

# Development of Ketorolac Tromethamine Mouth Dissolving Tablet Using Natural Disintegrating Agents

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Received: 10<sup>th</sup> Sep, 2025; Revised: 24<sup>th</sup> Oct 2025; Accepted: 6<sup>th</sup> Nov, 2025; Available Online: 1<sup>st</sup> December, 2025

## ABSTRACT

The present study focuses on the design & development of Ketorolac Tromethamine (KT) mouth dissolving tablets (MDTs) using natural disintegrating agents with dual intent to enhance disintegration and optimize mouthfeel for improved patient compliance. Natural disintegrants such as fennel, cumin, and coriander powders were incorporated at varying concentrations (2%, 4%, and 6%) and compared with the synthetic super disintegrants Croscarmellose sodium (CCS). KT, a potent non-steroidal anti-inflammatory (NSAID) known for rapid analgesic action, was chosen as the test substance for the investigation, and direct compaction is utilized for tablet preparation. Preformulation studies, including FTIR analysis, confirmed drug-excipient comparability. Evaluation of pre and post compression parameters confirmed excellent flowability, uniformity, and mechanical strength of all formulations. The optimized formulations (F3, F6, F9, F12) exhibited rapid disintegration (10 min), reduced wetting time (4-5 min), and friability fell within the standard range (< 1%). In vitro dissolution studies revealed not able improved drug release with F9 (6% coriander powder), showing 88.80% drug release in 60 minutes, comparable to the marketed product (F14). Dissolution efficiency (DE60 %) further supported the superior performance of F9 (75.98%) and F12 (77.20%), with F9 offering a natural alternative to synthetic disintegrants. Kinetic modeling indicated a non-Fickian diffusion mechanism for F9, driven by swelling and wicking action of coriander powder. Overall, the study established that natural disintegrants, especially coriander powder, not only enhance disintegration and dissolution but also improve patient-centric parameters like mouthfeel, making them ideal for MDT formulations. F9 was identified as the optimal formulation, offering an effective, stable, and natural alternative for fast-acting pain relief.

**Keywords:** Mouth Dissolving Tablets, Improved Mouth Feel, Improved Drug Dissolution, Patient Compliance, and Ketorolac Tromethamine.

**How to cite this article:** Kumar CSP, Thummala U, Bhaskararao P, Narla D, Kumar KK; Development of Ketorolac Tromethamine Mouth Dissolving Tablet Using Natural Disintegrating Agents. *Int J Drug Deliv Technol.* 2026;16(1): 447-458. DOI: 10.25258/ijddt.16.1.47

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Evolution of oral drug delivery approaches has led to create the mouth dissolving tablet (MDTs), which furnish a convenient and patient-friendly alternative to traditional tablets. MDTs are type of dosage form designated to rapidly dissolve in the mouth, bypass water requirement. According to several studies, the simplicity of these dose forms has led to their increased use, particularly among young, elderly, and dysphasia patients who have trouble swallowing regular tablets<sup>1</sup>.

Numerous research efforts have been made to enhance the formulation, disintegration time, flavour masking, and general patient acceptability of MDTs. For instance, studies by Mohamed and Ibrahim (2011) and Kamle and Chaudhari (2011) have demonstrated the potential of

Mouth-Dissolving Tablets in improving the bioavailability and reducing the gastrointestinal side effects of NSAIDs like Ketorolac tromethamine. Other researchers, such as prajapati et al. (2012) and Bindal and indurkhya (2013), have also explored the use of various super disintegrants and formulation techniques to develop Mouth-Dissolving Tablets with rapid disintegration and high dissolution rates.

KT, a powerful NSAID, is a suitable candidate for mouth dissolving formulations due to its rapid onset of analgesic action & effective control acute pain. The drug's pharmacological profile aligns well with the objectives of fast-dissolving dosage forms, where prompt therapeutic response is critical.

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In current study, KTMDTs were manufactured using the direct compaction method, a cost-effective & efficient technique that eliminates that need for granulation. This economical method of tablet preparation allows for a simplified manufacturing process, reducing production costs and making it an attractive option for pharmaceutical companies<sup>2,3</sup>.

A crucial factor in successful design of mouth dissolving tablets is selection of an appropriate disintegrants. Natural disintegrants, derived from plant-based sources, offer several advantages, including biocompatibility, biodegradability, and minimal toxicity. In current study, we researched the benefit of three natural disintegrants-fennel powder, cumin powder, and coriander powder in formulation of Ketorolac Tromethamine mouth dissolving tablets. These spice-derived powders were chosen for their fibrous composition, hygroscopic nature, and historical use in traditional medicine, which suggest potential for promoting rapid tablet disintegration to promote rapid tablet disintegration.

The results of this study aim to establish a viable natural alternative to synthetic disintegrants in development of Ketorolac Tromethamine mouth dissolving tablets. By demonstrating both disintegration efficiency and patient-friendly attributes of fennel, cumin, and coriander powders, this research contributes to the advancement of effective and natural Mouth-Dissolving Tablets<sup>4,5</sup>.

#### MATERIALS

The following materials were selected for the current study: Ketorolac Tromethamine are gifted by SK Health Care Private Limited, Batchupally, Hyderabad, and natural disintegrants including fennel powder, cumin powder, and coriander powder, which were obtained from domestic sources. Additionally, CCS, Mannitol, MCC, Mg. stearate, & talc are also gifted SK Health Care Private Limited, Batchupally, Hyderabad.

#### METHODS

##### FTIR Studies

Fourier Transform infrared (FTIR) spectroscopy is performed to investigate adverse interactions between Ketorolac Tromethamine and individual excipients or their physical mixtures. This study was crucial in determining comparability of drug with various excipients, ensuring stability & efficiency of mouth dissolving tablets. The FTIR analysis was performed using an Alpha 2 ECO-AT FTIR instrument with OPUS software, scanning samples within the 600-400  $\text{cm}^{-1}$  range. The samples were prepared by placing them on the ZnSe crystal surface, and spectra were recorded after a background scan. The drug and excipients were analyzed in specific ratios, matching their maximum concentrations in the tablet formulation, including 1:1:8 for fennel powder, cumin powder, coriander powder, and Croscarmellose sodium, 1:12 for Mannitol, 1:14 for Microcrystalline cellulose, and 1:0:3 for magnesium stearate and talc as shown in Table 1. These studies helped identify any possible interactions

between the ingredients, ensuring the formulation's stability and performance<sup>6</sup>.

**Table 1.** FTIR studies<sup>7</sup>

Sample No.	Name of Drug: Excipient	Drug: Excipient Ratio (at Maximum concentration)
S1	Ketorolac Tromethamine	1
S2	Ketorolac Tromethamine: Fennel powder	1:1.8
S3	Ketorolac Tromethamine: Cumin powder	1:1.8
S4	Ketorolac Tromethamine: Coriander powder	1:1.8
S5	Ketorolac Tromethamine: Croscarmellose sodium	1:1.8
S6	Ketorolac Tromethamine: Mannitol	1:12
S7	Ketorolac Tromethamine: Microcrystalline cellulose	1:14
S8	Ketorolac Tromethamine: Magnesium stearate	1:0.3
S9	Ketorolac Tromethamine: Talc	1:0.3

##### Analytical Method

The calibration curve of Ketorolac Tromethamine is generated using buffer (0.1N HCl, phosphate buffer, and water) with UV Spectrometer to assess system suitability. The process involved preparing a primary stock solution (1000 $\mu\text{g}/\text{ml}$ ) by dissolving Ketorolac Tromethamine in buffer, followed by creating a secondary stock solution (100 $\mu\text{g}/\text{ml}$ ) through dilution, and then preparing various concentrations (2-16 $\mu\text{g}/\text{ml}$ ) through further dilution. The lambda max of Ketorolac Tromethamine was determined using a central concentration (8 or 10 $\mu\text{g}/\text{ml}$ ). Subsequently, absorbance values were measured for all concentration vs absorbance. The  $R^2$  value was calculated to evaluate system suitability, ensuring the linearity and reliability of the calibration curve<sup>8,9</sup>.

##### Saturation solubility Studies:

Saturation solubility for Ketorolac Tromethamine is assessed in different media, including 0.1N Hydrochloric acid, water, and phosphate buffer, pH 6.8. Excessive quantity of Ketorolac Tromethamine loaded to each medium and shaken at 37°C for 24 hours to ensure equilibrium. After filtration, the concentration of Ketorolac Tromethamine in filtrate is measured by UV Spectrophotometer, and solubility values were calculated in  $\text{mg}/\text{ml}$ <sup>10,11</sup>.

##### Formulation Table for Ketorolac Tromethamine Mouth Dissolving Tablets

**Table.2.** Formulation Table for KT MDTs

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ketorolac Tromethamine	10	10	10	10	10	10	10	10	10	10	10	10	10
Fennel powder (2%, 4%, 6%)	6	12	18	-	-	-	-	-	-	-	-	-	-
Cumin powder (2%, 4%, 6%)	-	-	-	6	12	18	-	-	-	-	-	-	-
CCS (2%, 4%, 6%)	-	-	-	-	-	-	6	12	18	-	-	-	-
Mannitol	120	120	120	120	120	120	120	120	120	120	120	120	120
MCC	140	134	128	140	134	128	140	134	128	140	134	128	140
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Total Weight (mg)	300	300	300	300	300	300	300	300	300	300	300	300	300

The KT MDTs are manufactured by direct compaction method, with different% w/w natural disintegrant powders, including fennel (2%, 4%, 6% w/w), cumin (2%, 4%, 6% w/w), and coriander (2%, 4%, 6% w/w), as well as Croscarmellose sodium (CCS) (2%, 4%, 6% w/w), as a synthetic disintegrants. Each formulation contained 10% w/w Ketorolac Tromethamine, 40% w/w Mannitol, and 46.67-48.67% w/w MCC, with 1% w/w Mg. stearate and 1% w/w talc as lubricants<sup>12,13,14</sup>.

The procedure for preparing the Mouth-Dissolving Tablets involved accurately weighing the required quantities of Ketorolac Tromethamine, disintegrants, Mannitol MCC, Magnesium stearate, and Talc using an electronic balance. The ingredients were then sifted through a #40 mesh sieve to achieve uniform particle size distribution. The weighed ingredients were dry-mixed, where Ketorolac Tromethamine was blended with Mannitol and MCC by a poly bag or laboratory blender for ten minutes to ensure uniformity. Disintegrants were then incorporated into the mixtures and further blended for 5 minutes to ensure their even dispersion throughout the formulation. Mg. stearate & talc loaded last and agitated gently for 2-3 minutes using a tumbling blender to avoid over-mixing, which could adversely affect tablet hardness. The final powder mixis then compressed a a tablet by a tablet compression machine fitted with a 6mm round flat punch, with an optimized compression force to ensure uniform hardness and tablet integrity<sup>15,16</sup>.

## EVALUATION OF TABLETS

### Precompression parameters

Pre-compression tests evaluates flow properties and compressibility of tablet mixture. Angle of repose assessed the flowability for tablet mixture, with lower angles indicating better flow (Limits; <25° is considered as Excellent, 25° to 30° is considered as Good, 30° to 40° is considered as Passable, 40° to 50° is considered as Poor, >45° is considered as Very poor). Bulk density (BD) was assessed by gauging initial volume of precisely weighed quantity of tablet mixture, with higher values indicating better flow (limits in g/ml: > 0.5=Good, 0.3-0.5 =Moderate, < 0.3 = poor). Tapped density (TD) was evaluated by submitting the powder-filled measuring cylinder to tapping until a constant volume was reached. Carr's index (CI), calculated from BD&TD, flow properties were assessed (limits:< 10% is considered as Excellent, 11% to 15% is considered as Good, 16% to 20% is considered as Fair, 21% to 25% is considered as Passable, 26% to 38% is considered as Poor). Hausner's ratio (HR), also calculated from BD and TD, evaluated

flow properties (limits: 1.00-1.11 excellent, 1.12-1.18 good, 1.19-1.45 poor). These tests ensured the powder blend had optimal flow properties for uniform die filling during compression, contributing to consistent tablet quality<sup>17,18,19</sup>. The results were shown at Table.7.

### Post compression parameters

The post-compression tests evaluated various parameters for Ketorolac Tromethamine Mouth-Dissolving Tablets. The Uniformity of weight involves determining weight of each 10 tablets, calculating average weight, and assessing % deviation from mean (limits: ≤ 80mg ± 10%, >80mg and <250mg ± 7.5%, ≥ 250mg ± 5%). Tablet thickness was checked using a Vernier caliper on 10 samples. Friability test assessed physical stability by roasting 10 tablets in friabilator for 100 times, with a value ≤ 1.0% indicating adequate resistance to abrasion. Wetting time was assessed by positioning a tablet on folded tissue paper, moistened with 6ml of distilled water, and recording the water penetration time on the tablet's surface. Drug content was determined by crushing 10 tablets, dissolving the powder in phosphate buffer, and absorbance were taken at 323nm using UV-Visible Spectrophotometer. Disintegration test was conducted in a USP disintegrator, six tablets were tested using distilled water at temperature 37± 0.5°C, and documented the disintegration time<sup>20,21,22</sup> as shown at Table 8.

### In-vitro drug dissolution studies

The *In-vitro* drug dissolution study is conducted to characterize absorption pattern and bioavailability of Ketorolac Tromethamine. A pre-weighed tablet was immersed into 900ml of phosphate buffer at temp 37.0°C, and agitated at 50 rpm. Sample collection occurred at intervals outlined in the Table 9, diluted, and analyzed using UV spectrophotometry at 323 nm to determine cumulative % drug release<sup>23</sup>. The results were shown at Table 9. And the dissolution efficiency (DE<sub>60%</sub>) was performed<sup>24</sup> for *in vitro* dissolution studies and results were shown at Table 10.

### In-vitro drug release kinetics study

*In-vitro* drug release profile is characterized by number of kinetic profiles for determining the drug release mechanisms, such as zero-order kinetics (C%DUR time), first-order kinetics (log C%DUR vs time), Higuchi model (C%DR vs √time), and Peppas's release profile provides insights into the drug release behaviour, with Peppas's model specifically helping to identify the diffusion mechanism (Fickian or non-Fickian) based on the diffusion exponent (n). The evaluation demonstrated the correlation between payload delivery and duration, offering understanding into the system's performance, & the coefficient of determination (R<sup>2</sup>) was used to evaluate the fit of each model<sup>25,26</sup>. The results were shown at Table 11.

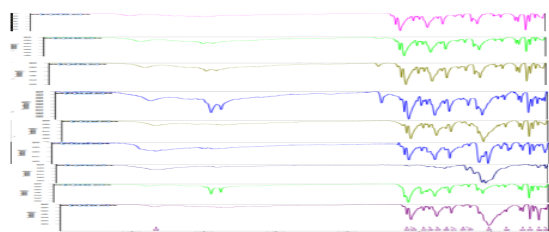
### Accelerated stability studies

The S1 formulation underwent accelerated stability testing for three months in accordance with ICH guidelines to

evaluate its physical and chemical stability under stress conditions. The tablets were stored under two different conditions: ambient room conditions with  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  temperature &  $60\% \pm 2\%$  RH, & accelerated conditions with  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  temperature &  $75\% \pm 2\%$  RH. Monthly evaluations were conducted to assess any changes in the tablet's physical characteristics and chemical stability, providing valuable insights into the formulation's stability profile and potential shelf-life. This study helped to predict the formulation's behaviour under long-term storage conditions and identify any potential stability issues<sup>27,28</sup>. The results were shown at Table 12,13 & 14.

**RESULTS & DISCUSSION**

**FTIR Studies**



**Fig.No. 1:** FTIR Spectras for powder mixes S1 to S9

**Table.3.** Comparative discussion of FTIR Spectras

$\lambda$ ( $\text{cm}^{-1}$ )	Key functional group	S 1	S 2	S 3	S 4	S 5	S 6	S 7	S 8	S 9
~3460 - 346	O-H stretching (broad, H-bonded)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~2920 - 2940	C-H stretching (aliphatic)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~1730 - 1745	C=O stretching (ester, acid)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~1600 - 1650	C=C or Amide I	✓	✓	✓	✓	✓	✓	✓	✓	✓
	(N-H bending/C=O)									
~1450	CH <sub>2</sub> bending (scissoring)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~1375	CH <sub>3</sub> symmetric bending	✓	✓	✓	✓	✓	✓	✓	✓	✓
~1230 - 1250	C-O-C stretching (ester/ether)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~1030 - 1100	C-O-C stretching (ether)	✓	✓	✓	✓	✓	✓	✓	✓	✓
~850 - 890	C-H out-of-plane (aromatic)	✓	✓	✓	✓	✓	✓	✓	✓	✓

The FTIR spectra of formulation S1 to S9 exhibited consistent peaks, indicating similar functional groups

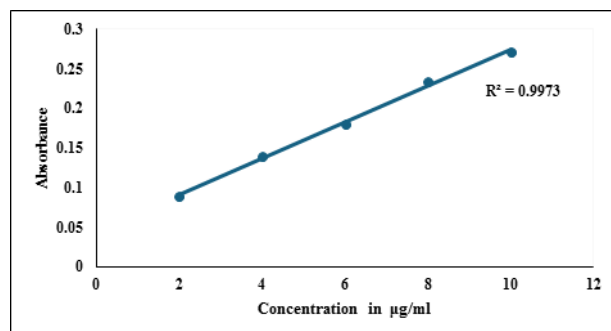
across all samples, which suggested the presence of Ketorolac Tromethamine in all formulations. The presence of a broad O-H stretch peak nearly  $3460\text{ cm}^{-1}$ , aliphatic C-H stretching peak between  $2910\text{--}2940\text{ cm}^{-1}$  and  $1030\text{--}1100\text{ cm}^{-1}$  were characteristics of Ketorolac Tromethamine's molecular structure. The consistency of these peaks across all nine formulations, despite varying excipients concentration, suggested that the drug's functional groups remained intact and unaffected by the presence of excipients. Moreover, the absence of significant peak shifts or new peak formulations in the spectra of S2-S9 formulations compared to the pure drug (S1) indicated no detectable chemical interactions or incompatibilities between Ketorolac Tromethamine and the excipients used, including Fennel powder, Cumin powder, Coriander powder, CCS, Mannitol, MCC, Mg. stearate, and talc. This suggested that formulation strategy was stable, and the excipients were compatible with Ketorolac Tromethamine, even at maximum concentrations. Overall, the FTIR study confirmed the presence of Ketorolac Tromethamine in all samples and demonstrated no evidence of interaction among the drug & excipients, supporting the potential for a stable and effective formulation.

**ANALYTICAL METHOD**

**Calibration curve**

**Table.4.** Ketorolac Tromethamine calibration curve using 0.1N Hydrochloric acid

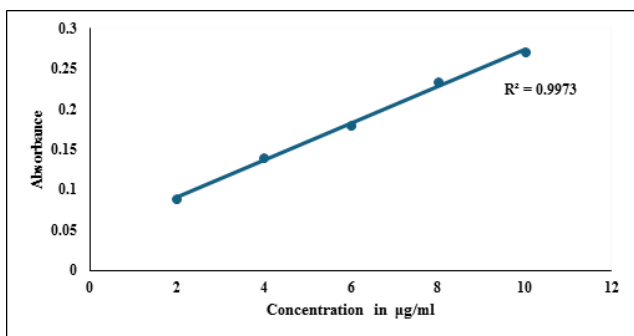
Concentration in $\mu\text{g/ml}$	Absorbance
2	0.089
4	0.139
6	0.18
8	0.234
10	0.271



**Fig.No. 2:** Ketorolac Tromethamine calibration curve using 0.1N Hydrochloric acid

**Table 5:** Ketorolac Tromethamine calibration curve using phosphate buffer, pH 6.8

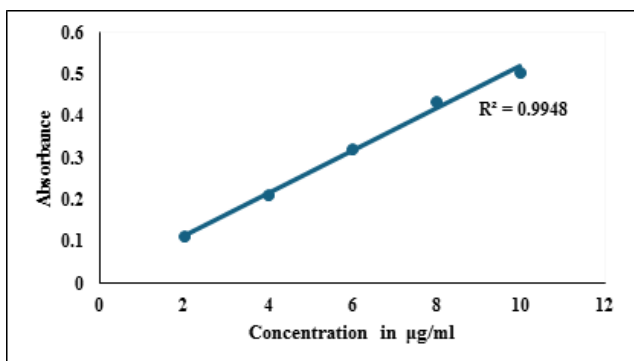
Concentration in $\mu\text{g/ml}$	Absorbance
2	0.110
4	0.235
6	0.277
8	0.338
10	0.426



**Fig.No. 4:** Ketorolac Tromethamine calibration curve using phosphate buffer, pH 6.8

**Table 6:** Ketorolac Tromethamine calibration curve in water as a buffer at 323 nm

Concentration in µg/ml	Absorbance
2	0.112
4	0.212
6	0.321
8	0.436
10	0.506



**Fig.No. 5:** Ketorolac Tromethamine calibration curve in water as a buffer at 323 nm

The development of standard calibration curves for Ketorolac Tromethamine involved three distinct buffers: 0.1 N Hydrochloric acid, phosphate buffer (pH 6.8) and water, with absorbance measurements taken at 323 nm. Across all three media, a robust liner relationship was observed between drug concentrations (2-10 µg/ml) and corresponding absorbance values, confirming adherence to Beer-Lambert’s law. Notably, the method exhibited excellent linearity in 0.1 N HCl, with a correlation coefficient ( $R^2$ ) of 0.9973, underscoring its suitability for quantitative estimation in acidic environments. pH phosphate buffer & water also demonstrated good linearity, with absorbance values increasing proportionally with concentration and yielding slightly higher values than 0.1 N HCl. This suggests improved solubility or enhanced optical response of the drug under neutral to slightly basic conditions. The consistent linearity across all three solvents confirms the reliability and robustness of the UV spectrophotometry method for estimating Ketorolac Tromethamine. Consequently, this method can be applied with confidence in *in vitro* drug release studies from

mouth-dissolving tablet formulation, accommodating different physiological pH environments. The method’s reliability across varied pH conditions support its utility in assessing drug release profiles under conditions mimicking both gastric and intestinal environments, thereby facilitating comprehensive formulation development and evaluation.

**Solubility studies**

**Table 7:** Solubility data of Ketorolac Tromethamine in various medias

Buffer	Concentration in mg/ml
0.1 N Hydrochloric acid	10
Phosphate buffer, pH 6.8	6
Distilled water	4

Solubility profile of Ketorolac Tromethamine demonstrated notable variation across different media, highlighting its pH-dependent nature. The drug exhibited the maximum solubility in 0.1 N HCl, reaching as much as 10 mg/ml, which reflects its favourable solubility in acidic environment like the stomach. In comparison, solubility decreased to 6 mg/ml in phosphate buffer, pH 6.8 & further declined to 4 mg/ml in the distilled water. These findings indicate that Ketorolac Tromethamine dissolves more readily under acidic conditions and becomes less soluble as the pH shifts towards neutral or slightly basic levels. This pH-dependent solubility behaviour is a key consideration in formulation of oral formulation, as it can influence both the drug’s dissolution rate and its subsequent bioavailability.

**PRECOMPRESSION PARAMETERS**

**Table.7.** Precompression parameters of Ketorolac Tromethamine fast dissolving tablets

Formulation	Angle of Repose (o)	Bulk Density (g/cm <sup>3</sup> )	Tapped Density (g/cm <sup>3</sup> )	Carr’s Index (%)	Hausners ratio
F1	29.12	0.42	0.48	12.5	1.14
F2	28.44	0.43	0.49	12.24	1.14
F3	27.85	0.44	0.50	12.00	1.13
F4	28.90	0.43	0.49	12.24	1.14
F5	27.42	0.44	0.50	12.00	1.13
F6	26.80	0.45	0.51	11.76	1.13
F7	28.10	0.42	0.47	10.63	1.12
F8	27.36	0.44	0.49	10.20	1.11
F9	26.94	0.45	0.50	10.00	1.11
F10	27.85	0.43	0.48	10.41	1.12
F11	26.64	0.44	0.49	10.20	1.11
F12	25.95	0.45	0.49	8.16	1.09
F13	30.28	0.41	0.48	14.58	1.17

The pre-compression evaluation of powder properties revealed that all formulations exhibited good to excellent flowability, compressibility, and compatibility, making them suitable for direct compression. The angle of repose ( $25.95^\circ$  to  $30.28^\circ$ ), BD ( $0.41$  to  $0.45\text{g/cm}^3$ ), TD ( $0.47$  to  $0.51\text{g/cm}^3$ ), CI ( $8.16\%$  to  $14.58\%$ ), and HR ( $1.09$  to  $1.17$ ) all indicated acceptable powder characteristics. Notably, formulations containing natural disintegrants, such as coriander and fennel powder, particularly at higher concentrations ( $6\%$ ), demonstrated improved flow and compressibility properties. Formulation F12 ( $6\%$  Croscarmellose sodium) and F9 ( $6\%$  coriander powder) showed the best overall performance, while F13, likely due to the absence of an effective disintegrants, exhibit inferior properties. These findings suggest that natural disintegrants can enhance the processing performance of Mouth-Dissolving Tablets, making them a promising option for improving tablet formulation.

### POST-COMPRESSION PARAMETERS

**Table.8.** Post-Compression variables for Ketorolac Tromethamine mouth dissolving tablets

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Disintegration time (min)	Wetting time (min)	Drug Content (%)
F1	299	3.2	3.8	0.71	45	10	98.2
F2	301	3.3	3.6	0.68	30	8	98.5
F3	300	3.3	3.5	0.65	20	7	99.1
F4	300	3.3	3.6	0.67	25	8	98.7
F5	299	3.2	3.4	0.62	15	6	99.3
F6	301	3.3	3.3	0.58	10	5	99.5
F7	298	3.2	3.7	0.69	35	9	98.9
F8	299	3.2	3.1	0.64	20	7	99.0
F9	300	3.3	3.7	0.59	10	4	99.6
F10	300	3.3	3.5	0.66	30	9	98.8
F11	301	3.2	3.4	0.60	15	6	99.4
F12	300	3.3	3.3	0.56	10	4	99.7
F13	301	3.4	4.2	0.88	50	12	97.6

The post-compression evaluation of the formulated tablets demonstrated excellent photochemical characteristics, confirming their suitability for pharmaceuticals use. Weight variation remained well within the acceptable IP limits for tablets weighing less than  $500$  mg, showing a deviation of less than  $2.5\%$ , with individual tablet weights ranging from  $298$  to  $301$  mg. This minimal variation, particularly evident in formulation's F2 and F12, indicates consistent powder flow and uniform die filling during

compression. Tablet thickness was also uniform, ranging between  $3.2$  and  $3.4$  mm, with negligible standard deviation, suggesting consistent tablet dimensions and no negative impact from the incorporation of natural disintegrants.

Tablet hardness values ranged from  $3.3$  to  $4.2$  kg/cm<sup>2</sup>, with F13, which lacked any disintegrant, likely leading to tighter packing and greater mechanical strength. Formulations containing  $6\%$  disintegrant-whether natural or synthetic (F3, F6, F9, F12), - showed slightly reduced hardness but remained within acceptable limits for Mouth-Dissolving Tablets, ensuring both mechanical stability and rapid disintegration. Friability values ranged between  $0.56\%$  and  $0.88\%$ , with F13 again showing the highest friability, while the optimized formulations with disintegrants (F6, F9, F12) demonstrated the lowest friability values, indicating superior mechanical resistance during handling and transportation.

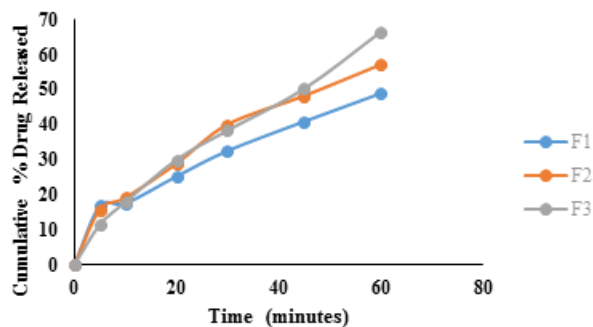
Disintegration time, a critical parameter for mouth-dissolving tablets, ranged from  $10$  to  $50$  minutes. F13, lacking a disintegrant, showed the longest disintegration time of  $50$  minutes. In contrast, formulations with  $6\%$  disintegrants (F6, F9, F12) exhibited rapid disintegration within  $10$  minutes, highlighting the role of both natural and synthetic disintegrants in promoting faster tablet breakdown. Wetting time, which reflects the tablet's ability to absorb saliva and begin disintegration, ranged from  $4$  to  $12$  minutes. F12 and F9 showed the shortest wetting time of  $4$  minutes, while F13 again displayed the longest time  $12$  minutes, underscoring the superior wicking effect of higher disintegrant concentrations. Drug content across all formulations was within pharmacopoeia limits ( $97.6\%$ - $99.7\%$ ), confirming uniform blending and excellent content uniformity.

In summary, all evaluated post-compression parameters affirmed the quality and performance of the formulated Mouth-Dissolving Tablets. Notably, formulations containing  $6\%$  fennel (F3), cumin (F6), and Coriander (F9) powders, as well as Croscarmellose sodium (F12), outperformed the disintegrant-free control (F13) in terms of rapid disintegration, shorter wetting time, and mechanical robustness. These finding support the effective use of natural disintegrants as functional, economical, and patient-friendly alternatives to synthetic disintegrants in the design of KT MDTs.

### In vitro Drugdissolution studies

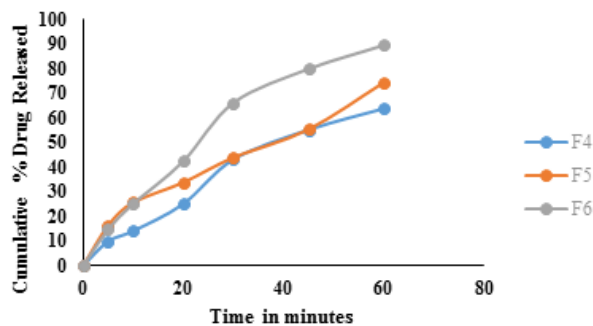
**Table 9:** Cumulative % drug dissolved data for Ketorolac Tromethamine fast dissolving tablets

Time (min)	Cumulative % Drug Dissolved													
	Fennel powder			Cummins powder			Coriander powder			CCS			F13	F14
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12		
5	16.80	15.72	11.44	9.86	16.254	14.61	16.25	18.62	38.72	13.53	16.25	20.46	13.22	82.95
10	17.54	19.19	17.90	14.07	25.594	25.06	14.80	23.93	54.27	15.89	28.87	32.69	13.66	93.55
20	25.22	28.86	29.96	25.03	33.79	42.38	23.58	38.36	74.37	20.63	45.69	71.79	19.9	98.66
30	32.52	40.08	38.36	43.12	43.87	66.14	30.51	46.76	78.37	27.40	64.85	88.80	23.31	99.21
45	40.92	48.24	50.25	55.18	55.35	79.86	44.39	67.41	84.23	41.66	82.58	90.26	30.54	--
60	48.96	57.19	66.50	63.78	74.37	89.52	58.29	77.85	88.80	58.46	84.95	99.32	37.1	--



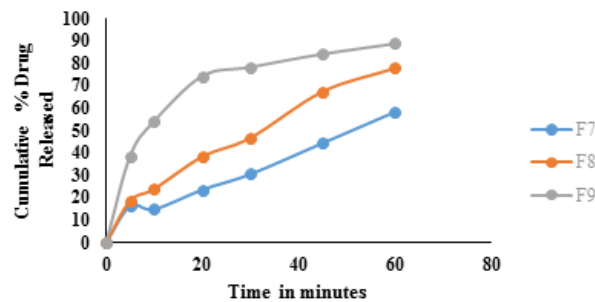
**Fig.No. 6:** *In vitro* Drug release study of Ketorolac Tromethamine Fennel Powder Formulations: F1-F3

F1, F2, & F3 containing fennel powder as a disintegrant, revealed distinct release profiles over 60 minutes. Initially, F1 showed the fastest release (16.80% at 5 minutes), but F3 ultimately outperformed others, achieving the highest cumulative release (66.50% at 60 minutes). The ascending order of formulations based on cumulative % drug dissolved at 60 minutes was F1 (48.96%) < F2 (57.19%) < F3 (66.50%). F3's superior dissolution profile suggests that the optimal concentration of fennel powder as a natural disintegrant enhanced disintegration and drug release characteristics, making it the most effective formulation.



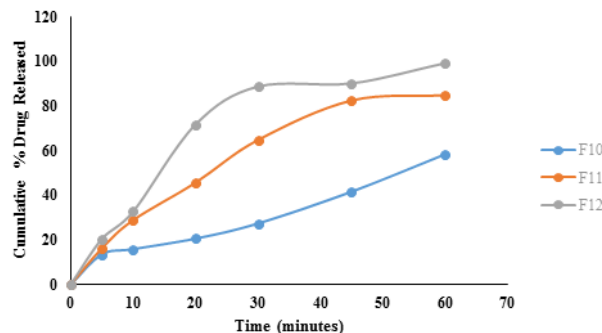
**Fig.No. 7:** *In vitro* Drug dissolution graph for Ketorolac Tromethamine Cumin Powder Formulations: F4-F6

F4, F5, & F6, containing cumin powder as a natural disintegrant, revealed distinct release profiles over 60 minutes. Initially, F5 showed the highest release (16.25% at 5 minutes), but F6 ultimately outperformed others, achieving the highest cumulative release (89.52% at 60 minutes). F6's superior performance was evident from the 20-minute mark onwards, suggesting optimal swelling and wicking action of cumin powder. The ascending order of formulations based on Cumulative % drug dissolved at 60 minutes was F4 (63.78%) < F5 (73.37%) < F6 (89.52%). F6's formulation demonstrated the most efficient *in vitro* drug release, highlighting success rate of cumin powder as natural disintegrating agent in promoting rapid and complete drug release.



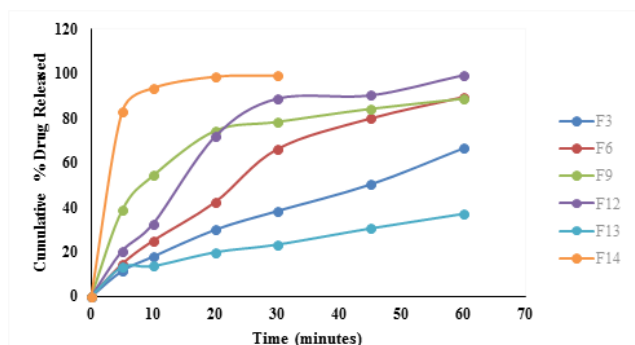
**Fig.No. 8:** *In vitro* Drug dissolution graph for Ketorolac Tromethamine coriander powder Formulations: F7-F9

F7, F8, & F9, containing coriander powder as a natural disintegrant, showed that F9 exhibit the fastest and most complete drug release, with 88.80% release at 60 minutes. F9 outperformed F8 and F7 though the study, with a significantly higher release rate from the initial 5-minute interval (38.72%). The ascending order of formulations based on cumulative % drug dissolved at 60 minutes was F7 (58.29%) < F8 (77.85%) < F9 (88.80%). F9's superior performance suggests an optimal concentration or interaction of coriander powder with the tablet matrix, highlighting its potential as a promising natural disintegrant. The results demonstrate the effectiveness of coriander powder in enhancing tablet disintegration and wettability, particularly in formulation F9.



**Fig.No. 9:** *In vitro* Drug dissolution graph for Ketorolac Tromethamine CCS (Croscarmellose sodium) Formulations: F10-F12

F10, F11, & F12, containing Croscarmellose sodium (CCS) as a synthetic super disintegrant, showed that F12 exhibited the most rapid and complete drug release, with 99.32% release 60 minutes. F12 outperformed F11 and F10 at time intervals, with a significantly higher release rate from the initial 5-minute mark (20.46%). The ascending order of formulations based on cumulative % drug dissolved at 60 minutes was F10 (58.46%) < F11 (84.95%) < F12 (99.32%). F12's superior performance confirms the potent disintegration capability of CCS when used at optimal levels, making it the most promising formulation. The results demonstrate the effectiveness of CCS in enhancing tablet disintegration and drug release, particularly in formulation F12.



**Fig.No. 10:** Comparative *In-vitro* Drug Dissolution Analysis: Formulations- F3, F6, F9, F12, F13, & F14

The *in vitro* dissolution study revealed significant differences in drug release profiles among the formulations. F14 exhibited the fastest and highest drug release, achieving 99.21% at 30 minutes. F12 also showed excellent dissolution, with 99.32% release at 60 minutes. F6 and F9 performed well, with > 88% release at 60 minutes, although F9 showed a slightly faster release rate. In contrast, F13 demonstrated poorest performance, with only 37.10% release at 60 minutes. The ascending order of formulations based on % drug released at 60 minutes was F13 < F3 < F6 < F9 < F12 < F14. Overall, F14 emerged as the best-performing formulation, while F12, F9, and F6 also showed promising results.

#### DISSOLUTION EFFICIENCY (DE60%)

**Table 10:** Dissolution efficiency of formulation from F1 to F13

Formulation code	DE60%
F1	32.96
F2	38.72
F3	39.88
F4	40.67
F5	45.56
F6	61.23
F7	33.87
F8	50.85
F9	75.98
F10	31.93
F11	62.43
F12	77.20
F13	24.73
F14	97.87

The Dissolution efficiency at 60 minutes (DE60%) was used to compare the performance of formulations F1 to F14, revealing significant variations in drug release profiles. F14 exhibited the highest DE60% (97.87%), indicating superior drug release, followed by F12 (77.20%) and F9 (75.98%), which contained 6% disintegrant. The absence of disintegrant in F13 resulted in the lowest DE60% (24.73%), the formulations ranked in descending order of DE60% where F14 > F12 > F9 > F11 > F6 > F8 > F5 > F4 > F3 > F2 > F7 > F1 > F10 > F13. The results demonstrate that optimized disintegrant selection, particularly natural disintegrants like fennel,

cumin, and coriander powders, can significantly enhance dissolution efficiency, F14 showed the best dissolution profile, highlighting the Importance of disintegrant selection in tablet formulations.

#### SELECTION OF BEST FORMULATION

Based on the comparative evaluation of all formulations, F14, the marketed reference product, showed highest drug release with a DE<sub>60</sub> % of 97.87%, serving as the reference standard. Among the test formulations, F12 exhibited the highest drug released with a DE<sub>60</sub>% of 77.20%, followed closely by F9 with a DE<sub>60</sub>% of 75.98%. Although F12 showed slightly superior performance, it was formulated using the synthetic disintegrant Croscarmellose sodium (CCS), whereas F9 incorporated coriander powder a natural disintegrant. Considering the growing emphasis on natural excipients due to their safety, biocompatibility, sustainability, and low toxicity, F9 emerged as the most suitable candidate among the tested formulations.

The formulations F9 showed significantly improved release behaviour compared to the control formulation F13, which lacked any disintegrant and displayed the lowest DE<sub>60</sub>% of 24.73%, a poor  $f_2$  value of 5.91, and the highest  $f_1$  value of 81.28. This highlight the critical role of disintegrant in promoting drug release. In contrast, F9 achieved favourable release kinetics, with an  $f_2$  similarity factor of 24.53 and an  $f_1$  dissimilarity factor of 32.79 when compared with the marketed formulations, indicating its considerable performance enhancement over control and synthetic free formulations.

The enhanced dissolution observed in F9 can be attributed to the mechanism of coriander as a natural disintegrant, which functions through both swelling and wicking. Upon contact with saliva, the natural fibers present in coriander observed water and swell, causing the tablet structure to rupture. At the same time, its porous texture promotes capillary action, drawing fluid into tablet matrix and facilitating rapid disintegration. This process result in fasted tablet breakup, increased surface area of drug dissolution, and consequently, improved bioavailability.

Given its strong performance, safety profile, and alignment with the current trend toward greener pharmaceutical technologies, F9- formulated with coriander powder (6% w/w)- is recommended as the final optimized formulation over those using synthetic disintegrants.

#### *In-vitro* pharmacokinetics data

**Table.11.** *In-vitro* pharmacokinetics data

Formulation n code	Zero-order kinetic s (R <sup>2</sup> )	First-order kinetic s (R <sup>2</sup> value)	Higuchi Plot (R <sup>2</sup> value)	Korsmeyer -Peppas plot (n-value)
F1	0.9939	0.9908	0.9749	0.4555

F2	0.9823	0.9952	0.9898	0.5441
F3	0.9944	0.9876	0.9851	0.6974
F4	0.9709	0.9872	0.9796	0.8028
F5	0.9911	0.9669	0.9720	0.5787
F6	0.9501	0.9902	0.9857	0.7569
F7	0.9830	0.9505	0.9239	0.5457
F8	0.9903	0.9801	0.9837	0.5955
F9	0.8001	0.9106	0.9056	0.3312
F10	0.9740	0.9335	0.9036	0.5749
F11	0.9277	0.9910	0.9781	0.6902
F12	0.8045	0.9765	0.9027	0.6903
F13	0.9948	0.9896	0.9665	0.4312
F14	0.7437	0.9723	0.8353	0.1002

The pharmaceutical evaluation of formulation F1-F14 was conducted using Zero-order, First-order, Higuchi, & Korsmeyer-peppas kinetics release profiles to estimate the drug release kinetics and mechanisms. F1, F3, F5, F8, and F13 exhibited strong zero-order kinetics with correlation coefficients (R<sup>2</sup>) greater than 0.99, indicating a consistent, concentration-independent drug release profile suitable for sustained-release applications. In contrast, several formulations, including F2, F9, F6, and F12, demonstrated a better fit with first-order kinetics (R<sup>2</sup> > 0.99), suggesting a concentration dependent release typical of immediate or fast-dissolving systems.

The Higuchi model also provided a good fit for many formulations, like F2, F3, F4, F6, F8, and F11, indicating diffusion-controlled drug release for a matrix system. Analysis through the Korsmeyer-Peppas model showed that most formulations had release exponent values (n) ranging from 0.45 & 0.89, which indicates anomalous (non-Fickian) transport, both diffusion & erosion play role in the release process. Notably, F4 and F6 exhibited higher n values, confirming a significant role of polymer relaxation in drug release. Meanwhile F14 (n = 0.1002) and F9 (n = 0.3312) followed by Fickian diffusion, indicating a rapid or burst release mechanism driven primarily by diffusion.

Overall, the majority of formulations conformed to first-order kinetics with anomalous transport as the dominant release mechanism. This dual behaviour underscores the influence of the disintegrant type-natural disintegrants such as fennel, cumin, and coriander and synthetic ones like Croscarmellose sodium (CCS)- in modulating the drug release rate. These findings highlight the feasibility of strategically combining natural and synthetic disintegrants to optimize release profiles, thereby enhancing bioavailability and ensuring therapeutic efficacy.

**Accelerated Stability study data for Formulation F9 (40°C ± 2°C / 75% RH ± 5%)**

**Table.12.** Precompression variables

Time point	Angle of repose(°)	Bulk density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Carr's index (%)	Hausner's ratio
Initial	26.94	0.45	0.50	10.00	1.11
1 <sup>st</sup> Month	27.05	0.45	0.50	10.20	1.11
2 <sup>nd</sup> Month	27.18	0.44	0.50	12.00	1.13
3 <sup>rd</sup> Month	27.34	0.44	0.51	13.72	1.16

Time (min)	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Disintegration Time (Sec)	Weighting Time (Sec)	Drug Content (%)
Initial	300 ±2.1	3.3 ±0.01	3.4 ±0.01	0.59 ±0.01	600 ±60	240 ±20	99.6 ±0.2
1 <sup>st</sup> Month	300 ±2.3	3.3 ±0.01	3.4 ±0.01	0.61 ±0.01	610 ±150	245 ±15	98.9 ±0.1
2 <sup>nd</sup> Month	301 ±2.5	3.3 ±0.01	3.5 ±0.02	0.65 ±0.04	130 ±30	260 ±30	98.3 ±1.02
3 <sup>rd</sup> Month	302 ±2.7	3.3 ±0.01	3.6 ±0.02	0.69 ±0.06	645 ±20	275 ±10	97.5 ±2.03

**Table.13.** Post-compression variables

Time (min)	Initial	1 <sup>st</sup> month	2 <sup>nd</sup> month	3 <sup>rd</sup> month
5	38.72	38.15	37.86	37.24
10	54.27	53.65	52.34	50.98
20	74.37	73.18	71.62	70.04
30	78.37	77.12	75.26	73.01
45	84.23	82.67	80.38	78.56
60	88.80	87.15	84.79	82.03

**Table.14.** In vitro dissolution study

Time (min)	Initial	1 <sup>st</sup> month	2 <sup>nd</sup> month	3 <sup>rd</sup> month
5	38.72	38.15	37.86	37.24
10	54.27	53.65	52.34	50.98
20	74.37	73.18	71.62	70.04
30	78.37	77.12	75.26	73.01
45	84.23	82.67	80.38	78.56
60	88.80	87.15	84.79	82.03

Formulation F9, containing coriander powder as a natural disintegrant, underwent 3 months of accelerated stability testing under ICH condition (40°C ± 2°C / 75% RH ± 5%). Pre-compression parameters remained within acceptable ranges, though a slight increase in angle of repose (from 26.94° to 27.34°) and Carr's index (10% to 13.72%) was observed, indicating minor reductions in flow and compressibility overtime. Bulk and tapped density values remained stable with minimal deviation, and Hausner's Ratio rose slightly, confirming marginal flow deterioration.

Post compression characteristics showed stable performance. Weight variation, thickness, and hardness remained consistent with minor increases. Friability

remained below 1%, suggesting tablets retained mechanical integrity. Disintegration time increased from 600 seconds, to 645 seconds, and wetting time extended from 240 to 275 seconds, indicating a gradual reduction in rapid disintegration ability. Drug content decreased slightly from 99.6% to 97.5%, still within Pharmacopoeial limits. In-vitro dissolution data reflect a gradual reduction in drug release at each time point. At 60 minutes, cumulative drug release dropped from 88.80% (initial) to 82.035 (3<sup>rd</sup> month), demonstrating slight decline in dissolution efficiency. Nonetheless, the release profile remained effective, with over 80% drug released even after 3 months. Overall, F9 demonstrated good stability with only marginal decline in flow, disintegration, and dissolution characteristics, validating its suitability for formulation development using natural disintegrants. The finding supports the feasibility of coriander powder-based Mouth-Dissolving Tablets with stable performance under accelerated storage conditions.

### CONCLUSION

The current investigation emphasized on the development of KT MDTs, by various natural disintegrants and synthetic disintegrants, with the aim to improve patient compliance, especially in populations requiring quick pain relief and ease of administration. The study began with FTIR compatibility studies, indicating negligible drug-excipient incompatibility, establishing chemical compatibility between Ketorolac Tromethamine and the selected natural disintegrants-fennel, cumin, and coriander powders – as well as with the synthetic disintegrant Croscarmellose sodium.

Pre-compression variables of all formulations, including bulk BD, TD, CI, HR, and angle of repose, are within acceptable limits, suggesting excellent flow characteristics and suitability for direct compaction. Post-compression evaluation showed that the tablets exhibited uniformity in weight (198-202 mg), hardness 93.0-3.8 kg/cm<sup>2</sup>, friability (<1%), and drug content (98.12% to 99.83%), ensuring mechanical integrity and content (98.12% to 99.83%), ensuring mechanical integrity and content uniformity across all batches.

Among the tested formulations, F9, which included 9% coriander powder, showed the best overall performance. It exhibited time for disintegration- 61 seconds, time for wetting - 53 seconds, and water absorption ratio- 78.12%, all indicative of its superior rapid disintegration behaviour. *In vitro* drug dissolution profile revealed a cumulative % drug release 97.87% at 30 minutes, closely matching and even surpassing the performance of the marketed reference product and synthetic disintegrant-based formulations such as F12 (97.91%). The release kinetics of F9 followed first-order release with non-Fickian (anomalous) diffusion, suggesting a synergistic mechanism of erosion and diffusion contributing to efficient drug release.

Notably, the study aligns with the therapeutic and pharmaceutical expectations for Ketorolac Tromethamine, which is often marketed in the form of chewable or orally

disintegrating tablets for fast pain relief. The selection of natural disintegrants such as fennel, cumin, and coriander was not only based on their disintegrating efficacy but also on their pleasant mouthfeel, taste-masking capability, and traditional usage as safe, natural, and consumer-friendly agents in mouth-freshening and culinary preparations. These organoleptically acceptable agents make the formulations more patient-centric and particularly suitable for pediatric, geriatric, and dysphagia populations who may otherwise struggle with conventional tablet forms.

The final phase of study-accelerated stability testing-demonstrated that F9 retained its physical and chemical characteristics over time, confirming its stability under ICH-recommended conditions. No substantial variation was seen in drug content, disintegration time, or dissolution profile after three months storage at 40°C/75% RH, ensuring the formulation's long-term reliability.

In conclusion, the study successfully formulated a mouth-dissolving tablet of Ketorolac Tromethamine by coriander powder (F9) is an effective natural disintegrant. This formulation combines fast onset with enhanced patient adherence, stability, & acceptable mouthfeel, meeting dual goals of pharmaceutical performance and patient-centric design. Thus, the findings support the viability of natural disintegrants as functional and organoleptically favourable alternatives to synthetic agents in the formulations of fast-dissolving oral dosage forms.

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