CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1249808

Available online at: http://www.iajps.com Research Article

FORMULATION AND *IN VITRO* EVALUATION OF ORO DISPERSIBLE TABLETS OF LORAZEPAM

Bommana Anusha[1]*, Girija Karike[2], Koppula Maheshwari[3], Ramya Sri Sura[4]

[1]Department of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar, Yenkapally (V), Moinabad (M), RR Dist. Hyderabad. 500075

[2,3]Department of Pharmaceutics, Joginpally B.R Pharmacy College, Bhaskar Nagar, Yenkapally (V), Moinabad (M), RR Dist. Hyderabad. 500075

[4] Department of Pharmaceutics, University of Technology, Osmania University, Hyderabad, Telangana.

Abstract:

The present investigation was done on lorazepam orodispersible tablets using super disintegrants. The prepared powder blend for all formulations was found to be within limits. Tablets were compressed using rotary tablet compression machine. Post compression studies like weight variation, hardness, thickness, friability, drug content, in vitro disintegration time were carried out which were found to be within limits. In vitro drug release studies revealed that Among all formulations F4 formulation were shown maximum drug release(99.99%) at 45 min. Among these three formulations F4 was considered as optimised formulation due to 2 mg of croscarmellose sodium.

Key words: *Lorazepam, Super disintegrants, Orodispersble tablets.*

Corresponding author:

Bommana Anusha,

Department of Pharmaceutics,
Bhaskar Pharmacy College,
Bhaskar Nagar, Yenkapally (V),
Moinabad (M), RR Dist.
Hyderabad. 500075

QR code

Please cite this article in press Bommana Anusha et al., ***Formulation And In Vitro Evaluation of Oro Dispersible Tablets of Lorazepam,*** *Indo Am. J. P. Sci, 2018; 05(05).*

INTRODUCTION:

FDT

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing.[1-2] 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 paediatric and geriatric patients1, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[2]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[3]

Oral dispersible tablets (ODT)is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.[4] US FDA defined ODT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Fast dissolving tablet' as a tablet that is to be placed in the Mouth. Where it disperses rapidly before swallowing.

Oral dispersible tablets are also called as Fast - dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fast dissolving tablets, rapimelts, porous tablets, quick dissolving tablet[5].

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Oral dispersible Tablets[6].Three main points stand out in the final guidance:

- Oral dispersible Tablets should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.
- The guidance serves to define the upper limits of the ODT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an ODT.

MATERIALS AND METHODS:

Materials Used:

Lorazepam was a gift sample Provided by Sura Labs, Dilsukhnagar. Crospovidone, Croscarmellosesodium, sodium starch glycolate, Sucralose, Talc, Magnesium Stearate, MCC were obtained from Sd fine Chem.Ltd. Mumbai, India.

METHODOLOGY

Analytical method development for Lorazepam:

a)Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λmax was found to be 240 nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Lorazepam was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2,4,6,8 and 10µg/ml respectively. The absorbance of each concentration was measured at respective (λmax) i.e., 240 nm.

Formulation development:

Drug and different concentrations of super disintegrants (Sodium starch glycolate, Cross caramellose Sodium, Cross povidone) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.

- The obtained blend was lubricated with magnesium stearate and glidant (Aerosil) was added and mixing was continued for further 5 min.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 1: Formulation table showing various compositions

Ingrediants	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lorazepam	1	1	1	1	1	1	1	1	1
Crospovidone	2	4	6	-	-	-	-	-	-
Croscarmellosesodium	-	-	-	2	4	6	-	-	-
sodium starch glycolate	-	-	-	-	-	-	2	4	6
Sucralose	3	3	3	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	36	34	32	36	34	32	36	34	32
Total weight	50	50	50	50	50	50	50	50	50

The tablets were prepared by using tablet compression machine. The hardness of the tablet was maintained as (2.2-3.0) kg/cm2

Evaluation of tablets:

Pre compression parameters:

Measurement of Micromeritic properties of powders

1.Angle of repose

The angle of repose of API powder is determined by the funnel method . The accurately weighed powder blend is taken in the funnel. The height of the funnel is adjusted in a way that the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on o the surface . The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$\tan \Theta = h/r$ ……(1)

Where , h and r are the height and radius of the powder cone.

Table 2: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (0)
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

2.Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in 100 ml graduated cylinder and the powder is leveled and the un setled volume , V0 is noted . The bulk density is calculated in g/cm3 by the formula.

Bulk density = M/V0 ……. (2)

V0 = apparent unstirred volume

M= Powder mass

3. Tapped density

The powder sample under test is screened through sieve No. 18 and the weight of the sample equivalent to 25 gm filled in 100ml graduated cylinder . The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V0 is noted . Tappings are proceeded further for an additional tapping 750 times and tapped volume , Vb is noted. The difference between two tapping volume is < 2%, Vb is considered as a tapped volume Vf . The tapped density is calculated in g/cm3 by the formula.

Tapped density = M/Vf …… (3)

M = weight of sample powder taken

Vf = Tapped volume

4. **Compressibility index**

The compressibility index of the powder blend is determined by Carr's index to know the flow character of a powder . This formula for Carr's index is as below :

Carr's Index (%) = [(TD-BD)/TD] x100 …… (4)

5. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation.

$H = Pt / \rho B$ ……(5)

Where ρT= tapped density, ρB = bulk density

Table 3: Scale of Flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Post compression parameters :

a) Thickness

The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation 3 batches were calculated. It passes the test for weight variation test if not more than 2 of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the % shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-friabilator . Accurately weighed six tablets were placed in The Roche friabilator and rotated at 25 RPM for 4 min. Percentage friability was calculated using the following equation.

Friability = ([w0-w]/w0) x 100

Where w0 = weight of tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions

d) Drug content

The content of drug carried out by 5 randomly selected tablets of each formulation. The 5 tablets were grinded to get powder, this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analysed spectrophotometrically at 240 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets . Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Lorazepam

Drug release from Lorazepam tablets was determined by using dissolution test USP 24 type II (paddle) . The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml . The whole study is being carried out at room temperature of 37˚ C and at a speed of 75 RPM.

5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10,15 , 20 , 25, 30, 35, 40,45 min) and appropriate dilution by UV spectrophotometer . The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipiennts in different proportions (in 1;1 ratio were to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm-1 and 550 cm-1.

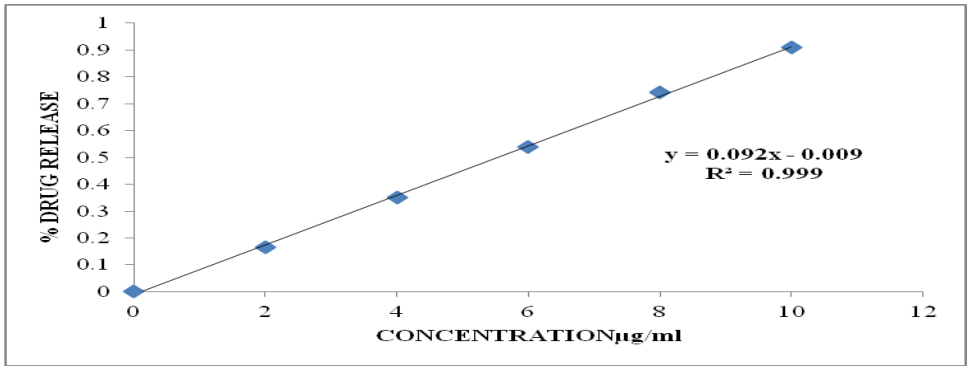
RESULTS AND DISCUSSION:

Preparation of calibration curve of Lorazepam

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of y = 0.092x - 0.009. Hence Beer-Lmbert's law was obeyed.

Table 4: Calibration curve data of Lorazepam in pH 6.8 phosphate buffer

Concentration	Absorbance
0	0
2	0.167
4	0.352
6	0.539
8	0.742
10	0.909



EVALUATION OF PRE-COMPRESION PARAMETERS OF POWDER BLEND

Table 5: Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density(gm/mL)	Tapped density (gm/mL)	Carr's index(%)	Hausner's ratio
F1	32.67	0.435	0.522	16.66	1.2
F2	29.08	0.429	0.518	17.18	1.2
F3	31.78	0.43	0.524	17.93	1.21
F4	30.64	0.432	0.528	18.18	1.22
F5	30.36	0.428	0.518	17.37	1.21
F6	31.05	0.42	0.51	17.64	1.21
F7	32.54	0.416	0.509	18.27	1.22
F8	29.67	0.417	0.515	19.02	1.23
F9	31.85	0.425	0.515	17.47	1.21

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.
- The bulk density of all formulations was found in the range of 0.416 -0.435 and tapped density was in the range of 0.509-0.528
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF LORAZEPAM ODTs

Table 6: Evaluation of post compression parameters of LORAZEPAM Fast dissolving tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm2	Friability (%loss)	Thickness (mm)	Drug content (%)	In vitro disintegration Time(min)
F1	49.1	5.10±0.4	0.225	3.77±0.007	97.93±0.04	29±4.5
F2	48.4	4.00±0.2	0.341	3.80±0.059	98.31±0.03	26±3.2
F3	49.3	6.24±0.4	0.314	3.78±0.006	96.94±0.02	30±3.2
F4	47.8	5.12±0.2	0.272	3.80±0.011	97.49±0.04	25±0.41
F5	48.2	6.24±0.5	0.331	3.79±0.010	99.25±0.02	31±4.12
F6	49.1	4.13±0.3	0.534	3.78±0.008	98.52±0.04	29±0.9
F7	48.6	5.34±0.2	0.249	3.80±0.007	97.80±0.03	30±0.12
F8	49.5	6.25±0.1	0.375	3.79±0.009	98.33±0.04	29±4.12
F9	49.8	4.21±0.3	0.295	3.78±0.009	99.75±0.03	28±0.12

Weight variation and Thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above. The average tablet weights of all the formulations were noted down.

Hardness and friability: All the ODT formulations were evaluated for their hardness using Monsanto hardness tester and the results are shown above. The average hardness for all formulations was found to be between (4.00±0.2-6.24±0.5) kg/cm2 which was found to be acceptable. Friability was determined to evaluate the ability of the tablets to with stand the abrasion during packing, handling and transpoting. All the ODT formulations were evaluated for their percentage friability using Roche friabilator and the results are shown above. The average percentage friability for all the formulations was between 0.225-0.375 which was found to be within the limit.

Drug content : All formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above . The assay values for all formulations were found to be in the range of (96.94±0.02 - 99.75±0.03.). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the ODT formulation comply with the standards given in IP.

***In vitro* disintegration time :** *In vitro* disintegration studies showed from 15-35 minutes. The F4 formulation showed very less in vitro disintegration time i.e. 30 minutes.

***IN VITRO* DRUG RELEASE SYUDIES OF LORAZEPAM**

Table 7: Dissolution data of LORAZEPAM

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	25.35	19.35	22.46	26.31	24.35	18.43	15.33	13.38	11.33
10	38.33	29.36	32.28	35.33	31.57	28.43	25.36	21.19	19.36
15	57.46	41.31	45.35	47.33	41.36	39.36	37.46	34.43	29.45
20	64.46	58.35	64.31	71.48	54.41	48.38	44.43	41.46	38.43
25	71.38	71.48	78.46	82.38	62.55	57.38	53.28	49.46	42.48
30	83.35	81.45	84.53	89.69	69.48	71.46	65.41	56.58	52.46
35	92.45	94.31	95.31	96.89	75.45	79.31	72.28	69.42	58.58
40	96.89	97.57	96.76	97.95	82.57	85.48	82.28	76.48	65.43
45	97.78	98.85	97.96	99.99	92.53	95.36	91.46	89.43	78.47

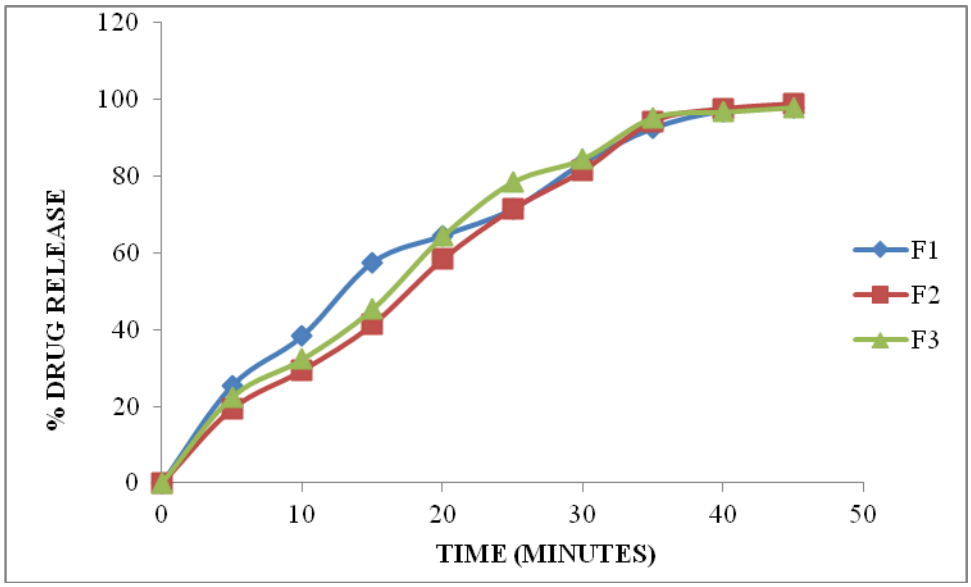


Fig.1: Dissolution profile of formulations F1,F2,F3

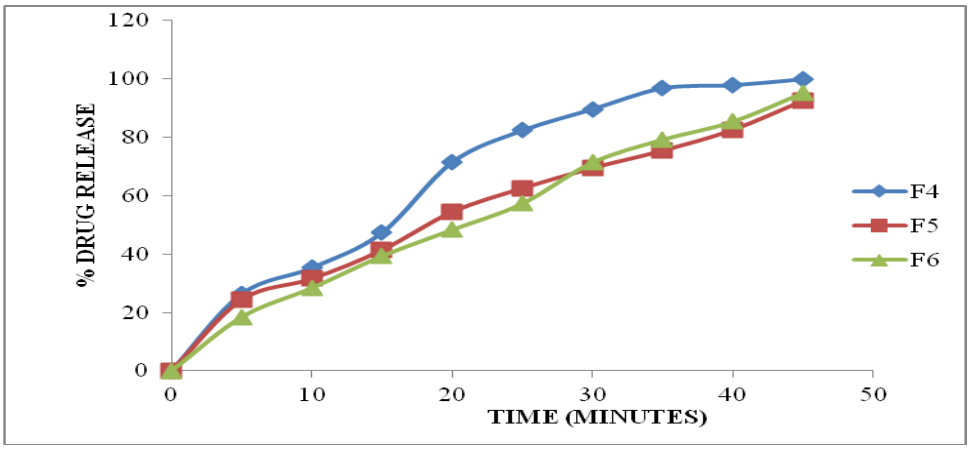


Fig.2: Dissolution profile of formulations F4,F5,F6

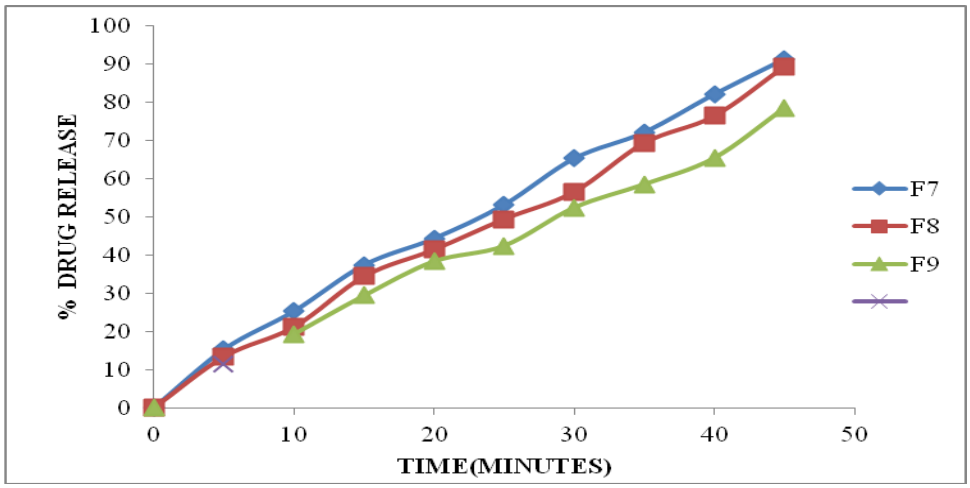


Fig.3: Dissolution profile of formulations F7,F8,F9

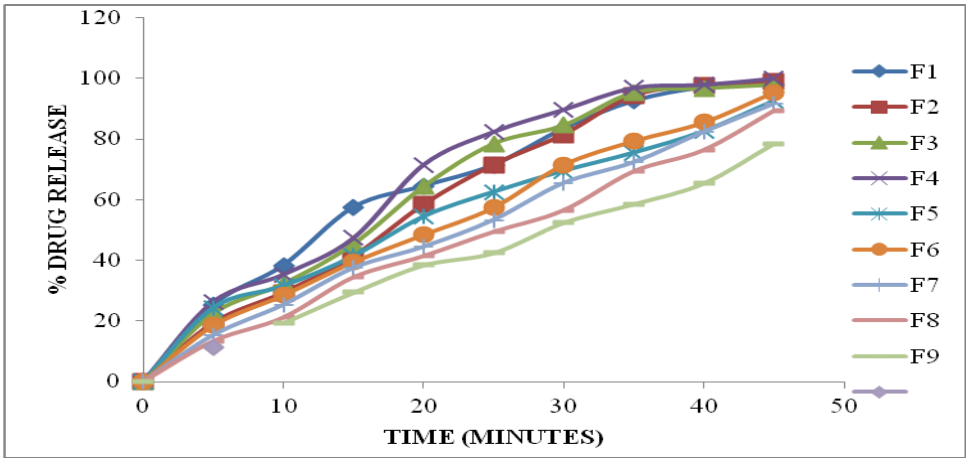


Fig. 4: Dissolution profile of all formulations F1-F9

FTIR RESULTS :

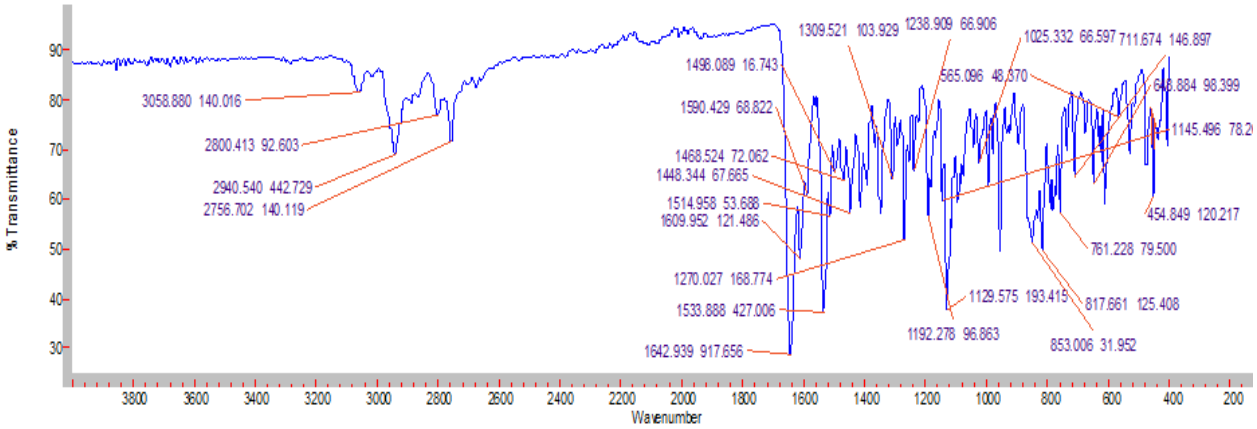


Fig.5 : FTIR of Lorazepam Pure Drug

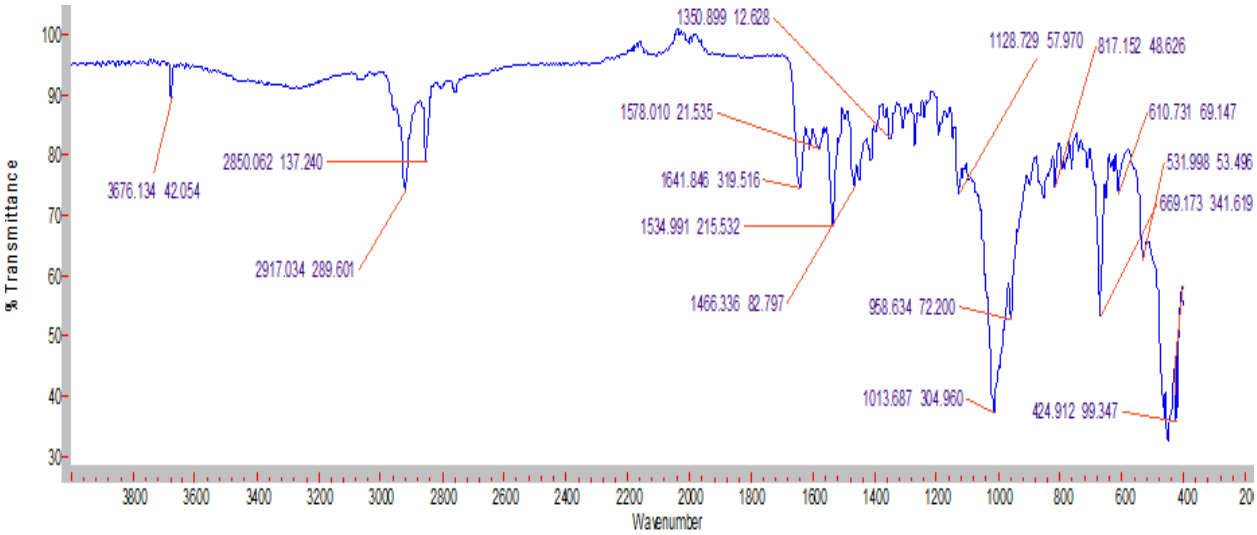


Fig. 6: FTIR of Lorazepam optimized formulation

Lorazepam was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions

CONCLUSION:

In the present study it can be concluded from the characterization of orally disintegrating tablets of Lorazepam that formulation containing Croscarmellose sodium is most acceptable. It was observed that to further increases the drug release from orally disintegrating tablets . The pre compression and post compression parameters have got in IP limits. The formulation F4 has got good results and it consider as optimized 98.89%.

ACKNOWLWDGEMENT:

The authors are thankful to **Sura Labs, Dilshukhnagar, Hyderabad,** T.S., India for providing the necessary facilities for the research work.

REFERENCES:

1. Sastry SV, Nyshdham JR, Fix JA. Recent technological advances in oral drug delivery: A review. Pharmaceutical Science and Technology Today. 2000; 3:138-45.

2. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmacy and Pharmacology. 1998; 50(4):375-82.
3. Debjit, B., Chiranjib, B., Krishnakanth., Pankaj., Margret, R., Fast Dissolving Tablets: An Overiew. *Journal. Chem. Pharm. Research*., 1(1), 163 – 177 (2009).
4. Jaysukh J Hirani1*, Dhaval A Rathod1 , Kantilal R Vadalia2, Orally Disintegrating Tablets: A Review , Tropical Journal of Pharmaceutical Research, April 2009; 8 (2): 161-172 .
5. Suresh, B., Rajender, M., Ramesh, G., Madhusudan Rao, Y., Orodispersible tablets: An overview. *Asian J Pharm*., 2(1), 2-11 (2008).
6. Indian Pharmacopoeia. 4th Ed, Ministry of Health and Family Welfare, Govt. of India. The 11.
controller of publications, New Delhi, 1996, pp. A-54.
7. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci, 2002; 15: 295-305
8. Simone SS, Peter CS, Fast dispersible ibuprofen tablets, European Journal of Pharmaceutical Sciences, 2002;15: 295–305.
9. In vitro dissolution. The United States pharmacopoeia, United States pharmacy convention, inc., Asian edition, 2000; 1941-1943.
10. Mishra D.N., Rapidly disintegrating oral tablets of meloxicam by direct compression method, Indian Drugs, 2006, 43, 117-121.