RESEARCH ARTICLE

Formulation Development and Evaluation of Effervescent Granules of Rizatriptan Benzoate

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Received: 19th January, 2024; Revised: 19th March, 2024; Accepted: 10th June, 2024; Available Online: 25th June, 2024

ABSTRACT

The present study describes the formulation and development of rizatriptan benzoate (RZB) effervescent granules and compares its dissolution rate against the conventional rizatriptan benzoate tablets. Earlier, placebo-effervescent granules were prepared to optimize the concentration of citric acid, NaHCO3 and tartaric acid and its effect on CO_2 content and effervescence time. Effervescent granules were prepared by direct sifting and blending of ingredients. Rizatriptan effervescent granules were prepared by the addition of RZB in the above-optimized placebo granule formula and evaluated for various physicochemical parameters. Later, the effervescent RZB granules were compared with the marketed RZB tablets for the dissolution rate. It was observed that RZB effervescent granules have the fastest dissolution rate compared with marketed RZB tablets. The optimized RZB effervescent granule formulation is quite superior to that of RZB conventional tablets to relieve the patients from migraine and the possible associated hyperacidity it.

Keywords: Placebo granules, Effervescent granules, Rizatriptan Benzoate, Dissolution.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.2.58

How to cite this article: Jadhav SJ, Gangurde AB, Jadhav JA. Formulation Development and Evaluation of Effervescent Granules of Rizatriptan Benzoate. International Journal of Pharmaceutical Quality Assurance. 2024;15(2):911-916.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Effervescent granules are soluble, have a high dissolution rate and are the most popular solid oral dosage form. Various analgesic, antacid, and cough formulations have been developed as effervescent granulates, which are convenient and stable dosage forms.[1] Effervescent formulations typically include a blend of active ingredients, acids or acid salts, and carbonates or bicarbonates. When these components are combined with water, they release carbon dioxide, producing effervescence.[2] The chemical reaction involved is illustrated below.

$C_6H_8O_7$ (aq) + 3$NaHCO_3$ (aq) → $Na_3C_6H_5O_7$ (aq) + 4H_2O + 3CO_2 (g) ↑

In above reaction, water acts as a catalyzing agent and it enhances the reaction rate, which makes the formulation unstable. Hence the manufacturing process is selected to avoid contact with water.[3] RZB is 5-HT1B/1D receptors agonist, which is widely used in the treatment of migraine headaches.[4] RZB conventional tablet is approved worldwide but effervescent granules/tablet is not approved; hence attempt was made to formulate an effervescent formulation of RZB and compare it with the currently marketed tablet formulation. RZB was chosen as its antimigraine drug with superior efficacy over other antimigraine drugs and having lesser side effects. Conventional RZB tablets have various limitations, such as low oral bioavailability (45%) due to high pre-systemic metabolism.[5] Swallowing a conventional tablet with water can exacerbate nausea and vomiting associated with migraines. Another limitation of oral treatment is the gastrointestinal disturbances often accompanying migraines.[6] The study was designed with the objective as, to enhance rate of dissolution for a quicker onset of action. To overcome the tablet swallowing issue as, an effervescent formulation is completely dissolved in liquid and the patient needs to drink liquid instead of swallowing the tablet and to enhance the permeability of the drug to increase the oral bioavailability.

Early in the development process, 3^3 factorial designs were used to manufacture the placebo granules. The concentrations of $NaHCO_3$, citric acid, and tartaric acid were chosen independent variables, while CO_2 content and effervescence time were regarded as dependent variables. The application of 3^3 factorial designs led to the logical optimization of acid content and its basis, as well as its influence on CO_2 release and effervescence time.

Based on the study design it was observed that F5 formulation gives higher CO_2 release and lesser effervescence time. Once the above factors were optimized, RZB effervescent

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granules were prepared by addition of RZB in an above optimised formula. Then the dissolution rate of these RZB effervescent granules was compared with that of the marketed RZB tablets.

MATERIAL AND METHODS

Materials

RZB (MSN), Citric acid (Merck), tartaric acid (Merck), sodium bicarbonate (Merck), orange flavor (International flavors and fragrances), colloidal silicon dioxide (Evonik Degusa), PEG-6000 (Canton), sucralose (Gangwal Chemicals), lactose (DFE Pharma), sodium stearyl fumarate (Merck).

Methods

Formulation of placebo effervescent granules

Placebo effervescent granules contain an acid source, either in combination or individually, an alkali source as sodium bicarbonate, lactose as a water-soluble diluent, glidant, lubricant, sweetener, and flavoring agent. Placebo granules were prepared by following process-Weighed all the ingredients, co-sifted lactose, acid source, alkali source through 30# ASTM sieve (A), co-sifted colloidal silicon dioxide, flavoring agent, sucralose, PEG 6000 through 30# ASTM sieve (B), mixed A and B blends in double cone blender for 15 minutes at 10 RPM (C). Sodium stearyl fumarate (SSF) passed through 40 sieve followed by blending with granules C, for 5 minutes. Temperature of NMT 25°C and relative humidity of NMT 25% was maintained throughout the process.[7]

Formulation optimization: placebo effervescent granules using 3^3 factorial design

After selecting the process for effervescent granulation, the components (excipients) and all formulation parameters were optimized using the design of the experiment (DoE). Independent variables X1 (Citric Acid), X2 (Sodium Bicarbonate) & X3 (Tartaric acid) were taken in design, Table 1. While trials were evaluated for dependent variables like effervescence time and CO_2 content.

Independent Variables

- Concentration of citric acid (X1)
- Concentration of sodium bicarbonate (X2)
- Concentration of tartaric acid (X3)

Dependent Variables

- CO_2 content
- Effervescence time

By running of design of experiment 3^3 factorial designs it shown 27 runs with their composition as Tables 2 and 3.

As per DoE software with 3^3 factorial designs, 27 batches were taken to optimize the formulation. Each trial was evaluated for effervescence time (ET), CO_2 release (CR), bulk density (BD), and flowability of granules.

Formulation of RZB containing Effervescent Granules (F30)

Based on placebo-effervescent trials, the formula has a composition similar to trial No. F5 was selected for manufacturing of RZB-containing effervescent granules. It was manufactured as follows- Weighed all the ingredients, co-sifted rizatriptan benzoate (7.267 mg), lactose, an acid source, alkali source through 30# ASTM sieve (A), co-sifted colloidal silicon dioxide, flavoring agent, sucralose, PEG 6000 through 30# ASTM sieve (B), mixed A and B blends in double cone blender for 15 minutes at 10 RPM (C). Sifted sodium stearyl fumarate through 40# ASTM sieve and mixed with granules C, for 5 minutes. Temperature of NMT 25°C and relative humidity of NMT 25% was maintained throughout the process.

Table 1: Independent Variables of 3^3 factorial design

Factor	*Lower value (-1)*	*Mid value (0)*	*Higher (+1)*
Concentration of citric acid (X1)	86	96	106
Concentration of tartaric acid (X2)	20	25	30
Concentration of sodium bicarbonate (X3)	111	126	141

Evaluation of Effervescent Granules of RZB

Physical evaluation

- *Bulk and tapped density (BD, TD)*

The appropriate amount of granules was weighed and added to the measuring cylinder and the volume occupied was recorded. The tapping was performed at every two seconds from a height of 2.5 cm until the volume stabilized.[7] BD, TD were determined.

BD = Granules Wt./Volume

TD= Granules wt. / Tapped volume

- *Carr's Index (CI)*

It was determined using below formula[8]

$$CI = [(TD - BD) \times 100] / [TD]$$

- *Hausner's ratio (HR)*

It was determined using below formula

$$HR = TD/BD$$

- *Angel of repose*

The cone's height (H) and base cone's diameter (D) were used to calculate the tan of the angle of repose (AR).[9]

Chemical Evaluation

Percent assay

The samples were analyzed at 225 nm to estimate the drug content using UV spectroscopy (JASCO V-730).[10]

Calibration curve of rizatriptan benzoate

A 10 mg sample of the drug was accurately weighed and dissolved in 100 mL of pH 6.8 phosphate buffer to get

Table 2: 3^3 Factorial design run trial batches

Ingredients (mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*	*F13*
Citric acid	106	106	106	86	106	96	106	106	86	86	86	96	96
Tartaric acid	25	20	20	20	25	20	20	30	30	30	25	25	25
Sodium bicarbonate	111	111	141	126	141	141	126	111	111	141	126	111	126
Lactose (DCL 11)	89.7	94.7	64.7	99.7	59.7	74.7	79.7	84.7	104.7	74.7	94.7	99.7	84.7
Sucralose	2	2	2	2	2	2	2	2	2	2	2	2	2
PEG 6000	6	6	6	6	6	6	6	6	6	6	6	6	6
Colloidal silicon dioxide	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
Strawberry flavor	1	1	1	1	1	1	1	1	1	1	1	1	1
SSF	6	6	6	6	6	6	6	6	6	6	6	6	6
Total	350	350	350	350	350	350	350	350	350	350	350	350	350

Table 3: 3^3 Factorial design run trial batches

Ingredients (in mg)	*F14*	*F15*	*F16*	*F17*	*F18*	*F19*	*F20*	*F21*	*F22*	*F23*	*F24*	*F25*	*F26*	*F27*
Citric acid	96	106	96	86	86	86	96	86	106	96	106	96	86	96
Tartaric acid	20	25	30	20	25	20	25	30	30	25	20	30	30	30
Sodium bicarbonate	126	126	111	141	141	111	111	141	126	111	141	141	126	126
Lactose (DCL 11)	89.7	74.7	94.7	84.7	79.7	104.7	99.7	74.7	69.7	99.7	64.7	64.7	79.7	79.7
Sucralose	2													
PEG 6000	6													
Colloidal silicon dioxide	3.3													
Strawberry flavor	1													
SSF	6													
Total	350	350	350	350	350	350	350	350	350	350	350	350	350	350

100 µg/mL stock solution. Aliquots ranging from 1.0 to 8.0 mL of the stock solution were then diluted to 100 ml with phosphate buffer at pH 6.8, resulting in serial dilutions of 1 to 8 µg/mL. The maximum absorbance of RZB was detected at 225 nm. Table 4 and Figure 1 shows the details of the calibration curve.

Drug release from the effervescent granule formulation i.e. Dissolution study

It was performed in pH 6.8 phosphate buffer (900 mL; 37°C ± 0.5°C) using USP II apparatus at 50 rpm. The test solutions were withdrawn at 5, 15, 30, and 45 minutes. Each time a 5 mL sample was taken, and equal volume was added. The samples were analyzed at 225 nm to calculate drug release.

Effervescence time

It was determined by adding a single dose in 250 mL of water. The effervescent time was recorded as the time taken for a clear solution to form. The resulting times fell within the acceptable ranges specified by the USP for this study.[10-16]

CO_2 release

After adding effervescent granules equivalent to one dose to 100 mL of 1N sulfuric acid solution, the weight changes were measured at the end of dissolution. The resulting weight difference was used to determine the CO_2 dosage amount (mg) per unit and was displayed accordingly.

pH of the effervescent solution

A pH meter can be used to find the solution's pH. After quick resolution, dissolve one unit dose granule in 200 mL of water at 21 to 25°C and check the pH.

Evaluation of RZB Conventional Tablets

Uniformity of thickness

Tablet thickness was measured using a Vernier caliper and the thickness.

Hardness test

The test was performed on ten randomly selected tablets. The tablet's hardness was determined using an Erweka Hardness tester and measured in Newton.

Weight variation test

To test for weight variability, the tablets were randomly selected and weighed individually.

Friability test

Initially, ten tablets were weighed to determine their initial weight. The tablets were then placed in the Roche friability, which was operated at 25 rpm for 4 minutes or up to 100 revolutions. Afterward, the tablets were reweighed to determine the final weight, and the percentage friability was calculated.

Table 4: Observation for standard calibration curve by UV

S. No.	*Concentration (µg/mL)*	*Absorbance (average) ± SD (n = 3)*
1	0	0 ± 0
2	1	0.155 ± 0.0040
3	2	0.296 ± 0.0044
4	3	0.411 ± 0.0046
5	4	0.502 ± 0.0031
6	5	0.648 ± 0.0030
7	6	0.812 ± 0.0036
8	7	0.881 ± 0.0066
9	8	1.052 ± 0.0201

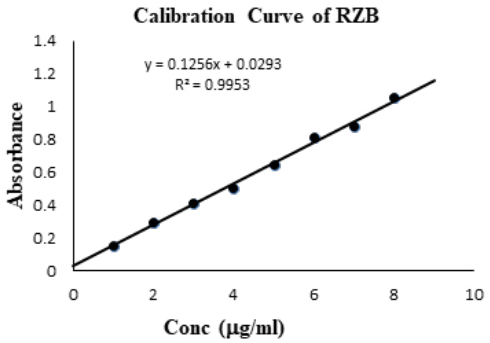

Figure 1: Linearity of RZB in pH 6.8 phosphate buffer

Table 5: Physical evaluation: Placebo and RZB effervescent granules

Formulation No.	*ET (Sec)*	*CR (mg)*	*BD*	*Td*	*CI*	*HR*	*AR*	*Flowability*
F1	41 ± 0.3	45 ± 0.3	0.41	0.49	16.32653	1.195122	36	Fair flow
F2	41 ± 0.6	48 ± 0.2	0.35	0.42	16.66667	1.2	37	Fair flow
F3	39 ± 0.2	117 ± 0.1	0.39	0.47	17.02128	1.2051282	36	Fair flow
F4	35 ± 0.3	91 ± 0.3	0.39	0.44	11.36364	1.1282051	32	Good flow
F5	23 ± 0.1	119 ± 0.2	0.42	0.48	12.5	1.1428571	32	Good flow
F6	35 ± 0.2	116 ± 0.1	0.34	0.42	19.04762	1.2352941	36	Fair flow
F7	34 ± 0.4	95 ± 0.2	0.39	0.48	18.75	1.2307692	36	Fair flow
F8	39 ± 0.1	51 ± 0.2	0.41	0.46	10.86957	1.1219512	33	Good flow
F9	43 ± 0.2	53 ± 0.3	0.36	0.42	14.28571	1.1666667	32	Good flow
F10	58 ± 0.2	114 ± 0.2	0.42	0.51	17.64706	1.2142857	36	Fair flow
F11	108 ± 0.2	93 ± 0.2	0.33	0.39	15.38462	1.1818182	32	Good flow
F12	99 ± 0.2	49 ± 0.1	0.45	0.51	11.76471	1.1333333	33	Good flow
F13	119 ± 0.1	97 ± 0.2	0.43	0.52	17.30769	1.2093023	37	Fair flow
F14	126 ± 0.2	85 ± 0.1	0.39	0.48	18.75	1.2307692	37	Fair flow
F15	129 ± 0.2	89 ± 0.1	0.34	0.44	22.72727	1.2941176	37	Fair flow
F16	144 ± 0.1	54 ± 0.3	0.42	0.48	12.5	1.1428571	34	Good flow
F17	139 ± 0.2	115 ± 0.2	0.4	0.48	16.66667	1.2	36	Fair flow
F18	125 ±	116 ± 0.3	0.41	0.49	16.32653	1.195122	36	Fair flow
F19	97 ± 0.1	55 ± 0.2	0.36	0.42	14.28571	1.1666667	32	Good flow
F20	91 ± 0.1	51 ± 0.1	0.37	0.46	19.56522	1.2432432	37	Fair flow
F21	88 ± 0.2	109 ± 0.2	0.39	0.46	15.21739	1.1794872	33	Good flow
F22	6 ± 1	84 ± 0.1	0.4	0.48	16.66667	1.2	37	Fair flow
F23	69 ± 0.2	58 ± 0.1	0.41	0.46	10.86957	1.1219512	33	Good flow
F24	75 ± 0.2	113 ± 0.2	0.42	0.5	16	1.1904762	37	Fair flow
F25	72 ± 0.2	108 ± 0.3	0.43	0.52	17.30769	1.2093023	37	Fair flow
F26	68 ± 0.2	91 ± 0.2	0.36	0.45	20	1.25	36	Fair flow
F27	51 ± 0.1	93 ± 0.1	0.4	0.48	16.66667	1.2	36	Fair flow
F30	22 ± 3	119 ± 3	0.44	0.51	13.72549	1.1590909	32	Good flow

RESULTS AND DISCUSSION

This research work deals with the development of effervescent RZB granules followed by tablets with a rapid dissolution rate compared with conventional formulation of RZB. The dissolution rates of effervescent granules and traditional tablets were studied. The physical parameters of the effervescent granules are presented in Table 5.

Table 6: Physical properties of conventional tablets

Formulation No.	Hardness	Thickness	Disintegration time	Weight variation
Marketed RZB Tablets	90-121 N	3.22 ± 0.21 mm	9–10 minutes	± 2.3%

Table 7: Chemical Prop: Placebo effervescent granules vs RZB effervescent granules

Formulation No.	*%Drug content*	*pH of effervescent solution*
F30	99.06	5.5
F38	99.51	NA

Table 8: %Drug release from effervescent granules vs conventional tablet

	%Drug release	
	Effervescent granules	*Marketed RZB tablet*
Time (Min)	*F30*	*F38*
0	00.00 ± 0.00	00.00 ± 0.00
5	72.01 ± 1.85	41.72 ± ± 3.25
15	85.34 ± ± 3.25	68.16 ± 3.55
30	90.55 ± 3.55	79.81 ± 4.10
45	101.15 ± 1.68	98.05 ± 3.56

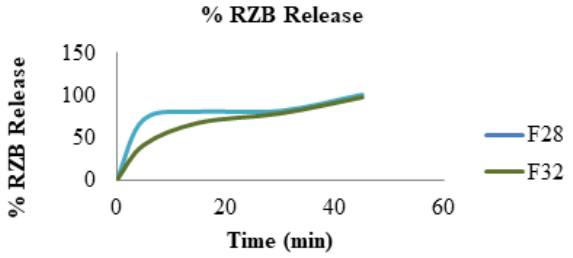

Figure 2: %Drug release from effervescent granules and tablet formulations of RZB

Table 9: Accelerated stability results

Test	*Initial*	*3 Month 40°/75% RH (HDPE bottle having moisture scavenger)*
%Drug content	99.06	99.01
%Moisture content	1.92	2.01
%Drug release at 45 minutes	101.15	98.90
Effervescent time (Second)	22	24
CO_2 release (mg)	119	117

Physical Evaluation: Placebo Effervescent Granules and RZB Effervescent Granules

Based on the above properties it is observed that placebo effervescent blend having formulation trial no. F5 has good flow properties, lesser effervescent time and a good amount of CO_2 release. Hence, for the preparation of RZB containing effervescent granules trial no. F5 is considered as a best formulation. Trial No. F30 contains RZB and has good flowability, with effervescent time- only 22 seconds and 119 mg of CO_2 release. Marketed RZB tablets also have good tableting properties, i.e., hardness, thickness, disintegration time, and weight variation, which is mentioned as follows in Table 6.

Chemical Evaluation: Placebo Effervescent Granules and RZB Effervescent Granules

Drug content

The drug content in the effervescent formulation and conventional tablet is within the acceptable limit of 90 to 110%. Values are mentioned in the Table 7.

Drug Release Comparative Evaluation: Effervescent Granules *vs* Conventional Tablet

Drug release from the effervescent granule formulation and conventional tablet formulation is given in the Table 8. Conventional tablet has slow drug release rate compared with effervescent granules. Graphical representation of the same is given in the Figure 2.

Accelerated Stability Testing of Optimized Formulation

F30 (optimized batch) was kept in a stability chamber at the accelerated condition as per ICH guidelines and studied for various parameters.[15] Results of the same is as follows in Table 9.

Stability study report shows that prepared effervescent granules are stable throughout the period of 3 months at accelerated conditions. All the analytical reports are well within acceptable limits. No significant changes were observed after three months of testing.

CONCLUSION

Optimized RZB effervescent formulation has good flowability, lesser effervescent time and the highest content of CO_2 release. Further, this formulation was compared with the marketed RZB tablet. Based on the above study, it was found that the rate of drug release/dissolution was very much faster in RZB effervescent formulation compared to that of conventional tablets. Ultimately it is assumed that faster rate of release absorption of the drug will be faster compared to conventional formulation. Also, the higher amount of alkali used in the formulation may neutralize the hyperacidity commonly associated with migraine. CO_2 may enhance the solubility and permeation of RZB through the paracellular pathway. Ultimately, contributing to enhanced therapeutic efficacy, patient relief, and compliance. All the above study suggests RZB effervescent formulation is superior to that of the traditional formulation. Further research will be conducted to compare the permeability of RZB effervescent granule formulation with conventional tablets, utilizing suitable permeation enhancers.

ACKNOWLEDGMENT

The authors would like to thank the management of KBHSS Trust's Institute of Pharmacy, Malegaon, Maharashtra, India, for providing the research facilities.

REFERENCES

1. Aulton ME. Pharmaceutics: the science of dosage form design. 2nd ed. New York: Churchill Livingstone; 2002.
2. Kabir AK, Huda NH, Jhanker YM, Shamin K. Formulation development of verapamil hydrochloride tablet by effervescent method. Stamford Journal of Pharmaceutical Sciences. 2010;3(1):34-37.
3. Ipci K, Öktemer T, Birdane L, Altintoprak N, Muluk NB, Passali D, Lopatin A, Bellussi L, Mladina R, Pawankar R, Cingi C. Effervescent tablets: a safe and practical delivery system for drug administration. ENT updates. 2016 Apr 1;6(1):46.
4. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD. Rizatriptan vs sumatriptan in the acute treatment of migraine: a placebo-controlled, dose-ranging study. Archives of neurology. 1996 Nov 1;53(11):1132-1137.
5. www.drugbank.com
6. Waikar SB, Shinde PS, Chandak KK, Umekar MJ, Bhoyar GS, Kolsure PK. Preformulation and thermodynamic study of rizatriptan benzoate nasal gel formulation. Journal of Pharmacy Research. 2009;2(5):986-990.
7. Patel SS, Patel NM. Development of directly compressible co-processed excipient for dispersible tablets using 32 full factorial design. Int J Pharm Pharm Sci. 2009;1(1):125-148.
8. Senthil A, Suresh Kumar P, Raju CH, Mohideen S. Formulation and evaluation of gastric oral floating tablet of glipizide. International Journal of Biological and Pharmaceutical Research. 2010;1(2):108-113.
9. Kaerger JS, Edge S, Price R. Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose. European journal of pharmaceutical sciences. 2004 Jun 1;22(2-3):173-179.
10. Patel N, Madan P, Lin S. Development and evaluation of controlled release ibuprofen matrix tablets by direct compression technique. Pharmaceutical development and technology. 2011 Feb 1;16(1):1-1.
11. The United State Pharmacopeia (USP), 46, NF41, USA: The United State Pharmacopeia Convention Inc; 2023
12. Akhtar SE, Hussain SO, Mandal SK. Formulation development and characterization effervescent tablets along with levocetirizine dihydrochloride. Asian Journal of Pharmaceutical and Clinical Research. 2020;13(8):124-130.
13. Kumari AS, Subhasish S, Kaushik DK, Annapurna MM. UV-spectroscopic methods for estimation of rizatriptan benzoate in pharmaceutical preparations. International Journal of ChemTech Research. 2010;2(1):653-659.
14. Jadhav S, Gangurde A. A Bird Eye View on Effervescent Drug Delivery System. International Journal of Drug Delivery Technology 2023;13(3):1046-1058.
15. Dekivadia M, Gudigennavar A, Patil C, Umarji B. Development & optimization of fast dissolving tablet of levocetirizine HCl. International Journal of Drug Development & Research. 2012 Apr;4(2):237-246.
16. Trocóniz IF, Armenteros S, Planelles MV, Benítez J, Calvo R, Domínguez R. Pharmacokinetic-pharmacodynamic modelling of the antipyretic effect of two oral formulations of ibuprofen. Clinical pharmacokinetics. 2000 Jun; 38:505-518.