COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF RIZATRIPTAN BENZOATE ORAL DISPERSIBLE TABLETS

SHEEBA F. R., KUNDAN CHAUDHARY
Mallige College of Pharmacy, Bangalore 90
Email: sheebagiles@gmail.com

Received: 25 Mar 2020, Revised and Accepted: 22 May 2020

INTRODUCTION

Nowadays, dispersible drug delivery systems are comprehensively used to expand bioavailability and patient compliance. Over the past three years, or dispersible tablets (ODTs) have gained considerable attention as a desired substitute to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. ODTs are solid dosage forms containing medicinal substances that disintegrate rapidly, usually within seconds, when placed on the tongue with or without the intake of water [1]. Usually, super disintegrants are added to a drug formulation to simplify the breakup or disintegration of tablet or capsule content into smaller particles that can dissolve more rapidly than in the absence of disintegrants. The faster the dissolution of the drug into the solution, the quicker is the absorption and onset of clinical effect. The bioavailability of certain drugs may increase due to the absorption of drugs in the oral cavity or also due to pregastric absorption of drug from saliva that pass down into the stomach [2]. Drug absorbed via “oral cavity” directly enters into systemic circulation by a jugular vein ensuring a rapid onset of action, avoidance of the first-pass metabolism, and drug degradation in gastric region and enzymatic hydrolysis in the intestine. The various technologies used to prepare ODT’s include direct compression, sublimation, tablet molding, spray drying and mass extrusion [3].

The new generation anti-migraine drug, rizatriptan benzoate is a potent and selective 5-hydroxytryptamine receptor agonist and is considered more effective than the traditional triptans for the treatment of acute migraine attack. Chemically it is 3-[2-(dimethylamino) ethyl]-5-(1H-1, 2, 4-triazol-1-ylmethyl) indole monobenzoate. A 10 mg dose of rizatriptan benzoate is equipotent to a 100 mg dose of sumatriptan, the traditional anti-migraine drug. The bioavailability of rizatriptan benzoate is about 45% which is superior to a poor 14-17% of sumatriptan [4].

The present study is to formulate rizatriptan oral dispersible tablets, by direct compression technique, using the various kinds of super disintegrants (Natural and Synthetic) along with studies of their role in tablet disintegration and dissolution, which are being used in the formulation to provide the safer and effective drug delivery with patient compliance.

MATERIALS AND METHODS

Rizatriptan Benzoate was obtained as a gift sample from Hetero Drug Ltd. Vishakhapatnam. Crospovidone, Sodium starch glycolate, Gellan gum, Karya gum and other excipients were obtained from Indian fine chemicals Mumbai. All other chemicals used were of analytical grade.

Formulation process

Oral dispersible tablets of Rizatriptan Benzoate were prepared by direct compression technique according to the formula given in table 1. The ingredients were sifted through a 20# mesh and then the required quantities weighed. All the ingredients except magnesium stearate and flavoring agents were uniformly blended. After mixing the drug and the excipients for 20 min, magnesium stearate and the flavoring agents were added and further mixed for an additional 2 min [5]. The tablet mixture was then compressed (8 mm diameter, concave punches) using a single punch tablet compression machine (Cadmach).

Preformulation studies

Calibration curve for rizatriptan benzoate

The standard calibration curve graph was obtained by preparing aliquots of standard solution of rizatriptan benzoate in 0.1 N HCl (pH 1.2) and the absorbance at 280 nm was measured after suitable dilution using UV/Visible spectrophotometer [6].

Drug-excipients compatibility studies

FT-IR spectroscopic study was performed to check the compatibility between drug, polymer and other excipients in the formulation. The FT-IR spectra of a drug alone and drug with polymers were obtained by KBr method and compared with the standard FT-IR spectrum of the pure drug.
Table 1: Formulation of an oral dispersible tablet of rizatriptan benzoate

| Ingredients          | Quantity (mg) present in each tablet |
|----------------------|--------------------------------------|
| Rizatriptan          | F1 7.27, F2 7.27, F3 7.27, F4 7.27, F5 7.27, F6 7.27, F7 7.27, F8 7.27, F9 7.27, F10 7.27, F11 7.27, F12 7.27 |
| Benzoate            |                                      |
| Sodiumstarch glycolate |                                      |
| Cross povidone      |                                      |
| Gellan gum          |                                      |
| Karya gum           |                                      |
| Mannitol            | 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18 |
| Magnesium stearate  | 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42, 1.42 |
| Sodium Saccharin    | 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5, 1.5 |
| Aerosil 200         | 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75, 0.75 |
| Microcrystalline cellulose101 | 113.56, 110.56, 107.56, 113.56, 110.56, 107.56, 106.06, 100.06, 94.06, 106.06, 100.06, 94.06 |

Note: Defined bulk weight per tablet is 100 mg containing rizatriptan benzoate equivalent to 5 mg of rizatriptan.

Evaluation of pre-compression parameters

**Bulk density**

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M) [7].

\[ \rho_b = \frac{M}{V_b} \]

**Tapped density**

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the drug excipients mixture was measured [8]. The tapped density (ρt) was calculated using the following formula.

\[ \rho_t = \frac{M}{V_t} \]

**Angle of repose**

Angle of repose (α) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the pile (r) was measured and the angle of repose was calculated.

\[ \alpha = \tan^{-1} \left( \frac{h}{r} \right) \]

**Carr’s Index**

Carr’s Index or % compressibility is helpful to determine flow properties of powder mixture, which is calculated as follows [8]:

\[ C = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \]

Where,

- ρt - Tapped density
- ρb - Untapped bulk density

**Hausner’s ratio**

Hausner’s ratio is an index of ease of powder flow; it is calculated by the following formula.

\[ \text{Hausner’s ratio} = \frac{\rho_t}{\rho_b} \]

Where,

- ρt - Tapped density
- ρb - Untapped bulk density

Post compression parameters

**Weight variation test**

Weight variation was determined by weighing 20 tablets individually; the average weight and percent variation of each tablet were calculated [9].

**Hardness test**

Hardness was determined using a Monsanto hardness tester. Three tablets were randomly picked from each batch and hardness is expressed in kg/cm². The mean and standard deviation were also calculated.

**Thickness of tablets**

The thicknesses of the tablets were determined by placing tablet between 2 arms of the Vernier Caliper. Five tablets were taken from each batch and average thickness values were calculated.

**Friability of tablets**

The friability of the tablets was determined for twenty tablets. Tablets were taken randomly from each batch. After weighing, the tablets were placed in the plastic chamber of the friability tester (Erweka tablets friability tester) for 100 revolutions [10]. The friability is evaluated by the following formula:

\[ F = \frac{(W_1 - W_2)}{W_1} \times 100 \]

Where,

- W1 is the weight of tablets before testing and
- W2 is the weight of tablets after testing.

**In vitro disintegration test**

Disintegration test was studied by placing one tablet in each tube of the basket and top portion of each tube was closed with disc. The disintegrating apparatus was run using water maintained at 37±2 °C. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiments were carried out in triplicate from each formulation [11].

**Drug content uniformity**

For the content uniformity test, ten tablets of each batch were weighed and powdered. Aliquot of this powder containing rizatriptan benzoate equivalent to 10 mg of rizatriptan was accurately weighed, suspended in approximately 100 ml of 0.1 N HCl and shaken for 15 min. Then the solution was filtered by using Whatmann filter paper and 5 ml of the filtrate was suitably diluted to 50 ml with the same buffer and analyzed spectrophotometrically at 280 nm. The amount of rizatriptan benzoate was estimated using the standard calibration curve of the drug. The study was carried out in triplicate for each batch of the formulation [6].

**In vitro dissolution studies**

*In vitro* dissolution of rizatriptan benzoate oral dispersible tablets was carried out in USP dissolution test apparatus Type II (Labindia, Mumbai) employing a paddle stirrer at 50 rpm using 500 ml of 0.1 N HCl (pH 1.2) at 37±0.5 °C as dissolution medium. One tablet was used
in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 280 nm. The volume withdrawn at each time interval was replaced with 5 ml of fresh dissolution medium to compensate loss. Cumulative percent of drug released was calculated and plotted against time [12]. The results are shown in fig. 1.

**Stability studies**

The selected formulation F9 was tested for its stability studies. Short-term stability studies were performed at temperature 40±2 °C over a period of 3 mo. five tablets were packed in amber coloured screw-capped bottles and kept in a stability chamber maintained at 40±2 °C. Samples were taken at 1 mo interval for their drug content estimation, including physical parameters. At the end of 3 mo period, the tablets were then evaluated for hardness, friability, in vitro disintegration time, wetting time, uniformity of content and assay [13].

**RESULTS AND DISCUSSION**

FTIR spectroscopic studies indicated that the drug is compatible with all the excipients. Oral dispersible tablets, each containing rizatriptan benzoate equivalent to 5 mg of rizatriptan, were prepared by direct compression method by using gelan gum, karya gum as natural superdisintegrant and sodium starch glycolate, crospovidone as synthetic superdisintegrants in different ratios, either alone or in combination. Directly compressible excipients, microcrystalline cellulose and mannitol were used as diluents to enhance mouth feel. Aerosil was used as a glidant and magnesium stearate was acting as lubricant. A total of twelve formulations were designed and evaluated for the comparative study of synthetic and natural superdisintegrant (table 1).

Table 2 and table 3 represents all the tablet precompression and post compression parameters evaluated. Bulk density was found to be between 0.350±0.002 and 0.370±0.002 gm/cm3 and tapped density between 0.370±0.002 and 0.370±0.002 gm/cm3 for all formulations. From density data carr’s index was calculated and found to be between 11.20±0.16 and 15.17±0.08 %, Hausner’s ratio was found below 1.17. Angle of repose was found to be in the range of 27.15±0.48 and 29.89±1.07°. All the formulation shows thegood blend properties for direct compression and hence tablets were prepared by using direct compression technology.

### Table 2: Evaluation of pre-compression parameters

| Formulation batch | Bulk density (gm/cm³) | Tapped density (gm/cm³) | Carr’s index (%) | Hausner’s ratio | Angle of repose (°) |
|-------------------|-----------------------|-------------------------|-----------------|----------------|-------------------|
| F1                | 0.31±0.0005           | 0.360±0.004             | 11.94±0.78      | 1.13±0.009     | 28.39±1.12        |
| F2                | 0.30±0.0001           | 0.340±0.002             | 11.20±0.16      | 1.12±0.002     | 29.89±1.07        |
| F3                | 0.31±0.0007           | 0.355±0.001             | 14.20±0.04      | 1.16±0.012     | 28.30±1.19        |
| F4                | 0.31±0.0003           | 0.359±0.003             | 13.64±0.07      | 1.15±0.007     | 29.60±1.09        |
| F5                | 0.31±0.0012           | 0.363±0.002             | 12.94±0.16      | 1.14±0.003     | 28.61±0.08        |
| F6                | 0.31±0.0015           | 0.360±0.001             | 13.05±0.23      | 1.15±0.017     | 29.39±1.17        |
| F7                | 0.305±0.020           | 0.358±0.002             | 14.08±0.09      | 1.17±0.015     | 29.35±0.05        |
| F8                | 0.30±0.0007           | 0.350±0.003             | 13.71±0.03      | 1.15±0.005     | 27.95±0.48        |
| F9                | 0.31±0.014            | 0.370±0.02              | 14.86±0.02      | 1.17±0.006     | 28.52±1.38        |
| F10               | 0.30±0.012            | 0.360±0.005             | 14.16±0.05      | 1.16±0.004     | 28.07±1.56        |
| F11               | 0.31±0.005            | 0.369±0.008             | 15.17±0.08      | 1.17±0.011     | 28.70±1.21        |
| F12               | 0.30±0.004            | 0.356±0.001             | 13.20±0.15      | 1.15±0.008     | 28.95±1.11        |

Note: All values are expressed as mean±SD. n=3.

Drug content was found to be high (≥99.87%) in all the tablet formulations. The tablets containing synthetic and natural superdisintegrants in different ratio showed in vitro disintegration time in the following order, combination of Crospovidone and karya gum>Crospovidone>gelan gum and combination of sodium starch glycolate>sodium starch glycolate. The tablets containing drug, crospovidone and karya gum ratio:1.5:1.5 combination showed faster disintegration (13 sec) than tablets containing drug and crospovidone alone ratio 1:3.

### Table 3: Evaluation of post compression parameters

| Formulation batch | Weight variation (mg) n=10 | Hardness (kg/cm²) | Thickness (mm) | Friability (%) n=10 | Drug content (%) | Disintegration time (sec) |
|-------------------|----------------------------|------------------|---------------|---------------------|-----------------|--------------------------|
| F1                | 151.20±0.7                 | 3.50±0.2         | 2.65±0.03     | 0.22±0.2            | 98.43±1.2       | 90±0.4                   |
| F2                | 149.95±1.1                 | 4.0±0.3          | 2.60±0.02     | 0.24±0.3            | 97.52±1.3       | 82±0.8                   |
| F3                | 152.23±2.4                 | 3.50±0.2         | 2.70±0.12     | 0.21±0.2            | 98.43±1.5       | 70±0.2                   |
| F4                | 152.45±0.9                 | 3.50±0.18        | 2.55±0.2      | 0.23±0.18           | 98.86±1.5       | 52±0.5                   |
| F5                | 151.36±0.6                 | 3.0±0.12         | 2.60±0.8      | 0.20±0.12           | 99.29±1.1       | 35±0.5                   |
| F6                | 150.7±0.9                  | 3.5±0.2          | 2.63±0.17     | 0.20±0.12           | 97.14±1.2       | 54±1.1                   |
| F7                | 151.95±2.0                 | 3.5±0.18         | 2.60±0.3      | 0.23±0.18           | 98.00±1.2       | 48±1.2                   |
| F8                | 149.59±1.3                 | 3.0±0.5          | 2.60±0.6      | 0.24±1.2            | 98.86±0.7       | 32±1.3                   |
| F9                | 151.29±1.0                 | 3.0±0.1          | 2.73±1.7      | 0.21±0.8            | 99.87±0.2       | 13±0.2                   |
| F10               | 152.3±0.7                  | 4.0±1.2          | 2.65±0.7      | 0.19±0.1            | 98.71±1.4       | 83±1.6                   |
| F11               | 151.34±1.4                 | 3.5±0.10         | 2.67±0.9      | 0.21±0.2            | 98.45±0.5       | 77±1.2                   |
| F12               | 152.3±4.0                  | 3.5±0.8          | 2.70±0.1      | 0.21±0.3            | 97.72±0.9       | 64±0.5                   |

Note: All values are expressed as mean±SD. n=3.

The thickness of the prepared tablets was found to be in the range of 2.5±0.02 to 2.7±0.17 mm, while the weight of all the tablets was found to be in the range of 149.5±1.3 to 152.4±1.9 mg. Hardness of the tablets was found to be in the range of 3.0±0.12 to 4.0±0.3 kg/cm and percentage weight loss in the friability test was less than 1% in all the batches, which was an indication of good mechanical resistance of the tablets. The values of tablet hardness and percent friability indicated good handling property of the ODTs.

The effect of superdisintegrants on the dissolution of rizatriptan from the ODTs tablets is shown as table 4. In vitro dissolution study on a best formulation (F9) exposed that more than 99.6% drug was released within 12 min and followed by formulation F6 crospovidone showed 96.25% within 12 min. From this dissolution, studies confirmed that the drug release increased to increase in the concentration of crospovidone.
CONCLUSION

From the present study, it can be concluded that a combination of natural and synthetic super disintegrants like karaya gum and crospovidone showed better disintegrating property than the most widely used synthetic super disintegrants like sodium starch glycolate and in the formulations of ODTs. These super disintegrating agents are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating, nontoxic in nature and biodegradable.

FUNDING
Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

ACKNOWLEDGMENT

The Authors acknowledge Mallige College of Pharmacy, Bengaluru for providing the necessary laboratory facilities to complete the work. The authors are also thankful to Director and Principal of Mallige College of Pharmacy Dr. Shiva Kumar Swamy for his motivation and support.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Rewar S, Singh CJ, Bansal BK, Pareek R, Sharma AK. Oral dispersible tablet: an overview; development, technologies and evaluation. Int J Res Dev Pharma Life Sci 2014;3(4, Suppl 6):1223-35.
2. Malay KB, Chotlilaya, Sumit Chakraborty. Overview of the oral dispersible tablet. Int J Pharma Tech Res 2012;4 Suppl 4:1712-20.
3. Kushagra K, Gauravi Xavier, Suresh KJ, Aashish P, Saksham K, Vipin, et al. Fast dissolving tablet-a novel approach. Int J Pharm Res Allied Sci 2016;5 Suppl 2:311-22.
4. Motilal M, Srikant K, Sivagirish Babu G, Ganendra K, Maninmaran V, Damoharan N. Formulation and evaluation of rizatRIPTAN benzoate orally disintegrating tablets. Int J Drug Dev Res 2012;4 Suppl 1:171-23.
5. Kuchekar BS, Badhan AG, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: a novel drug delivery system. Indian Drugs 2004;41:952-8.
6. Indian Pharmacopoeia. 4th ed. Vol. 2. New Delhi: The Controller of Publications; 1996. p. 735–6.
7. Sreedevi S, Sandip B. Formulation and evaluation of dispersible tablet of cefixime trihydrate. Int J Curr Pharm Res 2012;4 Suppl 9:243-9.
8. Sheetal B, Raval K, Sandip B. Formulation and evaluation of fast dissolving tablets of Amlodipine besylate by using sublimation technique. Int J Pharma Sci Rev Res 2011;6 Suppl 2:178-82.
9. Kangala Vijaya S, Geed Bharat R, Dashmukhi R, Chitimalla Ajay K. Preparation and evaluation of montelukast oral dispersible tablets by direct compression. Int Res Pharm 2012;3 Suppl 7:315-8.
10. Sunil Kumar BG, Felix JV, Vishwanath BA. Formulation and evaluation of dispersible tablet of cetirizine trihydrate. Int J Pharma Drug Analysis 2010;1 Suppl 9:185-68.
11. Duddeshnababu S, Sai Kishore V. Formulation and evaluation of fast dissolving tablets of Amlodipine besylate by using fenugreek seed mucilage and ocimum gum. Int J Pharm Bio Sci 2015:2 Suppl 1:1-12.
12. Laxmi CSR, Nitesh JP, Hitesh P, Sagar P. Formulation and evaluation of oral dispersible tablets of cinnarizine using sublimation technique. Int J Pharma sci Rev Res 2011;6 Suppl 2:178-82.
13. Kushagra K, Gauravi Xavier, Suresh KJ, Aashish P, Saksham K, Vipin, et al. Fast dissolving tablet-a novel approach. Int J Pharm Res Allied Sci 2016;5 Suppl 2:311-22.