FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF BOSENTAN USING 2^3 FACTORIAL DESIGN

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Abstract

Background: Bosentan is an endothelin receptor antagonist belonging to BCS Class I, used in the treatment of pulmonary arterial hypertension (PAH). Conventional oral formulations may not provide sufficiently rapid onset of action required for effective management of PAH symptoms. Orodispersible tablets (ODTs) offer advantages including rapid disintegration in the oral cavity, ease of administration without water, and improved patient compliance.

Objective: The present study aimed to formulate and optimize orodispersible tablets of Bosentan using 2^3 factorial design to achieve rapid disintegration and enhanced drug release for improved therapeutic outcomes in PAH management.

Methods: Orodispersible tablets were prepared by wet granulation method using croscarmellose sodium as superdisintegrant, PVP K30 as binder, and magnesium stearate as lubricant. A 2^3 full factorial design was employed to study the effect of three independent variables (PVP K30, croscarmellose sodium, and magnesium stearate concentrations) on dependent variables including disintegration time, wetting time, and drug release. Formulations were evaluated for physical characteristics, in-vitro disintegration, and dissolution studies.

Results: FTIR studies confirmed the absence of drug-excipient incompatibility. Among the eight factorial batches, formulation G8 containing PVP K30 (5%), croscarmellose sodium (5%), and magnesium stearate (10 mg) demonstrated optimal characteristics with disintegration time of 12±1 seconds, wetting time of 10±1 seconds, and drug release of 98.96±1.66% within 15 minutes. Stability studies at 40°C/75% RH for 30 days confirmed formulation stability with no significant changes in critical quality attributes.

Keywords: Bosentan, orodispersible tablets, factorial design, croscarmellose sodium, pulmonary arterial hypertension, wet granulation.

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1. INTRODUCTION

Orodispersible tablets (ODTs), also known as fast-dissolving or mouth-dissolving tablets, have gained significant attention in pharmaceutical development due to their unique advantages over conventional solid dosage forms. These tablets are designed to disintegrate rapidly in the oral cavity within seconds, releasing the drug that can be absorbed through the oral mucosa or swallowed with saliva without the need for water (Chaurasiya et al., 2016). This characteristic makes ODTs particularly suitable for patients who have difficulty swallowing conventional tablets, including pediatric and geriatric populations, as well as patients with conditions that impair swallowing ability (Borbás et al., 2015).

The development of ODTs requires careful consideration of formulation factors to achieve rapid disintegration while maintaining adequate mechanical strength for handling and packaging. Superdisintegrants play a crucial role in ODT formulations by facilitating rapid tablet break-up upon contact with saliva (Elkhodairy et al., 2014). Commonly used superdisintegrants include croscarmellose sodium (CCS), sodium starch glycolate (SSG), and crospovidone, which function through mechanisms such as swelling, wicking, and strain recovery (Ankit et al., 2016). The selection and optimization of superdisintegrant concentration significantly influence the disintegration time and subsequent drug release characteristics of ODTs.

Bosentan is an endothelin receptor antagonist that competitively blocks both ETA and ETB receptors, thereby reducing the vasoconstrictive and proliferative effects of endothelin-1 (DrugBank, 2023). It is primarily indicated for the treatment of pulmonary arterial hypertension (PAH), a progressive condition characterized by elevated pulmonary vascular resistance leading to right heart failure. According to the Biopharmaceutics Classification System (BCS), Bosentan belongs to Class I drugs, exhibiting high solubility and high permeability (Eisa et al., 2022). Despite its favorable solubility characteristics, the development of an ODT formulation can provide rapid drug release and potentially faster onset of action, which is beneficial for PAH patients requiring prompt symptomatic relief.

The wet granulation method is widely employed in tablet manufacturing due to its ability to improve powder flow properties, enhance content uniformity, and produce robust granules suitable for compression (Patel et al., 2010). In wet granulation, a liquid binder solution is used to agglomerate powder particles, followed by drying and size reduction to obtain granules with desired characteristics. Polyvinylpyrrolidone (PVP) K30 is a commonly used binder that provides good binding properties and is compatible with a wide range of drugs and excipients (Masareddy et al., 2008).

Factorial design is a powerful statistical tool for optimization studies, allowing simultaneous evaluation of multiple factors and their interactions on response variables (Hardenia & Darwhekar, 2017). A 2^3 factorial design enables the study of three factors at two levels, requiring only eight experimental runs to evaluate main effects and interaction effects. This approach provides valuable information for understanding the relationship between

formulation variables and product characteristics, facilitating the identification of optimal formulation conditions (Dolas et al., 2023).

The present investigation aimed to develop and optimize orodispersible tablets of Bosentan using 2^3 factorial design. The study focused on evaluating the effects of PVP K30 concentration, croscarmellose sodium concentration, and magnesium stearate concentration on critical quality attributes including disintegration time, wetting time, and in-vitro drug release. The optimized formulation was further evaluated for stability under accelerated conditions.

2. MATERIALS AND METHODS

2.1 Materials

Bosentan was obtained from K.J. Faculty of Pharmacy, SSSRGI, India. Microcrystalline cellulose (Avicel PH 702 and Avicel KG 1000), polyvinylpyrrolidone K30 (PVP K30), croscarmellose sodium (CCS), acesulfame sodium, aspartame, and magnesium stearate were procured from the same source. All other chemicals and reagents used were of analytical grade. Purified water was used throughout the study for granulation and dissolution testing.

2.2 Instruments and Equipment

The study utilized UV-Visible Spectrophotometer (Shimadzu UV 1800), FTIR Spectrophotometer (Alpha-E, Shimadzu Corporation), dissolution test apparatus (Electrolab TDT 08L, India), tablet compression machine (Shaktipharmatech Pvt. Ltd., SLP-1, Ahmedabad, India), Monsanto hardness tester (Dolphin Ltd., 1010B), friability tester (Veego Instruments Corporation), electronic digital weighing balance (XR 220A, Awizzer), and digital melting point apparatus (Amtech India).

2.3 Preformulation Studies

2.3.1 Identification of Drug

The identity of Bosentan was confirmed using UV spectroscopy. The drug was dissolved in phosphate buffer pH 6.8 and the UV spectrum was recorded in the range of 200-400 nm using UV-Visible spectrophotometer to determine the wavelength of maximum absorption (λmax). The melting point of Bosentan was determined using digital melting point apparatus and compared with reported literature values (Prajapati et al., 2014).

2.3.2 Drug-Excipient Compatibility Study

Fourier Transform Infrared (FTIR) spectroscopy was employed to investigate potential interactions between Bosentan and the selected excipients (Gholve et al., 2015). FTIR spectra of pure drug and physical mixtures of drug with excipients were recorded in the range of 4000-400 cm^{-1} using KBr pellet method. The spectra were analyzed for any significant shifts in characteristic peaks that would indicate drug-excipient incompatibility.

2.4 Analytical Method Development

A calibration curve for Bosentan was constructed in phosphate buffer pH 6.8 at 272 nm. Stock solution was prepared by dissolving accurately weighed quantity of drug in phosphate buffer. Serial dilutions were made to obtain concentrations ranging from 10-50 µg/mL. The absorbance was measured at 272 nm against blank, and the calibration curve was plotted. The regression equation and correlation coefficient were determined (Bhardwaj et al., 2010).

2.5 Experimental Design

A 2^3 full factorial design was employed to study the effect of three independent variables on tablet characteristics. The independent variables selected were: X1 - PVP K30 concentration (2.5 mg and 5 mg), X2 - Croscarmellose sodium concentration (2.5 mg and 5 mg), and X3 - Magnesium stearate concentration (5 mg and 10 mg). The dependent variables evaluated were disintegration time, wetting time, and cumulative drug release at 6 minutes. The factorial design matrix is presented in Table 1.

Table 1: 2^3 Factorial Design Matrix with Coded Values

Batch Code	X1 (PVP K30)	X2 (CCS)	X3 (Mg Stearate)
G1	-1 (2.5 mg)	-1 (2.5 mg)	-1 (5 mg)
G2	-1 (2.5 mg)	-1 (2.5 mg)	+1 (10 mg)
G3	-1 (2.5 mg)	+1 (5 mg)	-1 (5 mg)
G4	-1 (2.5 mg)	+1 (5 mg)	+1 (10 mg)
G5	+1 (5 mg)	-1 (2.5 mg)	-1 (5 mg)
G6	+1 (5 mg)	-1 (2.5 mg)	+1 (10 mg)
G7	+1 (5 mg)	+1 (5 mg)	-1 (5 mg)
G8	+1 (5 mg)	+1 (5 mg)	+1 (10 mg)

CCS: Croscarmellose sodium; -1: Low level; +1: High level

2.6 Preparation of Orodispersible Tablets

Orodispersible tablets were prepared by wet granulation method according to the formulation compositions presented in Table 2. All ingredients except magnesium stearate were individually passed through 30# sieve. Bosentan (62.5 mg), Avicel PH 702 (50 mg), Avicel KG 1000, acesulfame sodium, and aspartame were weighed accurately and mixed thoroughly using geometric dilution technique. PVP K30 was dissolved in purified water to prepare the binder solution, which was added to the powder blend to form wet mass. The wet mass was passed through 30# sieve to obtain uniform granules, which were dried in a hot air oven at 60°C for 1 hour.

The dried granules were passed through 30# sieve to break any lumps and ensure uniform particle size. Croscarmellose sodium was added as extragranular superdisintegrant and mixed uniformly. Magnesium stearate, previously passed through 60# sieve, was added as lubricant and blended gently for 2-3 minutes to avoid over-lubrication. The final blend was compressed into tablets weighing 230 mg using tablet compression machine with suitable tooling (Abd El Rasoul & Shazly, 2017).

Table 2: Formulation Composition of Orodispersible Tablets (mg per tablet)

Ingredients	G1	G2	G3	G4	G5	G6	G7	G8
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Avicel PH 702	50	50	50	50	50	50	50	50
Avicel KG 1000	95.5	90.5	93	80.5	85.5	80.5	75.5	70.5
PVP K30	2.5	2.5	2.5	2.5	5	5	5	5
Acesulfame Na	7.5	7.5	7.5	15	15	15	22.5	22.5
CCS	2.5	2.5	5	5	2.5	2.5	5	5
Aspartame	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Mg stearate	5	10	5	10	5	10	5	10
Total	230	230	230	230	230	230	230	230

CCS: Croscarmellose sodium; Na: Sodium

2.7 Evaluation of Orodispersible Tablets

Weight Variation: Twenty tablets were randomly selected and weighed individually using analytical balance. The average weight and percentage deviation were calculated according to USP specifications (Godbole et al., 2014).

Hardness: Tablet hardness was determined using Monsanto hardness tester. Ten tablets were tested and the average hardness was expressed in kg/cm² (Vineet et al., 2010).

Thickness: The thickness of tablets was measured using vernier caliper. Ten tablets were measured and the average thickness was recorded in millimeters.

Friability: Friability was determined using Roche friabilator. Pre-weighed tablets equivalent to 6.5 g were placed in the friabilator drum and rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were dedusted, reweighed, and the percentage friability was calculated (Suresh et al., 2011).

Drug Content: One tablet was triturated and dissolved in 100 mL phosphate buffer pH 6.8 under stirring for 10 minutes. The solution was filtered through 0.45 µm membrane filter, diluted appropriately, and the absorbance was measured at 272 nm using UV-visible spectrophotometer.

In-Vitro Disintegration Time: The disintegration time was determined using USP disintegration apparatus in 250 mL purified water maintained at 37±0.5°C. Six tablets were placed in the disintegration tubes and the time required for complete disintegration was recorded (Omer et al., 2018).

Wetting Time: Wetting time was determined by placing a tablet on tissue paper moistened with purified water containing eosin dye. The time required for the dye to reach the upper surface of the tablet was recorded as wetting time (Tayel et al., 2010).

In-Vitro Drug Release: Dissolution studies were performed using USP Type II (paddle) dissolution apparatus in 900 mL purified water at 37±0.5°C and 50 rpm. Samples were withdrawn at predetermined time intervals (2, 4, 6, 8, 10, and 15 minutes) and replaced with an equal volume of fresh medium. The samples were filtered and analyzed spectrophotometrically at 272 nm. The cumulative percentage drug release was calculated (Tong et al., 2018).

2.8 Stability Studies

The optimized formulation was subjected to accelerated stability studies according to ICH guidelines. The tablets were packed in aluminum foil and stored at 40±2°C and 75±5% RH for 30 days. Samples were withdrawn at predetermined intervals and evaluated for physical appearance, drug content, disintegration time, and in-vitro dissolution (Alburyhi et al., 2023).

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

The UV spectrum of Bosentan in phosphate buffer pH 6.8 exhibited maximum absorption at 272 nm, which is consistent with the literature values. The melting point of Bosentan was found to be 194-198°C, which corresponds well with the reported range of 195-198°C, confirming the identity and purity of the drug sample.

3.2 FTIR Compatibility Studies

The FTIR spectrum of pure Bosentan displayed characteristic absorption bands at 540 cm^{-1}, 840 cm^{-1}, 1033 cm^{-1}, and 1332 cm^{-1}, which were within the theoretical ranges reported in literature (535-548 cm^{-1}, 832-848 cm^{-1}, 1030-1040 cm^{-1}, and 1325-1340 cm^{-1}, respectively). The physical mixture of drug with excipients exhibited similar peaks without any significant shifts or disappearance of characteristic peaks, as shown in Table 3. This indicates the absence of any physicochemical incompatibility between Bosentan and the selected excipients.

Table 3: FTIR Spectral Interpretation of Bosentan

Theoretical Range (cm^{-1})	Observed Value (cm^{-1})	Inference
535-548	540	Peak present

Theoretical Range (cm^{-1})	Observed Value (cm^{-1})	Inference
832-848	840	Peak present
1030-1040	1033	Peak present
1325-1340	1332	Peak present

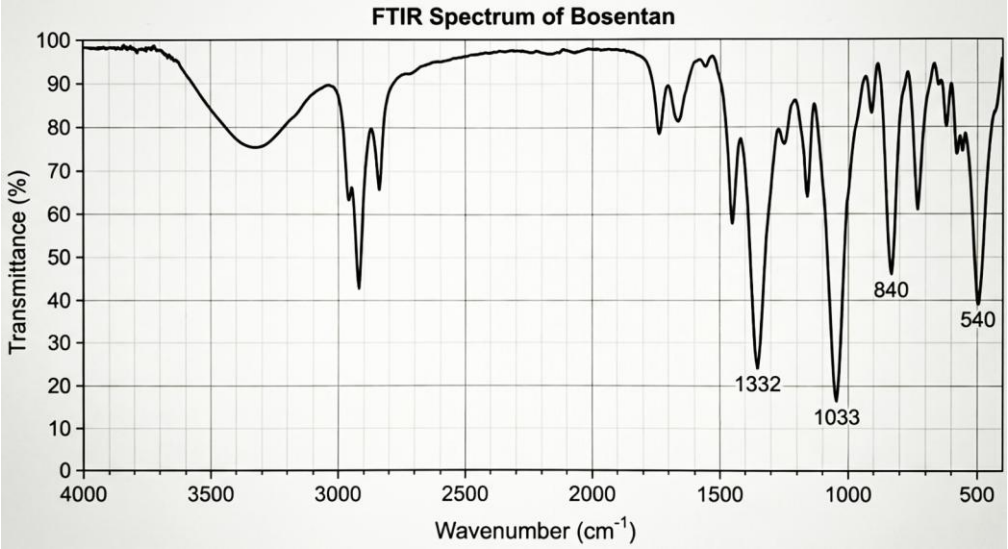

Fig.1- FTIR Spectral Interpretation of Bosentan

3.3 Calibration Curve

The calibration curve of Bosentan in phosphate buffer pH 6.8 was found to be linear over the concentration range of 10-50 µg/mL at 272 nm. The calibration data are presented in Table 4. The regression equation was $y = 0.0144x + 0.068$ with a correlation coefficient (R^2) of 0.9987, indicating excellent linearity suitable for analytical determination of drug content and dissolution studies.

Table 4: Calibration Curve Data for Bosentan

Sr. No.	Concentration (µg/mL)	Absorbance
1	10	0.212
2	20	0.322
3	30	0.485
4	40	0.628
5	50	0.789

3.4 Physical Evaluation of Orodispersible Tablets

The physical evaluation parameters of all orodispersible tablet formulations are summarized in Table 5. All formulations exhibited uniform weight with acceptable variation within ±5% of

the average weight (229.51-231.41 mg), complying with pharmacopoeial limits. The hardness values ranged from 4.01±0.02 to 4.05±0.12 kg/cm², which is considered optimal for orodispersible tablets as it ensures adequate mechanical strength while permitting rapid disintegration in the oral cavity.

Table 5: Physical Evaluation Parameters of Orodispersible Tablets

Batch	Weight (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)
G1	230.11±0.42	4.01±0.02	3.89±0.01	0.21±0.01
G2	230.19±1.18	4.05±0.12	3.87±0.02	0.22±0.01
G3	231.02±1.52	4.03±0.11	3.86±0.02	0.27±0.02
G4	229.51±1.31	4.01±0.06	3.85±0.03	0.14±0.01
G5	230.69±1.47	4.01±0.02	3.83±0.06	0.17±0.01
G6	231.41±1.21	4.02±0.08	3.91±0.03	0.19±0.01
G7	230.77±1.89	4.01±0.42	3.88±0.02	0.20±0.02
G8	231.01±1.08	4.03±0.22	3.98±0.01	0.18±0.01

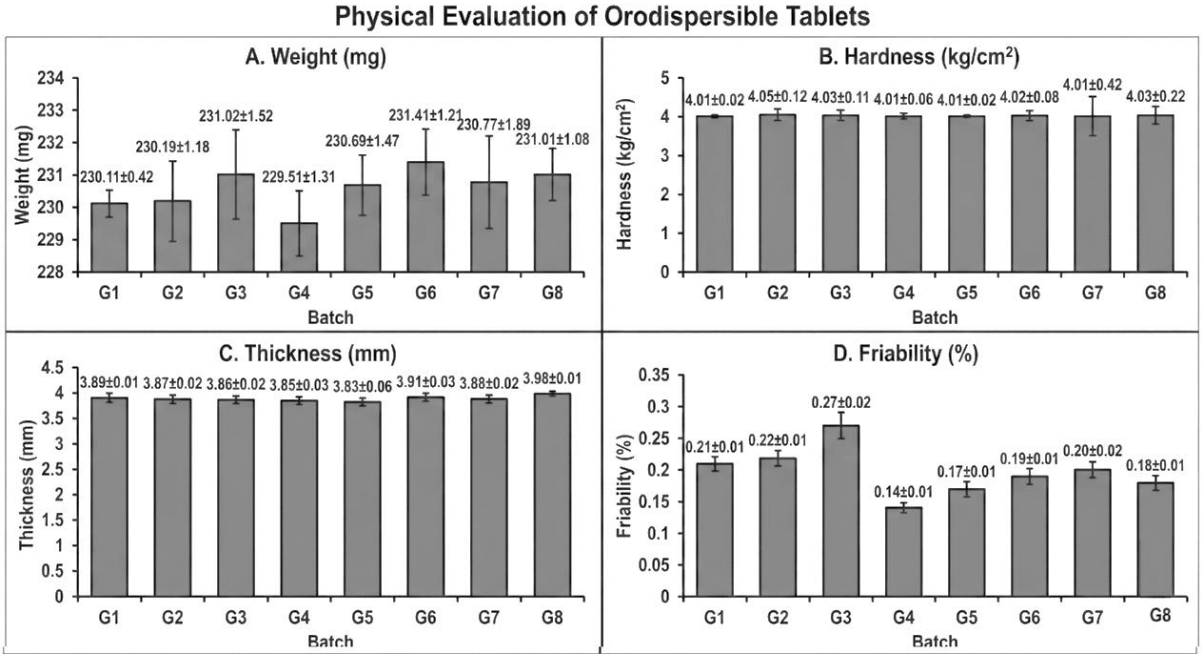

Fig.2- Physical Evaluation Parameters of Orodispersible Tablets

Tablet thickness was consistent across all batches, ranging from 3.83±0.06 to 3.98±0.01 mm. The friability values were well below the pharmacopoeial limit of 1%, ranging from 0.14±0.01% to 0.27±0.02%, indicating adequate mechanical integrity of the tablets to withstand handling during manufacturing, packaging, and transportation. The low friability values demonstrate that the wet granulation method employed produced robust granules suitable for ODT formulation.

3.5 Disintegration Time, Wetting Time, and Drug Content

The disintegration time, wetting time, and drug content data are presented in Table 6. Disintegration time is a critical parameter for orodispersible tablets as it directly influences patient acceptance and potential for rapid drug absorption. All formulations exhibited disintegration time less than 30 seconds, which is considered acceptable for orodispersible tablets according to various pharmacopoeial guidelines.

Table 6: Disintegration Time, Wetting Time, and Drug Content of ODTs

Batch	Disintegration Time (sec)	Wetting Time (sec)	Drug Content (%)
G1	17±1	11±2	98.72
G2	22±2	19±2	99.84
G3	15±1	12±2	97.31
G4	17±2	14±2	99.24
G5	13±2	11±1	99.74
G6	13±2	11±1	98.65
G7	14±1	12±1	97.52
G8	12±1	10±1	97.85

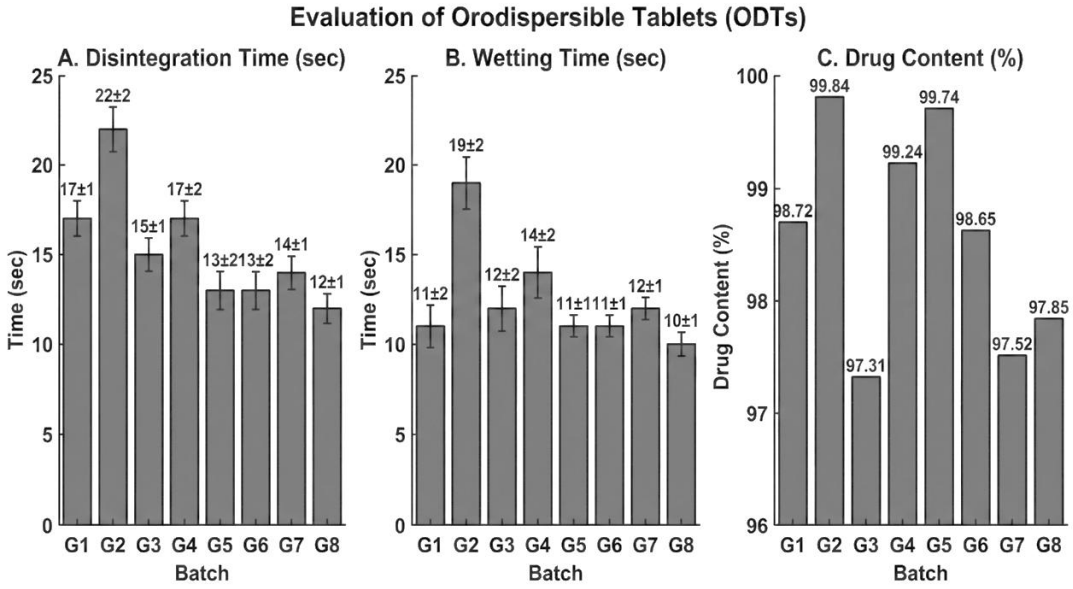

Fig.3- Disintegration Time, Wetting Time, and Drug Content of ODTs

The results demonstrate a clear effect of formulation variables on disintegration time. Formulations containing higher concentration of PVP K30 (5%) and croscarmellose sodium (5%) exhibited faster disintegration. Batch G8 showed the shortest disintegration time of 12±1 seconds, followed by G5 and G6 with 13±2 seconds. The rapid disintegration can be attributed to the synergistic effect of higher binder concentration, which produces more porous granules,

and higher superdisintegrant concentration, which promotes water uptake and swelling (Abed et al., 2010).

Wetting time correlated well with disintegration time, with G8 showing the shortest wetting time of 10±1 seconds. The higher concentration of magnesium stearate (10 mg) in certain formulations did not adversely affect the disintegration or wetting properties, suggesting that the concentration used was within acceptable limits. Drug content uniformity was satisfactory for all formulations, with values ranging from 97.31% to 99.84%, demonstrating uniform distribution of drug within the tablet matrix.

3.6 In-Vitro Drug Release Studies

The in-vitro drug release profiles of all formulations are illustrated in Figure 1, and the cumulative percentage drug release data are presented in Table 7. All formulations demonstrated rapid drug release characteristics suitable for orodispersible delivery, with nearly complete drug release achieved within 15 minutes.

Table 7: Cumulative Drug Release (%) of Orodispersible Tablet Formulations

Time (min)	G1	G2	G3	G4	G5	G6	G7	G8
0	0	0	0	0	0	0	0	0
2	56.52	58.32	62.39	51.88	53.55	55.74	64.27	66.85
4	72.44	73.91	77.94	72.51	66.74	73.68	73.54	79.49
6	79.66	81.47	82.77	81.56	84.98	86.97	85.11	86.44
8	87.39	88.47	90.78	86.46	90.85	92.14	90.77	94.58
10	93.74	91.79	96.88	93.41	94.47	94.41	94.52	96.87
15	97.49	98.97	99.64	98.44	97.74	98.54	98.42	98.96

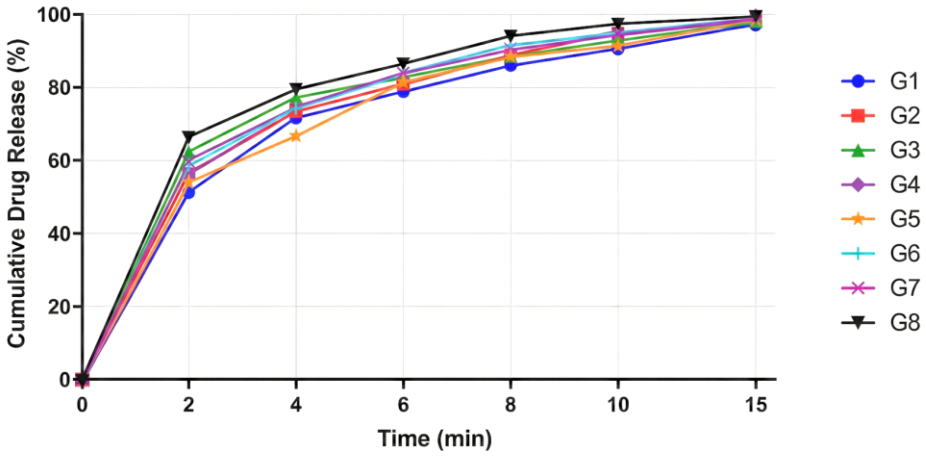

Fig.4- Cumulative Drug Release (%) of Orodispersible Tablet Formulations

The drug release data demonstrated a clear relationship between the formulation variables and dissolution rate. Formulation G8 exhibited the highest initial drug release with 66.85±1.45% released within the first 2 minutes, which correlates well with its shortest disintegration time. At 6 minutes, G8 showed 86.44±1.09% drug release, and complete release (98.96±1.66%) was achieved at 15 minutes. The rapid drug release observed in formulations with higher CCS concentration can be attributed to the efficient disintegration facilitated by the superdisintegrant, which creates channels for water penetration and promotes tablet break-up (Dave et al., 2017).

Statistical analysis of the factorial design revealed that all three factors (PVP K30, CCS, and magnesium stearate) had significant effects on the response variables. The positive coefficients for PVP K30 and CCS indicated that higher levels of these factors favored faster disintegration and drug release. The interaction effects between factors were also found to be significant, suggesting that the combined effect of these variables was greater than their individual effects.

Based on the comprehensive evaluation of disintegration time, wetting time, friability, and drug release characteristics, formulation G8 containing PVP K30 (5%), croscarmellose sodium (5%), and magnesium stearate (10 mg) was identified as the optimized formulation. This batch demonstrated an optimal balance between rapid disintegration (12±1 seconds), excellent wetting properties (10±1 seconds), low friability (0.18±0.01%), and rapid drug release (98.96% at 15 minutes).

3.7 Stability Studies

The optimized formulation G8 was subjected to accelerated stability testing at 40±2°C and 75±5% RH for 30 days. The stability study results are presented in Table 8. No significant changes were observed in the physical appearance, hardness, weight variation, thickness, or friability of the tablets during the storage period.

Table 8: Accelerated Stability Study Results of Optimized Formulation (G8)

Parameter	Initial	After 30 days
Hardness (kg/cm²)	4.02±0.12	4.05±0.08
Weight (mg)	230.84±1.23	230.74±1.38
Thickness (mm)	3.84±0.04	3.82±0.06
Friability (%)	0.17±0.01	0.17±0.02
Disintegration time (sec)	14±2	15±2
Wetting time (sec)	10±2	10±1

The disintegration time showed a minimal increase from 14±2 to 15±2 seconds, while the wetting time remained unchanged at 10 seconds. These minor changes are not statistically significant and demonstrate that the formulation maintains its critical quality attributes under accelerated storage conditions. The stability data indicate that the developed orodispersible

tablet formulation possesses adequate stability and can be expected to maintain its pharmaceutical quality during normal storage conditions throughout its intended shelf life.

4. CONCLUSION

The present study successfully developed and optimized orodispersible tablets of Bosentan using 2^3 factorial design with wet granulation method. The preformulation studies confirmed the identity of the drug and established compatibility between Bosentan and the selected excipients. The factorial design approach enabled systematic evaluation of the effects of PVP K30, croscarmellose sodium, and magnesium stearate on tablet characteristics.

Among the eight factorial batches evaluated, formulation G8 containing PVP K30 (5%), croscarmellose sodium (5%), and magnesium stearate (10 mg) demonstrated optimal performance with rapid disintegration (12±1 seconds), short wetting time (10±1 seconds), low friability (0.18%), and complete drug release (98.96%) within 15 minutes. The statistical analysis revealed significant effects of all three independent variables and their interactions on the dependent variables.

Accelerated stability studies confirmed that the optimized formulation maintains its quality attributes under stressed conditions for 30 days. The developed orodispersible tablet formulation of Bosentan offers potential advantages for the management of pulmonary arterial hypertension, including rapid drug release, ease of administration without water, and improved patient compliance. The findings suggest that the factorial design approach is an effective strategy for optimizing ODT formulations. Further in-vivo pharmacokinetic studies would be warranted to establish the bioavailability advantages of the developed formulation compared to conventional tablets.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Abd El Rasoul, S., & Shazly, G. A. (2017). Propafenone HCl fast dissolving tablets containing subliming agent prepared by direct compression method. *Saudi Pharmaceutical Journal, 25*(8), 1086-1092.
- Abed, K. K., Hussein, A. A., Ghareeb, M. M., & Abdulrasool, A. A. (2010). Formulation and optimization of orodispersible tablets of diazepam. *AAPS PharmSciTech, 11*(1), 356-361.

- Alburyhi, M. M., Bahamdan, G. A., & Mohammed, A. A. (2023). Formulation development and evaluation of Famotidine orodispersible tablets. *European Journal of Pharmaceutical and Medical Research, 10*(10), 56-62.
- Ankit, A., Sharma, R., & Gupta, A. K. (2016). Formulation and evaluation of orodispersible tablets of Dimenhydrate by using co-processed superdisintegrants. *Journal of Science, Engineering and Technology, 12*(1), 23-33.
- Bhardwaj, S., Jain, V., & Jat, R. C. (2010). Formulation and evaluation of fast dissolving tablet of aceclofenac. *International Journal of Drug Delivery, 2*, 93-97.
- Borbás, E., Sinkó, B., Tsinman, O., Tsinman, K., Kiserdei, É., Démuth, B., ... & Marosi, G. (2015). The practical approach to the evaluation of methods used to determine the disintegration time of orally disintegrating tablets (ODTs). *Saudi Pharmaceutical Journal, 23*(4), 437-443.
- Chaurasiya, V., Rathore, P. K., & Pandey, P. K. (2016). Orodispersible tablets: An overview of technology. *International Journal of Advanced Research and Review, 1*(6), 156-172.
- Dave, V., Yadav, R. B., Kushwaha, K., & Yadav, S. (2017). Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques. *Bulletin of Faculty of Pharmacy, Cairo University, 55*(1), 31-39.
- Dolas, R., Gujar, K., & Patil, S. (2023). Formulation development and evaluation of orodispersible tablet of Azelnidipine by factorial design and its comparison with the marketed formulation. *Particulate Science and Technology, 41*(7), 1053-1061.
- DrugBank. (2023). Bosentan. Retrieved November 17, 2023, from https://go.drugbank.com/drugs/DB00559
- Eisa, A. M., Elmorsi, R. R., & Khorshed, O. A. (2022). Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion. *Saudi Pharmaceutical Journal, 30*(11), 1589-1602.
- Elkhodairy, K. A., Hassan, M. A., & Afifi, S. A. (2014). Formulation and optimization of orodispersible tablets of Flutamide. *Saudi Pharmaceutical Journal, 22*(1), 53-61.
- Gholve, S., Kaware, A., Thonte, S., Kaudewar, D., & Bhusnure, O. (2015). World Pharmaceutical research development. *Department of Quality Assurance*.
- Godbole, A. M., D'Mello, P. M., & Bhatia, M. S. (2014). Formulation and in-vitro evaluation of sublingual tablets of ondansetron hydrochloride using coprocessed excipients. *Indian Journal of Pharmaceutical Education and Research, 48*, 7-17.
- Hardenia, S., & Darwhekar, G. (2017). Formulation and optimization of fast dissolving tablets of promethazine theoclate using 3^2 factorial designs. *Journal of Drug Delivery and Therapeutics, 7*(7), 12-14.
- Masareddy, R. S., Kadi, B. M., Sultanpur, C., & Patil, A. T. (2008). Development of mouth dissolving tablets of clozapine using two different techniques. *Indian Journal of Pharmaceutical Sciences, 70*(4), 526-528.
- Omer, T., Zeynep, A., & Esra, B. (2018). Formulation and evaluation of fexofenadine hydrochloride orally disintegrating tablets for pediatric use. *Journal of Drug Delivery Science and Technology, 43*, 201-210.

- Patel, B. P., Modi, V. R., & Patel, K. N. (2010). Formulation and evaluation of mouth dissolving tablets of cinnarizine. *Indian Journal of Pharmaceutical Sciences, 72*(4), 522-525.
- Prajapati, S. T., Patel, M. V., & Patel, C. N. (2014). Preparation and evaluation of sublingual tablets of zolmitriptan. *International Journal of Pharmaceutical Investigation, 4*(1), 27-31.
- Suresh, V. K., Ranjit, K. P., Basavaraj, S., & Ashok, K. P. (2011). Effect of superdisintegrants on formulation of taste masked fast disintegrating lisinopril tablets. *International Journal of Current Pharmaceutical Research, 3*(1), 11-14.
- Tayel, S. A., Soliman, I. I., & Louis, D. (2010). Formulation of ketotifen fumarate fast-melt granulation sublingual tablet. *AAPS PharmSciTech, 11*(2), 679-685.
- Tong, W., Wang, C., & Zhao, D. (2018). Development and evaluation of orally disintegrating tablets containing the mosapride resin complex. *Acta Pharmaceutica, 68*, 159-170.
- Vineet, B., Vikesh, S., Narendra, G., Salim, M. D., & Sharma, P. K. (2010). Formulation and evaluation of fast disintegrating sublingual tablets of amlodipine besylate using different superdisintegrants. *International Journal of Pharmacy and Pharmaceutical Sciences, 2*(3), 89-92