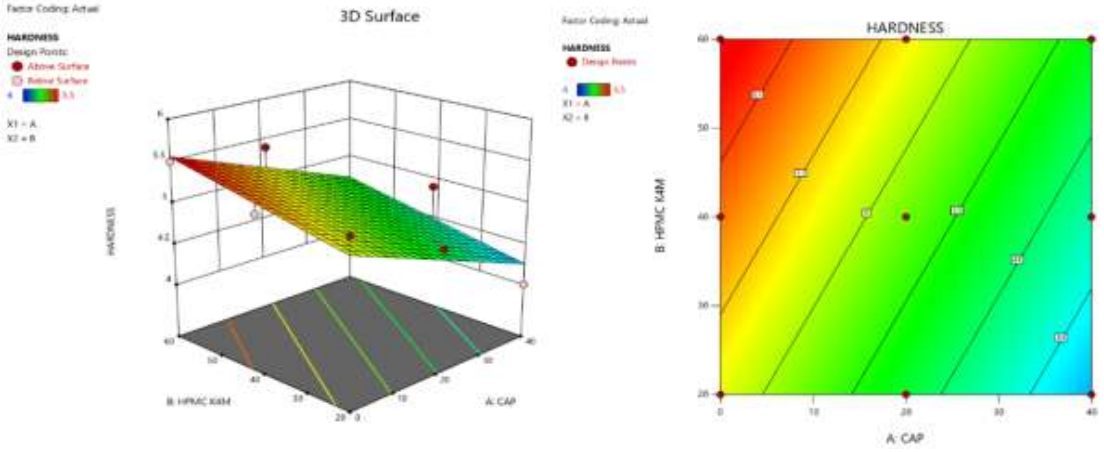

Figure 8: Contour plot and response surface plot showing the effect of concentration of CAP (X1) and HPMC K4M (X2) on hardness (Y2)

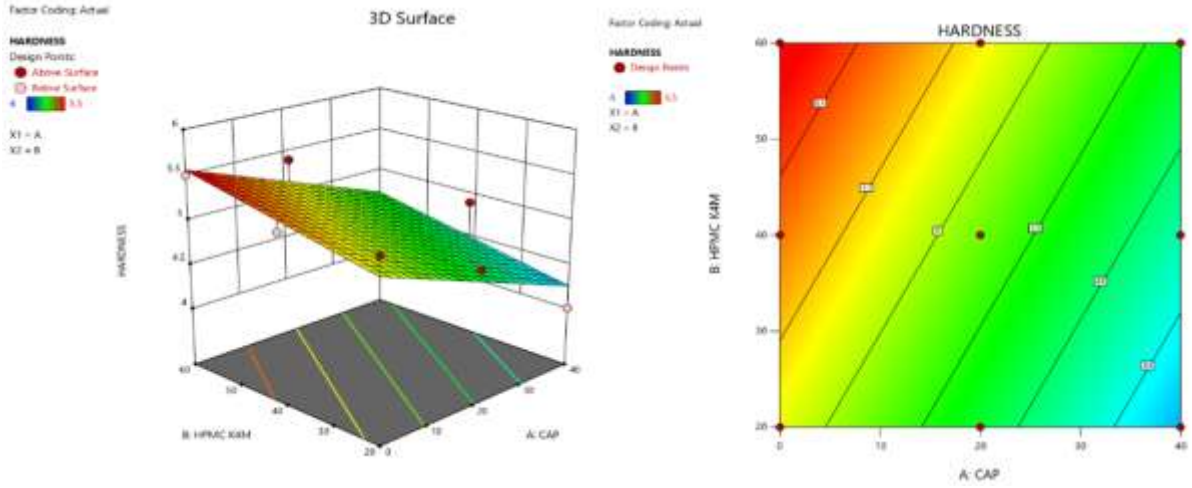

Figure 9: Optimization of matrix tablet of Torsemide (a) Desirability

Table 1: Composition of Torsemide matrix tablets prepared by wet granulation method.

	FORMULATIONS								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
INGREDIENTS									
Torsemide (API)	40	40	40	40	40	40	40	40	40
CAP	0	0	0	20	20	20	40	40	40
HPMC K4M	20	40	60	20	40	60	20	40	60
Guar gum	40	40	40	40	40	40	40	40	40
Lactose	91	71	51	71	51	31	51	31	11
Mg. Stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Starch paste	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2 : Micromeritic properties of APIs blend of all formulations.

Formulation batch code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)	Hausner's ratio
F1	30°21′±0.15	0.47±0.06	0.53±0.04	11.32±0.19	1.16±0.08
F2	27°36′±0.18	0.44±0.04	0.5±0.06	7.84±0.63	1.11±0.04
F3	27°20′±0.13	0.47±0.05	0.53±0.05	11.31±0.53	1.12±0.05
F4	25°54′±0.09	0.47±0.04	0.52±0.07	9.61±0.29	1.10±0.06
F5	30°06′±0.10	0.48±0.11	0.52±0.01	7.69±0.35	1.11±0.03
F6	29°12′±0.15	0.49±0.09	0.55±0.09	10.9±0.28	1.12±0.01
F7	28°56′±0.22	0.48±0.01	0.53±0.02	9.43±0.25	1.11±0.01
F8	26°58′±0.31	0.47±0.01	0.52±0.01	9.61±0.37	1.11±0.03
F9	30°36′±0.46	0.49±0.01	0.59±0.01	9.25±0.27	1.12±0.04

Table 3 : Physical evaluation of matrix tablet.

Formulation batch code	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content
F1	8.07±0.07	3.8±0.063	5.3±0.08	0.5±0.004	195.5±0.37	85.22±0.18
F2	8.08±0.02	3.9±0.051	5.2±0.07	0.5±0.006	196.2±0.41	86.71±0.5
F3	8.01±0.05	3.9±0.058	5.5±0.04	0.5±0.004	199.4±0.10	86.91±0.8
F4	8.05±0.07	3.89±0.047	4.8±0.02	0.5±0.003	195.6±0.19	87.89±0.21
F5	8.01±0.05	3.8±0.065	4.5±0.05	0.49±0.005	196.7±0.11	81.29±0.61
F6	8.05±0.07	3.9±0.036	5.4±0.09	0.51±0.008	195.4±0.40	80.44±0.65
F7	8.01±0.05	4.1±0.02	4±0.08	0.48±0.007	196.2±0.32	83.53±0.5
F8	8.04±0.07	4±0.08	4.9±0.04	0.51±0.010	194.9±0.24	82.41±0.9
F9	8.08±0.02	3.9±0.09	4.6±0.05	0.49±0.011	195.9±0.38	81.01±0.8

Table 4 : *In-vitro* dissolution data of Torsemide matrix tablets formulation (F1- F9).

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	35.13 ±0.40	33.96 ±0.38	31.96 ±0.61	1.86 ±0.39	1.71 ±0.28	1.57 ±0.29	2.71 ±0.51	1.86 ±0.29	1.71 ±0.39
2	63.75 ±0.1	60.75 ±0.29	57.75 ±0.34	4.30 ±0.38	3.86 ±0.36	3.43 ±0.36	4.74 ±0.54	4.01 ±0.39	3.86 ±0.36
3	85.28 ±0.42	82.28 ±0.36	79.28 ±0.68	55.03 ±0.38	53.77 ±0.34	52.41 ±0.38	47.37 ±0.49	46.30 ±0.37	44.70 ±0.48
4	92.64 ±0.45	89.64 ±0.41	86.64 ±0.29	69.72 ±0.61	68.45 ±0.39	66.55 ±0.45	61.14 ±0.51	59.95 ±0.39	57.82 ±0.45
5	97.41 ±0.39	94.41 ±0.39	91.41 ±0.39	74.64 ±0.41	73.01 ±0.37	71.70 ±0.42	66.40 ±0.41	64.75 ±0.29	62.54 ±0.42
6	99.83 ±0.38	96.74 ±0.49	93.25 ±0.38	77.05 ±0.42	75.39 ±0.36	73.79 ±0.48	69.23 ±0.42	67.60 ±0.41	66.11 ±0.43
7		98.06 ±0.39	97.06 ±0.41	79.79 ±0.28	78.16 ±0.39	76.67 ±0.49	72.11 ±0.45	71.18 ±0.42	69.58 ±0.46
8			99.25 ±0.29	82.46 ±0.51	80.54 ±0.39	78.77 ±0.41	74.43 ±0.36	72.86 ±0.43	70.97 ±0.43
9				85.08 ±0.29	83.19 ±0.31	81.53 ±0.43	76.99 ±0.38	75.36 ±0.36	73.44 ±0.42
10				87.67 ±0.48	85.87 ±0.32	83.71 ±0.45	79.70 ±0.39	77.84 ±0.39	75.86 ±0.41

Table 5 : Drug Release Kinetics of Formulation (F1- F9)

Formulation Code	First Order	Zero Order	Higuchi Matrix	Korsmeyer Peppas		Hixon Crowell	Best Fit Model
	R^2	R^2	R^2	R^2	n	R^2	
F1	0.9175	0.7915	0.9939	0.9965	0.44	0.8831	First order
F2	0.9174	0.8007	0.9951	0.9974	0.44	0.8853	First order
F3	0.9273	0.8242	0.9957	0.9966	0.47	0.8989	First order
F4	0.8830	0.9329	0.9020	0.9000	1.66	0.9171	Zero order
F5	0.8827	0.9305	0.9009	0.8984	1.68	0.9153	Zero order
F6	0.8828	0.9283	0.9000	0.8969	1.72	0.9138	Zero order
F7	0.8963	0.9375	0.9089	0.9087	1.5	0.9246	Zero order
F8	0.8958	0.9354	0.9071	0.9054	1.61	0.9229	Zero order
F9	0.8987	0.9364	0.9078	0.9069	1.6	0.9246	Zero order

Table 6 : ANOVA for Response-1 factorial model.

Source	Sum of Squares	df	Mean Square	F Value	p-value	
Model	345.24	5	69.05	53.91	0.0039	Significant
A-CAP	69.22	1	69.22	54.05	0.0052	
B-HPMC K4M	14.95	1	14.95	11.67	0.0420	
Residual	3.84	3	1.28			
Cor Total	349.08	8				

Table 7 : ANOVA for Response-2 factorial model.

Source	Sum of Squares	df	Mean Square	F Value	p-value	
Model	1.37	2	0.6842	7.32	0.0245	Significant
A-CAP	1.04	1	1.04	11.15	0.0156	
B-HPMC K4M	0.3267	1	0.3267	3.50	0.1107	
Residual	0.5606	6	0.0934			
Cor Total	1.93	8				

Table 8 : Stability data of optimized formulation

Observation	Initial	Accelerated condition 40℃ ± 2℃ / RH 75± 5% (After 30 days)
Hardness (kg/cm^2)	4.8	3.12
% Drug Content in1.2pH	84.07	81.12
% Drug Content in 6.8 pH	87.89	83.67
% DR at 10Hrs.	87.67	81.32

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