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FORMULATION AND EVALUATION OF OLANZAPINE LIQUISOLID COMPACT TABLETS

J.Ramesh*[1], B.Vijaya kumar[2], Y.Narasimha Reddy[3]
[1]Research Scholar Jawaharlal Nehru Technological University Kakinada, Kakinada, A.P. India.
[2]Jangaon Institute of Pharmaceutical Sciences, Jangaon, Warangal Dist, Telangana, India
[3]University College of Pharmaceutical Sciences, Warangal Dist, Telangana, India,
Email:rameshjadhav73@gmail.com

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Abstract

The main objective of the present study is to increase the solubility of olanzapine by using liquisolid compact technique. Liquisolid compacts were prepared by using a mathematical model to calculate required quantity of carrier, coating material to produce acceptable flowable, compressible admixture. In the present study peg-400 is selected as solvent. Avicel, aerosil were selected as carrier, coating material. Carrier coating ratios were taken as 3:1, 5:1, 7:1. Sodium starch glycolate, cross povidone and cross carmellose sodium were used as super disintegrants. Liquisolid compacts were subjected to precompression evaluation compressed tablets were subjected to post compression evaluation. FTIR studies showed that no interaction is occured between drug and other excipients. X -Ray diffraction studies prove that olanzapine is converted from crystalline form to amorphous form. From this study it concluded that liquisolid compact method used to enhance solubility of olanzapine.

Key Words: liquisolid compact, loading factor, carrier material, coating material.

Introduction

Low aqueous solubility of a drug is a technical challenge to converting it into suitable formulation for its better therapeutic action. Recently more than 40% of new drugs were developed in pharmaceutical industry were practically not soluble in water[1]. Drugs which are low in water shows slow release rate due to their limited solubility in gastro intestinal tract. For these drugs rate determining step in drug absorption is dissolution. So many techniques are proposed to increase dissolution of poor water soluble drugs like, solid dispersion, micronization, complexation, use of surfactant,

solid solution to improve the dissolution by reducing the crystalinity. Among these the most effective technique to increase dissolution is liquisolid compacts[2-7].

Liquisolid compact system refers to the converting the liquid drug, drug solution, drug suspension into dry, non adherent, free flowing and compressible form by mixing with carrier and coating material[8]. Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5] benzodiazepine) is a potential and most commonly used typical antipsychotic, for treatment of schizophrenia, acute mania in bipolar disorder, agitation associated with schizophrenia, and bipolar disorder[9-10]. The starting dose of OZ is a single evening dose of 10 mg and the usual maximum dose is 20 mg. It is practically insoluble in water and has only 60% oral bioavailability. Based upon individual patient characteristics dosage adjustments may be required.

Material and Method

Olanzapine was gifted by Natco laboratories Hyderabad, peg-400, avicel pH 102 and aerosil were purchased from E.Mecrk (India), cross povidone was purchased from SD fine chemicals (India).

Solubility study: The solubility study of olanzapine was carried out in different solvents by preparation of saturated solution in 0.1 N Hcl, 6.8 phosphate buffer and in peg-400. Excess amount of olanzapine was added to above solvents and shaking on shaker for 48 hrs at 25 ^{o}C. Then solutions were filtered and diluted with water and analyzed with uv-visible double beam spectrophotometer at 258 nm. (Elico SL 210)

Calculation Of Liquid Load Factor (L_f) Required Quantities Of Carrier (Q) And Coating (q) Materials: The formulation design was done by using mathematical model described by spires et al

In this study peg-400, avicel, aerosil were used as vehicle, carrier, coating material. The concentration of the drug solution were taken as 13%, 18% w/w, and carrier coating ratios were taken as 3:1, 5:1, 7:1.

Ratio of carrier and coating material was calculated by:

$$R = Q/q$$

Where Q is amount of carrier, q is amount of coating material.

Loading factor was determined by adding carrier material to drug solution until it produce good flow property and compressibility.

$$Lf = W/Q$$

Where W is weight of liquid medication, Q is weight of carrier material.

Loading factor was also calculated by using Φ-values of carrier, coating material and by using R value.

$$Lf = \Phi + \Phi\ (1/R)$$

Once, liquid loading factor was obtained, the appropriate quantities of carrier (Q) and coating (q) material required were calculated using following equations,

$$Q = W/Lf$$

$$q = Q/R$$

Preparation of liquisolid compacts:

Calculated amount of olanzapine is taken in a motor to this accurate amount of peg-400 is added and then mixed well. To this liquid medication add calculated amount of carrier material with continuous stirring until it produce wet mass. Then add coating material to the wet mass with gentle mixing. Finally add all other ingredient as given in table 1. The blended bulk was compressed as tablet by compression machiene[11].

Table 1: Formulation of liquisolid compacts.

	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Liquid medicament	13	13	13	18	18	18	13	13	13
Olanzapine	20	20	20	20	20	20	20	20	20
Peg-400	168	168	168	123	123	123	168	168	168
Avicel	205	343	480	150	251	351	480	480	480
Aerosil	68	69	69	50	50	50	69	69	69
Sodium starch glycolate	0	0	0	0	0	0	60	0	0
Cross povidone	0	0	0	0	0	0	0	60	0
Sodium cross carmellose	0	0	0	0	0	0	0	0	60

Total weight	461	600	737	343	444	544	797	797	797
R	3	5	7	3	5	7	7	7	7
Loading factor	0.82	0.49	0.35	0.82	0.49	0.35	0.35	0.35	0.35

Pre compression studies:

Infra red spectra analysis:

The infra red spectra studies were conducted on pure drug and physical mixture of liquid solid formulation. In this method KBr pellet technique was used. A base line correction was taken by using dried potassium bromide and then the spectrum of the pure olanzapine, liquid solid system was obtained.

X-Ray Powder diffraction (XRD) studies: X-ray powder diffraction studies were conducted to pure olanzapine, liquid solid compact physical mixture. These samples were exposed to Cu-K_α radiation at a scan rate of 1.5^0/ min over the 2θ range of 4-40^0C.

Flow property: Flow property of liquisolid compact physical mixture was evaluated by angle of repose, compressibility index and by hausner's ratio[12].

Post compression evaluation: Hardness: hardness of the tablet was determined by Monsanto hardness tester. It is expressed in Kg/cm^2.

Friability: friability was determined by roche friabilator. 20 tablets taken randomly and placed in roche friabilator after 100 revolutions friability was calculated by the following equation[13].

F= (1-Wo/W) 100

Wo = weight of the tablet before the test

W = weight of the tablet after the test

Disintegration time: disintegration time was determined by the using of disintegrating apparatus. 0.1 N Hcl is used as disintegrating medium. A tablet was placed in to each of the six tubes of the apparatus and one disk was added to each tube. The time was recorded after completion of the disintegration of the tablets. Dissolution: Drug release studies were conducted by using USP dissolution paddle apparatus. 900 ml of 0.1 N Hcl was taken as dissolution medium with rotation speed of 50 rpm. Temperature was maintained at 37^0 C ± 0.5 ^{0}C. at specific time intervals 5ml samples were withdrawn and at the same time 5ml of fresh solvent is added to dissolution medium to maintain sink condition. The

samples were analyzed by UV visible double beam spectrophotometer. The dissolution of the drug was expressed as percentage drug release.

Result and Discussion

Solubility study: solubility studies were conducted to decide which solvent is suitable for olanzapine. From the results (table 2) it is conformed that peg-400 is suitable for olanzapine because 132 mg olanzapine soluble in 1 ml of peg-400.

Table 2: solubility of olanzapine in different solvents.

Solvent	Solubility (mg/ml)
Peg-400	132
0.1 N Hcl	0.37
6.8 Phosphate buffer	0.16

Pre compression studies:

Infra red spectra analysis: Figure 1 shown olanzapine characteristic peak of NH stretching at 3237.25 cm^{-1}, CH stretching at 2927.62 cm^{-1}, C=C stretching at 1586.95 cm^{-1}, C=N stretching at 1419.32 cm^{-1} and C-N stretching at 1286.11 cm^{-1}. Figure 2 shown olanzapine liquisolid compact mixture character peaks from the results it observed that slight deviation occur in characteristic peaks which are in acceptable limit. So it is concluded that there is no interaction occur between olanzapine and other ingredients.

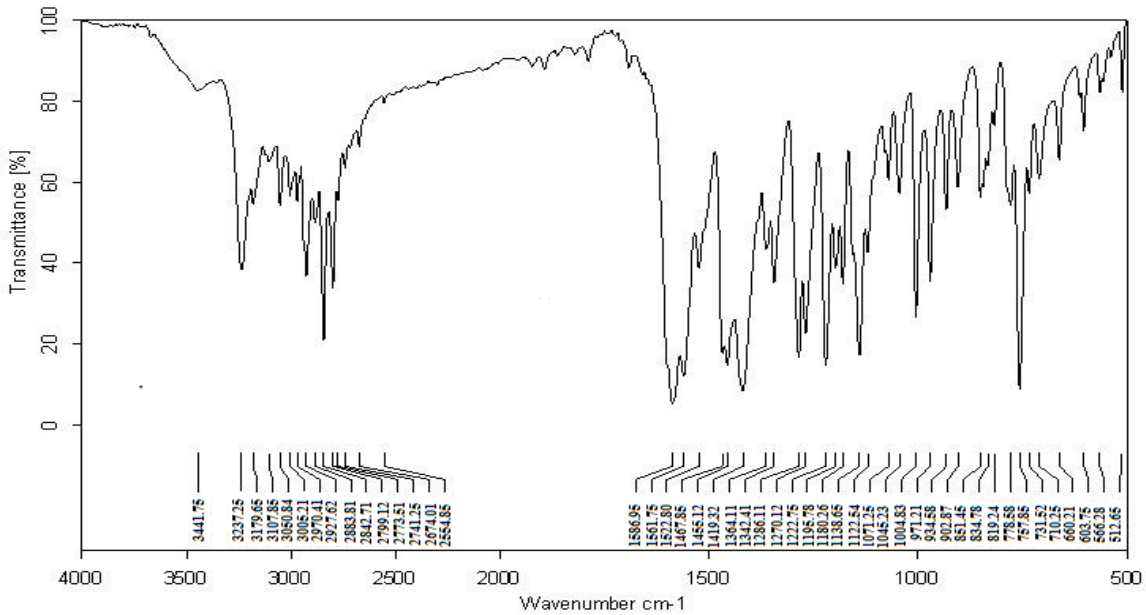

Figure 1: FTIR spectra of olanzapine.

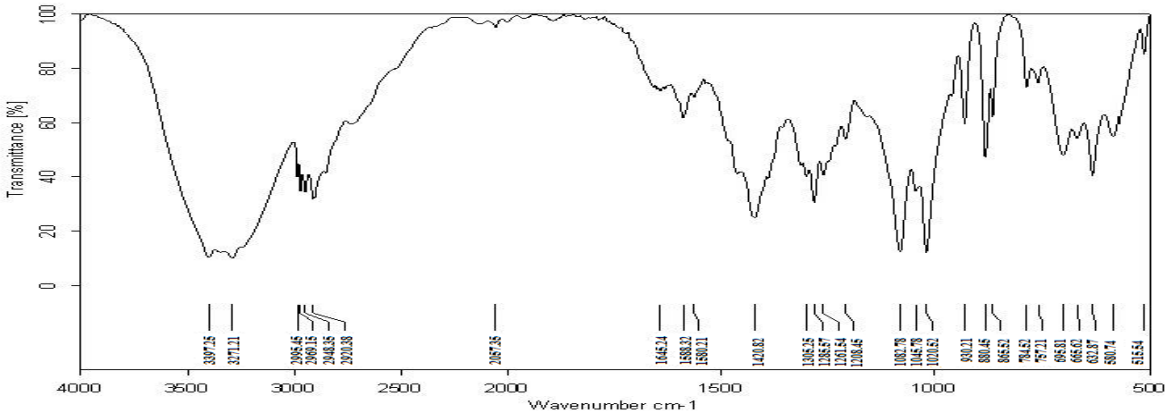

Figure 2: FTIR spectra of olanzapine liquisolid mixture.

XRD studies: XRD studies were used to determine crystalinity nature of the compound. Figure 3 shown X Ray diffraction pattern of olanzapine sharp peak at 8, 10, 12, 16 while liquisolid compact powder (Figure 5) shown sharp peak at 18 and 22. The absence of characteristic peak indicates drug converted from crystalline form to amorphous form.

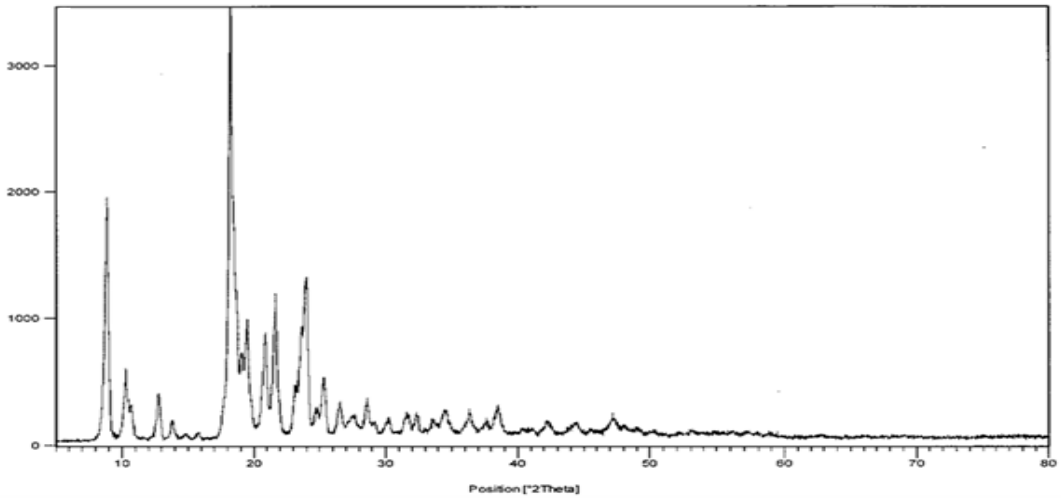

Figure 3: XRD spectra of olanzapine.

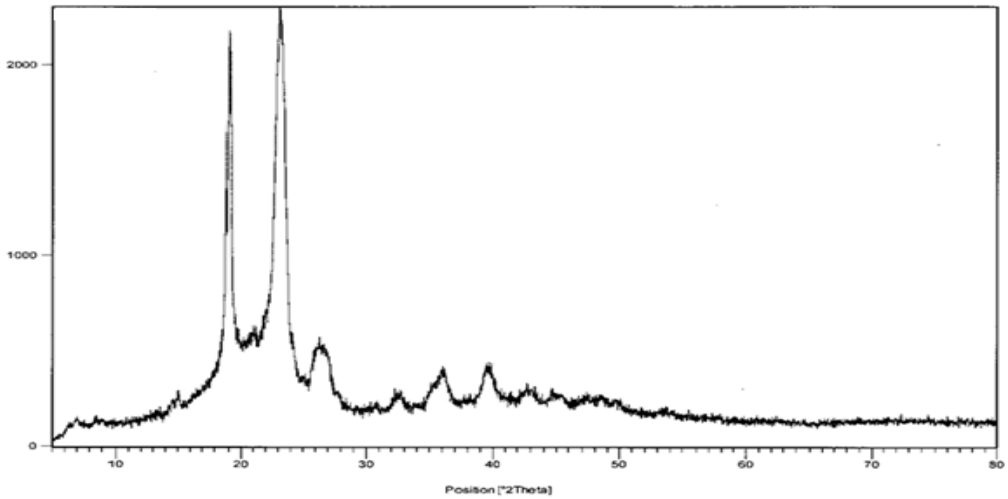

Figure 4: XRD spectra of avicel.

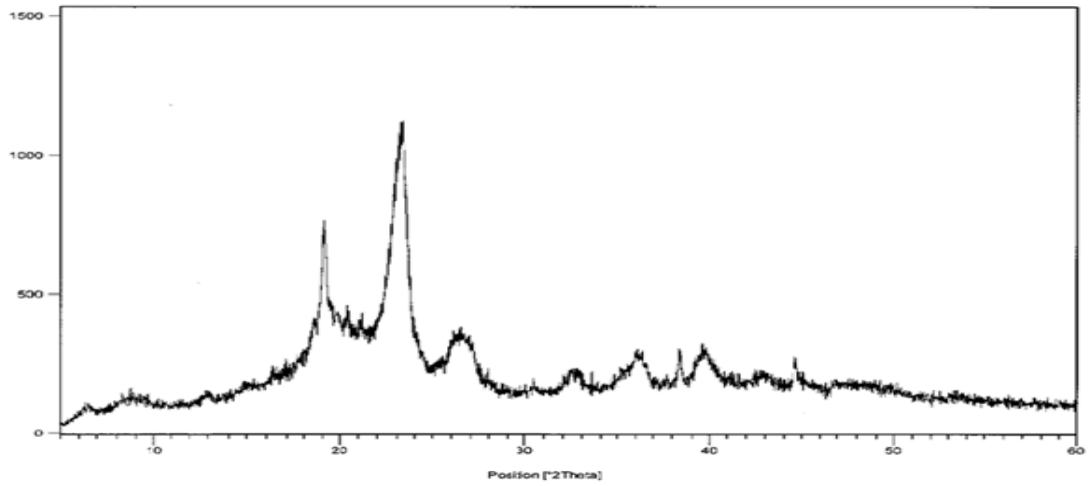

Figure 5: XRD spectra of olanzapine liquisolid compact mixture.

Flow property: physical mixture of liquisolid compact was subjected to angle of repose, Carr's index, and hausner's ratio. Results were given in the table 3. All the formulation showed angle of repose < 30^0 it indicates all the formulations shown good flow property. And results of Carr's index and hausner's ratio were proved all formulations shown good flow property.

Table 3: Flow property of liquisolid powder

	Angle of repose (θ)	Carr's index	Hausner's ratio
F1	25	15.60	1.18
F2	25	10.04	1.11
F3	30	9.12	1.10
F4	28	13.15	1.15
F5	19	10.80	1.12
F6	19	14.52	1.17
F7	28	12.81	1.15
F8	27	13.68	1.16
F9	30	17.01	1.20

Post compression evaluation: Prepared tablets were evaluated for the hardness, friability, disintegration time and assay. Results were shown in table 4. Hardness of all formulation was in the range of 4.3±0.2 to 4.5±0.2. All the formulation

had better hardness because on compression avicel molecules undergo plastic deformation and forms hydrogen bonding. Friability of all formulation was < 1%. It indicates all the formulation shown good mechanical strength. Disintegration time of all formulation showed lass than 2min due to the presence of avicel. Avicel is function as swellable disintegrant. In addition avicel has hydrophilic in nature it increases wetting of olanzapine this lead to tablet to be disintegrated quickly and decreases the disintegration time of the tablet. Super disintegrating agents also play a role in the decreasing disintegrating time of tablets. From the results it is concluded that cross povidone shown good disintegrating property than other disintegrants.

The drug content of liquisolid compact tablets was found to be in the range of 96.4±1.2 to 99.6±1.4 which is acceptable in limit.

Table 4: post compression evaluation.

	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (sec)	Assay (%)
F1	4.1±0.1	0.5	83±6.4	98.1±1.0
F2	4.2±0.3	0.3	71±3.6	97.2±1.9
F3	5.1±0.1	0.3	61±1.0	99.6±1.4
F4	4.4±0.2	0.6	90±2.0	96.9±0.9
F5	4.4±0.4	0.3	85±1.5	97.5±1.3
F6	4.5±0.2	0.6	73±2.0	96.4±1.2
F7	4.4±0.1	0.4	56±1.2	99.4±0.4
F8	4.3±0.2	0.4	51±1.0	98.0±1.7
F9	4.4±0.3	0.5	54±1.2	98.0±2.6

Dissolution: Drug release profiles of all formulation were shown in figure 6 and 7.

From the results it is observed that percent of olanzapine release from formulation F1-F3 was found to be in the range of 93% -101% in 60 min. From formulation F4-F6 % drug release was found to be in the range of 64%-73%. From the result it is concluded that concentration of drug in liquid medication is an important factor in drug release. F1-F3 formulation shown higher drug release than (contains 13% drug) F4-F6 formulation (contains 18% drug).

From the results it is observed that powder excipient ratio (R) also influence on dissolution. From the results it is concluded that drug release is direct relationship with powder excipient ratio (R). Formulation which has R value 7 showed better drug release than formulation which contain R value 5, the later shown better drug release than formulation which have R value 3.

Type of disintegrant also showed affect on dissolution (figure 7). F8 formulation contains cross povidone as disintegrants shown 101% drug release in 30 min. so F8 formulation is proved as best formulation.

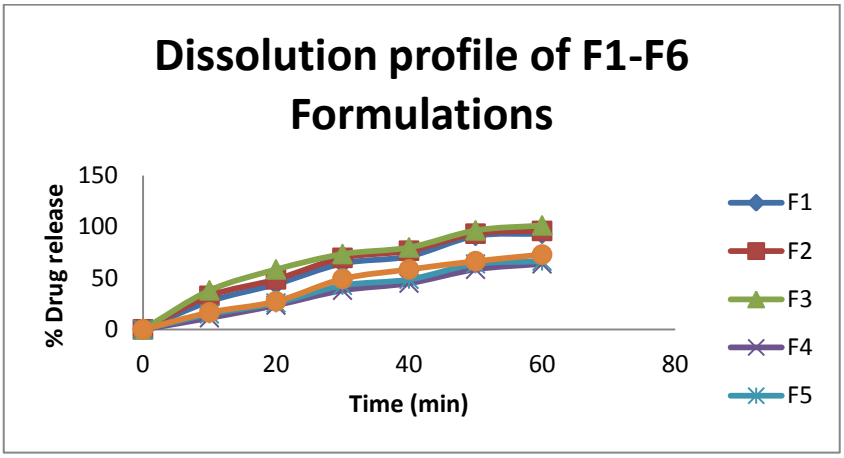

Figure 6: Dissolution Profile of F1 to F6 Formulations.

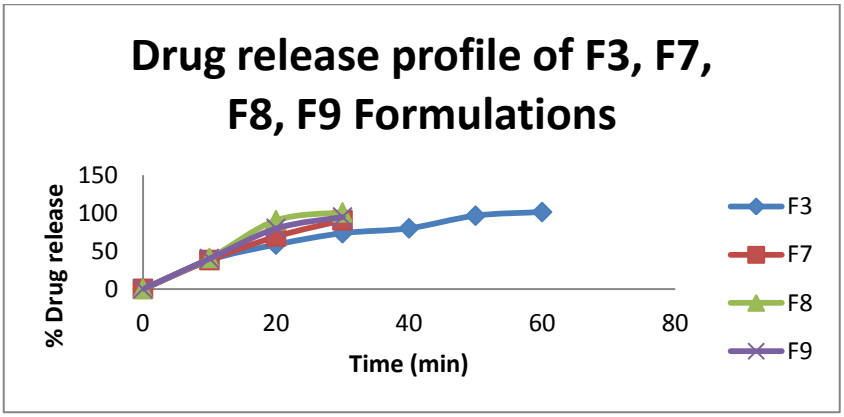

Figure 7: Dissolution profile of F3, F7, F8, F9 Formulations.

Conclusion

Solubility and drug release of poorly soluble drug olanzapine is enhanced by the liquisolid compact technique. In this study F8 formulation proved as best formulation it contains peg-400 as solvent and cross povidone as super disintegrant. The result of XRD showed that crystalline property of olanzapine is converted into amorphous form, and FTIR study showed that there is no interaction occurs between olanzapine and other ingredients. So it concluded that liquisolid compact technique is the best method to increase the solubility of olanzapine.

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Corresponding Author:

J.Ramesh*,

Email:*rameshjadhav73@gmail.com*