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Original Article

Development and *in vitro* evaluation of mefenamic acid orodispersible tablets prepared by direct compression

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Abstract

Mefenamic acid functions as a nonsteroidal anti-inflammatory drug (NSAID) of the fenamate class, which treats pain and inflammation by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes to decrease prostaglandin production. Mefenamic acid has strong therapeutic properties that help to treat arthritis and dysmenorrhea. The rapid dissolution of orodispersible tablets (ODTs) makes them an effective treatment option for patients with dysphagia. This study developed and evaluated mefenamic acid ODTs through direct compression while adding super-disintegrants, including croscarmellose sodium, crospovidone, and sodium starch glycolate, to improve drug release and disintegration speed. Pre-formulation analysis through FTIR spectroscopy showed that the drug and excipients maintained compatibility without detectable interactions. Product quality assessment included tests for hardness and weight variation, friability and disintegration time, dissolution studies, and stability testing. The performance of the formulation was evaluated through supplementary tests that measured the moisture uptake, wetting time, and water absorption ratio. The zero-order model provided the most accurate explanation of drug release kinetics among the model-dependent approaches, which included the zero-order, first-order, Higuchi, and Hixson-Crowell models. The combination of 7% croscarmellose sodium in formulation F1 produced the best results by enabling quick dissolution while maintaining the optimal disintegration time and improving drug absorption and patient compliance. Stability tests showed that the formulation structure remained consistent during the entire testing period, thus proving its durability. The direct compression method was effective for manufacturing stable mefenamic acid ODTs according to this research. This research demonstrates how super-disintegrants boost formulation performance, establishing ODTs as a promising drug delivery system for better therapeutic results and patient medication compliance.

Keywords: Mefenamic acid, Orodispersible tablets, NSAID, COX-1, Super-disintegrants.

1. Introduction

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) from the fenamate group that shows broad therapeutic use owing to its anti-inflammatory, analgesic, and antipyretic effects. The therapeutic benefits of this drug stem from its ability to block cyclooxygenase enzymes (COX-1 and COX-2), which control prostaglandin synthesis as pain and inflammatory mediators [1,2]. Mefenamic acid reduces prostaglandin synthesis to provide relief from arthritis, polyarthritis, acute pain, fever, and dental procedures. The primary application of mefenamic acid involves treating dysmenorrhea to minimize menstrual pain and discomfort [3,4]. Mefenamic acid exists as a crystalline substance with minimal water solubility (0.0041 g/100 mL at 25°C), leading to reduced bioavailability [5]. The compound exhibited better dissolution properties in alkaline hydroxides and ethanol. The BCS (Biopharmaceutics Classification System) class II designation of mefenamic acid demonstrates that its absorption depends on dissolution rate more than permeability so

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improving its solubility becomes essential for better therapeutic outcomes. Mefenamic acid requires protective storage containers because it degrades when exposed to light [5]. The development of orodispersible tablets (ODTs) represents a promising method for improving both bioavailability and patient compliance with mefenamic acid. The tablets dissolve or disintegrate quickly in the mouth without requiring water to function, while providing rapid drug effects. The unique properties of ODTs make them ideal for patients who struggle to swallow conventional tablets, including pediatric, geriatric, and disabled populations [6,7]. ODTs provide faster drug release, which enhances the therapeutic response while offering patients a convenient alternative to traditional dosage forms. The addition of super-disintegrant substances to ODTs enables rapid tablet disintegration after contact with saliva. The combination of enhanced drug absorption and accelerated onset of action results from this method [8]. Tablets can incorporate taste-masking technologies to enhance patient compliance because the unpleasant taste of mefenamic acid often discourages oral consumption, especially among pediatric and elderly patients [9]. The development of ODTs requires attention to environmental factors that affect drug stability because mefenamic acid shows sensitivity to temperature and humidity conditions [6].

This research focuses on developing and testing mefenamic acid orodispersible tablets, which improve dissolution speed and drug availability through patient-friendly features, including quick disintegration and taste masking. The development of mefenamic acid ODTs through optimized excipient selection with super-disintegrants and flavor masking agents will lead to improved therapeutic outcomes and patient adherence.

2. Materials and Methods

2.1. Materials

Analytical Weighing Balance: Shimadzu ATX224 (0.01 – 220g), Vernier Caliper**,** Vortex Mixer*:* SGS, Disintegration Test Apparatus: Pharma Test D-63512, Mortar and Pestle**,** Dissolution Apparatus (Type II**)**: Agilent 708-DS, Dryer: Black & Decker PX7, Filtration Assembly: Eyela A-1000S, Pfizer Tablet Hardness Tester**,** Roche Friabilator: Vankel Industries 1805, Ultrasonicator: DSA150-SK2 (5.7L), UV-Visible Spectrophotometer: Jasco V-530 Double Beam, pH Meter**,** Stability Chamber**,** Tablet Compression Machine: Rotary Multi Press, Sieve Assembly**,** Melting Point Apparatus**,** Fourier Transform Infrared Spectroscopy (FTIR)**,** Water Bath.

2.2. Excipients

Crospovidone (PVP-K30)**:** BASF, Croscarmellose Sodium**:** FMC Corporation, Sodium Saccharine**:** Suzhou Hope Technology Co., Ltd, Aspartame**:** Ajinomoto, NutraSweet, Mannitol**:** Roquette, Cargill, Magnesium Stearate**:** Peter Greven, Baerlocher, Talc**:** Imerys, Golcha Group, Sodium Starch Glycolate**:** DFMC, JRS Pharma, Menthol**:** Takasago International Corporation, Symrise AG, Flavorants**:** Firmenich, Givaudan, Microcrystalline Cellulose**:** FMC Corporation, Mingtai Chemical Co., Ltd

2.3. Active Pharmaceutical Ingredient (API)

The active pharmaceutical ingredient used in this study is mefenamic acid. The detailed specifications of the active ingredient are provided below:

The active ingredient in the formulation is Mefenamic acid**,** with batch number KAF74816. The assay value for this batch is 99.97%**,** ensuring that the content of the active pharmaceutical ingredient meets the required standards. The expiry date for this batch is November 26, 2015**,** which indicates the period until the product is guaranteed to retain its full potency and safety. The supplier of this batch is Livizon Group Fuzhou Fuxing Pharmaceuticals**,** a reputable source of pharmaceutical ingredients.

2.4. Pre-formulation studies

Pre-formulation studies were conducted to assess the physicochemical properties of the API and to identify suitable excipients for the tablet formulation. These studies are crucial to ensure that the API meets the required standards for use in tablet manufacturing and to determine compatibility with excipients.

2.5. Identification of API

The identification of the API (mefenamic acid) was confirmed through several analytical techniques, including. These methods allowed for the confirmation of the drug's identity and impurity assessment [10].

2.6. FTIR Analysis

The active pharmaceutical ingredient (API) mefenamic acid was subjected to Fourier Transform Infrared (FTIR) spectroscopic analysis to determine potential interactions with excipients used in the formulation. Chemical compatibility and excipient-drug interactions can be studied using FTIR spectroscopy because this technique reveals molecular changes by monitoring peak shifts in the IR spectra [11]. The BRUKER FTIR spectrophotometer recorded FTIR spectra between 4000 and 400 cm^{-1}. The detection spectrum enables researchers to identify functional groups and molecular vibrations of both drug substances and excipients. The research team analyzed the FTIR spectra of pure mefenamic acid, individual excipients, and the final formulations F1 to F5. The analysis focused on detecting shifts and changes or new peaks that appeared in the formulation spectra compared to the pure drug spectra. The stability and release performance of the final formulation could be affected by drug-excipient interactions when significant changes occur in the characteristic peaks. FTIR analysis confirmed the compatibility between mefenamic acid and selected excipients while providing essential data for optimizing the formulation to achieve stability and therapeutic performance [11].

2.7. Melting point determination

A standard melting point apparatus was used to determine the melting point of mefenamic acid and verify its drug identity and purity. A small amount of mefenamic acid was placed in a capillary tube before the apparatus gradually heated it. Scientists recorded the temperature at which the drug began to melt.

The assessment of compound purity relies heavily on this technique because impurities tend to decrease the melting points of substances (USP29-NF24, 2006). The laboratory-determined melting point of mefenamic acid was compared with values reported in the literature to validate drug authenticity and suitability for use in orodispersible tablet development. Confirmation of the quality of the active pharmaceutical ingredient (API) requires this essen-

tial step.

2.8. UV spectroscopy

A 10 µg/mL solution of mefenamic acid was prepared using 0.1 N NaOH for quantitative analysis. A UV spectrophotometer was used to measure the absorbance of the solution across the wavelength range of 250 to 300 nm. The maximum absorbance wavelength, λmax, emerged from the spectra because it served as a fundamental requirement for precise drug quantification through UV spectroscopy. The instrument received auto-zero calibration using a blank solution containing 0.1 N NaOH to remove any potential solvent interference. The λmax value obtained from this measurement serves as a reference point for analyzing mefenamic acid in pharmaceutical formulations [12]. The technique delivered a dependable noninvasive approach to drug concentration measurement, which maintained both formulation development precision and consistency.

2.9. Physicochemical properties

Several physicochemical properties of mefenamic acid have been evaluated, including:

The researchers examined the crystalline drug form to understand its stability characteristics and solubility behavior. Solubility tests of mefenamic acid in different solvents serve as a critical step for both bioavailability prediction and formulation design. The drug's melting point assessment included polymorph identification to maintain drug performance consistency [13]. The research team examined how light exposure affects the degradation of mefenamic acid because this drug is sensitive to light.

2.10. Particle size analysis

Sieve analysis was used to determine the particle size distribution of mefenamic acid to evaluate the flowability and compressibility properties of the drug powder essential for formulation development. The drug sample was sieved through a mesh that included both coarse (#8) and fine (#60) particles. Through sieving, the particles were separated into distinct size ranges to generate a complete understanding of the distribution pattern. Sieve analysis results will help pharmaceutical scientists select proper excipients and compression parameters for their formulations. The proper distribution of particle sizes enables optimal flow properties and tablet compaction uniformity, which directly affect drug dissolution and bioavailability. This study followed the standard analytical procedures outlined by USP29-NF24 (2006).

2.11. Moisture content

The moisture content of the granules was determined to assess its impact on the compressibility and stability of the tablet formulation. Excess moisture in the granules can adversely affect tablet hardness, friability, and shelf life, while too little moisture may lead to poor compaction during tablet formation. The moisture content was measured using standard methods outlined by USP29-NF24 (2006), typically involving the use of a moisture analyzer or oven drying technique. A known weight of granules was placed in a pre-weighed container and heated at a specified temperature until a constant weight was achieved. The difference in weight before and after drying was used to calculate the moisture content as a percentage.

2.12. Angle of repose

The flow properties of the powder mixture were evaluated by determining the angle of repose, which is an important parameter in assessing the powder's flowability. Poor flowability may lead to inconsistent tablet weight and content uniformity during compression. To determine the angle of repose, a known amount of powder was poured through a funnel onto a flat surface. The powder formed a cone, and the height (h) and radius (r) of the cone were measured. The angle of repose (θ) was then calculated using the following formula:

$\theta = \tan^{-1}(h/r)$

h=height of cone

r= radius of cone

2.13. Manufacturing of mouth-dissolving tablets: method selection and formulation development

2.13.1. Method selection

The direct compression method is the preferred approach for developing mefenamic acid mouth-dissolving tablets owing to its multiple beneficial characteristics. The direct compression method is preferred in tablet manufacturing owing to its simplicity, cost-effectiveness, and operational efficiency [14]. The direct compression method requires fewer production steps, thus enabling efficient large-scale tablet manufacturing. This method protects sensitive drugs such as mefenamic acid from both heat and moisture exposure during production. The method enables precise control of tablet properties, including hardness, disintegration, and dissolution characteristics, which are essential for fast-acting mouth-dissolving formulations. Direct compression manufacturers can precisely add excipients to improve the flow properties, moisture resistance, and drug interactions that determine tablet performance [15].

2.13.2. Formulation development

Five different formulations (F1–F5) were used to optimize the composition of mefenamic acid-containing mouth-dissolving tablets as shown in Table 1. The research team studied five different formulations containing different excipient types and concentrations to determine their effects on tablet properties, including disintegration time, dissolution rate, and mechanical strength. The formulation included disintegrants and binders and lubricants and glidants which were selected to optimize the dissolution and disintegration properties of the tablets. The inclusion of disintegrants such as sodium starch glycolate and croscarmellose sodium in the formulations enabled rapid tablet disintegration within the oral cavity thus accelerating the onset of action. The addition of microcrystalline cellulose as a binder helped maintain tablet integrity while ensuring uniform weight and content distribution. The addition of lubricants such as magnesium stearate helped reduce compression friction while improving the die ejection of tablets. The addition of colloidal silicon dioxide as glidant improved the flow properties of the powder blend which resulted in uniform tablet weight and contents varied in terms of the type and concentration of excipients to evaluate their impact on tablet properties, such as disintegration time, dissolution rate, and mechanical strength. The excipients used included disintegrants, binders, lubricants, and glidants, which were all chosen to enhance the

Table 1. Composition of formulations for mefenamic acid mouth-dissolving tablets.

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
Mefenamic acid	100	100	100	100	100
Sodium starch glycolate	-	-	-	-	10
Crospovidone	-	10	8	-	
Crosscarmilose sodium	14	-	-	10	-
MCC (Avicel)	35	39	41	39	39
Mannitol	45	45	45	45	45
Sodium saccharin	2	2	2	2	2
Magnesium stearate	1	1	1	1	1
Talc	3	3	3	3	3
Peppermint oil	qs	Qs	qs	qs	qs
Total	200	200	200	200	200

dissolution and disintegration characteristics of the tablets.

Disintegrants such as sodium starch glycolate and croscarmellose sodium were included to promote rapid tablet disintegration in the oral cavity, allowing for faster onset of action. Binders such as microcrystalline cellulose were incorporated to ensure tablet integrity during handling and to facilitate uniformity in weight and content. Lubricants such as magnesium stearate were added to reduce friction during compression and improve tablet ejection from the die. Glidants, such as colloidal silicon dioxide, were used to enhance the flow properties of the powder blend, ensuring a uniform tablet weight and content. These formulations aim to improve mefenamic acid dissolution by creating tablets that quickly disintegrate in the mouth before releasing the drug into the systemic circulation for pain relief [14]. The research team evaluated four different formulations by testing their hardness, disintegration time, dissolution rate, and friability to determine the optimal composition for mouth-dissolving tablets. The research methodology followed established guidelines for developing orally disintegrating tablets, focusing on excipient selection and formulation design to achieve rapid drug release and better patient compliance [15].

2.14. Steps in formulating mefenamic acid orodispersible tablets by direct compression method

A sensitive analytical balance was used to perform precise ingredient weight measurements. The master formula contained precise measurements of active pharmaceutical ingredient (API) and excipients to achieve proper formulation ratios. The weight of each component was measured with precision to ensure consistent formulation results. A 60-mesh sieve no was used to screen all components, including the API and excipients, to achieve uniform particle dimensions. The uniform distribution of particles during this step led to better tablet content uniformity and improved flow properties. A blender operated at 15 rpm mixed all ingredients except the lubricant and glidant for 10 min to create a uniform mixture. The powder blend received a sieved lubricant and glidant mixture for five more minutes of mixing. The distribution of the lubricant and glidant during this step resulted in the optimal tablet compaction and flow properties. A 10-station rotary tablet press compressed the final powder blend into 200 mg tablets. The tablet formation process utilized an 8 mm punch while achieving a production speed of 200-300 tablets per formulation. The tablet formation process at this stage creates uniform tablets, which are necessary for developing the intended orodispersible dosage form [14].

2.15. Post-compression parameters

The hardness of tablets was determined using a Monsanto hardness tester. Each tablet was subjected to breaking force, and the force at which the tablet broke was recorded in kg/cm². This measurement provided insight into the mechanical strength of the tablet and its ability to withstand physical stress during handling and transportation. To assess tablet weight uniformity, 20 tablets from each formulation were weighed individually. The average weight was calculated, and the percentage deviation from the average was determined to ensure the uniformity of the dosage form. Percentage deviation should comply with pharmacopeial standards [16]. The thickness of the tablets was measured using Vernier calipers. The average thickness was calculated along with the standard deviation to evaluate the consistency of the tablet size and shape. This ensured that the tablets met the required uniformity and specificity. The friability of the tablets was evaluated using a Roche Friabilator, which controlled the mechanical abrasion of the tablets. The tablets were weighed before and after the test, and the percentage of weight loss was calculated. A weight loss of ≤1% was considered acceptable, indicating that the tablets were sufficiently durable to withstand handling [14].

2.16. Invitro dissolution time

The USP Dissolution Apparatus II (paddle type) was operated according to a standard protocol [16] to perform dissolution testing. The dissolution medium included a phosphate-buffered solution (pH 6.8), which was maintained at 37 ± 0.5°C while stirring at 50 rpm. The study duration for the dissolution testing included multiple predetermined sampling points. The dissolution medium was sampled at predetermined time points, and 10 mL was withdrawn for filtration before spectrophotometric analysis at 285 nm to determine the drug concentration. The experiment maintained constant volume by using fresh buffer solution to replace withdrawn volumes according to [14]. The percentage dissolved was calculated using the following formula:

$$\% \text{ dissolved} = (AU / AS) \times (CS / L) \times 900 \times 100$$

where:

- AU = absorbance of the test solution
- AS = absorbance of the standard solution

- CS = concentration of mefenamic acid in the standard solution (mg/mL)
- L = tablet label stated (mg)
- 900 = volume of dissolution medium (mL)

2.17. Assay

The analysis of mefenamic acid served to measure the drug content of each tablet formulation. Each formulation received 20 tablets that were individually weighed before being powdered. A 100 mg sample of powdered tablet material was dissolved in 100 mL of 0.1 N NaOH solution to serve as the dissolving agent for the drug. The solution was diluted until it reached a concentration of 10 µg/mL. A UV spectrophotometer was used to measure the absorbance of the diluted solutions at a wavelength of 285 nm. The obtained spectra were compared with pure mefenamic acid standards to evaluate the drug concentrations in the samples. Drug content analysis measured the mefenamic acid levels in each formulation by expressing the results as percentage values [14].

2.18. Model dependent approaches

The dissolution profiles were analyzed using model-dependent approaches such as zero-order, first-order, Higuchi, and Hixson-Crowell models to understand the drug release kinetics.

2.18.1. Zero-order model

The zero-order kinetic model describes drug release where the dissolution occurs at a constant rate, independent of the drug concentration. This model is particularly relevant for controlled-release systems, ensuring a steady therapeutic effect over time. The equation representing the zero-order model is:

$\theta° - \theta t = K° t$

Rearrangement of equation yields

$\theta t = \theta° + K° t$

Where θt is the amount of drug dissolved in time t, θ° is the initial amount of drug in the solution (most times, θ° = 0) and K° is the zero-order release constant expressed in units of concentration/time.

2.18.2. First-order model

The first-order kinetic model describes drug release as an exponential process, where the rate of release is directly proportional to the amount of drug remaining in the dosage form. This model is commonly applied to systems where drug release decreases over time. The equation representing the first-order model is:

$dc/dt = - Kc$

Where K is first-order rate constant expressed in units per time.

Equation can be expressed as;

$\log C = \log C° - Kt / 2.303$

2.18.3. Higuchi model

The Higuchi model describes drug release from matrix systems based on Fickian diffusion, given by:

$ft = Q = A\sqrt{D(2C - Cs)\, Cs\, t}$

Where Q is the amount of drug released in time t per unit area A.

C is the drug initial concentration.

Cs is the drug solubility in the matrix media.

D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

Above described relationship is valid until all drug is depleted from the therapeutic system. Dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, is expressed by the following equation;

$$ft = Q = \sqrt{\frac{D\delta}{\tau}(2C - \delta Cs)\, Cs\, t}$$

Where D is the diffusion coefficient of the drug molecule in the solvent, δ is the porosity of the matrix, τ is the tortuosity of the matrix and Q, A, Cs and t have the meaning mentioned above.

The Higuchi model can be simplified as (generally known as the simplified Higuchi model)

$$f\,t = Q = KH \times t^{1/2}$$

KH is the Higuchi dissolution constant.

Higuchi model is plotted as cumulative percentage of drug release versus square root of time. This relationship can be used to describe the dissolution of drugs from different types of dosage forms for example matrix tablets with water-soluble drugs, transdermal formulations etc [17].

2.18.4.Hixson-Crowell model

This model focuses on changes in particle surface area:

In 1931 Hixson and Crowell two scientists found that regular area of particles is proportional to the cube root of its volume. They also derived the following equation;

$$W°\ 1/3 - Wt\ 1/3 = \kappa\, t$$

W° is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface volume relationship [17].

***2.19. In Vitro* dispersion time**

The standardized protocol guided the evaluation of tablet dispersion time in vitro. A phosphate-buffered solution (pH 6.8) followed the USP guidelines [16] to create a solution that mimicked human body conditions. The experimental setup included a 100 mL buffer solution, which was maintained at 37 ± 0.5°C using a thermostatically controlled water bath. A 250 mL borosilicate glass beaker was added to each tablet before adding the buffer solution.

A magnetic stirrer operating at 50 rpm provided gentle agitation to maintain uniform mixing. The study endpoint was when the entire tablet was dispersed without any remaining visible fragments. Three independent observers confirmed the endpoint under consistent lighting conditions to reduce the subjective variability [14].

2.20. Accelerated stability studies

The formulation underwent accelerated stability tests to determine its performance under extreme conditions, which helped predict the storage requirements and shelf life duration. The research followed the International Council for Harmonization (ICH) guidelines (ICH, 2003) during its execution. The stability chambers were maintained at a temperature of 60 ± 2 °C and 75 ± 5% relative humidity to store the formulations. The analysis of critical

parameters, including physical appearance, drug content, disintegration time, and in vitro dispersion time, occurred at predefined time points during a one-month study period.

2.20.1. Moisture uptake studies

The hygroscopic properties of the formulations were assessed using moisture-uptake experiments. The initial weight measurement involved ten tablets from each batch, which were placed in a desiccator with anhydrous calcium chloride for drying. The tablets were placed in a controlled humidity chamber with 75% relative humidity (RH) for two weeks according to [15] Weight gain from moisture absorption was calculated by weighing the tablets after storage. The percentage moisture uptake was determined using the following formula:

$$Moisture\ uptake = \frac{Final\ weight - Initial\ weight}{Intial\ weight} \times 100$$

2.20.2. Wetting time and water absorption ratio

The hydration and disintegration properties of the formulations were assessed by measuring wetting time and water absorption ratio. A circular tissue paper piece received amaranth dye solution through a petri dish (10 cm diameter) containing 10 mL of dye solution to measure the wetting time. Tablet placement on tissue paper was followed by a stopwatch recording of the time required for the dye solution to fully wet the tablet surface [14]. The water absorption ratio (R) was calculated using the following equation.

$$R = \frac{Wa - Wb}{W} \times 100$$

where Wb is the dry weight and Wa is the wet weight. Short wetting times and higher water absorption ratios are essential for optimizing the performance of orodispersible and fast-dissolving tablets.

2.21. Statistical analysis

The model-independent approach (f_1 and f_2) assessed dissolution profile similarity, identifying Formulation F2 as closest to F1. ANOVA confirmed significant differences among formulations ($F = 6.505$, $p < 0.05$), rejecting the null hypothesis. Results validate F2 as the most comparable to F1, with all formulations meeting similarity criteria.

3. Results

3.1. Compatibility between drugs and excipients

Evaluation of active drug compatibility with excipients represents a vital step in maintaining formulation stability and drug effectiveness [11]. FTIR analysis showed no significant changes in the spectra between the drug and excipients in any of the formulations. The spectra from F1 to F5 showed identical patterns to that of mefenamic acid alone, which confirmed no drug-excipient incompatibility. The excipient compatibility test of formulation F1 showed no peak shifts as shown in Fig.1, indicating that all the components were compatible. The stability of these formulations was confirmed by identical results obtained for F2, F3, F4, and F5.

3.2. Pre-formulation studies

The pre-formulation study evaluated the API and formulations (F1–F5) by assessing their essential powder flow characteristics through bulk density, tapped density, angle of repose, compressibility index, Hausner's ratio and moisture content measurements. The flowability tests demonstrated that API and F1 had excellent flow characteristics suitable for direct compression yet F2, F3, F4, and F5 displayed different levels of cohesiveness which might need glidant addition or granulation processes. The research results enable manufacturers to choose the best formulation which maximizes production efficiency and tablet uniformity and stability. The flow properties of the API and formulations F1 through F5 were assessed through bulk and tapped density measurements along with angle of repose determination, compressibility index evaluation, Hausner's ratio calculation, and moisture content analysis. The API exhibited excellent flow characteristics (Hausner's ratio = 1.09, compressibility index = 12.61%) and minimal moisture content (0.47%), making it ideal for direct compression applications. The flow properties of F1 showed good results (compressibility index = 11.74%); however, its Hausner ratio (1.12) indicated a slightly reduced flow compared to the API. The flow characteristics of F2 and F4 were passable with a Hausner's ratio of 1.26, indicating moderate cohesiveness; however, F3 and F5 showed fair flow (compressibility index = 15.77%) and could benefit from glidants or granulation for improvement. All formulations maintained excellent angle of repose values between 25.00° and 28.00°, but F5 exhibited the highest value at 28.00°, indicating a slightly reduced flowability. The lowest moisture content was detected in F1 at 0.36%, whereas F5 showed the highest content at 0.65%, which could affect product stability during storage. API and F1 demonstrated optimal processing capabilities, but F3, F4, and] F5 required flow-enhancing modifications to achieve manufacturing efficiency as shown in Table 2.

3.3. Post formulation studies

The post-formulation analysis of five formulations (F1–F5) containing 100 mg mefenamic acid in mouth-dissolving tablets appears in the Table 2. The evaluation of five formulations (F1–F5) includes measurements of thickness, hardness, friability, weight variation, assay, wetting time, dispersion time, in-vitro dispersion time, and water absorption ratio. The tablets measured between 3.20 mm and 3.36 mm in thickness which met packaging requirements. All formulations demonstrated similar hardness values between 3.8 kg/cm² and 4.0 kg/cm² which indicates tablets will maintain their structural integrity. The tablets exhibited outstanding strength as their friability values stayed below 1% USP limit and measured between 0.106%

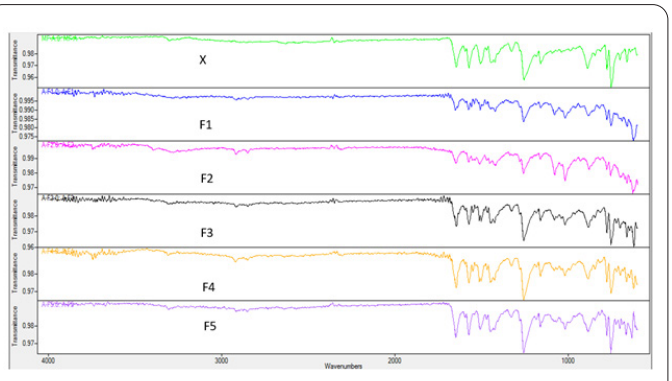

Fig. 1. Comparative spectra of all five formulations with mefenamic acid using Essential FTIR software.

Table 2. Comparative analysis of powder flow properties and classification of API and formulations and comprehensive post-formulation evaluation

Parameter	API	F1	F2	F3	F4	F5
Bulk Density (g/cm³) ± S. D	0.56 ± 0.007	0.56 ± 0.007	0.59 ± 0.006	0.57 ± 0.007	0.59 ± 0.005	0.57 ± 0.007
Tapped Density (g/cm³) ± S. D	0.66 ± 0.01	0.65 ± 0.01	0.72 ± 0.04	0.65 ± 0.01	0.71 ± 0.05	0.65 ± 0.03
Angle of Repose (°) ± S. D	25.12 ± 1.27	25.00 ± 1.29	27.06 ± 1.20	27.00 ± 1.23	26.00 ± 1.19	28.00 ± 1.34
Flow Property	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Compressibility Index (%) ± S. D	12.61 ± 1.04	11.74 ± 1.00	13.74 ± 1.23	15.77 ± 1.27	13.73 ± 1.05	15.77 ± 1.33
Flow Characteristic	Good	Good	Good	Fair	Good	Fair
Hausner's Ratio ± S. D	1.09 ± 0.01	1.12 ± 0.02	1.26 ± 0.02	1.14 ± 0.03	1.26 ± 0.03	1.14 ± 0.04
Flow Classification	Excellent	Good	Passable	Good	Passable	Good
Moisture Content (%)	0.47	0.36	0.58	0.57	0.63	0.65
Post formulations study						
S#NO	**Test**	**F1**	**F2**	**F3**	**F4**	**F5**
1.	Thickness (mm)	3.36 ± 0.14	3.22 ± 0.03	3.20 ± 0.06	3.22 ± 0.04	3.25 ± 0.13
2.	Hardness (kg/cm²)	4 ± 0.11	4 ± 0.44	4 ± 0.19	3.9 ± 0.26	3.8 ± 0.51
3.	Friability (%)	0.106 ± 0.005	0.196 ± 0.02	0.192 ± 0.01	0.167 ± 0.02	0.191 ± 0.006
4.	Weight Variation (mg)	199.30 ± 0.36	198.00 ± 0.11	203.00 ± 0.48	195.00 ± 0.86	182.00 ± 0.13
5.	Assay (%)	99.9971%	99.4406%	97.9701%	99.0334%	97.342%
6.	Wetting Time (sec)	16.50 ± 0.45	18.65 ± 0.23	30.50 ± 0.81	25.44 ± 0.65	28.5 ± 0.38
7.	D.T (sec)	14.50 ± 0.52	25.00 ± 0.54	20.50 ± 0.55	17.35 ± 0.58	16.18 ± 0.75
8.	In-vitro Dispersion Time (sec)	20 ± 1	25 ± 3	25 ± 3	34 ± 2	43 ± 2
9.	Water Absorption Ratio (%)	85.55 ± 0.24	67.73 ± 0.64	75.35 ± 0.55	56.71 ± 0.81	52.17 ± 0.73

and 0.196%. The weight measurements of the tablets complied with USP standards (±7.5%) while active ingredient tests showed results between 95–105%. F1 demonstrated the fastest disintegration time (16.50 seconds) and achieved the highest water absorption ratio (85.55%) among all formulations. The experimental results demonstrated that all tested formulations satisfied the required specifications for mouth-dissolving tablets.

3.4. Disintegration time, *In vitro* dispersion time and dissolution profile

This test determines how long it takes for the tablet to break down into small particles when placed in contact with a dissolution medium. The disintegration time for F1 tablets reaches 14.50 ± 0.52 seconds which demonstrates the fastest breakdown because its excipients were selected optimally to enhance disintegration speed. The longer disintegration times of F2 (25.00 ± 0.54 s) and F3 (20.50 ± 0.55 s) may stem from differences in excipient composition or compression force. The tablet break-up speeds of F4 and F5 fall between those of the other formulations because of the different formulation approaches. The test procedure evaluates the tablet dispersion by placing the tablet in a buffered solution (pH 6.8) under standardized experimental conditions. The measurement determines the speed at which the tablet breaks to release the drug. The dispersion time for F1 is 20 ± 1 s, which indicates quick dispersion, but F5 requires 43 ± 2 s to disperse, possibly because of excipient properties or compression differences. The correct drug absorption rate depends on the proper dispersion time of the orodispersible tablets [29].

The dissolution profile of mefenamic acid mouth-dissolving tablets demonstrates different drug release behaviors between formulations during specific time points. The drug release data at 30 seconds shows F5 achieves the highest release rate (25.6%) followed by F4 (24.1%) and F3 (22.2%) which indicates F5 demonstrates the fastest dispersion and disintegration properties. The drug release percentage at 1-minute shows F5 in the lead position with 43.0% followed by F4 at 41.3% and F1 at 35.7%. The drug release analysis shows F5 maintains its position as the most efficient formulation by achieving 60.8% drug release at 5 minutes while F1 and F2 demonstrate slightly lower release rates at 55.1% and 55.7% respectively. The drug release percentage of F5 reaches 82.2% after 10 minutes while F4 shows 80.9% and F3 shows 76.6%. The drug release profile of F1 reaches 99.9% at 15 minutes which demonstrates its status as the fastest formulation for rapid drug onset yet F5 (97.3%) and F2 (97.9%) maintain sustained drug release suitable for extended therapeutic effects. The experimental findings demonstrate F1 provides rapid relief but F5 delivers extended therapeutic as shown in Table 3.

Dissolution of all 5 formulations was found to be correlated to the concentration of super-disintegrant used. The higher the concentration of super-disintegrant in the formulation the less it takes time to disintegrate and dissolve. Formulations F1 showed the best results regarding its dis-

solution and other tests because of the increased amount of Croscarmellose sodium in it, followed by F4, F3, F2 and F5, with the cumulative percentage of drug release as 99.90%, 99.03%, 97.90%, 97.90% and 97.30% respectively (Table 3 & Fig. 2).

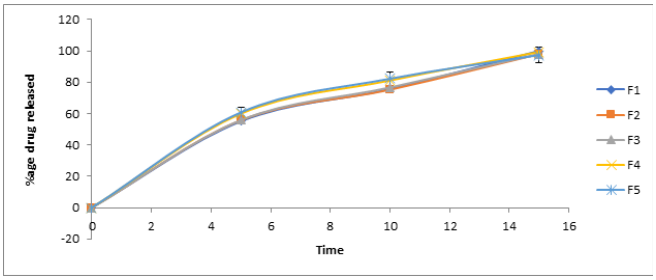

Fig. 2. Graphical presentation of Mefenamic acid release from formulations in 6.8 pH phosphate buffer.

3.5. Model independent approach and statistical analysis

Difference and similarity factors are the most appropriate model-independent approach with the help of which we can estimate which formulation or batch is most near to the standard. In this method, we used two factors i-e difference (f1) and similarity (f2) factors. The basic purpose of this approach is to assess dissolution profiles. As the name indicates, difference factors tell us how much difference is they're between two curves at every interval against time and enable us to detect relative error between the two curves. The similarity factor tells us the degree of the resemblance (%) present among the two curves of the dissolution data. The calculated f_1 and f_2 values are shown in Table 4. The model-independent approach was applied, and all five formulations were compared with the dissolution profile of the best formulations amongst these five i-e F1. No standard mouth-dissolving formulation of mefenamic acid present till now. Formulation F1 is taken as standard for other formulations in the study due to its better results. The results of this model-independent approach are displayed in Table 4. It can be seen that all five formulations pass the test successfully, but values of formulation F2 have the least difference factor and highest similarity index which indicates that formulation F2 was closer to the standard (F1). All the other formulations passed the test, which means that their curves were similar to the curve of standard formulation i-e F1 [17]. ANOVA is a statistical method used to analyze variation in data and determine if the null hypothesis holds true or if there are significant differences [18]. In the present study, the null hypothesis assumed that all five formulations had different dissolution rates due to varying ingredient concentrations. The ANOVA results, as shown in Table 4, revealed that the F value exceeded the critical F value, and the p-value was

Table 3. Disintegration time, *In-vitro* dispersion time and dissolution profile.

Test	**F1**	**F2**	**F3**	**F4**	**F5**
Disintegration Time (sec)	14.50 ± 0.52	25.00 ± 0.54	20.50 ± 0.55	17.35 ± 0.58	16.18 ± 0.75
In-vitro Dispersion Time (sec)	20 ± 1	25 ± 3	25 ± 3	34 ± 2	43 ± 2
		Dissolution Profile			
Test	**F1**	**F2**	**F3**	**F4**	**F5**
Drug Release at 30 Seconds (%)	20.3	21.1	22.2	24.1	25.6
Drug Release at 1 Minute (%)	35.7	36.3	37.6	41.3	43.0
Cumulative Drug Release at 5 min (%)	55.1	55.7	55.8	59.8	60.8
Cumulative Drug Release at 10 min (%)	75.6	75.2	76.6	80.9	82.2
Cumulative Drug Release at 15 min (%)	99.9	97.9	97.9	99.03	97.3

Table 4. ANOVA and comparison of results between formulations F1, F2, F3, F4, F5 and kinetic study of drug release profile of mefenamic acid in 6.8 pH phosphate buffers.

Formulation	**F1 (0-15)**	**F2 (50-100)**	**F1 vs. F2**	**F1 vs. F3**	**F1 vs. F4**	**F1 vs. F5**
F1	1.31	1.61	4.53	6.20	-	-
F2	90.02	88.71	68.63	63.59	-	-
			ANOVA Results			
Source of Variation	**SS**	**Df**	**MS**	**F**	**P-value**	**F crit**
Between Groups	11595.48	5	2319.096	6.505	0.003792	3.106
Within Groups	4278.007	12	356.5006			
Total	15873.9	17				

	Kinetic study of drug release profile							
Code	**Zero-order kinetic model**		**First order kinetic Model**		**Higuchi model**		**Hixson Crowell model**	
	K°	**R²**	**K°**	**R²**	**K°**	**R²**	**K°**	**R²**
F1	17.55	0.993	5.64235	0.753	105.9	0.976	0.309	0.900
F2	17.31	0.994	6.19507	0.808	104.5	0.977	0.225	0.937
F3	17.45	0.995	5.87265	0.811	105.4	0.978	0.225	0.949
F4	17.99	0.996	4.622121	0.786	108.8	0.982	0.243	0.953
F5	17.95	0.997	4.72115	0.846	108.6	0.984	0.200	0.931

less than 0.005 indicating rejection of the null hypothesis. This implies that all formulations exhibited similar dissolution rates in 6.8 pH buffer solution [19].

3.6. Kinetic modeling of drug release from tablet formulations

The table displays dissolution data for five tablet formulations (F1, F2, F3, F4, and F5), analyzed using different kinetic models: Zero-Order, First-Order, Higuchi, and Hixson-Crowell. The Zero-Order kinetic model demonstrates the most suitable fit for all formulations because its R^2 values approach 1.0 which indicates uniform drug release rates throughout the time period. The First-Order model exhibits lower R^2 values indicating the formulations deviate from strict first-order kinetics thus demonstrating that drug release rate depends on factors beyond the amount of remaining drug. The Higuchi model demonstrates excellent fit with high R^2 values for most formulations (F1, F2, F3) because it relies on diffusion mechanisms for drug release. The Hixson-Crowell model demonstrates reasonable fit for F3 and F4 formulations when applied to formulations with decreasing tablet surface area. The drug release data indicates zero-order kinetics as the primary mechanism while diffusion plays a substantial role in the process as shown in Table 4.

3.7. Stability studies

Stability studies play a crucial role in formulation development by assessing a product's potential for marketability and determining its expected shelf life. These studies, guided by International Conference on Harmonization (ICH) guidelines, provide insights into optimal storage conditions and duration of stability. Our project conducted stability studies at 40°C with 75% relative humidity, following ICH guidelines [20]. Over a month, tablets from each formulation underwent thorough examination for parameters like physical appearance, hardness, friability, assay, disintegration time, and wetting time at specific intervals, as detailed in Table 5.

The physical characteristics of five different formulations (F1 to F5) of mouth-dissolving tablets underwent comparison between initial values and one-month stability testing results in a tabular format. All formulations retained their "Nearly White" color appearance throughout the initial assessment and during the one-month stability period. The stability test revealed no substantial weight changes in the tablets across all formulations while demonstrating minimal standard deviation variations. The thickness measurements of all formulations stayed consistent throughout the month-long stability test period while showing minor standard deviation fluctuations. The tablet hardness showed minimal changes in formulations F2, F3 and F4 after one month of storage indicating minor effects from environmental conditions. All formulations demonstrated minimal changes in their friability percentages during storage indicating tablets maintained their structural integrity. The formulations maintained their dissolution efficiency because both disintegration time (D.T.) and wetting time exhibited minimal changes.

4. Discussion

This study provides essential information regarding the development and assessment of mefenamic acid mouth-dissolving tablets by examining drug-excipient compatibility, pre- and post-formulation characteristics, and dissolution patterns. FTIR spectroscopic analysis revealed that the drug substance maintained compatibility with all excipients without showing any substantial interactions. The findings match previous research which confirmed the compatibility of mefenamic acid with standard pharmaceutical excipients. FTIR analysis conducted by [21] on mefenamic acid and croscarmellose sodium demonstrated that these excipients did not chemically interact with the drug substance. The selected excipients demonstrated properties suitable for maintaining drug stability and integrity in mefenamic acid tablets.

The powder flowability and bulk density measurements from this study matched the typical requirements for manufacturing solid pharmaceutical dosage forms. The literature demonstrates that Excellent flowability is essential for achieving uniform powder compression during tablet manufacturing processes [22]. The formulation

Table 5. Physical est results of mouth-dissolving Tablets before and after stability studies.

S#NO	Test	F1	F2	F3	F4	F5
Color	Initial	Nearly White	Nearly White	Nearly White	Nearly White	Nearly White
	After 1 Month	Nearly White	Nearly White	Nearly White	Nearly White	Nearly White
Weight (mg) ± S.D	Initial	199.3 ± 0.36	198 ± 0.11	203 ± 0.48	195 ± 0.86	182 ± 0.13
	After 1 Month	199.3 ± 0.36	198 ± 0.11	203 ± 0.48	195 ± 0.86	182 ± 0.13
Thickness (mm) ± S.D	Initial	3.36 ± 0.14	3.22 ± 0.03	3.20 ± 0.06	3.22 ± 0.04	3.25 ± 0.13
	After 1 Month	3.36 ± 0.14	3.22 ± 0.03	3.20 ± 0.06	3.22 ± 0.04	3.25 ± 0.13
Hardness (kg/cm²) ± S.D	Initial	4 ± 0.11	4 ± 0.44	4 ± 0.19	3.9 ± 0.26	3.8 ± 0.51
	After 1 Month	4 ± 0.11	3.9 ± 0.41	3.9 ± 0.11	3.9 ± 0.13	3.8 ± 0.56
Friability (%) ± S.D	Initial	0.106 ± 0.005	0.196 ± 0.02	0.192 ± 0.01	0.167 ± 0.02	0.191 ± 0.006
	After 1 Month	0.107 ± 0.001	0.198 ± 0.02	0.194 ± 0.012	0.169 ± 0.023	0.197 ± 0.0061
Disintegration Time (sec)	Initial	14.50 ± 0.52	25.00 ± 0.54	20.50 ± 0.55	17.35 ± 0.58	16.18 ± 0.75
	After 1 Month	14.46 ± 0.52	24.63 ± 0.54	20.38 ± 0.55	17.30 ± 0.58	16.07 ± 0.75
Wetting Time (sec) ± S.D	Initial	16.50 ± 0.45	18.65 ± 0.23	30.50 ± 0.81	25.44 ± 0.65	28.5 ± 0.38
	After 1 Month	16.32 ± 0.45	18.46 ± 0.23	30.21 ± 0.81	25.16 ± 0.65	28.0 ± 0.38
Assay (%)	Initial	99.9971%	99.4406%	97.9701%	99.0334%	97.342%
	After 1 Month	99.9331%	99.43%	97.97%	99.00%	

utilizes croscarmellose sodium and microcrystalline cellulose, which demonstrate superior flow characteristics and have become standard ingredients in various pharmaceutical formulations owing to their processing benefits. According to Srinivasan et al., the tablet manufacturing process benefits from the optimal angle of repose and Hausner's ratio values measured in this study [13]. The post-formulation tests of tablet hardness, friability, weight variation, and disintegration time matched the expected results for the mouth-dissolving tablets. The therapeutic effectiveness of mefenamic acid depends on its rapid dissolution and bioavailability properties because this non-steroidal anti-inflammatory drug (NSAID) serves as a pain relief medication. All formulations passed the mechanical stability tests because their friability values remained well below the acceptable threshold of 1% while showing results comparable to those of the NSAID formulations studied by [21]. The rapid disintegration time (14.5 seconds observed in the F1 tablets confirmed their essential fast-release property for mouth-dissolving formulations. The research data support previous studies showing that formulations containing higher amounts of super-disintegrants, such as croscarmellose sodium, achieve faster disintegration and dissolution rates [23].

The dissolution profile of F1 showed outstanding results by releasing more than 75% of the drug content within 10 min, which meets the USP requirements for mouth-dissolving tablets. The rapid drug release mechanism of mefenamic acid is critical because it enables quick relief of pain and inflammation. The faster drug release in F1 occurs because higher concentrations of croscarmellose sodium accelerate tablet disintegration and drug release [24]. Our dissolution results match those of previous research on NSAID mouth-dissolving tablets, which demonstrated that optimized excipient ratios combined with super disintegrants lead to improved dissolution rates [25]. The dissolution profiles of these formulations showed varying drug release rates. The dissolution rate was fastest for F1, followed by F4, F3, F2, and F5, indicating that formulation components, especially disintegrant concentration, directly affect drug release speed. These findings align with existing research on mouth-dissolving drug tablets, which demonstrates that higher disintegrant concentrations lead to accelerated dissolution rates [15]. This study confirms that using multiple disintegrants in formulations creates a synergistic effect that enhances the dissolution rate performance.

The model-independent methods validated the consistency of the dissolution profile through similarity and difference factor analyses. The dissolution profiles of all formulations matched the reference formulation, and F1 achieved the highest similarity factor, indicating its superior drug release performance. The pharmaceutical industry relies heavily on this analytical method to maintain product consistency while evaluating new formulation dissolution profiles against established standards [26,27]. The research findings enhance the scientific understanding of the development of NSAID mouth-dissolving tablets. Several researchers agree that NSAID formulations require rapid disintegration and dissolution to deliver prompt pain relief. The therapeutic effectiveness of these dosage forms improves through the strategic use of croscarmellose sodium excipients and formulation parameter optimization according to [28,29]. The promising results from F1 indicate that future research should focus on optimizing the formulation through excipient combinations and nanocarrier or controlled-release system integration to enhance the clinical effectiveness of mefenamic acid mouth-dissolving tablets. These advancements could further improve patient compliance and therapeutic outcomes, similar to how Oliveira et al. (2020) explored lactose-free formulations for enhanced patient acceptability[30].

5. Future Directions

1. **Application to Other Drugs**: The formulation approach used in this study can be extended to other poorly water-soluble drugs or drugs with challenging physicochemical properties to enhance their bioavailability and patient compliance.
2.
3. **Exploration of Novel Excipients**: Future research could investigate the use of innovative excipients, such as super-disintegrants or taste-masking agents, to improve the sensory attributes and functionality of the tablets.
4. **Personalized Medicine**: The approach could be tailored to develop personalized orodispersible tablets by incorporating patient-specific doses or combinations of active ingredients, guided by pharmacogenomic insights.
5. **Pediatric and Geriatric Applications**: Further studies could focus on optimizing the formulation for specific patient populations, such as pediatric or geriatric patients, who often face challenges with swallowing conventional tablets.
6. **In Vivo Studies**: Conducting bioequivalence or pharmacokinetic studies in animal models or human subjects would validate the clinical utility of these formulations and provide more comprehensive data on their performance.
7. **Technology Integration**: Incorporating advanced manufacturing technologies like 3D printing or hot-melt extrusion could open new avenues for producing complex dosage forms with enhanced precision and scalability.
8. **Shelf Life and Storage Studies**: Extended stability studies under varied environmental conditions (temperature, humidity, etc.) could determine the long-term usability and robustness of the formulations.
9. **Sustainability in Drug Delivery**: Future work could explore the use of biodegradable or environmentally friendly excipients to ensure sustainable pharmaceutical practices in line with global trends.

Orodispersible tablets represent the dosage form of modern times because their attractiveness has grown steadily since their introduction while providing faster dissolution and improved swallowing capabilities compared to traditional oral therapies such as tablets and capsules. Fast-dissolving tablets can be produced through two main methods: matrix formation of highly porous structures and formulations containing effervescent excipients. The research demonstrated that mefenamic acid tablets were successfully produced through direct compression with croscarmellose sodium, cross povidone and sodium starch glycolate serving as super-disintegrants. The F1 formulation demonstrated superior performance among all five formulations because it contained 7% croscarmellose sodium as a super-disintegrant which led to optimal dissolution and disintegration and enhanced absorption and better patient compliance. The direct compression method provides a simple manufacturing process with minimal steps while offering convenient production of orodispersible

tablets. The zero-order kinetic model perfectly explained the drug release patterns of all five formulations tested in 6.8 pH buffer solution. This showed that the drug release patterns were independent of ingredient concentrations. The formulation showed no modifications throughout the testing duration and stability investigations revealed no significant alterations before or after the studies.

Abbreviations

F1 - Formulation 1; F2 - Formulation 2; F3 - Formulation 3; F4 - Formulation 4; F5 - Formulation 5; R^2 - Coefficient of Determination; K° - Rate Constant; SS - Sum of Squares; df - Degrees of Freedom; MS - Mean Square; P-value - Probability Value; F crit - Critical Value of F (from ANOVA table); ANOVA - Analysis of Variance; Higuchi Model - A model to describe the drug release from solid dosage forms; Hixson Crowell Model - A model for drug release based on particle size reduction

Conflict of interest

All the authors have no conflict of interest

Consent for publications

I hereby grant consent for the publication of this paper, including all associated data and findings, in relevant academic journals and platforms.

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