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"FORMULATION AND EVALUATION OF BILAYER TABLET OF ZIPRASIDONE HYDROCHLORIDE"

D.Singh Lodhi, *Dr. Dharwekar G.N*, Raj Sharma

1,1* Acropolis Institute of Pharmaceutical Educatioin & Research, Indore By -Pass Mangliya Indore (M.P)

2,2*Sagar Institute of Pharmacy & Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal Madhya Pradesh India-462036

***Corresponding Author: Mr. Devendra Singh Lodhi**

Sagar Institute of Pharmacy & Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal (M.P)-462036

Email-devendralodhi86@gmail.com

ABSTRACT

Ziprasidone is newer generation atypical antipsychotic drug used in the treatment of psyzophrenia it is a psychopharmacological agents or psychotropic drugs are those having primary effects on mental process and used for treatment of psychotic disorder. It has low propensity to cause extra pyramidal side effects or hyper lactatinaemia it is mildly sedating causes modest and little weight gain or blood sugar blood level. Ziprasidone has been reported to be an effective a typical newer generation antipsychotic drug for both positive and negative symptoms of schizophrenia. For treating a schizophrenic patient a combined action of an antipsychotic drug is needed i.e. For an immediate effect fast release of drug form formulation is desired and then a delayed release is needed .At present no existing formulation is having both type of action .In present work a bilayer tablet of Ziprasidone will be formulated in which one layer will provide a fast release to show an immediate effect and other layer will provide a sustain release of the drug and will be useful for maintaining the drug concentration in the diseased state .The major advantage of formulation will be reduction in the dosing frequency and enhancement of patient compliance and therapeutic effect. In the present research, the release profile will be studied.

Keyword: Bilayer Tablet, **RSPO**, RLPO, HPMC, Ziprasidone Hydrochloride

1.INTRODUCTION [1,2,3,4,5,6]:-

1. Oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Solid dosage form mainly used to deliverering the drug by oral dosage form which may be tablet, capsules, powder, pellets, granule, etc. Solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. Tablets are solid dosage forms usually obtained by single or multiple compressions of powders or granules. In certain cases tablets may be obtained by molding or extrusion techniques. They are uncoated or coated. Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled. They may have lines or break marks (scoring), symbols, or other markings. Tablets are single-dose preparations intended for oral administration. Some are intended to be swallowed whole, some after being chewed and some after being crushed, some are intended to be dissolved or dispersed in water before being taken and some are intended to be

retained in the mouth where the active ingredient(s)between APIs by physical separation and to is/are liberated. The terms Sustained release, prolongedenable the development of different drug release release, modified release, extended release or depotprofiles. Bi-layer tablet is suitable for sequential formulations are used to identify drug delivery systemsrelease of two drugs in combination and also for that are designed to achieve or extend therapeutic effectsustained release of tablet in which one layer is by continuously releasing medication over anfor immediate release as loading dose and extended period of time after administration of a singlesecond layer act as maintenance dose. So use of dose. There are several reasons for attractiveness ofbi-layer tablets is a very novel aspect for anti-these dosage forms: provides increased bioavailabilityhypertensive, diabetic, anti-inflammatory and of drug product, reduction in the frequency ofanalgesic drugs where combination therapy is administration to prolong duration of effective bloodoften used. Several pharmaceutical companies levels, reduces the fluctuation of peak troughare currently developing bi-layer tablets, for a concentration and side effects and possibly improvesvariety of reasons, patent extension. In general the specific distribution of the drug. Oral drug deliverytablet manufacturing principles remain the same, is the most preferred and convenient option as the oralthere is much more to consider because making route provides maximum active surface area among allmulti-layer tablets involves multiple often drug delivery system for administration of variousincompatible products, additional equipment and drugs. The attractiveness of these dosage forms is duemany formulation and operation challenges. The to awareness to toxicity and ineffectiveness of drugspresent research article provides an introduction when administered by oral conventional method in theto bi-layer tablet technology, challenges in bi-form of tablets & capsules. Usually conventionallayer tablet manufacturing, various tablet presses dosage form produces wide range of fluctuation in drugused, quality and GMP requirements for their concentration in the bloodstream and tissues withproduction various techniques used for bi-layer consequent undesirable toxicity and poor efficiency.tableting and recent developments in the field of The maintenance of concentration of drug in plasmabi-layer technology. Bi-layer tablets have been within therapeutic index is very critical for effectivedeveloped to achieve controlled delivery of treatment.

1**ADVANTAGE OF SOLID ORAL DOSAGE FORM**

- Usually used for oral administration and used for local & systemic effect
- Convenient and safe way of drug administration.
- Compared to liquid dosage form they are more physically & chemically stable.
- Enables more accurate dosing. Convenient to handle and can be Prepared in different ways according to their use.
- They can be mass produced, with quality-controlled production procedures giving an elegant.
- Preparation of consistent quality and low price.

2 BILAYER TABLET [5, 6, 7, 8] Bi-layer tablet is a new era for successful development of controlled release-sustain release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bi-layer tablets. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablets can be a primary option to avoid

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chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).In a combination therapy bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release and fast release of same drug in different layer.

REASON FOR CHOOSING BCS CLASS II DRUG FOR FORMULATION:

1. Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to sustain the drug release.
2. Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
3. Less risk of dose dumping.
4. Less inter and intra subject variability.
5. High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
6. Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
7. Transport of drug is independent of gastric emptying.

2. MATERIALS AND METHODS

2.1. Materials – Ziprasidone Hydrochloride was obtained as a gift sample from Ramdev I fully acknowledge and giving a special thanks to **Mr. Suneel Pandey** (M/S Ramdev Chemical Pvt.Ltd.) for providing me a gift sample of Ziprasidone, and **Ms. Kavita Dschuza** (M/S Evonik Degussa India Pvt.Ltd.) For providing a gift sample of EUDRAGIT RLPO, RSPO or **Ms.Sweta Sharma** (M/S Chouksey Laboratory Indore) for IR analysis of drug.. All the chemicals and reagents used were of analytical grade.

Table 2.1.

S.No	Material used	Manufacturer name
1	Ziprasidone Hydrochlorid	M/S Ramdev Chemical Pvt.Ltd.
2	Eudragit RLPO	M/S Evonik Degussa Pvt.Ltd
3	Eudragit RLPO	M/S Evonik Degussa Pvt.Ltd
4	Lactose	Lobachem Pvt.Ltd
5	Magenesium stearate	Lobachem Pvt.Ltd
6	Starch	Lobachem Pvt.Ltd
7	Talc	Lobachem Pvt.Ltd
8	Colloidal silicone dioxide	Lobachem Pvt.Ltd
9	MCC	Lobachem Pvt.Ltd
10	Aerosil	Lobachem Pvt.Ltd
11	Methanol	RFCL Limited
12	Ethanol	Shangshu Yanguan Chemical
13	Disodium hydrogen phosphate	Merck
14	Potassium dihydrogen phosphate	Merck

2.2. Drug identification [80-86]

- ✓ **Identification By UV**
  - ❖ **Calibration in Saline Phosphate buffer 7.4:-**

A)Preparation of buffer:- Dissolve 2.38gm of disodium hydrogen phosphate ,and 0.19

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gm of potassium dehydrogenate phosphate or 8.0 gm of Nacl was accurately weighed and taken in a 1000 ml of volumetric flask and mix slowly given a clear solution and finally volume was adjusted with distil water to produce sufficient volume. And pH was checked and adjusted if needed.

B) Preparation of stock solution :- 100 mg drug was accurately weighed and dissolved in 10 ml methanol then buffer was use to produce 100 ml. Then diluted with different concentration to make solution 2, 4, 6,7,10 µg/ml solution.

C) Sample determination:- Sample was taken and put in the Shimadzu-UV sample holder then g spectrum mode was selected and peak determined wavelength was note down then absorbance was taken of different concentration calibration curve was plotted.

2.3. FORMULATION OF ZIPRASIDONE (HCL) TABLET

- ❖ **Selection of Excipient:-**
- ✓ Eudragit RLPO and RSPO for combined release profile by combination of RL and RSPO in different ratio for delivering a sustain release formulation of Ziprasidone with no interaction of drug and polymer it should be time independent release profile of the drug.
- ✓ Lactose as diluents and bulking agent to increasing a bulk of drug.
- ✓ Starch as binder for make slurry of drug and Excipient to help a wet mass and granule formulation.
- ✓ Magnesium stearate as a lubricant for lubrication.
- ✓ Talc as glidant
  - ❖ **Selection of method**

Bilayer tablet of ziprasidone Hcl were prepared by wet granulation method using various concentration of polymer 10 % starch solution .All the ingredient were accurately weighed and passed with sieve no 22 then dry the granule at 60^{o}c at oven. Then again passed with 12 no sieve. Talc and magnesium stearate mix in the granule. Compress the tablet. In other layer Drug Mcc and starch passed through sieve no 40.All ingredients mixed in geometric proportion in a polybeg for 15 minute. Aerosil and magnesium stearate were passed through sieve 60 and mixed with above blend. Compressed the material to formulate a bilayer tablet. And we tried to formulate the tablet with the help of those method but the release rate cannot be show proper manner release so we choosing the direct compression for fast release and wet granulation method for the sustain release formula these are helpful to formulate the bilayer tablet of Ziprasidone tablet combining the both action.

Table 5.4.1 Formula for sustains release formulation (mg)

S. N	Ingredients	Quantity	F1 (1:1)	F2 (1:1)	F3(1:1:1)	F4 (1:2)	F5 (1:2)
1	Ziprasidone hcl	44	44	44	44	44	44
2	Eudragit RLPO	40	40	---	40	80	----
3	Eudragit RSPO	40	----	40	40	---	80
4	MCC	10	10	10	10	10	10
5	Starch	20	20	20	20	20	20
6	Talc	10	10	10	10	10	10
7	Magnesium stearate	10	10	10	10	10	10
8	Lactose	20	20	20	20	20	20
Tot		150	15	15	150	15	15

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al			**0**	**0**		**0**	**0**

Table 5.4. 2 Formula for fast release formulation (mg)

S/N	Ingredients	Quantity Taken
1	Ziprasidone Hcl	20mg
2	MCC	22mg
3	Colloidal silicone dioxide	2mg
4	Mg Stearate	1mg
5	Aerosil	5mg
Total 50mg/Tablet		50mg

Optimized Final Formula

S.No	Ingredients	Quantity
1	Ziprasidone Hcl	850mg
2	Eudragit RLPO	850mg
3	Eudragit RSPO	850mg
4	Lactose	100mg
5	Starch	300mg
6	Talc	40mg
7	Magnesium stearate	20mg
	For 20 tablet Total	**3000 mg**

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EVALUATION OF OPTIMIZED FORMULA: -[25-30]

5.6.1. Pre compression parameter

- ✓ **Bulk density:** It is determined by a powder of Ziprasidone placed in 100 ml measuring cylinder and measure the bulk volume and mass of powder sample and calculated by using the formula as given.

  Mass of the powder

  Volume of the Powder

  Bulk density= M/Vo

  Where M= Mass of powder taken
  Vo=Volume
- ✓ **Tapped density:** The powder sample under test was screened through sieve#18&10 ml of graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times the tapped density is calculated in g/cm3 by the formula. Tapped Density M/Vf

  Where M=Weight of powder taken V=Tapped volume
- ✓ **Percentage compressibility index** Based on the bulk density & Tapped density under the percentage compressibility granule was compound using cars compressibility index
- ✓ **Angle of Repose: -** It is defined as the maximum angle possible between the surface of a pile of the powder and horizontal place. And it is calculated by

  tanϴ=h/r

  Where h=height of pile
  r=radius of pile

A glass funnel is held in place with a clamp on a ring support cover a glass plate on a tripod stand measured the pile of powder height and radius.

S.No	Angle of Repose	Flow
1	<25	Excellent
2	25-30	Good

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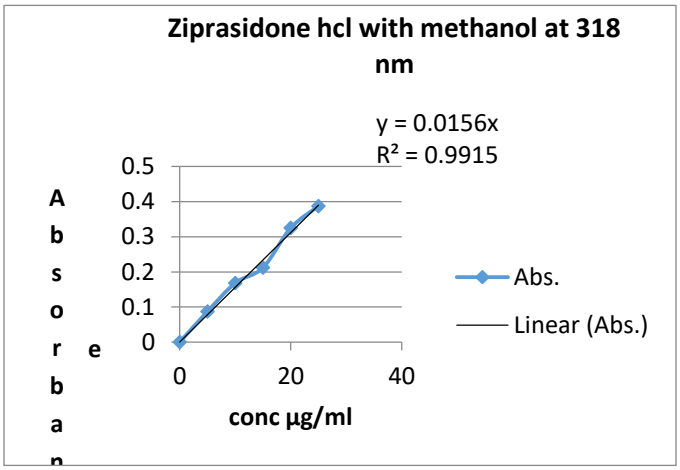
3	*30-45	Passable
4	>40	Very Poor

5.7. Post compression evaluation:-

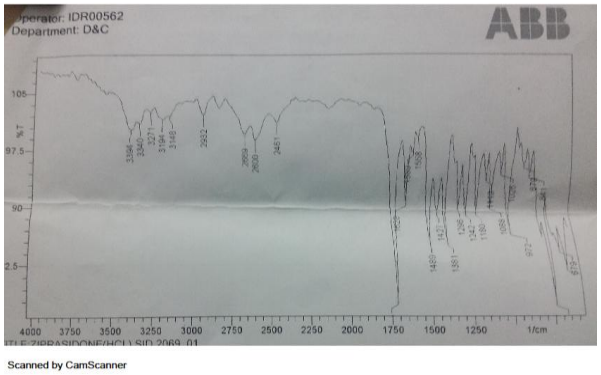
- ✓ **Weight Variation: -** 20 tablets were selected and weighed on digital weighting balance (Oahu's, USA), and average weight was determined. Then individual tablets were weighed, and the individual weight was compared with an average weight.
- ✓ **Thickness: -** Thickness of tablets was determined using vernier caliper (Indian Caliper Industries, Ambala, India). Three tablets from each batch were used, and an average value was calculated.
- ✓ **Hardness:-**The breaking strength of the tablets was measured using Pfizer hardness tester (Perfit). Four tablets from each formulation batch were tested individually, and the average reading was noted. Hardness measured in kg/cm^2.
- ✓ **Friability:-**Ten tablets were weighed and placed in a friabilator (Scientech, India), and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out de-dusted and reweighed. The percentage friability of the tablets was measured.
- ✓ **Invitro disintegration test:-**The test was carried out on 6 tablets using digital tablet disintegration tester (Veego, India). Distilled water at 37°C ± 2°C was used as a disintegration media, and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.
- ✓ **Drug content: -** A tablet was taken and weigh accurately and crush in a pestle mortar and dissolve in 40 ml of methanol filtered the solution and absorbance was taken peak was not detected so dilute the solution then absorbance was taken finally absorbance was taken and calculate the concentration and amount of drug release.

- ✓ **In vitro Dissolution Study:-**
Ziprasidone Hcl analyzed with the help of USP dissolution apparatus type II (Paddle) (Electrolab Pvt.ltd) speed was set 5o rpm.dissolution media pH 7.4 buffer solution with 1% SLS .And temperature maintained 37±2 °C and 5ml sample withdrawn at different time interval (0,15,30,45,60------) and sample analyzed .

6.1Preformulation study of Ziprasidone Hcl: - The Preformulation study of Ziprasidone was carried out by various parameters like melting point, solubility, and spectral analysis etc.



6.1.1 Identification by FTIR-Spectroscopy



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6.1.2 Estimation of Ziprasidone by UV in Methanol:-

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Table 6.1.2Estimation of Ziprasidone by UV in Methanol

S/N	Concentration µg/ml	Absorbance ±SD
1	2	0.041±0.0019
2	4	0.089±0.0034
3	6	0.125±0.0012
4	8	0.167±0.0021
5	10	0.21±0.0024

Fig: - 6.1.2.1 Calibration curve of Ziprasidone hydrochloride by UV in Methanol

S/N	Concentration µg/ml	Absorbance±SD
1	5	0.087±0.0012
2	10	0.168±0.0016
3	15	0.212±0.0023
4	20	0.325±0.0017
5	25	0.387±0.0032

6.1.3 Estimation of Ziprasidone in PH 7.4-

6.1.3.1 Table of estimation of Ziprasidone in PH 7.4

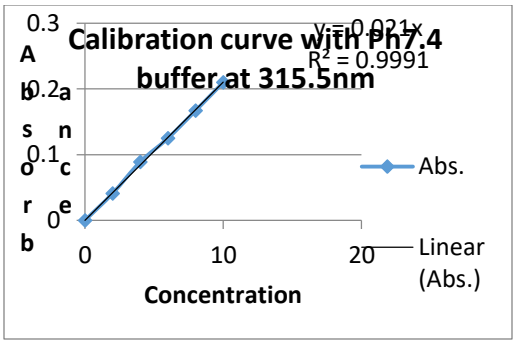

Fig:-6.1.3.2 Calibration curve with Ph 7.4 buffer

6.1.4 Solubility: - It was carried out in different solvent and found to be

S/N	Solvents	Solubility µg/ml
1	Methanol	100 µg/ml
2	Ethanol	100 µg/ml
3	Chloroform	1000 µg/ml
4	Ether	100 µg/ml
5	Distilled water	0.03 µg/ml

6.1.5 Melting point: - Melting point of Ziprasidone is determined by melting point apparatus and it was found to be.

S/N	Starting Point	End Point
1	293	295± 0.15
2	294	295±2
3	293	295±1

These results indicate that the given form of drug was pure.

6.1.6 Compatibility study: - It was carried out in stability chamber and Room temperature and

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observing the physical changes in compound and it was found to be.

S/N	Compound	75% RH,40°c Stability Chamber			
		15 days	30 days	45 days	Room temperature
1	**Drug+RSPO(1:1)**	No change	No change	No change	No change
2	**Drug+RLPO(1:1)**	No change	No change	No change	No change
3	**Drug Lactose(1:1)**	No change	No change	No change	No change
4	**Drug Starch(1:1)**	No change	No change	No change	No change

6.1.7 Density determination of granule of sustain release Ziprasidone and Eudragit RLPO, RSPO

S.No	Formulation Code	Bulk density	Tapped density	Angle of Repose	Carr's index	Hausner Ratio
1	Z1	0.514	0.618	26.8	16.6	1.201
2	Z2	0.516	0.620	26.4	16.4	1.186
3	Z3	0.524	0.625	26.40	16.1	1.171
4	Z4	0.524	0.623	26.22	16.3	1.192
5	Z5	0.511	0.570	26.44	16.2	1.210

6.1.8 for fast release Granule:-

S.No	Formulation Code	Bulk density	Tapped density	Angle of Repose	Carr's index	Hausner Ratio
1	Z1	0.514	0.618	26.8	16.6	1.201
2	Z2	0.516	0.620	26.4	16.4	1.186
3	Z3	0.524	0.625	26.40	16.1	1.171
4	Z4	0.524	0.623	26.22	16.3	1.192

6.2 For Post compression Evaluation of bilayer tablet of ziprasidone hydrochloride tablet it was found to be

S.No	Formulation	Hardness	Friability	Drug content Mg/tab	Weight Variation(mg)n=20 (mean±SD)
1	Z1	6.2±0.15	1.01	19	200±1.51
2	Z2	5.9±0.14	1.03	20	200±1.51
3	Z3	5.7±0.16	1.31	39	200±0.92
4	Z4	5.9±0.16	1.50	12	200±1.33
5	Z5	6.2±0.15	1.09	14	200±1.45

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6.3 Drug content, Dissolution and disintegration time of sustain release bilayer tablet of ziprasidone

6.3.1 Table of drug content and dissolution or disintegration time

S. No	Formulation	Drug content mg/ tab	Dissolution	Thickness (mm) n=10	Disintegration time
1	Z1	19± 0.05	33%	2.1±0 .2	5minute
2	Z2	20± 0.1	29%	2.2±0 .04	25minut e
3	Z3	39± 0.01	96.8%	2.2±0 .10	1 hours
4	Z4	12± 0.32	95.0	2.08± 0.3	58minut e
5	Z5	14± 0.32	33.19 %	2.66± 0.01	10minut e

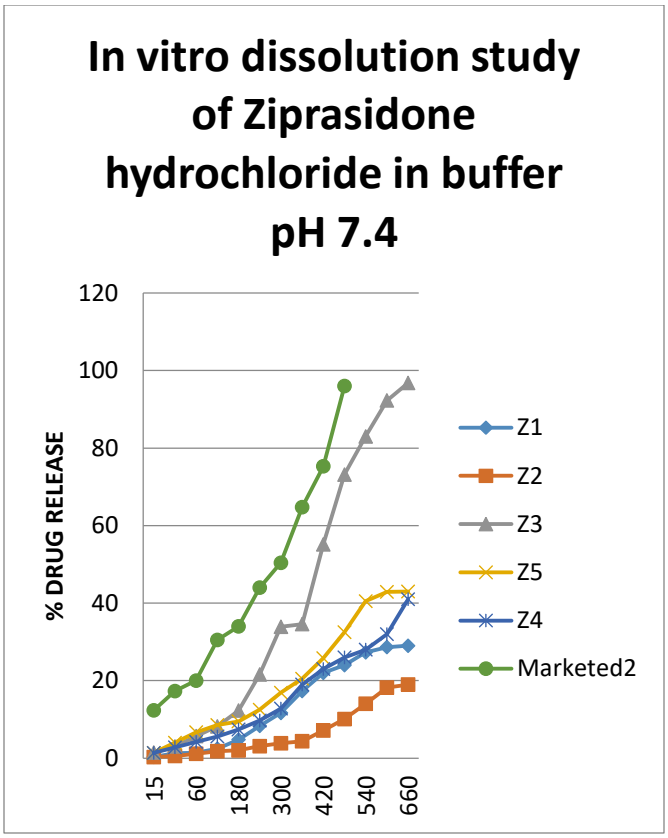

Fig 6.4.1 In vitro dissolution study of Ziprasidone hydrochloride bilayer sustain release formulation

These all formulation giving an invariable release or in proper release so we choose Z3 Formulation and study there release rate profile and compared with marketed product at different concentration. So these are the reason for rejecting this batch for formulation.

6.5.1 Table of release rate of final batch

S/N	Time	Log time	Cube root	Square root	Log % release	% Release
1	15	15	0.25	3.872	4.05	1.46±0.01
2	30	30	0.7	5.447	5.7	3.03±0.

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			8			25
3	45	45	0.80	6.708	7.4	4.5±0.21
4	60	60	0.90	7.745	8.2	5.7±0.31
5	90	90	0.96	9.486	9.5	7.4±0.03
6	120	120	1.02	10.954	11	8.2±0.35
7	150	150	1.03	12.247	12.3	9.5±0.35
8	180	180	1.07	13.416	18	11.0±0.36
9	240	240	1.10	15.491	21.6	12.3±0.035
10	300	300	1.13	17.320	22.6	18.0±0.36
11	360	360	1.23	18.973	28.6	21.6±0.31
12	420	420	1.24	20.237	33.9	22.6±0.32
13	480	480	1.28	21.237	34.6	28.2±0.36
14	540	540	1.29	24.494	47.2	33.9±0.35
15	600	600	1.31	25.690	55.2	34.6±0.52
16	660	660	1.34	26.832	65.2	47.2±0.32

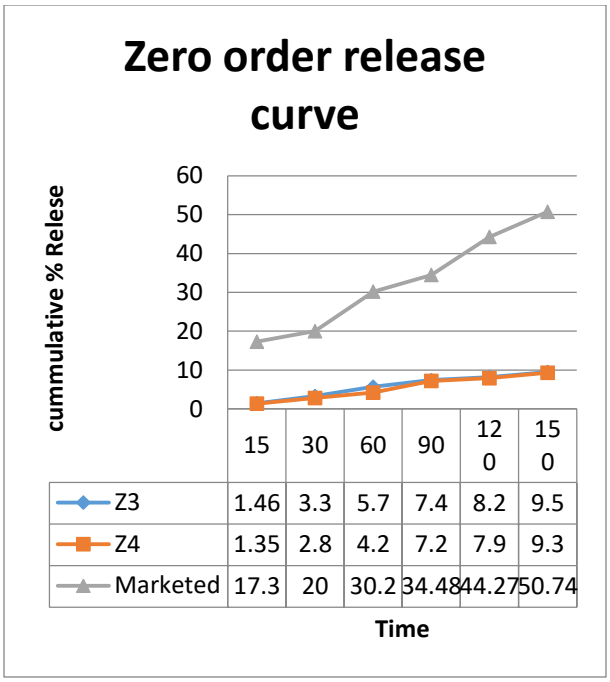

Fig:-6.5.2 Zero order release rate of final batch

6.6.2 Korsmeyer-Pepas model

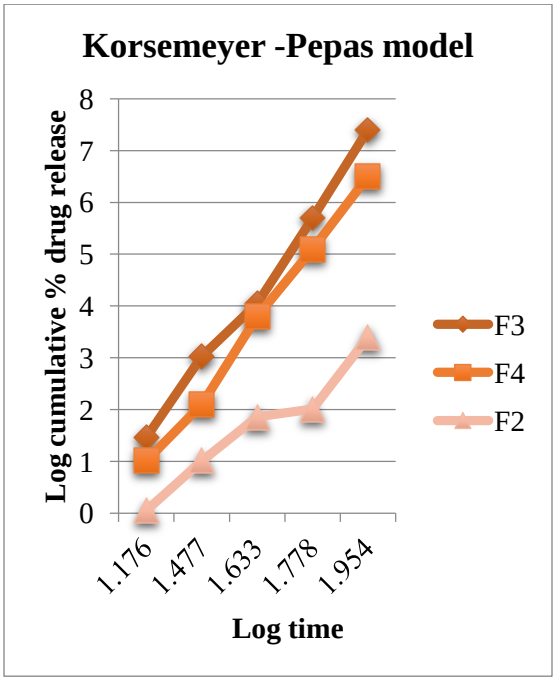

Fig:-6.5.3 Korsmeyer-Pepas model

6.5.4 Hixson Crowell's cube root curve

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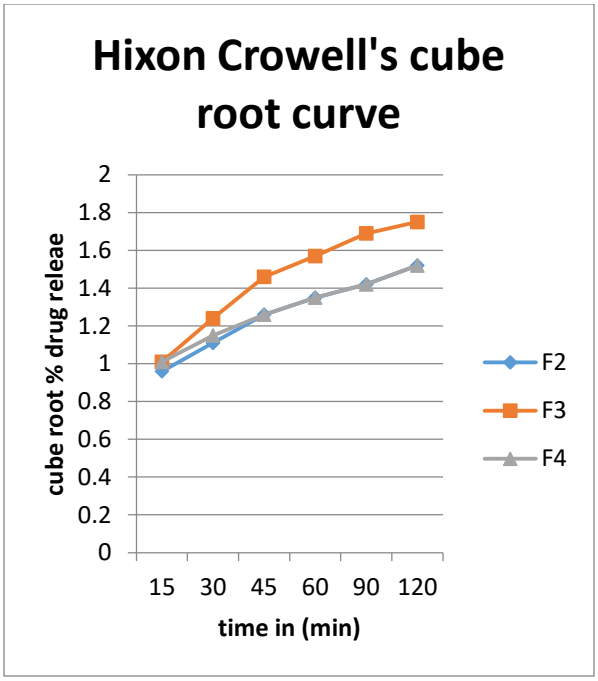

Fig: - 6.5.4.1 Hixson Crowell's cube root curve

6.5.5 First order release curve

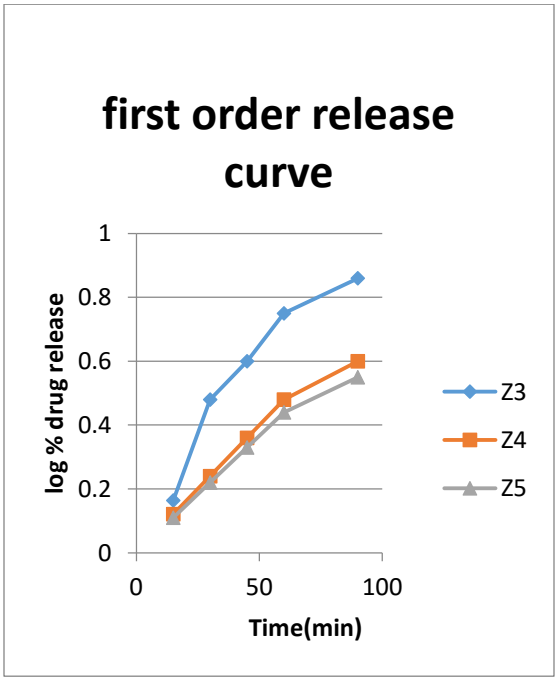

Fig 6.5.5 .1 First order release

6.6.1 Table of First order release, zero order release of formulation (ZF3-ZF5)

S.No	Time (min)	Hixon crowell	Zero order release	Korsemeyer Peppas model	Fisrst order release
1	15	1.01	5.7	1.46	0.164
2	30	1.24	7.4	3.3	0.48
3	45	1.46	8.2	5.7	0.6
4	60	1.57	9.5	7.4	0.75
5	90	1.69	11	8.2	0.86
6	120	1.75	12.3	9.5	0.91
7	150	1.83	18	8.2	1.04
8	180	1.98	21.6	11	1.08
9	240	2.02	22.6	18	1.25
10	300	2.25	28.6	22.6	1.33
11	360	2.46	33.9	33.9	1.45
12	420	2.59	34.6	47.2	1.67
13	480	2.79	47.2	65.3	1.92
14	540	2.8	91.2	84.1	1.95
15	600	3.01	96.8	96.8	1.96

6.6 Discussion & Conclusion

Formulation of bilayer tablet of Ziprasidone hydrochloride these drugs are atypical fifh generation atypical antipsychotic these help to treatment and controlling schizophrenia disease. in primary stage we studied and work on literature work and patent survey then working on next step of formulation so we studied various excipient profile and there action after selection of Excipient we select method of

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manufacturing. In formulation part primary performing preformulation in this step perform drug identity, solubility and compatibility. Compatibility study done and ratio of polymer(1:1:1) and (1:2:1) or (1:2:2) was putted on stability chamber for 45 days at 37 Degree temperature or 75%RH.and observed the physical appearance of drug and Excipient .Color and state of drug observed after this work formulate the formulation and formulate a different concentration of MCC and drug concentration for fast release of drug,(1:1),(1:1.5) or (1:2) and (1:3) these concentration of polymer containing formulation was made and release study will done and result was come to calculate the released and concentration ratio of the MCC were (1.1.5) are greater and helpful for fast release at desirable phenomenon .For Production of sustain release layer formulate different ratio of EUDRAGIT RLPO,RSPO (Z1 1:1) (Z21:1) (Z3(1:1:1 DRUG:RLPO:RSPO) and (Z4 1:2) (Z5 1:2) these concentration was taken and release rate study was taken and formula were optimized by release rate and optimized batch was formulate in large scale batch production then formulate and evaluate the tablet and result were correlate as standard specification and compare with marketed product .There release rate compare with (ZF1:Marketed) and (Z3:Marketed) . These are showing a better release rate. In future prospect these are beneficial for the patient of schizophrenia treatment and it will show better result and In present work a bilayer tablet of Ziprasidone formulated in which one layer will provide a fast release to show an immediate effect and other layer will provide a sustain release of the drug and will be useful for maintaining the drug concentration in the diseased state .The major advantage of formulation will be reduction in the dosing frequency and enhancement of patient compliance and therapeutic effect. In the present work we formulate a bilayer tablet of Ziprasidone hydrochloride and it helpful for patient and next generation.

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