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Formulation and Evaluation of Taste Masked Orodispersible Tablets of Lamotrigine

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ABSTRACT

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. The CDER defines ODT as "A solid dosage form containing medicinal substances which disintegrates rapidly within a matter of seconds, when placed upon tounge". The aim of this study was to formulate and evaluate stable orodispersible tablets of Lamotrigine. Lamotrigine is an Antiepileptic drug, the subsequent seizures condition requires fast onset of action of Lamotrigine, which can be easily obtained if it is given in orodispersible tablet form. Lamotrigine is slightly bitter drug so objective was to mask bitter taste of drug by formulating drug resin complex with use of ion exchange resin Kyron T-134. To formulate the Orodispersible tablets sodium starch glycolate in concentration 3, 4, and 4.25%. Crospovidone in 3, 4 and 4.5%. And Kyron T-314 in 4, 4.25, and 5% were used as a superdisintegrants.Among these superdisintegrants Kyron T-314 in concentration of 5% showed dissolution profile which matched with marketed product and also showed good mechanical strength. The tablets were prepared by direct compression method. The formulation of batch no.F9 was found to be optimized batch and taken forwarded for the stability study.

Key words: ODT, Taste masking, DRC, Superdisintegrants, Direct compression method.

I. INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form[1]. Among the pharmaceutical dosage form the conventional tablets seems to be most popular because of lower manufacturing cost[2]. Orodispersible tablets are also called as mouth-dissolving tablets, melt-in-mouth tablets, fast dissolving tablets, rapimelts, porous tablets, quick dissolving etc.[4]

The CDER defines ODT as "A solid dosage form containing medicinal substances which disintegrates rapidly within a matter of seconds, when placed upon tounge".[5]

Mouth dissolving tablets preferred alternative to conventional oral dosage form because of the numerous advantages like [6, 7]

- Administration without water
- Accuracy of dosage
- Easy portability
- Alternative to liquid dosage form
- Ideal for pediatric and geriatric patients
- Rapid onset of action
- Allows high drug loading
- Can be designed to leave minimal or no residue in the mouth after administration
- Provide a pleasant mouth feel
- Ease of administration for patients, those who are not co-operative

Aim of Present study was to formulate and evaluate stable Orodispersible tablets of Lamotrigine having good organoleptic properties, mechanical strength and rapid disintegration. This segment of formulation is designed for patients who are unable to swallow or refuse to swallow conventional oral formulations. Lamotrigine is an Antiepileptic drug and shows extensive first pass metabolism. It reveals us that it is suitable candidate for orodispersible tablet form. Lamotrigine is bitter drug so objective is to mask bitter taste of drug The primary treatment objectives for patient with epilepsy are maintenance of antiepileptic drug levels and prevention of subsequent seizures The subsequent seizures condition requires fast onset of action of Lamotrigine, which can be easily obtained if it is given in orodispersible tablet form.

MATERIALS

The lamotrigine drug was obtained as gift sample from labs and all other excipients including Kyron T-134 efficiently masked the

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bitter taste of Lamotrigine were obtained from Superdisintegrants such as sodium starch glycolate ,Crospovidone, Magnessium stearate were obtained from

II. METHODS

Taste Masking By Formation of Complexes with Ion Exchange Resins

Various resins supplied by Thermax India Ltd., Ion Exchange India Ltd. and Corel Pharmachem Ltd., were used to select the resin that showed excellent taste masking ability and optimum drug loading. Tulsion 339; Indion 204, 214; Kyron T-134 were used in 1:1 drug: resin ratios. 100 mg of each resin was allowed to swell separately in 50 ml of deionized water for 90 min. 100mg of Lamotrigine was added to each of them and stirred for 5 hrs. Each slurry was filtered and the residue i.e. resinate was washed again with 25 ml of deionized water. The combined filtrate was evaluated for drug content. The difference between amount of drug used initially and that remaining in the filtrate is the amount of drug loaded on the resin. The resin that showed optimum loading was subjected to optimization of drug loading process. Loading of Lamotrigine on Kyron T-134 was selected for further process. Batch process is the preferred method for loading a drug into finely divided ion exchange resins. Higher swelling efficiency in the batch process makes more surface area available for ion exchange. So batch process was selected

Formulation and development of Orodispersible Tablets Lamotrigine involves three steps

Method of Preparation:-

i) Dry Mixing:-

Mannitol, Kyron T314, Aspartame, Fruit flavour was weighed & passed through # 44 sieve and in it add drug resin complex ,mixed for 25 min.

ii) Lubrication:-

To the above step-I blend, add geometrically Talc and Magnesium stearate which were passed through # 60 sieve.

iii) Compression:-

Materials were compressed using 8 mm flat punch on compression machine. Tablet weight was maintained at 200mg

Composition of Lamotrigine Orodispersible Tablets

Ingredient Quantity (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug Resin Complex(eq. to 25.0mg of Lamotrigine)	125.0	125.0	125.0	125.0	125.0	125.0	125.0	125.0	**125.0**
Sodium Starch Glycolate	6.0	8.0	8.5	----	----	-----	----	----	**----**
Crospovidone	-----	-----	----	6.0	8.0	9.0	----	-----	**-----**
Kyron T314	-----	-----	-----	----	-----	----	8.0	8.5	**10.0**
Aspartame	1.75	2.0	2.25	2.25	2.25	2.25	2.25	2.25	**2.25**
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	**2.0**
Fruit Flavour	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	**2.0**
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	**2.0**
Mannitol	61.25	59.00	58.25	60.75	58.75	57.75	58.75	58.25	**56.75**
Total	200	200	200	200	200	200	200	200	**200**

III. EVALUATION PARAMETERS

PRECOMPRESSION PARAMETERS

1. Angle of Repose[15]

For determining angle of repose a funnel was mounted on a stand at a fixed height and a fix weighed quantity of Lamotrigine was poured through the funnel. Angle of repose was calculated as,

Angle of repose = tan-1 (height/ radius)

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2. Bulk density and Tap density[16]

The bulk density and tapped density of active material was calculated by using the formula,

Bulk density = Weight of substance / Final volume of substance (gm/ml)

Tap density = Weight of substance / Final volume after tap (gm/ml)

3.Compressibility Index and Hausner ratio[16]

In the recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The basic procedure to calculate the compressibility index and Hausner ratio involves measuring the bulk volume (V0) and final tapped volume (Vf). A 250 ml volumetric cylinder with 100 gm of the material was used for this purpose.

The calculations were done as:

Compressibility index = 100 (V0 - Vf)/V0

Hausner ratio = (V0)/ Vf

4.FT-IR Spectrophotometric Analysis[16]

To identified drug Lamotrigine IR spectrophotometric analysis was carried out by Kbr disc method, and recorded the spectrum in the range of 4000 cm-1 and 450cm-1 by using Shimadzu model.

5.Determination of λ max

Lamotrigine was accurately weighed and dissolved in 0.1N HCL to make concentration 1mg/ml. This solution was then suitably diluted to 100ml using distilled water to get a final solution of concentration 100µg/ml. UV spectrum was recorded over the wavelength range 200- 400 nm. by using UV Shimadzu 1800.

Evaluation of Orodispersible Tablets [16,17]

1. Hardness

Five tablets from each batch were selected and hardness was measured using hardness tester to find the average tablet hardness.

2. Dimensions of Tablet:

Thickness and diameter were measured using a digital Vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually

3 .Friability (%F)

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability,

%F =1-(loss in weight/ initial weight) 100

4. Weight Variation

Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 1996). 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in Table 26 and no tablets differ in weight by more than double that percentage.

Average weight of tablet (mg)	**Percentage difference allowed**
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

Limits for weight variation as per I.P. 1996

5. Uniformity of Content

Twenty tablets were selected randomly and powdered. A quantity of this powder equivalent to 25 mg of Lamotrigine was dissolved in 100 ml of 0.1N HCL, stirred for 60 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 0.1N HCL. Absorbance of this solution was measured at 267 nm using 0.1N HCL as blank and content of Lamotrigine was estimated.

6 . Disintegration Time

Disintegration time was determined using USP tablet disintegration apparatus (ED2L Electrolab, India) using 900 ml distilled water without disk at 37°C±2°C temperature. A tablet was placed in each of the six tubes of the apparatus. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

7. Wetting Time

A Petri dish containing 6 ml of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. Time required

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for the upper surface of the tablet to become wet was noted as the wetting time of the tablet

8. Dissolution Studies[16]

Dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1N HCL was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time interval of 5 to 30 min, filtered and amount of Lamotrigine released from tablets was determined by using U.V. Spectrophotometric analysis at 267 nm.

9.Stability Studies [18,19]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Long-term Testing: 25^0 C ± 20 C / 60 % RH ± 5 % for 12 Months.

30^0 C ± 20 C / 65 % RH ± 5 % for 12 Months

Accelerated Testing: 40^0 C ± 20 C / 75 % RH ± 5 % for 6 Months

Stability studies were carried out at 40^0 C / 75 % RH for the selected formulation for the period of 3 months.

- **Preformulation Study**
- **Confirmation of Drug**

Confirmation of drug was carried out by using infrared spectroscopy and UV spectroscopy

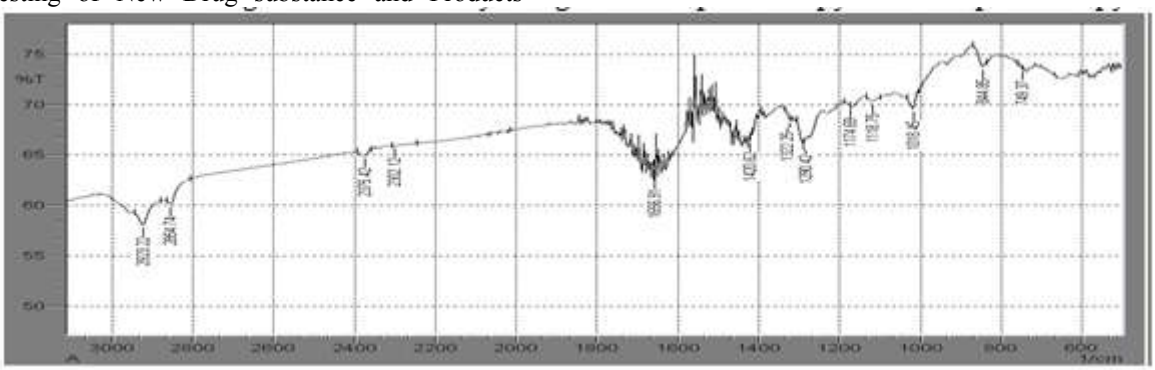

FIGURE: 1 FT-IR SPECTRUM OF LAMOTRIGINE

Wave No. (cm-1)	**Characteristic absorption**
2923.22 cm^{-1}	N-H Stretching
1420.62 cm^{-1}	N-H Bending
1656.91	N=N Stretching
2854.74 cm^{-1}	C-H Stretching
749.37 cm^{-1}	C-Cl bending vibration.

TABLE: 2 INTERPRETATION OF FTIR SPECTRUM OF LAMOTRIGINE

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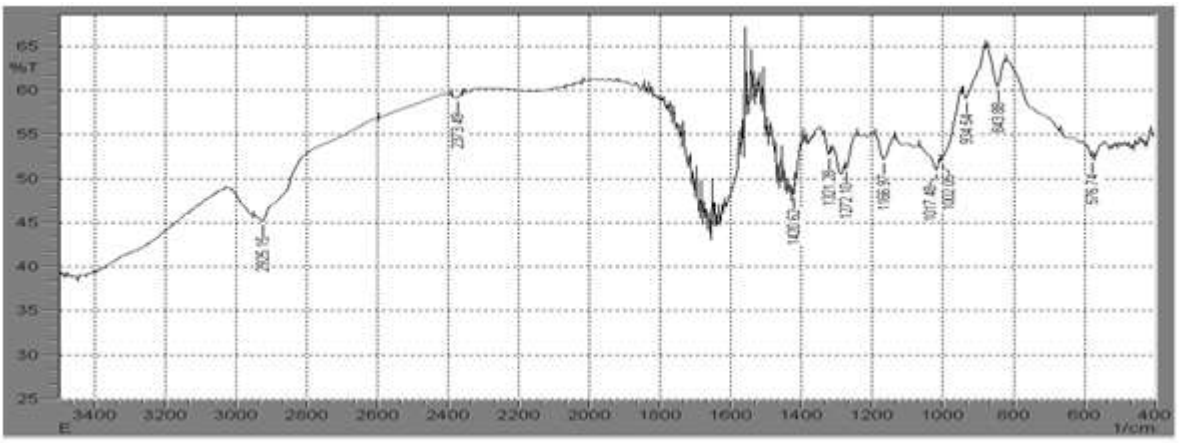

FIGURE:4 FTIR SPECTRA OF PHYSICAL MIXTURES OF LAMOTRIGINE AND SODIUM STARCH GLYCOLATE

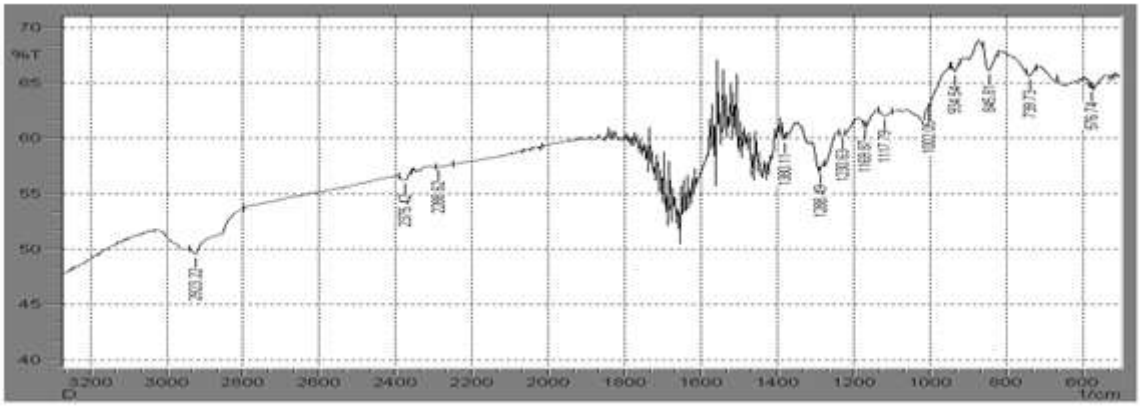

FIGURE:5 FTIR SPECTRA OF PHYSICAL MIXTURES OF LAMOTRIGINE AND CROSPOVIDONE

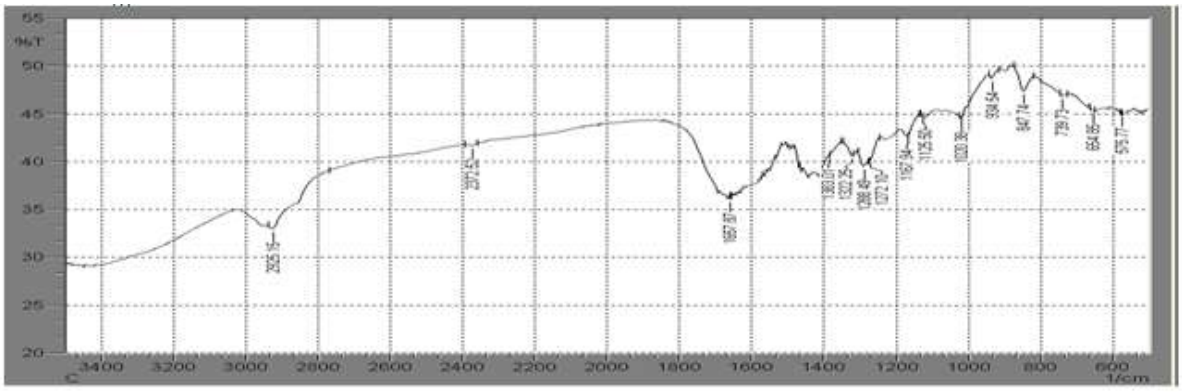

FIGURE:6 FTIR SPECTRA OF PHYSICAL MIXTURES OF LAMOTRIGINE AND KYRON-T-314

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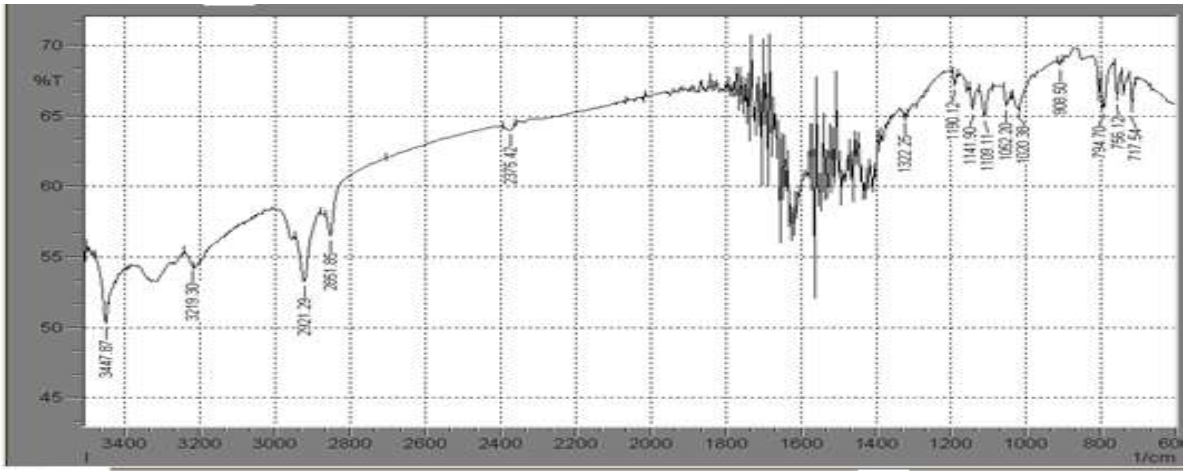

FIGURE:7 FTIR SPECTRA OF PHYSICAL MIXTURES OF DRUG RESIN COMPLEX

- **Organoleptic Properties of Lamotrigine**
- **Evaluation of Physical Properties of Drug**

Angle of Repose	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's Ratio	Compressibility Index (%)
33.73°	0.391	0.507	1.29	22.88

TABLE:5 PHYSICAL PROPERTIES OF DRUG

- **Precompression Parameter of Tablet Blend [15,16]**

Precompression parameters like angle of repose lose bulk density, tapped bulk density, compressibility index, and hausner's ratio of all batches of Lamotrigine .

Formulation Code	Bulk density (gm/ml)±SD	Tapped density(gm/ml)±SD	Hausner ratio	Compressibility index	Angle of repose
F1	0.584±0.0084	0.7258±0.0082	1.241	19.44	30.84±0.66
F2	0.6024±0.006	0.7544±0.009	1.252	17.49	31.40±0.287
F3	0.6122±0.0055	0.7358±0.0082	1.200	16.43	32.39±0.674
F4	0.6285±0.0062	0.7496±0.0095	1.192	16.15	33.99±1.072
F5	0.6428±0.0065	0.7826±0.0095	1.217	17.85	33.34±0.240
F6	0.6569±0.0068	0.7965±0.01	1.212	17.50	32.06±0.607
F7	0.6721±0.0071	0.7839±0.01	1.165	15.67	31.44±0.264
F8	0.7200±0.0082	0.8258±0.011	1.146	12.79	29.64±0.564
F9	**0.6715±0.0101**	**0.7659±0.009**	**1.140**	**12.28**	**28.66±0.531**

TABLE:8 PRECOMPRESSION PARAMETER OF TABLET BLEND

- **Physical evaluation of tablet formulations**

Postcompression parameter of orodispersible tablet like weight variation, thickness, hardness, friability, and drug content uniformity were evaluated

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Formulation Code	Weight Variation (mg)±SD	Hardness (kg/cm^2) ±SD	Diameter (mm) ±SD	Thickness (mm) ±SD
F1	200.11 ± 1.61	3.9 ± 0.20	7.8± 0.05	2.8 ± 0.03
F2	200.17 ± 1.32	3.8± 0.25	7.9± 0.03	2.8± 0.02
F3	199.62 ± 1.47	3.2 ± 0.17	8 ± 0.03	2.7± 0.02
F4	199.82 ± 1.46	3.0 ± 0.50	7.8± 0.00	2.5± 0.01
F5	200.87 ± 2.11	3.5 ± 0.63	7.9 ± 0.04	2.5 ± 0.04
F6	200.42 ± 1.68	3.5 ± 0.52	7.9± 0.03	2.8± 0.02
F7	201.11 ± 1.20	3.6± 0.24	7.9± 0.06	2.7± 0.04
F8	199.25 ± 1.42	3.4± 0.57	8 ± 0.03	2.6± 0.03
F9	**200.56 ± 1.63**	**3.5± 0.27**	**8 ± 0.03**	**2.6 ± 0.05**

TABLE:9 PHYSICAL EVALUATION OF TABLET FORMULATIONS

- **Evaluation of various parameters of tablets**

Formulation Code	Disintegration Time (s) ± SD	Friability% ± SD	% Assay ± SD	Wetting time Sec.
F1	85±1.02	0.87±0.02	98.44±1.02	55±0.65
F2	78±0.89	0.77±0.01	98.21±1.26	50±0.20
F3	71±1.21	0.8±0.04	99.18±0.85	46±0.90
F4	65±0.67	0.82±0.02	98.90±0.62	40±0.70
F5	59±0.96	0.79±0.03	97.53±1.08	34±0.83

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F6	54±0.82	0.76±00.02	98.02±0.96	32±0.22
F7	49±0.69	0.78±0.01	97.83±1.21	30±0.47
F8	47±0.77	0.81±0.03	98.28±1.05	24±0.19
F9	**45±0.81**	**0.74±0.01**	**99.63±0.8**	**21±0.26**

TABLE:10 EVALUATION OF VARIOUS PARAMETERS OF TABLETS

In-Vitro dissolution Study of orodispersible Tablet

Time in Min.	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	**0**
5	21.17	32.13	35.10	37.10	**39.3**
10	48.31	53.55	63.17	54.32	**57.11**
15	62.22	64.19	70.22	71.25	**73.24**
20	71.11	71.23	75.17	82.0	**84.50**
25	76.97	78.52	81.0	86.10	**88.30**
30	79.07	82.68	85.26	89.0	**90.89**

TABLE:11 CUMULATIVE % DRUG RELEASE LAMOTRIGINE FROM ORODISPERSIBLE TABLET

Time in Min.	**F6**	**F7**	**F8**	**F9**
0	0	0	0	**0**
5	40.10	41.75	45.43	**45.36**
10	61.3	65.31	71.23	**77.68**
15	75.52	77.64	84.41	**91.48**
20	85.37	88.52	91.45	**96.25**
25	89.35	91.32	93.45	**98.24**
30	93.40	94.76	96.24	**98.93**

TABLE:12 CUMULATIVE % DRUG RELEASE LAMOTRIGINE FROM ORODISPERSIBLE TABLET

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In-Vitro Dissolution Study

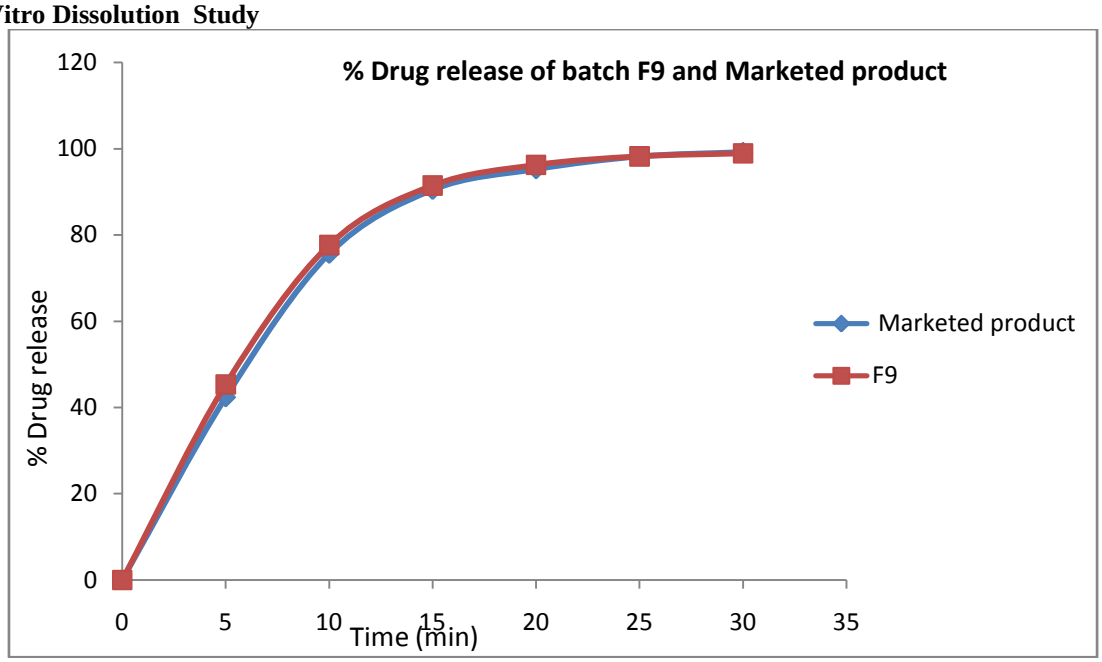

FIGURE:12 THE DISSOLUTION PROFILE OF BATCH F9 WAS MATCH WITH MARKETED PRODUCT

IV. CONCLUSION

Formulation development stage involves preformulation study of API. In that study all parameters of API passes the test. Drug-excipient compatibility by FTIR study shows no interaction between drug and exicipients. In Disintegration study Batch F9 as orodispersible tablet which shows 45 sec. time to disintegrate it, and this batch was optimized batch In Vitro dissolution study Batch F9 formulate as orodispersible tablet which shows 98.93 % of drug release in 30 min. is selected as optimized batch of orodispersible tablet formulation. Dissolution profile of this batch matched with dissolution profile of marketed product. Experiment conclude that orodispersible tablet is suitable for delivering drug with orodispersible drug delivery system which gives quick and rapid release of drug and to shows orodispersible release pattern

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