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FORMULATION AND *IN VITRO* EVALUATION OF MOUTH DISSOLVING TABLET OF OLANZAPINE USING SOLID DISPERSION TECHNIQUE

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ABSTRACT
In the present investigation solid dispersion of olanzapine has been prepared to improve its solubility. Further, using solid dispersion, mouth dissolving tablet was prepared to overcome the problem of swallowing. A Simplex Lattice design was applied using three factors, i.e. superdisintegrants like croscarmellose sodium(X_1) crospovidone(X_2), and sodium starch glycolate(X_3) in tablet formulation. Disintegration time and T_{50} (Time required to 50% drug release) taken as responses. Solid dispersion showed significant enhancement in solubility of olanzapine. For mouth dissolving tablet, batch containing 5% croscarmellose sodium alone had minimum disintegration time (44 sec.) and faster drug release (T_{50}: 40 sec) compared to other batches.

Key words: *Olanzapine; solid dispersion; solubility; mouth dissolving tablet; disintegration.*

INTRODUCTION

Recent advances in novel drug delivery system (NDDS) aims to enhance the safety and by formulating a convenient dosage form for administration to achieve better patient compliance. One such approach is formulation of mouth dissolving tablet (MDT). A rapidly disintegrating tablet is a dosage form placed in patient's mouth. Saliva rapidly dissolves the tablet, thus releasing the active ingredient which is swallowed with saliva as liquid. The pediatric and geriatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. The characteristic advantage of MDTs such as administration without water, anywhere, anytime leads to their suitability to pediatric and geriatric patients. They are also suitable for mentally ill, bedridden and traveling patients who do not have ready access to water. The rapid onset of action, increased bioavailability of these tablets makes it popular dosage form in current market.[1] However, poorly water soluble drugs, when administered orally, have shown to be slowly and unpredictably absorbed since their bioavailability is largely dependent on the dissolution process in the gastrointestinal tract. Several methods have been suggested to improve the dissolution characteristics of the poorly water-soluble drugs. However, the solid dispersion technique is more effective and is the widely used method for the enhancement of the dissolution rate of poorly water-soluble drugs.[2] A wide variety of water soluble carriers have been used for enhancing the aqueous solubility of drugs[3,4,5]. Several insoluble drugs have been shown to improve their solubility, dissolution rate and oral absorption when incorporated into a solid dispersion[6-9]. Olanzapine is classified as a thiobenzodiazepines. It is an atypical antipsychotic drug used in the treatment of schizophrenia. It is practically insoluble in water which is responsible for its high T_{max} value (6 hr) having only 60% oral bioavailability[7]. Olanzapine undergoes extensive first pass metabolism. Some schizophrenic patients hide a conventional tablet under their tongue to avoid its daily dose of an atypical antipsychotic. Also schizophrenic patients with dysphagia are not able to swallow conventional olanzapine tablet. To overcome these problems an attempt was made to formulate and evaluate MDTs of olanzapine using solid dispersion technique.

MATERIALS AND METHODS

Olanzapine was kindly supplied as a gift sample from Zydus healthcare, Ahmedabad, Gujarat, India. Croscarmelose sodium (Vivasol®) was provided as a gift sample from JRS Pharma, Germany. Sodium starch glycolate was obtained as a gift sample from Sanofi Aventis Pharmaceuticals, Ankleshwar, Gujarat, India. polyvinylpolypyrrolidone K-30 (PVP K-30) was purchased from Oxford Chemicals, Mumbai, India. Crospovidone (polyplasdone XL®), mannitol, microcrystalline cellulose, aerosil, magnesium stearate and other reagents were purchased from Crystal Chemicals, Himmatnagar, Gujarat, India. All other chemicals and reagents were of analytical grades.

Preparation of olanzapine solid dispersions

Solid dispersion containing olanzapine using PVP K-30 as a carrier in the proportion of 1:3, 1:5 and 1:10 were prepared by solvent evaporation method. In this method, accurately weighed quantities of carriers in the stated proportion were carefully transferred into beaker and dissolved in chloroform. To this solution accurately weighed quantities of olanzapine was added

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and allowed to dissolve. The solution was transferred to a petridish and solvent was allowed to evaporate at room temperature for 1 hour and then dried at 65° C for 6 hours in a hot air oven. The mass obtained in each case was crushed, pulverized and sifted through sieve No.80. All the solid dispersion was preserved in well-closed glass container till use.

Evaluation of prepared solid dispersions

a. Drug content estimation

Solid dispersion equivalent to 10 mg of drug was accurately weighed and added into 100 ml volumetric flask. To this 10 ml acetonitrile was added and further made up volume with phosphate buffer. This solution was stirred for 60 min, till the entire drug leached out. The solution was filtered and 1 ml was withdrawn from this solution and added into 10 ml volumetric flask and volume was made to 10 ml (10 ìg/ml) with phosphate buffer pH 6.8. Drug content was estimated by UV spectrophotometer (Shimadzu Inc.) at 253 nm, using phosphate buffer pH 6.8 as blank.

b. Saturation solubility studies

Saturation solubility study was performed according to method reported by Higuchi and Connors[8]. Excess quantities of solid dispersion, equivalent to 20 mg of drug were added to 10 ml distilled water in a vial and mixtures were shaken for 24 hrs in rotary flask shaker. After shaking, to achieve equilibrium, 2 ml aliquots were withdrawn at 1 h intervals and filtered through Whatman filter paper No. 41. The filtrate was analyzed spectrophotometrically at 253 nm. Shaking was continued until three consecutive readings were the same.

c. *In vitro* dissolution study of prepared solid dispersion

In vitro dissolution study of solid dispersion was conducted using USP dissolution apparatus II (Electrolab, Mumbai) at 50 rpm, using 900 ml phosphate buffer pH 6.8 as a dissolution media maintaining at 37 ± 0.5° C. Quantity of solid dispersion equivalent to 10 mg of drug was taken. 10 ml sample was withdrawn at time intervals of 5, 15, 30 up to 90 mins. and filtered through a 45µm filter paper, diluted and assayed at 253 nm using UV spectrophotometer. The volume of dissolution fluid was adjusted to 900 ml by replacing each 10 ml aliquot withdrawn with 10 ml of fresh phosphate buffer.

d. Differential scanning calorimetry (DSC):

Thermograms of pure olanzapine, PVP K-30 and solid dispersion were recorded (Shimadzu Inc.). About 5 mg of samples were sealed in aluminum pans and heated at a rate of 20°C /min. from 50-300ÚC under atmospheric air.

Formulation of mouth dissolving tablet using prepared solid dispersion

***Table 1**: Design Matrix for Simplex Lattice*

Batch No.	Coded Value			Actual Value (mg) (Superdisintegrant - 5%)		
	X1	X2	X3	X1	X2	X3
1	1	0	0	9	-	-
2	0	1	0	-	9	-
3	0	0	1	-	-	9
4	0.5	0.5	0	4.5	4.5	-
5	0.5	0	0.5	4.5	-	4.5
6	0	0.5	0.5	-	4.5	4.5
7	0.33	0.33	0.33	3	3	3

X1 = Croscarmellose sodium
X2 = Crospovidone
X3 = Sodium starch glycolate

***Table 2:** Formulation of Olanzapine Mouth Dissolving Tablet*

Ingredients (mg)	01	02	03	04	05	06	07
Solid dispersion (Drug:10 mg)	60	60	60	60	60	60	60
Microcrystalline cellulose	80	80	80	80	80	80	80
Mannitol	31.8	31.8	31.8	28.2	28.2	28.2	24.6
Croscarmelose sodium	9	-	-	4.5	4.5	-	3
Crospovidone	-	9	-	4.5	-	4.5	3
Sodium starch glycolate	-	-	9	-	4.5	4.5	3
Aspartame	1	1	1	1	1	1	1
Magnesium stearate	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Aerosil	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Total wt.	180	180	180	180	180	180	180

Simplex lattice design was adopted and seven batches were designed as shown in Table 1 with their code and actual value. Mouth dissolving tablets of olanzapine were prepared by direct compression method according to the formula given in Table 2 using optimized batch of solid dispersion (Drug: carrier ratio - 1:5). Various superdisintegrants with concentration of 5%, were used such as Sodium starch glycolate, croscarmellose sodium and crospovidone. All the required materials were passed through sieve No. 60 and mixed homogeneously for 15 min. Finally, Magnesium stearate and aerosil were added and mixed for 1 min. This blend was compressed using 8 mm size flat faced punch on rotary compression machine.

Mannitol improves patient compliance by imparting cool sensation and mild sweet taste. It flows well and improves flow properties of other materials. Microcrystalline cellulose act as a diluent as well as also play a role of adsorbent and keeps solid dispersion in a dry and free flowing form as PVP K-30 is a very hygroscopic material which can affect the flow property of tablet formulation. Aspartame was used as sweetener. It is an enhanced flavor system and also used as taste masking agent. The approximate sweetening power is 180-200 times to that sucrose. Aerosil was used as glidant and magnesium stearate as lubricant [9].

Evaluation of prepared tablets

Thickness

It was determined by using digital vernier caliper. It is expressed in mm.

Hardness

The hardness of the tablets was determined using Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). It is expressed in kg/cm^2.

Friability

Friability of the tablets was determined using Roche friabilator. It is expressed in %[10]. Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

Weight variation

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. To study weight variation, 20 tablets from each formulation were weighed and the test was performed according to the official method[11].

Uniformity of content

Drug content from the tablets was determined by taking tablets from each formulation. Twenty tablets from each formulation were accurately weighed and powdered. Powder equivalent to 10 mg of drug was weighed and added into 100 ml volumetric flask. Then it was dissolved in 10 ml acetonitrile. The volume of solution was made to 100 ml (100 ìg/ml). From this solution 1 ml was withdrawn and added into 10 ml volumetric flask and finally volume was made to 10 ml with phosphate buffer pH 6.8 (10 □g/ml), then solution was filtered with Whatman filter paper No. 41 and absorbance of the resulting solution was measured at 253 nm using UV spectrophotometer.

Disintegration time

The disintegration time for all formulations was carried out using a tablet disintegration test apparatus (Electrolab, Mumbai). Tablets were placed individually in each tube of the disintegration test apparatus. The water was maintained upto 900 ml at a temperature of 37±5^{0}C and the time taken for the entire tablet to disintegrate completely was noted.

***In vitro* dissolution study of prepared tablet**

In vitro dissolution study of mouth dissolving tablet was conducted using USP dissolution apparatus II at 50 rpm, using 900 ml phosphate buffer pH 6.8 as a dissolution media maintaining at 37 ± 0.5^{0}C. 10 ml sample were withdrawn at time intervals of 1, 2, 4, 6 upto 16 min. and filtered through a 45µm filter paper, diluted and assayed at 253 nm using UV/ Vis double beam spectrometer. The volume of dissolution fluid was adjusted to 900 ml by replacing each 10 ml aliquot withdrawn with 10 ml of phosphate buffer.

Statistical analysis

One way ANOVA with Students Paired't' test was applied to compare the dissolution rate of pure olanzapine with its solid dispersion. Simplex lattice design[4] was adopted to optimize the formulation variables. In this design, three factors were evaluated by changing their concentrations simultaneously and keeping their total conc. constant.

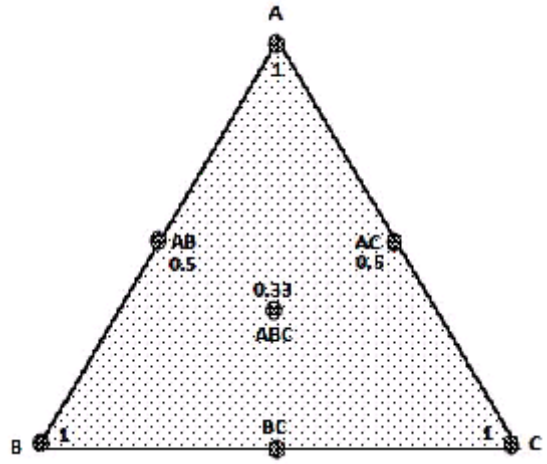

Fig. 1: *Schematic presentation of simplex lattice design*

A, B, C: Represents maximum amount of component A, B and C, respectively in formulation. AB, BC, AC: Represents equal amount of components A and B, B and C, A and C, respectively in formulation. ABC: Represents equal amount of component A, B, C in formulation

The simplex lattice design for three component system is represented by an equilateral triangle (Figure 1) in two dimensional spaces. Seven batches (O1 to O7) were prepared, one at each vertex (A, B, C), one at half way between vertices (AB, BC, AC) and one at the centre point (ABC). Each vertex represents, a formulation containing the maximum amount of one component, with the other two components at a minimum level. The half way between the two vertices represents, a formulation containing the average of the minimum and maximum amount of the two ingredients represented by two vertices. The centre point represents, a formulation containing one third of each ingredient. Croscarmellose sodium (X1), Crospovidone (X2), Sodium starch glycolate (X3) are independent variable and disintegration time and T_{50} (Time required to 50% drug release) taken as responses.

RESULTS AND DISCUSSION

a) Drug content estimation:

The drug content of solid dispersions was found to be in the range of ±5 % of the theoretical amount indicating the acceptability of method for preparation of solid dispersion.

b) Saturation solubility studies:

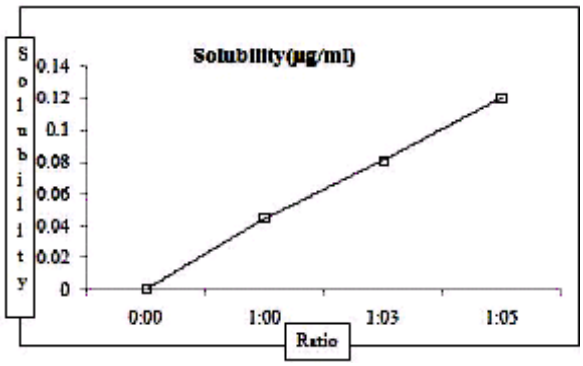

Fig. 2 : Saturation solubility studies

To study the effect of PVP k-30 in solubility improvement of pure drug, saturation solubility study was carried out with solid dispersions of different ratio in distilled water. The effect of PVP k-30 concentration upon the solubility of olanzapine is presented in Figure 2. The increase in solubility was linear with respect to the increment in weight fraction of the carrier. The solubility of drug was increased > 2.5 fold up to 1:5 drug : carrier ratio as compared to pure drug.

***In-vitro* dissolution study of solid dispersions**

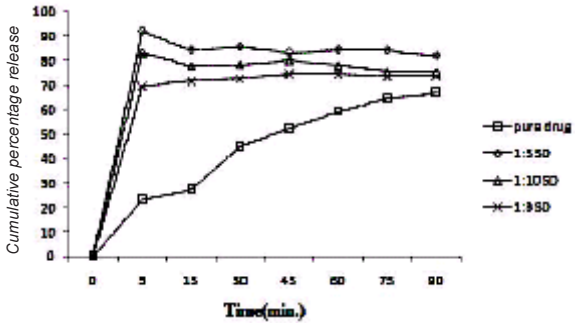

Fig.3 : *In-vitro* release profile of olanzapine from solid dispersion

The dissolution rate of olanzapine from various solid dispersions was studied and it was found that dissolution of olanzapine from all the solid dispersions was rapid and more than the pure drug. The rate of dissolution increases as concentration of PVP K-30 increases in solid dispersion upto 1:5 drug : carrier ratio (p = 0.005). Further improvement in concentration of PVP K-30 did not enhance the dissolution rate (Figure 3). This might be due to viscous boundary layer formed by PVP K-30 in higher amount surround drug particles which retard the drug release. The initial high drug release is observed at the 5 min. time point, and gets reduced at subsequent time points. This behavior is typical of a carrier effect which brings temporary supersaturation followed by the reprecipitation of part of the drug. Probably the initial rapid flux of the drug from the solid dispersion particles to the dissolution medium resulted in a high concentration, which got reduced with time. Slow dissolution was observed subsequently till the equilibrium concentration was reached.

a) Differential scanning calorimetry (DSC)

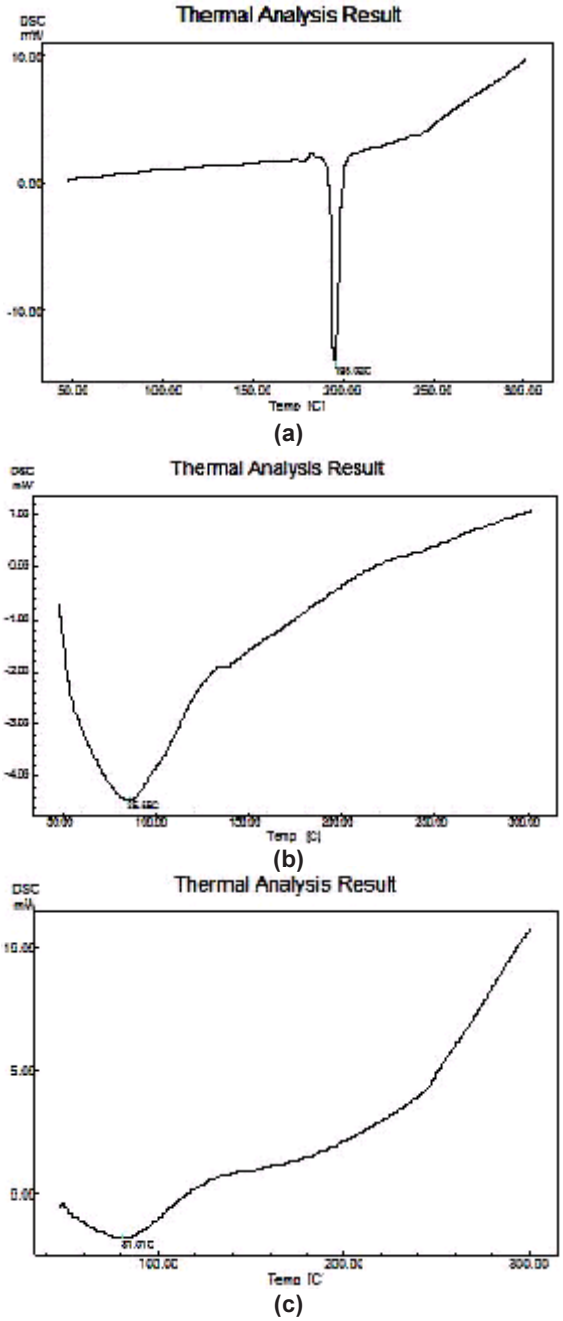

Fig. 4: DSC spectra: (a) olanzapine, (b) PVP K-30 and (c) Solid dispersion(1:5)

Supporting evidence for solid dispersion formation was also obtained from DSC studies. The DSC thermograms [Figure 4(a),(b),(c)], shows endothermic peak of olanzapine at 195.02°, which corresponds to its melting point, while PVP k-30 exhibited a typical broad endothermic peak at 85.56°. The disappearance or shifting of endothermic or exothermic peaks of drugs is mostly an indication of formation of solid dispersion which is observed in thermogram of solid dispersion where endothermic peak of olanzapine is completely absent. These observations clearly indicate strong evidences of dispersion of drug in carrier material; this would have assisted in increasing the release rate from the tested samples.

Evaluation of Mouth dissolving tablet

Table 3: Evaluation of Tablet Parameters

Batch	O1	O2	O3	O4	O5	O6	O7
Thickness* (mm)	3.23 ±0.42	3.13 ±0.74	3.26 ±0.64	3.34 ±0.9	3.14 ±0.25	3.04 ±0.43	3.25 ±0.50
Hardness* (kg/cm²)	2.59 ±0.21	2.51 ±0.32	2.56 ±0.29	2.73 ±0.34	2.78 ±0.25	2.67 ±0.10	2.71 ±0.43
Friability* (%)	0.82	0.87	0.85	0.79	0.78	0.76	0.80
Wt. variation* (%)	1.34 ±0.63	1.98 ±0.21	1.44 ±0.36	1.57 ±0.63	1.51 ±0.30	1.46 ±0.59	1.62 ±0.23
Content Uniformity*(%)	97.53 ±0.23	98.34 ±0.21	98.52 ±0.33	98.22 ±0.10	97.17 ±0.39	99.37 ±0.52	98.39 ±0.49
DT# (s)	44 ±0.3	57 ±0.4	182 ± 0.6	51 ±0.7	69 ±0.5	153 ±0.6	92 ±0.7

*O1 to O7 represents the various tablet formulations of olanzapine. *Each value represents a mean of 10 determinations. #Each value represents a mean of 20 determinations. $Each value represents a mean of 3 determinations*

All the prepared tablets showed acceptable pharmaceutical properties (Table 3). The hardness values of formulations were within the range of 2-3 kg/cm^2. Friability values of all formulations were less than 1% was an indication of good mechanical resistance of the tablets. In determinations of tablet weights, according to the IP less than 7.5% weight variation is acceptable in the tablet formulation having average weight between 80-250. All formulations were found to be within IP limits as per weight variation test. The uniformity of content was found within pharmacopoeial limits of 90-110%. All the batches have disintegration time within official limit of less than 3 mins. From all the batches evaluated formulation containing crosscarmellose sodium alone (5%) produced the best results as it shown minimum disintegration time.

In vitro dissolution study of prepared tablets

From the dissolution profile of all the batches (Figure 5) it was found that there was a fast drug release at initial state of dissolution. The initial rise in the drug release was dependent upon the effectivity and concentration of superdisintegrant. The bursting effect of superdisintegrant showed rise (shoot) in the drug release. From this study it was reported that decrease in the disintegration time showed faster drug release.

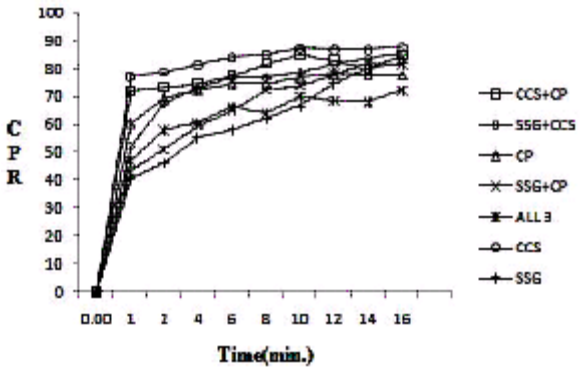

Fig. 5 : Dissolution profile of all batches
CPR : Cumulative percentage release

The batch containing 5% croscarmellose sodium alone shown fastest drug release as it had least disintegration time.

Selection of optimized batch

Table 4 : Selection of Optimized Batch

Batch	Disint. Time# (s)	T_{50} *,# (s)	Q10 ** (%)
O1	44	40	89
O2	57	47	76
O3	182	160	68
O4	51	43	86
O5	69	57	75
O6	153	110	70
O7	92	69	71

**T_{50}: Time required to release 50% of drug*
***Q10: Percentage of drug released in 10 min*
#Dependable variable

From all important evaluation parameters and results of dependable variables (Table 4), it was found that the batch containing 5% croscarmellose sodium alone shown minimum disintegration. As well as from dissolution profile it was concluded that the same batch had least T_{50} value (40 s) and maximum Q10 (percentage of drug released in 10 min.) value (89 %). So, batch O1 finalized as optimum batch amongst all the batches prepared and evaluated.

CONCLUSION

In the present investigation, solid dispersions has been prepared with PVP k-30 using different drug: carrier ratio (1:3, 1:5 and 1:10) and it was found that PVP K-30 improves solubility upto 1:5 drug:carrier ratio. Further improvement in PVP K-30 quantity did not significantly improve the solubility.

After that on a way to design proper dosage form of prepared solid dispersion having most patient compliance, mouth dissolving tablet was formulated. Now, to evaluate that whether in combination superdisintegrants can give far better results or not,

simplex lattice design has been applied and more seven batches has been prepared in combination of all three superdisintegrants and on the basis of different evaluation parameters optimized batch has been selected. Based on the results of different dependent variables it was finalized that batch O1 containing croscarmelose sodium alone proved as an optimized batch and combination of superdisintegrants did not significantly affect disintegration time as well as drug release from mouth dissolving tablet. Moreover, it is more preferable to produce desirable results with less no. of excipients for industrial applicability in terms of cost effectiveness. So, it was concluded that the method attempted here for development of mouth dissolving tablet of olanzapine using solid dispersion technique was simple, superior, reliable and effective in terms of cost and patient as well as industry compliance.

Further in future, different other methods for the improvement in solubility should be evaluated for poorly water soluble drugs and giving them desirable dosage form having good patient compliance.

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