



Article

NOVEL MULTIPARTICULATE SUBLINGUAL APPROACH FOR RAPID DELIVERY OF RIZATRIPTAN BENZOATE

Ram Gopal Singh¹ and Sunil Gupta^{1,2}

¹Institute of Biomedical Research and Education, Department of Pharmacy, Mangalayatan University, Beswan, Aligarh, 202146, Uttar Pradesh

^{1,2}Mangalayatan Institute of Pharmaceutical Education and Research, Mangalayatan University, Beswan, Aligarh, 202146, Uttar Pradesh

ABSTRACT

The present study focused on the development and evaluation of sublingual multiparticulate granules of rizatriptan benzoate intended for the acute treatment of migraine, with the aim of achieving rapid onset of action, improved patient compliance, and enhanced therapeutic effectiveness. Multiparticulate granules containing a therapeutic dose of 10 mg of rizatriptan benzoate were formulated using mannitol, starch powder, and starch paste, where mannitol served as the primary diluent to improve palatability and mask the bitter taste of the drug. The formulations were prepared and optimized by varying formulation and process parameters, including binder and disintegrant concentrations, mixing time, and drying conditions. The prepared granules were evaluated for physical characteristics, disintegration behaviour, drug content, content uniformity, mouthfeel, and solubility in simulated saliva. A stability-indicating HPLC method was developed and validated in accordance with ICH guidelines, and forced degradation studies were performed to confirm method specificity. The optimized formulation demonstrated rapid disintegration, acceptable mouthfeel, uniform drug distribution, and drug content within pharmacopeial limits. Solubility studies in simulated saliva indicated rapid drug availability, while stability studies revealed predictable degradation behaviour with effective protection. Overall, the findings indicate that sublingual multiparticulate granules of rizatriptan benzoate represent a scientifically robust and patient-friendly dosage form, offering rapid drug release, consistent dosing, and suitability for fast-acting migraine therapy.

Keywords: *Multiparticulate system, Rizatriptan Benzoate, Sublingual route, Rapid action, Analytical method development*

1. Introduction

1.1 Multiparticulate Drug Delivery Systems (MDDS)

Multiparticulate drug delivery systems consist of multiple discrete units such as pellets, granules, microspheres, or beads. Unlike monolithic dosage forms, MDDS distribute uniformly throughout the gastrointestinal tract, reducing localized drug concentration, minimizing irritation, and improving plasma concentration consistency. The division of dose into multiple subunits significantly lowers the risk of dose dumping and enhances patient safety, particularly

for drugs with narrow therapeutic indices. MDDS also allow formulation flexibility through differential coating and layering techniques, enabling immediate, delayed, sustained, or pulsatile drug release. [2,8,13]

1.2 Rationale for Sublingual Multiparticulate Delivery

The sublingual route enables rapid drug absorption by bypassing gastrointestinal degradation and hepatic first-pass metabolism. After oral administration, rizatriptan is completely absorbed, but its absolute bioavailability is only about 45% because a substantial amount of the absorbed drug is metabolized before reaching systemic circulation — this reflects the first-pass effect. Multiparticulates of rizatriptan can be advantageous when administered by this route due to their high surface area, rapid wetting in saliva, superior mucosal spreading, and improved patient comfort. Their small size allows better dose reliability compared with single-unit sublingual tablets.[8,9,15]

2. Drug Profile and Justification

2.1 Rizatriptan Benzoate

Rizatriptan benzoate is a selective 5-HT_{1B/1D} receptor agonist used in the acute treatment of migraine. Rapid onset of action is critical, especially during migraine attacks associated with nausea and difficulty in swallowing. Sublingual multiparticulate delivery enhances absorption, improves patient compliance, and ensures faster therapeutic plasma levels. Rizatriptan benzoate, administered at a therapeutic dose of 10 mg for the treatment of acute migraine attacks, was formulated using excipients such as mannitol, starch powder, and starch paste; among these, mannitol was specifically selected due to its pleasant cooling sensation and inherent sweetness, which effectively masks the bitter taste of rizatriptan benzoate, thereby improving palatability and patient acceptability, particularly for sublingual administration. [17,19]

3. Formulation Design

3.1 Selection of Excipients

Table 1: Selection of Excipients

Component	Function	Justification
Rizatriptan benzoate	API	Therapeutic dose ≤10 mg
Mannitol	Diluent	Sweet, cooling mouthfeel; highly water-soluble
Starch powder	Disintegrant	Rapid wetting and granule breakup
Starch paste	Binder	Mechanical strength without retarding disintegration

3.2 Formula Composition

Table 2: Formula Composition

Component	% w/w	Amount (mg)
Rizatriptan benzoate	1.0	10
Mannitol	90.0	900
Starch powder	5.0	50

Starch paste (dry eq.)	4.0	40
Total	100	1000

4. Optimization Variables

Table 3: Optimization Variables

Formulation	Mixing Time (min)	Drying Time (min)	Temp (°C)	Binder (g)	Disintegrant (%)
F1–F8	40–60	20–60	60–85	15–35	10–20

5. Evaluation of Multiparticulate Granules

5.1 Physical Characterization:

It was measured by the tapped density apparatus with the help of a graduated cylinder. Samples were weighed and transferred into a measuring cylinder and measured their bulk volumes, followed by the measurement of tapped densities of the blends using a tapped density apparatus. This method was selected for determining the tapped density of the samples, expressed as g/mL using the given formula:

$$\text{Bulk Density (Db)} = \text{Mass of Samples} / \text{Occupied Bulk Volume}$$

$$\text{Tapped Density (Dt)} = \text{Mass of Samples} / \text{Occupied Tapped Volume}$$

Angle of repose:

By using a simple funnel, angles of repose of the prepared formulation blends were determined. The funnel was held at a height of 25 cm from the base using a burette stand. Samples were introduced from the top of the funnel and were allowed to flow downwards until a maximum height “h” was received. By using a scale, the diameter of the heap, d, was measured and the angles of repose were calculated using the following formula:

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h/r),$$

where h = height of the sample and r = radius of the heap obtained. [3]

5.2 Disintegration

Multiparticulate granules rapidly disintegrated upon contact with saliva due to high surface area and starch-based disintegration. Disintegration times complied with pharmacopeial expectations for orally disintegrating systems (30 s–3 min). [3,4,18]

5.3 Drug content:

An accurately weighed quantity of rizatriptan benzoate sublingual granules equivalent to the labeled dose was transferred to a volumetric flask. A suitable solvent (phosphate buffer pH 6.8 or a methanol–water mixture) was added, and the mixture was shaken to achieve complete drug extraction. The solution was filtered to remove insoluble excipients, and the filtrate was appropriately diluted with the same solvent. The sample was analyzed using a validated UV spectrophotometric or HPLC method. Drug content was determined from the calibration curve. For uniformity of content, individual doses of granules were analyzed separately using the same procedure to ensure uniform drug distribution.

$$\text{Drug Content (\%)} = \text{Measured drug amount} / \text{Theoretical drug amount} \times 100$$

Table 4: Drug content of rizatriptan benzoate

Formulation Batch	Theoretical Content (mg)	Measured Content (mg)	Drug Content (%)
F1	10	9.85	98.5
F2	10	9.92	99.2
F3	10	9.88	98.8

Uniformity of drug content:

For content uniformity, ten individual doses of rizatriptan benzoate sublingual granules were randomly selected. Each dose was accurately weighed, transferred to a separate volumetric flask, and extracted with a suitable solvent (phosphate buffer pH 6.8 or methanol–water mixture) by thorough shaking. The solutions were filtered to remove insoluble excipients, suitably diluted, and analyzed individually using a validated UV spectrophotometric or HPLC method. Drug content was calculated from the calibration curve and expressed as a percentage, and the mean, standard deviation, and relative standard deviation (RSD) were determined to assess uniformity.

Table 5: Content uniformity of rizatriptan benzoate

Unit No.	Measured Drug Content (mg)	% of Label Claim
1	9.82	98.2
2	9.95	99.5
3	10.08	100.8
4	9.90	99.0
5	9.87	98.7
6	10.02	100.2
7	9.93	99.3
8	9.85	98.5
9	9.98	99.8
10	10.05	100.5

5.4 Dissolution Considerations

The classical method of Dissolution testing was modified to suit the purpose in case of sublingual dosage form, as sublingual absorption depends on mucosal permeation rather than gastrointestinal dissolution. Standard USP dissolution methods do not simulate the sublingual environment and are not scientifically relevant for this dosage form.

Therefore solubility studies were carried out in line with the recommendation of FDA. (FDA document)

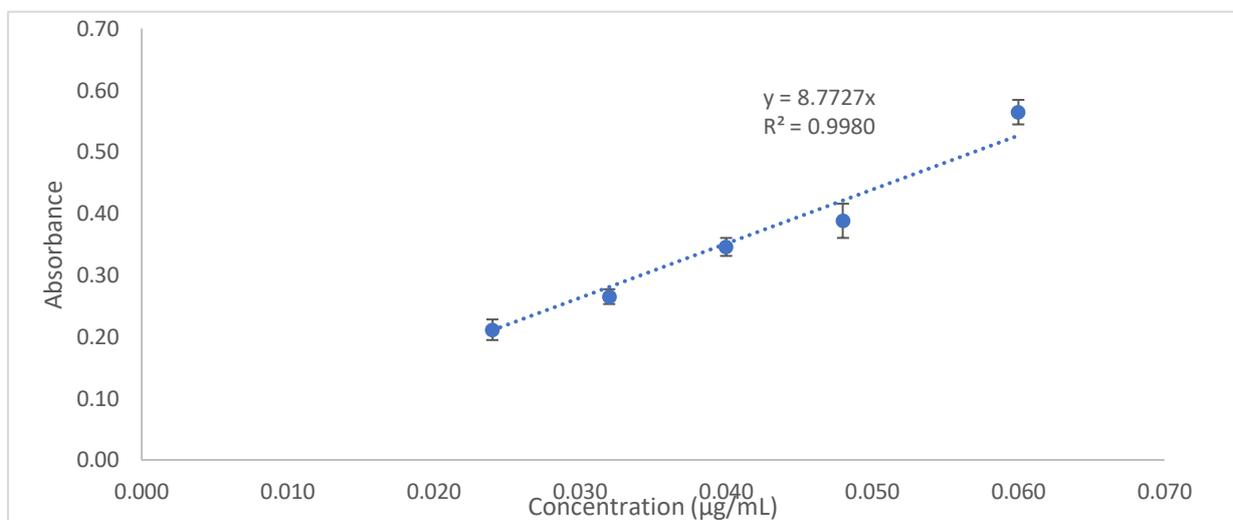
simulated saliva serves as a physiologically relevant medium that bridges the gap between in vitro testing and in vivo performance, helping to optimize formulation composition and predict the onset of therapeutic action for sublingual drug delivery systems.

Solubility study conducted instead of dissolution on the drug product. Specially (SD n=6) of product in small volume (e.g, 1 mL, 2 mL, 3 mL, 4mL and 5 mL) while stirring as a function

of time (e.g, 1 min, 2 min, 3 min, 5 min, 10 min) at pH 6.8 phosphate buffer (simulated saliva without enzymes) at 37-degree cent. [10,14,17,26]

Table 6: Solubility data of rizatriptan benzoate at pH 6.8 Buffer

Time	1 mL	2 mL	3 mL	5 mL
1	8.66	5.32	4.29	2.76
2	12.97	7.26	4.84	2.90
3	14.53	7.26	4.84	2.90
4	14.53	7.26	4.84	2.90



5.5 Mouthfeel

During preliminary evaluation using placebo granules the human volunteers reported that the granules passed through BSS sieve number 22 (about 700 micrometer) exhibited acceptable mouthfeel. Larger particles passed through BSS sieve number 18 were associated with grittiness, highlighting the importance of particle size control for patient acceptability.[1,4]

6. Analytical Method Development

6.1 Chromatographic Conditions

- Column: C18
- Mobile phase: buffer: Acetonitrile (70:30, v/v)
- Flow rate: 1.0 mL/min
- Detection: 225 nm
- Injection volume: 20 µL

6.2 Peak Purity

Peak purity was confirmed using PDA detection. Purity angle was consistently lower than the purity threshold, confirming absence of co-eluting impurities.

7. Method Validation (ICH Q2(R1))

- Linearity, accuracy, precision, specificity, robustness confirmed
- Robustness: small variations in flow rate, mobile phase, and wavelength showed no significant impact
- System suitability parameters complied with acceptance criteria. [21,22]

8. Forced Degradation Studies

8.1 Stress Conditions

To facilitate the formation of degradants, forced degradation study was conducted on rizatriptan solution under different conditions. [11,12]

Table 7: Stress Conditions

Stress Type	Condition
Oxidative	50% H ₂ O ₂ at 60 °C
Thermal	Dry heat 60–80 °C
Acid/Base	As per ICH
Photolytic	Visible light 1.2 million lux hours, 200 watt-hours/sq meter

The separation of degradation products of rizatriptan was carried out using High performance liquid chromatography followed by their identification at a wavelength of 225 nm. The forced degradation study on formulations was omitted because no evidence of drug excipients interactions was observed.

Mobile phase preparation:

- Granules equivalent to 10 mg of Rizatriptan were accurately weighed.
- Dissolved in mobile phase and sonicated for 10 minutes.
- Final dilution to 100 mL, filtered through 0.45 µm filter.

Table 8: Description of mobile phase

Parameter	Description
Column	C18, 250 mm × 4.6 mm, 5 µm
Mobile Phase	0.05 M Phosphate buffer (pH 3.0) : 6 M Acetonitrile (70:30)
Flow Rate	1.0 mL/min
Detection Wavelength	225 nm
Injection Volume	20 µL
Column Temperature	30°C
Run Time	10 minutes
Retention Time	~4.5 minutes

System suitability:

This method is suitable for routine quality control and stability analysis of Rizatriptan Granules. [12]

Parameter	Acceptance Criteria	Result
Retention Time (RT)	Consistent ($\sim 4.5 \text{ min} \pm 0.2 \text{ min}$)	4.5 min
Theoretical Plates	> 3000	4200
Tailing Factor	< 2	1.1
% RSD (5 Injections)	$\leq 2\%$	0.32%

8.2 Justification of Oxidative Conditions

High-strength H_2O_2 was required due to oxidative stability of rizatriptan. The conditions produced 10–20% degradation, fulfilling ICH requirements.

9. Stability Studies**9.1 Packaging**

- Paper sachets: proposed final packing
- Aluminium sachets: controlled pack to protect against moisture, oxygen, and light. [3,11]

9.2 Kinetic Analysis

Model	Rate Constant	R ²
Zero-order	0.46 %/month	0.991
First-order	0.01 %/month	0.985
Pseudo-order	0.01%/month	0.984

Zero-order kinetics best described degradation of rizatriptan.

10. Mass Balance

Mass balance values remained within 95–105%, confirming conservation of drug-related material and validating the stability-indicating nature of the method. [11,12]

11. Regulatory Justifications

- Dissolution testing: The classical method of Dissolution testing was modified to suit the purpose in case of sublingual dosage form.
- Ruggedness: Since the developed analytical method is to be used for research purpose only it will not be transfer to another laboratory therefore ruggedness was not carried out.
- Replicate stability testing: Not mandated by ICH Q1A(R2)

12. Conclusion

Multiparticulate sublingual granules of rizatriptan benzoate provide rapid disintegration, enhanced mucosal absorption, improved patient compliance, and robust stability. The formulation and analytical approach comply with ICH guidance and support the suitability of MDDS for fast-acting migraine therapy.

DISCUSSION

Multiparticulate Drug Delivery Systems: Scientific Rationale

Multiparticulate drug delivery systems were chosen to overcome the limitations of conventional single-unit dosage forms. The distribution of the dose into multiple discrete units minimizes localized drug concentration, reduces the risk of irritation, and provides more consistent plasma levels. This approach also lowers the risk of dose dumping, improving patient safety. Moreover, multiparticulates offer greater formulation flexibility, enabling modification of drug release through coating or compositional changes.

Suitability of Multiparticulate Systems for Sublingual Delivery

The sublingual route requires rapid wetting, fast disintegration, and efficient mucosal contact within a limited saliva volume. Multiparticulates are particularly advantageous under these conditions due to their high surface-area-to-volume ratio, which promotes rapid hydration and dispersion. Unlike conventional sublingual tablets that may feel bulky and uncomfortable, multiparticulates spread uniformly across the sublingual mucosa, improving contact with the absorption surface and enhancing drug permeation. The reduced risk of accidental swallowing further improves dose reliability and therapeutic predictability.

Justification for Rizatriptan Benzoate as a Model Drug

Rizatriptan benzoate is a fast-acting antimigraine agent where rapid onset of action is clinically critical. Oral administration is often compromised during migraine attacks due to nausea and vomiting. Sublingual multiparticulate delivery bypasses gastrointestinal transit and hepatic first-pass metabolism, resulting in faster systemic absorption. The physicochemical properties of rizatriptan, including high aqueous solubility, make it suitable for rapid mucosal absorption when formulated as small multiparticulate units.

Formulation Design and Excipient Selection

The formulation was designed to achieve rapid wetting, fast disintegration, acceptable mouthfeel, and adequate mechanical integrity. Mannitol was selected as the primary diluent due to its pleasant cooling sensation, sweetness, and high water solubility, which collectively enhance patient acceptability and promote rapid dissolution in saliva. Starch powder acted as a disintegrant, facilitating rapid granule breakup upon contact with saliva, while starch paste served as a water-soluble binder providing sufficient granule strength without significantly retarding disintegration. The balanced excipient composition ensured optimal sublingual performance.

Effect of Process Variables on Granule Characteristics

Variations in mixing time, drying time, temperature, binder concentration, and disintegrant concentration influenced granule formation and performance. Higher binder concentrations improved granule integrity but prolonged disintegration, whereas increased disintegrant levels reduced disintegration time. Drying temperature and duration affected residual moisture content, which in turn influenced stability and mouthfeel. Optimization of these parameters resulted in granules with rapid wetting, acceptable mechanical properties, and reproducible performance.

Disintegration Behavior of Multiparticulate Granules

Rapid disintegration is the most critical performance parameter for sublingual multiparticulates. The optimized granules demonstrated fast break up in saliva due to their small particle size, high surface area, and starch-based disintegration mechanism. These results

align with pharmacopeial expectations for orally disintegrating systems and confirm the suitability of multiparticulates for rapid sublingual drug delivery.

Drug content and Uniformity of content

The evaluation of drug content and uniformity of content of rizatriptan benzoate sublingual granules demonstrated that the granules contained 98.5–99.2% of the label claim, with a mean content of 99.2%, falling well within the acceptable pharmacopeial limits of 90–110%. Uniformity of content analysis of ten individual doses showed values ranging from 98.2% to 100.8%, with a mean of 99.45% and a low relative standard deviation of 0.87%, indicating homogeneous distribution of the drug throughout the granules. These results confirm that the granulation and mixing processes were effective, ensuring accurate dosing and uniformity, which is particularly important for sublingual administration where rapid dissolution in saliva and consistent therapeutic effect is required. Overall, the study establishes that the prepared sublingual granules meet pharmacopeial standards and are suitable for further evaluation and development.

Dissolution Study: Scientific Non-Relevance

Dissolution study is not applicable for sublingual granules in classical sense therefore dissolution method was used as recommended by FDA. Because pharmacopoeia does not specify any specific apparatus for sublingual dosage form. So that is why that dissolution method was modified. Sublingual drug absorption occurs through mucosal permeation in the presence of minimal saliva volume, whereas conventional dissolution testing employs large aqueous volumes that represent gastrointestinal conditions. For rizatriptan benzoate sublingual granules, rapid disintegration and mucosal absorption are more relevant indicators of performance than in-vitro dissolution, making dissolution testing scientifically unjustified.

Mouthfeel and Patient Acceptability

Mouthfeel is a critical determinant of patient compliance for sublingual formulations. Multiparticulates with particle sizes below 500 μm were found to be acceptable, whereas larger particles produced a gritty sensation. The optimized formulation balanced rapid disintegration with acceptable sensory characteristics, ensuring patient comfort without compromising drug release or absorption.

Analytical Method Performance and Peak Purity

The developed HPLC method demonstrated adequate specificity and sensitivity for rizatriptan benzoate. Peak purity analysis using PDA detection confirmed the absence of co-eluting impurities, establishing the method as stability-indicating. Minor variations in detection wavelength (225–227 nm) were observed in case of rizatriptan solution and its formulation under different conditions. This variation was attributed to solvent and pH effects and are consistent with UV spectroscopic principles.

Forced Degradation and Stability-Indicating Capability

Forced degradation studies conducted on the API under oxidative, thermal, acidic, and basic conditions successfully generated degradation products without complete destruction of the drug. Oxidative stress was observed in case of 50% hydrogen peroxide at 60 °C. This was above the ICH recommended conditions to achieve measurable degradation due to the inherent oxidative stability of rizatriptan. Thermal and Photolytic degradation of exposed samples

produced no additional peaks as compared to controlled samples, indicating thermal stability or formation of non-UV-detectable products. These outcomes are acceptable under ICH Q1A(R2) and confirm the robustness of the analytical method.

Stability Behavior and Kinetic Interpretation

Stability studies revealed a linear decline in assay over time under accelerated conditions, best described by zero-order kinetics. The high correlation coefficient supports a constant degradation rate, likely governed by environmental exposure rather than concentration-dependent reactions. The selected packaging system significantly influenced stability, with aluminium sachets providing superior protection against moisture and oxygen compared to paper sachets.

Mass Balance and Method Reliability

Mass balance values within 5% of the label claim, confirming that the degradation products were adequately accounted for and that no significant loss of drug-related material occurred during stress studies. This further validates the stability-indicating nature of the analytical method and the reliability of the degradation data.

Regulatory and Methodological Justifications

Certain tests, including dissolution, ruggedness, and replicate stability analysis, were not performed based on scientific and regulatory rationale. The multiparticulate nature of the formulation, intended sublingual route, and single-laboratory research scope justified these exclusions in accordance with ICH Q1A(R2) and Q2(R1).

References

1. Acceptability of placebo multiparticulate formulations in children and adults. (2018). *Scientific Reports*. 8:27446.
2. Al-Hashimi, N., Begg, N., Alany, R.G., Hassanin, H., & Elshaer, A. (2018). Oral modified release multiple-unit particulate systems: Compressed pellets, microparticles and nanoparticles. *Pharmaceutics*. 10(4):176.
3. Aulton, M.E., & Taylor, K.M.G. (2018). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. 5th ed. London: Elsevier.
4. Development of orally disintegrating tablet evaluation measures. (2024). *International Journal of Novel Research and Development*. 9(7):f946.
5. Dingalwar, A.A. (2024). Polyelectrolyte complex-based multiparticulate drug delivery system: A special emphasis on chitosan and alginate. *Asian Journal of Pharmacy*. 18(2).
6. Dixit, R.P., & Puthli, S.P. (2009). Oral strip technology: Overview and future potential. *Journal of Controlled Release*. 139(2):94–107.
7. Formulation of multiparticulate systems as lyophilised orally disintegrating tablets. (2011). *PubMed*.
8. Gavali, H., Nair, D., & Patel, D. (Year not specified). Multiparticulate drug delivery system and their processing techniques. *World Journal of Pharmaceutical Research*.
9. Ghebre-Sellassie, I., & Knoch, A. (2007). Pelletization techniques. In: Swarbrick J. (Ed.), *Encyclopedia of Pharmaceutical Technology*. 3rd ed. New York: Informa Healthcare. pp. 2728–2745.
10. Hearnden, V., Sankar, V., Hull, K., Juras, D.V., Greenberg, M., Kerr, A.R., et al. (2012). New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Advanced Drug Delivery Reviews*. 64(1):16–28.

11. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (2003). *ICH Q1A(R2): Stability testing of new drug substances and products*. Geneva: ICH.
12. International Council for Harmonisation (ICH). (2005). *ICH Q2(R1): Validation of Analytical Procedures—Text and Methodology*. Geneva: ICH.
13. Pabari, R.M., & Ramtoola, Z. (2012). Application of multiparticulate systems for oral drug delivery. *Advances in Pharmacoepidemiology and Drug Safety*. 1(1):1–7.
14. Patel, V.F., Liu, F., & Brown, M.B. (2011). Advances in oral transmucosal drug delivery. *Journal of Controlled Release*. 153(2):106–116.
15. Rajesh, N., Swetha, A., & Vidya, J.S. (Year not specified). Formulation and evaluation of multiparticulate drug delivery system. *World Journal of Pharmaceutical Research*.
16. Sachdeva, V., Alam, M.S., Kumar, R., & Kataria, M.K. (2013). Oral multiunit pellet extended-release dosage form: A review. *International Current Pharmaceutical Journal*. 2(10):177–184.
17. Shojaei, A.H. (1998). Buccal and sublingual drug delivery systems. *Indian Journal of Pharmaceutical Sciences*. 60(1):1–9.
18. Singh, M., Ullapu, P.R., Mariadoss, A.V.A., Kumar, S., & Kang, S.G. (2025). Development of pH-sensitive multiparticulates for orally disintegrating tablets of proton pump inhibitors: Physicochemical characterization and drug release studies. *Pharmaceutics*. 17(9):1187.
19. Singh, M.K., Mazumder, R., Padhi, S., & Singh, D.K. (2022). Formulation development and optimization of bioenhanced sublingual tablets of rizatriptan benzoate to combat migraine. *Indian Journal of Pharmaceutical Education and Research*. 56(2):91.
20. Sirisha, K., Vijaya Sri, K., Suresh, K., Kamalakar Reddy, G., & Devanna, N. (2013). A review of pellets and pelletization process—A multiparticulate drug delivery system. *International Journal of Pharmaceutical Sciences and Research*. 4(6):2145–2158.
21. Skoog, D.A., Holler, F.J., & Crouch, S.R. (2007). *Principles of Instrumental Analysis*. 6th ed. Belmont (CA): Thomson Brooks/Cole.
22. Snyder, L.R., Kirkland, J.J., & Dolan, J.W. (2010). *Introduction to Modern Liquid Chromatography*. 3rd ed. Hoboken (NJ): Wiley.
23. Sudhakar, Y., Kuotsu, K., & Bandyopadhyay, A.K. (2006). Buccal bioadhesive drug delivery—A promising option for orally less efficient drugs. *Journal of Controlled Release*. 114(1):15–40.
24. Systematic screening of particle-engineered polymers for the preparation of multiparticulates embedded orally disintegrating tablets. (2024). *Journal of Drug Delivery Science and Technology*. Article 101302.
25. Zakowiecki, D., et al. (2020). Preparation of delayed-release multiparticulate formulations and evaluation using biorelevant dissolution methods. *Journal of Drug Delivery Science and Technology*. 60:101986.
26. Zhang, H., Zhang, J., & Streisand, J.B. (2002). Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. *Clinical Pharmacokinetics*. 41(9):661–680.