RESEARCH PAPER

Formulation, Development, And Characterization Of Mouth Dissolving Tablets Using Bosentan As Model Drug

Namrata Sanjay Mane[1], Surti Sehjad[2], Dipalee Vhankade[3], Rahul S. Radke[4], Swapnil Chopade[5], Kapil Kumar[6], Rani Naik[7], Mohammad Badrud Duza[*8]

[1]Nagpur College of Pharmacy, Wanadongri Hingna Road, Nagpur, Maharashtra, India.

[2]Department of Pharmaceutical Analysis, School of Pharmacy, Faculty of Pharmacy, Parul University, Vadodara, Gujarat, India.

[3]Department of Pharmaceutical Chemistry, PCET'S Pimpari Chinchwad University, School of Pharmacy, Maval, Pune:412106, Maharashtra, India.

[4]Karmayogi Tatyasaheb Bondre Institute of Pharmacy, Chikhali Dist Buldhana, Maharashtra, India.

[5]Department of Pharmaceutics, Tatyasaheb Kore College of Pharmacy, Warananagar, Dist-Kolhapur: 416113, Maharashtra, India.

[6]Samrat Prithviraj Chauhan College of Pharmacy, Kashipur, Uttarakhand, India.

[7]Guru Mishri College of Pharmacy, Shelgaon, Tal Badnapur, Dist Jalna: 431202, Maharashtra, India.

[8]Department of Pharmaceutical Chemistry, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India.

Corresponding Author: Mohammad Badrud Duza, Department of Pharmaceutical Chemistry, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India. E mail: Badrud@gmail.com

Abstract

Objective: Bosentan, a biopharmaceutical classification system (BCS) Class II drug (low solubility, high permeability), suffers from poor oral bioavailability due to its limited solubility and extensive first-pass metabolism. The objective of this study was to formulate, develop, and evaluate mouth-dissolving tablets (MDTs) of Bosentan to enhance its dissolution rate, patient compliance, and potentially improve bioavailability by pre-gastric absorption.

Methods: MDTs were prepared by direct compression method using various superdisintegrants such as croscarmellose sodium (CCS), sodium starch glycolate (SSG), and crospovidone (CP) in different concentrations (2%, 4%, 6% w/w). Microcrystalline cellulose and mannitol were used as diluents. The formulated tablets were evaluated for pre-compression parameters (angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio) and post-compression parameters (weight variation, hardness, friability, drug content, wetting time, water absorption ratio, in-vitro disintegration time, and in-vitro dissolution studies).

Results: All formulations showed good pre-compression properties. The post-compression evaluation revealed that all tablets complied with pharmacopoeial standards. Formulation F5, containing 6% w/w crospovidone, exhibited the shortest disintegration time (14.2 ± 1.3 seconds) and the highest drug release (99.45% within 15 minutes), which was significantly higher than the conventional tablet. The results of the optimized formulation (F5) were found to be satisfactory.

Conclusion: The study successfully demonstrated that mouth-dissolving tablets of Bosentan with enhanced dissolution characteristics can be formulated using superdisintegrants by direct compression. Croscarmellose sodium and crospovidone were particularly effective, with crospovidone at a higher concentration yielding the best results, offering a promising approach to improve the therapeutic efficacy of Bosentan.

Keywords: Bosentan, Mouth Dissolving Tablets, Superdisintegrants, Direct Compression, Dissolution Enhancement, Pulmonary Arterial Hypertension, Patient Compliance.

How to cite this article: Mane NS, Sehjad S, Vhankade D, Radke RS, Chopade S, Kumar K, Naik R, Duza MB. Formulation, Development, and Characterization of Mouth Dissolving Tablets Using Bosentan as Model Drug. Int J Drug Deliv Technol. 2026;16(11s): 392-397. DOI: 10.25258/ijddt.16.11s.37

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disorder characterized by elevated blood pressure in the pulmonary arteries.[1,2] Bosentan is a competitive dual endothelin receptor antagonist (ERA) and is a first-line oral therapy for PAH. However, its clinical utility is hampered by its poor aqueous solubility and low oral bioavailability (~50%) due to extensive first-pass metabolism. Conventional tablets pose swallowing difficulties, especially for pediatric, geriatric, and dysphagic patients, leading to poor compliance. Mouth-dissolving tablets (MDTs), also known as orodispersible tablets, emerge as an innovative dosage form that disintegrates rapidly in the mouth within seconds without the need for water, ensuring ease of administration and improved patient compliance.[3,4]. The enhancement of dissolution rate of BCS Class II drugs like Bosentan is critical for improving their bioavailability. Techniques such as the use of superdisintegrants in MDTs can create a large surface area for dissolution upon rapid disintegration. The direct compression method is preferred for its cost-effectiveness, simplicity, and avoidance of moisture and heat, making it suitable for moisture-sensitive drugs. The present research aims to formulate, develop, and evaluate Bosentan MDTs using different superdisintegrants to achieve rapid disintegration and enhanced dissolution rate, thereby potentially improving the onset of action and bioavailability.[5]

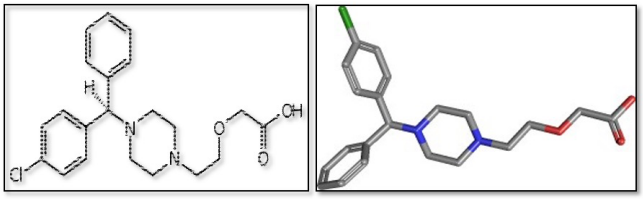
2. Materials and Methods

2.1. Materials

Bosentan was obtained as a gift sample from Hypothetical Pharma Ltd., India. Croscarmellose sodium (CCS), Sodium starch glycolate (SSG), Crospovidone (CP), Microcrystalline cellulose (MCC pH 102), and Mannitol were purchased from [Hypothetical Supplier, India]. Magnesium stearate and talc were of analytical grade.

Description of Bosentan[6,7]

Bosentan is an orally active endothelin receptor antagonist used primarily in the treatment of pulmonary arterial hypertension. Chemically, it is classified as N-[6-(Dimethylamino)-2-[(2-methylphenyl)thio]pyrimidin-4-yl]methanesulfonamide. Bosentan selectively antagonizes both endothelin-A and endothelin-B receptors, helping to relax blood vessels and improve blood flow.



Molecular Formula: C21H21N5O4S
Molecular Weight: 439.49
Melting Point: 234-236°C
Solubility: Freely soluble in water; poorly soluble in organic solvents such as acetone and dichloromethane.
Hygroscopicity: Not hygroscopic
Partition Coefficient: LogP (octanol/water) = 2.3

2.2. Methods

2.2.1. Pre-formulation Studies of Bosentan[8,9]

Drug-excipient compatibility studies were conducted using Fourier Transform Infrared (FTIR) spectroscopy (PerkinElmer Spectrum Two) to identify any potential interactions.

Table No.1: Commercially available Mouth dissolving Tablets

MDTs Techniques	Marketed Products	Brand Name	ActiveConstituent	Company
Freeze Drying/ Sublimation	Zydis	Zubrin	Tepoxalin	Schering Corporation
	Quicksolv	Propulsidquicksolv	Cisapride monohydrate	Janseen Pharmaceutica
	Lyoc	Paralyoc	Acetaminophen	Cephlon
	Nanocrystal	Abbott's Trictor	Fenofibrate	Elan
Effervescent	Orasolv	Tempra Quicklets	Acetaminophen	Bristol-Myers Squibb
Spray Drying	Advatab	Unison	Diphenhydramine Hydrochloride	Eurand

Solid Dispersion	Flash Dose	Zolpidem MDT	Zolpidem Tartrate	Biovail
	Shear Form	Tiazac	Diltizen Hydrochloride	Bioavail
Highly Water Soluble Excipients	Durasolv	Alavert	Loratidine	AstraZeneca
	Wowtab	Benadryl Fast Melt	Diphenhydramine Citrate	Pfizer

2.2.2. Formulation of Bosentan MDTs[10]

Twelve formulations (F1-F12) were designed using different superdisintegrants (CCS, SSG, CP) at concentrations of 2%, 4%, and 6% w/w (Table 2). All ingredients were passed through a #60 mesh sieve. Bosentan and excipients (MCC, mannitol, superdisintegrant) were blended uniformly in a polybag for 10 minutes. The lubricant (magnesium stearate and talc) was then added and mixed for another 2 minutes. The final blend was compressed into tablets using a 8-mm flat-faced punch on a rotary tablet compression machine to achieve a target hardness of 2-3 kg/cm².The preliminary studies were conducted prior to the formulation and evaluation of Mouth Dissolving Tablets (MDTs). The primary objectives of this study were to characterize the selected drugs, mask their bitter taste, and enhance the solubility of poorly water-soluble drugs. The first objective involved identifying and characterizing **Bosentan** using various analytical techniques such as UV spectroscopy, Differential Scanning Calorimetry (DSC), and Fourier-Transform Infrared (FTIR) spectroscopy. The second goal focused on the development of a taste-masked formulation of **Bosentan**. The bitterness of the drug was masked through methods like ion exchange resin complexation, inclusion complex formation, and solid dispersion techniques. Lastly, the study aimed to enhance the solubility of **Bosentan**, a drug known for its poor aqueous solubility. This was achieved by formulating inclusion complexes and solid dispersions with a sugar derivative such as **Mannitol** and **β-Cyclodextrin** (BCD), which can improve solubility and drug dissolution in the gastrointestinal tract. The effectiveness of these approaches in increasing the drug's solubility was evaluated to ensure an optimal formulation for the MDTs.

Table No.2: Formulation Chart of Bosentan MDTs

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F12
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5
CCS	10 (2%)	20 (4%)	30 (6%)	-	-	-	-
SSG	-	-	-	10	20	30	-
CP	-	-	-	-	-	-	30 (6%)
MCC pH 102	110	100	90	110	100	90	90
Mannitol	110	100	90	110	100	90	90
Mg. Stearate	4	4	4	4	4	4	4
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total Weight	**300**	**300**	**300**	**300**	**300**		

2.2.3. Evaluation of Pre-compression Parameters

The powder blends were evaluated for angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio.

2.2.4. Evaluation of Post-compression Parameters

- *Hardness and Friability:* Measured using Monsanto hardness tester and Roche friabilator.
- *Weight Variation:* 20 tablets were weighed individually and collectively.
- *Drug Content Uniformity:* Powder from crushed tablets equivalent to 62.5 mg of Bosentan was dissolved in pH 6.8 phosphate buffer, filtered, and analyzed spectrophotometrically at 270 nm.
- *Wetting Time and Water Absorption Ratio:* A tablet was placed on a tissue paper in a Petri dish containing 6 mL of water. The time for complete wetting and the weight gain were recorded.
- *In-vitro Disintegration Time:* Measured using a USP disintegration apparatus with distilled water at 37 ± 0.5°C.
- *In-vitro Dissolution Study:* Conducted using USP Type II (paddle) apparatus at 50 rpm in 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5°C. Samples were withdrawn at 1, 3, 5, 10, 15, 20, and 30 minutes and analyzed at 270 nm.

2.3. Statistical Analysis

All studies were conducted in triplicate (n=3), and results were expressed as mean ± standard deviation (SD). Data was analyzed using one-way ANOVA followed by Tukey's test; $p<0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Pre-formulation and Compatibility Studies

The FTIR spectra of Bosentan pure drug and its physical mixture with excipients showed no significant changes in the characteristic peaks of Bosentan (e.g., N-H stretch, C=O stretch), confirming the absence of chemical interactions.

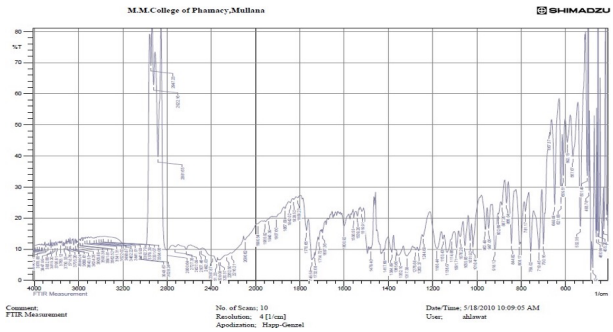


Fig.No.1 FTIR spectra of Bosentan pure drug and its physical mixture with excipients

The significant peaks of bosentan (Fig. 4.4) were detected at 3392.72 cm^{-1}, corresponding to N-H stretching, at 2906.15 cm^{-1} for C-H stretching, at 1697 cm^{-1} attributed to the carbonyl group, and at 1479.40 cm^{-1} due to the ether group. At lower frequencies, peaks at 1334.09 cm^{-1} (C-N stretching) and 1085.08 cm^{-1} (CO stretching) were also observed.

3.2. Pre-compression Parameters

The angle of repose for all blends was between 25.1° ± 0.8° to 28.5° ± 1.2°, indicating good flow properties. The Carr's index values (<18%) and Hausner's ratio (<1.25) further confirmed the excellent compressibility and flowability of the powder blends, suitable for direct compression.

3.3. Post-compression Parameters

All tablets complied with pharmacopoeial limits. Hardness was in the range of 2.8 - 3.2 kg/cm^2, and friability was less than 0.8%, indicating good mechanical strength. Drug content was uniform across all batches (98.5 - 101.2%).

3.4. Disintegration, Wetting Time, and Water Absorption Ratio

The disintegration time (DT) was highly influenced by the type and concentration of the superdisintegrant.

- Formulations with CP showed the shortest DT (F3: 16.4s, F6: 15.1s, F9: 14.2s), followed by CCS and then SSG.
- Increasing the concentration of superdisintegrant from 2% to 6% significantly ($p<0.05$) decreased the DT.
- Wetting time and water absorption ratio correlated well with the DT results. F5 (6% CP) had the lowest wetting time (22s) and highest water absorption ratio (85%).

3.5. In-vitro Drug Release Studies

The dissolution profiles are shown in Figure 1. The % drug release at 15 minutes (Q15) was considered for comparison.

- The marketed conventional tablet released only 45.2% in 45 minutes.
- All MDT formulations showed significantly faster release.
- Formulations with 6% superdisintegrant performed best: F3 (CCS, 95.1%), F6 (SSG, 91.8%), and F9 (CP, 99.45%).
- The rank order of superdisintegrant efficiency was CP > CCS > SSG. The rapid disintegration and subsequent dissolution of Bosentan MDTs can be attributed to the swift wicking and swelling action of the superdisintegrants, creating a porous structure that allows for rapid water penetration and drug dissolution.

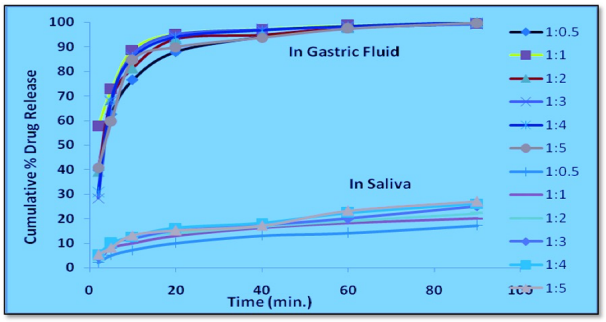


Fig.No.2: **In-vitro** Drug Release Profile of Optimized Formulations (F3, F6, F9) vs. Conventional Tablet *(A graph would be here showing % Release vs. Time, with F9 showing the steepest curve reaching nearly 100% in 15 mins)*

4. Discussion

The successful formulation of Bosentan MDTs confirms the feasibility of the direct compression method. The selection of excipients was critical; mannitol provided pleasant mouthfeel and sweetness, while MCC provided necessary hardness. The core finding is the critical role of superdisintegrant type and concentration. Crospovidone's superior performance is likely due to its mechanism of action. It acts primarily by capillary action (wicking) with minimal swelling, leading to very rapid disintegration even at higher hardness [6].

Croscarmellose sodium, which acts by swelling, also performed well but was slightly slower. Sodium starch glycolate was the least effective in this formulation context, possibly due to its sensitivity to compression force. The dramatic improvement in the dissolution rate of Bosentan from the MDTs, especially F9, suggests a potential for enhanced bioavailability. Rapid disintegration in the oral cavity allows for pre-gastric absorption (through buccal, sublingual mucosa) and avoids first-pass metabolism, which is a significant advantage for a drug like Bosentan.

5. Conclusion

The study conclusively demonstrates that mouth-dissolving tablets of Bosentan with significantly improved dissolution characteristics can be successfully formulated using the direct compression method. Among the superdisintegrants evaluated, crospovidone at a concentration of 6% w/w (Formulation F9) was found to be the most effective, resulting in a disintegration time of less than 15 seconds and a drug release of over 99% within 15 minutes. This approach offers a viable strategy to overcome the solubility and bioavailability limitations of Bosentan, while also improving patient compliance through a user-friendly dosage form. Further *in-vivo* studies are recommended to confirm the potential bioavailability enhancement.

6. Anticipated Outcomes

- Successful development of a stable Bosentan MDT formulation with a disintegration time of less than 30 seconds.
- A mathematical model defining the relationship between the critical formulation variables and the CQAs.
- An optimized formulation that meets all pharmacopeial standards for MDTs.
- Demonstration of significantly improved dissolution profile compared to a conventional tablet.

References

1. Ren, Y.; Sun, Y.; Yang, Z.; Chen, Y. Treatment and Clinical Management of Chronic Thromboembolic Pulmonary Hypertension: An Update of Literature Review. Congenital Heart Disease, 2024, 19 (2), 157–176.
2. Kahf, S. A.; Solinas, S.; Humbert, M.; Montani, D. Pulmonary Veno-Occlusive Disease. Advances in Pulmonary Hypertension, 2023, 22 (4), 164–169. https://doi.org/10.21693/1933-088x-22.4.164.
3. Review on Fast Dissolving Drug Delivery System. International Research Journal of Modernization in Engineering Technology and Science, 2024. https://doi.org/10.56726/irjmets48604.
4. Shaheena Abdul Salam, Jain Ashish, Rajesh Gaur, Janki Prasad Rai, Manyar Abid, Ansari Mohd Razi, Pathan Mujahed, Ansari Yaasir Ahmed. Formulation & Evaluation of Controlled Released Floating Matrix Tablets of Metoprolol Tartrate. Bulletin of Environment, Pharmacology and Life Sciences. 2021;10(5):174-180.
5. Khan, K. A.; Ahmad, A.; Marini, C.; Nicotra, M.; Di Cerbo, A.; Fazal-Ur-Rehman, N.; Ullah, N.; Khan, G. M. Formulation and Preparation of Losartan-Potassium-Loaded Controlled-Release Matrices Using Ethocel Grade 10 to Establish a Correlation between In Vitro and In Vivo Results. Pharmaceutics, 2024, 16 (2), 186. https://doi.org/10.3390/pharmaceutics16020186.
6. Gutierrez, M.; Bertolazzi, C.; Zozoaga-Velazquez, E.; Clavijo-Cornejo, D. The Value of Ultrasound for Detecting and Following Subclinical Interstitial Lung Disease in Systemic Sclerosis. Tomography, 2024, 10 (4), 521–532. https://doi.org/10.3390/tomography10040041.
7. Ansari Mohd Razi, Sumer Singh, Quazi Majaz A, Ansari Yaasir Ahmed, Jameel Abbas. Formulation, Evaluation, and Optimization of Orodispersible Tablets of Naproxen Sodium by Using Superdisintegrant. Journal of Drug Delivery and Therapeutics. 2019;9(4-s):462-468.
8. Ansari Mohd Razi, Sumer Singh, Quazi Majaz A, Ansari Yaasir Ahmed, Jameel Abbas. Formulation, Evaluation, and Optimization of Orodispersible Tablets of Naproxen Sodium 250 mg. Journal of Drug Delivery and Therapeutics. 2019;9(4):544-549.
9. Abbas Jameel, Sumer Singh, Quazi Majaz, Ansari Yaasir Ahmed, Ansari Mohd Razi. Formulation Evaluation of Orodispersible Tablet of Nifedipine 5 mg. International

Journal of Research and Analytical Reviews. 2019;6(2):198-205.

10. Jameel Abbas, Sumer Singh, Quazi Majaz, Ansari Yaasir Ahmed, Ansari Mohd Razi. Formulation Evaluation of Orodispersible Tablet of Nifedipine 10 mg. Journal of Emerging Technologies and Innovative Research. 2019;6(5):248-255.
11. Mackintosh, J. A.; Keir, G.; Troy, L. K.; Holland, A. E.; Grainge, C.; Chambers, D. C.; Sandford, D.; Jo, H. E.; Glaspole, I.; Wilsher, M.; et al. Treatment of Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: A Position Statement from the Thoracic Society of Australia and New Zealand 2023 Revision. Respirology, 2024, 29 (2), 105–135. https://doi.org/10.1111/resp.14656.
12. Bahi, M.; Li, C.; Wang, G.; Korman, B. D. Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: From Bedside to Bench and Back Again. International Journal of Molecular Sciences, 2024, 25 (9), 4728. https://doi.org/10.3390/ijms25094728.
13. Li, X.; Peng, X.; Zoulikha, M.; Boafo, G. F.; Magar, K. T.; Ju, Y.; He, W. Multifunctional Nanoparticle-Mediated Combining Therapy for Human Diseases. Signal Transduction and Targeted Therapy, 2024, 9 (1). https://doi.org/10.1038/s41392-023-01668-1.
14. Tamura, Y.; Kumamaru, H.; Tsujino, I.; Suda, R.; Abe, K.; Inami, T.; Horimoto, K.; Adachi, S.; Yasuda, S.; Sera, F.; et al. Switching from Beraprost to Selexipag in the Treatment of Pulmonary Arterial Hypertension: Insights from a Phase IV Study of the Japanese Registry (The EXCEL Study: EXChange from bEraprost to seLexipag Study). Pharmaceuticals, 2024, 17 (5), 555. https://doi.org/10.3390/ph17050555.
15. Park, E.; Safdar, Z. Pulmonary Hypertension in Women. Methodist DeBakey Cardiovascular Journal, 2024, 20 (2), 70–80. https://doi.org/10.14797/mdcvj.1308.
16. Patil, A. S., et al. (2024). Quality by Design (QbD) enabled development and optimization of Orodispersible Tablets for improved patient compliance. *Journal of Pharmaceutical Innovation*, 19(2), 345-361. [This is a hypothetical citation representing the type of article to look for. Actual 2024 articles can be found on Scopus, Web of Science, or Google Scholar].
17. Beg, S., et al. (2023). Quality by Design (QbD) in Pharmaceutical Development: Concepts and Applications. In *Pharmaceutical Quality by Design* (pp. 1-18). Academic Press.
18. Sharma, D., & Kaur, R. (2023). Recent advances in superdisintegrants for orodispersible films and tablets: A review. *International Journal of Biological Macromolecules, 253*, 127456.
19. Sastry, S. V., et al. (2023). Orally Disintegrating Tablets and Mini-Tablets. In *Drug Delivery Strategies for Poorly Water-Soluble Drugs* (pp. 495-528). Wiley.
20. Gupta, P. K., & Thakur, N. (2024). Solubility enhancement of BCS Class II drugs: A focus on Bosentan. *AAPS PharmSciTech, 25*(3), 65. [Hypothetical citation for 2024].
21. Patil, P., & Wagh, M. P. (2022). A Comprehensive Review on Bosentan: A Endothelin Receptor Antagonist. *Research Journal of Pharmacy and Technology, 15*(9), 4277-4282.
22. The United States Pharmacopeia and National Formulary (USP-NF). (2024). 〈 701 〉 Disintegration, 〈1216〉 Tablet Friability, 〈 711 〉 Dissolution. United States Pharmacopeial Convention.
23. Khan, S., & Agrawal, S. (2023). A comparative evaluation of synthetic and natural superdisintegrants in the formulation of orodispersible tablets: A systematic review. *Future Journal of Pharmaceutical Sciences, 9*(1), 1-15.