PREPRATION OF RIZATRIPTAN SUBLINGUAL TABLETS PREPARED BY DIRECT COMPRESSION WITH DIFFERENT POLYMERS IN VITRO EVALUATION

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ABSTRACT : Sublingual tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. The focus of present investigation was to improve solubility, bioavailability and to achieved rapid onset action. sublingual tablets of Nimodipine were prepared by direct compression technique. The aim of the research was to prepare and evaluate the Rizatriptan sublingual tablets by using direct compression technique.Rizatriptan is a headache medicine that narrows the blood vessels around the brain.Eight Formulations were formulated using excipients are the chitosan, povidine ,sodium starch glycol Friability, Disintegration time. In addition, the prepared tablets were also evaluated for weight variation, thickness, diameter, friability, content uniformity, wetting time and drug release studies. The eight formulations are done in this F6 formulation are release the drug up to the 8 hrs. combination sodium starch glycolate and Chitosan showed better results. So it is more effective in combination with Chitosan. All parameters are come within range of limits. The stability studies are done for 90days.The kinetic profile data is calculated it is fallow the zero order and higuchi model.

Key words: Rizatriptan , Dry granulation technique, FTIR studies, Polymers, Drug release studies , stability studies.

I. INTRODUCTION

The word ‘novel’ about the drug delivery system (DDS) is a search for something that will ultimately lead to minimizing the disadvantages associated with the existing dosage form (DF) and optimizing therapy while maximizing patient comfort[1]. Drug delivery system is a relatively modern term used in place of ‘dosage form’ to describe a system carrying a drug. The ideal form of DDS would be the ‘magic bullet’ envisioned by the 1908 Nobel Laureate Paul Ehrlich. His aim was, as he put it, to find chemicals which have special affinities for pathogenic organisms, to which they would go, and would be, as Ehrlich expressed it, ‘magic bullets’ but should have very little affinity for non-target cells.[2] Sublingual Delivery This is systemic delivery of drugs through mucosal membranes lining the floor of the mouth. Sublingual drug delivery system is enteral route of administration, but as far as absorption is concerned, it is oral trans mucosal type of drug absorption.[3]Sublingual drug delivery systems have been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms[4].Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. The aim of the research was to prepare and evaluate the Rizatriptan sublingual tablets by using direct compression technique.[5] Rizatriptan is a headache medicine that narrows the blood vessels around the brain. Rizatriptan also reduces substances in the body that can trigger headache pain, nausea, sensitivity to light and sound, and other migraine symptoms. Rizatriptan is used to treat migraine headaches.[6]

II. MATERIALS AND METHOD

2.1 Materials

Rizatriptan was collected as a gift sample from Hetero labs,Hyd , polymers and other excipients were purchased from Vijaya Chemicals, Hyd.

2.2 Methododology

Drug excipient compatability

Compatibility studies of Rizatriptan and the disintegrants were carried out by using Fourier Transform Infrared Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450

cm-1 using a FTIR by the KBr disc method[7]

Preparation of tablets by Direct compression method:

Different matrix embedded formulations of Rizatriptan were prepared by direct compression method using varying proportion of super disintegrants either alone or in combination. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, Various Super disintegrant agent and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 5–6 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.[8,9]

Formulation table:

Table :1 Formulation table for Rizatriptan sublingual tablets

INGREDIENS	F1	F2	F3	F4	F5	F6	F7	F8
Rizatriptan	5	5	5	5	5	5	5	5
Cross caramellose	2.5	5	7.5	10	-	-	-	-
Sodium starch glycolate	-	-	-	-	2.5	5	7.5	10
chitosan	10	10	10	10	10	10	10	10
Lactose	76.5	74	71.5	69	76.5	74	71.5	69
Saccharrine sodium	1	1	1	1	1	1	1	1
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Evaluation studies [10,11,12,13]

Bulk Density

Mass thickness is characterized as the mass of powder isolated by mass volume.

It is ascertained utilizing the accompanying condition:

Mass thickness = weight of test taken/volume noted

Tapped density

A precisely measured amount of the powder (W) was deliberately filled the graduated barrel and the volume (vo) was estimated.

Tapped thickness = weight of test taken/tapped volume

Where,

Vo = beginning volume

Vf = last volume.

Compressibility index

In view of the obvious mass thickness and the tapped thickness, the rate Compressibility of the mass medication was dictated by the accompanying recipe.

Carr's index = Tapped thickness - Bulk thickness/Tapped thickness X 100

Hausner's ratio

It shows the stream properties of the powder. The proportion of tapped thickness to the mass thickness of the powder is called Hausner proportion.

Hausner's proportion = Tapped thickness/Bulk thickness

Angle of repose

The stream attributes are estimated by point of rest. Edge of rest is characterized as the most extreme point conceivable between the surface of a heap of the powder and the even plane.

tanE = h/r

Where

h = tallness of heap

r = sweep of the base of the heap
E = edge of rest

Evaluation of tablets[14,15,16]

Weight variation

Twenty tablets were Characterized chosen from each group and exclusively weighed. The normal weight and standard deviation of 20 tablets was ascertained. The cluster finishes the test for weight variety test if not more then two of the individual tablet weight digress from the normal weight by more than the rate.

Thickness

Twenty tablets were evaluated chosen from each group and there thickness was estimated by utilizing vernier caliper. Thickness of three tablets from each cluster was estimated and mean was computed.

Hardness

Hardness demonstrates the capacity of a tablet to withstand mechanical stuns while taking care of. The hardness of the tablets was resolved utilizing Monsanto hardness analyzer. It is communicated in kg/cm2. Three tablets were arbitrarily picked and hardness of the tablets were resolved.

Friability

Friability test is performed to survey the impact of erosion and stuns, which may regularly make tablet chip, top or break. Roche friabilator was utilized for the reason. This gadget subjects various tablets to the consolidated impact of scraped spot and stun by using a plastic chamber that spins at 25 rpm dropping the tablets at separation of 6 creeps with every upheaval. Twenty tablets were weighed and set in the Roche friabilator, which was then worked for 25 rpm for 4 min. After unrest Tablets were dedusted and reweighed. Packed tablets ought not free over 1% of their weight.

The rate friability was estimated utilizing the recipe,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in rate
Wo = Initial weight of tablet
W = weight of tablets after insurgency

Content Uniformity

Twenty tablets from each clump were powdered and weighed precisely identical to 100 mg Rizatriptan . Break down the measured amount of powder into 100 ml of 6.8 phosphate support arrangement by blending it for 15 min. 1 ml of arrangement was pipette out into 10 ml volumetric flask.

In vitro drug release studies

In the USP drug release test for sublingual tablets, the breaking down mechanical assembly for oral tablets is utilized without the covering plastic plates, and 2 min is indicated as the satisfactory time confine for tablet deterioration satisfying the official necessities (<2 min) for the sublingual measurements frame. The test was done utilizing a tablet breaking down contraption. Refined water was utilized as the crumbling medium at 24 ± 0.2°C. The time required to acquire finish breaking down of the considerable number of tablets was noted.

Wetting time

The tablet was put at the focal point of two layers of permeable paper fitted into a petridish. After the paper was altogether wetted with refined water, overabundance water was totally depleted out of the dish. The time required for the water to diffuse from the wetted spongy paper all through the whole tablet was then recorded utilizing a stopwatch.

In vitro drug release studies

In-Vitro sedate discharge thinks about were done utilizing Tablet dissolusion apparatus USP II at 50 rpm. The disintegration medium comprised of 900 ml of Standard support pH 1.2 for the initial 2 hrs, trailed by pH 6.8 for residual timeframe. Temperature kept up at 37 ^{o} C. The example of 5ml was pulled back at foreordained time interims and a proportional measure of new disintegration liquid equilibrated at a similar temperature was supplanted. From that 5 ml test, 1 ml test was pulled back and set in a 10 ml volumetric flask. The aliquots were tested.

Swelling study

Swelling of tablet includes the assimilation of a fluid bringing about an expansion in weight and volume. Fluid take-up by the molecule might be because of immersion of slender spaces inside the particles or hydration of macromolecule. The fluid enters the particles through pores and tie to huge atom; breaking the hydrogen bond and bringing about the swelling of molecule. The degree of swelling can be estimated as far as % weight gain by the tablet. one tablet was weighed and set in a Petri plate containing 25 ml of 6.8 pH cushion arrangement. After

every interim the tablet was expelled from recepticle, evacuates overabundance of cushion by utilizing channel paper and weighed again up to 12 hours. The swelling list was ascertained utilizing following equation.

Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100

Where,

S.I. = Swelling list

Wt = Weight of tablet at time t

Wo = Weight of tablet before putting in the petri plate.

Drug release kinetics

The models utilized were zero request (condition 1) First request (condition 2) and Higuchi show (condition 3) and Koresmeyer Peppas display (condition 4).

Zero order kinetics

R = Ko t - (1)

R=cumulative percent tranquilize discharge

Ko=zero arrange rate steady

First order kinetics

log C = log Co – K 1 t/2.303 - (2)

where

C = total percent medicate discharge

K 1 = first request rate steady

Higuchi Model

R = K H t 0.5 - (3)

Where

R = aggregate percent medicate discharge

K H = higuchi display rate consistent

korsermeyer peppas :

M t/M α = k t n

log M t/M α = log k + n log t - (4)

where

k = korsermeyer peppas rate consistent

'M t/M α' is the partial medication discharge, n = diffusional type, which describes the instrument of medication discharge (Simon Benita, 2007).

The acquired relapse co-effective (which neared 0.999) was utilized to comprehend the discharge example of the medication from the Sublingual tablets.

Diffusional exponent (n)		Drug release mechanism
0.43	--	Fickian diffusion
0.43- 0.85	--	Anamolous (non- fickian) transport
0.85- 1	--	Case II transport
> 1	--	Supercase II transport

The obtained regression co-efficient (which neared 0.999) was used to understand the release pattern of the drug from the Sublingual tablets.

Stability studies

The sublingual tablets of Rizatriptan were set on plastic tubes containing desiccant and put away at surrounding conditions, for example, at room temperature, 40±2oc and icebox 2-8oc for a time of 3 months.[17]

III.RESULTS AND DISCUSSIONS

FT-IR Spectrum of Rizatriptan

FT-IR Spectra of Rizatriptan and F6 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Rizatriptan and polymer. It also confirmed that the stability of drug during microencapsulation process.

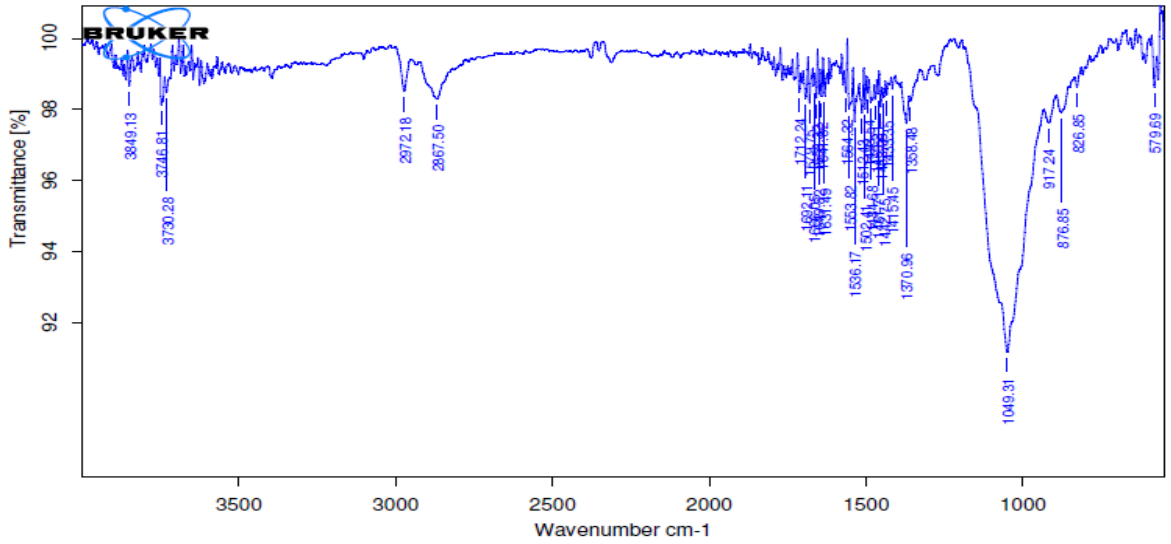

Fig.1. FTIR Studies of Rizatriptan

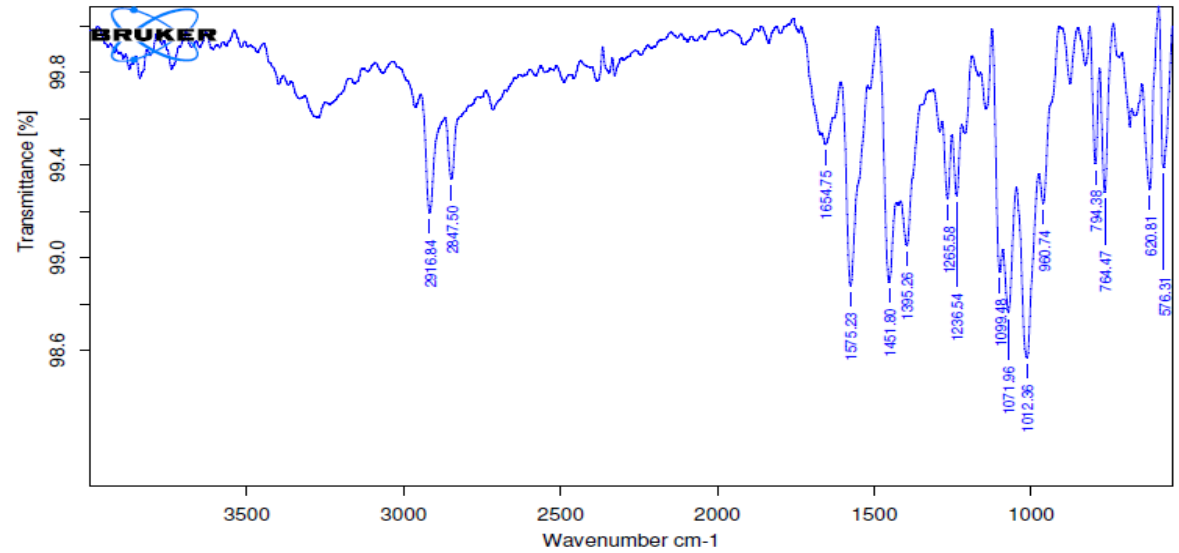

Fig.2. FTIR Studies of optimized formulation

Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.431-0.471

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.515-0.563.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to31^0

c) Compressibility index: Compressibility index was carried out, it found between 10% to 14.90 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table-: 2 Pre compression parameters of Rizatriptan sublingual tablets

S. no	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	**Angle of repose(0)**
F1	0.431	0.522	17.43	1.21	29^{0}c

F2	0.471	0.563	16.34	1.19	29^0c
F3	0.463	0.524	11.64	1.13	30^0c
F4	0.455	0.515	11.65	1.13	30^0c
F5	0.462	0.531	12.99	1.14	31^0c
F6	0.458	0.534	14.23	1.16	29^0c
F7	0.449	0.521	13.81	1.16	31^0c
F8	0.451	0.530	14.90	1.17	30^0c

Post compression parameters

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 2.3 mm to 2.6 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 3.24 to 3.46 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 95.20% and 98.55% of Rizatriptan , it complies with official specifications.

Disintegration Time:

In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 2.25 s, while the longest greatly exceeded 2.81 sec.

Wetting Time:

The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The shortest registered wetting time was 1.25 s, while the longest greatly exceeded 1.52 sec.

Table-: 3 Evaluation parameters of Rizatriptan sublingual tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Disintegration time(sec)	Wetting time (sec)
F1	99	2.3	3.24	0.52	96.10	54	125
F2	98	2.4	3.26	0.45	95.20	53	134
F3	100	2.6	3.28	0.54	98.55	51	155
F4	97	2.4	3.46	0.51	97.50	49	152
F5	100	2.5	3.40	0.53	96.58	45	128

F6	100	2.6	3.28	0.54	98.55	51	155
F7	97	2.4	3.46	0.51	97.50	49	152
F8	100	2.5	3.40	0.53	96.58	45	128

Dissolution studies

All the eight formulation of Rizatriptan sublingual tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-: 4 Dissolution Profile of formulation F1 to F8

%Drug Release								
Time(mins)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
10	25.36	26.39	25.98	24.59	26.79	23.40	24.80	23.85
20	35.26	36.29	37.59	39.65	34.56	32.71	33.10	32.71
30	50.26	49.67	50.26	49.99	48.26	48.56	46.29	47.36
40	62.35	59.66	61.29	64.26	63.54	65.30	59.80	60.55
60	70.26	70.98	71.29	73.29	72.59	72.28	70.60	73.60
80	79.36	81.26	82.29	83.96	83.85	82.10	81.90	82.26
100	86.26	87.26	88.99	90.26	89.56	89.25	90.64	88.25
120	93.26	95.35	94.68	93.48	94.56	98.48	95.51	90.58

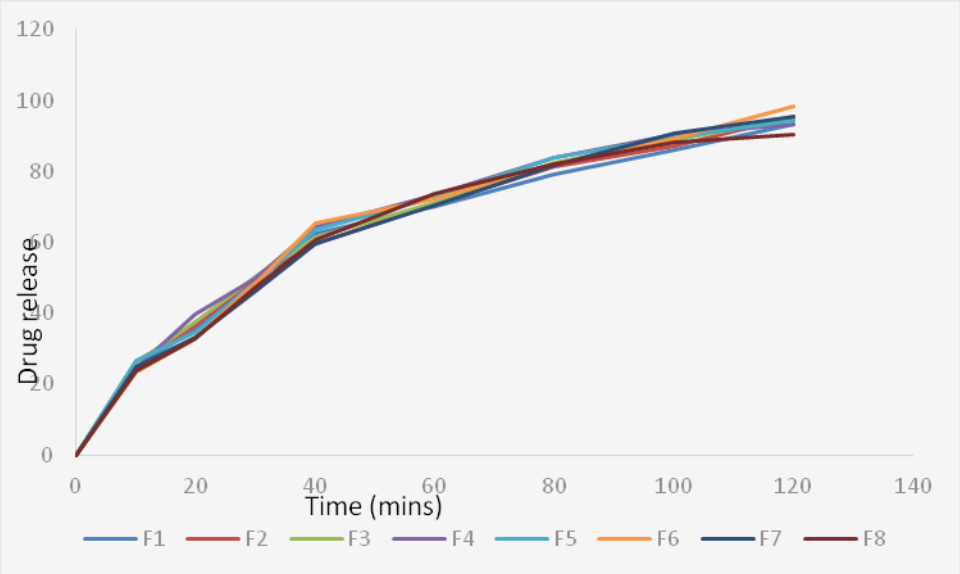

Fig.3. Percentage drug release of all formulations

Release order kinetics

Table-:5 Drug release kinetics of optimized formulation

Time (hrs)	% CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	**0**	**0**	**0**

10	23.4	3.16228	1	1.29864	76.6	1.90369
20	32.71	4.47214	1.30103	1.35984	67.29	1.88705
30	48.56	5.47723	1.47712	1.51135	51.44	1.82956
40	65.3	6.32456	1.60206	1.7626	34.7	1.62439
60	72.28	7.74597	1.77815	1.80079	27.72	1.56573
80	82.1	8.94427	1.90309	1.89845	17.9	1.31911
100	89.25	10	2	1.94226	10.75	1.09517
120	98.48	10.9545	2.07918	1.97918	1.52	0.67025

Zero order kinetics

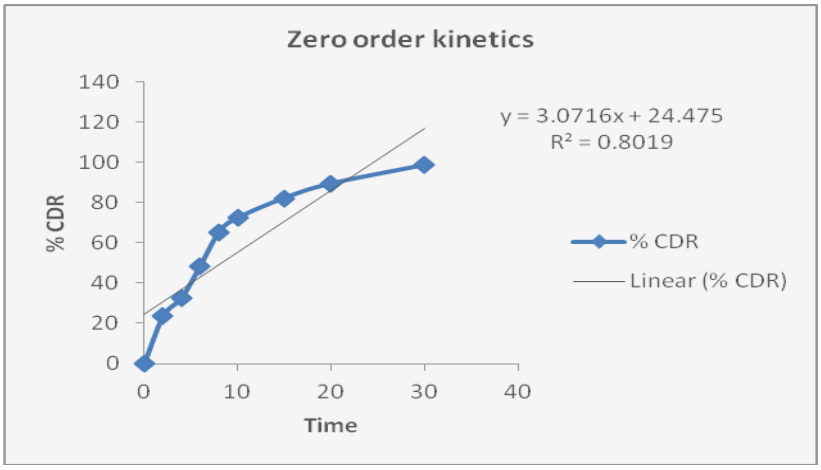

Fig.4. zero order plot for optimized formula

First order kinetics

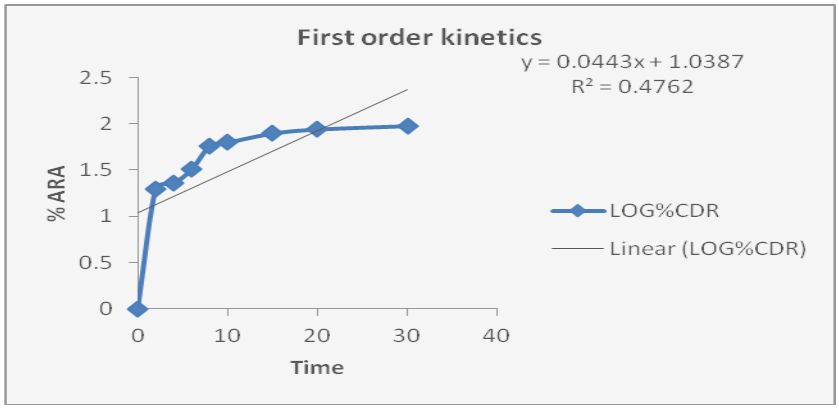

Fig.5. First order for optimized formula

Higuchi model

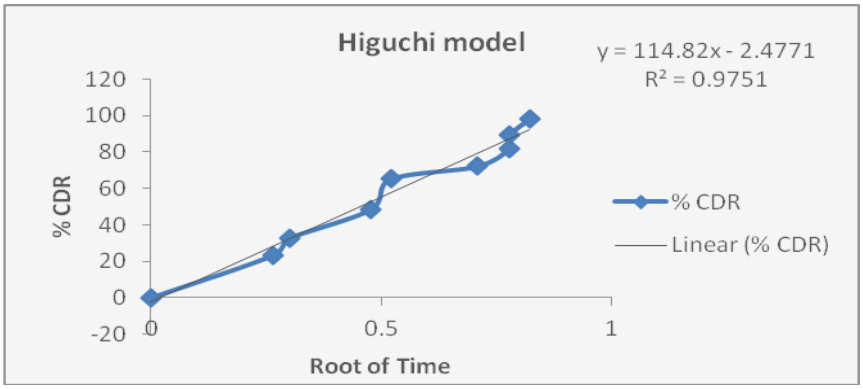

Fig.6. Higuchi plot for optimized formula

Korsmayer peppas

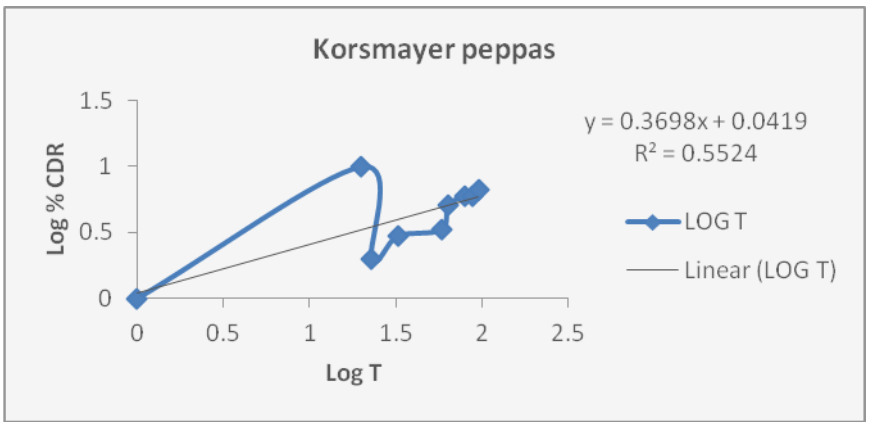

Fig.7. Korsmayer peppas plot for optimized formula

The drug release from the tablets was found to follow Zero order release based on the "r" value obtained for Zero order (0.801) and first order (0.476) for F6 formulation. Also, the drug release mechanism was found to be "Diffusion" based on the "r" value of 0.975 obtained for Higuchi's plot. Similarly, the drug release mechanism was found to be of Anomalous diffusion mechanism based on the "n" value of 0.552 obtained for Peppa's equation.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 6 months. Parameters quantified at various time intervals were shown.

Table-: 6 Stability studies of all formulations

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	25^0C/60%RH % Release	98.48	98.46	98.42	98.41	Not less than 85 %
F-6	30^0C/75% RH % Release	98.48	98.45	98.45	98.40	Not less than 85 %
F-6	40^0C/75% RH % Release	98.48	98.46	98.44	98.42	Not less than 85 %

IV. SUMMARY

The design, prepare and characterization of the sublingual tablets of the rizatriptan by using direct compression technique. In this formulation development first undergo for the pre formulation studies such as the color, odour, taste and solubility studies are done. The API and polymers compatability studies are done by the FTIR studies. For formulation studies the used excipients are the chitosan, povidine ,sodium starch glycolate and mannitol and talc were used. The eight formulations are done in this F6 formulation are release the drug up to the 8 hrs. combination sodium starch glycolate and Chitosan showed better results. So it is more effective in combination with Chitosan. It is compared to innovator it releases the drug. The post compression parameters are also done. Such as the weight variation, friability, thickness, disintegration are done. All parameters are come within range of limits. The stability studies are done for 90days.The kinetic profile data is calculated it is fallow the zero order and higuchi model

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