DEVELOPMENT AND EVALUATION OF NANOPARTICULATE SUBLINGUAL TABLET OF OLANZAPINE

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Abstract : The given study describes the formulation of nanoparticles and its delivery in the form of nanoparticles. Olanzapine is one of the most prescribed drug for the treatment of Schizophrenia. It belongs to 2nd generation antipsychotics. Olanzapine belongs to BCS class II and possess low solubility, So the aim of this study was to formulate and optimise the agglomerates of Olanzapine with enhanced solubility and dissolution characteristics. The Quasi Emulsion Solvent Diffusion Technique was used to prepare drug loaded agglomerates. The method involves use of the internal phase consisting of the good solvent and the external phase consisted of bridging liquid and poor solvent and the polymer. Process variables were evaluated and preliminary screening was carried out in concern to preparation of the agglomerates. Evaluation of the factorial batches was carried out like microscopy study, percentage yield, drug content, Micromeritic properties etc. The results indicates that Olanzapine was highly dispersed in agglomerates. Further the agglomerates were evaluated for parameters like FTIR, Drug content, Percentage yield and Dissolution. The prepared agglomerates were compressed in the form of Sublingual Tablet. Finally it was concluded that the formulated agglomerates have good dissolution characteristics as compared to that of pure drug as well as marketed formulation.

Key Words **- Nanoparticles, Quasi Emulsion Solvent Diffusion Technique, Crospovidone, Nanoparticulate Sublingual Tablet.**

1. INTRODUCTION

Schizophrenia is a complicated mental health disorder which shows symptoms like delusions, hallucinations, disorganized speech or behavior, and disturbed cognitive ability[1].It requires patience compliance for its successful treatment and sublingual drug delivery is proven to be an alternative for achieving it.

It is estimated that many of the compounds developed by the pharmaceutical industry tends to be poorly water soluble. A crucial property of a drug is solubility, especially aqueous system solubility which directly affects the dissolution rate of the drug. An improvement of oral bioavailability of poorly water soluble drugs remains one of the most challenging tasks of drug development.To overcome poor solubility, many approaches have been studied. They are generally salt formation, use of surfactant, use of prodrugs and Micronization. In Micronization, the particle size of a drug powder is reduced which increases the specific surface area and dissolution rates. However, many new drugs are so poorly soluble that Micronization is not sufficient, which motivated the development of nanoscale systems. By decreasing the particle size from a micron to a nanometer scale, there is a significant increase in the surface area and related dissolution rate. The Quasi Emulsion Solvent Diffusion Method allows the drug to be formulated in the form of agglomerates.

QESD method presents numerous advantages, in that it is a straightforward technique, rapid and easy to perform. In this method, the drug is dissolved in a good solvent which is added to the poor solvent containing the bridging liquid[5]. The organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size is dependent on the type of stabilizer, its concentrations and homogenizer speed. In order to produce small particle size, often a high-speed homogenization may be employed.

Olanzapine is a 2nd generation atypical antipsychotic.It shows less amount of extrapyramidal effects as compared to 1st generation antipsychotics and is one of the highly prescribed drug for schizophrenia[6]. Olanzapine have a high rate of hepatic first pass metabolism which makes it a favourable candidate for the Sublingual Drug Delivery but also Olanzapine is sparingly soluble in water. Thus inorder to increase its solubility in water, the particle size needs to be reduced into Nano scale or nanoparticle. The Nanoparticulate sublingual Table must rapidly dissolve into saliva, so its formulation must consist of ingredients that readily dissolves in water.

There have been some studies evaluating the effects of Crosspovidone, Crosscarmellose sodium and Sodium Starch Glycolate as superdisintegrant on the characteristics of oral solid dosage form. However, the differences of their effects on the characteristic of Sublingual Tablet are still unknown. Therefore, this study is aimed to compare the characteristics of Sublingual Tablet formulated by using Crospovidone, Croscarmellose sodium and Sodium Starch Glycolate as superdisintegrant.

2. METHODOLOGY

MATERIAL: THE OLANZAPINE WAS OBTAINED AS A GIFT SAMPLE FROM INTAS PHARMACEUTICALS,MATODA

2.1 METHOD OF PREPARATION OF OLANZAPINE NANOPARTICLES:

The weighed quantity of olanzapine was added to the good solvent(dichloromethane) and this internal phase was added to a poor solvent(water) consisting of 0.7% of polymer(PVPK-30) with a stirring speed of 2000rpm for 1 hour. Nine batches were prepared for the optimization of the formula.The obtained agglomerates were collected through filtration and used for further characterization and finally formulated in the form of sublingual tablets.

Table no.1 Composition of Factorial Batches

Batch No	X_1 Conc of Polymer(%)	X_2 Stirring speed
F-1	0.5	1500
F-2	0.5	2000
F-3	0.5	2500
F-4	0.75	1500
F-5	0.75	2000
F-6	0.75	2500
F-7	1	1500
F-8	1	2000
F-9	1	2500

Table no.2 Formula of Olanzapine Nanoparticulate Sublingual Tablet

Ingredients	T 1	T 2	T 3	T 4	T 5	T 6	T7	T8	T9
Olanzapine nanoparticles	11.77	11.77	11.77	11.77	11.77	11.77	11.77	11.77	11.77
Croscarmellose Na	5	10	15	-	-	-	-	-	-
Crospovidone	-	-	-	5	10	15	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	5	10	15
Mannitol	96.23	91.23	86.23	96.23	91.23	86.23	96.23	91.23	86.23
Sorbitol	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total weight(mg)	120	120	120	120	120	120	120	120	120

2.2 Preparation of Calibration Curve in Phosphate Buffer pH 6.8:

2.2.1 Preparation of stock solution: To prepare stock solution of 1000ug/ml, 100 mg of drug was added to the 100 ml volumetric flask and dissolved in phosphate buffer 6.8.The final volume was made upto 100 ml by using the phosphate buffer solution.

2.2.2 Preparation of Working sample solutions

From the stock solution (100ug/ml),accurately measured volume(0.5, 1, 1.5, 2, 2.5) is transferred to 10 ml volumetric flask and volume is made up with phosphate buffer to obtain the concentration of 5, 10, 15, 20 and 25 ug/ml respectively. The prepared solutions of olanzapine are analyzed for their absorbance at 226nm through the UV visible spectrophotometer by using phosphate buffer 6.8 as blank. The experiment was performed in triplicate, based on which the equation for the best line was generated.

2.2.3 Evaluation of Nanoparticulate Sublingual Tablet

Hardness:

The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.

Thickness: The thickness and diameter of the tablets was determined using a Vernier caliper. Five tablets from each formulation were used and average values were calculated.

Weight Variation:20 tablets were selected randomly.The average weight of the tablets was calculated and variation was determined.

Friability: In this test 10 tablets was weighed and placed in a Roche Friabilator test apparatus, and then the tablets was subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = 1 – (wt. of tablets after test/ wt. of tablets before test) x 100

Wetting time: A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of phosphate buffer pH 6.8. A tablet was kept on the paper, and the time for complete wetting was measured.

Water Absorption Ratio (%):A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of purified water. A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$R = 100 (Wa-Wb)/ Wb$$

Where, Wa and Wb are the weight after and before water absorption, respectively. The average value with standard deviation was recorded.

Drug content uniformity: 10 tablets were weighed and triturated. The tablet triturate equivalent to 5mg of the drug was weighed accurately, dissolved in phosphate buffer 6.8 and suitably diluted with phosphate buffer. The content of Olanzapine was determined spectrophotometrically at 226 nm against blank using UV-visible spectrophotometer**.**

***In vitro* disintegration time:** *In vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The water was maintained at a temperature of 37±0.5ºC and time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

***In vitro* Drug Release Study:** *In-vitro* dissolution study was performed by using USP dissolution testing apparatus II (Paddle method). Weighed tablets from different batches were kept in a flask of the apparatus containing 250 ml of dissolution medium(phosphate buffer pH 6.8). The temperature and speed were maintained at 37±0.5ºC and 50 rpm respectively. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 226nm against suitable blank using UV-visible spectrophotometer.

Comparision with Marketed formulation:
Formulated Olanzapine Nanoparticulate tablets were compared with a marketed product. Olanzapine sublingual tablets are not available in the market. Hence, the immediate release dosage form was selected for the purpose of comparision. Since comparison is done with immediate release preparation there's only one parameter which can be compared & that is in-vitro drug release.

3. RESULTS AND DISCUSSION

3.1 Calibration curve of Olanzapine: The wavelength of Olanzapine in phosphate buffer 6.8 was found to be 226nm.

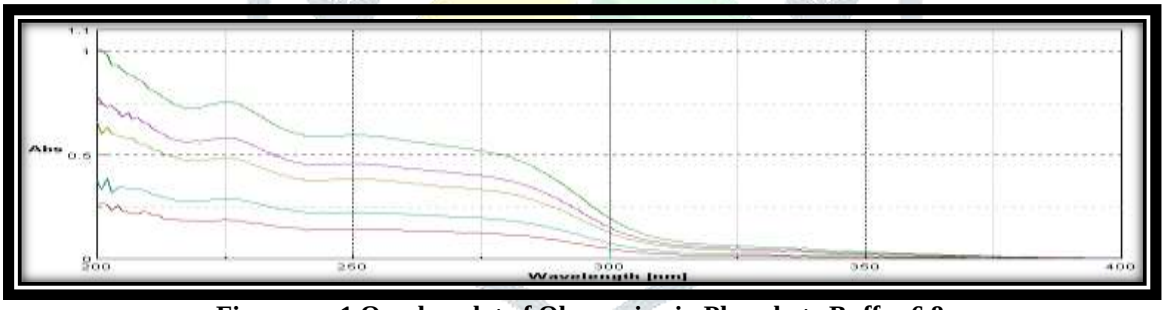

Figure no. 1 Overlay plot of Olanzapine in Phosphate Buffer 6.8

Table no.3 Calibration curve of Olanzapine in Phosphate Buffer 6.8

Concentration (ug/ml)	Absorbance at 226nm (n=3)
0	0
5	0.185
10	0.298
15	0.458
20	0.588
25	0.754

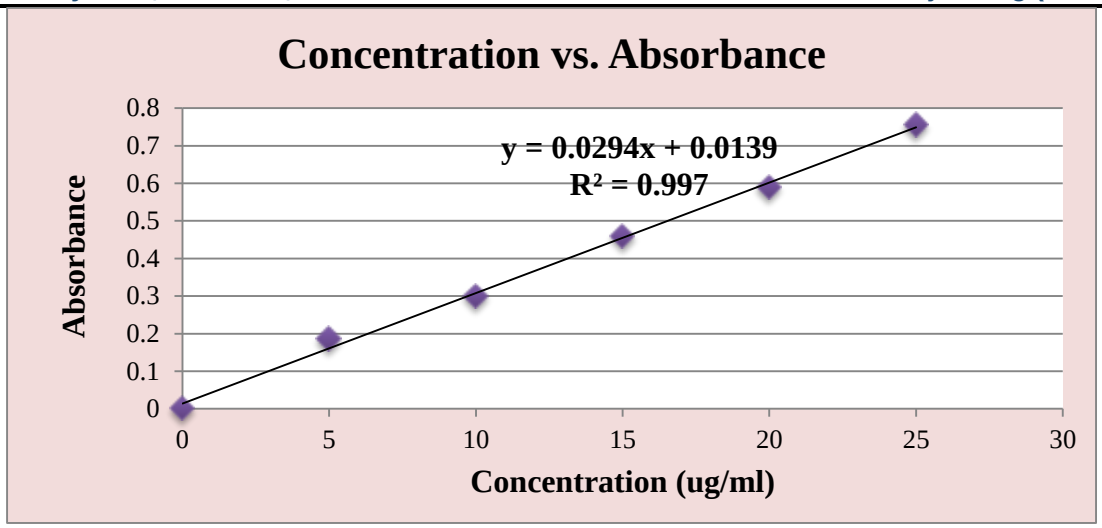

Figure no.2:Calibration curve of Olanzapine in Phosphate Buffer 6.8

3.2 FTIR Studies:

It can be concluded from the FTIR studies that there was no interaction between the drug and the excipients used in the formulation.

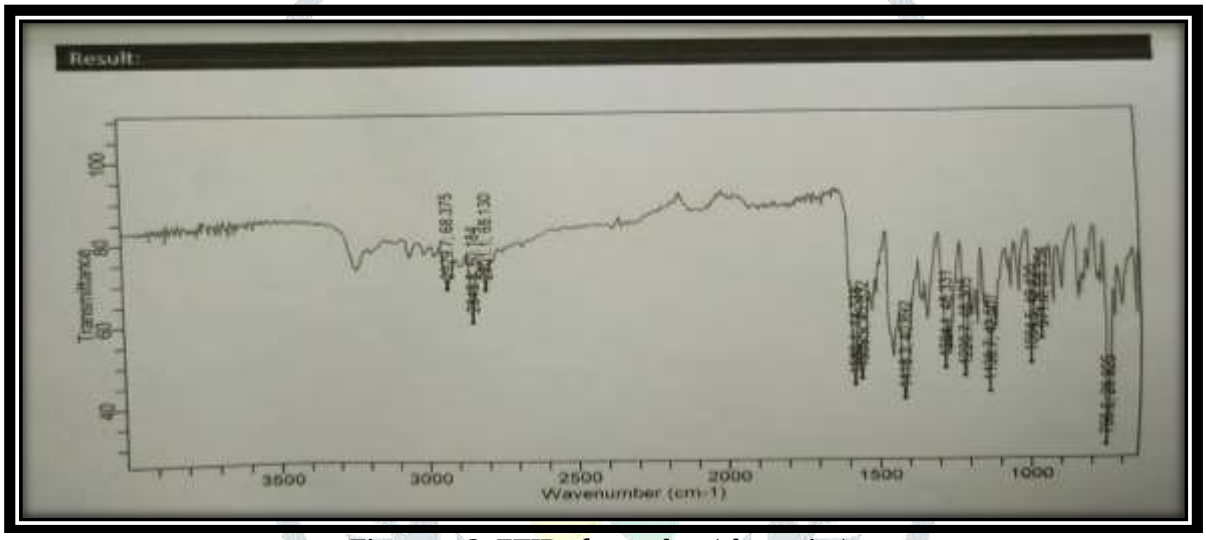

Figure no.3: FTIR of pure drug(olanzapine)

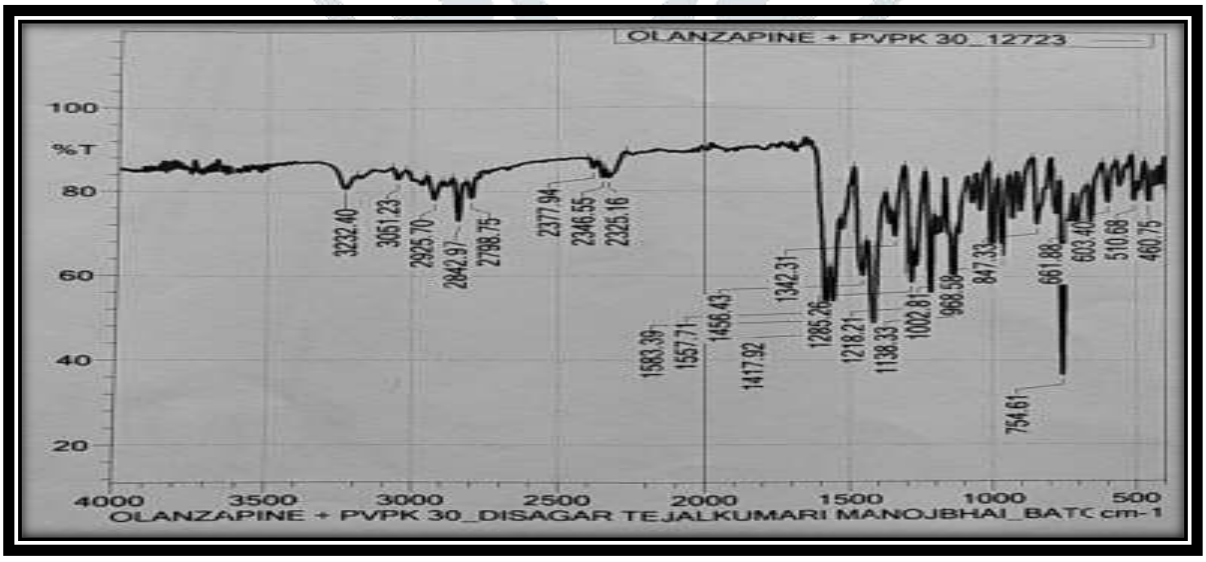

Figure no.4: FTIR of Olanzapine + PVPK-30

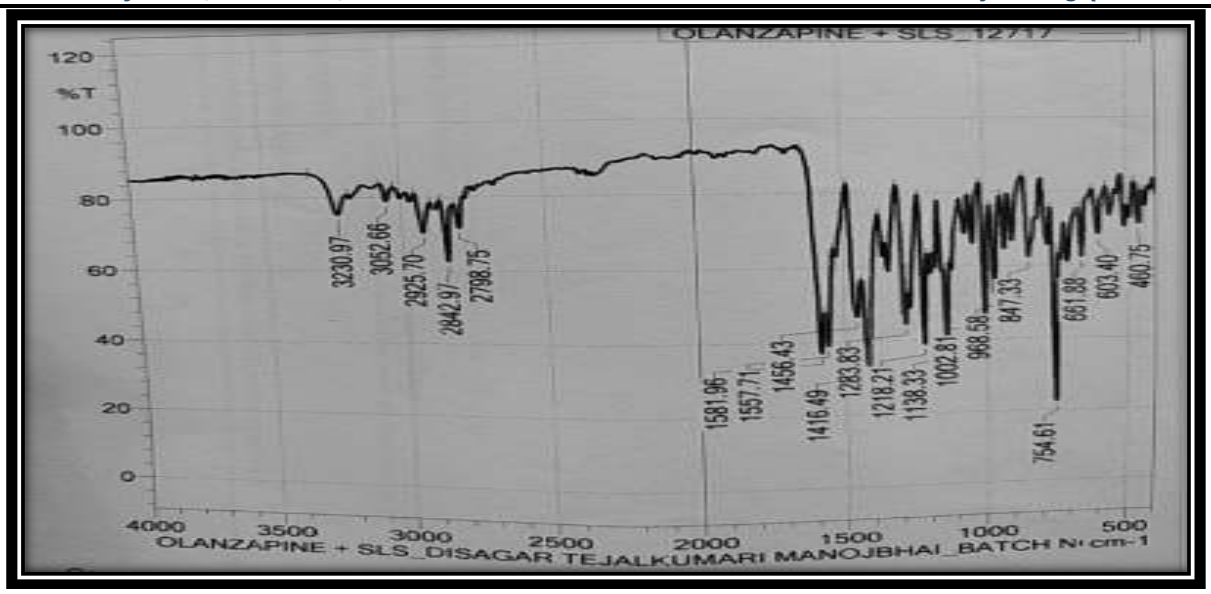

Figure no.5: FTIR of Olanzapine + SLS

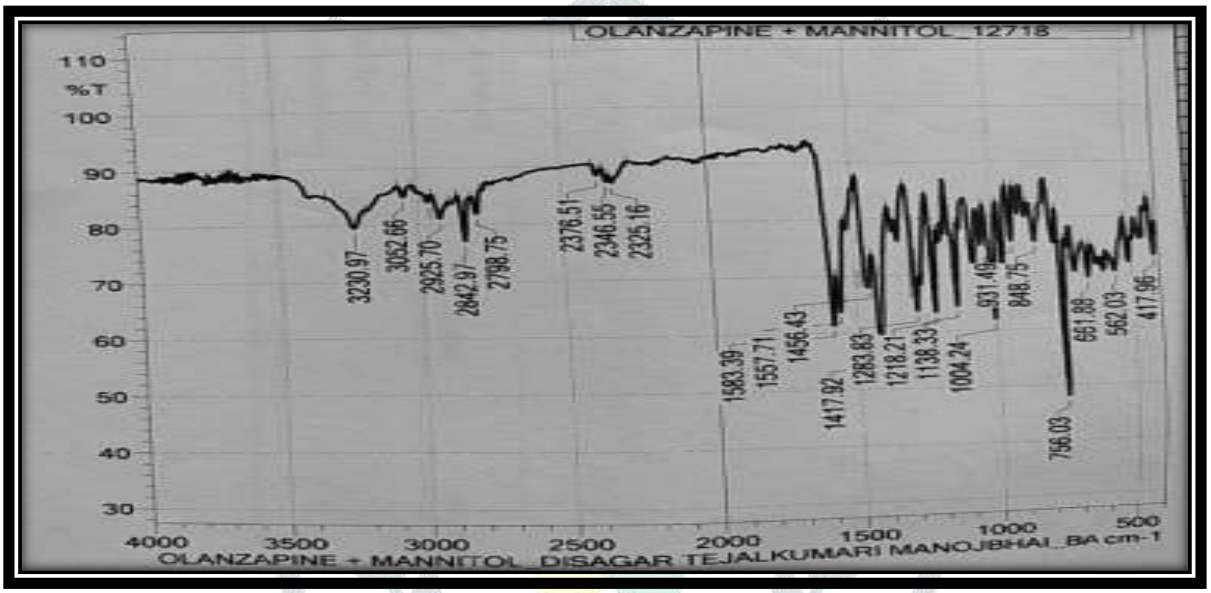

Figure no.6: FTIR of Olanzapine + Mannitol

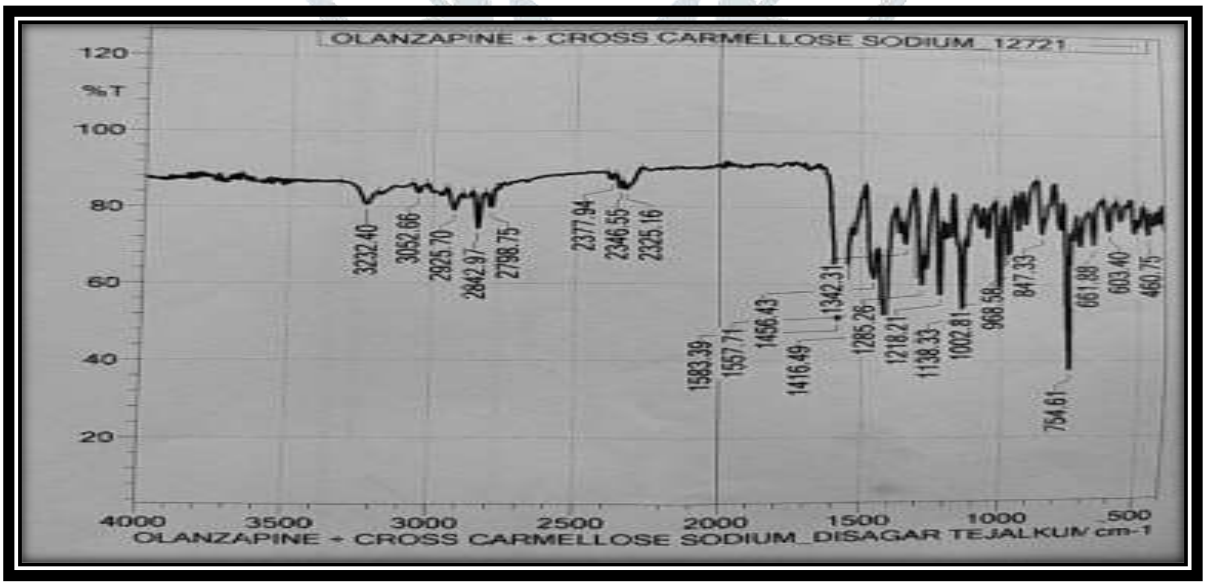

Figure no.7: FTIR of Olanzapine + Cross Carmellose Sodium

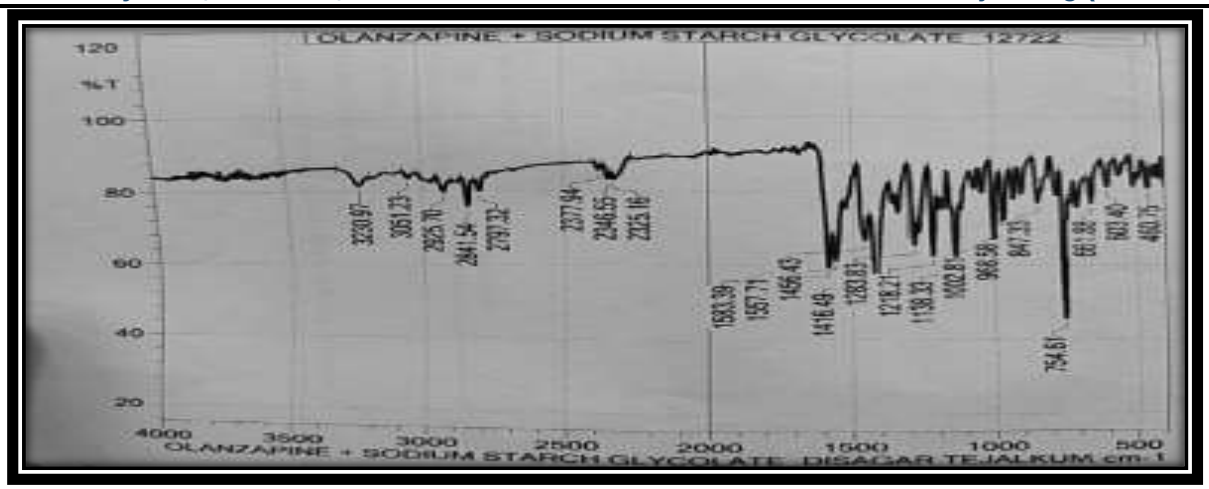

Figure no.8: FTIR of Olanzapine + Sodium Starch Glycolate

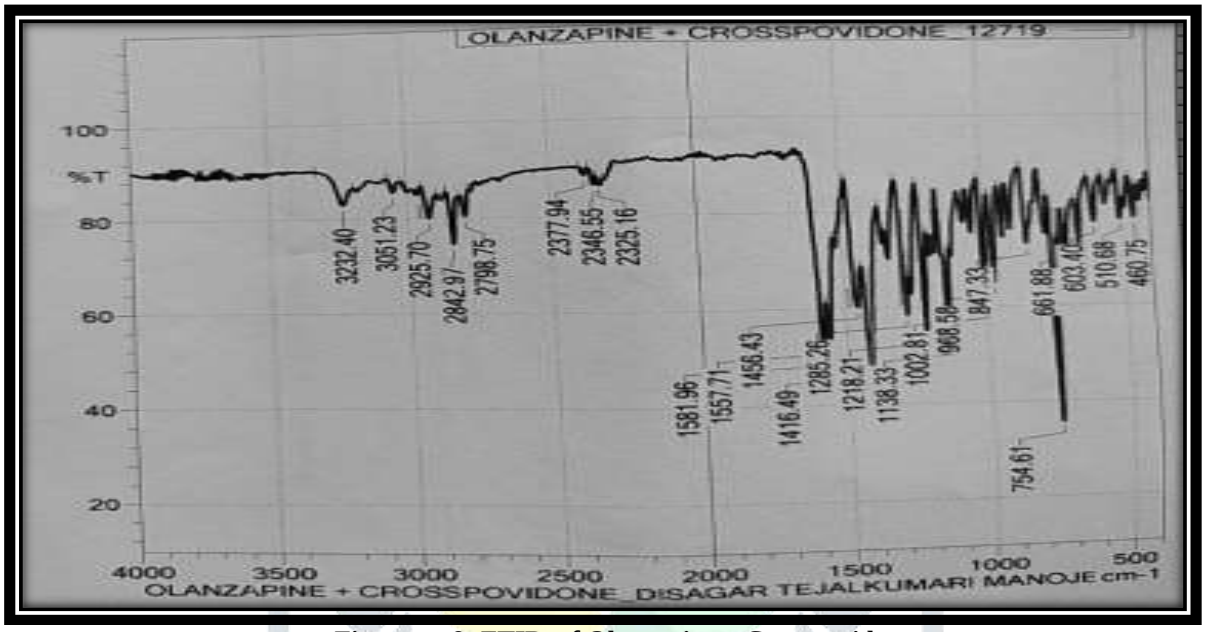

Figure no.9: FTIR of Olanzapine + Crosspovidone

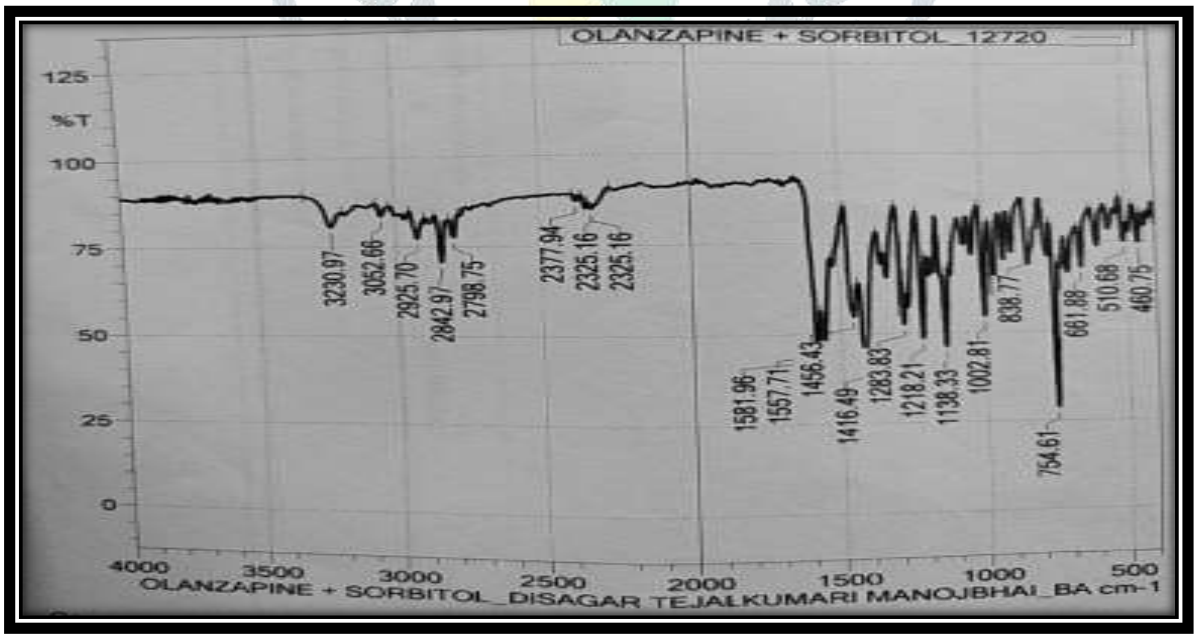

Figure no.10: FTIR of Olanzapine + Sorbitol

3.3 Evaluation Parameters of Nanoparticulate Sublingual Tablet

Table no.4 Post-Compression Parameters

Formulation	Hardness (Kg/cm^2)	Thickness (mm) ±SD	Disintegration Time (sec) n=6	Friability % ±SD
T1	3.633 ± 0.208	2.44 ± 0.01	46.333 ± 1.527	0.380±0.015
T2	3.366 ± 0.208	2.446 ± 0.032	47.666 ± 1.154	0.327±0.015
T3	3.466 ± 0.115	2.44 ± 0.01	39.333 ± 0.577	0.333±0.020
T4	3.500 ± 0.264	2.43 ± 0.02	45.666 ± 1.527	0.356±0.010
T5	3.466 ± 0.057	2.43 ± 0.02	36.333 ± 1.527	0.366±0.008
T6	3.300 ± 0.1	2.43 ± 0.02	32.666 ± 0.577	0.358±0.009
T7	3.333 ± 0.057	2.44 ± 0.01	47.000 ± 1.732	0.337±0.010
T8	3.500 ± 0.1	2.43 ± 0.02	45.333 ± 1.154	0.356±0.009
T9	3.600 ± 0.1	2.45 ± 0.01	36.333 ± 1.527	0.341±0.014

Table no.5 Post-Compression Parameters

Formulation	Weight variation (mg) ±SD (n=20)	Wetting time (Sec)	Water Absorption ratio(%) ±SD	Drug content (%) ± SD
T1	120.05±1.935	38.30±0.776	30.80±1.656	99.13±0.610
T2	121.05±1.532	36.88±0.602	34.38±2.085	98.26±1.585
T3	120.75±2.094	33.25±1.379	35.22±0.405	98.56±1.810
T4	120.8±1.913	36.91±1.595	34.55±1.888	97.87±1.169
T5	119.75±1.894	31.50±0.827	30.63±1.072	99.02±1.037
T6	121.5±2.179	29.78±1.536	36.64±1.872	99.23±1.192
T7	120.3±2.325	36.32±0.701	29.82±0.360	97.42±1.435
T8	120.9±1.972	34.0±0.744	31.14±0.665	98.71±1.209

T9	121.25±1.409	31.04±1.515	34.54±2.113	98.38±1.82

All values are expressed as mean ± standard deviation, n=3

From the above result it had been concluded that cross povidone is giving better result than Croscarmellose sodium. Hence these superdisintegrant were subjected for further investigation

Table no. 6 Dissolution rate of Drug from Sublingual Nanoparticulate Tablet

Time	F1	F2	F3
0	0	0	0
2	25.54 ± 1.014	39.07± 0.924	43.38± 2.00
4	36.28 ± 0.918	49.64 ± 1.413	51.24 ±1.827
6	56.42 ± 0.568	73.53 ± 1.606	77.01 ± 0.843
8	75.99 ± 0.730	89.52 ± 0.777	90.46 ± 0.824
10	88.16 ± 1.767	92.44 ± 1.756	94.04 ± 1.761

Table no. 7 Dissolution rate of Drug from Sublingual Nanoparticulate Tablet

Time	T4	T5	T6
0	0	0	0
2	34.26 ± 2.239	36.84 ± 0.756	49.46± 1.486
4	41.30 ± 1.197	47.23 ± 1.953	62.68 ± 1.645
6	64.72 ± 0.956	69.86 ±1.777	76.06 ± 0.552
8	79.88 ± 1.264	88.69 ± 1.459	85.92 ± 0.716
10	90.82 ± 0.766	91.88 ± 0.905	98.03 ± 1.422

Table no. 8 Dissolution rate of Drug from Sublingual Nanoparticulate Tablet

Time	T7	T8	T9
0	0	0	0
2	31.53 ± 1.928	38.67 ± 1.420	38.06± 1.324
4	51.40 ± 0.913	51.07 ± 1.743	56.95 ± 1.987
6	70.95 ± 1.670	60.08 ± 0.993	65.56 ± 1.359
8	78.63 ± 0.666	79.00 ± 0.872	72.00 ± 0.698
10	89.85 ± 1.870	91.03 ± 1.719	91.15 ± 0.704

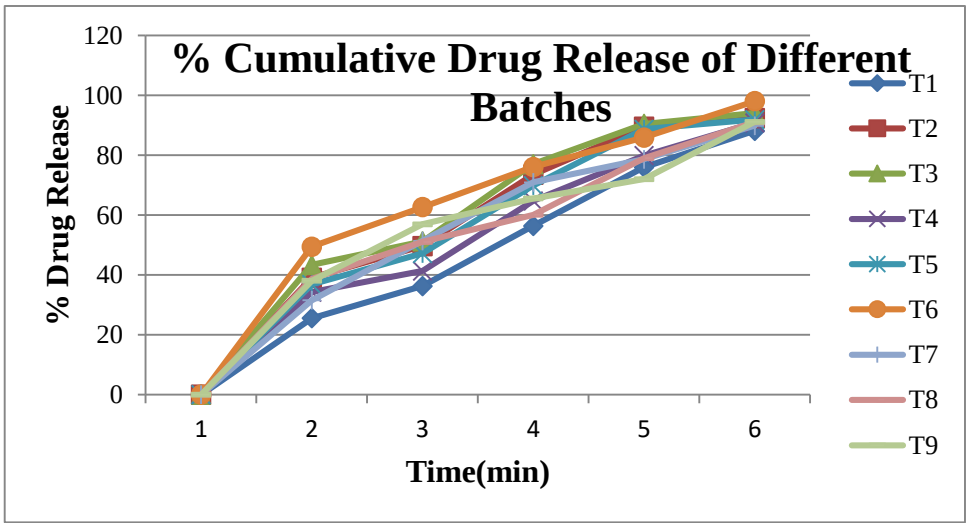

Figure:3 Cumulative Drug Release of Different Batches

3.4 Comparision with Marketed Formulation:

From the comparision of in vitro dissolution of the nanoparticulate sublingual Tablet and Marketed formulation it can be concluded that the nanoparticulate tablet shows better dissolution.

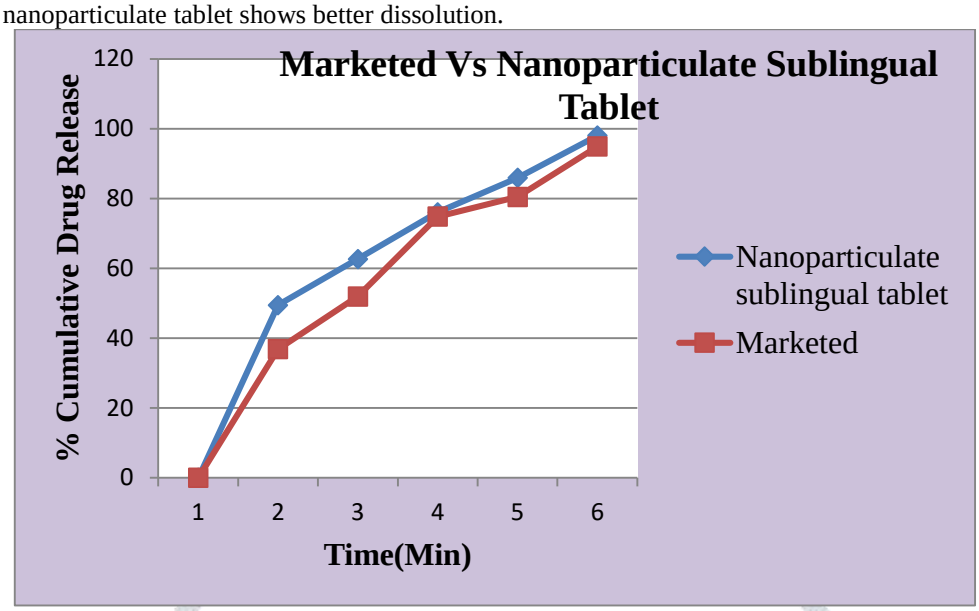

Figure:4 Comparison with Marketed Formulation

SUMMARY:

The spherical crystallization is the technique where in particle size enlargement is achieved. The technique involves modification of Nanoparticles characteristics and dissolution property. Particle size enlargement leads to show agglomeration of the crystalline drug with that of polymer and that finally leads to show improved the dissolution.

The present work was designed to develop Sublingual Tablet Containing Nanoparticle of Olanzapine by Quasi Emulsion Solvent Diffusion Technique to enhance the solubility and dissolution rate.The sublingual tablets were prepared using different superdisintegrants i.e. Crospovidone (CP), Croscarmellose sodium (CCS). Tablets prepared with Croscarmellose and Crosspovidone. It showed less disintegration time compared to CCS.

From all F1- F6 batches, F5 batch has Proper Spherical in shape & Size is selected. Disintegration time and Wetting time of the check point batch is 21±1.00 and 27±0.57 sec. The results are as expected thus, we can conclude that the statistical model is mathematically valid.

CONCLUSION

- The agglomerates were prepared using quasi emulsion solvent diffusion technique; the agglomerates showed improved solubility, micrometric properties as well as dissolution.
- The improved dissolution was achieved using the polymer that leads to convert the crystalline nature of the drug, finally the optimized batch is prepared with consideration to all of the factors and applying experimental design.

  The Nanoparticulate tablets were prepared, evaluated and the observed change in the Disintegration time as well as the dissolution data shows that the drug release of the prepared tablet is better than the marketed formulation.

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