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Development and *In vitro* evaluation of rizatriptan oro dispersible tablets

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Abstract
Orally disintegrating tablets (ODTs) are a modern form of tablets that when placed in the oral cavity, disperses rapidly. These tablets have advantages, particularly good applications for children and old patients who have a complication in chewing or swallowing solid dosage forms. Rizatriptan is a drug of choice in treatment of migraine headaches. Drug compatibility with excipients was checked by FTIR studies. In the present work, oral dispersible tablets of Rizatriptan were prepared by direct compression method with a view to enhance patient's compliance. To formulate oro dispersible tablets of Rizatriptan for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of motion sickness. Drug and excipient compatibility studies measured by using FTIR studies. Eight formulations having different concentrations of super disintegrants were prepared. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and *in vitro* disintegration time. Among the formulations tablets of batch F5 containing Croscarmellose showed superior organoleptic properties along with excellent in-vitro disintegration time and drug release as compared to other formulations. Hence croscarmellose is recommended as suitable disintegrate for the preparation of direct compression or dispersible tablets of Rizatriptan. It was concluded that the presence of a super disintegrant is desirable for orodispersion of tablets by direct compression method.

Keywords: Rizatriptan, super disintegrants, FTIR studies, direct compression technique, in-vitro drug release studies, Drug release kinetics

Introduction
The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients [1], but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water [2] Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc, are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets [3]. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate [4]. Superdisintegrants added in the formulation increase the drug release, thus increasing the bioavailability of drug [5]. Oro disintegrating tablets when placed in the mouth, disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva and can be swallowed as a liquid, without the aid of water [6].

Also, this dosage form offers an advantage of convenience of administration while travelling where there may not be an access to water [7] Rizatriptan benzoate is a potent and selective 5-HTIB/ID receptor agonist and is effective for the treatment of acute migraine. Rizatriptan is 5HT1D agonist, which serves to inhibit both dural vasodilatation and inflammation [8]. The present work was aimed to improve the bioavailability and efficacy of rizatriptan by preparing oral disintegrating tablets.

Materials

Rizatriptan was obtained from Hetero lab, HYD. Sodium starch glycolate, croscarmellose and crospovidone were procured from Synpharma Research Labs, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

Methodology

Fourier Transform Infrared Spectroscopy (FTIR) [9]

Fourier Transform Infrared (FTIR) Spectroscopy FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The spectra was recorded as a dispersion of the sample in potassium bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm-1 and the resolution was 1 cm $^{-1}$.

Table 1: Formulation table

S. No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Rizatriptan	10	10	10	10	10	10	10	10
2	Sodium starch glycolate	5	10	-	-	-	-	5	-
3	Crospovidone XL	-	-	5	10	-	-	5	5
4	Croscarmellose	-	-	-	-	5	10	-	5
5	Lactose	80	75	80	75	80	75	75	75
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2
8	Total wt	100	100	100	100	100	100	100	100

Preparation method

Direct compression technique [10]

Rizatriptan Oro dispersible tablets were prepared by direct compression method by using coprocessed super disintegrants like Crospovidone, Sodium Starch Glycolate and croscarmellose. Lactose as a diluent, Sodium saccharin as a sweetening agent, Mint as a flavor, Magnesium Stearate, Talc used as a lubricant and glident. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components and compressed into tablets of 100mg using 6mm round flat punches on 12-station rotary tablet machine.

Evaluation of tablet

Weight variations [11]

20 random FDTs weighed and average weight determined. Then individual tablet weighed separately to obtain % deviation from the average. The accepted deviation for tablets with average weight ≤ 130mg is 10%, for ≥130mg is 7.5%.

Thickness [12]

Thickness of tablet is crucial for patient acceptance and packaging hence to be controlled at ± 5% deviation from standard value. Vernier Calipers used for measurement of thickness of 10 FDTs

Hardness [13]

Hardness tester was used for determination of hardness of randomly picked 10 tablets and average of measured values reported.

Friability [14]

20 tablets randomly picked were weighed and subjected to friability test in Roche friabilator that rotated at 25 rpm for duration of 4min. the tablets were then reweighed after de-dusting and following equation was used to calculate percent loss in weight due to impact and abrasion,

%Friability= (Loss in weight/ Initial weight) X 100.

Content uniformity [15]

Randomly picked 20 tablets were powdered in a glass mortar after calculating their average weight and amount equal to 10 mg was dissolved in 100ml of phosphate buffer pH 6.8 and filtered followed by spectrometric determination of drug content at 268 nm

In-vitro disintegration time (DT) [16]

The DT of ODTs analyzed in USP device with six glass tubes measuring “3 long, open at the top, and held against 10” screen at lower end of the basket rack congregation. One tablet positioned in each tube with basket rack positioned in 1000ml beaker containing buffer at 37± 2 0C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

In- Vitro Release study [17]

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37±1º C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whatman filter paper. The filtrate was analyzed by U.V. spectrophotometer (Labindia) at 268 nm. The drug release was plotted against time to determine the release profile of various batches.

Kinetics of drug release [18]

To study kinetics data obtained from *in vitro* release were plotted in various kinetic models.

- **Zero-order equation**
  %R = Kt
- **First order equation**

Log% unreleased = Kt / 2.303

- **Higuchi equation**

  $\%R=Kt^{0.5}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

- **Korsmeyer-Peppas equation:** $\%R=Kt^{n}$

This model is widely used, when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms as:

Stability studies [19]

Accelerated three months stability tests were carried out for the optimized ODT in a stability chamber at 40 °C / 75 % RH post wrapping the ODTs in aluminum foil and sealing into ambered bottles

Results and Discussion

Fourier Transformation Infra-red (FTIR) analysis

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).

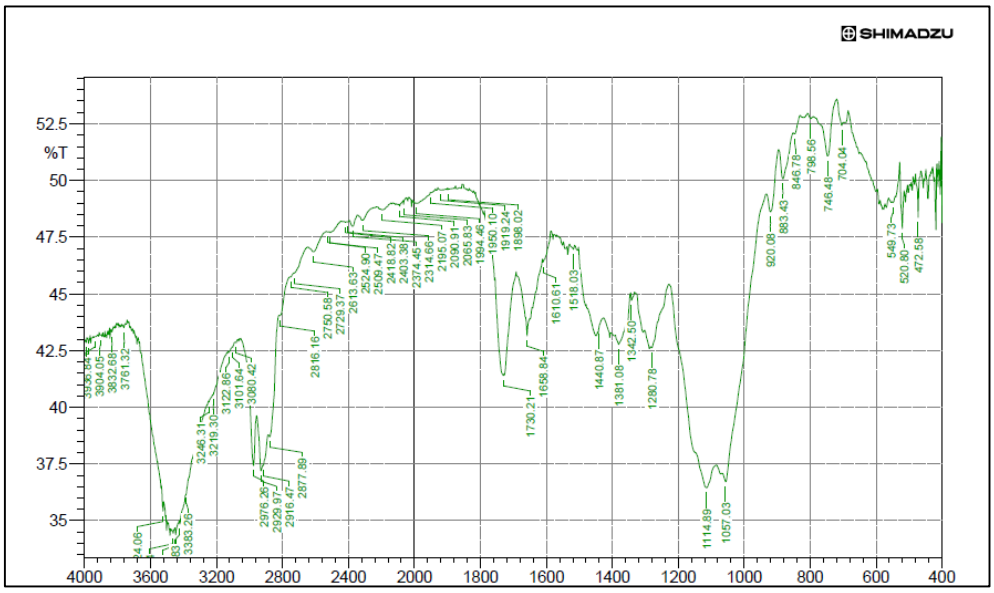

Fig 1: FT-IR Sample for Rizatriptan

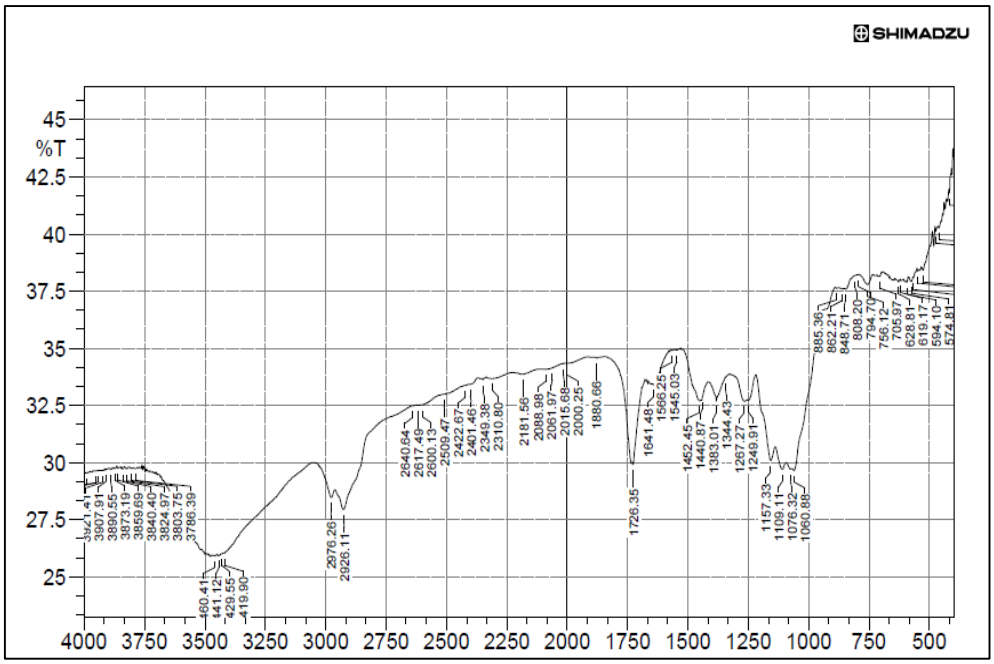

Fig 2: FT-IR Sample for physical mixture of drug and Excipients

In the present study, it has been observed that there is no chemical interaction between Rizatriptan and the super disintegrants used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and excipients. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation studies

Table 2: Evaluation Parameters for Rizatriptan oro dispersible tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation	100	100	99	98	100	101	99	100
Thickness (mm)	2.3	2.5	2.1	2.4	2.6	1.9	2.3	2.4
Hardness (kg/cm^2)	3.56	4.12	3.65	3.18	3.16	3.24	3.48	3.24
Friability (%)	0.54	0.48	0.43	0.53	0.52	0.57	0.59	0.48
Disintegration time	36	41	43	40	32	36	38	34
Drug content	90.24	89.24	88.47	90.71	92.35	91.27	89.25	91..25

Uniformity of weight

All the prepared fast dispersible tablets of Rizatriptan were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±5%.

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 3.18 to 4.12 kg/cm^2. The friability values were found to be in the range of 0.43 to 0.57%.

Uniformity of drug content:

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 88.47 to 92.35 percent (which was within the acceptable limits of ±5%.).

All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

***In vitro* Dissolution studies**

The dissolution conditions used for studying the drug release from oro dispersible tablet:

Apparatus: USP apparatus II (Paddle)
Agitation speed (rpm): 50 rpm
Medium: 6.8 pH Phosphate buffer
Volume: 900 ml
Temperature: 37.0±0.5 °C
Time: 5, 10, 15, 30, 45 and 60min

***In-vitro* dissolution Profiles for tablets**

Table 3: *In vitro* drug release studies of all formulations

Time (min)	F1	F 2	F 3	F 4	F5	F 6	F 7	F 8
0	0	0	0	0	0	0	0	0
5	26.39	20.25	25.86	25.58	28.95	22.60	20.52	25.99
10	48.25	32.18	38.88	35.17	46.55	30.56	32.14	25.20
15	50.18	48.56	52.45	50.26	52.21	42.38	48.13	40.59
30	70.56	70.93	68.49	69.12	76.38	58.96	52.53	63.89
45	80.93	79.50	78.93	80.21	89.96	72.24	78.10	83.58
60	90.25	93.48	93.63	95.12	98.42	92.96	91.23	96.55

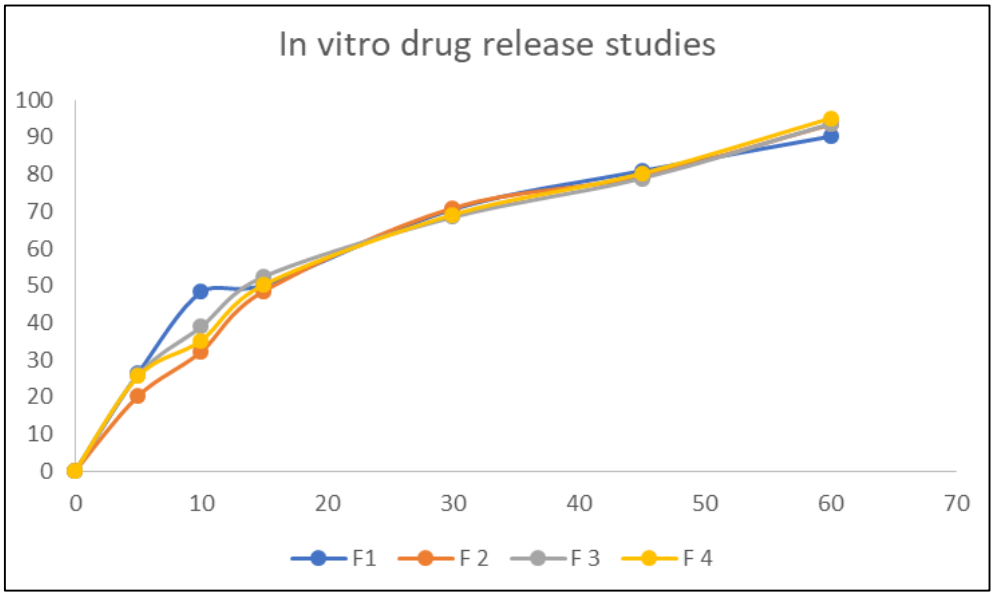

Fig 3: *In vitro* drug release studies for (F1-F4) formulation

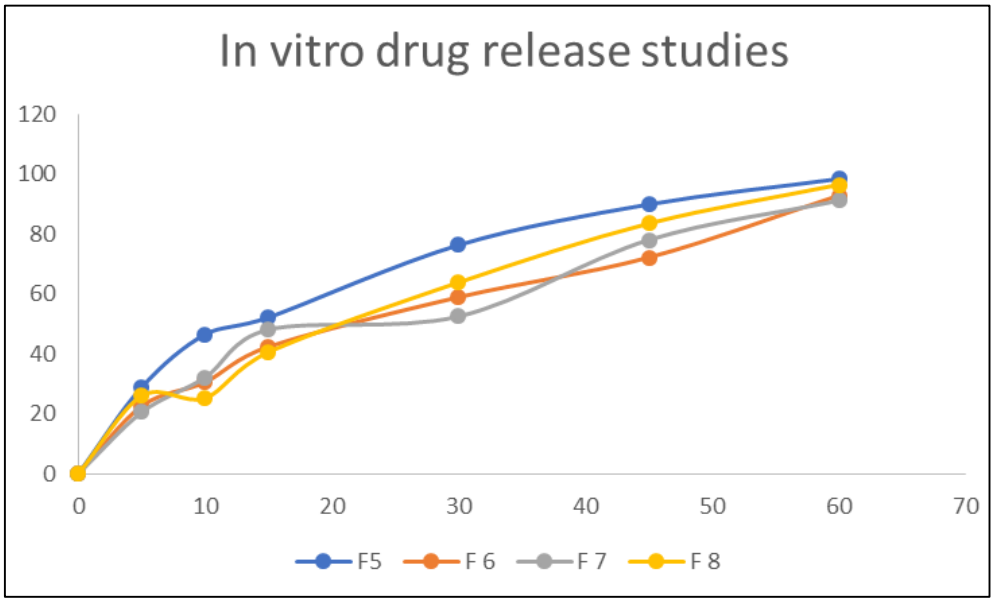

Fig 4: *In vitro* drug release studies for (F5-F8) formulation

Among all formulations, F5 shows better drug release when compared with all other formulations. So formulation F5 selected as optimized formula.

Drug release kinetics

Zero order kinetics

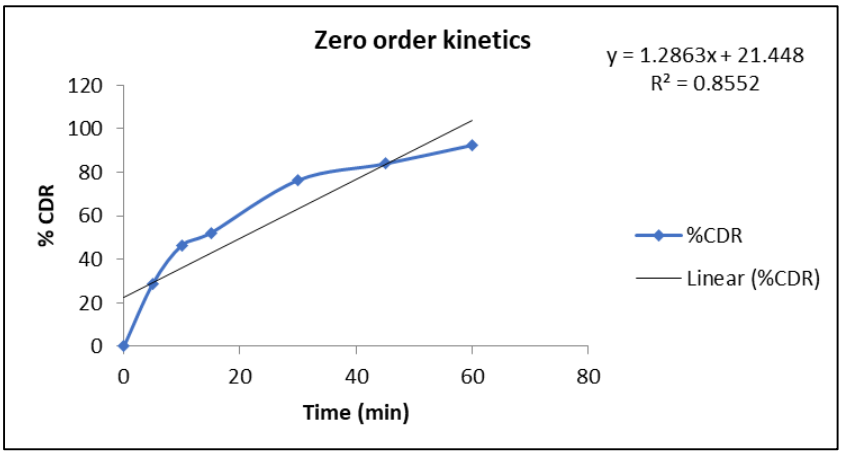

Fig 5: Zero order kinetics of optimized formulation

First order kinetics

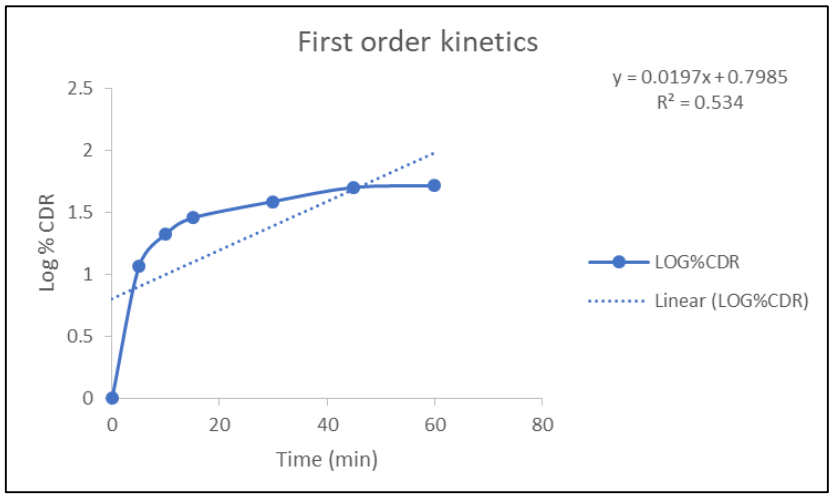

Fig 6: First order kinetics of optimized formulation

Higuchi model

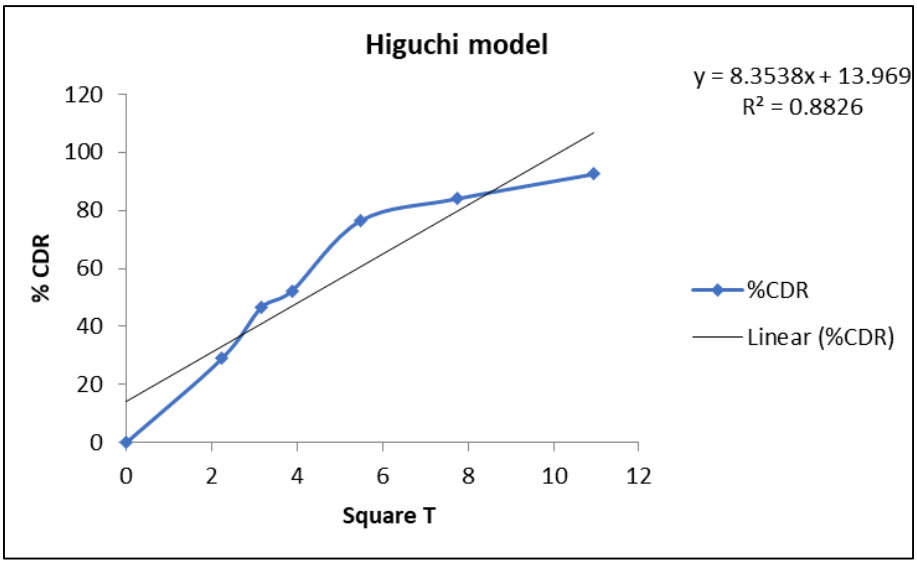

Fig 7: Higuchi model of optimized formulation

Krosmeyer peppas

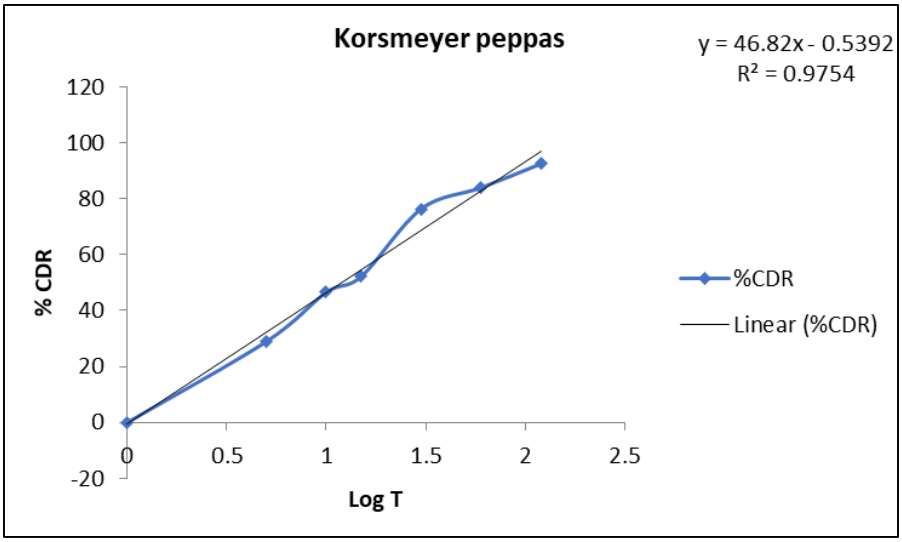

Fig 8: Korsmeyer poppas of optimized formulation

Stability studies

Table 4: Stability Studies of Optimized Formulation

S. NO	Time in days	Physical changes	% Drug release		
			Oro dispersible tablet		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	98.42	98.42	98.42
2.	30	No Change	97.89	97.56	97.50
3.	60	No Change	96.25	96.28	96.54
4.	90	No Change	95.10	95.27	95.20

There was no significant change in physical and chemical properties of the tablets of formulation F5 after 90 days, parameters like % drug release and assay values at various conditions(at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table and dissolution profile.

Conclusion

The aim of the present study was to formulate and evaluate for orodispersible tablets containing Rizatriptan for the management of migraine. After pre-formulation studies it was decided to prepare oro dispersible tablets prepared by direct compression method. In the above studies F5

formulation showed promising results. It was further supported by FTIR analysis which showed that F5 had no interaction with excipients. The stability studies were carried out for the optimized formulation for 3 months and it showed acceptable results. The kinetic studies of the formulations revealed that dissolution is the predominant mechanism of drug release. So F5 formulation was considered as the optimized formulation.

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