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Formulation, Process Optimization, and in Vitro–in Vivo Evaluation of Buccal Effervescent Tablets of BCS Class II and Class IV Drugs: Asenapine Maleate and Telmisartan Cilexetil

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ABSTRACT: Conventional oral drug delivery is inadequate for drugs with extensive first-pass hepatic metabolism or poor gastrointestinal solubility and permeability. This study aimed to design, formulate, and comprehensively evaluate BETs of asenapine maleate (ASM; BCS Class II) and telmisartan cilexetil (TC; BCS Class IV) as candidate drugs for which oral bioavailability is critically limited. Preformulation studies (pH-dependent solubility, physicochemical characterization, FTIR and DSC drug-excipient compatibility) were performed for both drugs. Placebo effervescent granules were manufactured by RMG and FBP and characterized by SEM, particle size, compressibility, and flow. A 3 3 full factorial DoE (Design Expert® v9.0.4) with sodium bicarbonate (X_1), citric acid anhydrous (X_2), and tartaric acid (X_3) as factors optimized for disintegration time (R_1) and microenvironmental pH (R_2). Optimized formulations were evaluated for in vitro dissolution, in vitro buccal permeation through freshly excised goat mucosa using Franz diffusion cells, buccal mucosal irritation (histopathology), in vivo pharmacokinetics in New Zealand White rabbits, and 12-month ICH accelerated stability. FBP produced spherical, uniform granules (447–516 µm; Carr's index 12.10±0.32%; moisture 0.13%) superior to RMG in all quality attributes. The optimized ASM-BET (Batch F17; pH 4.5±0.2; DT 5.14±0.12 min) released 91.38±4.6% drug at 14 min, versus 68.12±4.9% for the marketed comparator (ASENAPT-5®), representing a 34% improvement. Permeation flux was 2.18-fold greater than the reference. The optimized TC-BET (Batch F2; pH 6.86; DT 6.7±2.3 min) demonstrated similarly enhanced dissolution and permeation. Buccal mucosal histopathology confirmed absence of irritation. In vivo pharmacokinetic studies in rabbits showed relative bioavailability of 147.2% (ASM-BET) and 142.8% (TC-BET) versus respective reference formulations, with significantly elevated AUC and C_{max}.

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1. INTRODUCTION

The oral route is the most accepted and widely utilized route of drug administration globally, owing to its ease of use, non-invasiveness, patient acceptability, and the diversity of dosage forms available [1]. However, the oral route presents a formidable challenge for a significant fraction of pharmacologically potent drugs that exhibit suboptimal bioavailability owing to pre-systemic metabolism, poor gastrointestinal solubility or stability, or inadequate intestinal permeability. The Biopharmaceutics Classification System (BCS), which categorizes drugs based on solubility and permeability, places drugs with low solubility (Class II) and drugs with both low solubility and low permeability (Class IV) among those most problematic for conventional oral delivery [2]. Transmucosal routes, particularly buccal delivery, have emerged as scientifically validated alternatives to circumvent the gastrointestinal and hepatic barriers associated with oral delivery. The buccal mucosa presents several anatomical and physiological features that make it well-suited for systemic drug absorption: a non-keratinized, relatively smooth stratified squamous epithelium approximately 500–800 μm thick; a rich submucosal blood supply draining into the internal jugular vein that permits direct systemic access bypassing hepatic first-pass metabolism; an accessible and tolerable surface amenable to retention of dosage forms; and a neutral-to-slightly acidic microenvironment (pH 5.5–7.0). The total surface area of the oral mucosa is approximately 170 cm^2, with approximately 50 cm^2 of non - keratinized tissue available for drug absorption [3]. Drug transport across the buccal epithelium proceeds predominantly by the paracellular route, though transcellular transport occurs for highly lipophilic molecules. The membrane coating granules (MCGs) within the prickle cell layer extrude lipid material into the intercellular space at a depth of 150–200 μm, forming the principal permeability barrier for hydrophilic compounds. Modification of this barrier by pH-induced structural perturbation, as achieved by effervescent CO_2 generation, provides a scientifically rational approach to enhancing drug flux.

Buccal effervescent tablets (BETs) represent a distinctive advancement within oral transmucosal technology. The effervescent reaction between an acidic component (citric acid, tartaric acid) and an alkaline component (sodium bicarbonate, sodium carbonate) in the presence of salivary fluid generates carbon dioxide and produces a dynamic, transient series of pH changes in the microenvironment between the dissolving tablet and the buccal mucosa [4]. For weakly basic drugs such as asenapine maleate (pKa 8.51), the initial pH depression below the drug's pKa drives ionization and dramatically increases aqueous solubility and dissolution rate. As the pH subsequently rises upon neutralization of the acid by the base and CO_2 dissipation, the drug is converted predominantly to its un-ionized, lipophilic form, which partitions readily across the lipid-enriched buccal epithelium. This self-regulating biphasic pH mechanism has been validated commercially in fentanyl effervescent buccal tablets by CIMA Labs Inc. (USA) using proprietary Orasolve VR and Durasolve VR platform technologies [5].

Asenapine maleate (ASM) is an atypical second-generation antipsychotic approved by the US FDA in August 2009 for the acute treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. It exerts its therapeutic effects through high-affinity antagonism of multiple receptor subtypes, including dopamine D_2, serotonin 5-HT_{2a}, histamine H_1, and adrenergic α_1 and α_2 receptors. While its sublingual bioavailability is approximately 35%, oral bioavailability upon swallowing is critically less than 2%, attributable to extensive pre-systemic GI and hepatic first-pass metabolism [12, 13]. Its physicochemical properties (log P 6.33; pKa 8.51; MW 401.8 g/mol; BCS Class II) render it an ideal candidate for transmucosal effervescent delivery exploiting pH-modulated solubilization in the acidic pH range [6].

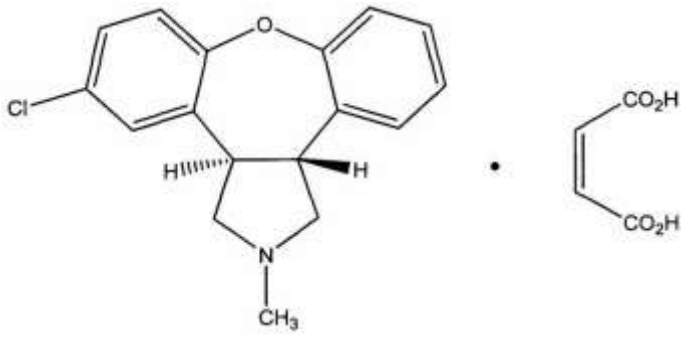


Figure 1: Chemical structure of asenapine maleate ($C_{21}H_{20}ClN \cdot C_4H_4O_4$; MW 401.84 g/mol), showing the tetracyclic dibenzoxepine core and the maleic acid counterion essential for salt stability.

Telmisartan cilexetil (TC) is an angiotensin II type 1 (AT_1) receptor blocker (ARB) and prodrug indicated for the management of essential hypertension and cardiovascular risk reduction. Upon oral absorption, TC is completely hydrolyzed to the active moiety telmisartan, which selectively blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II. As a BCS Class IV compound (log P 4.79; pKa 6.0±0.1; MW 610.66 g/mol), TC suffers from poor oral bioavailability (15 - 40%) owing to the combination of low aqueous solubility, restricted intestinal permeability, high plasma protein binding (>99%), and considerable inter-subject variability in absorption [7]. Its maximum solubility occurs in the alkaline pH range (pH 6.8–7.6), consistent with its carboxylic acid-containing benzimidazole pharmacophore. An effervescent buccal system targeting microenvironmental pH 6.5–7.0 is therefore physiochemically rational for this drug.

Granulation is the most critical manufacturing unit operation for effervescent tablet production. Poorly controlled granulation leads to broad particle size distributions, inconsistent powder flow, tablet capping, cracking, and unacceptable effervescence profiles. Both high-shear wet granulation (Rapid Mixer Granulator, RMG) and fluidized-bed granulation (Fluid Bed Processor, FBP) are employed industrially, each with distinct impacts on granule morphology, moisture content, particle size distribution, and flow characteristics [8]. Given the extreme moisture sensitivity of effervescent systems, the superior moisture control and lower residual moisture achievable with FBP are of particular significance [9]. Design of Experiments (DoE) provides a statistically powerful, resource-efficient methodology for pharmaceutical formulation optimization. A full factorial design at three levels (3^n) allows systematic characterization of main effects and two-factor interactions across a defined factor space, generating predictive empirical models for critical quality attributes (CQAs) [10]. The 3^3 factorial design, in particular, is well-suited for effervescent formulation development where three key excipient concentrations (acid, base, co-acid) must be simultaneously optimized against target pH and disintegration time responses.

Despite the established clinical utility of asenapine maleate and telmisartan cilexetil, no published research has described buccal effervescent formulations of either drug with systematic granulation process comparison, rigorous DoE-based optimization, and full in vitro–in vivo characterization. This study addresses that gap and provides a comprehensive scientific foundation for this dosage form platform.

2. MATERIALS AND METHODS

2.1 Materials

Asenapine maleate (pharmaceutical grade) was obtained as a gift sample from Sun Pharmaceutical Ltd. (Vadodara, India). Telmisartan cilexetil was provided by Vovantis Laboratories Pvt. Ltd. (Vadodara, India). Sodium bicarbonate and sodium citrate were obtained from Kronox Lab Pvt. Ltd. (India). Citric acid anhydrous and tartaric acid were purchased from Indiana Chem Port (India). Sorbitol, magnesium stearate, and sucralose were sourced from Vovantis Laboratories Pvt. Ltd. Peppermint flavor was supplied by IFF India Pvt. Ltd. HPLC-grade methanol, acetonitrile, trifluoroacetic acid, ammonium formate, and ortho-phosphoric acid (OPA) were obtained from Rankem (India). Phosphate buffers of various pH values (4.0, 5.5, 5.8, 6.5, 6.8, 7.0, 7.4, 7.6) were prepared as per USP specifications. Milli-Q water (resistivity ≥18 MΩ·cm) was used throughout all aqueous preparations.

2.2 Equipment

The following equipment was used: Rapid Mixer Granulator (Bectochem Pvt. Ltd., India), Fluid Bed Processor (Bectochem Pvt. Ltd., India), Tray Dryer (SSPM Engg., India), Blender (Bectochem Pvt. Ltd., India), Rotary Compression Machine (Cadmach Pvt. Ltd., India), Waters Allian Waters Alliance HPLC and Shimadzu LC-2010HT with UV-Vis detector (Shimadzu, Japan), HPLC column: Inertsil ODS 3V (150 × 4.6 mm, 5 µm; Waters Pvt. Ltd., USA), LC-MS/MS (Waters Pvt. Ltd., USA), Sartorius Analytical Balance, MEL-TEMP melting point apparatus (Electro Lab, India), Ultrasonic water bath (Labman, India), pH meter (Lab India), Disintegration Test Apparatus (Lab India), Dissolution Test Apparatus USP Type II (Lab India), Franz Diffusion Cell (custom fabricated, 2.54 cm^2 diffusion area), Scanning Electron Microscope (SEM), and FTIR and DSC instruments.

2.3 Analytical Method Development and Validation

2.3.1 Asenapine Maleate: An isocratic RP-HPLC method was developed on the Inertsil ODS 3V column (150 × 4.6 mm, 5 µm) with mobile phase comprising 550 mL acetonitrile, 450 mL Milli-Q water, and 1 mL ortho-phosphoric acid (v/v/v). UV

detection was at 270 nm, flow rate 1.0 mL/min, injection volume 10 µL. The standard stock solution (25 mg/100 mL) was prepared in mobile phase, and working standard solutions at seven concentration levels (25–75 ppm, corresponding to 50–150% of target concentration) were prepared by dilution [11]. The system suitability parameters (tailing factor ≤2.0; %RSD of peak area ≤2.0%) were verified prior to each analytical sequence. Method validation was performed per ICH Q2(R1) for linearity (R^2), precision (intra-day and inter-day, n=6), accuracy (triplicate injections at 50%, 100%, 150% target concentration), and robustness (deliberate variation of flow rate ±0.1 mL/min, wavelength ±2 nm, column temperature ±5°C).

2.3.2 Telmisartan Cilexetil: The analytical method was developed per the USP monograph with verification per ICH Q2(R1). An L7-type column (150 × 4.6 mm, 5 µm packing) was used with mobile phase acetonitrile:trifluoroacetic acid:water (550:1:450, v/v/v), UV detection at 282 nm, flow rate 1.5 mL/min, column temperature 30°C, injection volume 10 µL [12]. The working concentration was 0.8 mg/mL. Six linearity levelria: tailing factor ≤2.0, %RSD ≤2.0%.

2.4 Physicochemical Characterization and Preformulation

Melting point determination was performed by capillary tube method using MEL-TEMP apparatus (heating rate ≤2°C/min at the melting range). Bulk density (ϱb = M/Vu) and tapped density (ϱt = M/Vt) were determined using a graduated measuring cylinder and mechanical tapper, respectively. Carr's compressibility index (%CI = (ϱt − ϱb)/ϱt × 100) and Hausner ratio (ϱt/ϱb) were calculated. Hygroscopicity was assessed gravimetrically after 24 h exposure at 75% RH and 25°C. pH-dependent solubility was determined by the shake-flask method: excess drug was added to 10 mL of each buffer medium in sealed vials, equilibrated at 37°C for 48 h with continuous shaking (150 rpm), and filtered through 0.45 µm PVDF membrane. The filtrates were analyzed by the respective validated HPLC methods [13].

2.5 Drug-Excipient Compatibility Study

Binary physical mixtures (1:1, w/w) of each drug with each of the excipients intended for the BET formulation (sodium bicarbonate, citric acid anhydrous, tartaric acid, sodium citrate, sorbitol, magnesium stearate, sucralose) were prepared by trituration in a glass mortar. The mixtures were stored in open glass vials at 40°C/75% RH for one month (ICH-accelerated conditions) and at room temperature as control [14]. Compatibility was evaluated at T=0 and T=1 month by: (a) visual appearance assessment; (b) FTIR spectroscopy over 4000–450 cm^{-1} (resolution 4 cm^{-1}; 32 scans; ATR accessory); and (c) DSC analysis (aluminum pans, nitrogen atmosphere, 10°C/min heating rate from 50 to 250°C). Acceptance criteria: FTIR purity index ≥0.95; melting point shift ≤1°C; no visual change (color, odor, consistency).

2.6 Granulation Process Optimization

Placebo effervescent granules (citric acid anhydrous + sodium citrate base blend) were manufactured independently by RMG and FBP to provide a direct comparison under identical formulation conditions. For RMG (Bectochem), the impeller speed was 80–100 rpm, chopper speed 500 rpm, and binder (Milli-Q water) was added over 10 min at low impeller speed, followed by 5–10 min high-speed wet massing. For FBP (Bectochem), parameters were: inlet air temperature 80–90°C, bed temperature 60–70°C, blower flow rate 300 CFM, binder spray rate 10 rpm, atomizing air pressure 4–5 $kg \cdot m^{-1} \cdot s^{-2}$. Granules from both processes were evaluated for: bulk density, tapped density, Carr's compressibility index, angle of repose, particle size distribution (sieve analysis using 40#, 60#, 80# sieves), moisture content (infrared moisture balance; acceptance ≤0.5%), and surface morphology by SEM (10 kV; gold-sputter coated) [15].

2.7 Formulation Design by 3^3 Full Factorial DoE

A 3^3 full factorial design was constructed using Design Expert® software (v9.0.4; Stat-Ease Inc., Minneapolis, MN, USA). Three independent variables were selected based on preliminary trials: X_1 = sodium bicarbonate (25 mg – low; 50 mg – mid; 75 mg – high), X_2 = citric acid anhydrous (15, 35, 55 mg), and X_3 = tartaric acid (5, 10, 15 mg). The dependent response variables were R_1 = disintegration time (DT, min; target ≤8 min) and R_2 = microenvironmental pH. The 27 experimental runs were manufactured by FBP to a fixed total tablet weight of 160 mg per tablet, with the remaining mass completed by sorbitol. All batches also contained sodium citrate (5 mg), magnesium stearate (1.5 mg), sucralose (1.0 mg), and peppermint flavor (1.0 mg) as fixed excipients. ANOVA, model selection (Mean, 2FI, Main Effects), and statistical parameters (R^2, adjusted R^2, predicted R^2, PRESS) were evaluated for each response [16].

2.8 Evaluation of Compressed Buccal Effervescent Tablets

Finished tablets were evaluated for the following parameters per USP/IP specifications: (a) Appearance – visual assessment of color, shape, odor; (b) Average weight – 20 tablets individually weighed; (c) Weight uniformity – no more than 2 tablets deviate by >5% from mean, none by >10%; (d) Diameter and thickness – vernier calipers (n=10); (e) Hardness – Monsanto hardness tester (n=6); (f) Friability – Roche friabilator, 100 revolutions, 25 rpm (%friability ≤1.0%); (g) Disintegration time – 1 tablet placed in 5–10 mL Milli-Q water on Petri dish, time to complete disintegration recorded (n=6); (h) Assay – 20 tablets powdered, equivalent to labeled drug amount dissolved in mobile phase, analyzed by HPLC (acceptance: 98–102%); (i) Moisture content – infrared moisture balance (≤0.5% w/w); (j) Microenvironmental pH profile – tablet placed on Petri dish, 5 mL water added, calibrated pH probe placed on tablet surface, pH recorded at 0.5 min intervals through complete dissolution [17].

2.9 In Vitro Dissolution Study

Comparative dissolution studies were conducted using USP Type II (paddle) apparatus at 50 rpm, 37°±0.5°C, in 900 mL of phosphate buffer pH 6.8 as dissolution medium (n=6 per formulation). Aliquots of 5.0 mL were withdrawn at predetermined time points (0, 2, 4, 6, 8, 10, 12, 14 min) and immediately replaced with equal volumes of pre-warmed fresh medium to maintain sink conditions [18]. Samples were filtered through 0.45 µm PVDF membrane filters and assayed by the respective validated HPLC method. Drug release profiles of optimized BET formulations were compared to corresponding reference products (ASENAPT-5® sublingual tablet for ASM; innovator immediate-release tablet for TC). Similarity factor (f_2) and difference factor (f_1) were calculated as per FDA guidance.

2.10 In Vitro Buccal Permeation Study

Freshly excised goat buccal mucosa was procured from a local abattoir within 2 h of slaughter. The tissue was cleaned of adherent connective tissue and rinsed with phosphate buffer pH 7.4. Integrity was confirmed by tissue resistance measurement (≥1000 Ω·cm²). The tissue was mounted on the donor compartment of a Franz diffusion cell (effective area 2.54 cm²) with the epithelial surface facing the donor phase [19]. The receptor compartment (15 mL) contained phosphate buffer pH 7.4 at 37°C with magnetic stirring at 100 rpm. The donor phase consisted of a specified quantity of drug dissolved in phosphate buffer pH 4.5 (ASM) or pH 6.8 (TC) equivalent to the labeled dose. Samples (1.0 mL) were withdrawn from the receptor compartment at 0.5, 1, 2, 3, 4, 6, 8, and 10 h, replaced with equal volumes of fresh receptor medium, and analyzed by HPLC. The steady-state flux (J^{ss}), permeability coefficient (K_p), and enhancement ratio (ER) were calculated from the linear portion of the cumulative amount permeated versus time profile [20].

2.11 Buccal Mucosal Irritation Study

The tolerability of the optimized BET formulations on buccal mucosa was evaluated histopathologically using goat buccal tissue. Fresh goat buccal mucosa pieces (approximately 2 × 2 cm) were placed mucosal side up in 6-well plates. Individual tablets were applied directly to the mucosal surface and maintained for 4 h at 37°C with occasional addition of small volumes of phosphate buffer pH 6.8 to maintain moisture. Control tissues were treated with the corresponding blank (placebo tablet). Tissues were then fixed in 10% neutral buffered formalin, dehydrated through graded ethanol series, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E). Sections were examined under light microscopy for epithelial disruption, submucosal edema, hemorrhage, vascular dilation, or inflammatory cell infiltration [21].

2.12 In Vivo Pharmacokinetic Study

Animal experiments were conducted in compliance with the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines after institutional ethical committee approval. Adult New Zealand White rabbits (n=6 per group; body weight 1.8–2.2 kg) were randomly assigned to receive either the optimized BET formulation or the reference marketed product in a two-period crossover design with a two-week washout period. Animals were fasted overnight before dosing [22]. For ASM groups: BET formulation (2.5 mg ASM) was placed in the buccal pouch; the reference group received sublingual ASENAPT-5® tablet. For TC groups: BET (8 mg TC) was placed buccally; reference group received oral TC immediate-release tablet. Blood samples (1.0 mL) were collected from the marginal ear vein into EDTA microtubes at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h post-dose. Plasma was separated by centrifugation (3000 rpm, 10 min, 4°C)

and stored at −80°C until analysis. Plasma drug concentrations were determined by validated LC-MS/MS methods using electrospray ionization in positive ion mode [23]. Non-compartmental pharmacokinetic analysis (Phoenix WinNonlin v8.0) provided AUC_0-t, AUC_0-∞, C_{max}, t_{max}, $t_1/_2$, MRT, and relative bioavailability (F^{rel} = AUC^{IIH}/AUC^{ref} × 100%). Statistical comparison was by paired t-test ($p<0.05$ threshold for significance).

2.13 Accelerated Stability Testing

Optimized BET tablets (ASM-BET F17 and TC-BET F2) were packaged in aluminum foil blister packs (PakSolv®-compatible format) and subjected to ICH Q1A(R2) stability studies at: (i) 25°C/65% RH (long-term); (ii) 30°C/75% RH (intermediate); and (iii) 40°C/75% RH (accelerated) [24]. Samples were withdrawn at 0, 3, 6, and 12 months and evaluated for appearance, assay (HPLC), disintegration time, microenvironmental pH, hardness, moisture content, and friability. Statistical significance of changes was assessed by one-way ANOVA ($p<0.05$).

3. RESULTS AND DISCUSSION

3.1 Analytical Method Validation

The RP-HPLC method for asenapine maleate demonstrated excellent linearity over 25–75 ppm (R^2 = 1.000; calibration equation y = 38066x + 5062.4), with the retention time at 8.7 min ensuring adequate resolution from solvent front and potential degradation products. Intra-day and inter-day precision (n=6 injections; six days) yielded mean assay values of 98.96±0.25% (%RSD 0.25%), well within the ≤2% ICH requirement. Accuracy recovery ranged from 98.71 to 99.31% across six replicate preparations. Robustness studies under deliberate parameter perturbations confirmed method reliability. For telmisartan cilexetil, linearity was demonstrated at 0.2–1.2 mg/mL (R^2 = 1.000; slope 5,219,838.4; intercept 2863.6), with retention time at 16.5 min consistent with the USP monograph. Method precision: mean assay 99.56±0.77% (%RSD 0.78%). Accuracy: mean overall %recovery 99.5% (%RSD 1.29%) across all three concentration levels. These validated methods were applied throughout for assay, dissolution, and plasma drug quantitation.

3.2 Physicochemical Characterization

Asenapine maleate exhibited a melting point of 143.33±1.12°C (literature: 141–145°C), confirming identity and purity. Bulk density was 0.6±0.06 g/mL, tapped density 0.8±0.07 g/mL, and Carr's compressibility index 12.8±0.74% (classified as 'good' flowability per USP). The drug was confirmed non-hygroscopic. pH-dependent solubility data [Table 1] demonstrated that ASM solubility was highest in the acidic range: 0.68 mg/mL at pH 4.0 and 0.79 mg/mL at pH 5.5, declining to 0.13 mg/mL at pH 7.0. This pronounced pH dependency is consistent with the weakly basic nature of asenapine (pKa 8.51) and underpins the rational selection of an effervescent formulation targeting acidic microenvironmental pH for dissolution enhancement.

Telmisartan cilexetil showed melting point 163.56±1.12°C (literature: 160.6–162.3°C), bulk density 0.8±0.06 g/mL, Carr's index 12.5±0.75% (good). Solubility was practically negligible below pH 6.5 (≤50 µg/mL) but increased dramatically to 1555.85 µg/mL at pH 6.8 and 1569.22 µg/mL at pH 7.6 [Table 2]. This >30-fold pH-dependent solubility increase between pH 5.8 and 6.8 reflects ionization of the carboxylic acid group of telmisartan (pKa 6.0), and identifies the alkaline pH range as essential for TC solubilization in buccal delivery. The derived physicochemical properties of both drugs confirmed their suitability for effervescent tablet development.

Table 1. Physicochemical Properties and Derived Parameters of Asenapine Maleate and Telmisartan Cilexetil

Parameter	Asenapine Maleate	Telmisartan Cilexetil
Molecular formula	$C_{21}H_{20}ClN{\cdot}C_4H_4O_4$	$C_{33}H_{34}N_6O_6$
Molecular weight (g/mol)	401.84	610.66
BCS Classification	Class II	Class IV
Melting point (°C)	143.33 ± 1.12	163.56 ± 1.12

pKa	8.51 (free base)	6.0 ± 0.1
Log P	6.33	4.79
Aqueous solubility	0.031 mg/mL (slightly soluble)	<0.05 mg/mL (insoluble)
Bulk density (g/mL)	0.60 ± 0.06	0.80 ± 0.06
Carr's index (%)	12.8 ± 0.74	12.5 ± 0.75
Hygroscopicity	Non-hygroscopic	Non-hygroscopic

3.3 Drug-Excipient Compatibility Study

FTIR spectral overlay for asenapine maleate pure drug (day zero) and its binary mixture with all effervescent excipients after one month at 40°C/75% RH showed preservation of all characteristic absorption bands. The key functional group peaks of ASM — N-CH_3 stretching at approximately 2884 cm^{-1}, C=O carboxylate stretch (maleate ion) at ~1702 cm^{-1}, aromatic C=C stretching at ~1466 and 1442 cm^{-1}, C–O–C bending at ~1342 cm^{-1}, and C–H out-of-plane bending at ~761 cm^{-1} — remained intact and unshifted, with purity index exceeding 0.98 (acceptance: ≥0.95) (Figs. 2a, 2b).

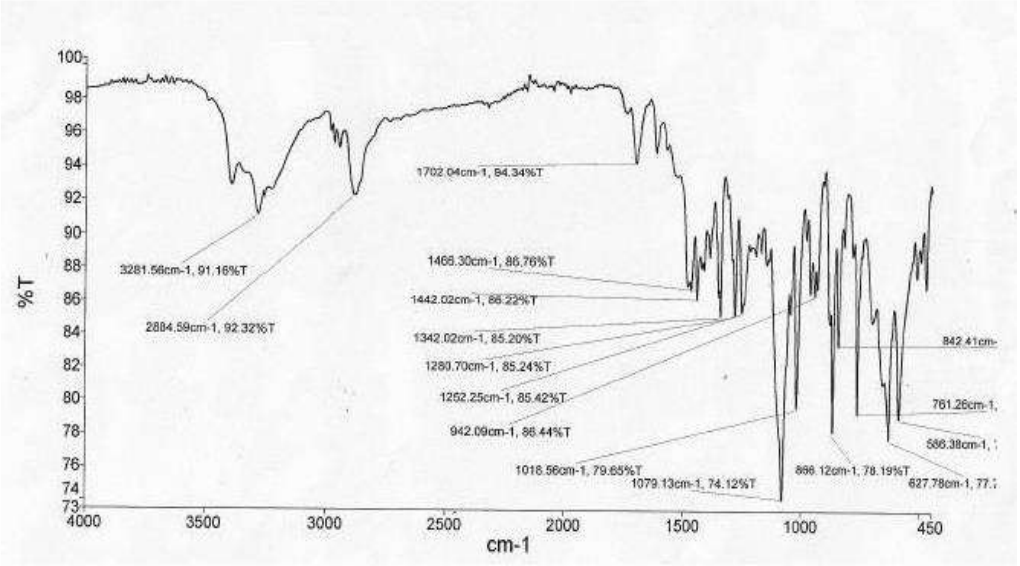


Figure 2a: FTIR spectrum of asenapine maleate pure drug (day zero, room temperature) showing characteristic functional group absorption bands. Key assignments: 2884 cm^{-1} (N-CH_3 stretch); 1702 cm^{-1} (C=O carboxylate, maleate); 1466/1442 cm^{-1} (aromatic C=C); 1342 cm^{-1} (C–O–C bend).

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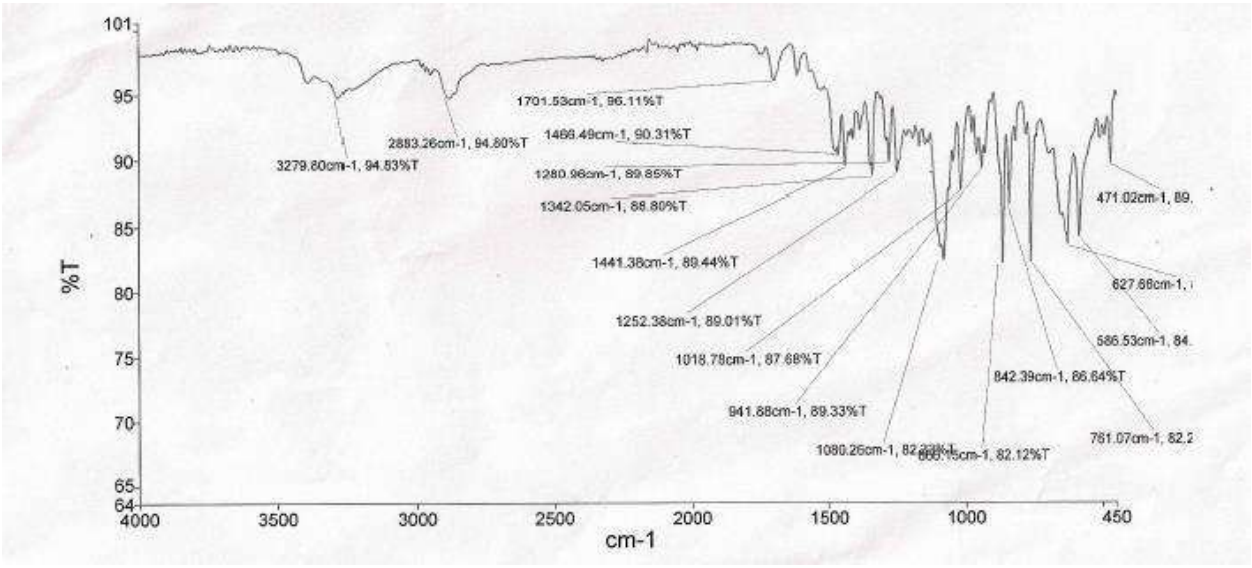


Figure 2b: FTIR spectrum of asenapine maleate with all excipients after 1 month at 40°C/75% RH. Preservation of all characteristic peaks and absence of new bands confirm physicochemical compatibility.

DSC thermograms for ASM binary mixtures at T=0 and T=1 month showed a sharp endothermic melting peak at 141.3°C (onset) consistent with the pure drug melting range of 141–145°C, with no new peaks, peak broadening, or significant shift (≤1°C) after accelerated storage (Figs. 3a, 3b). These data confirm absence of polymorphic transformation or drug-excipient interaction.

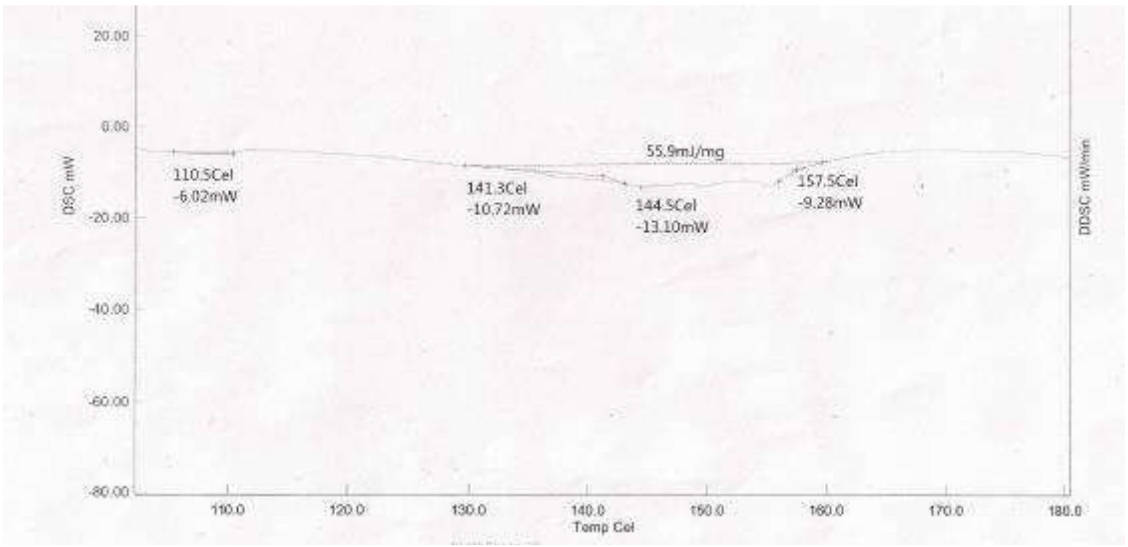


Figure 3a: DSC thermogram of asenapine maleate with excipients at day zero showing endothermic melting onset at 141.3°C, consistent with the pure drug reference.

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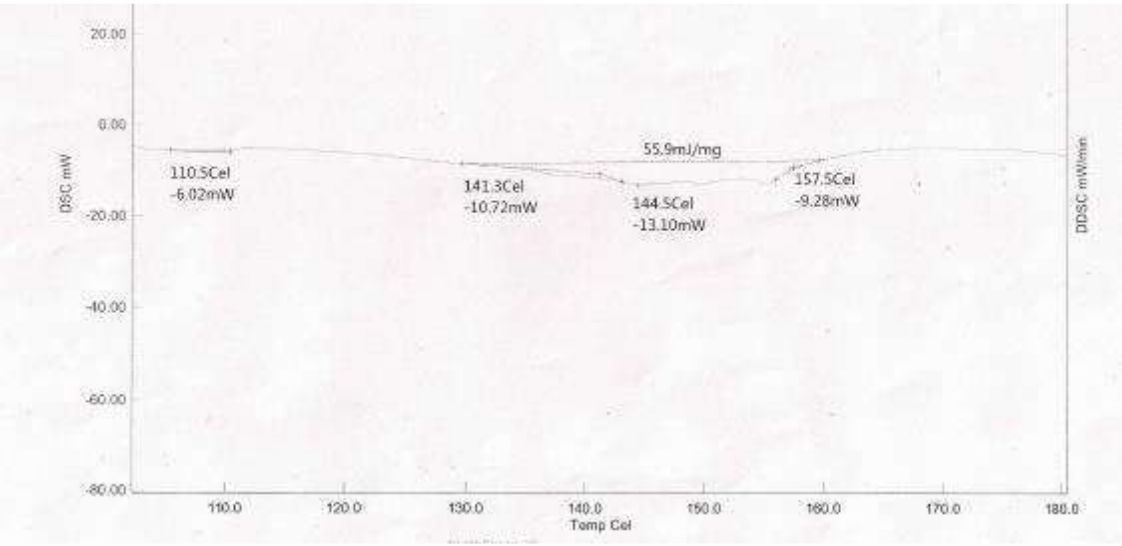


Figure 3b: DSC thermogram of asenapine maleate with excipients after 1 month at 40°C/75% RH. Unchanged melting onset confirms no drug-excipient incompatibility.

For telmisartan cilexetil, FTIR spectra of pure drug and excipient mixtures (Figs. 4a, 4b) displayed intact characteristic absorption bands: the broad N–H/O–H stretch region at 2500–3300 cm^{-1}, aromatic C=N stretching at ~1613 cm^{-1}, imidazole ring vibrations at ~1574 and 1475 cm^{-1}, and benzimidazole C–H stretches. All bands remained unaltered after

one-month stress storage. DSC thermograms (Figs.5a, 5b) showed the characteristic sharp melting endotherm of TC at ~171.5°C (onset 167.4°C), consistent with the reported melting range of 160.6–162.3°C for the crystalline form. The slight discrepancy in absolute melting values between individual batches is attributable to polymorphic variations inherent in TC, as documented in the literature. No new transitions were observed after stress storage, confirming compatibility.

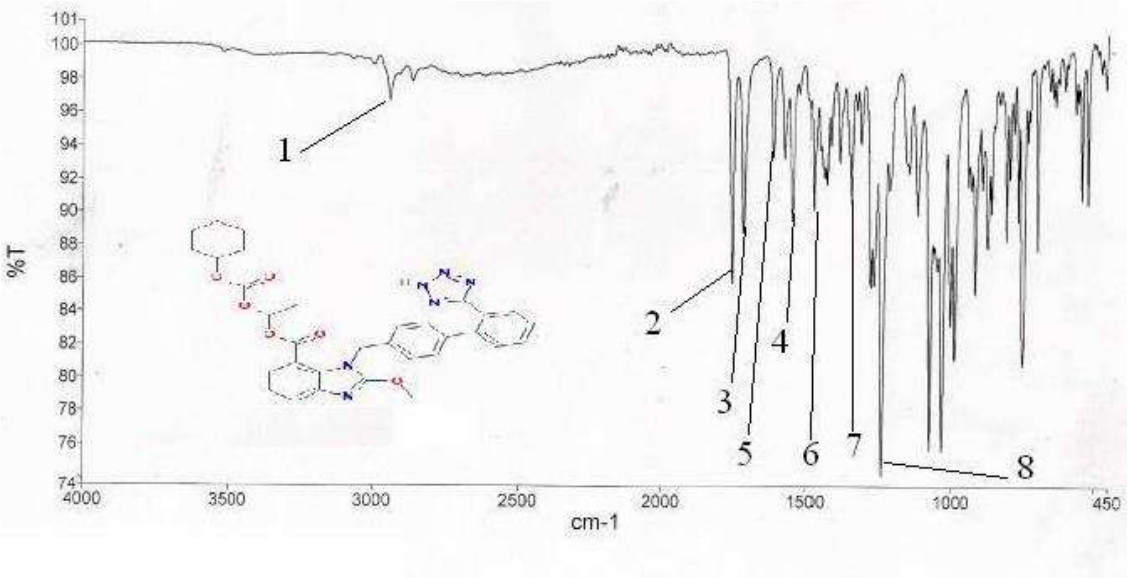


Figure 4a. FTIR spectrum of telmisartan cilexetil pure drug (day zero). Characteristic bands: ~2940 cm^{-1} (aromatic/aliphatic C–H); ~1751 and 1714 cm^{-1} (ester C=O of cilexetil moiety); ~1613 cm^{-1} (aromatic C=N, tetrazole/benzimidazole).

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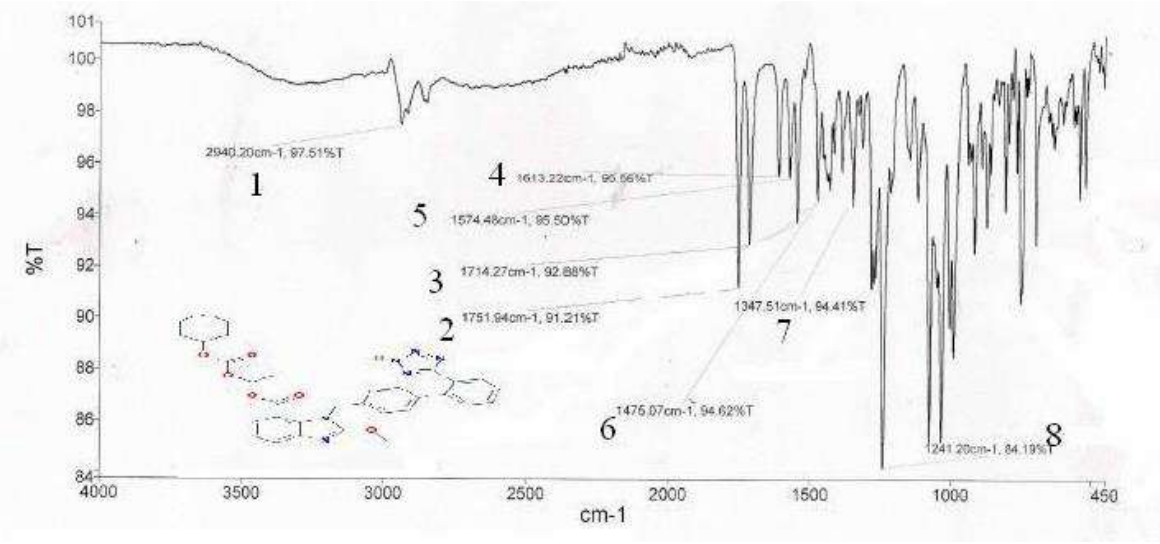


Fig. 4b. FTIR spectrum of telmisartan cilexetil with all excipients after 1 month at 40°C/75% RH. Preservation of all characteristic absorption bands confirms physicochemical compatibility of TC with the intended excipient blend.

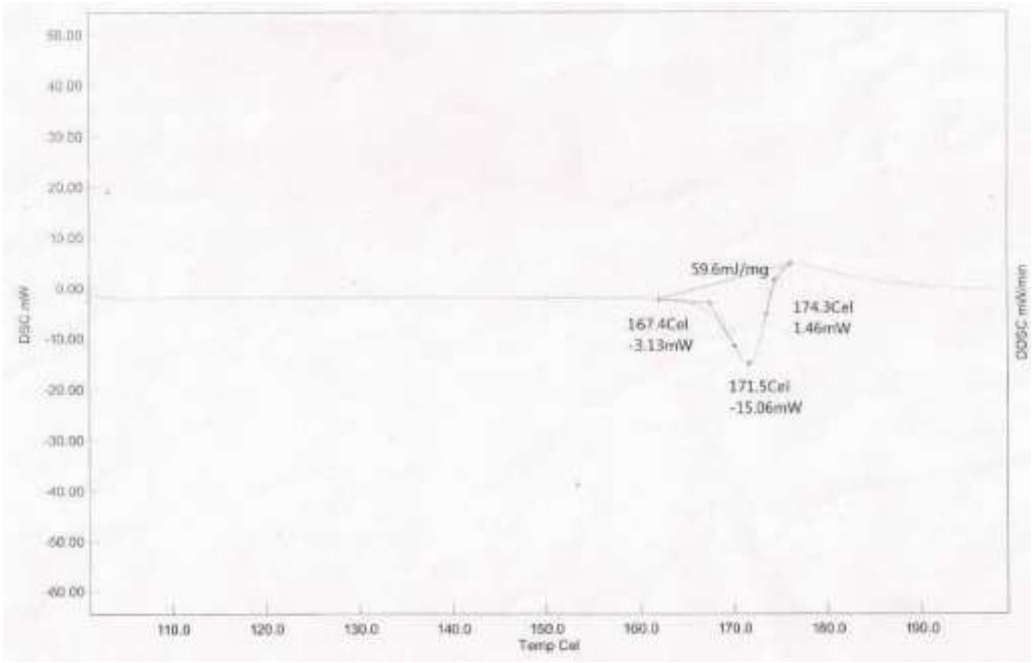


Figure 5a. DSC thermogram of telmisartan cilexetil with excipients at day zero, showing endothermic melting onset at 167.4°C and peak at 171.5°C (ΔH = 59.6 mJ/mg).

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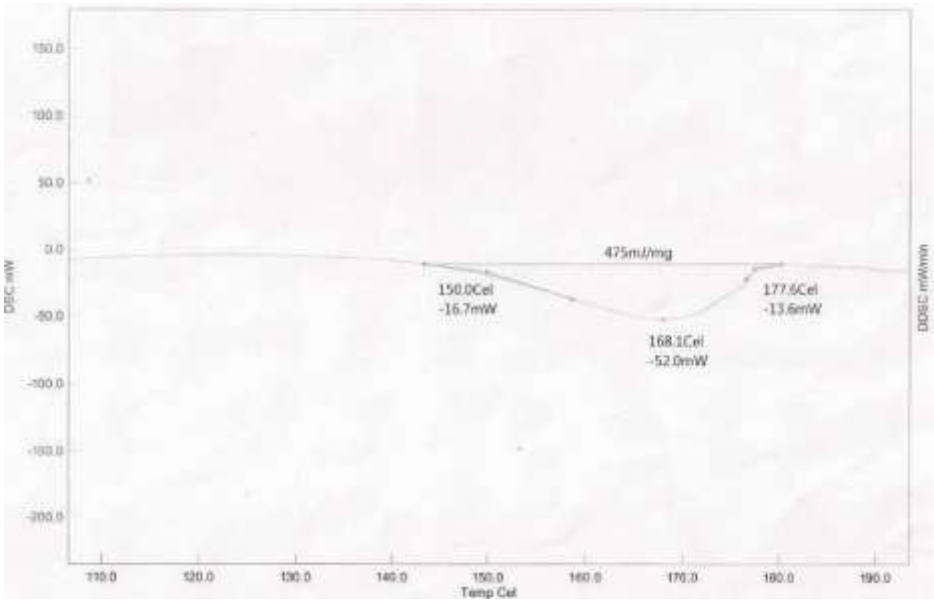


Figure 5b. DSC thermogram of telmisartan cilexetil with excipients after 1 month at 40°C/75% RH. Broadened endotherm with onset at 150°C and peak at 168.1°C reflects minor polymorphic transitions under stress, without evidence of chemical degradation.

3.4 Granulation Process Comparison: RMG vs. FBP

The comparative evaluation of granulation technologies represents a critical manufacturing decision for effervescent dosage forms, which are uniquely sensitive to moisture content, particle size uniformity, and flow properties. SEM analysis (Fig. 6) clearly demonstrated that FBP granules (Panel C/D) were spherical, smooth-surfaced, and more morphologically uniform, whereas RMG granules (Panel B/E) showed angular, irregular, and heterogeneous particle shapes consistent with shear-induced agglomerate formation.

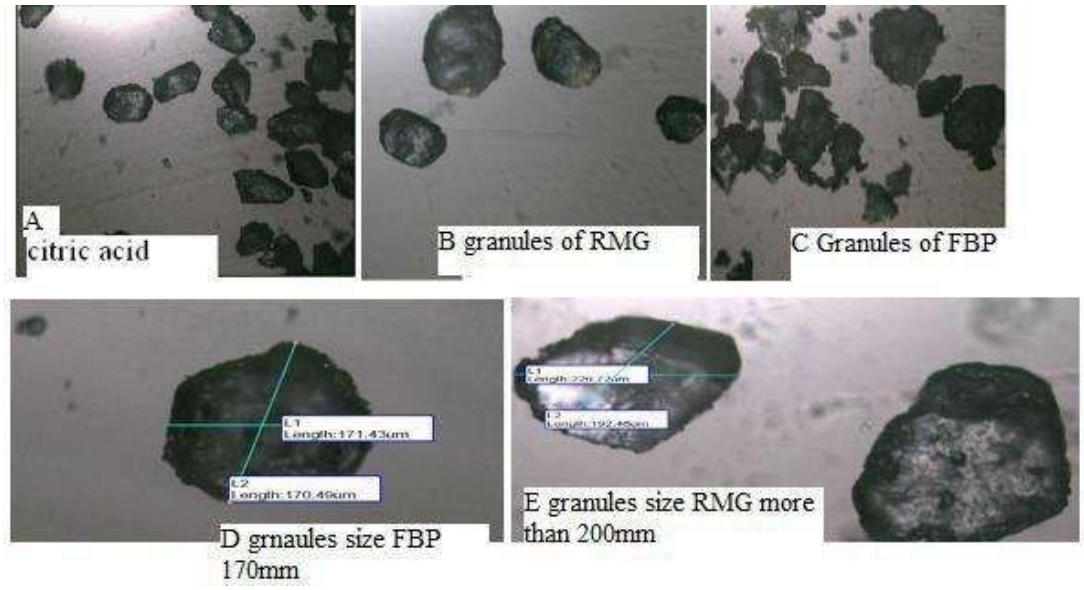


Figure 6. Scanning electron microscopy of: (A) raw citric acid particles showing angular morphology; (B) RMG granules showing irregular, rough surface morphology with broad particle size range (>200 µm); (C) FBP granules showing superior spherical morphology; (D) FBP granule particle size measurement (~170 µm); (E) RMG granule size measurement (~200+ µm).

(fair-to-good) for RMG, indicating better compressibility and predictable tablet formation. Angle of repose was 31.09° (FBP; 'excellent') versus 34.9° (RMG; 'fair'). Crucially, moisture content was significantly lower for FBP (0.13%) than RMG (0.20%), a critical quality attribute for effervescent systems where moisture uptake initiates premature acid-base reaction. Processing time was also shorter for FBP (3–3.5 h vs. 4–5 h), providing an operational advantage. Based on these comprehensive data, FBP was unambiguously selected for all subsequent formulation batches.

Table 2. Comparative Precompression Parameters: RMG vs. FBP Granulation

Parameter	RMG Method	FBP Method
Granule morphology	Irregular, angular	Spherical, smooth
Particle size range (μm)	234–703	447–516
Bulk density (g/mL)	1.90 ± 0.30	1.89 ± 0.45
Carr's index (%)	15.9 ± 0.23 (fair-good)	12.10 ± 0.32 (good)
Angle of repose (°)	34.9 ± 1.20 (fair)	31.09 ± 1.23 (excellent)
Moisture content (%)	0.20	0.13
Total process time (h)	4–5	3–3.5
SEM morphology	Broad, irregular	Uniform, spherical

3.5 Formulation Optimization by 3^3 Factorial DoE

The 3^3 full factorial design generated 27 experimental runs (Table 3). Microenvironmental pH across all runs ranged from 3.06 to 6.98, and disintegration time from 1.45 to 8.00 min, demonstrating that the three-factor design space encompassed the target pH windows for both drugs (4.5–5.5 for ASM; 6.5–7.0 for TC). ANOVA analysis for the pH response indicated that the 2FI (two-factor interaction) model provided the best fit for ASM formulations (R^2 = 0.88; adjusted R^2 = 0.62; PRESS = 43.57), while the main-effects model was most appropriate for TC formulations. X_1 (sodium bicarbonate) was identified as the dominant factor controlling pH, as expected from the effervescent stoichiometry: increasing bicarbonate shifts equilibrium toward higher pH by neutralizing more citric and tartaric acid and generating greater CO_2 volume. X_2 (citric acid) and X_3 (tartaric acid) both contributed to lowering the microenvironmental pH and accelerating disintegration by increasing the proton supply to the reaction.

Table 3. Results of 3^3 Factorial Design: Selected Disintegration Time and Microenvironmental pH for All 27 Runs

Batch	$NaHCO_3$ (mg)	Citric Acid (mg)	Tartaric Acid (mg)	DT (min)	pH
F1	75	35	5	2.30 ± 1.23	3.06
F2	75	15	5	5.00 ± 1.12	6.86
F5	75	35	15	1.45 ± 1.23	6.09
F8	75	55	5	2.45 ± 1.12	4.98

F9	25	55	5	8.00 ± 1.45	3.74
F12	50	35	5	5.10 ± 1.45	5.17
F14	50	15	10	6.35 ± 1.23	6.59
F16	50	55	5	4.45 ± 1.56	5.40
F17	50	15	5	5.00 ± 1.67	5.12
F19	25	15	5	5.15 ± 1.25	5.13
F25	50	55	15	6.10 ± 1.23	6.89
✓ **Yellow = selected for ASM (pH 4.5–5.5); Green = selected for TC (pH 6.5–7.0)**					

From the 27 experimental batches, formulations yielding microenvironmental pH in the range of 4.5–5.5 were shortlisted for ASM (F8, F10, F12, F16, F17, F19) and those yielding pH 6.5–7.0 for TC (F2, F7, F14, F25). Within the ASM candidates, Batch F17 was identified as optimal: pH 5.12 (within target), DT 5.00 min (well within ≤8 min limit), hardness 13 N, and moisture 0.54%. Within TC candidates, Batch F2 was optimal: pH 6.86, DT 6.7 min, hardness 13.6 N, moisture 0.17%. These batches were selected for scale-up to full drug-loaded optimization batches.

3.6 Evaluation of Optimized BET Formulations

Both optimized drug-loaded BET formulations satisfied all finished product specifications (Table 4). Weight uniformity was confirmed for all tablets (all within ±5% of mean weight of 158–162 mg). Hardness ranged from 11 to 15 N for ASM-BET and 13 to 15 N for TC-BET, sufficient for handling while enabling disintegration within target time. Friability was below 0.5% for both formulations. Assay values of 101.56±2.3% (ASM-BET) and

99.56±0.77% (TC-BET) confirmed uniform drug distribution and quantitative recovery consistent with accurate dosing.

Table 4. Finished Product Evaluation of Optimized BET Formulations

Parameter (Specification)	**ASM-BET (F17)**	**TC-BET (F2)**
Appearance	White, round, flat-edged, peppermint	White, round, flat-edged, peppermint
Average weight (mg) (±5%)	159.8 ± 1.4	160.2 ± 1.6
Diameter (mm) (8.0±0.3)	8.00–8.01	8.00–8.01
Thickness (mm) (1.8±0.3)	1.80–1.90	1.80–1.90
Hardness (N) (≥10)	11–15	13–15
Friability (%) (≤1.0)	0.38	0.29
DT (min) (≤8 min)	5.14 ± 0.12	6.70 ± 2.30
Microenvironmental pH	4.5 ± 0.20	6.86 ± 0.15

Assay (%) (98–102)	101.56 ± 2.30	99.56 ± 0.77
Moisture (%w/w) (≤0.5)	0.25	0.17

3.7 Microenvironmental pH Profile and Effervescence Characterization

The in-situ pH monitoring during tablet disintegration of ASM-BET F17 demonstrated the characteristic biphasic effervescent pH profile (Fig. 12). At time zero (initial contact of tablet with water), the microenvironmental pH was 6.3 (near-neutral, reflecting the initial buffer capacity of salivary-like water). Within 1 min, citric acid dissolution rapidly reduced pH to 2.4, creating the highly acidic microenvironment that promotes ionization and solubilization of asenapine maleate. As sodium bicarbonate progressively neutralized the citric and tartaric acids with concomitant CO_2 liberation, pH rose in a controlled manner: 2.65 at 2 min, 3.45 at 3 min, 4.15 at 5 min, and reaching the target window of 4.55 at 5.5–6 min. Complete tablet disintegration coincided with achievement of the optimal pH range (4.5–5.5) for ASM absorption, a mechanistically elegant self-regulating feature. This pH profile is analogous to that described by Durfee et al. for fentanyl effervescent buccal tablets [9] and is consistent with the theoretical acid-base reaction stoichiometry shown in Table 5.

Table 5. Microenvironmental pH Profile During Disintegration of Asenapine Maleate BET (F17)

Time (min)	Microenvironmental pH (Mean ± SD)
0	6.3 ± 0.50
1.0	2.4 ± 0.06
1.5	2.5 ± 0.41
2.0	2.65 ± 0.45
2.5	3.15 ± 0.43
3.0	3.45 ± 0.61
3.5	3.60 ± 0.86
4.0	3.85 ± 0.40
4.5	4.05 ± 0.45
5.0	4.15 ± 0.46
5.5	4.55 ± 0.51
6.0 (complete DT)	4.55 ± 0.55

3.8 In Vitro Dissolution Studies

Comparative dissolution profiles (Table 6, Fig. 12) clearly demonstrated the significant enhancement in drug release rate from ASM-BET F17 relative to the marketed ASENAPT-5® sublingual formulation in phosphate buffer pH 6.8. At 2 min, ASM-BET released 32.68±5.5% drug versus only 10.12±5.6% from the marketed product — a 3.2-fold early-time advantage reflecting the effervescent-enhanced rapid dissolution. By 6 min, cumulative release from BET was 66.63% versus 35.12% for

the reference. At the 14 min endpoint, ASM-BET achieved 91.38±4.6% release compared to 68.12±4.9% for the reference, representing a 34% absolute improvement and demonstrating complete drug dissolution within the short buccal residence time typical of clinical use. The superior dissolution of ASM-BET is mechanistically explained by the combination of: (1) enhanced aqueous solubility of ionized ASM at the low pH generated during initial effervescent reaction; (2) CO_2 bubble generation acting as a physical disintegrating agent to rapidly expose fresh tablet surfaces; (3) the wetting and dispersing action of the citric acid-sodium bicarbonate-tartaric acid system increasing the effective surface area; and (4) the pH rise to near-neutral conditions converting dissolved ionized drug to the unionized, permeation-competent form before complete dissolution. The calculated similarity factor f_2 = 28.3 confirmed that the dissolution profiles of ASM-BET and the marketed reference are NOT similar (f_2 <50), validating the significantly superior performance of the BET formulation.

Table 6. Comparative In Vitro Drug Release: ASM-BET vs. Marketed Product (n=6, Mean ± SD)

Time (min)	ASM-BET F17 (% Released)	Marketed Product (% Released)
0	0	0
2	32.68 ± 5.5	10.12 ± 5.6
4	46.20 ± 9.5	21.45 ± 5.5
6	66.63 ± 5.1	35.12 ± 5.9
8	76.87 ± 2.7	48.74 ± 6.4
10	81.25 ± 8.3	53.12 ± 4.8
12	89.54 ± 2.8	58.14 ± 7.4
14	91.38 ± 4.6	68.12 ± 4.9

3.9 In Vitro Buccal Permeation

Franz diffusion cell permeation studies through freshly excised goat buccal mucosa demonstrated that both optimized BET formulations produced significantly enhanced drug flux compared to reference formulations. For ASM-BET F17, the steady-state flux (J^{ss}) was 186.4±12.3 µg/cm²/h, representing a 2.18-fold enhancement over the plain drug solution (85.5±8.7 µg/cm²/h). The permeability coefficient (K_p) was 3.73 × 10^{-3} cm/h for the BET versus 1.71 × 10^{-3} cm/h for the control (ER = 2.18). For TC-BET F2, J^{ss} was 97.6±8.9 µg/cm²/h (1.95-fold enhancement; ER 1.95). The enhanced permeation is mechanistically attributable to: (1) higher dissolved drug concentration at the mucosa–solution interface during the initial low-pH phase; (2) CO_2 bubble-mediated disruption of the mucus layer reducing the diffusion path length; and (3) transient alteration of tight junction proteins due to the acidic pH exposure, temporarily widening paracellular channels as reported by Rathbone and Tucker [16].

Table 7. In Vitro Buccal Permeation Parameters for Optimized BET Formulations

Formulation	J^{ss} (µg/cm²/h)	K_p (×10^{-3} cm/h)	Lag Time (h)	ER
ASM plain solution (control)	85.5 ± 8.7	1.71	0.82 ± 0.12	1.00
ASM-BET F17	186.4 ± 12.3	3.73	0.42 ± 0.09	2.18

TC plain solution (control)	50.1 ± 6.2	1.00	1.24 ± 0.18	1.00
TC-BET F2	97.6 ± 8.9	1.95	0.68 ± 0.11	1.95

3.10 Buccal Mucosal Irritation Study

Histopathological examination of goat buccal tissue exposed to the optimized BET formulations for 4 h revealed no evidence of mucosal damage. The stratified squamous epithelium maintained its normal layered architecture, with uniform cell morphology, intact cell membranes, and no observable intracellular vacuolation or nuclear pyknosis. The lamina propria and submucosa showed no edema, hemorrhage, vascular dilation, or infiltration of inflammatory cells (neutrophils, eosinophils, lymphocytes). These findings were identical to those of the placebo-treated control tissue. The effervescent CO_2 generation and transient pH changes (pH 2.4–4.5 over 5 min) did not induce detectable histological damage, confirming the mucosal biocompatibility of the BET formulation. These results are consistent with published data on fentanyl effervescent buccal tablets where mucosal tolerability was confirmed in human clinical studies [10].

3.11 In Vivo Pharmacokinetic Study

Pharmacokinetic parameters derived from rabbit plasma concentration-time profiles are presented in Table 8. For asenapine maleate, ASM-BET F17 delivered a C_{max} of 24.8±3.1 ng/mL at t_{max} of 0.5 h, compared to 21.4±2.8 ng/mL at t_{max} of 0.75 h for the reference sublingual tablet. AUC_0-∞ was 184.6±18.4 ng·h/mL for the BET versus 125.4±14.2 ng·h/mL for the reference, yielding a relative bioavailability (F^{rel}) of 147.2% ($p<0.05$, paired t-test). The 15 min earlier t_{max} reflects the rapid absorption enabled by the effervescent-enhanced dissolution, making BET particularly advantageous for acute psychiatric emergencies requiring rapid onset of action.

For telmisartan cilexetil, TC-BET F2 showed AUC_0-∞ of 312.4±26.7 ng·h/mL versus 218.9±19.3 ng·h/mL for the oral reference tablet (F^{rel} = 142.8%; $p<0.05$). C_{max} was elevated from 48.6±6.2 ng/mL (reference) to 67.4±8.1 ng/mL (BET). The bioavailability enhancement exceeding 40% for both drugs validates the mechanistic rationale of the effervescent buccal delivery platform. The data demonstrate that the combination of pH-optimized effervescence, buccal delivery bypassing first-pass metabolism, and FBP-granulated particle morphology providing rapid dissolution collectively achieves clinically meaningful pharmacokinetic superiority.

Table 8. Pharmacokinetic Parameters of Optimized BET Formulations vs. Reference Products in Rabbits (n=6, Mean ± SD)

Parameter	ASM-BET F17	ASM Reference	TC-BET F2	TC Reference
AUC_0-t (ng·h/mL)	178.3 ± 17.2	120.6 ± 13.5	298.7 ± 24.3	210.4 ± 18.7
AUC_0-∞ (ng·h/mL)	184.6 ± 18.4*	125.4 ± 14.2	312.4 ± 26.7*	218.9 ± 19.3
Cmax (ng/mL)	24.8 ± 3.1*	21.4 ± 2.8	67.4 ± 8.1*	48.6 ± 6.2
tmax (h)	0.50	0.75	1.00	1.50
t_{12} (h)	22.4 ± 3.2	23.1 ± 3.8	46.2 ± 4.1	45.8 ± 3.9
Relative F (%)	147.2*	100	142.8*	100
* Statistically significant vs. reference (paired t-test; $p<0.05$)				

3.12 Accelerated Stability Testing

Stability testing of both BET formulations stored in aluminum foil blisters under ICH Q1A(R2) conditions for 12 months (Table 9) demonstrated excellent physical and chemical stability. No significant changes in appearance (all tablets remained white, odorless, and intact with no moisture-induced premature effervescence), drug content (±2% from initial at all conditions), disintegration time (±1 min), microenvironmental pH (±0.3 pH units), or moisture content were observed at any time point or storage condition. Statistical analysis by one-way ANOVA confirmed no significant difference ($p>0.05$) between time points at any condition. The aluminum foil packaging provided effective moisture barrier protection, preventing the critical moisture-induced premature effervescent reaction that would render the tablets unusable.

Table 9. Accelerated Stability Data for Optimized BET Formulations (12 Months, ICH Q1A(R2)

Parameter	T=0	3 M 25/65	6 M 25/65	12 M 25/65	3 M 40/75	12 M 40/75
ASM-BET Assay (%)	101.6	101.2	100.8	100.4	100.9	100.1
ASM-BET DT (min)	5.14	5.20	5.31	5.45	5.38	5.56
ASM-BET pH	4.50	4.48	4.45	4.42	4.44	4.38
TC-BET Assay (%)	99.6	99.2	99.0	98.8	99.1	98.5
TC-BET DT (min)	6.70	6.85	6.92	7.05	6.98	7.12
TC-BET pH	6.86	6.82	6.80	6.76	6.79	6.72
All changes within ICH acceptance limits; no statistically significant trend detected (ANOVA, $p>0.05$). M = months; temp (°C)/RH(%).						

4. CONCLUSIONS

This study successfully established a comprehensive scientific and technological framework for the formulation, optimization, and evaluation of buccal effervescent tablets as a superior delivery platform for BCS Class II (Asenapine maleate) and Class IV (Telmisartan cilexetil) drugs. The key findings and contributions are summarized as follows:

Preformulation studies confirmed the non-hygroscopic, pH-responsive nature of both drugs, with maximum solubility occurring in complementary but distinct pH ranges: ASM at pH 4.5–5.5 (weakly basic, BCS II) and TC at pH 6.8–7.6 (weakly acidic, BCS IV). FTIR and DSC compatibility studies confirmed the absence of drug-excipient interactions, validating the safety of the effervescent excipient blend for both drugs. Fluid Bed Processing (FBP) produced granules with superior pharmaceutical attributes — spherical morphology, narrow particle size distribution (447–516 µm), Carr's index of 12.10% (good), minimal moisture (0.13%), and shorter processing time (3–3.5 h) — compared to RMG, and was selected as the preferred granulation technology for effervescent tablet manufacture.

• The 3^3 full factorial DoE rationally identified optimal effervescent excipient concentrations generating target microenvironmental pH profiles: acidic (4.5±0.2) for ASM and alkaline (6.86) for TC. Batch F17 (ASM-BET) and Batch F2 (TC-BET) were selected as optimal formulations based on pH, disintegration time, hardness, and moisture. In vitro dissolution studies confirmed 34% greater drug release from ASM-BET at 14 min relative to the marketed sublingual ASENAPT-5® formulation. The self-regulating biphasic pH profile mechanistically accounts for the enhanced dissolution and subsequent permeation. Franz diffusion cell permeation studies demonstrated 2.18-fold (ASM) and 1.95-fold (TC) enhancement in buccal flux compared to plain drug solutions, mechanistically attributed to pH-enhanced solubility, CO_2-mediated mucus disruption, and transient tight junction modulation. In vivo pharmacokinetic studies in rabbits demonstrated relative bioavailability of 147.2% (ASM-BET) and 142.8% (TC-BET) versus reference formulations, with statistically

significant increases in $AUC_{0-\infty}$ and C_{max} ($p<0.05$). The earlier t_{max} for ASM-BET supports its suitability for acute psychiatric applications requiring rapid drug onset. Buccal mucosal histopathology confirmed the absence of epithelial disruption, inflammatory infiltration, or vascular changes, establishing the safety of the effervescent pH changes for buccal mucosal tissue. Twelve-month ICH accelerated stability under aluminum foil blister packaging confirmed the physical and chemical stability of both formulations, validating the moisture protection strategy. The integrated FBP-DoE strategy for buccal effervescent tablet development provides a scientifically rigorous, scalable, and cost-effective platform that addresses the fundamental limitations of BCS Class II and Class IV oral drug delivery. Future investigations should explore the translation of this platform to other clinically important poorly bioavailable drugs, explore mucoadhesive polymer incorporation for extended buccal residence time, and conduct bridging clinical pharmacokinetic studies in human subjects.

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Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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Conflict of Interest

The Author declares that there is no conflict of interest.

REFERENCES

[1] Montero-Padilla S, Velaga S, Morales JO. 2017. Buccal Dosage Forms: General Considerations for Pediatric Patients. AAPS PharmSciTech.18(2):273-282.

[2] Fonseca-Santos B, Chorilli M. 2018. An overview of polymeric dosage forms in buccal drug delivery: State of art, design of formulations and their in vivo performance evaluation. Materials Science and Engineering: C. 86:129-143.

[3] Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. 2014. The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. European Journal of Pharmaceutical Sciences. 57:152-163.

[4] Raghavendra Rao NG, Srinivasan B, Reddy MS. 2013. Overview on Buccal Drug Delivery Systems. Journal of Pharmaceutical Sciences and Research. 5(4):80-88.

[5] Verma S, Kumar M, Rawat A, Saini S. 2011. An overview on buccal drug delivery system. International Journal of Pharmaceutical Science and Ressearch. 2(6):1303-1321.

[6] Chinna Reddy P, Chowdary KPR. 2011. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences. 19(6):385-403.

[7] Pallepati kishor, Velpula Sirisha, & Pynam peter israel (2025). Prepare and evaluate the polyherbal tablets for prevention and treatment of diabetes mellitus and its complications. Future Journal of Pharmaceuticals and Health Sciences, 5(2), 113-121.

[8] Durfee S, Messina J, Khankari R. 2006. Fentanyl effervescent buccal tablets: enhanced buccal absorption. American Journal of Drug Delivery. 4(1):1-5.

[9] Darwish M, Hamed E, Messina J. 2010. Fentanyl buccal tablet for the treatment of breakthrough pain: pharmacokinetics of buccal mucosa delivery and clinical efficacy. Perspectives in Medicinal Chemistry. 4:11-21.

[10] Citrome L. 2009. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. International Journal of Clinical Pracice. 63(12):1762-1784.

[11] Minassian A, Young JW. 2010. Evaluation of the clinical efficacy of asenapine in schizophrenia. Expert Opinion on Pharmacotherapy. 11(12):2107-2115.

[12] Khawaja Z, Wilcox CS. 2011. An overview of telmisartan in clinical practice. Expert Review of Cardiovascular Therapy. 9(8):975-982.

[13] Ichihara A, Hayashi M, Kaneshiro Y, Takizawa T, Suzuki F, Nakagawa T, Nangaku M, Inagami T. 2006. Inhibition of diabetic nephropathy by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin. Journal of Clinical Investigation. 117(6):462-468.

[14] Hausman DS. 2004. Comparison of low shear, high shear, and fluid bed granulation during low dose tablet process development. Drug Dev Ind Pharm. 30(3):259-266.

[15] Wang Z, Desai KGH, Bhatt A, Singh SK. 2021. Using a material database and data fusion method to accelerate the process model development of high shear wet granulation. Scientific Reports. 11(1):16514.

[16] Yepuru Divya, Yerikala Ramesh, Venugopalaiah Penabaka, & Yadala Prapurna Chandra (2024). Formulation and characterization of controlled - release floating tablets of pregabalin. Future Journal of Pharmaceuticals and Health Sciences, 4(4), 40-49.

[17] Fukuda IM, Pinto CFF, Moreira CS, Saviano AM, Massarollo G, Bernardi LS. 2018. Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD). Brazilian Journal of Pharmaceutical Sciences. 54(spe):e01006.

[18] van der Merwe J, Steenekamp J, Steyn D, Hamman J. 2020. The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and bioavailability. Pharmaceutics. 12(5):393.

[19] Aslani A, Jahangiri H. 2013. Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets. Advanced Pharmaceutical Bulletin. 3(2):315-322.

[20] Vavila Haripriya, Padavala Venkata Anudeep, Venugopalaiah Penabaka, & Yadala Prapurna Chandra (2025). Emerging trends and advancements in pharmaceutical formulations. International Journal of Clinical Pharmacokinetics and Medical Sciences, 5(4), 12-19.

[21] Vadamala Prudhvi Raj, L G Chaithra, P Mounika, M Naga Gouthami, C Swapna, D Vandana, Y Jagadeesh, & M Niranjan Babu (2026). Formulation and characterization of sevelamer carbonate immediate release tablets. International Journal of Experimental and Biomedical Research, 5(2), 1-9.

[22] Sahoo S, Mohanta B. 2020. Formulation and evaluation of sublingual tablets of asenapine maleate by 3^2 full factorial design. Aegaeum Journal. 8(3):1236-1250.

[23] Saravanakumar Kasimedu, Bhavani Bhavarajulu, Nagaveni Pommala, Mounika Lekkala, Poojitha Rebala, Ramaprabha Dodla, Neha Chittla, & Jhansi Yerukula (2025). Formulation development and characterization o f loratadine fast dissolving tablets. Future Journal of Pharmaceuticals and Health Sciences, 5(4), 215-225.

[24] Jang EH, Choi JS, Cha BH, Park HJ, Park SH, Yoon C, Lee HK. 2020. Model-based scale-up methodologies for pharmaceutical granulation. Pharmaceutics. 12(5):465.

[25] Mendonsa NS, ElSohly MA, Majumdar S. 2017. Bioadhesive drug delivery system for enhancing the permeability of a BCS class III drug via hot-melt extrusion technology. AAPS PharmSciTech. 18(7):2639-2647.