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FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF RIZATRIPTAN BENZOATE SUSTAIN RELEASE TABLET DOSAGE FORM

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ABSTRACT

The present study was formulation development and in vitro evaluation of rizatriptan benzoate sustain release tablet dosage form. the sustained release tablets containing Rizatriptan Benzoate were prepared by wet granulation method and their evaluation were carried out. The *in-vitro* drug release studies from the developed formulation F10 was found to be most promising formulation and maintained excellent release of 94.67% up to 12 hrs, extended the duration period. It shows the sustained release characteristics. The formulation F1-F10 follows the release of Higuchi‘s model. The results of the *in-vitro* release data were fitted to the Korsmeyer Peppa‘s equation, the value of ‗n‘ was found to be less than 0.500,indicating the drug release follows Fickian mechanism.

KEYWORDS: Rizatriptan Benzoate, wet granulation method, Higuchi‘s model, Fickian mechanism.

INTRODUCTION

A tablet is a pharmaceutical oral dosage form (oral solid dosage or OSD) or solid unit dosage form. Tablets may be defined as the solid unit dosage form of medicament or medicaments with suitable excipients. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose.

Tablets are prepared either by moulding or by compression. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrant to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.[1]

Migraine is a common disorder characterised by severe, throbbing and unilateral headache often associated with nausea, vomiting, giddiness and fatigue lasting for several hours, in the classical migraine, a brief ‗aura‘ of visual disturbances occurs prior to the headache. An attack is triggered by factors like stress, anxiety, excitement, food and hormonal changes. The triggering factors stimulate the release of vasoactive substances from nerve endings which are responsible for the events that follow. The peptide neurotransmitters released, the most important of which is calcitonin gene-related peptide (CGRP) is a powerful vasodilator.[2]

Rizatriptan Benzoate is the benzoate salt form of Rizatriptan, a member of the triptan class of compounds with anti-migraine property. Rizatriptan Benzoate is a highly selective $5HT_1$-like receptor agonist introduced as a new treatment for migraine. It is indicated for the acute relief of migraine and cluster headache. Oral administration is reported to be free of substantial side effects. The compound appears to be a significant advance over the use of ergotamine and other agents in the treatment of migraine.

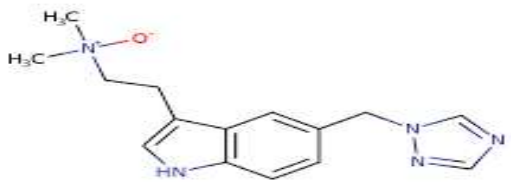

Figure 1: Chemical structure of Rizatriptan Benzoate.

Experimental Work

Materials

Rizatriptan Benzoate, Eudragit RSPO collected from Yarrow Chem. products, Mumbai. HPMC, Ethyl cellulose, Lactose, Talc are collected from nice chemicals Pvt. Ltd, Mumbai.

METHODOLOGY[3]

PREFORMULATION STUDY

Objective of preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico-chemical parameter of new drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in preformulation study.

COMPATIBILITY STUDY

Formulation table

Table No. 1: Formulation of Rizatriptan Benzoate.

S. no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10 (mg)
1	Rizatriptan	10	10	10	10	10	10	10	10	10	10
2	HPMC	50	75	100	-	-	-	-	-	-	82.78
3	Ethyl cellulose	-	-	-	50	100	150	-	-	-	70.425
4	Eudragit RSPO	-	-	-	-	-	-	50	75	100	64.155
5	Lactose	214	189	164	214	189	164	214	189	164	46.64
6	Microcrystalline	30	30	30	30	30	30	30	30	30	30
7	Magnesium	3	3	3	3	3	3	3	3	3	3
8	Talc	3	3	3	3	3	3	3	3	3	3

PRE- COMPRESSION PARAMETER[4]

- Angle of repose (θ):
- Bulk density (ρ_b):
- Tapped density (ρ_t):
- Carr's index or compressability index:
- Hasuner's ratio:
- Standard values for angle of repose, compressibility index and hausner's ratio

POST COMPRESSION PARAMETER

- Thickness
- Weight variation
- Drug content
- Hardness
- Friability

IN-VITRO DISSOLUTION STUDIES

Dissolution Parameters
Medium: Phosphate buffer of pH 6.8
Apparatus: USP type-2 Paddle
RPM: 50
Temperature: 37± 0.5°C
Volume: 900 ml
Wavelength: 226nm

In-Vitro drug release studies[5-6]

Procedure

The dissolution test apparatus was kept as per the above conditions. One tablet was placed in each basket and the apparatus was run. After specified interval of time, 1ml of liquid was withdrawn from the zone midway between the top of rotating paddle and surface of dissolution medium. The 1ml of withdrawn sample is diluted up to 10ml with the dissolution medium and mixed well. The instrument was switched on and stabilized. The instrument was made up to zero and then the absorbance of blank and sample was measured at 226nm using dissolution medium as blank.

KINETIC ANALYSIS OF *IN-VITRO* RELEASE STUDY[7]

ZERO ORDER KINETICS

The zero order kinetics can be obtained by plotting cumulative percentage drug released Vs time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$\mathbf{C = k_0 t}$$

Where,
k_0 = Zero order rate constant in concentration / time t = time in hrs

FIRST ORDER KINETICS

First order release would be predicted by the following equation

$$\mathbf{Log\ C = Log\ C_0 - Kt/\ 2.303}$$

Where
C = Amount of drug remained at time (t)
C_0 = Initial amount of drug
K = First order rate constant

When the data is plotted as log cumulative percent drug remaining versus time, yield a straight line, indicating that the release follow first order kinetics. The constant _K' can be can be obtained by multiplying 2.303 with the slope value.

HIGUCHI MODEL

The graph was plotted with % cumulative drug release Vs square root of time yields a straight line indicating that the drug was released by diffusion mechanism.

$$\mathbf{Q = Kt^{1/2}}$$

Where,
K = Constant reflecting design variable system (Differential rate constant)
T = Time in hours
The drug release rate is inversely proportional to the square root of time.

HIXSON AND CROWELL EROSION EQUATION

To evaluate the drug release with changes in the surface area and the diameter of the particles, the data were plotted using Hixson and Crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hrs

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t$$

Where,

Q_t = Amount of drug released at time t

Q0 = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation[49]

KORSMEYER EQUATION/ PEPPA'S MODEL

To study the mechanism of drug release from the sustained release layer, the release data were also fitted to the well known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behaviour from the polymeric systems, when the release mechanism is not known or more than one type of release is involved.

$$M_t / M_\alpha = Kt^n$$

Where,

M_t / M_α = fraction of drug released at a time_t'

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system

n = Diffusion exponent related to the mechanism of the release.

Mechanism of drug release as per Korsmeyer equation / Peppa's model

Table No. 2: kinetic study.

SL.NO	n VALUE	DRUG RELEASE
1.	< 0.45	Fickian release
2.	0.45 < N < 1.0	Non- Fickian release
3.	> 1.0	Case II transport

If slope value (n) less than 0.5 or less, the release mechanism is ―Fickian diffusion‖ and if 0.5< n <1 it follows ―Non-Fickian diffusion‖ (anomalous transport). The drug release follows zero order release and Non-Fickian case II transport, if the value is 1. For the values of n higher than 1, the mechanism of drug released is regarded as Non-Fickian case II transport.[5]

RESULTS

Compatibility studies

The FTIR spectrum of Rizatriptan Benzoate, HPMC, Ethyl cellulose, Eudragit RSPO are represented in the below figures. The most intensive band at 884.30 in the spectra was attributed to the stretching vibration of CH absorption band at 3374.23 indicated the presence of -OH stretching vibration sharp absorption band 2676.05 at indicated the presence of SH.

All the functional groups Rizatriptan Benzoate were maintained in the sustained release formulation. The results indicate that no chemical interaction occurred between Rizatriptan Benzoate and polymers.

Calibration curve of Rizatriptan Benzoate

The standard curve of Rizatriptan Benzoate was determined in phosphate buffer pH 6.8 by using UV-Visible spectrophotometer at 226 nm. Graph was plotted by taking concentrations (mcg/ml) on X- axis vs absorbance (nm) on Y-axis and it follows the Beer's law.

Table No.3: calibration curve.

S No	Concentration (mcg|ml)	Absorbance (nm) at 226nm
1	0	0
2	1	0.121
3	2	0.244
4	3	0.38
5	4	0.515
6	5	0.655

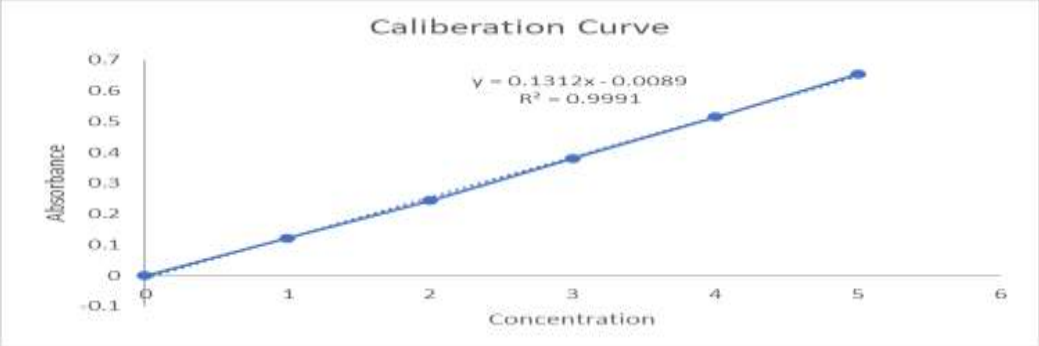

Figure No. 11: Calibration curve of Rizatriptan Benzoate.

Table 4: Various Parameters (Pre & Post Compression).

S.No.		VALUES
PRE-COMPRESSION PARAMETERS		
1.	Angle of repose	23°84′ to 29°08
2.	Bulk density	0.26 to 0.30 g/mL
3.	Tapped density	0.30 to 0.36 g/mL.
4.	Carr's index or % compressibility index	21.58% to 22.7%.
5.	Hausner's ratio	1.21 to 1.28
POST COMPRESSION STUDIES		
6.	Hardness test	5.3 to 6 kg/cm^3
7.	Friability	0.346 to 0.706%
8.	Thickness (mm)	7.1 to 7.4mm.
9.	Drug content analysis (%)	93.47 to 96.84

***IN-VITRO* DRUG RELEASE CHARACTERISTCS**

The sustained release matrix tablets were prepared by using Rizatriptan Benzoate with various polymers. *In-vitro* drug release studies were carried out in trial (n=3) basis for all formulations.

COMPARATIVE RELEASE PROFILE OF RIZATRIPTAN BENZOATE FROM F1 TO F10.

Table No. 5: Comparative Release Profile Of Rizatriptan Benzoate From F1 To F10.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	22.36	23.86	25.25	21.6	22.43	26.7	23.30	21.69	28.9	15.76
1	41.96	34.29	32.09	28.84	31.81	37.04	29.43	29.92	34.60	22.08
2	51.83	38.68	42.76	39.13	43.56	49.9	36.94	38.97	46.25	26.30
3	59.19	47.37	47.40	45.52	47.12	57.52	44.46	43.74	53.16	40.74
4	63.27	55.70	57.06	51.03	51.49	63.41	51.21	51.97	62.23	54.48
5	66.10	59.23	60.83	57.58	59.23	66.69	62.05	59.08	70.63	63.45
6	72.10	62.65	68.19	62.16	63.24	72.45	70.53	65.97	78.59	72.06
7	79.11	69.45	71.96	71.58	72.13	79.15	72.04	78.21	82.18	78.24
8	84.38	77.93	88.67	78.90	77.30	84.24	78.43	84.48	87.10	81.24
9	85.25	88.46	91.08	85.18	86.93	90.97	85.88	90.94	91.08	83.89
10	90.04			90.32	90.43	92.27	91.54	92.36	94.31	85.11
11										91.84
12										94.67

KINETIC VALUES OF FORMULATION F1 TO F10

Table No. 6: Kinetic Values Of Formulation F1 To F10.

Formulation	Zero order	First order	Higuchi plot R^2	Korsmeyer & peppa's plot		Hixson crowell	Possible mechanism
	R^2	R^2		R^2	n	plot R^2	
F1	0.511	0.972	0.974	0.954	0.412	0.954	Higuchi Model, Fickian
F2	0.724	0.917	0.980	0.974	0.417	0.938	Higuchi Model, Fickian
F3	0.770	0.909	0.980	0.975	0.436	0.948	Higuchi Model, Fickian
F4	0.813	0.950	0.989	0.987	0.441	0.976	Higuchi Model, Fickian
F5	0.756	0.940	0.986	0.983	0.444	0.965	Higuchi Model, Fickian
F6	0.665	0.968	0.987	0.995	0.404	0.972	Higuchi Model, Fickian
F7	0.809	0.954	0.990	0.979	0.437	0.979	Higuchi Model, Fickian
F8	0.845	0.951	0.984	0.979	0.431	0.977	Higuchi Model, Fickian
F9	0.666	0.986	0.994	0.990	0.417	0.988	Higuchi Model, Fickian
F10	0.841	0.977	0.980	0.975	0.408	0.989	Higuchi Model, Fickian

SUMMARY

In the present study sustained release Rizatriptan Benzoate tablet formulations were prepared and evaluated by using HPMC, Ethyl cellulose and Eudragit RSPO (50, 75, 100 mg) at various concentrations.

The compatibility study of drug and polymer composition was studied by using FT-IR. The spectrum of drug and polymer showed the major characteristics of absorption bands of polymers in HPMC, Ethyl cellulose and Eudragit RSPO with negligible difference of absorption band values. So, FT-IR spectra shows there are no change in nature and position of absorption band indicating no chemical reaction between drug and polymer.

Optimization was carried out using Stat-Ease software. A randomized 2^3 Full Factorial design was selected. Based on Central composite design the polymers concentration should be optimized. The optimized formula should be selected on the basis of ANOVA for reduced linear model, Desirability and lack of fit value. Stability studies were carried out for optimized formulation and are complies within the limit.

The physical characteristics of tablets were evaluated for thickness, hardness, weight variation and friability. All the formulation provides good weight uniformity and thickness. The parameters like hardness and friability were within acceptable limit. All the batches showed uniform thickness. The average percentage deviation of the 20 tablets of each formulation was less than 7.5% as per IP limit; hence all the formulation passed the test for uniformity of weight as per official requirements. % Friability of all the formulation was below 1% indicating that the friability is within the acceptable limit.

The drug content of Rizatriptan Benzoate of all formulations (F1-F10) was present within the acceptable limit (93.47 – 96.84%) which indicates the uniform amount of drug present in all formulations.

The *in-vitro* release characteristics were studied in 900 ml of pH6.8 for upto 12 hrs. Using USP type 2 paddle type apparatus. The results of this study show F1-F9 formulations fit into Higuchi model and the F10 (96.84%) with higher concentration show the higher release rates at sustained period of time. The *in-vitro* drug release studies from the developed formulation F10 was found to be most promising formulation and maintained excellent release of 94.67% up to 12 hrs, extended the duration period. It shows the sustained release characteristics.

To know the mechanism of drug release from these formulations, the data were treated according to Zero order, first order, Higuchi model, Hixson and crowell model and Korsmeyer and peppas model. The formulation f1 to f10 shows higher regression values for higuchi‘s model as the plot shows regression value for (0.974- 0.994). To confirm the release mechanism the data were fitted into korsemeyer peppa‘s equation with slope values ranging from (0.404- 0.444). This result suggests that the release of drug follows Fickian release mechanism.

CONCLUSION

In the present study, concluded that the sustained release tablets containing Rizatriptan Benzoate were prepared by wet granulation method and their evaluation were carried out. The *in-vitro* drug release studies from the developed formulation F10 was found to be most promising formulation and maintained excellent release of 94.67% up to 12 hrs, extended the duration period. It shows the sustained release characteristics. The formulation F1-F10 follows the release of Higuchi‘s model. The results of the *in-vitro* release data were fitted to the Korsmeyer Peppa‘s equation, the value of _n‘ was found to be less than 0.500,indicating the drug release follows Fickian mechanism.

BIBLIOGRAPHY

1. Verma P, Thakur AS, Deshmukh K, Jha AK, Verma S. Routes of drug administration. International Journal of Pharmaceutical Studies and Research, 2010 Jul; 1(1): 54-9.
2. http:/en.wikepiedia.org/wiki/Tablets.
3. Reddy AM, Sindhura J, Lakshmi BN, Reedy AA, Sri DN, Kumar MN, Babu PS. Formulation and evaluation of bilayered tablets of Rizatriptan Benzoate by using hydrophilic polymers. Der Pharmacia Lettre, 2016; 8(5): 189-206.
4. Bharath Kumar R, Vedavathi T. Formulation and evaluation of Rizatriptan Benzoate oral disintegrating tablets and comparision of disintegrating property between super disintegrants and simple disintegrants. The Pharma Innovation, 2012; 1(9): 73-92.
5. Bonthagarala B, Poornima G, Nama S, Suresh N. Formulation and evaluation of Sublingual tablets of Rizatriptan. Indian Journal of Pharmaceutical Science and Research, e-ISSN No-2248-9126, Print ISSN NO-2248-9118, 2013; 3(2): 69-73.
6. Marabathuni VJ, Dinesh P, Ravikumar R, Yamini P, Kiran PS, Hussain SP, Rao CM. Chitosan based sustained release mucoadhesive buccal patches containing amlodipine besylate (AMB). Asian J Res Pharm Sci, 2017 Jun 28; 7: 97-104.
7. Marabathuni VJ, Bhavani M, Lavanya M, Padmaja K, Madhavi N, Babu P, Rao CM. Formulation and evaluation of mouth dissolving Tablets of carbamazepine. Asian Journal of Pharmacy and Technology, 2017; 7(3): 137-43.