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TO MASK THE BITTER TASTE OF RIZATRIPTAN BENZOATE AND DEVELOP WATER DISPERSIBLE TABLETS BY USING INDION 234 AND KYRON T-114

Vikrant V. Chilate*[1], Harsha V. Sonaye[2] and Dr. C. A. Doifode[3]

*[1,2]Taywade Institute of Diploma in Pharmacy, Koradi, Nagpur, Maharashtra.
[3]Taywade College of Pharmacy, Koradi, Nagpur, Maharashtra.

***Corresponding Author: Vikrant V. Chilate**
Taywade Institute of Diploma in Pharmacy, Koradi, Nagpur, Maharashtra.

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ABSRACT
Rizatriptan benzoate is anti migraine drug. Report indicates that, it has very bitter taste, which deters its use in geriatrics patient thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy. To mask the bitter taste of Rizatriptan benzoate and develop water dispersible tablets by using the combination of Indion 234 and Kyron T-114a well palatable and patient compliant Rapid disintegrating tablet could be successfully prepared using direct compression method. The prepared optimized tablet showed rapid disintegration as well as rapid dissolution. Thus the rapid disintegrating tablet of bitter drug having better taste and pleasant mouth feel can be successfully formulated.

KEYWORDS: Rizatriptan benzoate, Indion 234, Kyron T-114 and water dispersible tablets.

INTRODUCTION

Over the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing. Since the development cost of a new drug molecule is very high, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy, bioavailability together with reduced dosing frequency and the production of more cost effective dosage forms[1] to fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as dispersible tablet, which disintegrate rapidly in small amount of water, usually in a matter of few seconds. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.[2]

Since the development cost of a new drug molecule is very high, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy, bioavailability together with reduced dosing frequency and the production of more cost effective dosage forms.[1] Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.[2] There is need for non-invasive delivery systems persists due to patients poor acceptance of and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.[3]

MATERIALS AND METHODS

Material: Rizatriptan benzoate from Alkem Labs. Ltd. Mumbai, Indion 234, KYRON T-114 from Vama Pharma, Nagpur, Glycine, Microcrystalline cellulose, Sodium starch glycolate, Cross povidone, Aspartame, Sodium carboxymethyl cellulose, Magnesium stearate, Aerosil.

Methods

Characterization of drug and excipients

Characterization of drug: The characterization of drug was carried out by conducting various tests including;
Appearance: Appearance of the drug was visually recorded by physical texture of drug.

Organoleptic properties: These are preliminary characteristics of any substance, which are useful in the identification of specific material. Taste of sample was tested by panel of tastes following physical properties of drug were studied. Color, Taste, Odor.

Determination of melting range: It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals melting ranges are very sharp and constant. Since the crude drug contains the mixed chemicals they are described with certain melting range.

Procedure: Melting range was determined using glass capillary method. Drug filled capillary was placed in melting range apparatus containing liquid paraffin as heating medium and melting range was noted by using thermometer.[4]

Solubility analysis: The saturation solubility of Rizatriptan benzoate was determined by the equilibrium solubility method. Excess quantities of drug were added in to the 5 ml of each of distilled water, phosphate buffer (pH 6.8) and 0.1 M HCl contained in 25 ml glass vials and were shaken at constant temperature 37±1ºC over a period of 24 hr. Analysis of the drug solutions was carried out by recording absorbances at previously determined λ_{max} values using respective medium as blank.[5]

Loss on drying: LOD test is designed to measure the amount of water and volatile matters in the drug when dried under specified conditions.

Procedure: Accurately about 1 g Rizatriptan benzoate was weighed and the powder was kept in oven for 6 hr at 105ºC. At interval of 2 hr the moisture content was calculated.[5]

Spectral analysis of drug: λ_{max} and IR spectrum of Rizatriptan benzoate were determined.

A. Determination of λ_{max} in UV range: Quantity of 10 mg of drug was accurately weighed and transferred to previously dried 100 ml volumetric flask and dissolved using 10 ml distilled water. Final volume was made up to 100 ml with distilled water. From this stock solution, suitable dilutions were made and solution of 50 µg/ml concentrations was scanned in the range of 400 nm to 200 nm using distilled water as blank and λ_{max} was noted. Similarly, the λ_{max} values for solutions of drug in 0.1M HCl and phosphate buffer pH 6.8 were determined using corresponding solution as blank.

B. Preparation of standard calibration curve of drug

i. Preparation of standard calibration curve in distilled water: The stock solution 5(100 µg/ml) was prepared by dissolving accurately weighed 10 mg of drug in distilled water. The solutions in the concentration range of 10-100 µg/ml were prepared by appropriate dilutions of the stock solution. The UV absorbance of these solutions were recorded at previously reported λ_{max} value and calibration curve was plotted.

ii. Preparation of standard calibration curve in 0.1 M HCl: The stock solution (100 µg/ml) was prepared by dissolving accurately weighed 10 mg of drug in 0.1M HCl. The solutions in the concentration range of 10-100 µg/ml were prepared by appropriate dilutions of the stock solution. The UV absorbance of these solutions were recorded at previously reported λ_{max} value and calibration curve was plotted.

iii. Preparation of standard calibration curve in phosphate buffer pH 6.8: The stock solution (100 µg/ml) was prepared by dissolving accurately weighed 10 mg of drug in phosphate buffer pH 6.8. The solutions in the concentration range of 10-100 µg/ml were prepared by appropriate dilutions of the stock solution. The UV absorbance of these solutions were recorded at previously reported λ_{max} value and calibration curve was plotted.

C. Determination of infra red spectra: Spectral analysis was carried out by using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 –400 cm^{-1}. The procedure consisted of dispersing a sample of PZQ in KBr and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.[6]

Thermal behavior by differential scanning calorimetry: Thermal behavior of drug was studied by differential scanning calorimetry.

Procedure: The differential calorimetric scanning of drug was carried out by placing sample in aluminum crucible and heating at the rate of 10^0C/min in the range of 30 to 600^0C. Air was purged at the rate 50 ml/min.

X-ray diffraction: Dissolution properties of drug particles are affected greatly by nature and extent of crystallinity present in them. An amorphous or the metastable form dissolves faster because of the associated higher levels of internal energy and greater molecular mobility. These together enhance the thermodynamic properties of these forms as compared to crystalline state.

X-ray scattering measurements on Rizatriptan benzoate was carried out at a voltage of 40 kV and current of 25 mA using Cr as a tube anode material. The solid were exposed to Cu –K radiation angles from 10°-70°.[7]

Characterization of excipients

Appearance: Appearance of different excipient viz. crystalline, amorphous, smooth, greety etc was characterize by physical texture.

Organoleptic characteristics: Organoleptic properties was determine as per the procedure mentioned in above section.

Flow characterization

A. Bulk density: Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.

Procedure: A quantity of 15.0 g of drug powder was passed through 20# sieve to break any agglomerates formed during the drug storage. This quantity was introduced into a 50 ml measuring cylinder. The powder was level without compacting it and the apparent volume was measured.[5]

Bulk density = weight of sample in gram / volume occupied by the sample.

B. Tapped density: A quantity of 15.0 g of excipients was passed through 20# sieve to break any agglomerates formed during storage. This quantity was introduced into a 50 ml measuring cylinder. The graduated cylinder containing a known mass of blend was tapped for a fix time. Cylinder was tapped for 500 times initially and the tapped volume (V_1) was measured to the nearest graduated units repeated the tapping was repeated for additional 750 times and tapped volume (V_2) was measured to the nearest graduated units. If the difference between the two volumes is less than 2 percent then volume (V_2) is taken rather again tapping for additional 1250 times.[8]

Tapped density = Wt. of sample in g / Tapped volume

C. Hausner's ratio and Compressibility index: In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast and popular methods for predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.[8]

i. Hausner's ratio: Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density.[8] Hausner's ratio was calculated using following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

ii. Compressibility index: The compressibility index measures the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume which is due to rearrangement of packing occurring during tapping.[8] It is indicated as Carr's compressibility index (CI) and calculated using following formula,

$$\text{CI \%} = \frac{(\text{Tapped density} - \text{Bulk density})100}{\text{Tapped density}}$$

D. Angle of repose: Irregular flow of powders from the hopper produces tablets with non uniform weights. As a result content uniformity and dose precision cannot be achieved in production of tablets and capsules. Angle of repose is defined as the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane.[5]

Procedure: The angle of repose was determined by the glass funnel method. The height of the funnel was adjusted in a way that the tip of the funnel just touched to the apex of the hip of the powder. The accurately weighed quantity of powder blend was passed through the funnel. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using following formula,

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

Where, h = Height of pile.r = Radius of the base of pile.θ = Angle of repose.

Particle size: Measurement of particle size involves the electromagnetic sieve shaking of the sample through the series of successively arranged sieves (Sieve No. 20, 30, 40, 60, 80, 100 and receiver) and weighing the portion of the sample retained on each sieve and calculation of same.

Masking of bitter taste of drug using various techniques: The techniques used for masking the bitter taste of Rizatriptan benzoate was;

1) Ion exchange resin: Weak cation exchange resin: Kyron T-114, Indion 234.

2) Rizatriptan benzoate and ion exchange resin complex: Complex of Rizatriptan benzoate with weak cation exchange resins (Indion 234 and Kyron T114) were prepared. Resin was activated before preparation of Rizatriptanbenzoate: resin complex.[39] Following steps were carried out to prepare these complex.[9]

a) Activation/purification of resin: Resins were purified by following procedure.

Accurately about 5 g of the resin was weighed, added in a beaker containing 100 ml deionised water and stirred with magnetic stirrer for 15 min. Dispersion was filtered with Whatman filter paper (No. 41). The resin was consequently washed with methanol (50 ml) and then with deionised water to remove organic and colored impurities. The wet resin was treated with 0.1 M HCl (100 ml) for 1 hr with the help of magnetic stirrer. The dispersion was filtered and rinsed with deionised water for several times. The washing was continued with deionised water till the pH of the filtrate comes near to neutral. The resin was drained on a buchner funnel using mild suction and dried overnight at 50ºC.[10]

b) Preparation of drug:resin complex (Resinate): The drug resin complex was prepared by batch process using variable proportions of resins. An accurately weighed quantity of activated resin was dispersed in a beaker containing 100 ml of deionised water and stirred for 20 min with the help of magnetic stirrer. Required quantity of Rizatriptan benzoate was slowly added with continuous stirring. Stirring was continued for 3 hr. During stirring the pH of the dispersion was frequently

checked and adjusted to required value using 1M NaOH solution. The complex formed was separated from dispersion by filtration (Whatman paper-No. 41) and washed with deionised water (3-4 portions of 25 ml each) to remove uncomplexed drug. The complex formed was dried overnight and stored in tightly closed container.[4] Complex of drug:resin in different ratio were prepared using above procedure. All these resinate were evaluated for its taste masking ability and loading of drug/drug content.

Table No 1: Composition of resinate of Rizatriptan benzoate with Indion 234 and Kyron T-114.

Sr. No.	Complex code	Complex of Rizatriptan benzoate and resin	Ratios of Rizatriptanbenzoate:resin
1	C1	Rizatriptanbenzoate:Indion 234	1:1
2	C3	Rizatriptanbenzoate:Indion 234	1:3
3	C5	Rizatriptanbenzoate:Indion 234	1:5
4	C7	Rizatriptanbenzoate:Indion 234	1:7
5	K1	Rizatriptanbenzoate:Kyron T-114	1:1
6	K3	Rizatriptanbenzoate:Kyron T-114	1:3
7	K4	Rizatriptanbenzoate:Kyron T-114	1:4
8	K5	Rizatriptanbenzoate:Kyron T-114	1:5

Evaluation of taste modified drug samples: The modified drug samples were evaluated for the following characteristics.

Characterization for probable interaction of drug and excipients

A.U V spectroscopy: Modified drug powders equivalent to 10 mg of Rizatriptan benzoate were dissolved separately in 0.1 M HCl and the final volume was made up to 100 ml. The solutions were appropriately diluted and were scanned in the UV range of 200-400 nm to note the shift in λ_{max} value. However, in case of modified powders of drug resin complex, dried gels prepared with PEG 6000, the acidic solutions were stirred for about 2 hr and the solutions were filtered and the filtrates were appropriately diluted before scanning in the UV range.

B. Infra red spectroscopy: IR absorption spectra of taste modified drug samples were recorded as per the procedure mentioned in section.

Evaluation of taste of Rizatriptan benzoate and its taste modified forms by panel method

The taste modified drug powders were evaluated for change in bitter taste of Rizatriptan benzoate by appointed panel of tastees. Healthy human volunteers of either sex in the age group of 20-30 yrs were selected. Informed consents were obtained from them. Procedure of test was orally described to them before start of the test. The procedure was carried out as follows,

Coding of drug and its taste modified forms was done using non overlapping abbreviations. About 5 ml dispersion of drug powder (equivalent to unit dose) in water was used. Dispersion was held in oral cavity for 15 sec by the volunteers. Content was spit off from oral cavity by the volunteers into wash basin. The oral cavity was rinsed with sufficiently large volume of purified water until the after taste of drug is completely ceased. Same procedure was followed for all the taste modified form of Rizatriptan benzoate. The volunteers were asked to rate both pure drug as well as the individual modified drug samples i.e. resinates in the scale of 0 to 4 as follows,

0 - No bitter taste, 1 - Slightly bitter taste, 2 - Moderately bitter taste, 3 - Strong bitter taste, 4 - Very strong bitter taste

The scores from each volunteer were compared carefully and the most suitable approach (ratio 0-1) was judged.[11]

Effect of various parameters on drug loading in resinate: The drug: resin complex selected by panel of tastees were studied for various parameters affecting drug loading. The drug loading efficiency of the resin can be affected by various parameters. viz. concentration of the resin, pH, soaking time, stirring time and temperature. So it becomes necessary to study the effect of these parameter on resinate preparation.

i. Effect of pH on drug loading: Four separate resinates of drug: resin (Rizatriptan benzoate: Kyron T-114) in the selected ratio (1:4) were prepared at five different pH and studied for effect. An accurately weighed activated resin (300 mg) was dispersed in a beaker containing 100 ml of deionised water and stirred for 20 min with the help of magnetic stirrer. Rizatriptan benzoate (1.2 g) was slowly added to it with constant stirring. The pH of dispersion was adjusted to the specific pH by using 1 M NaOH and stirring continued to 3 hr. During Stirring pH of dispersion was frequently checked. The amount of the drug loaded at different pH was determined.[12]

Table No. 2: Effect of pH on drug loading.

Sr. No.	Drug :resin	Complex of Rizatriptan benzoate and resins	pH
1	1:4	Rizatriptan benzoate: Kyron T-114	5
2	1:4	Rizatriptan benzoate: Kyron T-114	6
3	1:4	Rizatriptan benzoate: Kyron T-114	7
4	1:4	Rizatriptan benzoate: Kyron T-114	8
5	1:4	Rizatriptan benzoate: Kyron T-114	9

ii. Effect of soaking time on drug loading

Five separate resinates of Rizatriptan benzoate with Kyron T114 (1:4) were prepared. About 1.2 g activated resin was weighed and soaked in deionised water (100 ml) for 0, 10, 20, 30 and 40 min respectively. After specified time Rizatriptan benzoate (300 mg) was accurately weighed and added to it. The pH was adjusted to previously selected value, stirring was continued for 3 hr. The amount of the drug loaded at different soaking time was determined.[13]

Table No. 3: **Effect of soaking time on drug loading.**

Sr. No.	Drug: Resin	Complex of Rizatriptan benzoate and resins	Time (min)
1	1:1	Rizatriptan benzoate: Kyron T-114	0
2	1:4	Rizatriptan benzoate: Kyron T-114	10
3	1:4	Rizatriptan benzoate: Kyron T-114	20
4	1:4	Rizatriptan benzoate: Kyron T-114	30
5	1:4	Rizatriptan benzoate: Kyron T-114	40

iii. Effect of stirring time on drug loading: Four different resonates of Rizatriptan benzoate with resin (1:4) was prepared by soaking 1.2 g of activated resin (30 min) into 100 ml of deionised water. 300 mg of Rizatriptan benzoate was added to each with constant stirring. The pH was adjusted to previously selected value and stirring was continued for 2, 3, 4 and 5 hr respectively. The amount of the drug loaded at different stirring time was determined.[14]

Table No. 4: Effect of stirring time on drug loading.

Sr.No.	Drug :resin	Complex of Rizatriptan benzoate with resins	Time (hr)
1	1:4	Rizatriptan benzoate: Kyron T-114	2
2	1:4	Rizatriptan benzoate: Kyron T-114	3
3	1:4	Rizatriptan benzoate: Kyron T-114	4
4	1:4	Rizatriptan benzoate: Kyron T-114	5

iv. Effect of temperature on drug loading: Resinates of Rizatriptanbenzoate: Kyron T114 (1:4) were prepared by soaking 1.2 g of activated resin (30 min) in deionised water (100 ml). 300 mg of Rizatriptan benzoate was added to it with constant stirring. The pH was adjusted to previously selected value and stirring was continued for 5 hr at room temperature. The same procedure was performed at 20ºC, 40ºC and 60ºC using temperature controlled magnetic stirrer for 5 hr. The drug loading efficiency of resinates prepared at different temperature were determined.[15]

Table No. 5: Effect of temperature on drug loading.

Sr.No	Drug :resin	Complex of Rizatriptan benzoate with resins	Temperature (^{0}C)
1	1:4	Rizatriptan benzoate: Kyron T-114	20^{0}C
2	1:4	Rizatriptan benzoate: Kyron T-114	40^{0}C
3	1:4	Rizatriptan benzoate: Kyron T-114	60^{0}C
4	1:4	Rizatriptan benzoate: Kyron T-114	Room temperature(44^{0}C)

After studying the effects of various parameters on drug loading, most suitable resinate was prepared.

Organoleptic properties: Organoleptic properties viz. color, odor taste and appearances were evaluated by following the same procedure as per the procedure mentioned in above section.

Flow properties: The flow properties viz. angles of repose, bulk density, tapped density and compressibility index of taste modified samples were determined as per the procedure mentioned in above section.

X-ray diffraction: Resinate was evaluated by X- ray diffraction studies for any structural changes due complex formation. It was carried out as per the procedure mentioned in section.

Drug content: The drug content of taste modified sample was determined using following method; Taste

modified drug powder equivalent to 10 mg of Rizatriptan benzoate was accurately weighed and transferred in 250 ml volumetric flask containing 0.1 M HCl. Sonicated for 15 min, stirred using magnetic stirrer for 30 min and filtered. Further dilutions were made and UV absorbances at λ_{max} 225 nm were recorded.

Formulation of water dispersible tablets using most suitable approach of taste masking

Ingredients mentioned in tables were used for the formulation of taste modified dispersible tablets of Rizatraptan benzoate by direct compression method. The ingredients were weighted, mixed in geometrical order and compressed by 8 mm size punch to get a tablet of 200 mg weight using 12 station single rotary Rimak tablet compression machine.

Table No 6: Composition of water dispersible tablets of Drug: Kyron T-114 (1:4) complex with superdisintegrants.

Name of the ingredient	Quantity (mg)									
	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug Kyron T-114 resinate *(25%)	50	50	50	50	50	50	50	50	50	50
Microcrystalline cellulose (pH 101)	134	126	122	122	126	122	122	126	122	122
Sodium starch glycolate	….	4	4	8	…	….	….	4	4	8
Croscarmellose sodium	….	4	8	4	4	4	8	….	….	…
Crospovidone	….	….	…..	…	4	8	4	4	8	4
Aspartame (5%)	10	10	10	10	10	10	10	10	10	10
Magnesium stearate (0.5%)	1	1	1	1	1	1	1	1	1	1
Aerosil (1%)	2	2	2	2	2	2	2	2	2	2
Orange flavor (0.5%)	1	1	1	1	1	1	1	1	1	1
Orange color (1%)	2	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200	200

SSG: CCS: CP =1:1, 1:2, 2:1* Equivalent to 10 mg of Rizatriptan benzoat Total weight of tablet 200 mg.

Evaluation of taste masked water dispersible tablets: The water dispersible tablets were evaluated for following parameters;

1) Appearance 2) Weight variation 3) Friability 4) Disintegration time 5) Wetting time 6) Water absorption ratio 7) Uniformity of dispersion 8) Drug release study (*In-Vitro*) 9) Dimensions 10) Hardness 11) Drug content

Appearance: Tablets were examined for texture, any surface flaws like cracks and chips.

Weight variation: 20 tablets of each formulation batch were weighed individually using an electronic balance. The average weight was calculated and individual tablet weight was then compared with average value and the deviation was recorded.[5]

Friability: Weight of 10 tablets of each formulation type was recorded and these tablets were then subjected to combined effects of abrasion and shocks in a plastic chamber that revolved at 25 rpm for 4 min (100 revolutions) to make the impact from a height of six inches with each revolution. Test was carried out for 100 revolutions. The tablets were then deducted and weighed again and percent friability was calculated by the following formula;[5]

$$\%F = (W_o - W) / W_o \times 100$$

Where, F = friability W_o = ***initial weight of the ten tablets*** W = final weight of the ten tablets.

Disintegration time (*in vitro*): The disintegration time was determined by using USP tablet disintegration test apparatus using 900 ml of deionised water without disk. For this, 6 tablets of each formulation were used and the disintegration test was conducted at following test conditions.

Apparatus : Disintegration test apparatus
Disintegration medium : Distilled water
Frequency of raising and lowering of basket rack assembly : 28 to 32 cycles.
Temperature of medium : 37±2^{o}C
End point : No residue of the tablet left on the screen of the apparatus except soft mass with no palpably hard core.

The individual tablets were placed in each tube and the test carried out. The time required for complete disintegration of tablet was noted.[5]

Wetting Time: A piece of tissue paper was folded twice and placed in a small petridish (internal diameter=6.5cm) containing 10 ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured.

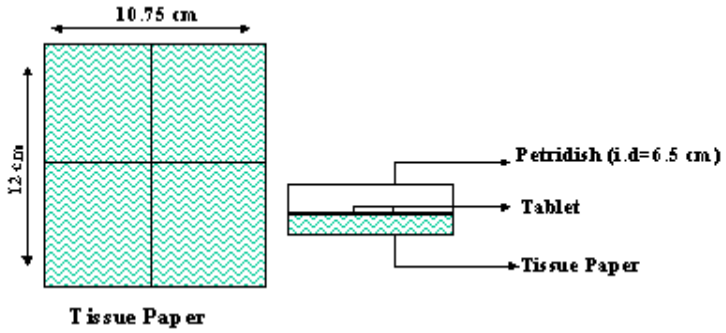


Fig. 1: Schematic illustration of the measurement of wetting time of tablets.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R was determined using equation,

$$R = 100 \times (Wa-Wb) / Wb$$

Where, Wa = weight of the tablet before water absorption, Wb = weight of the tablet after water absorption. Three tablets from each formulation were analyzed and standard deviation was also determined.[16]

Uniformity of dispersion: Two tablets of each formulation were used. The tablets were dropped into 100 ml of water contained in a beaker. The dispersion was stirred to allow complete disintegration of tablets and was then passed through a sieve (sieve No. 22, #710µm). The mesh was observed for any residues of tablets.[17]

Drug release study (*in-vitro*)

i) Drug release of Rizatriptan benzoate in 0.1 M HCl

The drug release of Rizatriptan benzoate from dispersible tablets was estimated using dissolution test carried out as under.

ii) Drug release of Rizatriptan benzoate in distilled water

This study was performed in distilled water. From each formulation 2 tablets were crushed. A quantity of powder equivalent to 100 mg of Rizatriptan benzoate as well as unmodified Rizatriptan benzoate was accurately weighed and transferred to 10 ml of distilled water in different test tubes. The suspensions were shaken for 60 sec. Absorbances of filtrates were measured at previously reported λ_{max} value.

Dimensions: Dimensions such as thickness of the tablets were measured using digital Vernier caliper.

Hardness: From each dispersible formulation 3 tablets were selected randomly. Monsanto hardness tester was used to check the hardness. Individual tablet was held along its axis between two jaws of the tester and scale was adjusted to zero. A constant force was then applied by rotating the knob until the tablet was fractured. Hardness was noted in kg/cm^2.

Drug content: Two tablets of each formulation were used. The tablets were weighed and crushed. A quantity of powder equivalent to 100 mg of Rizatriptan benzoate was accurately weighed and transferred to 100 ml volumetric flask to which small volume of 0.1 M HCl was added to disperse the contents. Final volume was adjusted to 100 ml using 0.1 M HCl. The dispersion was stirred for 2 hr using magnetic stirrer and then allowed to settle. Solution was filtered through Whatman filter paper (No.41). Appropriate dilution of filtrate was made using 0.1M HCl and the UV absorbance was recorded.[18]

Taste evaluation: Taste of water dispersible Rizatriptan benzoate tablets was evaluation by panel of tastees. It was carried out as per the procedure mentioned in above section.

Comparison of optimized batch with marketed preparation: The optimized formulation of water dispersible tabletwas compared with marketed preparation for various testing parameters as per the procedure mentioned in section.

Stability study of water dispersible tablets

The dispersible tablets of optimized formulation was selected and stored at the controlled environmental conditions (temperature 40 ± 2^0C and RH 75 ± 5%) for 30 days. Tablets were wrapped using aluminium foil and kept at above specified condition in environmental control chamber. The tablets were tested at the interval of every 15 days for changes in appearance, disintegration time (*in-vitro)*, hardness, friability, assay, uniformity of dispersion, drug release (*in-vitro)* and the findings were recorded as per the procedure mentioned in section.[19]

RESULTS AND DISCUSSION

Characteristics of drug and excipients

Characteristics of Rizatriptan benzoate

Organoleptic characteristic: Organoleptic properties were determined as per the procedure given in experimental part and the results are illustrated.

Discussion: The organoleptic characteristics of drug are matching with those reported in the U.S.P.

Melting range: Melting range were determined as per the procedure given in experimental part and the results are 178-180^{0}C.

Discussion: From the result it was observed that melting range of Rizatriptan benzoate have good agreement with those reported in the U.S.P.

Saturation solubility: Saturation solubility was determined as per the procedure given in experimental part and the results are illustrated in the table.

Table No. 7: Saturation solubility study of Rizatriptan benzoate.

Sr. No.	Medium	Solubility
1	Purified water	Soluble
2	0.1 M HCl	Slightly soluble
3	0.01 M HCl	More soluble
4	pH 6.8 Phosphate buffer	Soluble
5	pH 7.4 Phosphate buffer	Soluble

From the results of saturation solubility. It was observed that Rizatriptan benzoate was more soluble in 0.01 M HCl, slightly soluble in 0.1 M HCl and soluble in water. Saturation solubility data of Rizatriptan benzoate have good agreement with those reported in the U.S.P.

Loss on drying: Loss on drying was determined as per the procedure given in experimental part and the results are 0.48%.

Spectrum analysis of Rizatriptan benzoate

A. Determination of λ_{max} in UV range: λ_{max} of Rizatriptan benzoate was determined in distilled water, 0.1 M HCl and phosphate buffer pH 6.8, as per the procedure given in experimental part.

Table No. 8: λ_{max} values of Rizatriptan benzoate in different solvents.

Sr. No.	Type of solvent	λ_{max} value (nm)
1	Distilled water	225.2
2	0.1 M HCl	225.4
3	phosphate buffer pH 6.8	225.1

λ_{max} of Rizatriptan benzoate in distilled water, 0.1 M HCl and phosphate buffer pH 6.8 was found to be 225.2 nm, 225.4 nm and 225.1 nm respectively. The observed values are in good agreement with the reported value in U.S.P. (225 nm).

B. Standard calibration curve: Standard calibration curves of Rizatriptan benzoate in distilled water, 0.1M HCl and phosphate buffer pH 6.8 were found to be linear (R^2 = 0.997- distilled water, 0.998-HCl and 0.998-phosphate buffer pH 6.8 over the concentration range of 10-100 µg/ml. Hence, it obeys Beer-Lambert's law in the range of 10-100 µg/ml.

C. Determination of infra red spectra

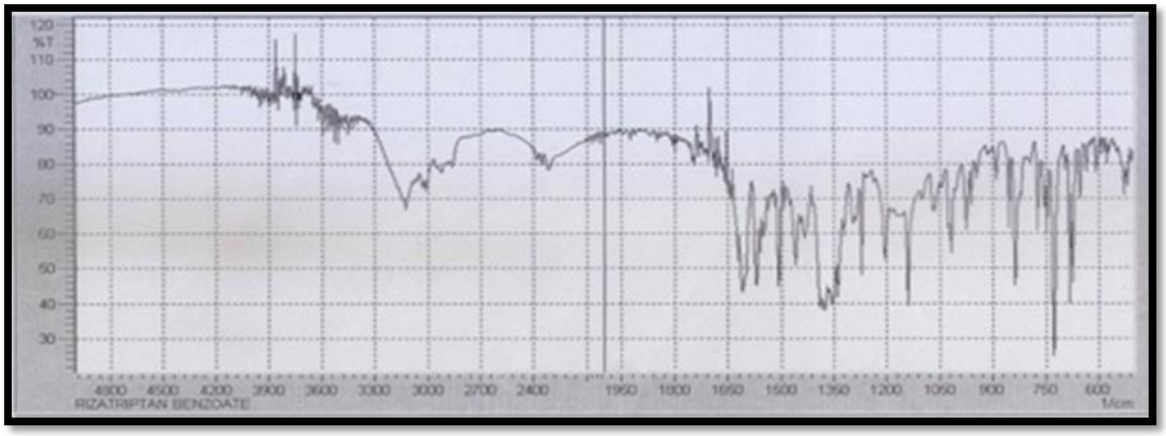


Fig. 2: IR spectrum of Rizatriptan benzoate.

Table 9: Interpretation of IR spectrum of Rizatriptan benzoate.

Sr. No.	Wave number (cm^{-1})	Corresponding functional group with type of molecular vibration
1	3430	N-H stretching of amide
2	2938, 2888	CH_3, CH_2 stretch
3	1608, 1505	C=C and C=N stretch
4	1569	NH bend
5	1446, 1377	CH_2, CH_3 bend
6	1271, 1140, 1016	C–N stretch
7	888, 853, 836, 794, 772	CH and CN out of plane bend

The IR spectrum of Rizatriptan benzoate indicated presence of peaks corresponding to the major functional groups in the structure of drug supporting its identity.

Thermal behavior by differential scanning calorimetry: The differential calorimetric scanning of drug was carried out as per the procedure given in experimental part.

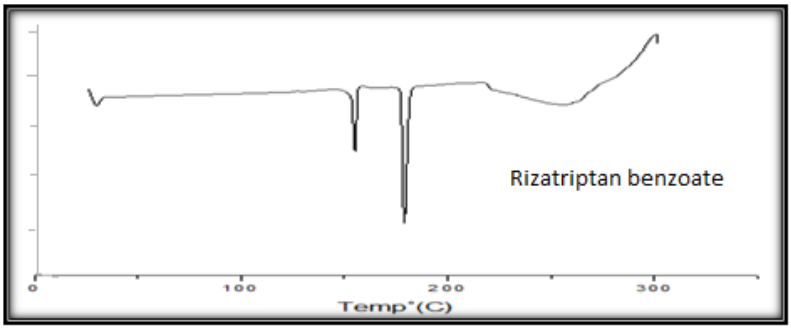


Fig. 3: DSC thermogram of Rizatriptan benzoate: Thermogram of Rizatriptan benzoate revealed sharp endothermic peak at 178^{0}C corresponding to its melting range.

X- ray diffraction studies

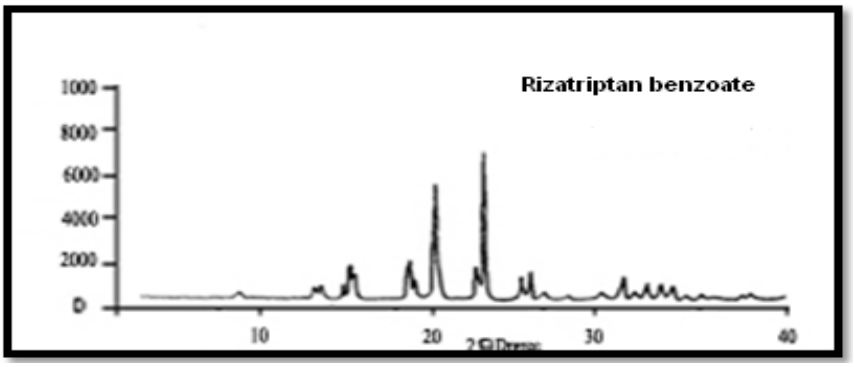


Fig 4: X- ray diffraction spectrum of Rizatriptan benzoate.

X-ray diffraction spectrum of Rizatriptan benzoate exhibitednumerous distinctive peaks indicating its amorphous nature. Based on the findings of preformulation studies, the sample of Rizatriptan benzoate was considered to be of good quality and purity. Hence, no attempt was made for further characterization.

Characterization of excipients

II. Ion exchange resin (Indion 234 and Kyron T-114)

Organoleptic properties: Oraganoleptic properties of Indion 234 and Kyron T 114 were determined as per the procedure given in experimental part and the results are illustrated.

2. Flow properties: Flow properties of individual resins viz. bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were determined by following the procedure mentioned in experimental part and the results are illustrated in table.

Table No. 10: Flow properties of resins.

Sr. No.	Parameters	Ion exchange resin	
		Indion 234	Kyron T 114
1	Bulk density	0.62	0.69
2	Tapped density	0.72	0.88
3	Hausner's ratio	1.16	1.21
4	Carr's index	16.12	27.5
5	Angle of repose	24.20	21.80

3. Melting range: Melting range of Indion 234 and Kyron T-114 were determined as per the procedure given in experimental part and the results are 78^0C-80^0C and 130^0C-132^0C respectively.

4. Particle size: Particle size was determined as per the procedure given in experimental part and the results are illustrated in table.

Table No. 11: Particle size of resins.

S.N	Resin	Specification	Observed
1	Indion 234	Retention on 100 number mesh (% w/w) = ≤0.9%	0.5%
2	Kyron T-114	Retention on 100 number mesh (% w/w) = ≤1%	0.64%

5. Loss on drying: Loss on drying of Indion 234 and Kyron T-114 were determined as per procedure given in experimental part and the results are 2.8% and 3.2% respectively.

6. IR spectrum analysis: Spectrum analysis was carried out as per the procedure.

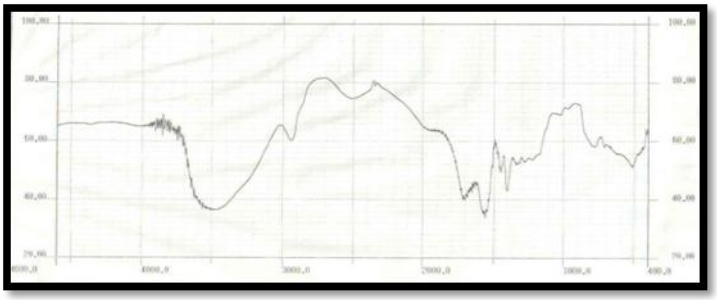


Fig. 5: IR spectrum of Indion 234.

Table No. 12: Interpretation of IR spectrum of Indion 234.

SN	Wave number (cm^{-1})	Corresponding functional group with type of molecular vibration
1	3450	O-H stretching
2	1704	C=O stretching of aryl acid
3	1568	C=C stretching in aromatic ring

The IR spectrum of Indion 234 revealed presence of all peaks associated with major functional groups in the structure of Indion 234 supporting identity of polymer with that of reported in literature.

ii) IR spectrum of Kyron T 114

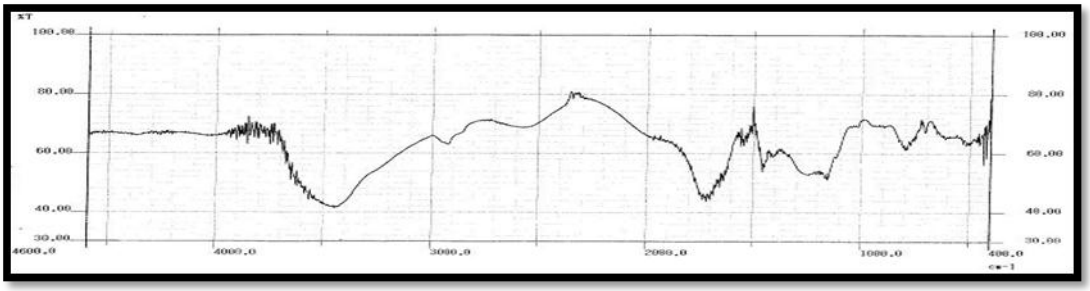


Fig 6: IR spectrum of Kyron T114.

Table 13: Interpretation of IR spectrum of Kyron T114.

Sr. No.	Wave number (cm^{-1})	Corresponding functional group with type of molecular vibration
1	3420	O-H stretching
2	1715	C=O stretching
3	1680	C=C stretching
4	1460	CH_3 bending

The IR spectral analysis revealed presence of major functional groups in the structure of Kyron T-114 supporting the identity of the resin sample. Based on the findings of preformulation studies, the sample of Indion 234 and Kyron T-114 was considered to be of good quality and purity. Hence, no attempt was made for further characterization.

Masking of bitter taste of drug using various techniques

Ion exchange resin: Different types of resin in the variable ratio with drug were taken Complex were prepared as per the procedure mentioned in experimental part and evaluated for masked of bitter taste.

Evaluation of taste modified drug samples

Characterization of probable interaction of Rizatriptan benzoate with excipients

A. UV spectra of taste modified forms of Rizatriptan benzoate

λ_{max} value of physical mixture of Rizatriptan benzoate and sucrose in 0.1 M HCl was found to be 225.1 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm, Indicating absence of any probable interaction between them. λ_{max} value of physical mixture of Rizatriptan benzoate and glycine in 0.1 M HCl was found to be 225.2 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm. So no any probable interaction was observed. λ_{max} value of physical mixture of Rizatriptan benzoate and Aspartame in 0.1 M HCl was found to be 225.1 nm which was near to λ_{max} of pure. Rizatriptan benzoate 225 nm. Indicating absence of any probable interaction between them. λ_{max} value of physical mixture of Rizatriptan benzoate and Indion 234 in 0.1 M HCl was found to be 225.3 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm. Indicating absence of any probable interaction between them. λ_{max} value of physical mixture of Rizatriptan benzoate and Kyron T-114 in 0.1 M HCl was found to be 225.3 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm. Indicating absence of any probable interaction between them. λ_{max} value of physical mixture of Rizatriptan benzoate and PEG 4000 in 0.1 M HCl was found to be 225.2 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm. Indicating absence of any probable interaction between them. λ_{max} value of physical mixture of Rizatriptan benzoate and PEG 6000 in 0.1 M HCl was found to be 225.2 nm which was near to λ_{max} of pure Rizatriptan benzoate 225 nm. Indicating absence of any probable interaction between them.

Table No. 14: λ_{max} values of Rizatriptan benzoate and its taste modified forms in 0.1 M HCl.

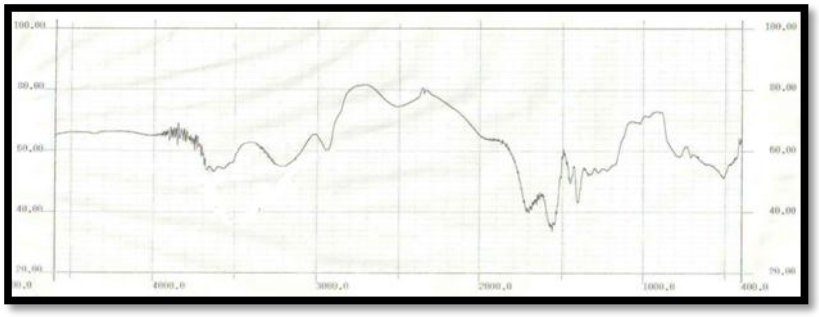
Sr No.	Type of approach for masking bitter taste	λ_{max} value
1	Unmodified drug	225
2	Complexation with Indion 234	225.3
3	Complexation with Kyron T-144	225.4

The scanning of taste modified forms of Rizatriptan benzoate were performed in 0.1 M HCl. Which compiles with the λ_{max} reported in U.S.P.(225 nm).

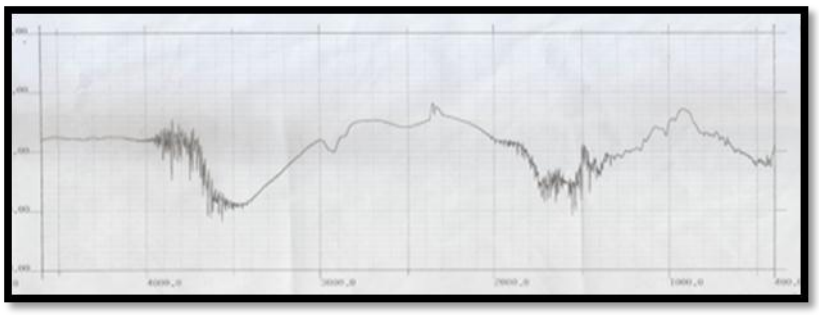
B. Infrared spectra of Rizatriptan benzoate and its taste modified forms: spectrum was determined as per procedure given in experimental part and the results are illustrated as following,

IR of Rizatriptan benzoate with ion exchange resin complex (Kyron T-114 and Indion 234)

A



E



F

Fig. 7: IR spectra of Rizatriptan benzoate (A), complex of Rizatriptan Benzoate with Indion 234 (E), Complex of Rizatriptan benzoate with Kyron T-114 (F).

From the IR study, it was observed that, there was no interaction between drug and excipients. Thus, considered for further study.

Evaluation of taste of Rizatriptan benzoate and its taste modified forms by panel of tastees: Evaluation of taste was carried out as per the procedure given in experimental part and the results are illustrated as following table.

Table 15: Taste evaluation of Rizatriptan benzoate and ion exchange resin with Indion 234 and Kyron T-114 by panel of tastes.

Name of resinate	Taste masked code	Score assigned by the volunteers					Effectiveness value
		V_1	V_2	V_3	V_4	V_5	
Rizatriptan benzoate	Pure drug	4	4	4	4	4	
Indion 234	C1	3	3	2	3	2	2.6
	C3	3	2	2	1	2	2
	C5	2	2	2	1	1	1.6
	C7	0	2	1	2	1	1.2
Kyron T-114	K1	2	3	2	2	3	2.4
	K3	1	2	2	1	1	1.4
	K4	0	0	0	0	0	0
	K5	0	0	0	0	0	0

0 = No bitter taste, 1 = Slightly bitter taste, 2 = Moderately bitter taste, 3 = Strong bitter taste, 4 = Very strong bitter taste. **V_1, V_2, V_3, V_4, V_5 – Volunteers.**

From the result it was observed that batch K4 and K5 has least score that is 0. As concentration of resin increased the loading efficacy of resin was decreased. To reduce the bulk of tablet, K4 was selected for further study. Based on the results of taste masking it was concluded that, physical mixture of drug with complex of drug with Kyron T-114 (K4) exhibited better taste masking. Hence, batch K4 was selected for further study.

Effect of various parameters on drug loading: A selected resinate of Rizatriptan benzoate with Kyron T-114 in the ratio of 1:4 was further studied for the effect of various parameters viz. pH, soaking time, stirring time and temperature on drug loading.

Table 16: Effect of pH on drug loading: Rizatriptan benzoate: Kyron T114 (1:4).

Resinate code	pH	% Drug loading
RP_1	5	91.30±0.37
RP_2	6	92.01±0.64
RP_3	7	93.66±0.38
RP_4	8	95.01±0.64
RP_5	9	89.36±0.52

1) Effect of pH on drug loading: Initially as the pH was increased from 5 to 8, drug loading also increased, but further increased in pH, drug loading was decreased. The pH of the dispersion affects both solubility and the degree of ionisation of drug and resin. Results can be attributed to the fact that Kyron T-114 has a pKa between 6-8 with complete ionisation in this range offering maximum loading. Resinate RP_4 exhibited 95.01% drug loading at pH 8 and was selected for further study.

2) Effect of soaking time on drug loading: Effect of soaking time on drug loading of Kyron T-114 was studied as per the procedure mentioned in section and the results are depicted in table.

Table 17: Effect of soaking time on drug loading.

Rizatriptan benzoate: Kyron T-114 (1:4)		
Resinate code	**Soaking time (min)**	**% Drug loading**
RP_4S_1	0	87.07±0.74
RP_4S_2	10	90.99±0.53
RP_4S_3	20	93.02±0.55
RP_4S_4	30	95.09±0.67
RP_4S_5	40	95.17±0.21

The results of soaking time on drug loading revealed that as soaking time was increased from 0-30 min the drug loading also increased. Further increment in soaking time does not affect drug loading significantly. This may be due to maximum swelling and hydration properties of Kyron T-114 that affects the rate of ion exchange. Resinate RP_4S_4 given 95.09%, drug loading at 30 min and was selected for further study.

3) Effect of stirring time on drug loading

Effect of stirring time on drug loading was studied as per the procedure given under section and the results are illustrated in table.

Table 18: Effect of stirring time on drug loading.

Rizatriptanbenzoate:Kyron T114 (1:4)		
Resinate code	**Stirring time (hr)**	**% Drug loading**
$RP_4S_4St_1$	2	93.25±0.41
$RP_4S_4St_2$	3	95.46±0.37
$RP_4S_4St_3$	4	94.79±0.64
$RP_4S_4St_4$	5	95.75±0.41

Effect of stirring time on drug loading revealed that percentage drug loading was increased with increased in stirring time but the increment is not much significant. Hence, stirring time of 5 hr ($RP_4S_4St_4$) was selected for further study.

4) Effect of temperature on drug loading: Effect of temperature on drug loading was studied as per the procedure mentioned in section and the results are illustrated in table.

Table 19: Effect of temperature on drug loading.

Rizatriptan benzoate: Kyron T-114 (1:4)		
Resinate code	**Temperature $^oC(\pm 2^oC)$**	**% Drug loading**
$RP_4S_4St_4T_1$	Room tempe.(44)	94.93±0.76
$RP_4S_4St_4T_2$	20	91.97±0.24
$RP_4S_4St_4T_3$	40	94.66±0.55
$RP_4S_4St_4T_4$	60	95.46±0.49

Efficient drug loading on Kyron T114was observed uniformly in the experimental range of 20°C-60°C. Higher temperature during resonate formation may increase ionisation of drug and resin. It also increases the diffusion rate of ions. Results of effect of tem perature on drug loading revealed that, temperature does not affect

the drug loading efficiency significantly. Hence, resinate was prepared at room temperature. The most suitable resinate was prepared using drug: KyronT114 in the ratio of 1:4, at pH 8, with soaking time of 30 min and stirring time of 5 hr at room temperature.

Organoleptic properties: Oraganoleptic properties were determined as per the procedure given in experimental part.

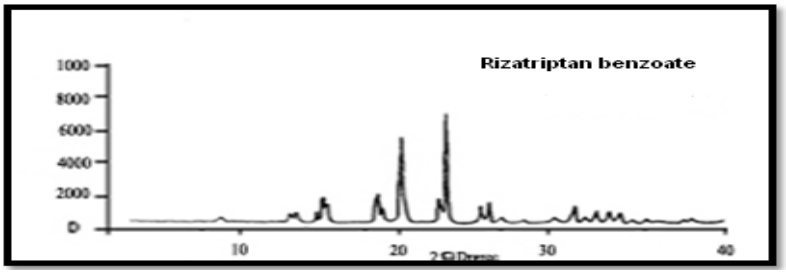
I. Kyron T-114 (K4): The Characteristics of K4were determined and used for further study.

Flow properties: Flow properties were determined as per the procedure given in experimental part and the results are illustrated in the table.

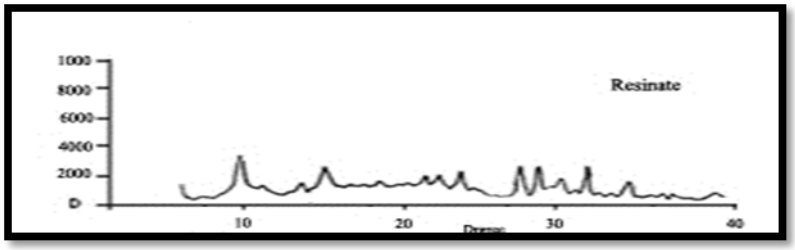
Table No. 20: Flow properties of K4.

Sr. No.	Flow parameters	Observationof optimized batch
1	Angle of repose	34.51^0
2	Bulk density	0.64
3	Tapped density	0.7142
4	Hausner's ratio	1.3468
5	Carr's index	25.75

X- ray diffraction studies: X-ray diffraction pattern of Rizatriptan benzoate with Kyron T-114 was studied as per the procedure given in experimental part 7.1.1.8 and spectrum is depicted in Fig.



a



b

Fig 8: X- ray diffraction spectrum of Drug (a) and resinate (b)

X-ray diffraction spectrum of Rizatriptan benzoate with Kyron T-114 (1:4) exhibitsnumerous distinctive peaks indicating its amorphous nature. Based on the findings of preformulation studies, the sample of Rizatriptan benzoate was considered to be of good quality and purity. Hence, no attempt was made for further characterization.

Contents of drug: Content of drug were determined as per the procedure given in experimental part 7.3.7 and the results are illustrated in the following table.

I. Content of Rizatriptan benzoate in K4: content of drug were determined as per the procedure given in experimental part and the results are 99.98 ± 0.63.

Formulation of water dispersible tablets using Kyron T-114

Water dispersible tablets of taste masked Rizatriptan benzoate were prepared using Drug: Kyron T-114 (1:4) complex with different concentrations of superdisintegrant viz. sodium starch glycolate, Croscarmellose sodium, crospovidone. Prior to compression, the mixture blends of each formulation batch were evaluated for flow properties/precompression parameters like bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose. All these parameters were studied and the results were given in table 32.

Table No. 21: Precompressional parameters of powder blend used for direct compression method.

Formulations	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility (%)	Hausner's ratio	Flowability
F0	23.32±0.01	0.56±0.11	0.70±0.04	16.21 ± 0.18	1.12± 0.06	Excellent
F1	24.58±0.02	0.57±0.02	0.68±0.08	15.22 ± 0.11	1.1± 0.04	Excellent
F2	25.23±0.03	0.55±0.01	0.71±0.07	16.82 ± 0.20	1.14± 0.08	Excellent
F3	21.23±0.01	0.59±0.06	0.69±0.01	15.69 ± 0.25	1.17± 0.06	Excellent
F4	29.16±0.08	0.57±0.02	0.65±0.13	13.38 ± 0.14	1.15± 0.08	Excellent
F5	24.01±0.07	0.58±0.01	0.66±0.07	16.60 ± 0.16	1.19± 0.06	Excellent
F6	22.08±0.01	0.62±0.04	0.71±0.21	14.52 ± 0.18	1.16± 0.09	Excellent
F7	23.24±0.04	0.58±0.03	0.68±0.06	15.41 ± 0.14	1.17± 0.10	Excellent
F8	29.35±0.08	0.55±0.04	0.71±0.07	13.61 ± 0.16	1.15± 0.11	Excellent
F9	24.23±0.02	0.56±0.06	0.73±0.01	15.69 ± 0.25	1.17± 0.09	Excellent
F	24.38±0.02	0.54±0.04	0.68±0.08	15.21 ± 0.11	1.14± 0.04	Excellent
F10	29.16±0.08	0.57±0.02	0.65±0.13	13.38 ± 0.14	1.15± 0.08	Excellent
F11	26.01±0.07	0.52±0.01	0.63±0.07	16.60 ± 0.16	1.19± 0.06	Excellent
F12	22.08±0.01	0.62±0.04	0.72±0.21	14.42 ± 0.18	1.16± 0.09	Excellent
F13	28.24±0.04	0.58±0.03	0.68±0.03	15.21 ± 0.14	1.17± 0.10	Excellent
F14	24.35±0.08	0.59±0.04	0.64±0.07	14.61 ± 0.16	1.15± 0.11	Excellent
F15	21.23±0.04	0.59±0.06	0.69±0.01	15.69 ± 0.25	1.17± 0.06	Excellent
F16	25.01±0.07	0.58±0.01	0.66±0.07	16.60 ± 0.16	1.19± 0.06	Excellent
F17	29.08±0.03	0.62±0.04	0.72±0.11	14.52 ± 0.28	1.16± 0.09	Excellent
F18	28.24±0.04	0.58±0.06	0.68±0.08	15.41 ± 0.14	1.17± 0.11	Excellent

(Mean ± standard deviation n=3)

The mixture blends of all the formulation batches had bulk density in the range of 0.55-0.62 g/cm^3 and tapped density in the range of 0.68-0.72 g/cm^3. All formulations had compressibility index between 13.38-6.68 and Hausner's ratio less than 1.26**,** indicating excellent flowability.

Evaluation of taste masked water dispersible tablets

Water dispersible tablets were formulated by direct compression method using different types and concentrations of superdisintegrants viz. sodium starch glycolate, Croscarmilose sodium and crospovidone. All the formulation batches were evaluated for various tests viz. appearance, thickness and diameter, weight variation, friability, hardness, disintegration time, uniformity of dispersion, wetting time, wetting volume, water absorption ratio, dispersion time, assay and drug release.

I. Evaluation of water dispersible tablets: All the tests were performed as per the procedure mentioned in experimental part 7.5 and the results are illustrated in table.

Table No. 22: Evaluation of formualation code F0-F9 water dispersible tablets.

Formulation Code	Physical appearance	Hardness test (Kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation
F0	Orange colored, smooth, free from cracks	3.6± 0.021	4.35 ± 0.24	0.64±0.22	Passed
F1	Orange colored, smooth, free from cracks	3.9± 0.011	4.30 ± 0.14	0.74±0.12	Passed
F2	Orange colored, smooth, free from cracks	3.7± 0.082	4.32 ± 0.15	0.58±0.13	Passed
F3	Orange colored, smooth, free from cracks	3.8± 0.013	4.34 ± 0.13	0.63±0.09	Passed
F4	Orange colored, smooth, free from cracks	3.6± 0.014	4.36 ± 0.11	0.52±0.15	Passed
F5	Orange colored, smooth, free from cracks	3.8± 0.016	4.34 ± 0.05	0.41±0.07	Passed
F6	Orange colored, smooth, free from cracks	3.8± 0.015	4.32 ± 0.03	0.55±0.16	Passed
F7	Orange colored, smooth, free from cracks	3.7± 0.089	4.30 ± 0.06	0.83±0.06	Passed
F8	Orange colored, smooth, free from cracks	3.8± 0.094	4.34 ± 0.11	0.42±0.15	Passed
F9	Orange colored, smooth, free from cracks	3.8± 0.014	4.30 ± 0.06	0.95±0.07	Passed

(Mean ± standard deviation n=3)

Table No. 22cont…..

Formulation Code	Wetting time (Sec)	Water absorption ratio	*In-vitro* dispersion time (Sec)	*In-vitro* disintegration time (Sec)	Drug content (%)	Uniformity of dispersion
F0	82.26± 1.6	72.43± 0.26	126.20 ± 0.13	242.24 ± 1.7	98.32 ± 1.2	Passed
F1	23.24 ± 1.8	98.13± 0.14	29.09 ± 0.01	31.36 ± 1.8	99.12 ± 1.1	Passed
F2	21.18 ± 2.1	87.04± 0.15	26.98 ± 0.05	33.38 ± 1.7	98.61 ± 1.8	Passed
F3	21.34 ± 1.3	93.25± 0.13	28.12 ± 0.04	28.46 ± 0.8	98.17 ± 1.9	Passed
F4	19.29 ± 1.6	92.09± 0.11	27.99 ± 0.04	24.44 ± 1.3	99.39 ± 1.9	Passed
F5	23.18 ± 1.9	96.59± 0.05	29.10 ± 0.13	31.32 ± 1.4	99.61 ± 1.9	Passed
F6	20.58 ± 1.2	96.19± 0.03	26.98 ± 0.11	28.31 ± 1.1	99.46 ± 1.5	Passed
F7	24.51 ± 0.6	88.34± 0.06	31.00 ± 0.15	26.39 ± 1.5	99.12 ± 1.8	Passed
F8	18.55 ± 1.1	97.51± 0.06	24.97 ± 0.16	19.18 ± 1.4	99.52± 1.9	Passed
F9	22.45± 1.2	94.25± 0.13	30.21 ± 0.04	21.36 ± 1.8	99.14 ± 1.7	Passed

(mean ± standard deviation n=3)

All batches (except F0) given disintegration time below 1 min (19-33 sec). The dispersion time for all formulation batches were between 24-31 sec, also all batches passed the test for uniformity of dispersion. Water absorption ratio of all formulations was found to be in between 87-98%. This results in fast wetting of tablets as reflected from wetting time (18-23 sec). The drug content of all formulation batches was found to be in the range of 98.17-99.61, which was within the acceptable limit as per U.S.P.

b. Drug release (*in-vitro*): The release of Rizatriptan benzoate from water dispersible tablets was estimated in 0.1M HCl as per the procedure mentioned in section and the results are illustrated in fig.

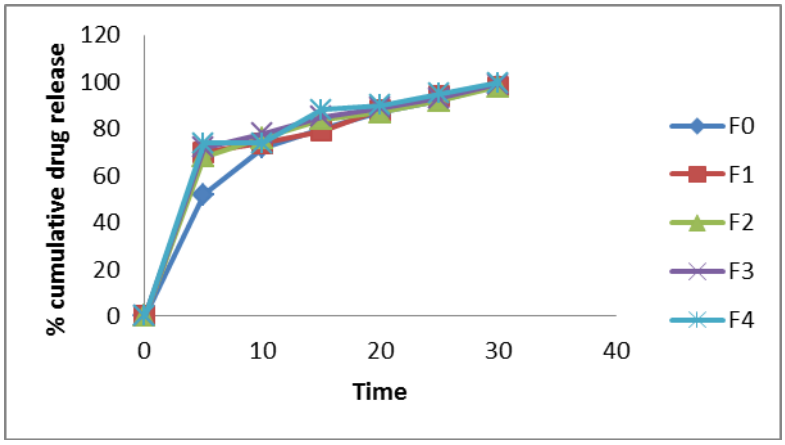


Fig 9: Release profiles of baches F0 – F4 in 0.1N HCl.

Table No. 35: Drug release of batches F5 to F9 in 0.1 M HCl.

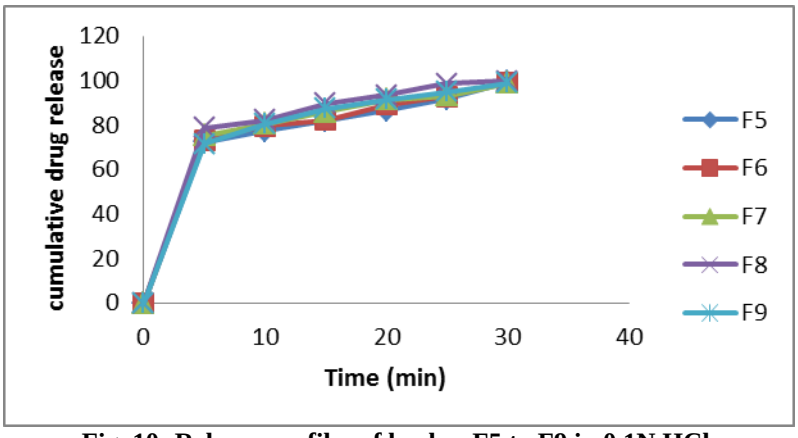


Fig. 10: Release profiles of baches F5 to F9 in 0.1N HCl.

In vitro dissolution study revealed that all formulation batches released 98% the drug within 30 min. It was observed that as the concentration of super disintegrants increases disintegration time of tablets decreases, F8 have least disintegration time i.e 19.18 ± 1.4 Formulation F8 containing 2% sodium starch glycolate and 4% crospovidone released 78.58±0.04% drug in five min and 99.78±0.06% drug in 30 min. This was might be due to easy swelling ability of sodium starch glycolate with crospovidone.

II. Evaluation of formulation code F10-F18: All the tests were performed as per the procedure mentioned in experimental part and the results are illustrated in table.

Table No. 23: Evaluation of formulation batch F10-F18 of water dispersible tablets.

Formulation code	Hardness test (Kg/cm^2)	Thickness (mm)	Friability (%)	Wetting time (Sec)	Weight variation
F	3.6 ± 0.013	4.12 ± 0.02	0.53	74.42± 1.3	Passed
F10	3.7 ± 0.011	4.14 ± 0.04	0.52	35.41 ± 1.8	Passed
F11	3.8 ± 0.012	4.14 ± 0.05	0.57	21.03 ± 2.1	Passed
F12	3.8 ± 0.018	4.15 ± 0.017	0.59	28.15± 1.3	Passed
F13	3.7 ± 0.020	4.13 ± 0.04	0.66	21.01 ± 1.6	Passed
F14	3.8 ± 0.018	4.15 ± 0.03	0.69	24.15 ± 1.9	Passed
F15	3.8 ± 0.015	4.15 ± 0.14	0.67	27.12 ± 1.2	Passed
F16	3.8 ± 0.013	4.13 ± 0.04	0.70	38.78 ± 0.6	Passed
F17	3.7 ± 0.018	4.15 ± 0.12	0.71	22.44 ± 1.1	Passed
F18	3.8 ± 0.018	4.15 ± 0.17	0.69	28.15± 1.3	Passed

(mean ± standard deviation n=3)

Table No. 36cont……

Formulation Code	Water absorption ratio	*In-vitro* dispersion time (Sec)	Drug content (%)	*In-vitro* disintegration time (Sec)	Uniformity of dispersion
F	79.23± 1.4	124.43± 0.03	99.60 ± 1.8	272. ± 1.4	Passed
F10	94.23 ± 1.8	37.19 ± 0.01	98.72 ± 1.1	29.00 ± 1.8	Passed
F11	96.07 ± 2.1	21.15 ± 0.04	99.60 ± 1.8	18.7 ± 1.4	Passed
F12	97.68 ± 1.3	32.78 ± 0.05	99.28 ± 0.4	21.36 ± 0.8	Passed
F13	97.68 ± 1.6	22.09 ± 0.04	99.44 ± 1.1	30.3 ± 1.3	Passed
F14	99.44 ± 1.9	23.01 ± 0.13	99.91 ± 1.5	21.23± 1.4	Passed
F15	86.33 ± 1.2	32.98 ± 0.11	99.05 ± 0.8	28.40 ± 1.1	Passed
F16	98.41 ± 0.6	24.15 ± 0.15	99.28 ± 1.6	27.5 ± 1.5	Passed
F17	97.61 ± 1.1	18.67 ± 0.16	99.49 ± 1.4	19.1 ± 1.4	Passed
F18	97.68 ± 1.3	21.15 ± 0.04	99.18 ± 0.8	21.26 ± 1.4	Passed

All batches (except F) given disintegration time below 1 min (18-30 sec).

The dispersion time for all formulation batches were between 18-37 sec, also all batches passes the test for uniformity of dispersion. Water absorption ratio of all formulations was found to be in between 86-99%. This results in fast wetting of tablets as reflected from wetting time (21-38 sec). The drug content of all formulation batches was found to be in the range of 98.72 -99.91, which was within the acceptable limit as per U.S.P. for water dispersible tablets.

b. Drug release of formulation batches F11-F18: The *in vitro* release of Rizatriptan benzoate from water dispersible tablets was estimated in distilled water and 0.1M HCl as per the procedure given in the experimental part 7.5.8 and the results are illustrated in table 8.39.

i. Dissolution release profile of formulation batches F10-F18 in distilled water

Medium: Distilled water **Speed:** 50 RPM **Volume:** 900ml.

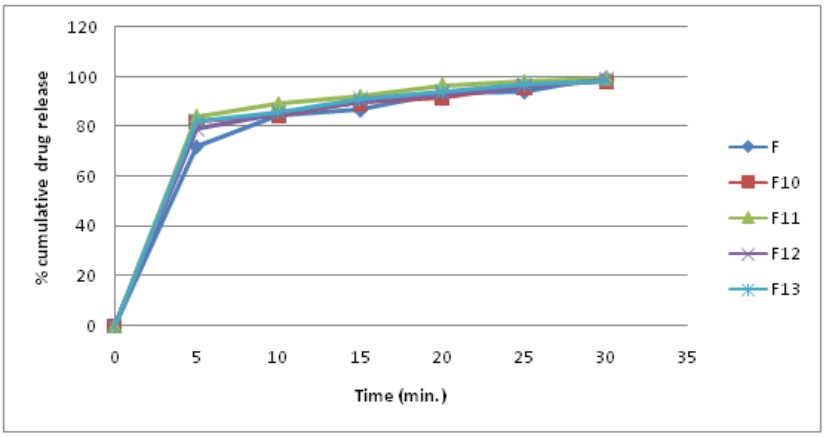


Fig. 11: Drug release profile of batches F10 to F13 in distilled water.

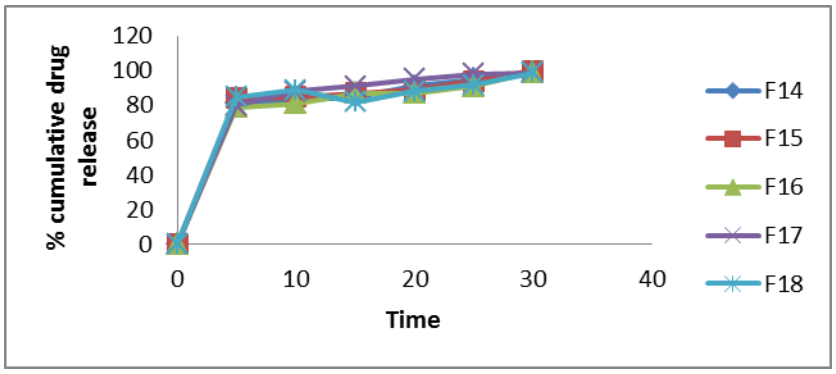


Fig. 12: Drug release profile of batches F14 to F18 in distilled water.

In vitro dissolution study of the prepared water dispersible tablets revealed that all formulation batches released approximately 99% the drug within 30 min. From the result it was observed that percent drug release of batch F17 found to be relevantly more faster than the other batches.

ii. Dissolution release profile of formulation batches F10-F18 in 0.1 M HCl

The *In Vitro* release of Rizatriptan benzoate from water dispersible tablets was estimated in distilled water and 0.1M HCl as per the procedure given in the experimental part and the results are illustrated in table.

Medium: 0.1 M HCl **Speed:** 50 RPM **Volume:** 900ml

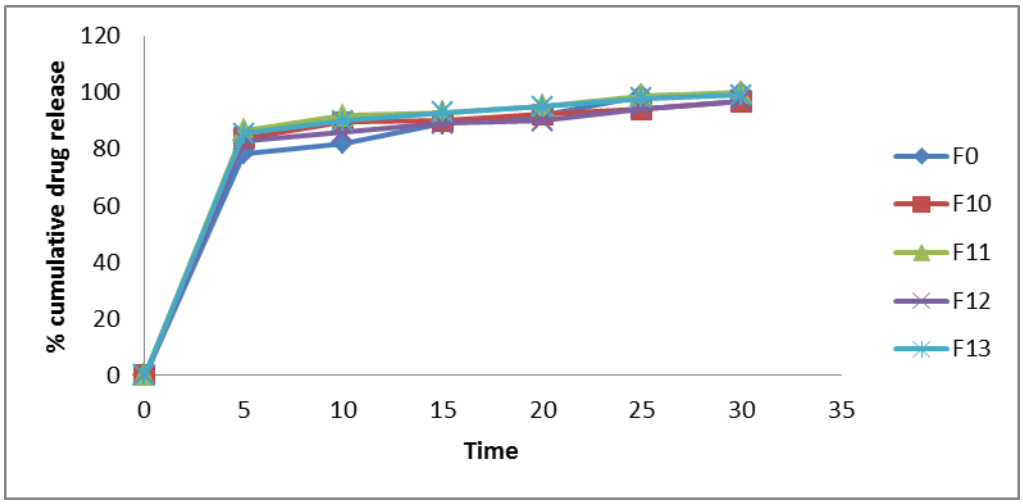


Fig. 13: Drug release profile of batches F10 to F13 in 0.1 M HCl.

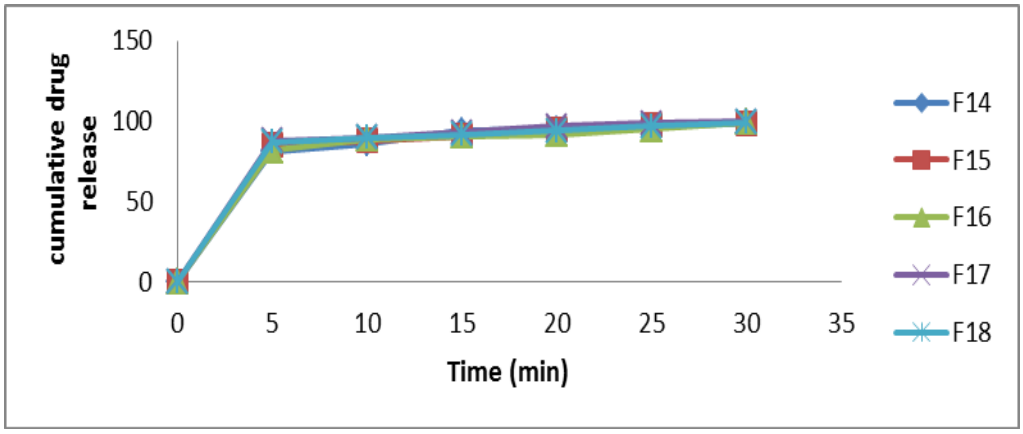


Fig. 14: Drug release profile of baches F14 - F18 in 0.1 M HCl.

From the result it was observed that percent drug content of batch F17 found to be rapid release than other batches of drug:sweetner (aspartame) physical mixture.Based on the results of disintegration time, dispersion time, wetting time, wetting volume and *in vitro* drug release formulation F8 and F17 were showing the best result than any other batches, these baches were illustrated for further taste evaluation study.

Evaluation of taste water dispersible Rizatriptan benzoate tablets: Taste evaluation of formulation batches F8, F17 and marketed tablets of water dispersible Rizatriptan benzoate tablets by panel of tastes were carried out as per procedure given in experimental part and the results are illustrated in the table.

Table 24: Taste evaluation of Marketed tablets, Formulation batch F8 and batch F17 by panel of tastes.

Formulation batch	1	2	3	4	5	Average effectiveness
Marketed preparation (M)	3	4	4	3	3	3.6
Formulation baches F8	0	0	0	0	0	0
Formulation baches F17	1	0	1	0	0	0.4

0 = No bitter taste, 1 = Slightly bitter taste, 2 = Moderately bitter taste,
3 = Strong bitter taste, 4 = Very strong bitter taste

Formulation batches F8 exhibited least or no bitterness of drug. Where as formulation batch F17 exhibited slightly bitterness Hence Formulation code F8 was selected as optimized batch for the formulation. It was concluded that batch F8 exhibited maximum % cumulative drug release than batch F17 and showing best taste mask result. Thus further study of formulation batch F8 was illustrated on stability.

Comparison of optimised batch (F8) with marketed formulation

The optimised formulation F8was compared with available marketed formulation. All the evaluation tests were carried as per the procedure given in experimental part and the results are illustrated in table.

Table No. 25: Comparative evaluation of optimised batch with marketed formulation.

Evaluation parameters	Marketed preparation (M)	Optimised formulation (F8)
Appearance	Cream coloured, free from cracks	Orange colored, smooth, free from cracks
Thickness *(mm)	4.08±0.05	4.25 ±0.11
Diameter* (mm)	8.59 ±0.26	7.99 ±0.04
Weight variation(mg)	Passes	Passes
%Friability	0.92	0.42
Hardness* (kg/cm2)	2.8 ±0.15	3.8 ±0.09
Disintegration time*(sec)	22.04 ±0.15	19.18±1.4
Uniformity ofdispersion*	Passes	Passes
Wetting time*(sec)	16.33 ±1.52	18.55±1.1
Water absorption ratio*	98.7	97.51±0.06
Dispersion time* (sec)	26.06 ±0.08	24.97 ± 0.16
Assay*	98.91 ±0.99	99.52 ±1.9
Taste	Slightly bitter	Sweet

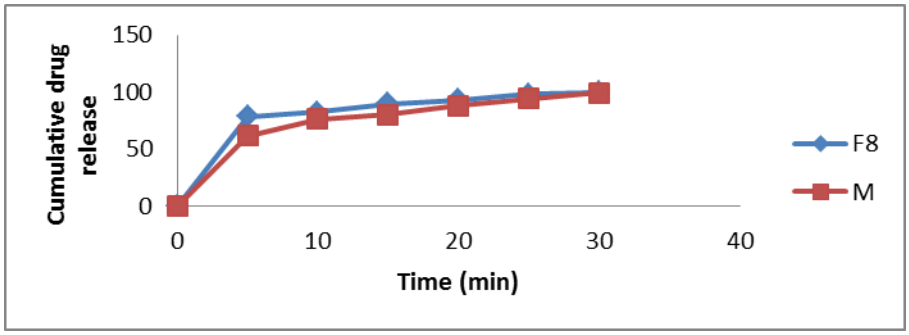


Fig. 15: *In vitro* release of drug of batch F8 and Marketed product in 0.1M HCl.

The comparative evaluation of optimised formulation (F8) with marketed formulation (M) revealed that F8was superior than marketed formulation. The disintegration time for batch F8 was less (19 sec) as compared to marketed formulation (22 sec). Also the rate of drug release from batch F8 was faster than marketed formulation Taste of formulation batch (F8) was tasteless where as taste of marketed batches was slightly bitter. From the result formulation batch F8 was selected as optimized batch So further stability study was done on formulation batch F8.

Data of stability of developed formulation of water dispersible tablets of Rizatriptan benzoate

From the result batch F8 was selected as optimized batch and stability study was done as per the procedure given in experimental part and result are illustrated in the table.

Table No. 26: Stability study of optimized batch F8.

Parameters	Stability study after		
	0 day	15 days	30 days
Physical appearance	Orange colored, smooth, free from cracks	Orange colored, smooth, free from cracks	Orange colored, smooth, free from cracks
Hardness (Kg/cm^2)	4.33 ± 0.28	4.00 ± 0.50	3.91± 0.43
In-vitro disintegration time (sec)	18-20	18-19	17-19
Drug content	99.83 ± 1.24	99.31± 0.79	99.47±0.17
Weight variation	Passes	Passes	Passes
Uniformity of dispersion	Passes	Passes	Passes

(mean ± standard deviation n=3)

DISCUSSION

Results of stability study revealed that, there was no significant change in the optimised formulation (**F8)** during stability period. Thus the formulation was found to be stable.

CONCLUSION

From the findings of various physical and chemical tests it can be concluded that Procured Rizatriptan benzoate and excipients are of finest quality. Also all the formulation excipients are compatible with Rizatriptan benzoate. The bitter taste of Rizatriptan benzoate was successfully masked by Drug: Kyron T-114 (1:4) complex than Drug: INDION 123 (1:5) physical mixture. Water dispersible Rizatriptan benzoate tablets were developed by using Drug: Kyron T-114 (1:4) complex passed all the criteria for water dispersible tablet. The exaggerated conditions of temperature and humidity (40°C±2°C, 75±5%RH) have minimally affected the water dispersible tablets over the period of 1 month. However, elaborate studies are needed for extended period to assure the greater stability.

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