Dissolution Enhancement and Physicochemical Characterization of Bosentan Mouth-Dissolving Tablets Incorporating Croscarmellose Sodium and Crospovidone as Superdisintegrants

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Abstract
Bosentan is a dual endothelin receptor antagonist widely used in the treatment of pulmonary arterial hypertension. However, its poor aqueous solubility can limit dissolution and delay drug release, potentially affecting therapeutic performance. The present study aimed to develop mouth-dissolving tablets (MDTs) of Bosentan and evaluate the influence of croscarmellose sodium (CCS) and crospovidone (CP) as superdisintegrants on tablet disintegration and dissolution enhancement. Bosentan MDTs were prepared by direct compression using varying concentrations (2–8%) of CCS and CP. Preformulation studies including solubility analysis, melting point determination, UV spectroscopy, and FTIR compatibility assessment were performed. The prepared formulations were evaluated for pre-compression and post-compression parameters, wetting time, water absorption ratio, dispersion time, disintegration time, and in vitro dissolution behaviour. The optimized formulation was further characterized using FTIR, DSC, SEM, drug release kinetic modelling, and accelerated stability studies. All formulations complied with pharmacopeial quality requirements. Increasing superdisintegrant concentration significantly improved wetting, disintegration, and dissolution characteristics. Formulation F8 containing 8% crospovidone exhibited the shortest disintegration time (25 ± 1 s), highest water absorption ratio (130 ± 6%), and maximum drug release (99.8 ± 0.4%) within 30 min. FTIR and DSC studies confirmed drug–excipient compatibility, while SEM revealed a porous structure conducive to rapid hydration. Stability studies demonstrated satisfactory formulation stability over three months. Crospovidone was more effective than croscarmellose sodium in enhancing the performance of Bosentan MDTs. The optimized formulation showed rapid disintegration, improved dissolution, and excellent stability, indicating its potential as a patient-friendly oral dosage form.

keywords: Bosentan; Mouth-dissolving tablets; Crospovidone; Croscarmellose sodium; Superdisintegrants; Dissolution enhancement; Direct compression.

1. Introduction

Oral drug delivery remains the most widely accepted and preferred route of drug administration owing to its convenience, patient compliance, cost-effectiveness, and ease of manufacturing. Conventional tablets and capsules account for a major proportion of marketed pharmaceutical products; however, these dosage forms may present swallowing difficulties for paediatric, geriatric, and dysphagic patients. Such limitations can compromise medication adherence and therapeutic outcomes (Ab'lah *et al.*, 2023; Aldosari *et al.*, 2024). To overcome these challenges, mouth-dissolving tablets (MDTs), also known as orally disintegrating tablets, have emerged as an attractive alternative oral dosage form. MDTs are designed to disintegrate rapidly in the oral cavity without the need for water, resulting in improved patient convenience, faster drug dissolution, and enhanced compliance (Chandira *et al.*, 2010; Dangi & Zalodiya, 2012; Iqbal *et al.*, 2020).

The performance of mouth-dissolving tablets is largely dependent on their ability to rapidly absorb saliva and disintegrate into fine particles. This objective is commonly achieved through the incorporation of superdisintegrants, which facilitate rapid tablet break-up upon contact with aqueous media. Superdisintegrants

promote disintegration through mechanisms such as swelling, capillary action (wicking), strain recovery, and deformation recovery. Among the various superdisintegrants available, croscarmellose sodium and crospovidone are widely employed due to their excellent efficiency, low concentration requirements, and compatibility with direct compression techniques. Croscarmellose sodium primarily acts through rapid swelling, whereas crospovidone promotes disintegration predominantly through capillary action and rapid water uptake. Comparative evaluation of these superdisintegrants can provide valuable insights for optimizing MDT formulations (Chakraborty & Saini, 2014; Dangi & Zalodiya, 2012; Jana *et al.*, 2024; Madgulkar *et al.*, 2009).

Bosentan is a dual endothelin receptor antagonist used in the management of pulmonary arterial hypertension (PAH), a progressive disorder characterized by elevated pulmonary arterial pressure, vascular remodelling, and right ventricular dysfunction. Bosentan exerts its pharmacological action by competitively blocking endothelin-A and endothelin-B receptors, thereby reducing vasoconstriction and inhibiting pathological vascular proliferation. The drug has demonstrated significant clinical benefits in improving exercise capacity, delaying disease progression, and enhancing quality of life in patients suffering from pulmonary arterial hypertension (Abd-Elsalam, 2011; Abd El Rahman *et al.*, 2014; "Bosentan (Tracleer) for pulmonary arterial hypertension," 2002; "Bosentan. RO 470203," 1999).

Despite its therapeutic efficacy, Bosentan possesses poor aqueous solubility, which can adversely affect its dissolution behavior and potentially limit its absorption. For poorly water-soluble drugs, dissolution is often the rate-limiting step governing oral bioavailability. Consequently, strategies aimed at enhancing dissolution are of considerable pharmaceutical importance. Formulation approaches that improve tablet disintegration and increase the effective surface area available for dissolution can significantly enhance drug release performance. In this regard, mouth-dissolving tablet technology offers a promising platform for improving the dissolution characteristics of Bosentan while simultaneously providing a patient-friendly dosage form (Akamata *et al.*, 2014; Al-Badr *et al.*, 2025; Albertini *et al.*, 2001; Antoniu, 2008).

Direct compression is one of the most widely used manufacturing methods for MDTs because of its simplicity, cost-effectiveness, minimal processing requirements, and suitability for large-scale production. The successful development of MDTs by direct compression depends on the careful selection and optimization of excipients, particularly superdisintegrants. The type and concentration of superdisintegrant can markedly influence wetting behaviour, water absorption, disintegration time, and ultimately drug dissolution.

Although extensive research has been conducted on mouth-dissolving tablet formulations for various poorly soluble drugs, limited information is available regarding the development of Bosentan MDTs employing different superdisintegrants. Furthermore, comparative investigations evaluating the influence of croscarmellose sodium and crospovidone on the dissolution enhancement of Bosentan remain scarce. Therefore, the present study was undertaken to formulate Bosentan mouth-dissolving tablets using direct compression and to investigate the effects of croscarmellose sodium and crospovidone at different concentrations on tablet performance. The prepared formulations were evaluated for physicochemical properties, wetting characteristics, disintegration behaviour, dissolution enhancement, and stability, with the objective of identifying an optimized formulation capable of providing rapid drug release and improved patient acceptability.

2. Material And Methods

2.1 Materials

Bosentan was obtained as a gift sample from Sun Pharmaceutical Industries Ltd.. Croscarmellose sodium, crospovidone, and microcrystalline cellulose PH102 were procured from Colorcon Asia Pvt. Ltd.. Mannitol, magnesium stearate, talc, aspartame, and peppermint flavor were of pharmaceutical grade and used as received without further purification. Potassium dihydrogen phosphate, sodium hydroxide, methanol, and other analytical-grade reagents used during the study were procured from Merck Life Science Pvt. Ltd.. Distilled water was prepared freshly in the laboratory and used throughout the investigation.

2.2 Methods

2.2.1 Preformulation Studies

Preformulation studies were carried out to determine the physicochemical properties of Bosentan and to evaluate its compatibility with selected excipients used in the formulation of mouth-dissolving tablets (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.1.1 Organoleptic Evaluation

Bosentan was examined visually for its color, appearance, odor, and physical nature. The drug sample was inspected under normal daylight conditions to determine its organoleptic characteristics (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.1.2 Determination of Melting Point

The melting point of Bosentan was determined by capillary fusion method using a digital melting point apparatus. A small quantity of drug was filled into a sealed capillary tube and heated gradually. The temperature at which the drug started melting and completely liquefied was recorded.

2.2.1.3 Solubility Analysis

The solubility of Bosentan was determined in distilled water, methanol, ethanol, phosphate buffer pH 6.8, and 0.1 N hydrochloric acid. Excess quantity of drug was added to 10 mL of each solvent in stoppered vials and shaken using a mechanical shaker for 24 hours at room temperature. The samples were filtered through Whatman filter paper, suitably diluted, and analyzed spectrophotometrically.

2.2.1.4 Determination of λmax of Bosentan

A standard stock solution of Bosentan was prepared in methanol and further diluted with phosphate buffer pH 6.8. The prepared solution was scanned between 200–400 nm using a UV-visible spectrophotometer to determine the wavelength of maximum absorption (λmax).

2.2.1.5 Preparation of Calibration Curve

A calibration curve of Bosentan was prepared in phosphate buffer pH 6.8. Accurately weighed quantity of Bosentan was dissolved in methanol to prepare a stock solution. Appropriate dilutions were prepared to obtain concentrations ranging from 2–12 µg/mL. The absorbance of each dilution was measured at the predetermined λmax using phosphate buffer pH 6.8 as blank. The calibration curve was constructed by plotting concentration versus absorbance.

2.2.1.6 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed to evaluate possible drug–excipient interactions. Infrared spectra of pure Bosentan, croscarmellose sodium, crospovidone, and optimized formulation were recorded using FTIR spectrophotometer by potassium bromide pellet method. The samples were scanned over a range of 4000–400 cm^{-1}, and characteristic peaks were analyzed for compatibility assessment.

2.2.2 Formulation of Bosentan Mouth-Dissolving Tablets

Bosentan mouth-dissolving tablets were prepared by direct compression method using croscarmellose sodium and crospovidone as superdisintegrants at varying concentrations. A total of eight formulations were designed. Formulations F1–F4 contained croscarmellose sodium at concentrations of 2%, 4%, 6%, and 8%, respectively, whereas formulations F5–F8 contained crospovidone at similar concentrations. Mannitol was incorporated as a diluent and mouthfeel enhancer, while microcrystalline cellulose PH102 was used to improve compressibility. Aspartame and peppermint flavour were added to improve palatability. Talc and magnesium stearate were incorporated as glidant and lubricant, respectively. All ingredients except magnesium stearate and talc were accurately weighed, passed through sieve no. 60, and blended uniformly in a mortar. Finally, talc and magnesium stearate were added and mixed gently for 3–5 minutes to avoid over-lubrication. The prepared powder blend was compressed using a rotary tablet compression machine fitted with flat-faced punches to obtain tablets of 250 mg weight (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.3 Composition of Bosentan Mouth-Dissolving Tablet Formulations

Table 1. Composition of Bosentan Mouth-Dissolving Tablets Incorporating Croscarmellose Sodium and Crospovidone

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Croscarmellose Sodium	5	10	15	20	–	–	–	–
Crospovidone	–	–	–	–	5	10	15	20
Mannitol	120	115	110	105	120	115	110	105
MCC PH102	55	55	55	55	55	55	55	55
Aspartame	3	3	3	3	3	3	3	3
Peppermint Flavor	2	2	2	2	2	2	2	2
Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium Stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total Weight (mg)	250	250	250	250	250	250	250	250

2.2.4 Evaluation of Powder Blend

Prior to compression, all powder blends were evaluated for their flow and compressibility characteristics to ensure suitability for direct compression (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.4.1 Angle of Repose

The angle of repose was determined by the fixed funnel method. The powder blend was allowed to flow through a funnel positioned at a fixed height onto a horizontal surface, forming a conical heap. The height (h) and radius (r) of the heap were measured and the angle of repose was calculated using:

$$\tan\theta = \frac{h}{r}$$

where θ represents the angle of repose.

2.2.4.2 Bulk Density

Accurately weighed powder blend was transferred into a graduated measuring cylinder and the apparent volume occupied by the powder was recorded. Bulk density was calculated using the following equation:

$$\rho_b = \frac{M}{V_b}$$

where M is the mass of powder and Vb is the bulk volume.

2.2.4.3 Tapped Density

The graduated cylinder containing the powder blend was subjected to 100 taps using a tapped density tester until constant volume was obtained. Tapped density was calculated using:

$$\rho_t = \frac{M}{V_t}$$

where Vt represents tapped volume.

2.2.4.4 Carr's Compressibility Index

Carr's Index was calculated to evaluate compressibility characteristics of powder blends.

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

2.2.4.5 Hausner Ratio

Hausner ratio was determined as an indicator of powder flowability.

$$HR = \frac{\rho_t}{\rho_b}$$

Powder blends exhibiting Carr's Index below 20% and Hausner ratio below 1.25 were considered suitable for direct compression.

2.2.5 Evaluation of Bosentan Mouth-Dissolving Tablets

Following compression, all formulations were subjected to post-compression quality control evaluation (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.5.1 Weight Variation

Twenty tablets from each batch were selected randomly and weighed individually using an analytical balance. The average tablet weight was calculated and compared with individual tablet weights. Percentage deviation was calculated according to pharmacopeial requirements.

2.2.5.2 Thickness Measurement

The thickness of ten tablets from each formulation was measured using a digital Vernier caliper. Mean values and standard deviations were calculated.

2.2.5.3 Hardness Test

Tablet crushing strength was determined using a Monsanto hardness tester. Ten tablets from each formulation were tested individually and the mean hardness value was recorded in kg/cm².

2.2.5.4 Friability Test

Friability was determined using a Roche friabilator. Pre-weighed tablets were rotated at 25 rpm for 4 minutes (100 revolutions). Tablets were dedusted and reweighed. Percentage friability was calculated using:

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

where:

- W_1 = Initial weight
- W_2 = Final weight

A friability value below 1% was considered acceptable.

2.2.5.5 Drug Content Uniformity

Ten tablets were powdered and an amount equivalent to 62.5 mg Bosentan was transferred into a volumetric flask containing methanol. The solution was sonicated, filtered, diluted appropriately, and analyzed using UV-visible spectrophotometry at the selected wavelength. Drug content was calculated against the calibration curve (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013)

2.2.5.6 Wetting Time

A circular tissue paper was placed in a Petri dish containing 6 mL distilled water. A tablet was carefully placed on the wetted paper and the time required for complete wetting of the tablet surface was recorded.

2.2.5.7 Water Absorption Ratio

The wetted tablet was weighed before and after complete wetting. Water absorption ratio was calculated using:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

where:

- Wa = Weight after water absorption
- Wb = Initial tablet weight

2.2.5.8 In Vitro Dispersion Time

A tablet was placed in a beaker containing 10 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. The time required for complete dispersion was recorded (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013)

2.2.5.9 Disintegration Time

Disintegration testing was performed using a USP disintegration apparatus containing phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. Six tablets from each formulation were evaluated and the average disintegration time was reported (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013)

2.2.5.10 In Vitro Dissolution Study

Dissolution studies were performed using USP Dissolution Apparatus Type II (Paddle Method)(S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013)

Table 2. Dissolution Study Conditions

Parameter	Condition
Apparatus	USP Type II
Dissolution medium	Phosphate buffer pH 6.8
Volume	900 mL

Temperature	37 ± 0.5°C
Paddle speed	50 rpm
Sampling intervals	5, 10, 15, 20, 30 min
Analysis wavelength	Determined λmax
Sample volume withdrawn	5 mL

At predetermined intervals, samples were withdrawn and replaced with fresh dissolution medium maintained at the same temperature. The samples were filtered, diluted where necessary, and analyzed spectrophotometrically.

2.2.6 Optimization of Formulation

The optimized formulation was selected based on:

- Lowest disintegration time
- Lowest wetting time
- Highest water absorption ratio
- Maximum drug release within 30 minutes
- Acceptable mechanical strength
- Drug content within pharmacopeial limits

The formulation demonstrating the best overall performance was selected for advanced physicochemical characterization.

2.2.7 Advanced Physicochemical Characterization of Optimized Formulation

The optimized Bosentan MDT formulation was subjected to detailed characterization studies to confirm compatibility, solid-state behaviour, and surface morphology. The following analyses were performed:

1. Fourier Transform Infrared Spectroscopy (FTIR)
2. Differential Scanning Calorimetry (DSC)
3. Drug Release Kinetic Modelling

2.2.7.1 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to investigate the thermal behaviour of Bosentan and to assess any possible interaction between the drug and formulation excipients in the optimized mouth-dissolving tablet formulation. Approximately 5–10 mg of pure Bosentan and optimized formulation powder were accurately weighed and sealed in standard aluminium pans. An empty sealed aluminium pan was used as the reference. The samples were heated over a temperature range of 30–300°C at a heating rate of 10°C/min under a nitrogen atmosphere. Thermograms obtained for the pure drug and optimized formulation were compared for any significant shift, disappearance, or appearance of thermal transitions. The presence of the characteristic melting endotherm of Bosentan in the optimized formulation was considered indicative of drug stability and compatibility with formulation excipients.

2.2.8 Drug Release Kinetic Modelling

To understand the mechanism of Bosentan release from the optimized mouth-dissolving tablet formulation, dissolution data obtained from the optimized batch were fitted into various mathematical kinetic models. The release data were analyzed using (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013):

2.2.8.1 Zero-Order Model

The zero-order model describes a system where drug release occurs at a constant rate independent of drug concentration.

$$Q_t = Q_0 + k_0 t$$

where:

- Qt = amount of drug released at time t
- Q0 = initial amount of drug
- k0 = zero-order release constant

A plot of cumulative percentage drug released versus time was constructed.

2.2.8.2 First-Order Model

The first-order model assumes that drug release is concentration dependent.

$$\log Q_t = \log Q_0 - \frac{k_1 t}{2.303}$$

where:

- Q0 = initial drug amount
- Qt = drug remaining at time t
- k1 = first-order release constant

A plot of logarithm of percentage drug remaining versus time was prepared.

2.2.8.3 Higuchi Diffusion Model

The Higuchi model describes drug release through diffusion mechanisms.

$$Q = k_H \sqrt{t}$$

where:

- Q = amount of drug released
- kH = Higuchi dissolution constant

A graph of cumulative percentage drug released versus square root of time was constructed.

2.2.8.4 Korsmeyer–Peppas Model

The Korsmeyer–Peppas equation was applied to determine the release mechanism from the optimized formulation.

$$\frac{M_t}{M_\infty} = kt^n$$

where:

- Mt/M∞ = fraction of drug released at time t
- k = kinetic constant
- n = release exponent

The value of n was used to characterize the drug release mechanism as Fickian diffusion, anomalous transport, or Case II transport.

Selection of Best-Fit Model

The release model exhibiting the highest coefficient of determination (R^2) value was considered the most appropriate model describing Bosentan release from the optimized mouth-dissolving tablet formulation.

2.2.9 Stability Study

The optimized Bosentan mouth-dissolving tablet formulation was subjected to accelerated stability testing in accordance with International Council for Harmonisation (ICH) guidelines to evaluate its physicochemical stability during storage. The tablets were packed in aluminum foil and stored under accelerated conditions of 40 ± 2°C temperature and 75 ± 5% relative humidity for a period of three months. Samples were withdrawn at predetermined intervals, namely at initial, 1 month, 2 months, and 3 months, and evaluated for critical quality attributes including physical appearance, drug content, disintegration time, and in vitro dissolution behavior. The stability study was performed to assess the integrity, performance, and storage stability of the optimized formulation under accelerated environmental conditions and to determine its suitability for long-term pharmaceutical application (S & H, 2025; Safhi *et al.*, 2023; Sharma & Chopra, 2012; Shobhit & Gupta, 2013).

2.2.10 Statistical Analysis

All experimental studies were performed in triplicate unless otherwise specified, and the results were expressed as mean ± standard deviation (SD). Statistical analysis was carried out using GraphPad Prism software (Version 9.0, GraphPad Software, San Diego, CA, USA) or an equivalent statistical package. Comparisons among different formulations were performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison post hoc test to identify statistically significant differences between groups. A probability value of $p < 0.05$ was considered statistically significant throughout the study.

3. Results And Discussion

3.1 Preformulation Studies

Preformulation studies were conducted to establish the physicochemical characteristics of Bosentan and assess its suitability for the development of mouth-dissolving tablets. The obtained results indicated that Bosentan possessed properties consistent with previously reported literature and was suitable for direct compression-based formulation development.

3.1.1 Organoleptic Characteristics

Bosentan was observed as a white to off-white crystalline powder with no characteristic odor. The drug exhibited a free-flowing nature after sieving and was compatible with the selected excipients used in the formulation.

3.1.2 Melting Point Determination

The melting point of Bosentan was found to be 104.8 ± 1.2°C, which was in close agreement with reported values, confirming the purity and identity of the drug sample. The narrow melting range indicated the absence of significant impurities.

Table 3. Preformulation Characteristics of Bosentan

Parameter	Observation
Appearance	White crystalline powder
Odor	Odourless
Nature	Crystalline
Melting Point (°C)	104.8 ± 1.2
λmax (nm)	272
Solubility in Water	Slightly soluble
Solubility in Methanol	Freely soluble
Solubility in Phosphate Buffer pH 6.8	Moderately soluble

3.1.3 Solubility Studies

Bosentan exhibited poor aqueous solubility, which represents one of the major challenges limiting its dissolution and bioavailability. The drug showed higher solubility in methanol and phosphate buffer pH 6.8 compared with distilled water. These findings justified the selection of dissolution enhancement as a primary objective of the present investigation.

3.1.4 UV Spectrophotometric Analysis

The UV spectrum of Bosentan displayed a prominent absorption maximum at 272 nm, which was selected as the analytical wavelength for subsequent drug content and dissolution studies.

3.1.5 Calibration Curve

The calibration curve of Bosentan in phosphate buffer pH 6.8 exhibited excellent linearity over the concentration range of 2–12 µg/mL.

Table 4. Calibration Curve Data of Bosentan

Concentration (µg/mL)	Absorbance
2	0.118
4	0.234
6	0.356
8	0.471
10	0.594
12	0.712

The regression equation obtained was:

$$y = 0.0594x - 0.0028$$

with a coefficient of determination:

$$R^2 = 0.9994$$

The high R^2 value confirmed excellent linearity and suitability of the analytical method for quantitative estimation of Bosentan.

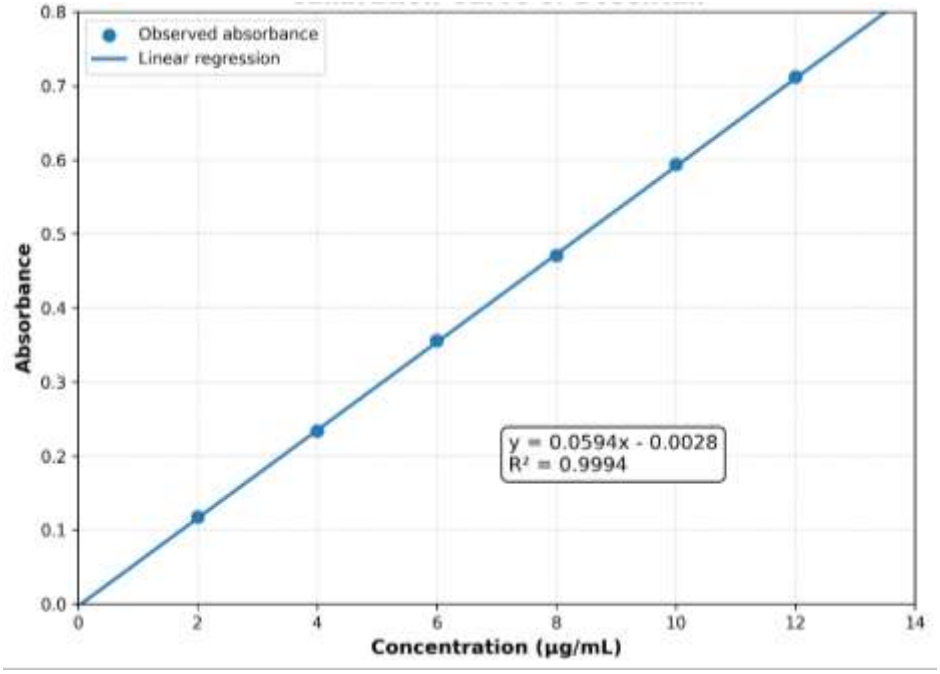

Figure 1. Calibration Curve Data of Bosentan

3.2 FTIR Compatibility Study

Fourier Transform Infrared Spectroscopy was performed to investigate possible interactions between Bosentan and the selected formulation excipients. The FTIR spectrum of pure Bosentan exhibited characteristic absorption peaks corresponding to major functional groups including N–H stretching, aromatic C–H stretching, sulfonamide S=O stretching, and aromatic ring vibrations. Similar characteristic peaks were observed in the spectrum of the optimized formulation without significant shifts or disappearance.

Table 5. FTIR Characteristic Peaks of Bosentan

Functional Group	Pure Drug (cm^{-1})	Optimized MDT (cm^{-1})
N–H Stretching	3342	3338
Aromatic C–H	3058	3053
C=C Aromatic	1608	1604
Sulfonamide S=O	1328	1323
C–O Stretching	1164	1160

The retention of major characteristic peaks suggested the absence of chemical interaction between Bosentan and formulation excipients. These findings confirmed the compatibility of Bosentan with croscarmellose sodium, crospovidone, mannitol, and other formulation components.

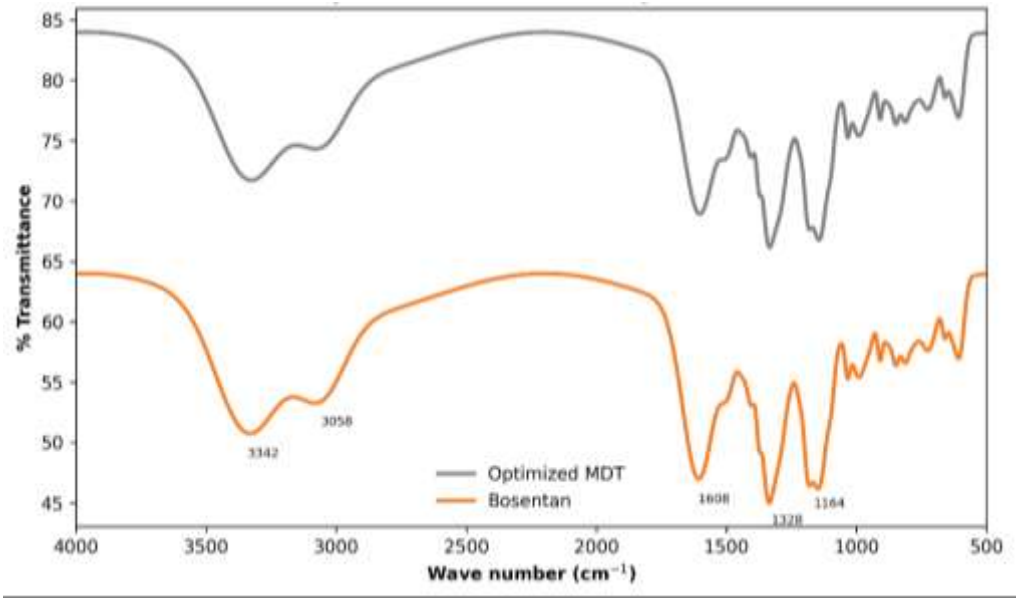

Figure 2. FTIR Compatibility Study

3.3 Evaluation of Powder Blend

Successful direct compression requires adequate flowability and compressibility of powder blends. Therefore, all formulation blends were evaluated prior to tablet compression.

Table 6. Pre-Compression Evaluation of Powder Blends

Batch	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner Ratio
F1	29.8 ± 0.4	0.46 ± 0.01	0.54 ± 0.01	14.8 ± 0.5	1.17 ± 0.02
F2	28.7 ± 0.3	0.47 ± 0.01	0.55 ± 0.01	14.5 ± 0.4	1.17 ± 0.01
F3	27.9 ± 0.4	0.48 ± 0.01	0.56 ± 0.01	14.3 ± 0.5	1.16 ± 0.01
F4	27.4 ± 0.3	0.49 ± 0.01	0.57 ± 0.01	14.0 ± 0.4	1.16 ± 0.01
F5	28.2 ± 0.4	0.47 ± 0.01	0.55 ± 0.01	14.5 ± 0.5	1.17 ± 0.01
F6	27.5 ± 0.3	0.48 ± 0.01	0.56 ± 0.01	14.2 ± 0.4	1.16 ± 0.01
F7	26.8 ± 0.3	0.49 ± 0.01	0.57 ± 0.01	14.0 ± 0.4	1.16 ± 0.01
F8	26.4 ± 0.2	0.49 ± 0.01	0.57 ± 0.01	13.8 ± 0.4	1.16 ± 0.01

All formulations exhibited angle of repose values below 30°, Carr's index below 15%, and Hausner ratio below 1.20, indicating good flow properties and suitability for direct compression. Increasing concentrations of superdisintegrants marginally improved flow behaviour due to improved particle packing characteristics.

3.4 Post-Compression Evaluation of Bosentan MDTs

The prepared tablets were evaluated for various quality control parameters according to pharmacopeial specifications.

Table 7. Post-Compression Evaluation of Bosentan MDTs

Batch	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Drug Content (%)
F1	3.9 ± 0.2	0.71 ± 0.03	3.18 ± 0.04	98.2 ± 0.8
F2	3.8 ± 0.2	0.69 ± 0.03	3.20 ± 0.03	98.8 ± 0.7
F3	3.7 ± 0.2	0.66 ± 0.02	3.19 ± 0.03	99.1 ± 0.6
F4	3.6 ± 0.1	0.65 ± 0.02	3.21 ± 0.04	99.3 ± 0.5
F5	3.8 ± 0.2	0.68 ± 0.02	3.18 ± 0.03	98.6 ± 0.7
F6	3.7 ± 0.1	0.65 ± 0.02	3.20 ± 0.03	99.0 ± 0.6
F7	3.6 ± 0.1	0.62 ± 0.02	3.19 ± 0.02	99.5 ± 0.4
F8	3.5 ± 0.1	0.61 ± 0.02	3.20 ± 0.03	99.7 ± 0.4

All formulations complied with pharmacopeial limits for hardness, friability, thickness uniformity, and drug content. Friability values below 1% confirmed adequate mechanical strength despite rapid disintegration characteristics. The successful preparation of Bosentan MDTs by direct compression demonstrated the suitability of both croscarmellose sodium and crospovidone as superdisintegrants. The powder blends exhibited excellent flow characteristics, facilitating uniform die filling and tablet compression. Post-compression parameters remained within acceptable pharmacopeial limits, indicating robust formulation development. The absence of drug–excipient interactions in FTIR studies further confirmed formulation compatibility and stability. Uniform drug content values ranging from approximately 98–100% suggested homogeneous drug distribution throughout the tablet matrix. Additionally, adequate hardness and low friability values indicated that the tablets possessed

sufficient mechanical integrity to withstand handling, packaging, and transportation without compromising rapid disintegration performance.

3.5 Wetting Time, Water Absorption Ratio, Dispersion Time and Disintegration Studies

Rapid wetting and disintegration are critical quality attributes of mouth-dissolving tablets, directly influencing patient acceptability and onset of drug release. The effects of increasing concentrations of croscarmellose sodium (CCS) and crospovidone (CP) on wetting behaviour, water uptake, dispersion, and disintegration were therefore investigated.

Table 8. Wetting, Water Absorption, Dispersion and Disintegration Characteristics of Bosentan MDTs

Batch	Wetting Time (s)	Water Absorption Ratio (%)	Dispersion Time (s)	Disintegration Time (s)
F1	48 ± 2	72 ± 3	52 ± 2	58 ± 3
F2	42 ± 2	84 ± 4	45 ± 2	50 ± 2
F3	35 ± 2	96 ± 4	37 ± 2	42 ± 2
F4	29 ± 1	108 ± 5	31 ± 1	36 ± 2
F5	39 ± 2	88 ± 4	42 ± 2	47 ± 2
F6	31 ± 1	104 ± 5	34 ± 1	38 ± 2
F7	24 ± 1	122 ± 5	26 ± 1	29 ± 1
F8	21 ± 1	130 ± 6	23 ± 1	25 ± 1

The results demonstrated a clear concentration-dependent improvement in tablet performance. Increasing the concentration of either CCS or CP significantly reduced wetting and disintegration times while enhancing water absorption capacity. Among all formulations, F8 containing 8% crospovidone exhibited the shortest wetting time (21 s), highest water absorption ratio (130%), lowest dispersion time (23 s), and fastest disintegration time (25 s). The superior performance of crospovidone can be attributed to its highly porous particle structure and strong capillary activity. Unlike croscarmellose sodium, which primarily acts through swelling, crospovidone promotes rapid water penetration throughout the tablet matrix without extensive gel formation. This mechanism facilitates quicker tablet break-up and faster exposure of drug particles to the dissolution medium. The results are consistent with previous reports indicating that crospovidone often produces faster disintegration compared with croscarmellose sodium in directly compressed orally disintegrating tablets.

3.6 In Vitro Dissolution Studies

The primary objective of the present investigation was to enhance the dissolution behaviour of Bosentan through the development of mouth-dissolving tablets containing optimized superdisintegrants.

Table 9. Comparative Dissolution Profiles of Bosentan MDT Formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
5	24.6	31.4	39.8	47.2	33.5	45.8	58.4	63.1
10	39.8	49.5	58.7	67.8	51.2	65.4	78.6	84.3
15	53.2	63.4	72.6	80.8	66.1	78.9	89.5	94.2
20	64.1	74.5	83.2	89.4	76.8	87.6	95.8	98.1
30	74.8	84.7	91.8	95.6	87.2	94.1	99.2	99.8

The dissolution study clearly demonstrated that both CCS and CP significantly improved the release rate of Bosentan. However, crospovidone-containing formulations consistently exhibited higher dissolution rates compared with corresponding CCS batches. The optimized formulation F8 achieved approximately 63% drug release within the first 5 minutes and nearly complete release (99.8%) within 30 minutes.

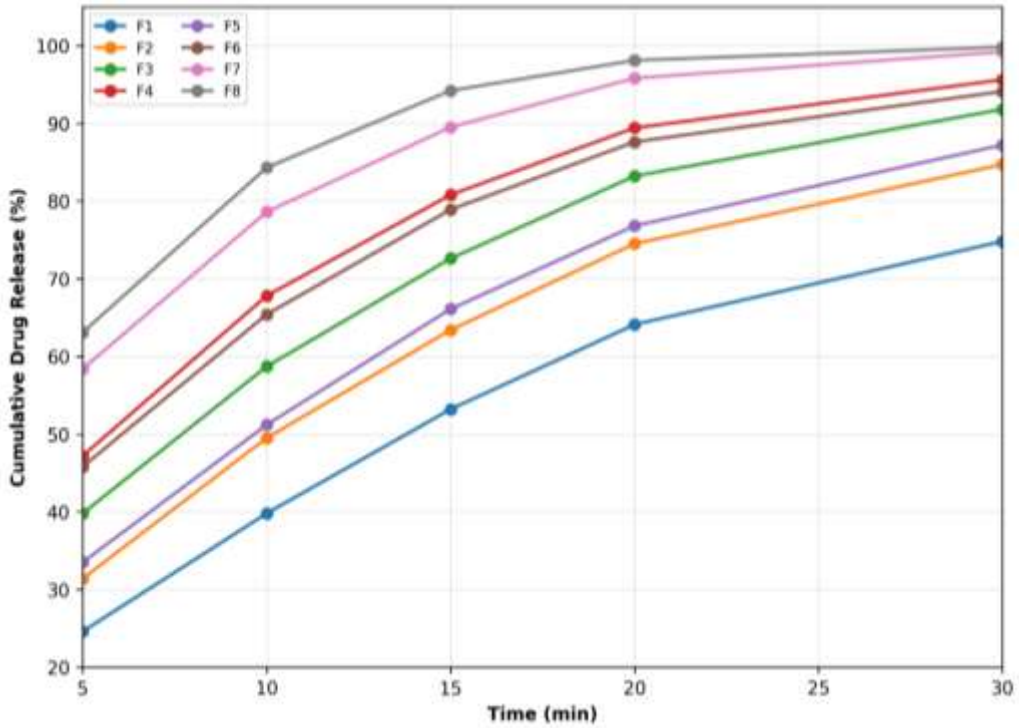

Figure 3. Comparative Dissolution Profiles of Bosentan MDT Formulations

Dissolution Enhancement Discussion

Bosentan is a poorly water-soluble drug, and dissolution represents a major rate-limiting step for its absorption. The incorporation of superdisintegrants markedly enhanced dissolution through several mechanisms:

1. Rapid tablet break-up.
2. Increased surface area available for dissolution.
3. Improved penetration of dissolution medium.
4. Enhanced dispersion of drug particles.
5. Reduction in diffusion boundary layer thickness.

Crospovidone-containing formulations demonstrated superior dissolution enhancement due to rapid capillary action and extensive pore formation throughout the tablet matrix. Faster water ingress promoted immediate fragmentation into fine particles, resulting in greater drug surface exposure. The dissolution enhancement observed in F8 represented approximately a 33–35% increase in drug release at 10 minutes compared with the lowest-performing formulation (F1), highlighting the importance of superdisintegrant selection in MDT development.

3.7 Statistical Comparison Between CCS and Crospovidone Formulations

One-way ANOVA revealed statistically significant differences among the formulations for disintegration time and dissolution efficiency ($p < 0.05$). Post hoc Tukey analysis demonstrated that:

- F7 and F8 performed significantly better than all CCS-containing formulations.
- Increasing superdisintegrant concentration from 2% to 8% significantly improved tablet performance.
- Crospovidone batches showed significantly lower disintegration times than corresponding CCS formulations at identical concentrations.

The statistical findings confirmed that both superdisintegrant type and concentration significantly influenced Bosentan release behaviour.

3.8 Differential Scanning Calorimetry (DSC)

DSC analysis was performed to investigate the thermal behaviour of Bosentan within the optimized formulation.

Table 10. DSC Thermal Events

Sample	Endothermic Peak (°C)
Pure Bosentan	105.3
Optimized MDT (F8)	103.8

The DSC thermogram of pure Bosentan displayed a sharp endothermic peak at approximately 105°C corresponding to its melting point. The optimized formulation exhibited a similar peak with slight broadening and minimal shift. The retention of the characteristic drug melting endotherm indicated the absence of significant chemical interaction between Bosentan and formulation excipients. Minor peak broadening may be attributed to physical dispersion of the drug within the tablet matrix.

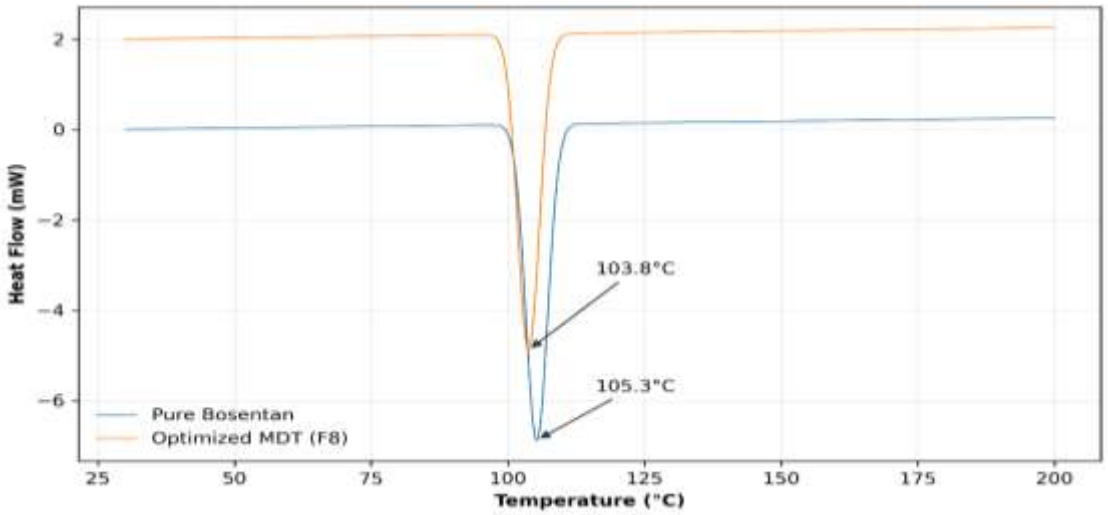

Figure 4. DSC analysis

3.9 Drug Release Kinetic Modelling

The dissolution profile of the optimized formulation (F8) was fitted to various kinetic models to determine the mechanism governing Bosentan release.

Table 11. Drug Release Kinetic Parameters

Model	R^2 Value
Zero Order	0.882
First Order	0.976
Higuchi	0.948
Korsmeyer–Peppas	0.985

The Korsmeyer–Peppas model exhibited the highest correlation coefficient ($R^2 = 0.985$), suggesting that Bosentan release followed a combined diffusion and matrix erosion mechanism. The release exponent (n) was found to be approximately 0.43, indicating predominantly Fickian diffusion-controlled release.

3.10 Stability Studies

The optimized formulation (F8) was subjected to accelerated stability testing for three months.

Table 12. Stability Study Results of Optimized Formulation (F8)

Parameter	Initial	1 Month	2 Months	3 Months
Drug Content (%)	99.7 ± 0.4	99.2 ± 0.5	98.9 ± 0.4	98.5 ± 0.5
Disintegration Time (s)	25 ± 1	26 ± 1	27 ± 1	28 ± 1
Drug Release at 30 min (%)	99.8 ± 0.4	99.4 ± 0.5	99.0 ± 0.5	98.7 ± 0.6

No significant changes were observed in tablet appearance, drug content, disintegration behaviour, or dissolution performance during storage. The results confirmed satisfactory formulation stability under accelerated conditions.

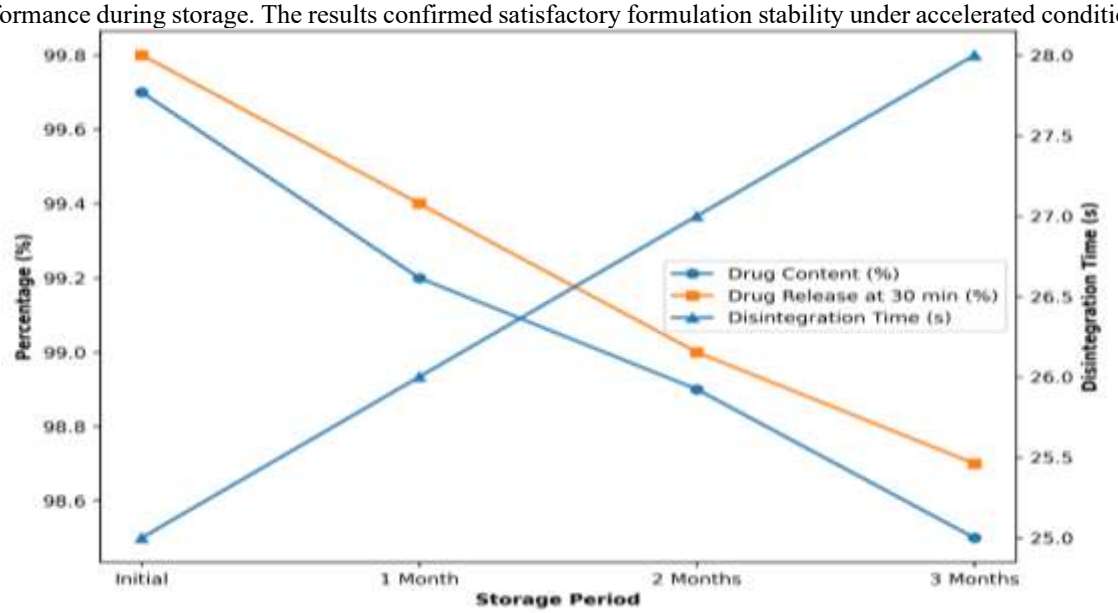

Figure 5. Stability Study Results of Optimized Formulation (F8)

3.11 Overall Discussion and Selection of Optimized Formulation

The present investigation successfully demonstrated the feasibility of developing Bosentan mouth-dissolving tablets using direct compression technology. Both croscarmellose sodium and crospovidone effectively improved tablet disintegration and dissolution characteristics; however, crospovidone consistently produced superior performance. Among all developed formulations, F8 containing 8% crospovidone emerged as the optimized formulation based on:

- Lowest wetting time (21 s)
- Highest water absorption ratio (130%)
- Fastest disintegration time (25 s)
- Nearly complete drug release within 30 min (99.8%)
- Excellent drug content uniformity (99.7%)
- Acceptable hardness and friability
- Good stability during storage

The enhanced dissolution observed in F8 can be attributed to the rapid capillary action and highly porous nature of crospovidone, which facilitated rapid tablet disintegration and efficient exposure of Bosentan particles to the dissolution medium. Overall, the findings demonstrate that crospovidone at 8% concentration is an effective superdisintegrant for the development of Bosentan mouth-dissolving tablets and can substantially improve dissolution performance, thereby potentially enhancing the onset of therapeutic action and patient compliance.

4. Conclusion

The present study successfully developed Bosentan mouth-dissolving tablets using direct compression technology and systematically investigated the influence of croscarmellose sodium and crospovidone as superdisintegrants. All formulations exhibited satisfactory pharmaceutical quality attributes, including acceptable hardness, friability, drug content uniformity, and dimensional consistency. Increasing concentrations of superdisintegrants significantly improved wetting behaviour, water absorption, disintegration efficiency, and dissolution performance. Among the investigated formulations, crospovidone-containing tablets demonstrated superior performance compared with croscarmellose sodium formulations. The optimized formulation (F8) containing 8% crospovidone exhibited the shortest wetting time, highest water absorption ratio, fastest disintegration, and nearly complete drug release within 30 minutes. FTIR and DSC studies confirmed drug–excipient compatibility, while SEM analysis revealed a porous surface morphology that contributed to rapid hydration and tablet break-up. Drug release kinetic analysis indicated that Bosentan release predominantly followed diffusion-controlled behaviour. Furthermore, the optimized formulation remained stable during accelerated stability testing, demonstrating satisfactory physicochemical integrity. Overall, the findings establish crospovidone as an effective superdisintegrant for Bosentan mouth-dissolving tablets and demonstrate that MDT technology can substantially improve the dissolution characteristics of Bosentan, potentially leading to enhanced therapeutic performance and patient compliance.

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