FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS CONTANING AZILSARTAN MEDOXOMIL

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Abstract: The aim of the study was to formulate develop and evaluate the fast-dissolving tablets of Azilsartan Medoxomil. Azilsartan medoxomil is an Angiotensin-II receptor antagonist that is used in the treatment of hypertension. It is having less side effects as compared to other angiotensin receptor antagonist. Azilsartan medoxomil is having low solubility hence solubility was enhanced by solubility enhancement technique. Solid dispersion was prepared by using Poloxamer 188 for solubility enhancement. The preliminary trials were performed by using different Superdisintegrants Plantago ovata was used as Superdisintegrant in combination with Crosspovidone. The prepared formulation was then evaluated by using various parameters. Finally, it was concluded that the formulated fast dissolving tablets have good dissolution characteristics as compared to that of pure drug.

Key Words **– Fast Dissolving tablets, Hypertension, Poloxamer 188, Plantago ovata, Solubility enhancement technique, Solid dispersion.**

1. INTRODUCTION:

Hypertension is defined as the clinical condition where in the blood strain inside the arteries is persistently elevated. It is the most common disease observed nowadays. The normal Systolic blood pressure is 140 mmHg and the normal diastolic blood pressure is 90mmHg. Hypertension may arise due to high salt intake, intake of alcohol, smoking, lifestyle changes and many other factors.

Fast dissolving tablets are the novel drug delivery system that disintegrate into smaller granules which slowly dissolve in mouth. Geriatric, pediatric and mentally ill patients experience difficulty in swallowing tablets which may lead to poor patient compliance hence to overcome such problems an innovative drug delivery system was developed known as fast dissolving tablets or fast disintegrating tablets. Fast dissolving tablets are also called as Orodispersible tablets. Various Natural and Synthetic Superdisintegrants are used in the formulation of fast dissolving tablets. Superdisintegrants such as plantago ovata, banana powder, crosspovidone, sodium starch glycolate, crosscarmellose sodium are used for increasing the disintegration time and better action.

Azilsartan medoxomil is an angiotensin II receptor antagonist used in the treatment of hypertension. It is having less side effects as compared to other angiotensin receptor antagonist and it more effective. It is having less solubility. It is insoluble in water, soluble in methanol. Hence, solubility enhancement techniques were used to increase solubility. Poloxamer 188 was used as a carrier for solubility enhancement. Solid dispersions were prepared using poloxamer 188 as carrier.

2. METHDOLODGY

MATERIAL: THE AZILSARTAN MEDOXOMIL WAS OBTAINED AS GIFT SAMPLE FORM CTX LIFESCIENCES PVT, LTD. SURAT

METHOD OF PREPARATION OF SOLID DISPERSION

Weigh the required quantity of Azilsartan medoxomil. After that Azilsartan medoxomil and poloxamer were dissolved in the sufficient quantity of methanol in the ratio 1:1, 1:2, 1:3, 1:4 in a separate china dish. The solvent is evaporated at 45°C in a hot air oven until dried solid mass remains in the dish. The solid mass is then pulverized and passed through sieve no. 60 and kept in a desiccator.

METHOD OF PREPARATION OF FAST DISSOLVING TABLETS:

Crosspovidone, Plantago ovata, Isomalt, Microcrystalline cellulose, Magnesium stearate were weighed and passed through sieve 60 mesh size separately. Solid dispersion equivalent to Azilsartan were mixed in geometric proportion to get a uniform mixture. All the ingredients were weighed and mixed in geometrical order and tablets were compressed using flat round punch on a tablet machine.

Table no.1 Formula of Fast dissolving tablets of Azilsartan medoxomil

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Azilsartan medoxomil	40	40	40	40	40	40	40	40	40
Plantago ovata	4	6	8	4	6	8	4	6	8
Crosspovidone	4	4	4	6	6	6	8	8	8
Isomalt	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	20	18	16	18	16	14	16	14	12
Total weight	200 mg								

2.1 Determination of λ max

2.1.1 Preparation of standard stock solution

In order to determine λ max of drug. 100 mg drug was weighed accurately and transferred to a 100 ml volumetric flask, the volume was adjusted to 100 ml with suitable solvent, to get a 1000 µg/ml stock solution, further stock solution was diluted suitably to get 10 µg/ml for Azilsartan medoxomil solution, which was analyzed by UV Visible double beam spectrophotometer at 200 to 400 nm against suitable solvent as a blank solution.

2.1.2 Preparation of calibration curve of Azilsartan medoxomil in Phosphate buffer pH 6.8

From stock solution (1000 µg/ml), 100 µg/ml solution was prepared by diluting 10ml of stock solution with phosphate buffer pH 6.8 in volumetric flask. Accurately measured standard working sample solutions (0.8,1.0,1.2,1.4,1.6 ml) were transferred to a series of 10 ml volumetric flask and diluted to obtain concentration of 8,10,12,14,16 µg/ml. The absorbance of prepared solution was measured at 248nm using UV- visible spectrophotometer.

2.2 Evaluation of Fast Dissolving tablets.

Pre-Compression parameters.

2.2.1 Angle of repose: The angle of repose was determined by funnel method. The powder was allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of powder from the funnel mouth forms a pile of powder at the surface, this was continued until the pile touches the stem tip of the funnel. A rough circle was drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula

$\tan \theta = h / r$

Where, θ= angle of repose

h= height of the pile

r = average radius of the powder cone

2.2.2 Bulk density: Bulk density of powder was determined by pouring gently 10gm of powder into a 50 ml graduated cylinder. The volume occupied by the powder was recorded. The bulk density was calculated as follows:

$$\text{Bulk Density (gm/ml)} = \frac{\text{weight of powder in gram}}{\text{Volume of bulk powder}}$$

2.2.3 Tapped density: 10 gm powder was poured gently into a 50ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume is obtained. Volume occupied by the powder after tapping was recorded and tapped density was calculated as follows:

$$\text{Tapped Density (gm/ml)} = \frac{\text{weight of powder in gram}}{\text{Volume of tapped powder}}$$

2.2.4 Carr's index: One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index (I) which was determined by the following equation.

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100$$

2.2.5 Hausner's ratio: Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A higher Hausner's ratio is considered to be an indication of poor flow property. Tapped density and bulk density were measured and the Hausner's ratio was calculated using the following equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post Compression parameters

2.2.6 Hardness: It is the force required to break a tablet by compression in the radial direction. In the present study the crushing strength of the tablet was measured on the day of compression, using Pfizer Hardness Tester. An average of three observations is reported.

2.2.7 Friability: Friability of each batch was measured in the Roche Friabilator. Ten pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then re-weighed and the percentage of weight loss was calculated and limit should not more than 1% as per IP. Friability was calculated by following formula

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

2.2.8 Weight variation: Weight variation study was performed by weighing 20 tablets of each batch formulation by using electronic balance and test was performed according to IP.

2.2.9 Disintegration time: This test is performed by taking one tablet in a beaker containing phosphate buffer pH 6.8. The time required for complete dispersion of tablet was measured.

2.2.10 Wetting time: This test is performed by placing a piece of tissue paper folded twice in a petridish with 10 cm diameter. 10 ml of water was added to the petri dish. A tablet was placed on the surface of tissue paper. The time required for complete wetting was measured as wetting time.

2.2.11 In-vitro Dissolution study: USP Dissolution Test Apparatus Type II (Electrolab) was used with paddle stirred at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C, as the dissolution medium. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content (i.e., amount of drug dissolved from tablet) The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium. And then Cumulative % of drug release was calculated.

3. Result

3.1 Calibration curve of Azilsartan medoxomil:

Azilsartan medoxomil shows maximum absorbance at 248nm in phosphate buffer pH 6.8 respectively and shows linearity range of 8-16 µg/ml.

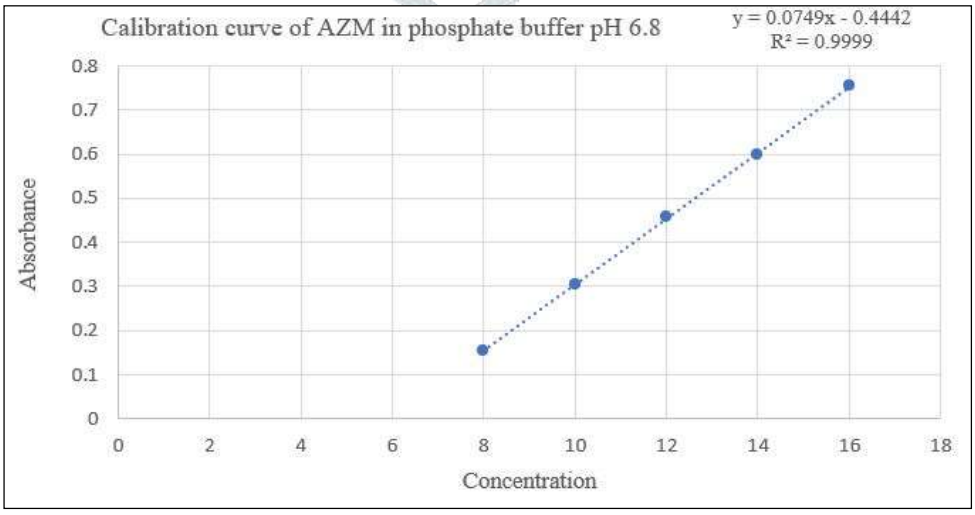

Fig 1: Calibration curve of Azilsartan medoxomil at 248nm

3.2 FTIR studies:

IR spectra of drug were shown as the peaks obtained in the spectra of drug correlates with functional groups of Azilsartan medoxomil which confirms purity of drug. All the characteristic peaks respective to their functional groups of drugs are shown and comparison of graph done which reveal no interaction with polymer and drug mixture.

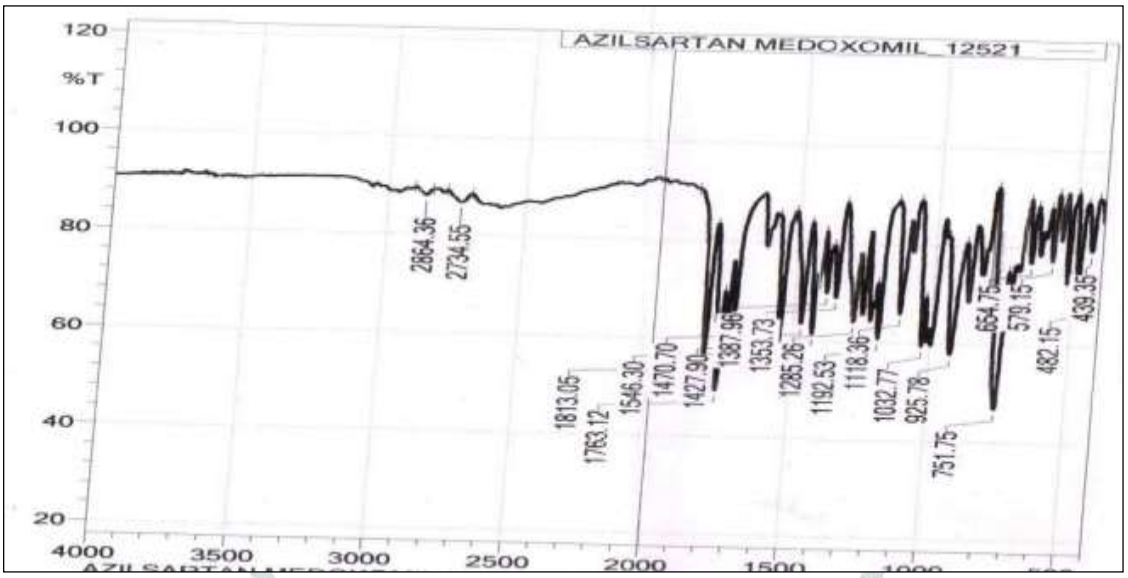

Fig 2: FTIR spectra of Azilsartan medoxomil

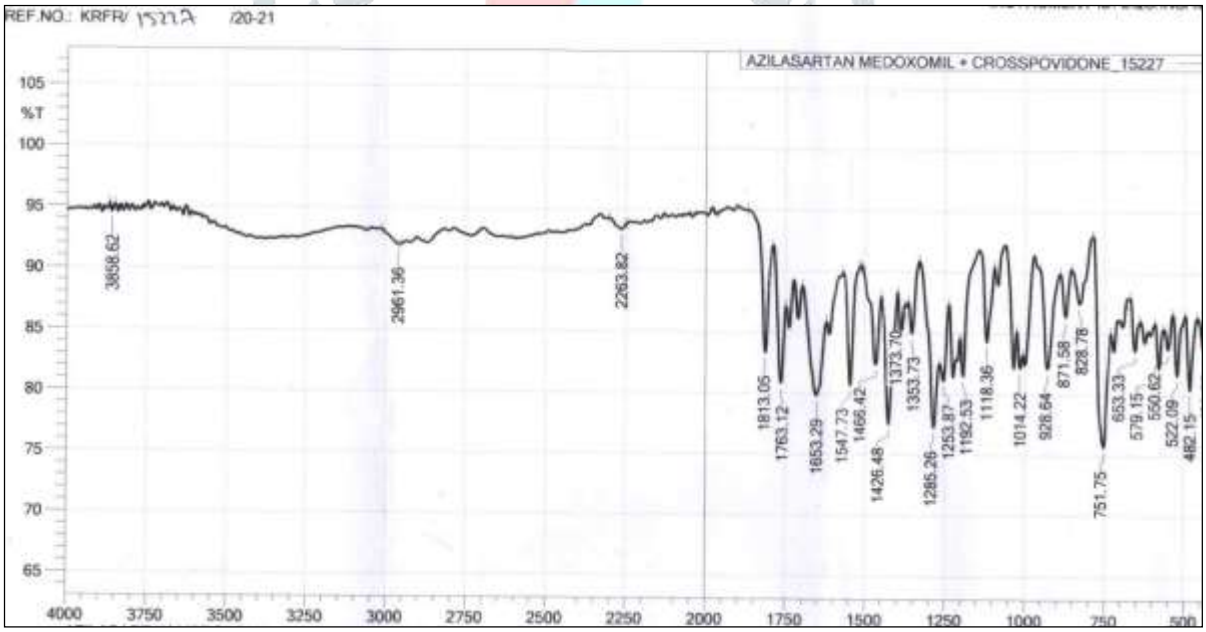

Fig 3: Fig FTIR spectra of Azilsartan medoxomil with Crosspovidone

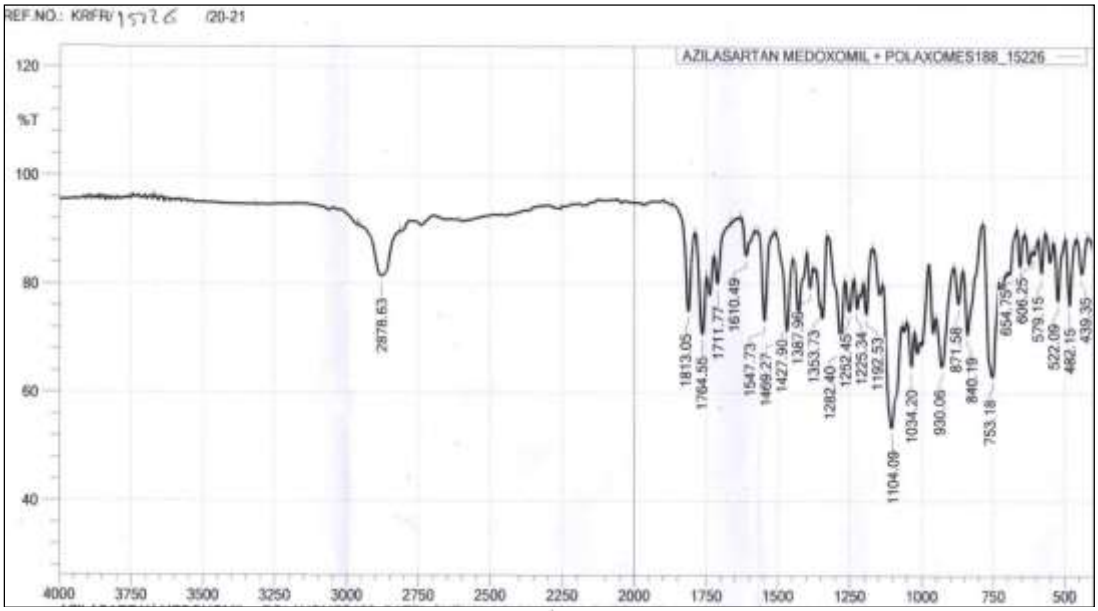

Fig 4: Fig FTIR spectra of Azilsartan medoxomil with Poloxamer 188

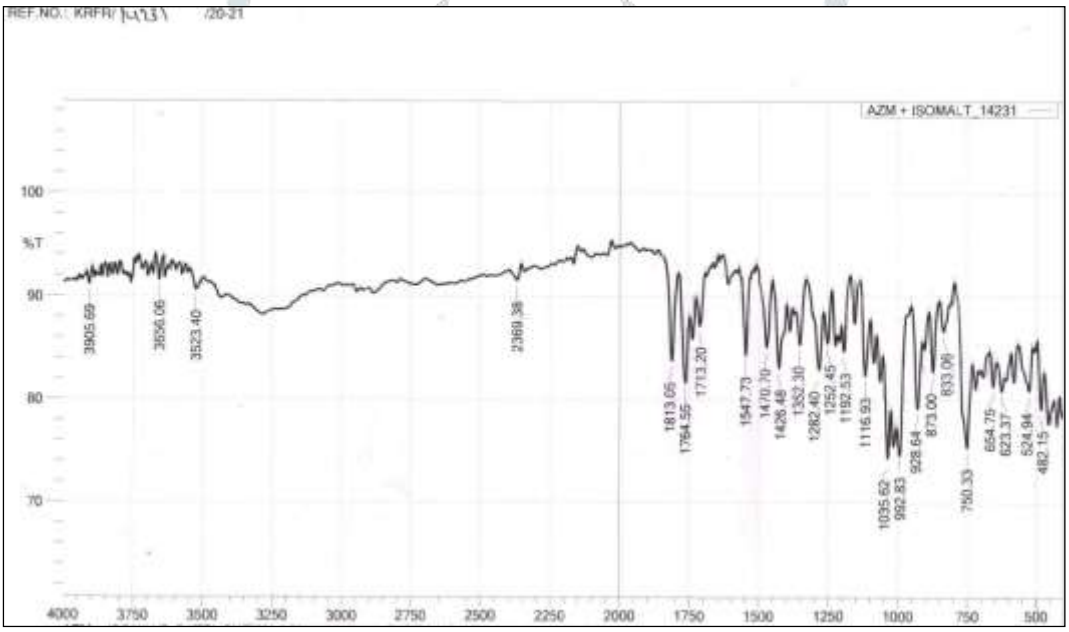

Fig 6: FTIR spectra of Azilsartan medoxomil with Isomalt

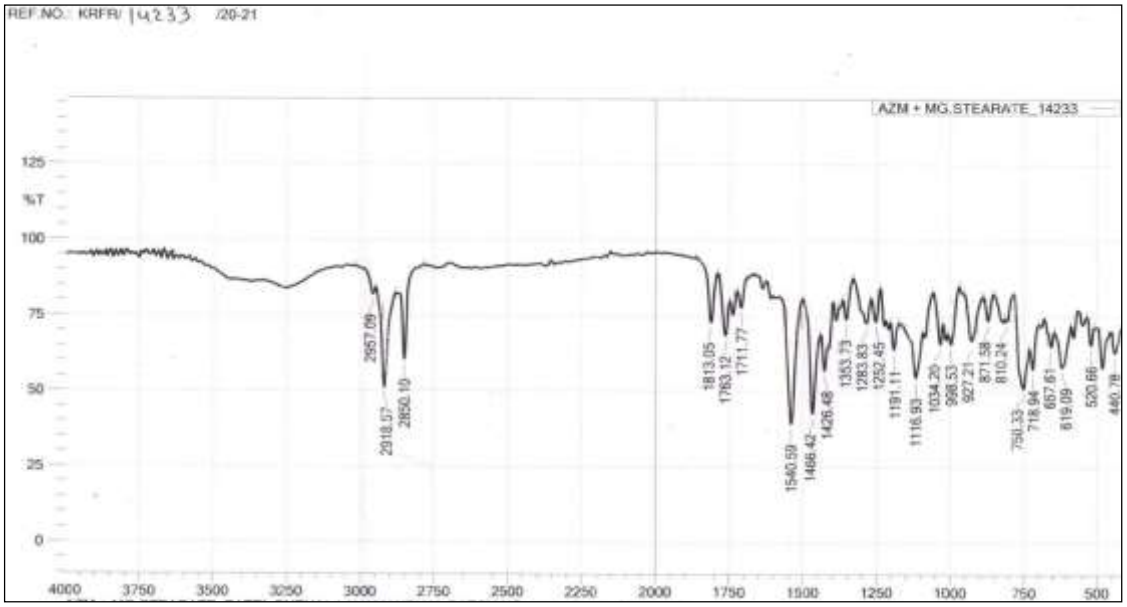

Fig 7: FTIR spectra of Azilsartan medoxomil with Magnesium stearate

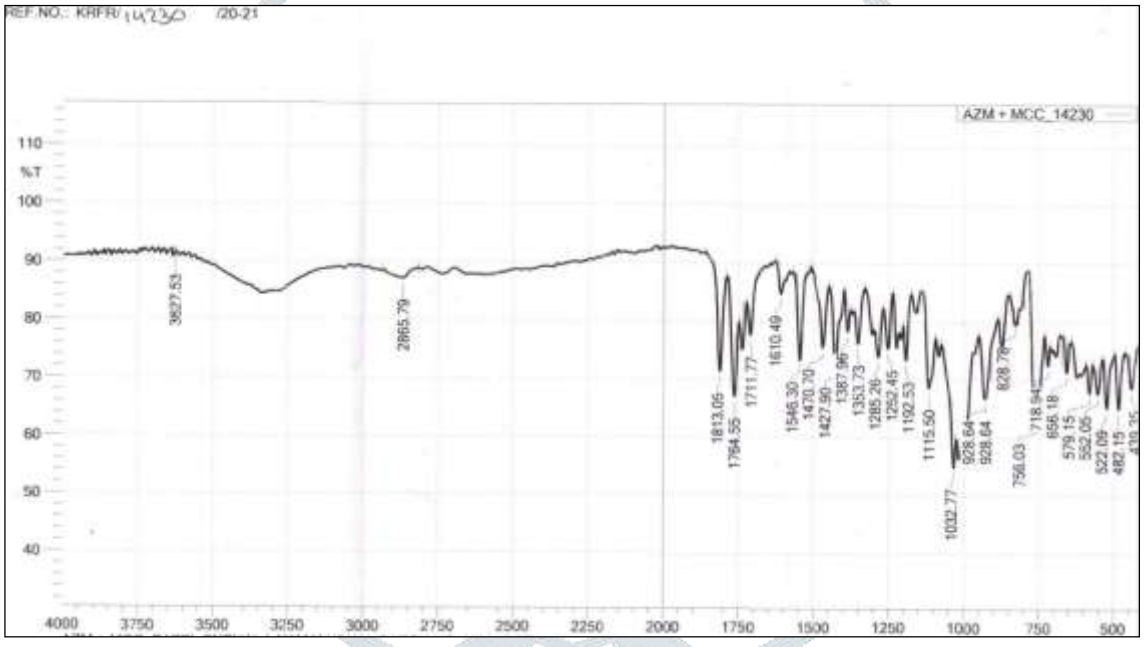

Fig 8: FTIR spectra of Azilsartan medoxomil with Microcrystalline cellulose

3.3 Evaluation of Batches

Sr. No.	Angle of Repose	Bulk density	Tapped density	Hausner's ratio	Carr's index	Hardness	%Friability	Disintegration time (sec)	Weight variation	Wetting time
1.	28.37	0.517	0.577	1.11	10.32	3.9	0.02	56	200.2	55
2.	28.35	0.600	0.682	1.13	11.9	3.6	0.30	48	199.98	47
3.	27.22	0.519	0.556	1.07	6.7	3.2	0.58	38	198.05	37
4.	26.87	0.535	0.600	1.12	11.9	4.1	1.10	54	201.4	52
5.	26.82	0.527	0.556	1.05	6.7	3.8	0.64	46	199.98	44
6.	28.35	0.519	0.556	1.07	6.9	3.4	0.90	36	198.8	35
7.	28.37	0.600	0.682	1.13	11.9	3.8	0.85	52	199.89	51
8.	26.87	0.517	0.577	1.11	10.32	3.5	0.64	44	201.5	42
9.	28.34	0.535	0.600	1.12	10.35	3.6	0.80	34	199.99	32

Table no 2: Evaluation data of batches

Sr. No	Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0	0	0	0	0	0	0	0	0
2.	3	48.97	50.84	53.98	56.8	59.0	56.95	60.2	64.25	70.01
3.	6	58.86	59.3	65.89	69.07	62.7	7.98	71.9	73.98	78.75
4.	9	67.80	69.46	70.89	72.98	75.6	73.57	77.86	81.0	84.65
5.	12	71.05	71.3	72.97	75.0	78.65	76.5	79.61	82.5	86.01
6.	15	78.05	80.69	79	83.66	86.4	84.65	85.36	89.57	92.41

Table no 3: % Drug release

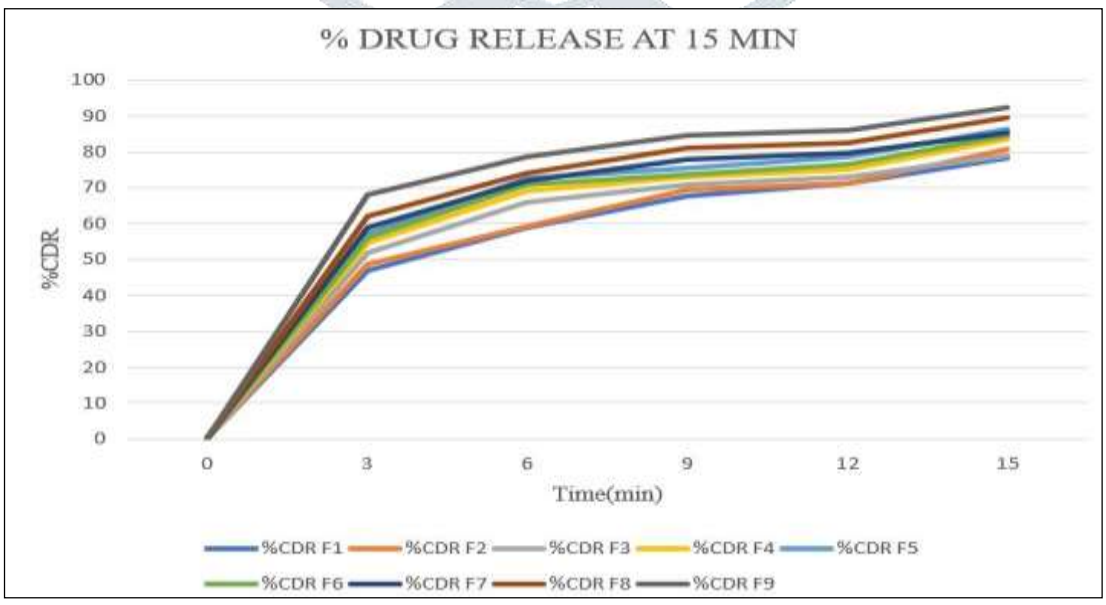

Fig 9: %CDR of Factorial batches

4. CONCLUSION:

Fast Dissolving Tablets of Azilsartan medoxomil was successfully formulated by using Direct Compression method and was developed at a satisfactory level. Formulation F9 with 8mg Plantago ovata and 8mg Crosspovidone shows best disintegration time. Formulation F9 shows the highest % drug release 92.41%.

5. REFERENCES:

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