

Research article**FORMULATION AND EVALUATION OF DUAL-MECHANISM
TASTE-MASKED ORODISPERSIBLE TABLETS OF ZOLMITRIPTAN
USING ION-EXCHANGE RESIN AND SUPERDISINTEGRANT
OPTIMIZATION FOR RAPID ONSET OF ACTION****Mr. V. Arunachalam^{1*}, Dr. G. Mariyappan², Dr. J. Karthi³, Mr. Prakash Murugan⁴**

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ABSTRACT

Zolmitriptan, a second-generation triptan, is employed for the immediate management of migraines. Its medicinal efficacy is constrained by its intensely bitter flavor and by migraine-related gastroparesis and vomiting, which prolong gastric medication transit and hinder the onset of effect. The objective of this study was to formulate and assess dual-mechanism taste-masked orodispersible tablets (ODTs) containing zolmitriptan by ion-exchange resin complexation and the optimization of superdisintegrants for enhanced palatability and swift disintegration and release. A drug-resin complex (DRC) was produced utilizing the cation-exchange resin Kyron T-114 through a batch method by modifying the drug:resin ratio (1:1–1:6), pH (4–6), and stirring duration (30–120 min). The enhanced complex (DRC5; ratio 1:5, pH 6, 90 min) demonstrated a drug loading efficiency of $89.1 \pm 0.4\%$, a yield of $91.3 \pm 0.6\%$, an $8.4 \pm 0.2\%$ drug release in simulated salivary fluid (pH 6.8, 2 min), and a $95.2 \pm 0.3\%$ release in 0.1

N HCl (5 min). Six ODT formulations (F1–F6) incorporating DRC5 with croscarmellose sodium, or sodium starch glycolate (3% and 6% w/w) were developed using direct compression and evaluated for pre- and post-compression attributes, in-vitro dissolution, and release kinetics. Formulation F6 (6% w/w sodium starch glycolate) exhibited the shortest wetting time (20 s), swift disintegration (16 s), and the highest drug release ($98.2 \pm 0.5\%$ at 10 min), surpassing the normal zolmitriptan tablet ($62.4 \pm 0.4\%$ at 10 min) under comparable conditions. The optimal alignment with the release data from F6 was achieved by first order kinetics ($R^2 = 0.972$), and the Korsmeyer–Peppas exponent ($n = 0.51$) suggested anomalous (non-Fickian) transport, which aligns with a coupled diffusion–erosion mechanism. FTIR analysis revealed no interaction between the medication and excipient, and F6 demonstrated both physical and chemical stability over three months under accelerated circumstances ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$). The dual-mechanism approach is a scalable direct-compression system that could improve taste, onset, and adherence in acute migraine treatment.

Keywords: Zolmitriptan, orodispersible tablets, ion-exchange resin, Kyron T-114, taste masking, superdisintegrant, migraine, Korsmeyer–Peppas kinetics.

1. INTRODUCTION

Migraine is a persistent neurovascular disorder and a significant contributor to global disability. Approximately 12–15% of the global population is impacted, with a significant female majority (approximately 3:1). In addition to the distress caused by headaches, migraines considerably affect occupational efficiency, social interactions, and overall quality of life, and they continue to be inadequately recognized and treated in numerous regions. Current pathophysiological theories include the activation of the trigeminovascular system, altered cerebral pain processing, and the secretion of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), alongside diminished serotonergic activity at 5-HT_{1B/1D} receptors. Triptans, which are selective agonists of the 5-HT_{1B/1D} receptors, continue to be the primary abortive treatment as they target particular migraine pathways instead of inducing generic pain relief.

Zolmitriptan ((S)-4-{{[3-(2-dimethylaminoethyl)-1H-indol-5-yl]methyl}-1,3-oxazolidin-2-one; C₁₆H₂₁N₃O₂, molecular mass 287.4 g mol⁻¹; somewhat basic, pK_a 9.5; shown structure in Figure) (1) is a second-generation triptan exhibiting robust 5-HT_{1B/1D} agonistic activity and an advantageous pharmacokinetic profile, with a pre-systemic (pre-gastric) absorption aspect that is

anticipated to confer a little onset-of-action advantage compared to first-generation medications [8,9]. However, two primarily separate challenges constrain its applicability in clinical settings. Initially, 80% of individuals suffer from gastric stasis, while 30–50% endure nausea or vomiting during migraine episodes, leading to a postponement in gastric emptying and drug passage, which consequently delays the time to peak plasma concentration ($T_{\max}$) and may result in a complete loss of the ingested dose. Secondly, zolmitriptan possesses a notably acrid flavor, which holds therapeutic significance when formulating a dosage that is intended to disintegrate or dissolve in the mouth [10].

The initial challenge is to develop an appealing platform for orodispersible tablets (ODTs) that dissolve within seconds upon saliva contact, necessitate no water for consumption, and allow for at least partial buccal/pre-gastric absorption, which is beneficial during an acute episode complicated by dysphagia or vomiting. Directly compressed ODTs offer an industrially viable substitute for lyophilized (e.g., Zydis®) or sublimation-based systems, eliminating the necessity for specialist freeze-drying apparatus, and when suitable superdisintegrants are utilized, ensure fast disintegration [14,15]. The characteristic that renders an ODT therapeutically beneficial, namely oral disintegration, simultaneously engenders the issue of taste-masking, as any bitter medication released in the mouth prior to ingestion is perceptibly tasted and may undermine adherence, particularly in pediatric, geriatric, and dysphagic populations.

Several types of taste masking tactics have been described including the use of sweeteners/flavors, polymer or lipid microencapsulation, cyclodextrin complexation and ion-exchange resin (IER) complexation [18,19]. Among these, IER complexation is especially appropriate for weakly basic pharmaceuticals like zolmitriptan: the protonated compound establishes a reversible ionic complex with sulfonic-acid functionalized cation-exchange resins, which predominantly remains stable at the near-neutral pH of saliva (~6.8), yet dissociates swiftly upon contact with the elevated hydrogen-ion concentration of gastric fluid (pH 1–2) [20,21,22] (mechanism depicted in Figure 4). This pH-responsive, ion-exchange release technology facilitates taste masking without covalent modification of the pharmaceutical compound, so avoiding the regulatory intricacies associated with prodrug methodologies [23].

Nevertheless, taste masking by itself does not guaranty rapid disintegration and dissolution, which are primarily influenced by the type and quantity of superdisintegrant incorporated in the tablet matrix [14,24]. The majority of the released zolmitriptan ODT formulations have enhanced

either taste masking or disintegration independently^[25,26,27,28]. The compatibility of the two methodologies for simultaneous use remains uncertain. Resin particles possess a somewhat coarse and hydrophobic nature, potentially hindering rather than facilitating water absorption caused by superdisintegrants. A dual mechanism design featuring an improved drug-resin complex integrated within a superdisintegrant-optimized ODT matrix has been explored for other active compounds^[29], although it has not been comprehensively detailed for zolmitriptan to our knowledge.

The current investigation was designed to formulate and assess dual mechanism taste-masked orally disintegrating tablets (ODTs) of zolmitriptan utilizing (i) ion exchange resin (Kyron T-114) complexation for taste masking and pH-responsive release, and (ii) optimization of superdisintegrant type/concentration (crospovidone, croscarmellose sodium, and sodium starch glycolate) for swift disintegration, with the goal of creating a patient-friendly, rapidly acting oral dosage form for acute migraine treatment.

2. MATERIALS AND METHODS

2.1. Materials

Zolmitriptan was a complimentary sample of pharmacopeial caliber and employed accordingly. All reagents employed in this research were of pharmacopeial quality and utilized in their received form: Kyron T-114 (a polacrilin-type cation-exchange resin), crospovidone, croscarmellose sodium, sodium starch glycolate, mannitol, direct-compression grade lactose monohydrate (Lactose DCL 21), aspartame, lemon flavoring, talc, and magnesium stearate. Hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, and potassium bromide (spectroscopic grade) were of analytical reagent caliber. A commercially available standard zolmitriptan tablet (2.5 mg; Zomig®) was procured locally and employed as a reference in the dissolution experiments. All preparations were conducted using distilled water.

2.2. Preformulation Study

The organoleptic characteristics (hue, scent, and visual aspect) of zolmitriptan were assessed using direct visual and olfactory inspection in natural light. The equilibrium solubility was assessed using the shake-flask technique. Constant amounts of distilled water, 0.1 N hydrochloric acid (pH 1.2), and phosphate buffer (pH 6.8) were augmented with an excess of the medication, and the mixtures were agitated until equilibrium was achieved. The suspensions

underwent filtration (0.45 μm), were suitably diluted, and analyzed spectrophotometrically^[30,31]. A conventional solution was analyzed between 200–400 nm utilizing a UV-visible spectrophotometer, and the wavelength of peak absorption (λ_{max}) was determined. The compliance with the Beer–Lambert law was validated by least-squares linear regression analysis of the concentration–absorbance data derived from a five-point calibration curve (2–10 $\mu\text{g mL}^{-1}$) produced in triplicate at λ_{max} . The compatibility between the drug and excipient was assessed using Fourier-transform infrared (FTIR) spectroscopy (KBr pellet technique, 4000–400 cm^{-1}) on both pure zolmitriptan and the optimal physical mixture of the drug and excipient. The spectra were analyzed for peak retention, shifts, or the appearance of new bands^[32,33].

2.3. Selection and reasoning for the ion-exchange resin

Zolmitriptan is a somewhat basic compound ($\text{pK}_a = 9.5$) including a tertiary amine group, capable of being protonated in acidic to neutral pH environments and forming a reversible ionic bond with negatively charged sulfonic acid resin sites. Consequently, a cation-exchange resin (Kyron T-114) was chosen instead of anion-exchange or non-ionic adsorptive carriers due to (i) the drug-resin complex's stability at salivary pH, which reduces oral exposure to the unbound drug, (ii) the high H^+ concentration in gastric fluid facilitating swift and nearly total release, (iii) the resin's pharmacological inertness and lack of absorption, and (iv) the absence of required covalent modifications to the drug.

2.4. Formation of the zolmitriptan-Kyron T-114 pharmaceutical-resin combination

The combination of zolmitriptan and Kyron T-114 was manufactured using a batch ion-exchange method. Kyron T-114 was purified using distilled water to remove soluble contaminants, treated with 1 N HCl (30 minutes, gentle agitation), subsequently filtered, and rinsed until the effluents were neutral. The activated resin was immersed in distilled water for 30 minutes at room temperature to reveal the ion-exchange sites. Concurrently, zolmitriptan (5 mg per batch) was solubilized in distilled water, with the pH modified using dilute HCl or NaOH as required for each batch. The expanded resin was thereafter incorporated gradually into the pharmaceutical solution while maintaining continuous magnetic agitation for the designated duration. Six formulations (DRC1–DRC6) were created by methodically varying the drug-to-resin ratio, pH, and agitation duration, as detailed in Table 2. Upon completion, the complex underwent filtration, was gently rinsed with distilled water (to eliminate surface-adsorbed, unbound drug without dislodging weakly bound drug), dried in a hot-air oven at 40 $^{\circ}\text{C}$ until a constant weight

was achieved, passed through a #60 sieve, and subsequently stored in a securely sealed, light-resistant container before assessment.

2.5. Evaluation of drug–resin complex

The percentage yield was calculated as the ratio of the actual weight of the dried complex produced to the theoretical total weight of the medicine and resin used, expressed as a percentage. The efficiency of drug loading and complexation was assessed indirectly. The supernatant of each batch was examined spectrophotometrically at λ_{max} to measure the concentration of unbound (free) drug. The quantity of medication incorporated was determined by subtracting the final amount from the initial quantity. The ratio of the loaded fraction to the initial charge provided the efficiencies of loading and complexation. The in vitro efficacy of taste masking was evaluated by dissolving a quantity of DRC corresponding to 5 mg of zolmitriptan in 10 mL of simulated salivary fluid (phosphate buffer, pH 6.8) at a temperature of 37 ± 0.5 °C with mild agitation for 2 minutes (simulating oral residence duration), followed by prompt filtration and spectrophotometric analysis; a release of ≤ 10 –15% was deemed satisfactory for taste masking. The gastric release profile was examined by introducing an equivalent quantity of DRC into 0.1 N HCl (pH 1.2) at a temperature of 37 ± 0.5 °C, extracting aliquots at 1, 2, 5, 10, and 15 minutes (with volume replacement), and calculating the cumulative percentage of drug released. A target of ≥ 80 % release within 5-15 minutes was established for fast post-swallowing accessibility. The ideal DRC-batch was chosen based on the maximum loading efficiency and yield, lowest release at pH 6.8, swift release in 0.1 N HCl, and acceptable repeatability of the procedure.

2.6. Formulation of orodispersible tablets using direct compression

The enhanced drug-resin combination was included into ODTs using direct compression technique. Six experimental formulations (F1–F6; Table 3) were developed to evaluate three superdisintegrants: crospovidone, croscarmellose sodium, and sodium starch glycolate, at two concentrations (3% and 6% w/w). The quantity of mannitol was adjusted to maintain a consistent tablet weight of 250 mg. All components were filtered using a #60 mesh. The DRC was combined with mannitol and Lactose DCL 21 in a laboratory mixer, followed by the incorporation of aspartame and lemon flavor to improve taste. The selected superdisintegrant was thereafter incorporated and blended thoroughly. Talc and magnesium stearate were included

and blended gradually (2–3 min) to reduce excessive lubrication. The final blend was compacted using a singular rotary tablet press equipped with appropriately sized punches to achieve a target mass of 250 mg per tablet. The compressed tablets were housed in secure containers shielded from humidity for analysis.

2.7. Evaluation of powder blends (precompression criteria)

The powder blends were analyzed prior to compaction. The angle of repose was determined using the fixed funnel technique. The bulk and tapped densities were assessed prior to and following mechanical tapping to a uniform volume with a graduated cylinder, which facilitated the computation of Carr's compressibility index and Hausner ratio. Standard pharmacopeial interpretive scales were utilized for the angle of repose (<25°, excellent; 25-30°, good; 30-40°, passable; >40°, poor), Carr's index (5-15%, excellent; 12-16%, good; 18-21%, fair; 23-35%, poor; >35%, very poor), and Hausner ratio (1.00-1.11, excellent; 1.12-1.18, good; 1.19-1.25, fair; >1.25, poor).

2.8. Evaluation of tablets (post-compression parameters)

The fluctuation in weight was assessed by individually weighing twenty tablets from each batch using an analytical balance, adhering to the pharmacopeial standard of $\pm 7.5\%$ for tablets weighing between 130 and 324 mg. The thickness was assessed utilizing a digital caliper (n=5). The hardness (crushing strength) was assessed using a Monsanto hardness tester (n=3). The Roche friabilator was utilized to assess friability (tablets pre-weighed, 25 rpm, 100 revolutions/4 min), with an acceptable threshold of less than 1% weight reduction. The consistency of drug content was assessed by pulverizing a single tablet and dissolving the powder corresponding to one dose in an appropriate solvent, followed by filtration, dilution, and spectrophotometric analysis at λ_{max} . The wetting duration was characterized as the interval required for water to ascend to the upper surface of a tablet placed on a water-saturated tissue disk. The water absorption ratio was determined by comparing the weights of the tablet before and after soaking. The in vitro disintegration duration was assessed by placing a tablet in simulated saliva (pH 6.8) at a temperature of 37 ± 0.5 °C and recording the time required for complete breakdown. An acceptance standard of less than 30 seconds was implemented, aligning with pharmacopeial standards for ODTs [34,35].

2.9. In vitro dissolution test

In vitro dissolving experiments were conducted utilizing the USP Type II (paddle) equipment with 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C and the paddle revolving at 50 rpm. Given that the key clinical focus for an ODT is swift early phase release, samples (5 mL) were extracted at 2, 5, 10, 15, 20, 25, and 30 minutes, with each extraction compensated by an equivalent volume of fresh medium equilibrated to the dissolution medium's temperature. Samples were subjected to filtration and analyzed spectrophotometrically at λ_{max} . The cumulative percentage of drug release was determined by adjusting for the volume extracted at each interval. The commercially available traditional zolmitriptan tablet was evaluated as a reference in comparable conditions to assess the clinically meaningful onset-of-release advantage of the enhanced ODT.

2.10. Kinetics of drug release

The dissolution data of the optimized formulation was analyzed using linear regression to fit it to zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson–Crowell release models based on the respective transformed plots (cumulative % released vs. time; log % remaining vs. time; cumulative % released vs. $\sqrt{\text{time}}$; log cumulative % released vs. log time, excluding $t = 0$; and the cube root of the initial percentage remaining minus the cube root of the percentage remaining at time t , against time, respectively). The adequacy of each model was evaluated using the coefficient of determination (R^2), while the release exponent (n) from the Korsmeyer–Peppas equation was analyzed based on the established criteria for a device of this configuration ($n \leq 0.45$ indicates Fickian diffusion; $0.45 < n < 0.89$ signifies anomalous/non-Fickian transport; $n = 0.89$ denotes Case-II transport; $n > 0.89$ represents Super Case-II transport).

2.11. Selection of the best formulation

The chosen optimized ODT formulation was determined by a comprehensive set of criteria: minimal in vitro disintegration duration, brief wetting time, superior water absorption ratio, maximal and swift cumulative dissolution, and satisfactory mechanical characteristics (hardness, friability, weight variation, and drug content adhering to pharmacopeial standards).

2.12. Accelerated stability studies

The refined formulation underwent a short-term accelerated stability assessment in accordance with ICH Q1A(R2)^[37], maintained at 40 ± 2 °C/ $75 \pm 5\%$ RH for a duration of three months, with sampling conducted at 0 (baseline), 1, 2, and 3 months. Tablets were assessed at each interval for

their physical characteristics, hardness, friability, drug concentration, in vitro disintegration duration, and dissolution efficacy. The formulation was deemed stable when there were no notable alterations in physical appearance, the drug content remained within $\pm 5\%$ of the original value, and no major variations were seen in disintegration or dissolution characteristics.

2.13. Statistics analysis

All assessments were conducted a minimum of three times ($n = 3$), unless specified differently, and are presented as mean $\pm$ standard deviation. Calibration curve and release kinetic parameters (slope, intercept, and R^2) were derived by linear regression (least-squares fitting).

3. RESULTS AND DISCUSSION

3.1. Preformulation studies

Zolmitriptan was verified as a white to off-white, odorless crystalline powder, aligning with documented attributes and affirming the identification and purity of the utilized medicinal sample. The lack of a specific scent is advantageous for an orodispersible formulation; nonetheless, the extensively recognized bitter flavor of the medication required the taste-masking approach implemented in this study.

The solubility of zolmitriptan at equilibrium was influenced by pH (Table 1), exhibiting peak solubility in 0.1 N HCl ($8.5 \pm 0.3 \text{ mg mL}^{-1}$), moderate solubility in pH 6.8 phosphate buffer ($3.2 \pm 0.2 \text{ mg mL}^{-1}$), and minimal solubility in distilled water ($1.8 \pm 0.1 \text{ mg mL}^{-1}$). This trend aligns with the protonation of the tertiary amine in acidic environments and substantiates the reasoning behind an ion-exchange approach: increased ionization and solubility at gastric pH promote swift drug release from the resin, whereas diminished solubility at salivary pH correlates with lower free-drug availability for taste detection when the drug is bound.

The ultraviolet spectrum of zolmitriptan exhibited peak absorbance at 223 nm (Figure 1), which was utilized for all following spectrophotometric analyzes. The associated calibration curve ($2\text{--}10 \text{ }\mu\text{g mL}^{-1}$; Figure 2) exhibited linearity ($y = 0.0567x - 0.0045$; $R^2 = 0.9997$), validating adherence to the Beer–Lambert law and reinforcing the dependability of the analytical technique employed for drug-loading, dissolution, and content-uniformity assessments.

The FTIR spectra of unadulterated zolmitriptan and the combination of the medication with excipients are juxtaposed in Figure 3. The spectra of the unadulterated drug exhibited distinctive absorptions at 1734.98 cm^{-1} (C=O stretch), 1637.31 cm^{-1} (aromatic C=C stretch), 1459.22 cm^{-1}

(C–N stretch), 1258.15 cm^{-1} (C–O stretch), and 1022.60 cm^{-1} (aromatic ring vibration). All of these bands were preserved, with no notable alterations or emergence of new peaks, in the spectra of the drug–excipient mixture (slight variations in relative peak intensity were due to dilution by excipients). These results demonstrate the lack of significant chemical interactions between the medication and excipients, affirming the compatibility of Kyron T-114, the chosen superdisintegrants, and the other formulation excipients with zolmitriptan.

Table 1. Physicochemical characteristics of zolmitriptan.

Parameter	Value / description
Chemical name	(S)-4-[[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]methyl]-1,3-oxazolidin-2-one
Molecular formula	$\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$
Molecular weight	287.4 g mol^{-1}
pKa	9.5 (weakly basic)
Aqueous solubility (this study)	$1.8 \pm 0.1\text{ mg mL}^{-1}$ (water); $8.5 \pm 0.3\text{ mg mL}^{-1}$ (pH 1.2); $3.2 \pm 0.2\text{ mg mL}^{-1}$ (pH 6.8)
λ_{max} (UV)	223 nm
Organoleptic properties	White to off-white, odourless crystalline powder; bitter taste
Oral bioavailability (reported)	40%, with partial pre-systemic absorption

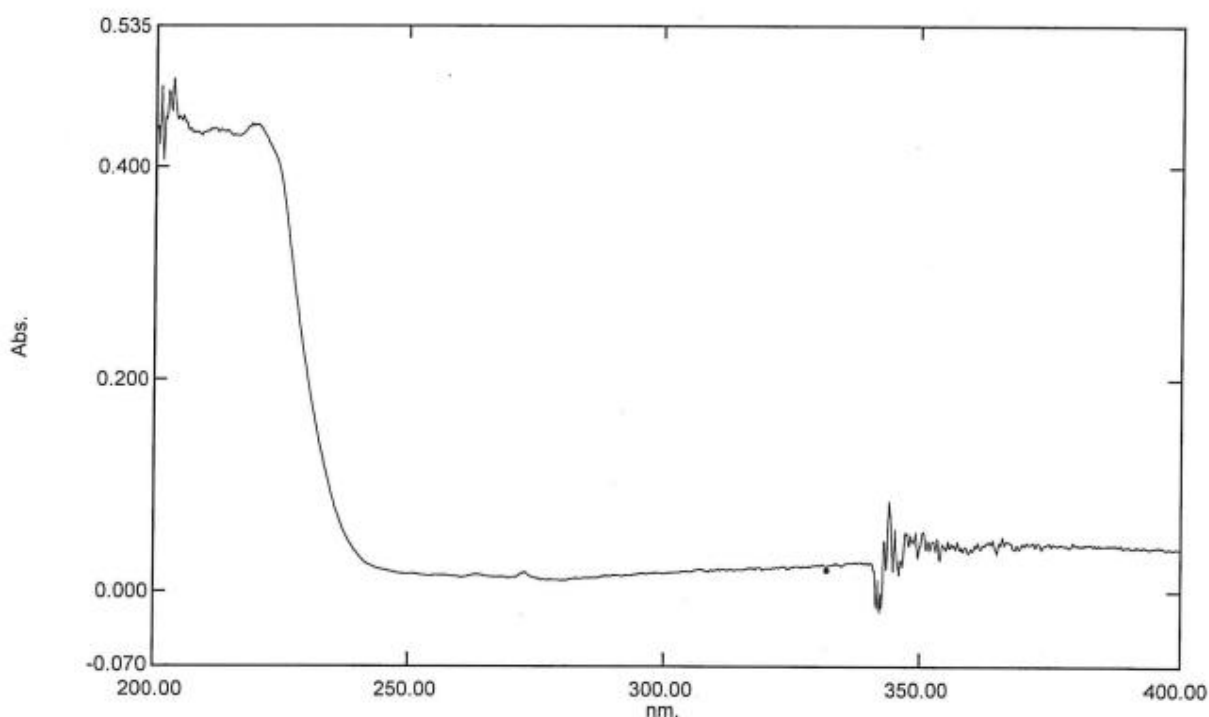


Figure 1: UV absorption spectrum of zolmitriptan showing λ_{max} at 223 nm

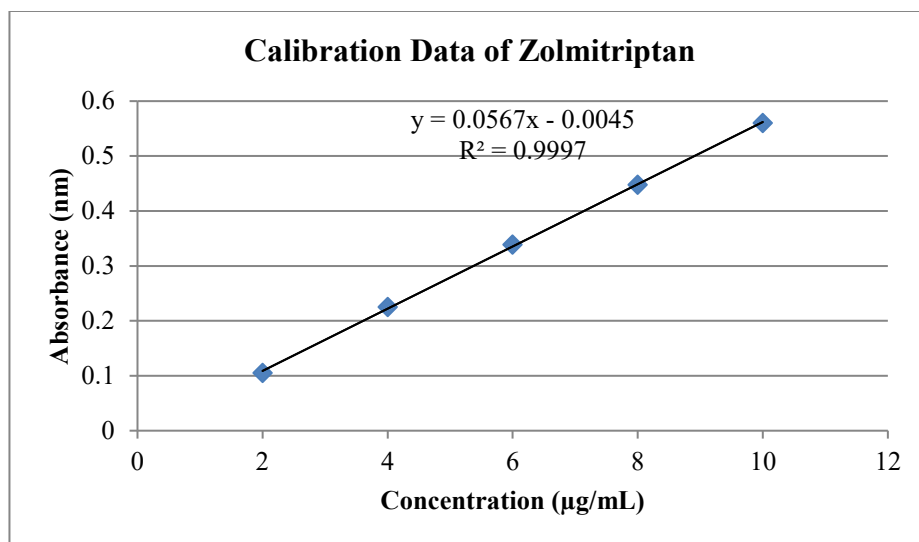


Figure 2: Calibration curve of zolmitriptan at 223 nm (2–10 µg mL⁻¹).

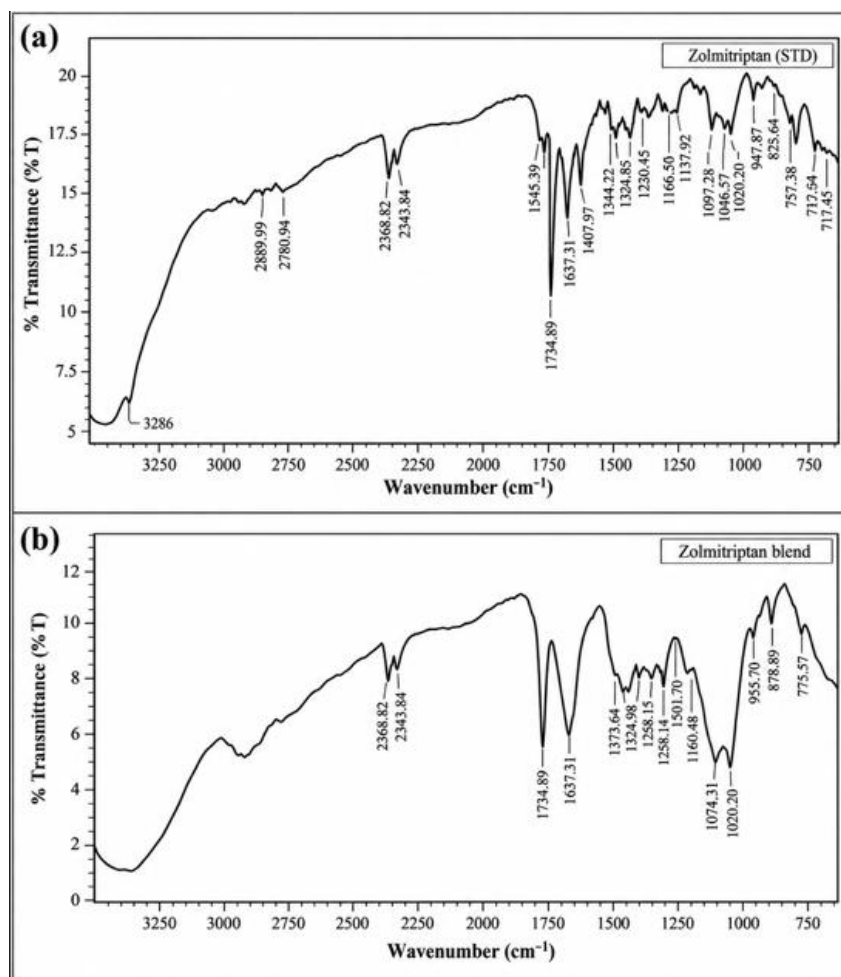


Figure 3: FTIR spectra of (a) pure zolmitriptan and (b) the optimized zolmitriptan–excipient physical blend, showing retention of characteristic drug absorption bands with no evidence of chemical interaction.

3.2. Optimization of zolmitriptan-Kyron T-114 drug-resin complex

The ion-exchange mechanism involved in taste masking and gastric release, dependent on pH, is schematically represented in Figure 4. The effect of drug:resin ratio, pH and stirring duration on the complexation performance is summarized in Table 2 and Figure 5. The drug loading efficiency increased gradually with the increasing proportion of resin from $65.4 \pm 0.8\%$ (DRC1, 1:1) to $91.4 \pm 0.3\%$ (DRC6, 1:6), reflecting the greater availability of ion-exchange sites at higher resin loadings. The efficiency also improved as the pH increased from 4 to 6, consistent with the maintained protonation and favorable electrostatic interaction with the sulfonic-acid groups of the resin in this range. The percentage yield increased parallelly from $72.3 \pm 0.6\%$ (DRC1) to $92.5 \pm 0.4\%$ (DRC6).

The taste-masking efficiency, expressed as cumulative drug release in simulated salivary fluid (pH 6.8, 2 min), increased monotonically with the resin amount and decreased from $22.4 \pm 0.5\%$ (DRC1) to $6.8 \pm 0.1\%$ (DRC6). The generally acknowledged criterion for satisfactory in-mouth flavor masking of 10% was first achieved at DRC5 ($8.4 \pm 0.2\%$). All batches released most of their drug load rapidly in 0.1 N HCl, with DRC5 providing the highest release at 5 min ($95.2 \pm 0.3\%$) and DRC6, despite its slightly higher loading efficiency, showing a slightly lower gastric release ($94.8 \pm 0.5\%$), perhaps due to a modestly longer diffusional path length through the thicker resin shell at the highest resin loading that would not materially affect taste masking but could marginally slow the terminal phase of ion-exchange release.

Using a combination of drug loading efficiency (89.1%) and yield (91.3%) with effective taste masking (8.4% release at pH 6.8), rapid gastric release (95.2% at 5 min) and more economical resin utilization than DRC6, batch DRC5 (1:5 drug:resin ratio, pH 6, 90 min stirring) was selected as the optimized drug-resin complex and carried forward into tablet formulation.

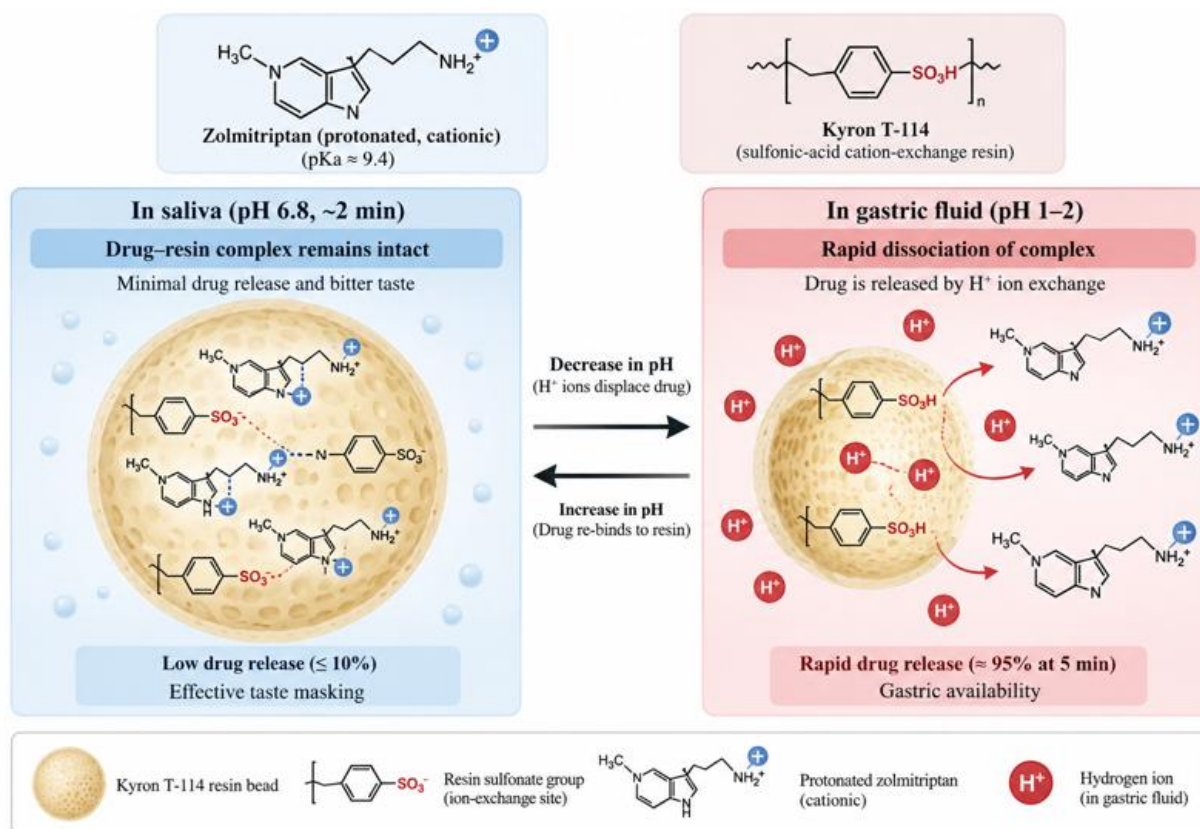


Figure 4: Proposed pH-dependent ion exchange mechanism of the zolmitriptan -Kyron T-114 complex : The drug -resin complex remains largely intact in saliva (pH 6.8) thus reducing the perception of bitter-taste and dissociates rapidly on exposure to gastric fluid (pH 1-2) as H^+ ions displace the protonated drug from the resin's sulfonic-acid sites.

Table 2. Formulation and assessment of zolmitriptan-Kyron T-114 drug-resin complexes (DRC1-DRC6).

Batch	Drug:resin ratio	pH	Stirring time (min)	Drug loading efficiency (%)	Yield (%)	Release, pH 6.8 2 min (%)	Release, 0.1 N HCl 5 min (%)
DRC1	1:01	4	30	65.4 ± 0.8	72.3 ± 0.6	22.4 ± 0.5	82.5 ± 0.7
DRC2	1:02	4	60	72.8 ± 0.6	78.6 ± 0.8	18.6 ± 0.4	86.4 ± 0.5
DRC3	1:03	5	60	80.2 ± 0.5	84.5 ± 0.7	14.8 ± 0.3	89.8 ± 0.6
DRC4	1:04	5	90	85.6 ± 0.7	88.2 ± 0.5	11.5 ± 0.2	92.4 ± 0.4
DRC5*	1:05	6	90	89.1 ± 0.4	91.3 ± 0.6	8.4 ± 0.2	95.2 ± 0.3
DRC6	1:06	6	120	91.4 ± 0.3	92.5 ± 0.4	6.8 ± 0.1	94.8 ± 0.5

*DRC5 was selected as the optimized drug-resin complex. Values are mean $\pm$ SD ($n = 3$).

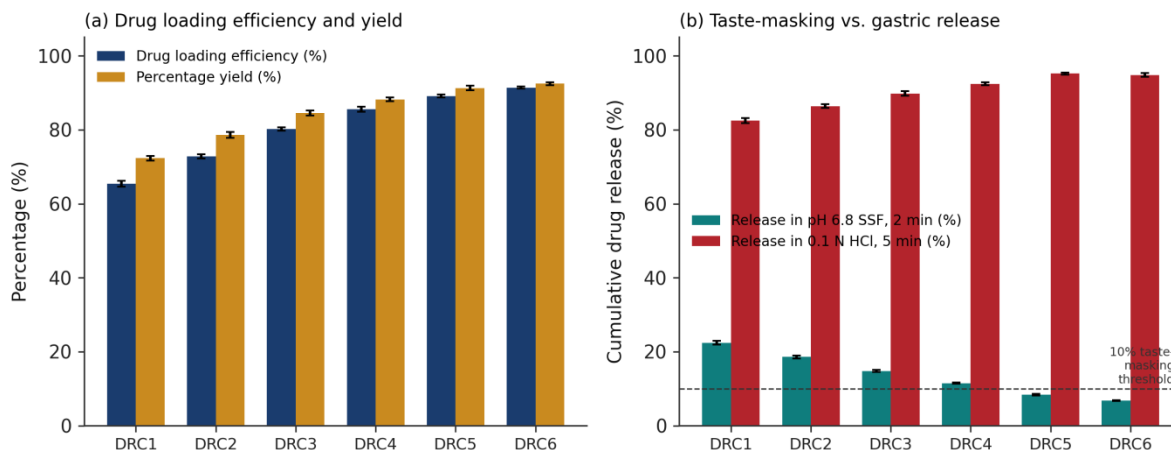


Figure 5: Evaluation of zolmitriptan–Kyron T-114 drug–resin complexes (DRC1–DRC6): (a) drug loading efficiency and % yield and (b) cumulative drug release in simulated salivary fluid (pH 6.8, 2 min) against 0.1 N HCl (5 min). Error bars are $\pm$ SD (n = 3).

3.3. Evaluation of powder mixtures before compression

The final compositions of the formulations F1–F6 developed as detailed in Section 2.6 are summarized in Table 3.

Table 3. Composition of the zolmitriptanorodispersible tablet formulations (F1–F6, mg/tablet).

Ingredient	F1	F2	F3	F4	F5	F6
Zolmitriptan–Kyron T-114 complex (eq. 5 mg drug)	25.00	25.00	25.00	25.00	25.00	25.00
Crospovidone	7.50	15.00	–	–	–	–
Croscarmellose sodium	–	–	7.50	15.00	–	–
Sodium starch glycolate	–	–	–	–	7.50	15.00
Mannitol	138.50	131.00	138.50	131.00	138.50	131.00
Lactose DCL 21	65.00	65.00	65.00	65.00	65.00	65.00
Aspartame	5.00	5.00	5.00	5.00	5.00	5.00
Lemon flavour	2.00	2.00	2.00	2.00	2.00	2.00
Talc	4.00	4.00	4.00	4.00	4.00	4.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00
Total tablet weight	250.00	250.00	250.00	250.00	250.00	250.00

Pre-compression properties of the six powder blends are summarised in Table 4. The results of angle of repose ($25.2\text{--}33.5^\circ$), Carr's index ($10.0\text{--}16.6\%$) and Hausner ratio ($1.11\text{--}1.20$) together revealed good-to-excellent flow and compressibility for all the batches, further confirming the feasibility of direct compression as the way of manufacture. Formulation F6 (6% w/w sodium

starch glycolate) showed the best flow properties of the set (angle of repose 25.2°; Carr's index 10.0%; Hausner ratio 1.11) which is consistent with the rather dense, free flowing particle shape of sodium starch glycolate at this loading .

Table 4. Pre-compression parameters of the powder blends (F1-F6).

Batch	Angle of repose (°)	Bulk density (g cm ⁻³)	Tapped density (g cm ⁻³)	Carr's index (%)	Hausner ratio
F1	29.5	0.42	0.49	14.3	1.16
F2	27.8	0.44	0.5	12	1.13
F3	31.2	0.41	0.48	14.6	1.17
F4	28.6	0.43	0.49	12.2	1.14
F5	33.5	0.4	0.48	16.6	1.2
F6	25.2	0.45	0.5	10	1.11

3.4. Evaluation of orodispersible tablets post compression

The post-compression characteristics are summarized in Table 5. The disintegration behavior of the optimized formulation has been represented photographically in Figure 6. All six formulations fulfilled the pharmacopeial criteria for weight variation and showed good uniformity of thickness, hardness (2.8–3.3 kg cm⁻², which represents an ideal compromise for ODTs, which would need to balance handling strength and disintegrability) and friability (0.60–0.82%, all below the 1% threshold). Drug content was found to be in the range of 94.8-98.5% showing adequate content uniformity throughout the batches.

Functional (disintegration related) characteristics discriminated the formulations better. Wetting time was 20 s (F6) to 38 s (F5) Water absorption ratio was 60% (F5) to 85% (F6) In-vitro disintegration time was 16 s (F6) to 34 s (F5). Sodium starch glycolate (F5, F6) and crospovidone (F1, F2) were superior to croscarmellose sodium (F3, F4) in terms of disintegration time at comparable 3%/6% w/w loading. At the higher (6%) loading level, F6 was superior to F2 (highest performing crospovidone batch). This ranking is mechanistically consistent with the relatively high swelling capacity of sodium starch glycolate (which can increase in volume several-fold on hydration, rapidly generating internal disruptive pressure within the tablet matrix) compared with the wicking/capillary-dominated action of crospovidone and the more moderate swelling of croscarmellose sodium^[14,24]. Hence, formulation F6 was selected as optimum formulation of ODT and was carried out for dissolving, kinetic and stability studies due to its

shortest wetting time, maximum water absorption ratio, fastest disintegration and highest drug concentration.

Table 5. Post compression properties of zolmitriptanorodispersible tablet formulations (F1-F6).

Batch	Weight variation (mg)	Thickness (mm)	Hardness (kg cm ⁻²)	Friability (%)	Drug content (%)	Wetting time (s)	Water absorption ratio (%)	Disintegration time (s)
F1	248 ± 2	3.2	3	0.72	96.2	32	68	28
F2	249 ± 1	3.3	3.2	0.65	98.1	22	82	18
F3	247 ± 3	3.1	2.9	0.78	95.4	35	65	30
F4	250 ± 2	3.2	3.1	0.7	97.3	26	75	22
F5	248 ± 2	3.1	2.8	0.82	94.8	38	60	34
F6*	250 ± 1	3.3	3.3	0.6	98.5	20	85	16

*F6 was selected as the optimized ODT formulation.

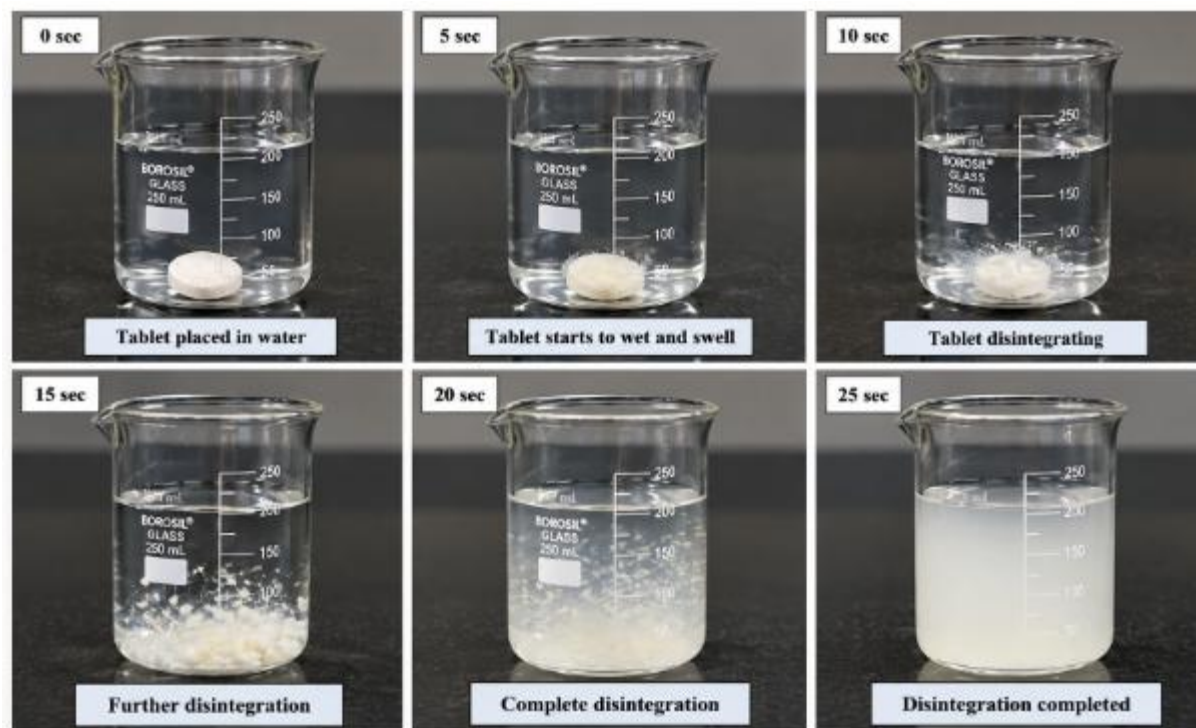


Figure 6: Time-lapse in-vitro disintegration of the optimized orodispersible tablet formulation (F6) in water at 0, 5, 10, 15, 20, 25 sec showing complete disintegration in about 25 sec under unagitated condition (in-vitro disintegration time under standard test conditions: 16 ± 1 sec).

3.5. In-vitro dissolution experiments

The dissolution profiles of F1–F6 are presented in Figure 7 a. All formulations exhibited rapid drug release, indicative of efficient tablet disintegration, but F6 was consistently the fastest and

most complete, releasing 34.2% at 2 min, 66.8% at 5 min, and 98.2% at 10 min, thereby achieving complete release ($\geq 99.4\%$) by 15 min. Among the set, formulation F5 (3% sodium starch glycolate) had the slowest rate of release, which is in agreement with its considerably longer wetting and disintegration times.

The comparative dissolution study against a marketed conventional zolmitriptan tablet (Figure 7b) showed a clear benefit of the optimized ODT in the clinically relevant early phase. F6 released 66.8 and 98.2% of its drug load at 5 and 10 min, respectively, compared to 34.6 and 62.4% for the marketed tablet at the same time points, which corresponds to an approximately 1.6-fold increase in the fraction released at 10 min. Both products ultimately achieved $>95\%$ release by 30 min, demonstrating that the main benefit of the improved ODT is in the rate of drug release, not the ultimate extent of drug release. The accelerated in vitro release profile is a favorable indicator, as early therapeutic plasma concentrations are pharmacodynamically important for aborting a migraine attack, although a formal in vitro–in vivo correlation would be required to confirm a corresponding pharmacokinetic ($T_{\max}$ -lowering) benefit.

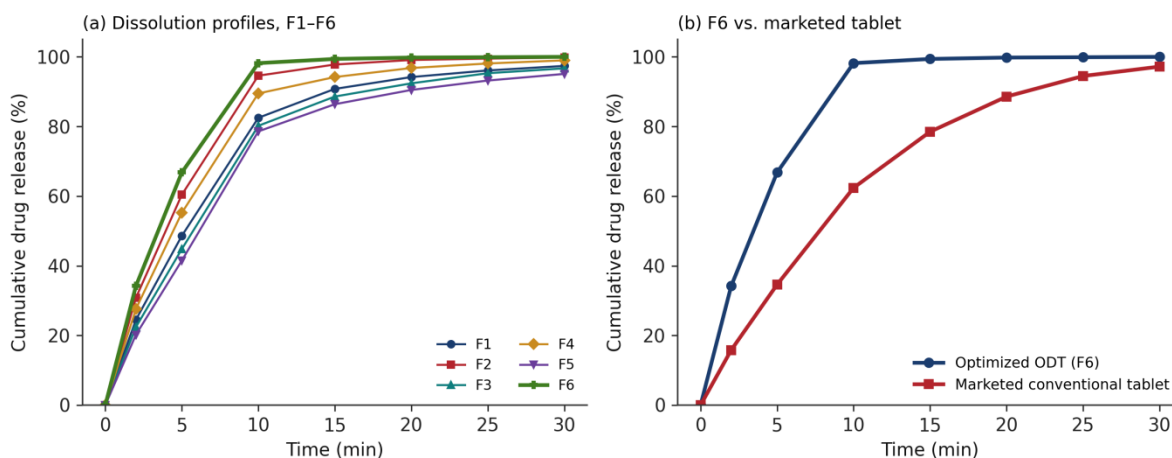


Figure 7: (a) In vitro dissolution profiles of formulations F1–F6 in phosphate buffer (pH 6.8); (b) comparative dissolution profile of the optimized formulation (F6) versus a marketed conventional zolmitriptan tablet.

3.6. Kinetics of drug release

The release-kinetic characteristics of the improved formulation (F6) derived by linear regression of the respective altered dissolution plots are summarized in Table 6 and Figure 8. The best overall fit was obtained by the first-order model ($R^2 = 0.972$) followed by the Higuchi ($R^2 = 0.930$), Korsmeyer–Peppas ($R^2 = 0.920$) and Hixson–Crowell ($R^2 = 0.912$) models, whereas the

zero-order model performed poorly ($R^2 = 0.767$) as expected for a concentration-dependent, immediate-release system rather than one that exhibits constant-rate release.

The prevalence of first order behavior is in accordance with rapid release driven by concentration gradient typical of quick release oral dose formulations. The similarly good fit to the Higuchi model indicates a significant diffusional component, which may represent the residual ion-exchange process where medication must dissolve from the resin matrix even after the tablet has disintegrated. The Korsmeyer–Peppas release exponent ($n = 0.51$) is in the range $0.45 < n < 0.89$ for anomalous (non-Fickian) transport, which suggests that the release was not only controlled by simple Fickian diffusion but by a combination of diffusion (from the drug–resin complex) and disintegrant-induced matrix swelling and erosion. This is mechanistically consistent with the purposely dual-mechanism design of the formulation, where two concurrent processes, rapid superdisintegrant mediated tablet breakup and ion-exchange mediated drug liberation from the resin, together dictate the overall release profile, instead of either process alone.

Table 6. Parameters of the kinetic models of release for the optimized formulation (F6).

Model	R^2	Release exponent (n)	Inference
Zero-order	0.767	–	Poor fit; release is not rate-independent of concentration
First-order	0.972	–	Best overall fit; concentration-dependent release
Higuchi	0.93	–	Strong diffusional contribution
Korsmeyer–Peppas	0.92	0.51	Anomalous (non-Fickian) transport — coupled diffusion/erosion
Hixson–Crowell	0.912	–	Consistent with surface-area/particle-dimension changes during rapid disintegration

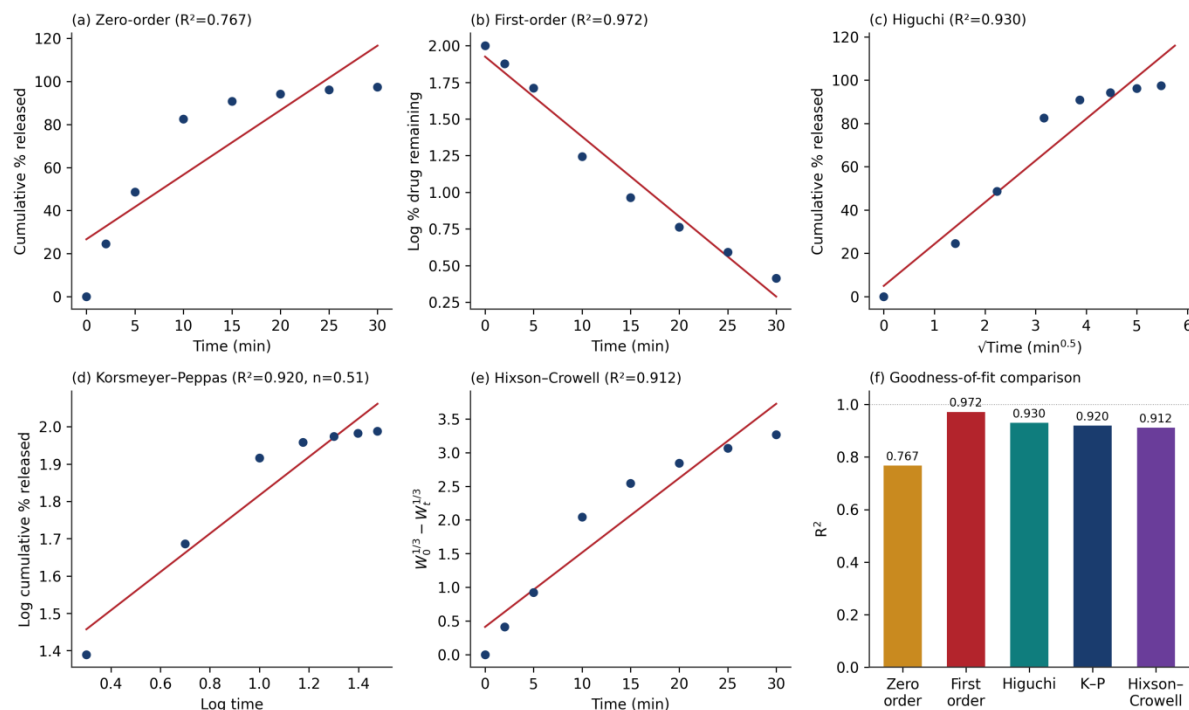


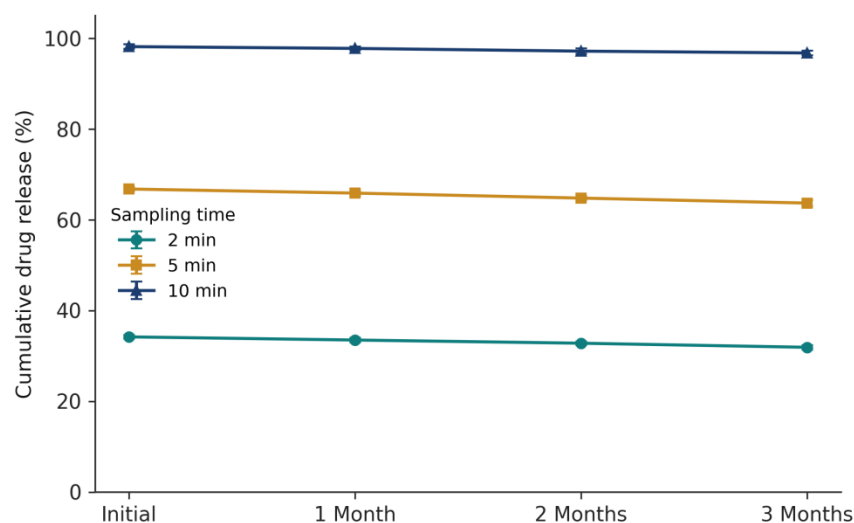
Figure 8: Release kinetic modeling of the optimized formulation (F6): (a) zero order, (b) first order, (c) Higuchi, (d) Korsmeyer–Peppas and (e) Hixson–Crowell plots, (f) goodness-of-fit (R^2) comparison between models.

3.7. Accelerated stability studies

The optimized formulation showed no noticeable change in appearance, color or surface properties at any sampling interval during accelerated storage ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$, 3 months) (Table 7, Figure 9). The hardness was somewhat reduced from 3.3 ± 0.1 to $3.2 \pm 0.1 \text{ kg cm}^{-2}$ and the friability was slightly enhanced from $0.60 \pm 0.02\%$ to $0.70 \pm 0.03\%$. These values were nevertheless within acceptable mechanical limits. The in vitro disintegration time rose from $16 \pm 1 \text{ s}$ to $22 \pm 2 \text{ s}$, perhaps indicating small moisture-related changes in tablet porosity, but remained well within the expected performance range for an ODT. Drug content showed a minor drop from $98.5 \pm 0.4\%$ to $97.3 \pm 0.5\%$ and cumulative dissolution after 10 min reduced from $98.2 \pm 0.5\%$ to $96.8 \pm 0.5\%$. These variations are within the typical test variability and well within the $\pm 5\%$ acceptance range for drug content as pre-specified. These results suggest that the optimized dual-mechanism ODT is physically and chemically stable under accelerated conditions. Confirmatory long-term/intermediate stability studies at labeled storage conditions, according to ICH Q1A(R2), would be required before a definitive shelf-life claim could be assigned [37].

Table 7. Accelerated stability statistics of improved formulation (F6), $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$.

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	White, smooth tablets	No change	No change	No change
Hardness (kg cm^{-2})	3.3 ± 0.1	3.3 ± 0.2	3.2 ± 0.2	3.2 ± 0.1
Friability (%)	0.60 ± 0.02	0.63 ± 0.03	0.67 ± 0.02	0.70 ± 0.03
Disintegration time (s)	16 ± 1	18 ± 1	20 ± 2	22 ± 2
Drug content (%)	98.5 ± 0.4	98.1 ± 0.5	97.8 ± 0.6	97.3 ± 0.5
Drug release at 10 min (%)	98.2 ± 0.5	97.8 ± 0.4	97.2 ± 0.6	96.8 ± 0.5

**Figure 9: Effect of accelerated storage ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$) on cumulative in vitro drug release from optimal formulation (F6) at 2, 5 and 10 min for 3 months. Error bars are $\pm \text{SD}$ ($n = 3$).**

3.8. Comparison with prior work and study limitations

These results are consistent with previous reports for zolmitriptan ODTs^[25,26,27,28] where quick disintegration and taste masking were usually considered as two different formulation goals. By contrast, the current dual-mechanism design explicitly co-optimises an ion-exchange drug-resin complex for taste masking with a superdisintegrant-optimised tablet matrix for rapid disintegration, and the kinetic analysis provides direct mechanistic evidence (anomalous transport, $n = 0.51$) that both processes contribute concurrently to the observed release profile, rather than resin incorporation simply providing inert bulk to an otherwise conventional superdisintegrant-driven system. The strategy is broadly generalizable to additional bitter, weakly basic actives needing a prompt onset oral therapy^[29].

There are some limitations of this study that should be taken into account while interpreting the findings. The taste-masking effectiveness was only examined using an indirect in vitro surrogate

(drug release in simulated salivary fluid), and a human taste-panel or electronic-tongue assessment would offer more direct corroboration of palatability^[16]. Dissolution and stability findings are in vitro only, and no pharmacokinetic or in vitro–in vivo correlation study was performed; the extent to which the observed acceleration in dissolution translates into a clinically relevant reduction in $T_{\max}$ remains to be determined. Finally, the three-month accelerated stability data support, but do not replace, the long-term real-time stability data needed to assign a formal shelf-life.

4. SUMMARY AND CONCLUSION

A dual mechanism, taste-masked orodispersible tablet of zolmitriptan was successfully developed by combining ion-exchange resin complexation (Kyron T-114) with superdisintegrant optimization. The improved drug-resin combination (DRC5; 1:5 ratio, pH 6, 90 min) demonstrated a favorable balance between drug loading (89.1%), yield (91.3%) and pH-dependent release, with the salivary-phase release limited to 8.4% and the gastric-phase release reaching 95.2% within 5 min. The inclusion of 6% w/w sodium starch glycolate (formulation F6) led to the shortest disintegration time (16 s) and the fastest and most complete dissolution among the formulations studied, with drug release around 1.6-fold faster than a marketed conventional tablet at 10 min. Kinetic study of the release showed mostly first-order, anomalous (non-Fickian) transport (Korsmeyer–Peppas $n = 0.51$), which agreed with the designed combination of disintegrant-driven matrix disassembly and ion-exchange-mediated drug release. FTIR analysis confirmed medication excipient compatibility and the improved formulation was found to be physically and chemically stable for three months under ICH accelerated storage conditions. Collectively, these findings support the dual-mechanism concept as a scalable, direct-compression platform to improve the palatability, onset of effect and potential compliance of oral zolmitriptan therapy for acute migraine. Future study should include human taste panel validation, pharmacokinetic/in vitro–in vivo correlation investigations, long-term (real-time) stability testing, and pilot scale process validation to facilitate clinical translation.

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.
2. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. *Neurol Clin*. 2009;27(2):321-334.
3. Lipton RB, Stewart WF. Migraine epidemiology and burden. *Cephalalgia*. 2001;21(1):3-9.
4. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev*. 2017;97(2):553-622.
5. Hargreaves RJ, Shephard SL. Pathophysiology of migraine-new insights. *Can J Neurol Sci*. 1999;26(Suppl 3):S12-S19.
6. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review. *Drugs*. 2000;60(6):1259-1287.
7. Slassi A. Recent advances in 5-HT_{1B/1D} receptor antagonists and agonists and their potential therapeutic applications. *Curr Top Med Chem*. 2002;2(6):559-574.
8. Charlesworth B, Dowson AJ. Review of zolmitriptan and its clinical applications in migraine. *Expert Opin Pharmacother*. 2002;3(7):993-1005.
9. Sweetman SC, editor. *Martindale: The Complete Drug Reference*. 41st ed. London: Pharmaceutical Press; 2024.
10. Silberstein SD, Shah J, Chan EK, Lissin D. Oral drug delivery in migraine: advantages and disadvantages. In: *Migraine Pain Management*. 2025:397-408.
11. Ahmed Kassem A. Formulation approaches of triptans for management of migraine. *Curr Drug Deliv*. 2016;13(6):882-898.
12. Parkash V, Maan S, Yadav SK, Jogpal V. Fast disintegrating tablets: opportunity in drug delivery system. *J Adv Pharm Technol Res*. 2011;2(4):223-235.
13. Al-Khattawi A, Mohammed AR. Compressed orally disintegrating tablets: excipients evolution and formulation strategies. *Expert Opin Drug Deliv*. 2013;10(5):651-663.
14. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. *Crit Rev Ther Drug Carrier Syst*. 2004;21(6):433-476.
15. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. *J Pharm Pharmacol*. 1998;50(4):375-382.
16. Hu S, Liu X, Zhang S, Quan D. An overview of taste-masking technologies: approaches, application, and assessment methods. *AAPS PharmSciTech*. 2023;24(2):67.

17. Dobetti L. Fast-melting tablets: developments and technologies. *Pharm Technol Eur.* 2001;13(9):44-50.
18. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. *Drug DevInd Pharm.* 2004;30(5):429-448.
19. Vishvakarma V, Kaur M, Nagpal M, Arora S. Role of nanotechnology in taste masking: recent updates. *Curr Drug Res Rev.* 2023;15(1):1-4.
20. Gupta S, Benien P, Sahoo PK. Ion exchange resins: transforming drug delivery systems. *Curr Drug Deliv.* 2010;7(3):252-262.
21. Anand V, Kandarapu R, Garg S. Ion-exchange resins: carrying drug delivery forward. *Drug Discov Today.* 2001;6(17):905-914.
22. Jeong SH, Park K. Drug-resin complexes for taste masking. *Expert Opin Drug Deliv.* 2008;5(7):771-783.
23. Vijay S, Chandrasekar D. Ion exchange resins and their applications. *J Drug DelivTher.* 2014;4(5):115-123.
24. Patel DM, Patel MM. Optimization of fast dissolving tablets. *Int J Pharm SciNanotechnol.* 2008;1(2):120-126.
25. Peera NH, Lohithasu D, Sahoo SK, Naidu MS, Kumar KM, Kumar VA. Formulation development and evaluation of oral disintegrating tablets of zolmitriptan. *Pharm Lett.* 2013;5:324.
26. Singh S, Shah D. Development and characterization of mouth dissolving tablet of zolmitriptan. *Asian Pac J Trop Dis.* 2012;2(Suppl 2):S457-S464.
27. Egla M, Hammid SN. Design zolmitriptanliquisolidorodispersible tablets and their in vitro evaluation. *J Chem Pharm Res.* 2016;8(11):232-242.
28. Deshpande KB, et al. Development and evaluation of zolmitriptan orally disintegrating tablets. *Int J Pharm Sci Res.* 2019;10(5):2201-2210.
29. Miksusanti M, Apriani EF, Ahmadi A, Shiyan S, Permata D, Wijaya VA. Formulation and characterization of Sambiloto extract orally dissolving films: a dual mechanism for probiotic growth and antibacterial action. *Int J App Pharm.* 2025;17(2):198-203.
30. Gaisford S, Saunders M. *Essentials of Pharmaceutical Preformulation.* Chichester: John Wiley & Sons; 2012.
31. Bharate SS, Vishwakarma RA. Impact of preformulation on drug development. *Expert Opin Drug Deliv.* 2013;10(9):1239-1257.
32. Patel P, Ahir K, Patel V, Manani L, Patel C. Drug-excipient compatibility studies: first step for dosage form development. *PharmaInnov J.* 2015;4(5 Pt A):14-20.
33. Serajuddin ATM, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, Varia SA. Selection of solid dosage form composition through drug-excipient compatibility testing. *J Pharm Sci.* 1999;88(7):696-704.
34. *European Pharmacopoeia.* 11th ed. Strasbourg: Council of Europe/EDQM; 2023.
35. *United States Pharmacopeial Convention.* USP 47-NF 42. Rockville, MD: USP Convention; 2024.
36. Uddin R, Saffoon N, Sutradhar KB. Dissolution and dissolution apparatus: a review. *Int J Curr Biomed Pharm Res.* 2011;1(4):201-207.
37. ICH Harmonised Tripartite Guideline. *Stability Testing of New Drug Substances and Products Q1A(R2).* Geneva: International Council for Harmonisation; 2003.