SHORT COMMUNICATION

DESIGN AND EVALUATION OF RIVAROXABAN EFFERVESCENT GRANULES

ABSTRACT

The present investigation is concerned with the formulation and development of rivaroxaban (RN) effervescent granules using a dry granulation process. A 2^3 factorial design was employed using Design-Expert® software to develop an ideal formulation. Formulations were evaluated, and showed outstanding flow characteristics, compositions with low moisture content contributing to their stability, effervescence time of less than 180 seconds and *in vitro* profile of over 90% for 30 minutes.

Keywords: Rivaroxaban, effervescent granules, *in vitro* dissolution, moisture content

INTRODUCTION

Effervescent granules serve as effective and easily dissolving dosage form, providing a simple and efficient delivery method for new chemical entities. These granules infused with water just before administration, rapidly disperse due to the internal release of carbon dioxide. They offer advantages such as enhanced flowability, wetness, particle size homogeneity, and stability, making them particularly beneficial for individuals with difficulty in swallowing pills[1]. The specific focus of this study involves the preparation of immediate-release effervescent granules containing a unit dose of rivaroxaban, achieved using citric acid and tartaric acid[2].

MATERIALS AND METHODS

A gift sample of rivaroxaban was provided by the Hyderabad-based Alphamed Formulation Pvt. Ltd.; citric acid, tartaric acid, and sodium lauryl sulphate were procured from SD Fine Chemicals, Mumbai. Sodium bicarbonate was purchased from Merck, Mumbai. Hydrochloric acid was from Thermo Fisher Scientific India Pvt. Ltd.

Preparation of rivaroxaban effervescent granules using 2^3 factorial designs

A three-factor plan for optimization has been used. The independent factors, as well as the dependent variables, were chosen. In the three categories, there were two independent variables. The highest and lowest factor values were marked as +1 and -1.

Developing effervescent granules of rivaroxaban

By employing tartaric acid, citric acid and sodium bicarbonate in the dry granulation process, rivaroxaban effervescent granules were prepared. The acids and alkalis were weighed and transferred to a china dish, thoroughly mixed with a glass rod, and heated for 5 minutes in a water bath until a wet mass was formed. The resultant granules were dried in a hot air oven at 50 °C after the wet mixture was passed through sieve no.10 and 22[3].

Evaluation of rivaroxaban effervescent granules

Angle of repose

To calculate the angle of repose, granules were allowed to freely flow down a funnel on graph paper that was placed on a horizontal surface. The angle of repose was determined from this equation by measuring the height and diameter of the resulting cone curve[4].

$$\text{Tan } \theta = \frac{h}{r}$$

Bulk density

A dry 100 mL cylinder was filled with 16 g of a granular blend without being compacted. The apparent unsettled volume, V_0, was measured after the granules had been thoroughly leveled without being compacted. The following formula was used to determine the bulk density[5].

$$\text{Bulk density } (\rho) = \frac{M}{V_0}$$

Determination of tapped density

Accurately weighed quantity of granules were transferred to measuring cylinder. The sample was tapped 500 times after observing its initial amount. Unless there is a difference of less than 2% between consecutive measurements, taped volume is not measured.

$$\text{Tapped density } (\rho) = \frac{M}{V_f}$$

Table I: Formulation chart of rivaroxaban effervescent granules using design expert

Formula	Rivaroxaban	A Sodium bicarbonate	B Citric acid	C Tartaric acid	Response R1 Effervescence time ± SD	Response R2 Disintegration time within 5 mins ± SD
I	0.2	3.7	2.4	2	88 ± 0.57	2.59 ± 2.5
II	0.2	3.7	2.8	2	75 ± 0.57	2.5 ± 2.1
III	0.2	3.7	2.4	4	112 ± 0.1	3.1 ± 2.7
IV	0.2	3.7	2.8	4	101 ± 0.57	3 ± 3.5
V	0.2	5.1	2.4	2	60 ± 0.57	2.3 ± 2.3
VI	0.2	5.1	2.8	2	67 ± 0.1	2.15 ± 3.2
VII	0.2	5.1	2.4	4	127 ± 0.57	3.22 ± 2.2
VIII	0.2	5.1	2.8	4	131 ± 0.57	3.41 ± 2.1

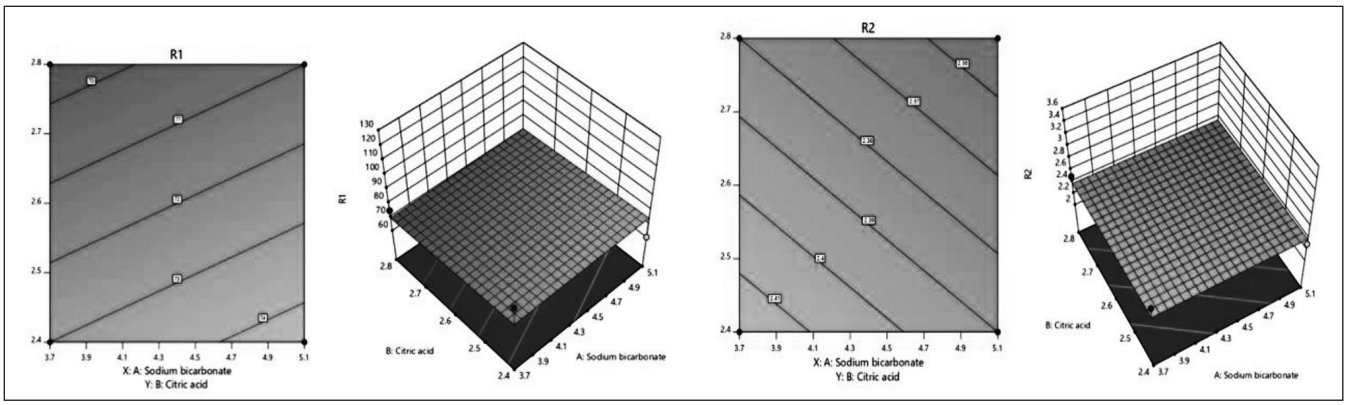

Fig. 1: Contour plot and 3D response surface plot of response R1 and R2

Carr's index

The following equation should be used to compute the values of the Carr's index, which represents the flow characteristics of the powder combination[7].

$$\text{Carr's index} = \frac{[(\text{Tapped density-Bulk density})}{\text{Tapped density}]} \times 100$$

Determination of Hausner's ratio

The tapped-to-bulk density ratio is known as the Hausner's ratio[8].

Estimating the effervescence time

Single dose of granules is taken in a beaker containing 100 mL of water in order to measure effervescence *in vitro.* The duration of *in vitro* effervescence was calculated[9].

Determination of moisture content

The granules were reduced to a fine powder in a dry mortar. Accurately weighed 0.5g sample was quickly tranfer to a titration vessel and mixed until the Karl Fischer reagent was entirely dissolved[10].

$$\text{Moisture content} = \frac{V \times F}{\text{Weight of sample}} \times 100$$

Disintegration time

A single administration of the effervescent granules should be dissolved in 200 mL of water at 25°C in glassware. The numerous gas bubbles that were forming around each granule ought to have disappeared and are now either dissolved or dispersed throughout the water[11].

Determination of drug content

Weighing was done before the effervescent granules were dissolved in the acetonitrile-water solvent. The stock solution was used to make subsequent dilutions, and the resultant dilution concentration was determined at 249 nm. Drug content was determined by employing the following equation:

Drug content = (absorption × dilution factor) slope[12]

Dissolution studies

In a covered jar, 900 mL of 0.1 N HCl with 0.2% SLS dissolution medium was added, and the temperature was held constant at 37±0.5°C[13] . The paddle was set at 50 revolutions per minute, with each sample being obtained at a separate time. 5 mL of the dissolving media were extracted and replaced with an identical volume maintained at 37±0.5°C. After the sample was taken out, it was filtered using Whattman filter paper, diluted with 0.1N HCl, and quantified with a UV spectrophotometer at 249 nm[14].

RESULTS

Optimization studies of the batches by factorial design

Formulations of rivaroxaban effervescent granules using Design-Expert® are depicted in Table I. Effervescence time and disintegration time within 5 mins are taken as response R1 and response R2. Contour plot and 3D response surface graph are depicted in the Fig. 1.

Flow properties of the granules

The bulk density ranged from 0.43 to 0.63. The tapping density ranged from 0.61 to 0.95. A range of 23.90 to 33 was discovered for the angle of repose. The prepared granules Carr's index results fall in the range of 12.1 to 14.3. The values of Hausner's ratio are found to be between 1.13 to 1.29.

Effervescence time determination

The effervescence time values ranged from 60 to 131 sec. The resulting ranges were acceptable.

Moisture content

The moisture content varied from 0.01±0.006 and peaked at 0.06 ± 0.01.

Disintegrating time

The disintegrating time values ranged from 2.15± 3.2 to 3.41 ± 2.1 mins.

Determination of drug content

The percentages of drug content ranged from 96.81 ± 0.10 – 99.12 ± 0.03.

Dissolution study

Within 5 minutes, all 8 formulae had a very good release profile. The burst of the granules into tiny particles, aided by the creation of effervescence, improves rivaroxaban solubility.

DISCUSSION

The rivaroxaban effervescent granules were prepared by dry granulation process. The Design-Expert® software had showed the equation for factorial formulations, Response R1 (Effervescence time) = 94.25+ 0.75A -1.75B+22.25C and Response R2 (Disintegration time within 5 mins) = 2.78+ 0.0138A- 0.0188B+ 0.3987C. Since both A and C have positive coefficients, it was concluded that A & C showed direct affect on the response R1 and R2. All 8 formulae had excellent flow qualities, according to the data. The relatively low level of moisture shows the granules capacity to maintain their effervescence quality and free flow ability. All the batches showed disintegrating time within 5 minutes, which was within the acceptable range. All the batches have a drug content value of more than 90%. F6 has the highest rate of drug release (98% in less than 30 minutes). The good amount of carbon dioxide released may be responsible for F6's good release pattern.

CONCLUSION

The granules were prepared by dry granulation technique with citric acid, tartaric acid and sodium bicarbonate. 2^3 factorial design was employed, and the formulation was optimized using a Design-Expert® software. Formulated granules gave satisfactory results for various physicochemical properties, effervescence time, disintegrating time and *in vitro* drug release. F6 has shown disintegration time in 2.15 mins and the highest drug release, thereby qualifying the suitability of rivaroxaban effervescent granules.

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