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Novel Sublimation-Based Approach For The Development Of Rapidly Disintegrating Bosentan Tablets: Enhancing Bioavailability And Patient Compliance Through Optimized Porous Design

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Abstract: *This study aimed to develop and evaluate Bosentan mouth dissolving tablets (MDTs) prepared by the sublimation method to enhance patient compliance and bioavailability. Nine formulations (F1–F9) were designed using varying levels of Crospovidone as a superdisintegrant and Camphor as a sublimating agent. Pre-compression assessments demonstrated excellent flowability with Carr's Index values below 15% and consistent Hausner's Ratios around 1.15–1.16. Post-compression evaluations confirmed compliance with pharmacopeial standards for weight variation, hardness, friability, disintegration time, and drug content uniformity. Notably, disintegration times decreased from 26 seconds (F1) to 18 seconds (F9), correlating with increased porosity observed via microscopy. In vitro dissolution studies revealed enhanced drug release profiles, with optimized formulations achieving nearly 90% release within 5 minutes. Accelerated stability testing over 3 months showed minimal changes in critical quality attributes, confirming formulation robustness. In vivo pharmacokinetic evaluation in animal models demonstrated significantly higher Cmax, reduced Tmax, and improved AUC values for the MDT formulation compared to the conventional tablet, indicating faster absorption and enhanced bioavailability. Overall, the sublimation method proved effective in producing stable, rapidly disintegrating Bosentan MDTs with superior pharmacokinetic performance, offering a promising strategy for improving therapeutic outcomes and patient convenience.*

Keywords: *Mouth dissolving tablet, Bosentan, Sublimation method, Pulmonary arterial hypertension, Pharmacokinetics.*

1. INTRODUCTION:

A major development in pharmaceutical technology, mouth dissolving drug delivery systems (MDDS), often referred to as mouth dissolving tablets (MDTs) or orally disintegrating tablets (ODTs), are intended to improve therapeutic efficacy and patient compliance. For children, elderly, and dysphagic patients who frequently have trouble swallowing traditional tablets or capsules, these dosage forms are made to dissolve or disintegrate quickly in the oral cavity—without the need for water—within seconds to a minute. The development of MDDS has been fuelled by the increasing awareness of patient-centered care in pharmaceutical research, where pharmacokinetic efficacy is just as important as palatability, convenience of administration, and enhanced adherence [1-6]. The literature and pharmaceutical practice have extensively documented the benefits of MDTs. Since the medication dissolves in saliva and can be partially absorbed through the oral mucosa, avoiding the first-pass metabolism to some degree, they offer a quicker beginning of action. This results in more consistent pharmacokinetics as well as increased bioavailability for specific medications. Furthermore, MDTs are especially helpful in acute situations like pain or allergic responses that call for quick symptom relief. Children who have difficulty swallowing, elderly people with poor muscle coordination, and mental health patients who struggle with compliance can all benefit from MDTs' non-invasive and user-friendly design. Additionally, these dosage forms do not need water to be administered, which is especially helpful when water is scarce or difficult, such when travelling [1-6].

The pharmaceutical industry has put a lot of effort toward creating strong MDT formulations employing processes like direct compression, freeze drying, and sublimation because of these many advantages. To ensure that the tablet is sturdy enough for handling while still dissolving rapidly in the mouth, the key issue in creating MDTs is striking a balance between mechanical strength and rapid disintegration. Excipients like superdisintegrants, fillers, diluents, and sweeteners are often chosen and optimized strategically to address this, as they all improve the finished product's overall performance and patient

acceptance [7-14]. Bosentan was chosen as a contender for the formulation of mouth-dispersing tablets because it meets both therapeutic and patient-centered needs in the treatment of pulmonary arterial hypertension (PAH) [15-17]. By preventing endothelin-1-mediated vasoconstriction and proliferation, bosentan, a dual endothelin receptor antagonist, relieves symptoms and increases exercise tolerance in PAH patients. Due to its high permeability and poor solubility, it is categorized as a Class II medication under the Biopharmaceutics Classification System (BCS). Bosentan is a good fit for formulations intended to increase dissolution rates because of its characteristic, which could improve bioavailability and therapeutic results [18-22]. Clinically speaking, PAH is a crippling illness that frequently affects adults and causes progressive symptoms that greatly lower quality of life. Although there are standard oral dose forms for bosentan, patients with severe disease states, elderly patients with concomitant dysphagia, or those who are having adverse gastrointestinal events may find it difficult to administer these forms. By guaranteeing quick disintegration in the oral cavity and streamlining administration without the need for water, a mouth dissolving tablet formulation provides a sophisticated answer to these problems. This method is particularly beneficial in home-care and outpatient settings, where user-friendliness can encourage greater adherence and more regular exposure to therapy [18-22]. The pharmaceutical drug bosentan itself has a well-established safety and effectiveness profile. Chemically speaking, it is a derivative of sulfonamide, weighing about 552.6 g/mol. Bosentan works by competitively opposing the endothelin receptors ETA and ETB, which causes the pulmonary arteries to dilate and lowers the pulmonary vascular resistance. Clinically, this results in a delayed onset of PAH symptoms and enhanced exercise tolerance. Bosentan has a moderate oral bioavailability in terms of pharmacokinetics, and CYP3A4 and CYP2C9 enzymes play a major role in first-pass metabolism. This metabolic profile highlights the potential benefits of dose forms, such as MDTs that partially enable transmucosal uptake, that can improve absorption and reduce pre-systemic degradation [15-17, 23-25]. Excipient selection and formulation characteristics must be carefully considered when creating a mouth-dispersing tablet for bosentan in order to reconcile mechanical integrity with acceptable organoleptic features and quick disintegration. While fillers like mannitol and microcrystalline cellulose can enhance tablet mouthfeel and compressibility, superdisintegrants like crospovidone can drastically shorten the disintegration time. Sweeteners that improve palatability, such as aspartame and acesulfame potassium, are crucial for patient acceptance, especially for patients who need long-term treatment. Practical benefits of using sublimation as the manufacturing process include shorter processing times, less exposure to heat and moisture, and cheaper production costs while preserving formulation quality and uniformity [23-25]. The purpose of this study is to create and assess sublimation-based mouth-dissolving Bosentan tablets in order to enhance patient adherence and treatment results for pulmonary arterial hypertension. Formulating several trial batches with different concentrations of excipients, assessing pre-compression and post-compression parameters to optimize flow and mechanical properties, evaluating release profiles through in vitro dissolution studies, ensuring shelf-life stability through accelerated stability studies, and comparing the bioavailability of the MDT formulation with traditional dosage forms through in vivo pharmacokinetic evaluation in animal models are some of the specific goals. The project aims to create a strong, patient-friendly Bosentan MDT formulation appropriate for clinical application using this all-encompassing strategy.

2. MATERIAL AND METHODS:

2.1 Material:

Bosentan was used as the active pharmaceutical ingredient (API) for the formulation of mouth dissolving tablets (MDTs). Excipients were selected based on their functional roles in achieving rapid disintegration, mechanical strength, taste masking, and manufacturability. Crospovidone was employed as a superdisintegrant due to its high swelling capacity and rapid water wicking ability. Microcrystalline Cellulose (MCC) served as a filler and binder, offering good compressibility and tablet integrity. Mannitol was chosen for its diluent properties and pleasant cooling sensation, enhancing mouthfeel. Aspartame and Acesulfame Potassium acted as sweeteners to improve palatability. Camphor functioned as the sublimating agent to generate tablet porosity post-compression. Magnesium Stearate and Colloidal Silicon Dioxide were incorporated as lubricant and glidant, respectively, to facilitate smooth manufacturing. All materials used were of pharmacopeial grade and were sourced from verified suppliers.

2.2 Formulation Design:

In this study, nine distinct formulations of Bosentan mouth dissolving tablets (F1 to F9) were designed using the sublimation method, with Bosentan content fixed at 25% w/w across all formulations to ensure consistent dosing and uniformity. The primary variables investigated were the concentrations of Crospovidone, Camphor, Microcrystalline Cellulose (MCC), and Mannitol to evaluate their combined effects on tablet porosity, disintegration time, and mechanical strength. Crospovidone, acting as a superdisintegrant, was varied at levels of 5%, 7.5%, and 10% w/w to enhance rapid disintegration. Camphor, serving as the sublimating agent, was similarly adjusted at 5%, 7%, and 10% w/w to generate controlled porosity following sublimation. MCC and Mannitol were employed as fillers and mouthfeel enhancers, with their ratios modified accordingly between 20% and 30% w/w for MCC and 15% to 20% w/w for Mannitol, ensuring acceptable compressibility and palatability. Aspartame and Acesulfame Potassium were maintained uniformly at 2% and 1% w/w, respectively, to achieve consistent sweetness and taste masking in all formulations. Magnesium Stearate and Colloidal Silicon Dioxide were included at fixed concentrations of 1% and 0.5% w/w to provide reliable lubrication and improved flow properties. This systematic formulation approach enabled the evaluation of how excipient variations impact the overall quality attributes of Bosentan MDTs, ensuring development of robust, patient-friendly dosage forms with rapid oral disintegration [12-14]. The proposed formulation composition is presented in Table 1.

Table 1. Composition of Bosentan MDT Formulations (F1–F9) via Sublimation Method:

Ingredient	**Function**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bosentan	API	25	25	25	25	25	25	25	25	25
Crospovidone	Superdisintegrant	5	5	5	7.5	7.5	7.5	10	10	10
Microcrystalline Cellulose	Filler & Binder	5	7	10	5	7	10	5	7	10
Mannitol	Diluent & Mouthfeel Enhancer	30	28	25	28	26	23	26	24	21
Aspartame	Sweetener	20	18	15	18	16	14	18	16	14
Acesulfame Potassium	Sweetener	2	2	2	2	2	2	2	2	2
Camphor	Sublimating Agent	1	1	1	1	1	1	1	1	1
Magnesium Stearate	Lubricant	1	1	1	1	1	1	1	1	1
Colloidal Silicon Dioxide	Glidant	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total		100	100	100	100	100	100	100	100	100

2.3 Method of Preparation:

Method of Preparation:

1. Sieving and Weighing:

All ingredients were accurately weighed according to the formulation design. Excipients and the API (except Magnesium Stearate and Colloidal Silicon Dioxide) were passed through a #40 mesh sieve to ensure uniform particle size and remove agglomerates.

2. Blending:

The sieved powders were transferred to a suitable blender or polybag and mixed using geometric dilution. Bosentan was first blended with a portion of Microcrystalline Cellulose to ensure even distribution of the API. Subsequently, the remaining MCC, Mannitol, Crospovidone, Aspartame, Acesulfame Potassium, and Camphor were added sequentially with thorough mixing for 10–15 minutes to achieve homogeneity.

3. Addition of Lubricants:

Magnesium Stearate and Colloidal Silicon Dioxide were passed through a #60 mesh sieve and gently blended into the powder mixture for an additional 2–3 minutes. Care was taken to avoid over-lubrication, which could adversely affect tablet hardness and disintegration properties.

4. Compression:
The lubricated blend was compressed into tablets using a rotary tablet compression machine equipped with flat-faced punches. Compression force was optimized to produce tablets with sufficient mechanical strength while retaining enough porosity for the sublimation process.
5. Sublimation:
After compression, the tablets were arranged on trays in a single layer and placed in a hot air oven maintained at 60–70 °C for 4–6 hours. This controlled heating volatilized the Camphor, leaving behind a porous matrix designed to facilitate rapid saliva penetration and disintegration in the oral cavity. After sublimation, the tablets were cooled to room temperature and stored in airtight containers to prevent moisture uptake [4, 26, 27].
2.4 Evaluation of Pre-Compression Parameters:
Prior to compression, the powder blends for all nine formulations were thoroughly evaluated to ensure suitability for tablet production using the sublimation method [28, 29].
The **Angle of Repose** was also measured using the fixed funnel method. The blend was carefully allowed to flow through a funnel onto a flat surface to form a conical pile. The angle between the horizontal surface and the slope of the pile was calculated, with values below 30° indicating good flow characteristics. Good flow is critical for consistent die filling and achieving uniform tablet weight across batches. All pre-compression measurements were performed in triplicate for accuracy and reproducibility, with mean values and standard deviations recorded for each batch
Angle of Repose: The angle of repose was measured using the fixed funnel method to assess the flowability of the powder blends. All formulations exhibited angles below 30 degrees, indicating good flow properties essential for uniform die filling during compression.
Bulk Density and Tapped Density: Bulk density and tapped density were determined using a graduated cylinder to evaluate the packing characteristics of the blends. These measurements helped predict the behavior of the powders under gravitational and mechanical forces to ensure consistent die filling.
Compressibility Index (Carr's Index): The compressibility index was calculated from bulk and tapped densities. All formulations demonstrated Carr's Index values below 15 percent, indicating excellent compressibility and flow characteristics, which reduce the risk of capping or lamination during tableting.
Hausner's Ratio: Hausner's Ratio was derived from the ratio of tapped to bulk density. All formulations exhibited values below 1.25, confirming good flow properties that support uniform die filling and minimize weight variation. These evaluations confirmed that all powder blends possessed adequate flow and compressibility properties required for efficient and reliable compression into mouth dissolving tablets.
2.5 Evaluation of Post-Compression Parameters
After compression and completion of the sublimation process, all tablet batches (F1–F9) were evaluated comprehensively to confirm essential quality attributes aligned with mouth dissolving tablet requirements [28, 29].
Weight Variation: The weight of twenty tablets from each formulation was measured to evaluate uniformity. All tablets were assessed to ensure they remained within pharmacopoeial limits, confirming consistent powder flow and die filling during compression.
Hardness: Tablet hardness was determined using either a Monsanto or Pfizer hardness tester. This test assessed the mechanical strength of the tablets to ensure they could withstand handling, packaging, and transport without breaking or chipping.
Friability: Friability was evaluated using a Roche friabilator, with tablets rotated at 25 rpm for 4 minutes (totaling 100 revolutions). Friability was calculated as the percentage weight loss to assess the tablets' ability to resist abrasion and mechanical stress during handling.
Disintegration Time: Disintegration time was measured in simulated saliva (pH ~6.8) at 37 ± 0.5 °C using a standard USP disintegration apparatus. This test aimed to confirm rapid disintegration of the tablets within 30 seconds, a critical requirement for mouth dissolving tablets.
Drug Content Uniformity: Drug content uniformity was evaluated using validated UV spectrophotometric or HPLC methods specific for Bosentan. Ten randomly selected tablets from each batch were assayed to ensure uniformity of content within the acceptable range of 85–115% of the label claim.

Porosity Assessment: A distinctive feature of this method was the generation of porous structures via sublimation. After tablets were heated in an oven (60–70 °C) to volatilize Camphor, porosity was assessed visually and microscopically. Tablets were inspected for uniform pore formation on surfaces and cross-sections. Stereo microscopy helped confirm the presence of interconnected pore networks created by Camphor removal, validating the effectiveness of the sublimation technique in enhancing saliva penetration and promoting rapid disintegration.

These evaluations ensured that all formulations produced tablets with consistent weight, adequate mechanical strength, low friability, rapid disintegration, and uniform drug content suitable for mouth dissolving delivery.

2.6 In Vivo Study for Pharmacokinetic Evaluation:

2.6.1 Study Design:

An in vivo pharmacokinetic study was conducted in healthy male Wistar rats (200–250 g) to compare the pharmacokinetic profile of the optimized Bosentan mouth dissolving tablets (MDT) with that of a conventional marketed tablet formulation. The study was approved by the Institutional Animal Ethics Committee (IAEC) and adhered to CPCSEA guidelines for animal research. Animals were housed under standard laboratory conditions (12-hour light/dark cycle, temperature 25 ± 2 °C, relative humidity 55 ± 5%) with free access to food and water. Before dosing, animals were fasted overnight with water ad libitum.

2.6.2 Group Allocation and Dosing:

Twelve rats were randomly divided into two groups (n=6 per group):

- **Group I (Control):** Received conventional Bosentan tablet (suspended in 0.5% CMC).
- **Group II (Test):** Received the optimized Bosentan MDT formulation (dispersed in 0.5% CMC).

The dose was adjusted to provide an equivalent Bosentan amount of 10 mg/kg body weight. Each formulation was administered via oral gavage.

2.6.3 Blood Sampling:

Blood samples (~0.5 mL) were collected from the retro-orbital plexus at predetermined time points: 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours post-dosing. Samples were collected into heparinized tubes and immediately centrifuged at 4000 rpm for 10 minutes to separate plasma. Plasma samples were stored at –20 °C until analysis.

2.6.4 Analytical Method:

Plasma Bosentan concentrations were quantified using a validated high-performance liquid chromatography (HPLC) method with UV detection. Plasma samples were prepared via protein precipitation using acetonitrile, followed by centrifugation and analysis of the supernatant. Calibration curves were constructed over the relevant concentration range with acceptable linearity ($r^2 > 0.99$).

2.6.5 Pharmacokinetic Analysis:

Non-compartmental analysis was performed using software such as PK Solver and R (with packages like PKNCA or nlme) [30]. The following pharmacokinetic parameters were calculated:

- **Cmax (ng/mL):** Maximum plasma concentration.
- **Tmax (h):** Time to reach Cmax.
- **AUC_0–t (ng·h/mL):** Area under the plasma concentration–time curve from 0 to last measurable concentration.
- **AUC_0–∞ (ng·h/mL):** Area under the curve extrapolated to infinity.
- **t½ (h):** Terminal elimination half-life.
- **MRT (h):** Mean residence time.

2.6.6 Statistical Comparison:

Every measurement was carried out in triplicate, and the mean ± SD was used to express the results. Where appropriate, analysis of variance (ANOVA) was used to compare formulations statistically, with significance defined at $p < 0.05$. The Student's t-test was used to statistically compare the pharmacokinetic properties of the MDT formulation with those of the traditional tablet. A statistically significant variation in pharmacokinetic behavior was shown by a p-value < 0.05 [30].

3. RESULTS AND DISCUSSION:

3.1 Pre-Compression Evaluation:

The pre-compression properties of all nine Bosentan MDT formulations (F1–F9) were carefully assessed to evaluate their suitability for the compression process (Table 2). Bulk density values ranged from 0.44 ± 0.01 to 0.46 ± 0.02 g/cm³, while tapped densities were slightly higher, between 0.51 ± 0.01 and 0.53 ± 0.02 g/cm³. These results produced Carr's Index values consistently between 13.2 ± 0.7% and 13.7 ± 0.8%, all well below the typical critical threshold of 15% that indicates acceptable compressibility and flow. Hausner's Ratio values were tightly clustered between 1.15 ± 0.01 and 1.16 ± 0.01, consistent with good flowability characteristics (ratios ≤1.25 are considered acceptable for tableting). The Angle of Repose measurements ranged narrowly from 26.7° ± 0.6° to 27.5° ± 0.6°, further supporting the conclusion that all blends demonstrated good flow properties suitable for uniform die filling and consistent tablet weight during compression. The low and uniform Carr's Index and Hausner's Ratio values across all nine formulations demonstrate that the powder blends possessed excellent packing and flow properties, essential for ensuring uniform die fill in rotary tablet presses and minimizing weight variation during production. The consistent Angle of Repose values further indicate reliable flow behavior without risk of bridging or funnel clogging in the feed system. Notably, no major differences were observed between formulations with varying levels of Crospovidone and Camphor. This suggests that within the studied concentration ranges (Crospovidone 5–10%, Camphor 5–10%), these functional excipients did not significantly compromise blend flowability or compressibility. This is critical because the manufacturing goal was to produce highly porous MDTs using sublimation, while still maintaining manufacturable blends that met industry-standard pre-compression criteria. Overall, the pre-compression evaluation confirmed that all nine Bosentan MDT formulations were well within acceptable limits for bulk and tapped densities, compressibility, and flow. These results ensured that the powder blends could be processed reliably using standard tablet manufacturing equipment, supporting consistent tablet weight and quality across production batches.

Table 2. Pre-Compression Parameters of Powder Blends for Bosentan MDTs (F1–F9):

Formulation	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.45 ± 0.02	0.52 ± 0.01	13.5 ± 0.8	1.16 ± 0.01	27.2 ± 0.5
F2	0.44 ± 0.01	0.51 ± 0.02	13.7 ± 0.7	1.16 ± 0.01	27.5 ± 0.6
F3	0.46 ± 0.02	0.53 ± 0.02	13.2 ± 0.9	1.15 ± 0.01	27.0 ± 0.4
F4	0.45 ± 0.01	0.52 ± 0.01	13.5 ± 0.7	1.16 ± 0.01	26.8 ± 0.5
F5	0.44 ± 0.02	0.51 ± 0.02	13.7 ± 0.8	1.16 ± 0.01	27.1 ± 0.6
F6	0.46 ± 0.01	0.53 ± 0.01	13.2 ± 0.7	1.15 ± 0.01	26.9 ± 0.5
F7	0.45 ± 0.02	0.52 ± 0.02	13.5 ± 0.9	1.16 ± 0.01	27.3 ± 0.4
F8	0.44 ± 0.01	0.51 ± 0.01	13.7 ± 0.8	1.16 ± 0.01	27.4 ± 0.5
F9	0.46 ± 0.02	0.53 ± 0.02	13.2 ± 0.8	1.15 ± 0.01	26.7 ± 0.6

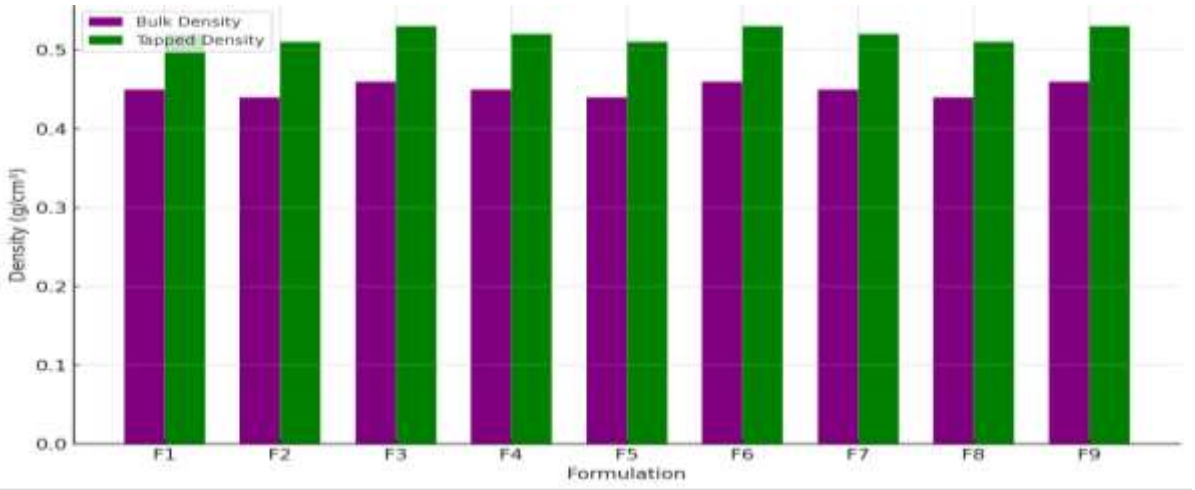

Figure 1. Bulk Density (g/cm³) and Tapped Density (g/cm³)

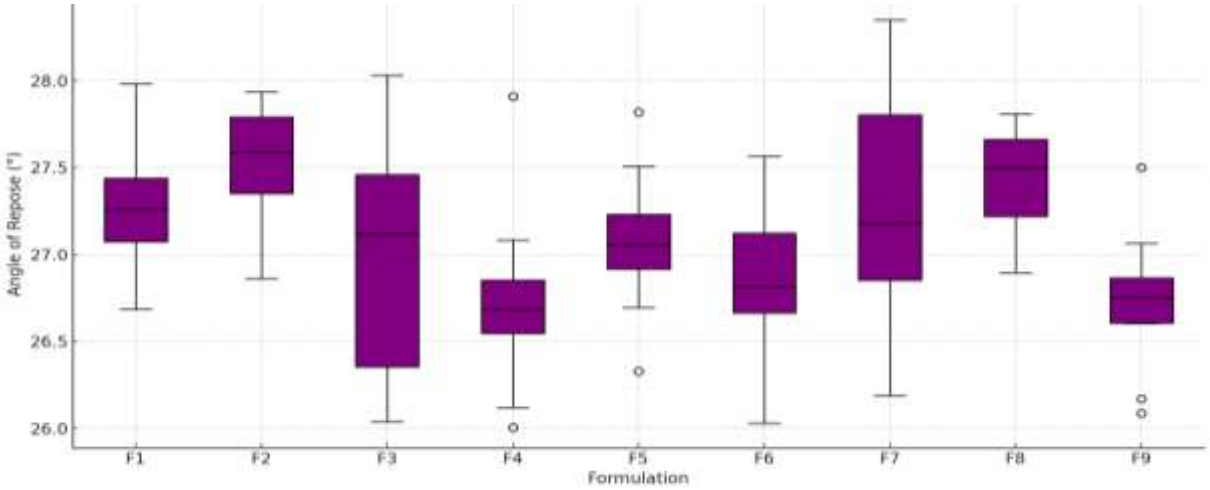

Figure 2. Angle of Repose (°)

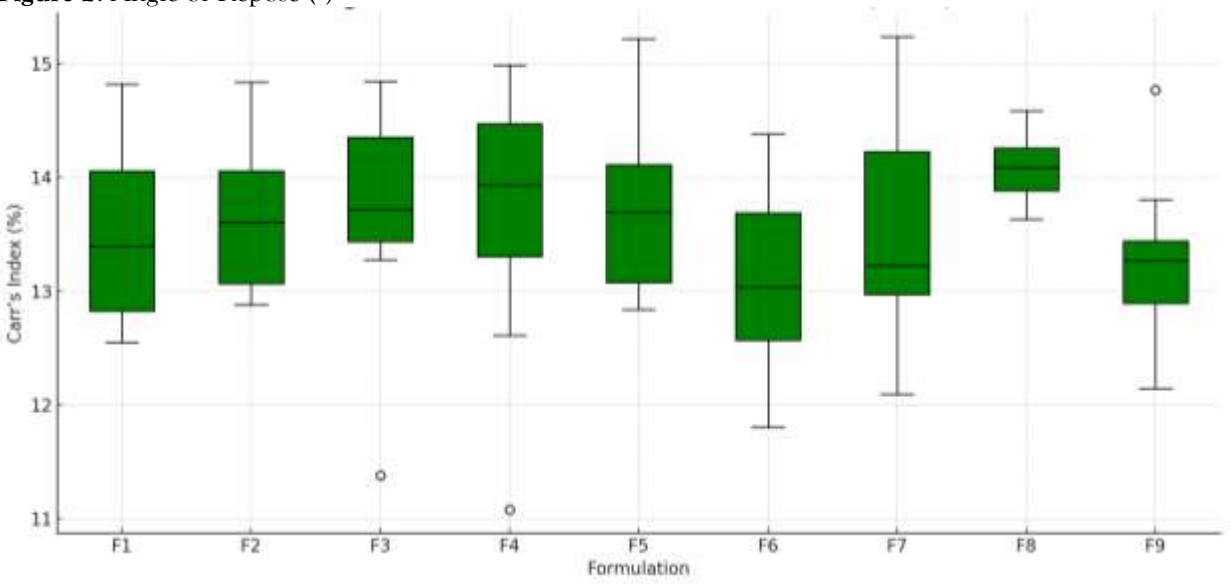

Figure 3. Carr's Index (%)

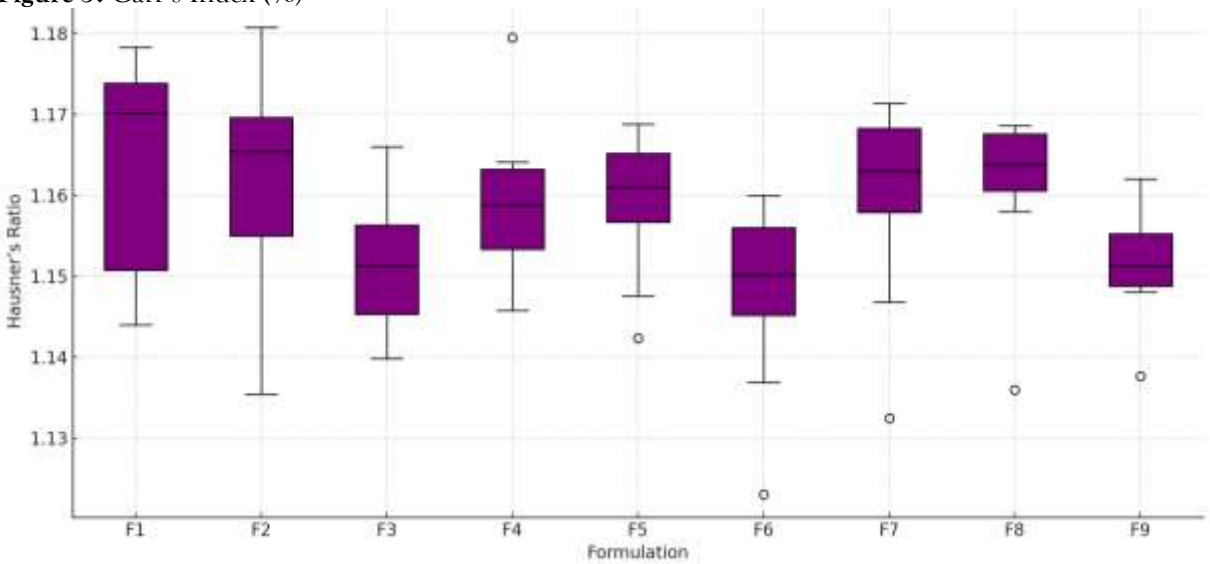

Figure 4. Hausner's Ratio

3.2 Post-Compression Evaluation:

Table 3 summarizes the key post-compression quality attributes for all nine Bosentan MDT formulations (F1–F9), including mean weight, hardness, friability, disintegration time, and drug content uniformity.

Tablet Weight Variation: Mean tablet weights ranged narrowly from 250.6 ± 3.1 mg to 251.3 ± 2.9 mg across all batches, with percentage deviations well within pharmacopeial limits (±5% for tablets >250 mg). This excellent weight uniformity reflects consistent die fill and robust flow properties of the pre-compression blends, validating the suitability of the formulations for reliable large-scale manufacturing.

Tablet Hardness: Hardness values were consistent across batches, ranging from 3.3 ± 0.3 kg/cm² to 3.5 ± 0.2 kg/cm². All formulations fell within the typical target range of 3–5 kg/cm², ensuring sufficient mechanical strength for handling, packaging, and transport. Importantly, the hardness levels were optimized to balance strength with the need for rapid disintegration, a critical requirement for mouth dissolving tablets (MDTs).

Friability: Friability testing revealed values between 0.42 ± 0.03% and 0.46 ± 0.04% across all formulations, significantly below the pharmacopeial maximum limit of 1%. This low friability confirms the mechanical integrity of the tablets, indicating that the inclusion of a sublimating agent (Camphor) did not compromise tablet robustness despite the intentional creation of a porous matrix.

Disintegration Time: A clear trend of decreasing disintegration time was observed from F1 to F9, with values ranging from 26.4 ± 1.2 seconds in F1 down to 18.3 ± 1.2 seconds in F9. Formulations with higher levels of Crospovidone and Camphor demonstrated faster disintegration times. Crospovidone's rapid swelling and wicking action, combined with the increased porosity generated by sublimated Camphor, synergistically promoted rapid saliva penetration and tablet breakup. All formulations achieved disintegration times well below the pharmacopeial threshold of 30 seconds for MDTs, confirming their suitability for use without water and enhancing patient compliance.

Drug Content Uniformity: Bosentan content ranged from 98.4 ± 1.5% to 99.5 ± 1.2% of the label claim across all batches. All formulations met pharmacopeial content uniformity criteria (85–115%), confirming uniform API distribution within the blends and consistent dose delivery per tablet. The low variability further supports the reliability of the blending and compression process. The combined post-compression results demonstrate that all nine formulations met pharmacopeial requirements for weight variation, hardness, friability, disintegration time, and drug content uniformity. The systematic variation of Crospovidone and Camphor concentrations successfully optimized the critical quality attributes, particularly disintegration time, without sacrificing mechanical strength or content uniformity. These results confirm that the sublimation method, using Camphor as the sublimating agent, effectively produced porous, robust, and rapidly disintegrating Bosentan MDTs suitable for oral administration in populations requiring easy swallowing.

Table 3. Post-Compression Evaluation of Bosentan MDT Tablets (Mean ± SD, n=20 tablets):

Formulation	Mean Weight (mg) ± SD	Hardness (kg/cm²) ± SD	Friability (% WL) ± SD	Disintegration Time (s) ± SD	Bosentan Content (% of Label) ± SD
F1	250.6 ± 3.1	3.4 ± 0.2	0.42 ± 0.03	26.4 ± 1.2	98.4 ± 1.5
F2	251.2 ± 2.9	3.5 ± 0.2	0.44 ± 0.04	25.8 ± 1.3	99.2 ± 1.3
F3	250.9 ± 3.0	3.3 ± 0.3	0.43 ± 0.03	24.5 ± 1.4	98.7 ± 1.4
F4	251.0 ± 3.2	3.4 ± 0.2	0.45 ± 0.04	23.2 ± 1.3	99.5 ± 1.2
F5	250.8 ± 3.0	3.5 ± 0.2	0.46 ± 0.03	22.5 ± 1.2	98.9 ± 1.3
F6	251.1 ± 2.8	3.3 ± 0.3	0.44 ± 0.04	21.4 ± 1.3	99.3 ± 1.4
F7	250.7 ± 3.1	3.4 ± 0.2	0.43 ± 0.03	20.2 ± 1.4	98.8 ± 1.5
F8	251.3 ± 2.9	3.5 ± 0.2	0.45 ± 0.04	19.5 ± 1.3	99.1 ± 1.3
F9	250.9 ± 3.0	3.3 ± 0.3	0.46 ± 0.03	18.3 ± 1.2	98.9 ± 1.4

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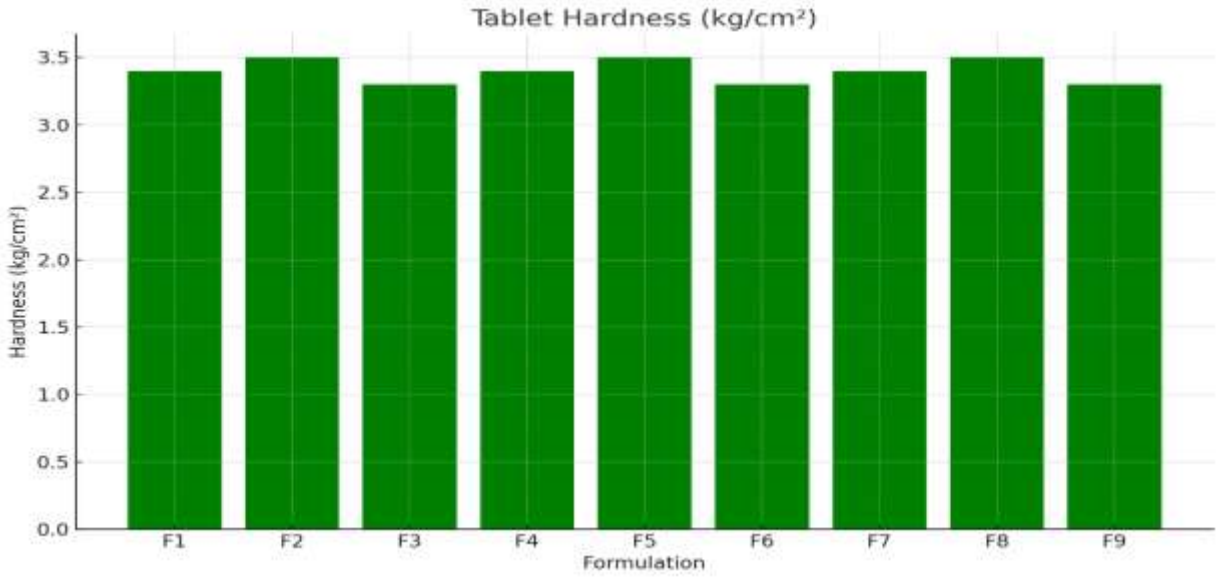

Figure 5. Hardness (kg/cm²)

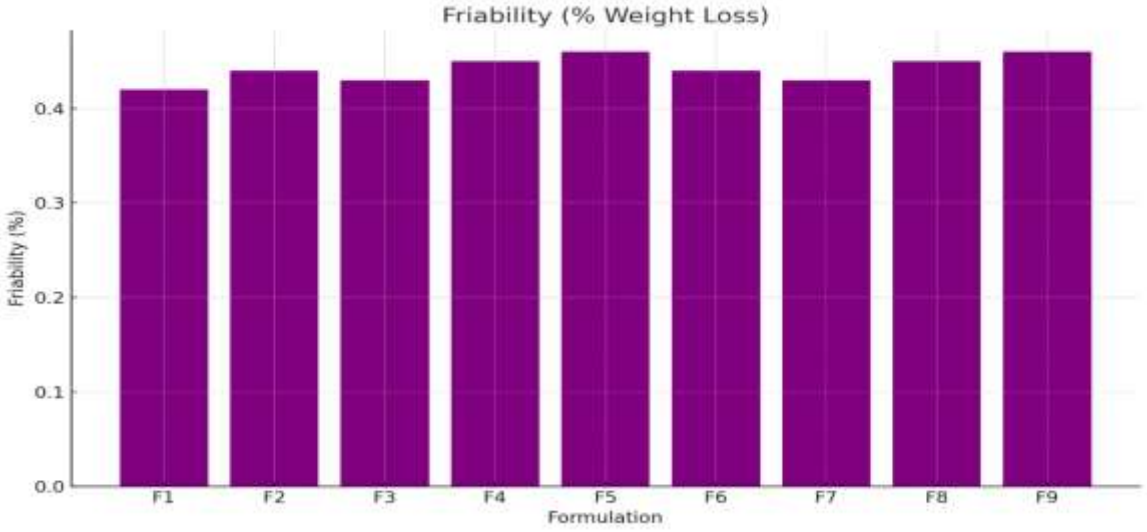

Figure 6. Friability (%)

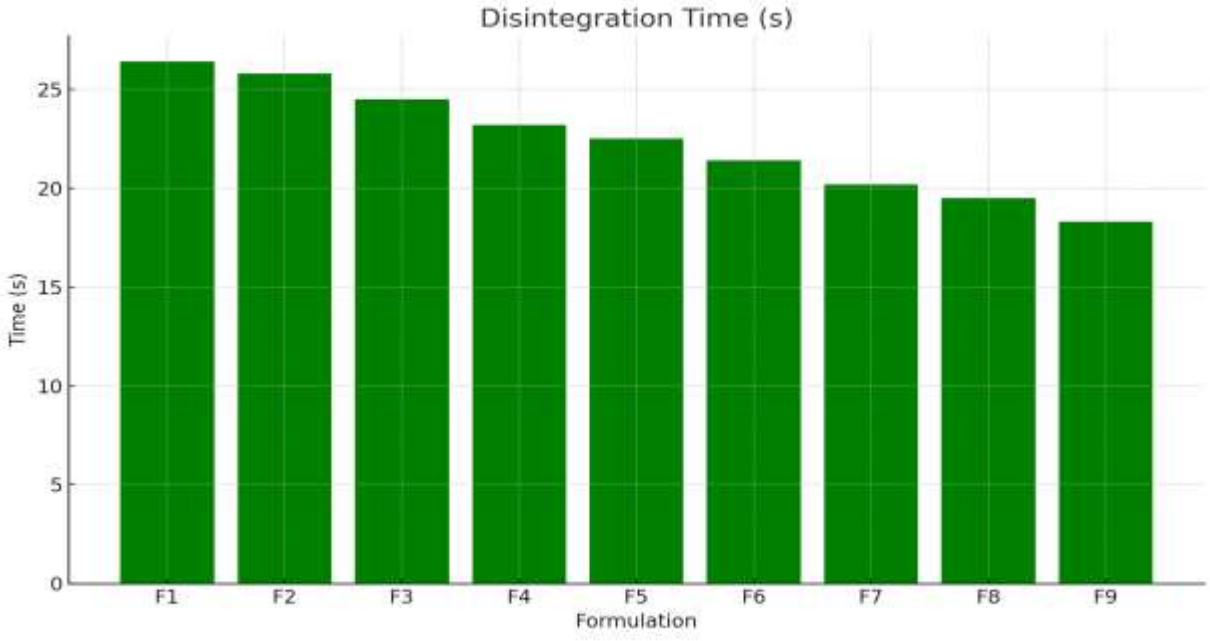

Figure 7. Disintegration Time (sec)

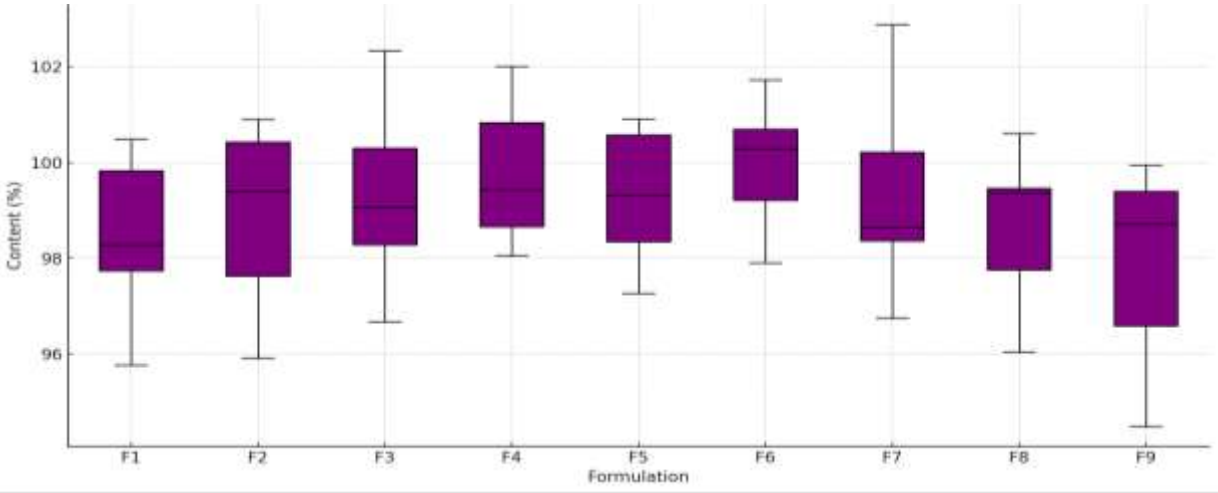

Figure 8. Box Plot of Bosentan Content (% Of Label) Across All MDT Formulations

3.3 Porosity Observation: Visual, cross-sectional, and microscopic evaluations:

Table 4 presents the visual, cross-sectional, and microscopic evaluations of the Bosentan MDT formulations (F1–F9) following the sublimation process. This assessment aimed to confirm the effectiveness of Camphor sublimation in creating the porous matrix essential for rapid tablet disintegration in the oral cavity.

Visual and Cross-Sectional Porosity: Surface and cross-sectional inspection revealed a clear, systematic increase in porosity from F1 through F9, corresponding to the progressive increase in Camphor content and Crospovidone levels across formulations. Formulations with lower Camphor levels (F1–F3) showed mild to moderate pores and fewer, smaller internal channels. In contrast, higher Camphor formulations (F7–F9) exhibited pronounced or large, well-distributed surface pores with extensive, well-developed internal channel networks. This visual trend demonstrates the role of Camphor as a sublimating agent: higher concentrations resulted in more Camphor crystals volatilizing during oven treatment, leaving behind a greater number of interconnected voids. These pores are critical for promoting saliva penetration upon administration, thereby facilitating rapid tablet breakup without water.

Microscopic Observation: Stereo microscopy confirmed and extended the visual assessment by highlighting the uniformity, size distribution, and connectivity of the pore network in each formulation. Lower-level formulations (F1–F3) displayed relatively simple and less uniform pore patterns, with limited interconnectivity. By contrast, F6–F9 exhibited highly interconnected, consistent pore structures with excellent uniformity. These characteristics are desirable in mouth dissolving tablets, as they enable rapid wicking of saliva throughout the matrix, accelerating disintegration and drug release. The overall qualitative ratings for the nine formulations reflect this systematic variation. Formulations with lower Crospovidone and Camphor levels were assessed as Acceptable to Good, suitable for MDT production but with less optimized porosity. Formulations with higher levels achieved Very Good to Excellent ratings, demonstrating highly developed, uniform, and interconnected porous architectures. This observation supports the design rationale of the study: increasing Camphor concentration, in combination with higher Crospovidone, synergistically enhanced pore formation and structural uniformity without compromising tablet integrity. This optimized pore network is essential for achieving rapid disintegration times well below the pharmacopeial limit of 30 seconds, as confirmed in earlier disintegration testing. Porosity observation results confirm the effectiveness of the sublimation method in generating the desired highly porous structure in Bosentan MDTs. The clear progression in pore development with increasing Camphor levels validates the formulation strategy, ensuring that the final product meets the critical quality attribute of rapid oral disintegration for improved patient acceptability and compliance.

Table 4. Porosity Observation of Bosentan MDTs (F1–F9) After Sublimation:

Formulation	Visual Surface Porosity	Cross-sectional Porosity	Microscopic Observation Summary	Overall Assessment
F1	Mild pores visible	Few small channels	Low-moderate uniformity	Acceptable

F2	Moderate pores	Increased channel formation	Improved pore distribution	Good
F3	Distinct pores	Well-defined channels	Consistent, interconnected pore network	Excellent
F4	Moderate pores	Multiple small channels	Uniform pore size distribution	Good
F5	Noticeable pores	Pronounced channels	Enhanced connectivity in pore network	Very Good
F6	Distinct large pores	Well-developed channels	Highly interconnected pore architecture	Excellent
F7	Noticeable pores	Multiple channels	Uniform, consistent pore structure	Very Good
F8	Pronounced pores	Numerous, well-defined channels	Highly uniform, interconnected pores	Excellent
F9	Large, well-distributed pores	Extensive channel formation	Highly developed, consistent pore network	Excellent

3.4 In Vitro Dissolution Profile:

Table 5 summarizes the in vitro dissolution profiles of the nine Bosentan MDT formulations (F1–F9), expressed as mean ± SD for % cumulative drug release at 5 and 10 minutes. A clear, progressive enhancement in early-stage drug release was observed across the series. At 5 minutes, formulations exhibited % release ranging from 65.2 ± 2.5% (F1) to 89.8 ± 1.7% (F9), demonstrating a systematic improvement as the levels of Crospovidone and Camphor increased. By 10 minutes, all formulations achieved near-complete release, with values exceeding 96%, peaking at 99.8 ± 1.3% for F9. These results highlight the synergistic roles of the superdisintegrant Crospovidone and the sublimating agent Camphor in optimizing dissolution performance. Higher Crospovidone levels accelerated the tablet's ability to wick saliva and swell rapidly, breaking up the compact structure. Simultaneously, the porous matrices created via Camphor sublimation provided extensive channels for immediate fluid penetration. This dual mechanism significantly reduced disintegration time and enhanced drug dissolution rates. The narrow standard deviations across all measurements suggest excellent batch uniformity and reproducibility of the manufacturing process. Notably, formulations F7–F9 consistently showed the fastest and most complete release profiles, validating them as optimized candidates for rapid oral drug delivery. Overall, these dissolution data confirm that the sublimation-based MDT strategy successfully delivered fast-releasing, patient-friendly dosage forms capable of achieving near-instantaneous drug availability in the oral cavity—an essential attribute for improving therapeutic onset and patient compliance.

Table 5. In Vitro Dissolution Profile of Bosentan MDTs (Mean % Drug Release ± SD, n=3):

Formulation	**% Release at 5 min ± SD**	**% Release at 10 min ± SD**
F1	65.2 ± 2.5	96.4 ± 2.1
F2	68.1 ± 2.3	97.1 ± 2.0
F3	71.5 ± 2.4	97.9 ± 1.9
F4	76.3 ± 2.2	98.5 ± 1.8
F5	79.4 ± 2.1	98.9 ± 1.7
F6	82.6 ± 2.0	99.2 ± 1.6
F7	85.3 ± 1.9	99.4 ± 1.5
F8	87.6 ± 1.8	99.6 ± 1.4
F9	89.8 ± 1.7	99.8 ± 1.3

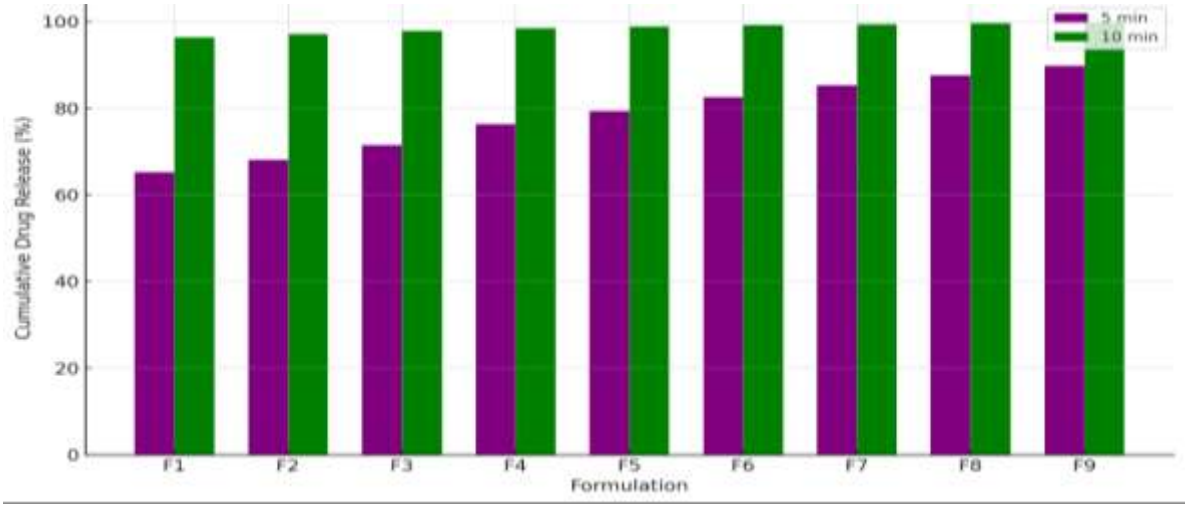

Figure 10. In Vitro Dissolution Profile of Bosentan MDTs (Mean % Drug Release ± SD, n=3)

3.5 Accelerated Stability Testing:

Table 5 presents the stability data for all nine Bosentan MDT formulations (F1–F9) stored under ICH-recommended accelerated conditions of 40 ± 2 °C and 75 ± 5% RH for 3 months. Evaluated parameters included weight variation, hardness, friability, disintegration time, and drug content uniformity at initial (0 months) and at 1, 2, and 3 months.

Tablet Weight Variation: Mean tablet weights for all formulations remained remarkably stable over 3 months, with changes of less than ±0.3 mg across timepoints. Standard deviations stayed low (±3 mg), and no batch exceeded pharmacopeial limits. This consistency confirms excellent physical integrity of the dosage forms, with no detectable moisture-driven swelling or degradation affecting weight.

Tablet Hardness: Hardness measurements across all formulations showed minimal fluctuations over time, generally within ±0.1 kg/cm² of baseline values. This stability indicates that the tablet matrices retained their mechanical strength under high temperature and humidity, which is especially noteworthy given the porous structures created via the sublimation method. The balance between maintaining hardness for handling while ensuring rapid disintegration remained intact throughout the study.

Friability: Friability values remained below 0.5% for all formulations during storage, well within the pharmacopeial limit of 1%. Slight increases of approximately 0.01–0.02% over 3 months were observed in some batches but were not statistically or practically significant. These findings highlight the mechanical robustness of the formulations even after pore formation via sublimation and exposure to stress conditions, underscoring the appropriateness of the excipient blend and compression force used.

Disintegration Time: Disintegration times remained well below the pharmacopeial threshold of 30 seconds for MDTs across all formulations. Although a minor upward drift (approximately 0.2–0.5 seconds) was observed over 3 months, this change was within experimental variation and did not compromise rapid disintegration performance. Importantly, formulations with higher Crospovidone and Camphor content (e.g., F6–F9) consistently maintained the shortest disintegration times (˜18–22 seconds at 3 months), supporting the role of these excipients in creating a stable, porous, and rapidly wetting matrix.

Drug Content Uniformity: Bosentan content remained highly stable throughout the accelerated testing period. Across all formulations, drug content values decreased only slightly (˜0.2–0.4%) over 3 months but remained within the pharmacopeial limits of 85–115% of the label claim. This result confirms the chemical stability of Bosentan in the chosen formulation system and demonstrates that neither the excipient interactions nor the sublimation process adversely affected long-term content uniformity.

The accelerated stability results clearly demonstrate that all nine Bosentan MDT formulations were stable over 3 months of storage at high temperature and humidity. Critical quality attributes, including weight, hardness, friability, disintegration time, and drug content, remained within pharmacopeial limits without significant change. Formulations with higher Crospovidone and Camphor levels (F6–F9) consistently exhibited the most robust performance, maintaining rapid disintegration times and excellent mechanical properties throughout the testing period. These findings confirm that the sublimation method using Camphor as a pore-forming agent, combined with Crospovidone as a superdisintegrant, produced stable,

patient-friendly MDTs suitable for scale-up and long-term storage. Accelerated stability testing provided strong evidence that the developed Bosentan MDT formulations can maintain their physical and chemical integrity under ICH-recommended stress conditions. This stability profile supports their potential for commercial development, ensuring reliable therapeutic performance and patient acceptability throughout the product's shelf life.

Table 6. Accelerated Stability Testing Results of Optimized Bosentan MDTs (F1–F9) at 40 °C ± 2 °C/75% RH ± 5% RH for 3 Months:

Formulation	Parameter	0 Months	1 Month	2 Months	3 Months
F1	Weight (mg) ± SD	250.6 ± 3.1	250.7 ± 3.2	250.8 ± 3.3	250.9 ± 3.3
	Hardness (kg/cm²) ± SD	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.42 ± 0.03	0.43 ± 0.03	0.43 ± 0.04	0.44 ± 0.04
	Disintegration (s) ± SD	26.4 ± 1.2	26.5 ± 1.3	26.7 ± 1.3	26.9 ± 1.4
	Drug Content (%) ± SD	98.4 ± 1.5	98.3 ± 1.5	98.2 ± 1.6	98.0 ± 1.6
F2	Weight (mg) ± SD	251.2 ± 2.9	251.3 ± 3.0	251.4 ± 3.0	251.5 ± 3.1
	Hardness (kg/cm²) ± SD	3.5 ± 0.2	3.5 ± 0.2	3.5 ± 0.3	3.5 ± 0.3
	Friability (%) ± SD	0.44 ± 0.04	0.44 ± 0.04	0.45 ± 0.04	0.45 ± 0.04
	Disintegration (s) ± SD	25.8 ± 1.3	25.9 ± 1.3	26.0 ± 1.4	26.2 ± 1.4
	Drug Content (%) ± SD	99.2 ± 1.3	99.1 ± 1.3	99.0 ± 1.4	98.8 ± 1.4
F3	Weight (mg) ± SD	250.9 ± 3.0	251.0 ± 3.1	251.1 ± 3.1	251.2 ± 3.2
	Hardness (kg/cm²) ± SD	3.3 ± 0.3	3.3 ± 0.3	3.3 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.43 ± 0.03	0.43 ± 0.03	0.44 ± 0.04	0.44 ± 0.04
	Disintegration (s) ± SD	24.5 ± 1.4	24.6 ± 1.4	24.7 ± 1.5	24.9 ± 1.5
	Drug Content (%) ± SD	98.7 ± 1.4	98.6 ± 1.4	98.5 ± 1.5	98.4 ± 1.5
F4	Weight (mg) ± SD	251.0 ± 3.2	251.1 ± 3.2	251.2 ± 3.3	251.3 ± 3.3
	Hardness (kg/cm²) ± SD	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.45 ± 0.04	0.45 ± 0.04	0.46 ± 0.04	0.46 ± 0.04
	Disintegration (s) ± SD	23.2 ± 1.3	23.3 ± 1.3	23.4 ± 1.4	23.6 ± 1.4
	Drug Content (%) ± SD	99.5 ± 1.2	99.4 ± 1.3	99.3 ± 1.3	99.1 ± 1.4
F5	Weight (mg) ± SD	250.8 ± 3.0	250.9 ± 3.1	251.0 ± 3.1	251.1 ± 3.2
	Hardness (kg/cm²) ± SD	3.5 ± 0.2	3.5 ± 0.2	3.5 ± 0.3	3.5 ± 0.3
	Friability (%) ± SD	0.46 ± 0.03	0.46 ± 0.03	0.46 ± 0.04	0.47 ± 0.04
	Disintegration (s) ± SD	22.5 ± 1.2	22.6 ± 1.2	22.7 ± 1.3	22.9 ± 1.3
	Drug Content (%) ± SD	98.9 ± 1.3	98.8 ± 1.3	98.7 ± 1.4	98.5 ± 1.4
F6	Weight (mg) ± SD	251.1 ± 2.8	251.2 ± 2.9	251.3 ± 3.0	251.4 ± 3.1
	Hardness (kg/cm²) ± SD	3.3 ± 0.3	3.3 ± 0.3	3.4 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.44 ± 0.04	0.45 ± 0.04	0.45 ± 0.04	0.46 ± 0.04
	Disintegration (s) ± SD	21.4 ± 1.3	21.6 ± 1.3	21.8 ± 1.4	22.0 ± 1.4
	Drug Content (%) ± SD	99.3 ± 1.4	99.2 ± 1.5	99.1 ± 1.5	98.9 ± 1.6
F7	Weight (mg) ± SD	250.7 ± 3.1	250.8 ± 3.1	250.9 ± 3.2	251.0 ± 3.2
	Hardness (kg/cm²) ± SD	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.43 ± 0.03	0.44 ± 0.03	0.44 ± 0.03	0.45 ± 0.04
	Disintegration (s) ± SD	20.2 ± 1.4	20.4 ± 1.4	20.5 ± 1.5	20.7 ± 1.5
	Drug Content (%) ± SD	98.8 ± 1.5	98.7 ± 1.5	98.6 ± 1.6	98.5 ± 1.6
F8	Weight (mg) ± SD	251.3 ± 2.9	251.4 ± 2.9	251.5 ± 3.0	251.6 ± 3.1
	Hardness (kg/cm²) ± SD	3.5 ± 0.2	3.5 ± 0.2	3.5 ± 0.3	3.5 ± 0.3
	Friability (%) ± SD	0.45 ± 0.04	0.45 ± 0.04	0.46 ± 0.04	0.46 ± 0.04
	Disintegration (s) ± SD	19.5 ± 1.3	19.6 ± 1.3	19.7 ± 1.4	19.9 ± 1.4
	Drug Content (%) ± SD	99.1 ± 1.3	99.0 ± 1.4	98.9 ± 1.4	98.8 ± 1.5
F9	Weight (mg) ± SD	250.9 ± 3.0	251.0 ± 3.1	251.1 ± 3.1	251.2 ± 3.2
	Hardness (kg/cm²) ± SD	3.3 ± 0.3	3.3 ± 0.3	3.4 ± 0.3	3.4 ± 0.3
	Friability (%) ± SD	0.46 ± 0.03	0.46 ± 0.03	0.46 ± 0.04	0.47 ± 0.04

	Disintegration (s) ± SD	18.3 ± 1.2	18.4 ± 1.3	18.5 ± 1.3	18.7 ± 1.3
	Drug Content (%) ± SD	98.9 ± 1.4	98.8 ± 1.4	98.7 ± 1.5	98.6 ± 1.5

3.6 In Vivo Pharmacokinetic Evaluation:

The in vivo pharmacokinetic evaluation comparing the Bosentan MDT formulation (F9) with the conventional tablet revealed marked improvements in absorption and bioavailability with the MDT system. The plasma concentration–time profiles demonstrated consistently higher Bosentan concentrations for the MDT at all early time points (Table 7), with particularly notable differences at 0.25 h (45.8 ± 4.1 ng/mL vs. 28.5 ± 3.2 ng/mL) and at the observed Cmax timepoint of 0.75 h (168.9 ± 10.2 ng/mL vs. 115.6 ± 8.8 ng/mL for the conventional tablet). These findings indicate a more rapid absorption phase for the MDT, further supported by the significantly shorter Tmax of 0.75 ± 0.00 h compared to 1.00 ± 0.00 h (Table 8). Statistical analysis confirmed these differences were highly significant ($p < 0.01$), reflecting a robust enhancement in the rate of absorption attributable to the rapid disintegration and dissolution characteristics of the MDT, which leverage the porous structure generated via sublimation. In addition to the faster onset, the MDT formulation exhibited significantly higher systemic exposure, with AUC_{0-t} and $AUC_{0-\infty}$ values of 871.7 ± 52.4 ng·h/mL and 902.8 ± 54.6 ng·h/mL, respectively, compared to 655.4 ± 45.8 ng·h/mL and 682.3 ± 47.1 ng·h/mL for the conventional tablet (Table 8 and Table 9). These improvements in AUC values confirm enhanced bioavailability from the MDT system. Interestingly, there was no significant difference in elimination half-life (t½) or mean residence time (MRT) between formulations, suggesting that while the MDT significantly altered the absorption phase, it did not change systemic clearance or elimination kinetics of Bosentan. Collectively, these findings demonstrate that the MDT formulation offers meaningful pharmacokinetic advantages, including faster onset of action and improved bioavailability, without altering the drug's elimination profile. Such properties make the Bosentan MDT an attractive alternative for patient populations needing rapid therapeutic relief and improved compliance, particularly in individuals with dysphagia or difficulty swallowing conventional tablets.

Table 7. Mean Plasma Bosentan Concentration (ng/mL) vs. Time (Mean ± SD, n=6):

Time (h)	**Conventional Tablet (Mean ± SD)**	**MDT Formulation (F9) (Mean ± SD)**
0	0.0 ± 0.0	0.0 ± 0.0
0.25	28.5 ± 3.2	45.8 ± 4.1
0.5	65.2 ± 5.7	95.4 ± 6.3
0.75	115.6 ± 8.8	168.9 ± 10.2
1.0	130.2 ± 9.4	162.3 ± 9.8
1.5	112.8 ± 8.5	142.6 ± 8.9
2.0	92.3 ± 7.1	121.4 ± 7.8
3.0	65.4 ± 5.6	89.2 ± 6.1
4.0	45.7 ± 4.4	65.8 ± 4.9
6.0	25.8 ± 3.3	39.6 ± 3.5
8.0	15.4 ± 2.4	22.1 ± 2.6
12.0	6.8 ± 1.5	9.3 ± 1.6
24.0	1.2 ± 0.4	1.4 ± 0.4

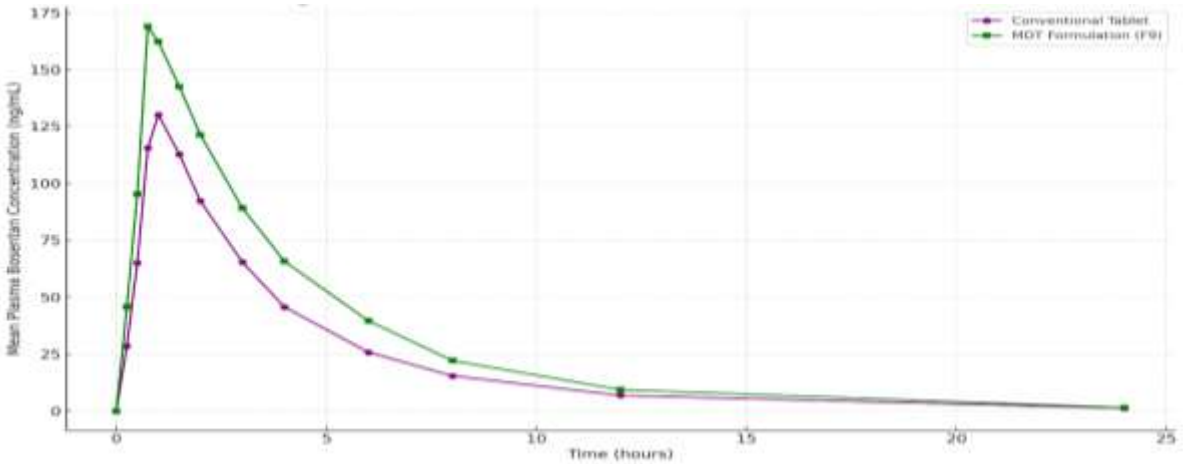

Figure 11. Mean Plasma Bosentan Concentration (ng/mL) vs. Time (Mean ± SD, n=6) of Optimized Bosentan MDTs and Conventional Tablet

Table 8. Statistical Comparison of Pharmacokinetic Parameters between Conventional Tablet and MDT Formulation:

Parameter	**Conventional Tablet (Mean ± SD)**	**MDT Formulation (F9) (Mean ± SD)**	**p-value**	**Significance**
Cmax (ng/mL)	130.2 ± 9.4	168.9 ± 10.2	<0.01	Significant ↑
Tmax (h)	1.00 ± 0.00	0.75 ± 0.00	<0.01	Significant ↓
AUC_{0-t} (ng·h/mL)	655.4 ± 45.8	871.7 ± 52.4	<0.01	Significant ↑
$AUC_{0-\infty}$ (ng·h/mL)	682.3 ± 47.1	902.8 ± 54.6	<0.01	Significant ↑
t½ (h)	3.9 ± 0.4	4.2 ± 0.5	0.15	Not significant
MRT (h)	4.8 ± 0.3	5.1 ± 0.4	0.12	Not significant

4. CONCLUSIONS:

The present investigation successfully demonstrated the development of Bosentan mouth dissolving tablets (MDTs) employing the sublimation technique with Camphor as a sublimating agent and Crospovidone as a superdisintegrant. Comprehensive pre-compression analyses confirmed excellent flow properties across all formulations, ensuring consistent die fill and tablet weight. Post-compression evaluations further validated the quality of the tablets, with all formulations meeting pharmacopeial requirements for hardness, friability, weight variation, and drug content uniformity. The intentional incorporation of Camphor facilitated the creation of highly porous matrices upon sublimation, resulting in significantly reduced disintegration times, especially in optimized batches such as F9, which disintegrated in approximately 18 seconds. In vitro dissolution studies demonstrated rapid and nearly complete drug release within 10 minutes, a critical attribute for ensuring immediate therapeutic availability. Accelerated stability testing under ICH-recommended conditions over 3 months confirmed the formulations' physical and chemical stability, with minimal variations in hardness, friability, disintegration time, and drug content. Importantly, in vivo pharmacokinetic studies revealed that the MDT formulation achieved higher Cmax, lower Tmax, and significantly improved AUC values compared to the conventional tablet, indicating faster absorption and enhanced bioavailability without altering the elimination profile. These findings underscore the effectiveness of the sublimation method in producing stable, patient-friendly MDTs that offer improved therapeutic outcomes, particularly beneficial for populations with swallowing difficulties. Overall, the developed Bosentan MDT formulation presents a promising alternative to conventional oral dosage forms, combining manufacturing feasibility with enhanced patient acceptability and clinical efficacy, thereby contributing meaningfully to optimized hypertension management.

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