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Sravan Kumar Aligeti
Research Scholar, Department of Pharmaceutics, JNTUK, Kakinada, Andhra Pradesh, India

Veerareddy Prabhakar Reddy
Palamuru University, Mahabubnagar, Telangana, India

G Girija Sastri
Andhra University, Vishakhapatnam, Andhra Pradesh, India

Corresponding Author
Sravan Kumar Aligeti,
Research Scholar, Department of Pharmaceutics, JNTUK, Kakinada, Andhra Pradesh, India

A novel solubility enhancement approach of poorly soluble drug: Ziprasidone by liquid compacts

Sravan Kumar Aligeti, Veerareddy Prabhakar Reddy and G Girija Sastri

Abstract
Liquisolid system refers to the formulations that are formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, non adherent, free flowing and compressible powder mixture by blending with suitable carrier and coating materials. Hence the dissolution step, a pre-requisite for drug absorption, is by passed and better bioavailability of poorly soluble drug is achieved. The purpose of this study is to develop novel a liquisolid technique to enhance the dissolution rate of poorly water soluble drug Ziprasidone. The main components of a liquisolid system are a non-volatile solvent, carrier and coating materials and a disintegrant. F5 of Ziprasidone was showing 99.6% release hence it was considered as optimized formula, F5 formulation having 50% drug concentration in Cremophore, with R value 25 and Lf value 0.312 was showing 99.6% release. Hence it can be appealed for further research of Ziprasidone.

Keywords: Ziprasidone, liquisolid compacts, coating material

Introduction
Many techniques are being employed for the solubility enhancement of poorly soluble drugs to resolve the bioavailability issue due to inadequate dissolution rate. Various approaches make use of hydrophilic polymers as solubility enhancers acting through a variety of mechanisms such as amorphization, co-solvency, and micelle formation or inclusion complexes. These techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, glass solutions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics. Due to this set-back, industrial feasibility of the final dosage form becomes very difficult. The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation. With the liquisolid technology as described and patented by Spireas, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients. Three major components in the formulation of liquisolid compacts are liquid medication, carrier and coat material. Other excipients such as use of disintegrant or release retarding polymers for modification of release profile are used as per the objective and need of the formulation. The first component i.e. liquid medication can either be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles. Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols or glycerin are best suitable as „liquid vehicle". The solubilization of the drug in a non-volatile solvent keeps the drug in uniformly and molecularly dispersed form. This creates opportunity to enhance the drug release. The liquid medication is incorporated into the second component of the system i.e. the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the third component i.e. coat materials. Thus, an apparently dry, free flowing and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material. The third component i.e. coat material avoids the re-aggregation of the liquisolid particles and imparts higher flow characteristics. The coating also assists the drylooking character of the system. Many times, amorphous silicon dioxide (colloidal silica) is used as coating material. Liquisolid formulation containing a drug solution or drug suspension of poorly soluble drugs in a solubilizing vehicle shows enhanced drug

release due to increased surface area of drug available for release, increased aqueous solubility of the drug by co-solvency and improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability [1].

Drug Profile

Drug name: Ziprasidone

Solubility: soluyble in foirmic acid insolubole in methanol and n-hexane

Physical state: light pink to pink colour powder

Melting point: >300 °C

C**AS NO:** 146939-27-7

Molecular formula: $C_{21}H_{21}ClN_4OS$

Molecular weight: Average:412.936,

Monoiso topic: 412.112459711

Bioavailability: The systemic bioavailability of ziprasidone is 100% when administered intramuscularly and 60% when administered orally with food.

Half-life:7 hours

Protein binding: 99%

Dose: 20,40,60, 80mg

Category: Antipsychotic Agents

Pharmacology: Ziprasidone's affinities for most of the dopamine and serotonin receptors and the α_1-adrenergic receptor are high and its affinity for the histamine H_1 receptor is moderate. It also displays some inhibition of synaptic reuptake of serotonin and norepinephrine, though notdopamine.

Ziprasidone's efficacy in treating the positive symptoms of schizophrenia is believed to be mediated primarily via antagonism of the dopamine receptors, specifically D_2. Blockade of the 5-HT_{2A} receptor may also play a role in its effectiveness against positive symptoms, though the significance of this property in antipsychotic drugs is still debated among researchers. Blockade of 5-HT_{2A} and 5-HT_{2C} and activation of 5-HT_{1A} as well as inhibition of the reuptake of serotonin and norepinephrine may all contribute to its ability to alleviate negative symptoms. The relatively weak antagonistic actions of ziprasidone on the α_1-adrenergic and H_1 receptors likely in part explain some of its side effects, such as sedation and orthostatic hypotension. Unlike many other antipsychotics, ziprasidone has no significant affinity for the mACh receptors, and as such lacks any anticholinergic side effects.

Pharmacokinetic Properties

Absorption: Ziprasidone absorption is optimally achieved when administered with food. Without a meal preceding dose, the bioavailability of the drug is reduced by approximately 50%

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and a1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Excretion: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Mechanism of Action

Ziprasidone's antipsychotic activity is likely due to a combination of its antagonistic function at D2 receptors in the mesolimbic pathways and at 5HT2A receptors in the frontal cortex. Alleviation of positive symptoms is due to antagonism at D2 receptors while relief of negative symptoms are due to 5HT2A antagonism.

Adverse Effects

Hypersalivation,Respiratorydisorders,Nausea,Vomiting,Drymouth,Constipation,Dyspepsia,Dizziness,Tremor,Dystonia,Akathisia,Parkinsonism,Musclerigidity,Rash,TachycardiaOrthostatic hypotension, Diarrhea, Anorexia, Myalgia Rhinitis, Cough, Anxiety, Abnormal vision, Spasmodic movement.

Storage: store at 15-20 ^{0}C keep out of childrens reach [2].

Materials and Methods

Methodology of Ziprasidone

Preparation of standard calibration curve

Determination of λ max

Ziprasidone (10mg) was weighed accurately and transferred in 10 ml volumetric flask. It was dissolved in methanol and filtered it. Then filtered solution diluted up to mark with phosphate buffer (pH 7.4). The final solution contained 1000 µg of Ziprasidone per ml of the solution. The solution (1ml) was diluted further to 10 ml with the same solvent methanol. The final solution contained 100 µg of Ziprasidone per ml of the solution as a stock solution. The resultant solution is scanned in the range of (200-400nm) by Ultra visible Spectrophotometer (UV-1700 Shimadzu corporation, Japan) to get absorption maximum (λ max).

Preparation of Calibration curve

From the above prepared stock solution, different concentration (10 to 80µg/ml) solutions are prepared using distilled water. The absorbances of these solutions are measured at λmax (260nm) by UV- spectrophotometer (UV-1700 Shimadzu Corporation, Japan). A standard curve is plotted using concentration on X axis and the absorbance

obtained on Y-axis.

Preformulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug-Excipients compatibility studies

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

Analytical method development

Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The χ maxwas found to be 260nm. Hence all further investigations were carried out at the same wavelength [3].

Preparation of standard graph in 0.1 N HCl

100 mg of Ziprasidone was dissolved in methanol 5 ml, volumetric flask make upto 100 ml of 0.1 N hydrochloric acid, from this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with 0.1 N HCl, from this secondary stock was taken separately and made up to 10 ml with 0.1 N hydrochloric acid, to produce 10, 20, 30, 40, 50, 60, 70, 80 µg/ml respectively. The absorbance was measured at 260 nm by using a UV spectophotometer.

Preformulation studies

Solubility studies

For the selection of best non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in five different non volatile solvents. Excess amount of pure drug was adding to the non volatile solvents. From this obtained saturation solution were shaking on the rotary shaker for 48 hours at 25 ^{0}C under constant vibration. After 48 hours period the saturated solution were filtered through a filter paper, and analyzed by UV spectrophotometer. The liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution is tremendously increased.

Calculation of loading factor (L_f)

Loading factors were calculated for different carriers, using various solvents. By using L_f = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder.

Formulation development

Preparation of liquid solid tablets

Preparation of drug solution

For the preparation of liquid solid compacts of Ziprasidone, a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquid solid powders containing Dimethylacetamide, Castor oil, Tween 80 as the liquid medicament, Avicel as carrier and Aerosil as the coating material is selected for the preparation of liquid solid compacts. Various ratios of carrier to coating materials are selected. According to solubility of Ziprasidone, desired quantities of drug and vehicle were accurately weighed in a beaker and then stirred with constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing

The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder.

In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles.

In the third stage, the powder was scraped off the mortar surfaces by means of aluminium spatula and then blended with a calculated quantity of disintegrant (5%) for another 30sec, in a manner similar to the one used in the first stage, producing the final liquid solid formulation to be compressed. The tablets were prepared by compressing the thoroughly mixed materials using 6 mm round, flat and plain punches on a 8 station tablet machine (Karnavathi India). The thickness of the tablet was 3.6mm [4].

Strategy 1

Using 10%, 20%, concentration of drug in vehicle, Aviel, Avicel as carrier material and with different carrier and coating material ratios batches were developed and evaluated.

Table 1: Composition of liquisolid tablets

Formulation	Ziprasidone (20mg) and dimethylacetamide	Ziprasidone (20mg) and Castor oil	Ziprasidone(20mg) and tween 80	Carrier: Coating Ratio R	Liquid Load factor L_f	Avicel (mg)	Aerosil (mg)	Super disintegrant (ssg)	Total tablet weight (mg)
F1	10%	-	-	20	0.171	100	50	5	197.17
F2	20%	-	-	20	0.171	110	50	5	209.17
F3	30%			20	0.171	120	50	5	221.17
F4	40%	-		20	0.171	130	50	5	233.17
F5	50%	-		20	0.171	140	50	5	245.17
F6		10%		20	0.171	100	50	5	197.17
F7		20%	-	20	0.171	110	50	5	209.17
F8		30%		20	0.171	120	50	5	221.17
F9		40%		20	0.171	130	50	5	233.17
F10		50%		20	0.171	140	50	5	245.17
F11			10%	20	0.171	100	50	5	197.17
F12			20%	20	0.171	110	50	5	209.17
F13			30%	20	0.171	120	50	5	221.17
F14			40%	20	0.171	130	50	5	233.17
F15			50%	20	0.171	140	50	5	245.17

Formulation	Ziprasidone(20mg) and DMSO	Ziprasidone (20mg) and Linseed oil	Ziprasidone(20mg) and Solutol hs 15	Carrier: Coating Ratio R	Liquid Load factor L_f	Avicel (mg)	Aerosil (mg)	Super disintegrant (ssg)	Total tablet weight (mg)
F16	10%	-	-	20	0.171	100	50	5	197.17
F17	20%	-	-	20	0.171	110	50		209.17
F18	30%			20	0.171	120	50	5	221.17
F19	40%	-		20	0.171	130	50	5	233.17
F20	50%	-		20	0.171	140	50	5	245.17
F21		10%		20	0.171	100	50	5	197.17
F22		20%	-	20	0.171	110	50	5	209.17
F23		30%		20	0.171	120	50	5	221.17
F24		40%		20	0.171	130	50	5	233.17
F25		50%		20	0.171	140	50	5	245.17
F26			10%	20	0.171	100	50	5	197.17
F27			20%	20	0.171	110	50	5	209.17
F28			30%	20	0.171	120	50	5	221.17
F29			40%	20	0.171	130	50	5	233.17
F30			50%	20	0.171	140	50	5	245.17

Evaluation of liquisolid tablets

Pre compression parameters

Measurement of Micromeritic Properties of Powders

Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$\tan \theta = h/r$ …… (1)Where, h and r are the height and radius of the powder cone.

Bulk density

The power sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 …….. (2)

M = Powder mass

V_0 = apparent unstirred volume

Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are preceded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.

Tapped density=M/V_f ..... (3)

M =weight of sample power taken

V_f =tapped volume

Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 …….. (4)

Hausner's ratio
The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation. [58]
H = ρT / ρB Where ρT = tapped density, ρB = bulk density

Post compression parameters
Thickness
The thicknes of liquisolid tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Weight variation
Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate frm the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Friability
The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.
Percentage friability was calculated using the following equation.

$$\text{Friability} = ([\, w_O - w] / w_O) \times 100$$

Where; w_O = weight of the tablet at time zero before revolution.
w = weight of the tablet after 100 revolutions.

Assay
The content of drug in five randomly selected liquisolid tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in 0.1 N HCl by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 260 nm using UV sectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test
Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated [5-6].

***In vitro* dissolution test of Ziprasidone liquid solid tablets**
Drug release from Ziprasidone liquid solid tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were 0.1N HCl as the dissolution medium of quantity 900ml. The whole study is being carried out at a temperature of 37^0 C and at a speed of 50rpm.
5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20 mimutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer at 260nm. The concentrationwas calculated usingstandard calibration curve [7].

Powder x-ray diffraction studies
Powder X-ray diffraction pattern of Ziprasidone, Avicel PH102, Aerosil 200 and liquisolid formulation (Best formulation) are studied using X-ray diffractometer (XRD-462, Digaku, Japan) with CuKα radiation. Voltage and current are set 40 kV and 30 mA respectively. All pattern scanned over range 3-50o 2θ angle with a scan speed of 20/min

Assessment and comparison of drug dissolution rates
The dissolution rate Ziprasidone is the amount of drug (in µg) dissolved per minute by each tablet formulation during first 10 min is calculated by the following equation (Shashidher Burra *et al*., 2011 and Spireas *et al*., 1998)

$$DR = (M \times D)1000$$

Where,
M = Total amount of pure drug in each tablet (in µg)
D = Percentage of drug dissolved in the first 10 minutes

Selection and evaluation of best formulation
The best formulation is selected depending on the results obtained from solubility studies in various non-volatile liquid vehicles and *in vitro* release studies

a) Comparison with directly compressed tablets
The *invitro* release of best formulation is compared with directly compressed tablets are prepared by mixing all tablet excipients, except non-volatile liquid vehicle (Amal Ali Elkordy *et al*., 2012 and Spiro Spireas *et al*., 1998)

b) Infrared spectroscopic studies for best formulation
Liquisolid formulation (Best formulation) is subjected to infrared Spectroscopic studies as per the procedure already discussed in compatibility studies.

c) Differential Scanning Colorimetric (DSC) studies for best formulation
DSC was performed using Shimadzu differential scanning calorimeter Mettler, in order to assess the thermotropic properties and thermal behaviour of the pure drug, and the liquisolid formulation (Best formulation). About 5 mg of the sample were sealed in the aluminium pans and heated at the rate of 10 °C/min, covering a temperature range of 30 °C to 300 °C. (*Jabbar et al.* 2013)

d) Release Kinetics Studies
1. Zero – order model
Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation: Qt = Q0 + K0t
Where, Qt is the amount of drug dissolved in time t,
Q0 is the initial amount of drug in the solution,
K0 is the zero order release constant and
"t" is time in hours.
Expressed in units of concentration/time.

Graph: X- axis is time in hours and Y- axis is% cumulative drug release.

2. First order model

The release of the drug which followed first order kinetics can be expressed by the equation:

observed in final formulation, which indicates that the pioglitazone was molecularly dispersed and in an amorphous form (Sanjeev Gubbi *et al*., 2009 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013)

log Qt = log Q0 + Kt / 2.303

Where, Q0 is the initial concentration of drug,

Qt is cumulative amount of drug released per unit surface area,

k is the first order rate constant and "t" is the time.

Graph: X- axis is time in hours and Y- axis is log% cumulative drug release.

3. Hixon Crowell model

Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. The equation describes the release from systems where there is a change in surface area and diameter of particles. They derived the equation:

W01/3 - W1/3 = KHC *t

Where, W0 is the initial weight of particle,

W is the weight of particle, KHC is Hixon Crowell release rate constant and "t" is time.

4. Higuchi model

Higuchi model describes the drug release from several type of matrices initially conceived for planar systems, then extended to different geometrics and porous systems. It was derived by higuchi in 1961. For higuchi release kinetics equation Q = KH t 0.

Where, Q is amount of drug released per unit surface area of the dosage form

KH is Higuchi release rate constant and

"t" is time.

5. Korsmeyer – Peppas model

Koresmeyer derived a simple relationship which describes drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Koresmeyer – Peppas model equation, (Mt/M) = Km tn

where, Mt is amount of drug released at time t,M is total amount of drug in dosage form,Km is kinetic constant,n is diffusion and release exponent and t is time in hours.[8]

d) Stability studies

The best formulation of three batches is stored at 40° C ± 2°C and relative RH 75% ± 5% for two months. The best formulation is evaluated using dissolution test, drug content, physical appearance, hardness and thickness. The above tests of best formulations are compared with those of freshly prepared tablets [9].

***In-vivo* evaluation of liquisolid compacts of Ziprasidone**

Animal study

The study protocol (VAAGESWARI COLLEGE OF PHARMACY/IAEC/00/2019–2020) was prepared and approved by the Institutional Ethics Committee of (Reg. no.:VCP/COLOGY/007/3/2016).

Male Wistar albino rats weighing 250–300 g were obtained for study. These rats had free access to a normal standard diet and tap water. Animals were kept in these facilities for 1 week before the experiment and fasted overnight before the experiments, but were allowed water ad libitum. The rats were divided into three groups of six rats per group. Groups 1–3 were administered pure

Ziprasidone, triturated marketed Ziprasidone formulation, and optimized formulation of the liquisolid system, respectively, in suspension form. A dose equivalent to 10 mg/kg of Ziprasidone was administered orally to each of the animals. The oral suspension was prepared with 5% PEG and the dosing volume was 1ml for each animal. Blood samples were collected into anticoagulant-containing tubes from the right femoral artery at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 48 h following the administration of each drug. Plasma was separated after centrifugation of the blood sample at 3000 rpm for 15 min and stored at−20°C until analysis of Ziprasidone [10].

Sample extraction

Ziprasidone was extracted from the plasma sample by adding haloperidol 10 µg/mL) as the internal standard (IS), and 50 µl of 0.1NHCl to 50 µl of plasma and 6ml of diethyl ether was added to this mixture. Then, the mixture was vortex mixed for 4min and centrifuged for 15 min. The organic layer was separated and transferred into a clear tube and evaporated under a gentle stream of air at 35°C. The residue was reconstituted in 500 µl mobile phase and a 20 µl aliquot was injected into the HPLC system [11].

Analysis by the high-performance liquid chromatography method

The plasma samples were analyzed using a HPLC system (PU-2080; Jasco Inc., Hachioji, Tokyo, Japan). Fifty microliters of haloperidol (10µg/ml) was used as an IS. The UV detector (UV-2075) was set at 225 nm. An analytical column (Kromasil, AKzo Nobel India Ltd., Navi-Mumbai, Maharashtra, India; 100 C-

18; 10 µ, 300×4.0 mm2) was eluted with a mixture of a 20 mmol/l PBS (pH 3.4) and acetonitrile (60: 40, v/v) at a flow rate of 1.2 ml/min at 30°C [12-14].

Pharmacokinetic analysis

The pharmacokinetic parameters of Ziprasidone were estimated using the noncompartment method. The area under the plasma concentration–time curve

(AUC) was calculated using the linear trapezoidal method. Maximum plasma concentration (Cmax) and the time to reach the maximum plasma concentration (tmax) were read directly from the plasma concentration–time data. The terminal elimination rate constant (ke) was estimated from the slope of the terminal phase of the log plasma concentration–time points fitted by the method of least squares and then the terminal elimination half-life (t1/2) was calculated as 0.693/k. [15].

Statistical analysis

The data were presented as their mean±SD and for the *in-vivo* data the one-way analysis of variance, followed by a posteriori testing using the Dunnett correction. A P-value less than 0.05 was considered to be significant.

Results and Discussion

Ziprasidone

Preparation of standard calibration curve

The λmax of Ziprasidone was determined by scanning the

(10µg/ml) solution of drug in phosphate buffer Ph 7.4 by UV-spectrophotometer and it was found to be 260nm The absorbance of the solution (10-80 µg/ml) was measured in UV-spectrophotometer at 260 nm. The linear correlation coefficient was found to be γ = 0.9997. The results were shown in the calibration graph of Ziprasidone and λmax of Ziprasidone

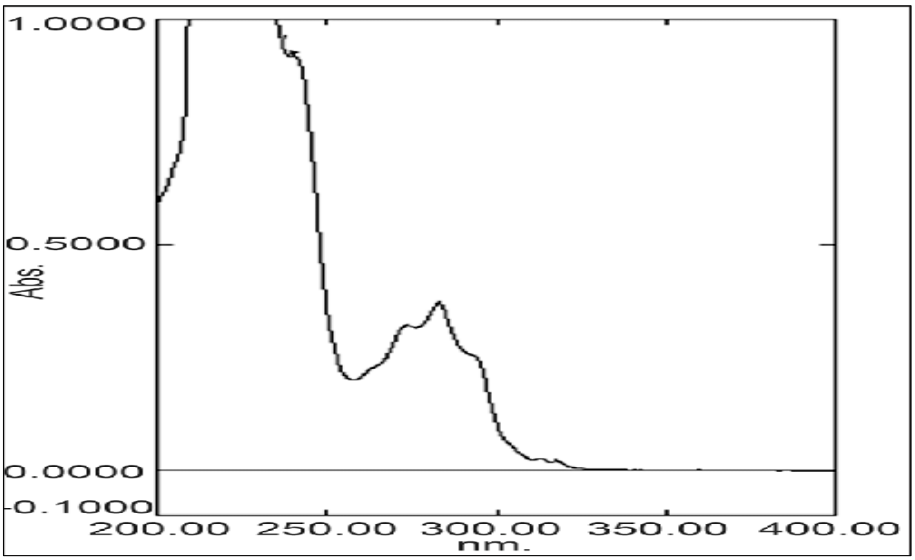

Fig 1: λmax of Ziprasidone

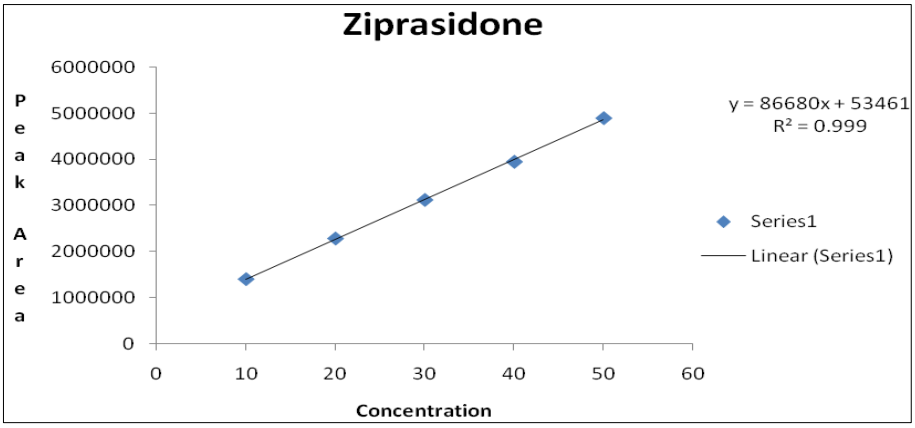

Fig 2: calibration curve of Ziprasidone

Analytical Method-Solubility studies of Ziprasidone

Solubility studies of Ziprasidone were carried in water and in different solvents. To each 10ml of solutions, drug was added and kept on the orbital shaker at100 rpm for 2 hrs. Then the conical flasks were removed from orbital shaker and kept aside over night to equilibrate dissolved and undissolved portion of drug. On the next day samples were filtered. A volume of filtrate was taken and appropriate dilutions were made, filtered, degassed and injected in to HPLC. Using the standard calibration curve the quantity of drug dissolved was calculated.

Linearity for Ziprasidone

Chromatographic Conditions

Column: YMC pack c18 150*4.6mm, i.d., 5µm
Mobile Phase: 0.02M Ammonium Dihydrogen Phosphate: methanol Ph 3.5 (60:40)
Injection Volume: 20 micro liters
Lambda max: 260 nm
Flow: 1 ml/min
Runtime: 10 min
Rt: 3.440 min

Preparation of Linearity Solutions

Accurately weighed 10 mg of ZIPRASIDONE working standard solution into a 100ml volumetric flask, to this add 70 ml of mobile phase to get clear solution after make up the solution up to the mark with same solvent (stock Solution) 100µg/ml.

From the above stock solution Pipette out a series of solution into separate 10 ml volumetric flasks 1ml,2ml,3ml,4ml,5ml separately make up the solutions with the mobile phase to get concentration of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and50µg/ml.

These solutions are injection into HPLC system based on the areas obtained in the HPLC chromatogram, plot graph between concentrations vs. peak area. (r2<0.99)

Linearity for Ziprasidone

Chromatographic Conditions

Column: Inertsil ODS c18 150*4.6mm, i.d., 5µm
Mobile Phase: Phosphate buffer: methanol having Ph 3.0 (70:30 v/v)
Injection Volume: 10 µl
Lambda max: 260 nm

Flow: 1 ml/min
Runtime: 10 min
Rt: 1.736 min

Preparation of Linearity Solutions

Accurately weighed 10 mg of Ziprasidone working standard solution into a 100ml volumetric flask, to this add 70 ml of mobile phase go get clear solution after make up the solution up to the mark with same solvent (stock Solution) 100µg/ml.

From the above stock solution Pipette out a series of solution into separate 10 ml volumetric flasks 1ml, 2ml, 3ml, 4ml, 5mlseperately…make up the solutions with the mobile phase to get concentration of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and 50µg/ml.

These solutions are injection into hplc system. based on the areas obtained in the hplc chromatogram, plot graph between concentrations vs. peak area. (r2<0.99)

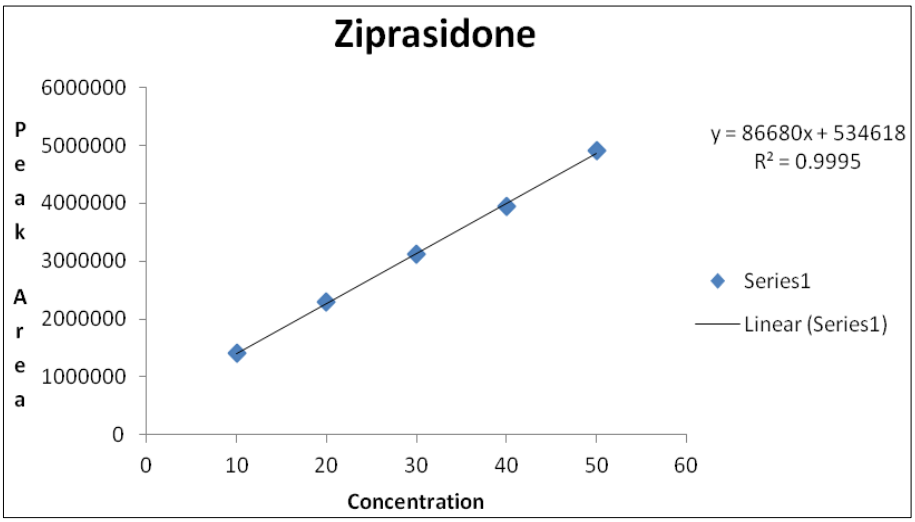

Fig 3: calibration curve of Ziprasidone

Evaluation parameters of tablets

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors' list is long and includes physical, mechanical as well as environmental factors Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio.

As the angle of repose (Θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive andlow if the powder is non cohesive. F1, F5 and F9 (θ=33.9±0.4,θ=33.5±0.5,θ=33.5±0.5) were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable.

Powders showing Carr's index (%) up to 21 are considered of acceptable flow properties. In addition to Carr's index, Hausner found that the ratio $D_{Bmax/DBmin}$ was related to the inter particle friction, so, he showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow.

Therefore F1, F5, F6, F9 were selected as acceptably flowing as they had average Ci(%) of 14.2±0.3, 12.5±0.6, 13.3±0.9; 10.4±0.1 respectively and average Hausner's ratios of 1.16±0.01;1.11±0.02; 1.15±0.01; 1.17±0.02; in the same order.

Finally, formulae F3, F5, F7, F12, were proven to be acceptably flowing according to either the angle of repose, Carr's index and Hausner's ratio were compressed into tablets and subjected for further evaluation while the rest of formulae were nominated as having unacceptable flowability and therefore excluded from further investigation.

At this microenvironment, it may be possible that the infinite amounts of PEG 400 diffusing with the drug molecules out of a single liquisolid particle and excessive amount of Avicel PH 200 responsible for its disintegration property. F1 and F5 formulations also showed the higher dissolution profiles (96.4%, 98.4%) when compared to the rest of the three formulations in 10% (F2=94.6%, F3=93.4, F4=92.3) and 20% (F6=95.3, F7=93.3, F8=90.14). This may be due to the higher amount of Aerosil ® PH 200 which aid in adsorbing excessive amount of liquid in the physical mixture.

Liquisolid formulations (F9,F10, F11, F12) containing 30% drug solution in the Figure 7.6 showed lowest drug release profiles (92.3%, 89.4%, 87.3%,85.1%) when compared to 10% drug solution and 20% drug solution, Because of various amount of vehicle, in these formulations drug is dispersed in the solvent, formed as drug suspension further showing no change in drug state. But, these formulations are showing excellent flow properties may be due to different concentration of vehicle. These evaluation parameter of these four formulations observed in acceptable range.

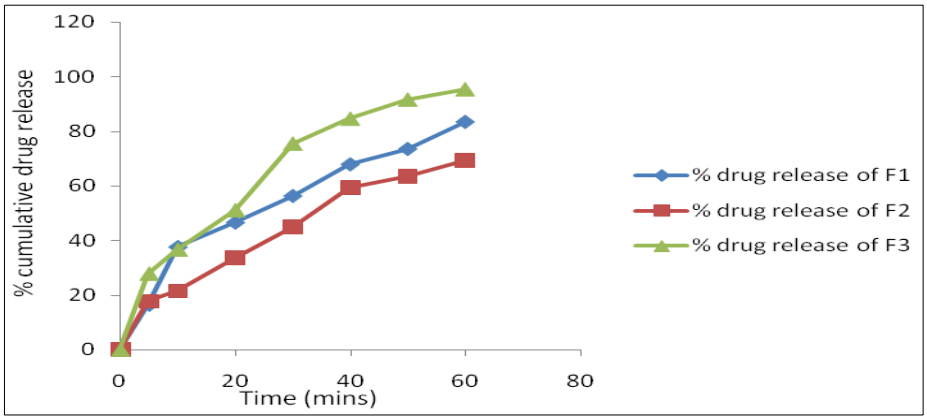

Fig 4: *In-vitro* Dissolution studies of f1, f2, f3

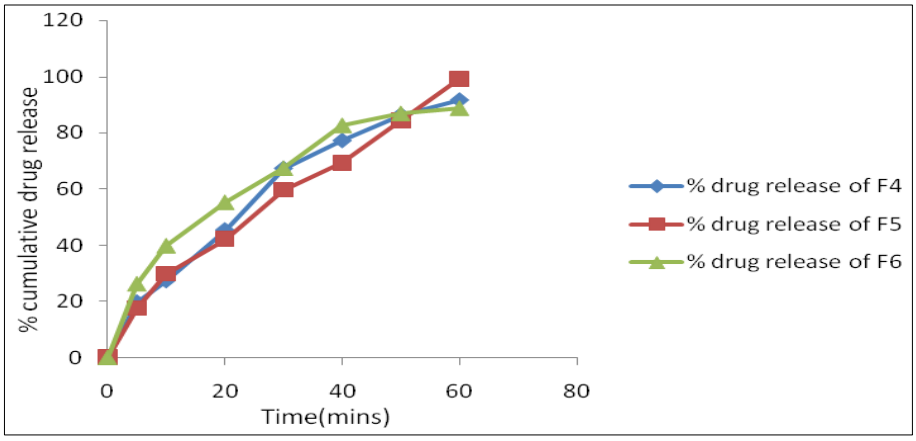

Fig 5: *In-vitro* Dissolution studies of f4, f5, f6

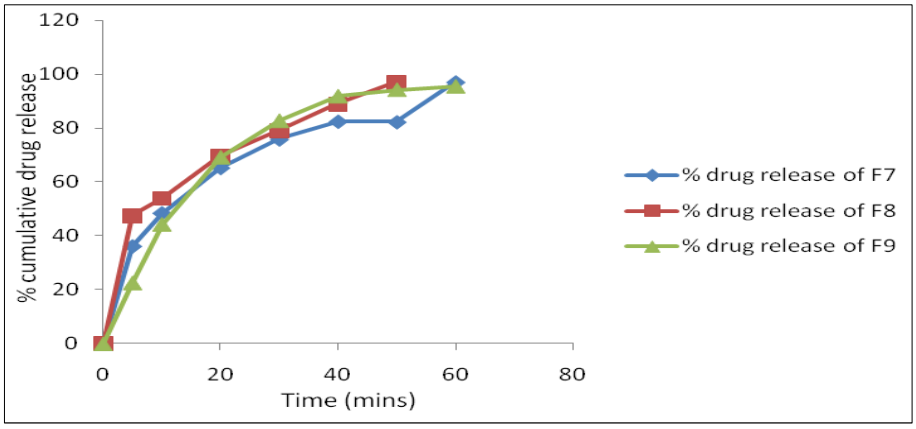

Fig 6: *In-vitro* Dissolution studies of f7, f8, f9

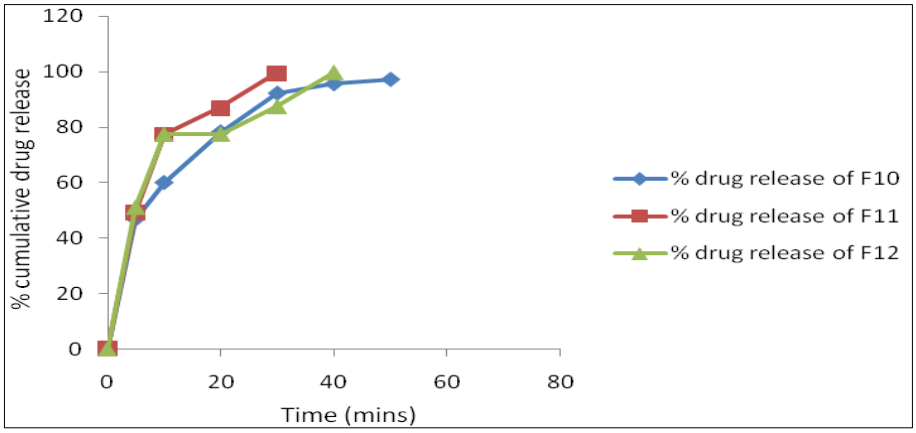

Fig 7: *In-vitro* Dissolution studies of f10,11,f12

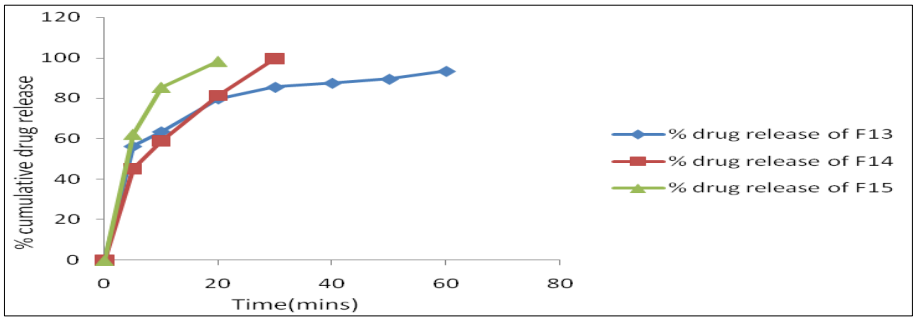

Fig 8: *In-vitro* Dissolution studies of f13, f14, f15

Of the all liquisolid formulations prepared F5 was found to be optimized formulation as it showing desired release of 99.6%.Hence it is considered as optimized formula.

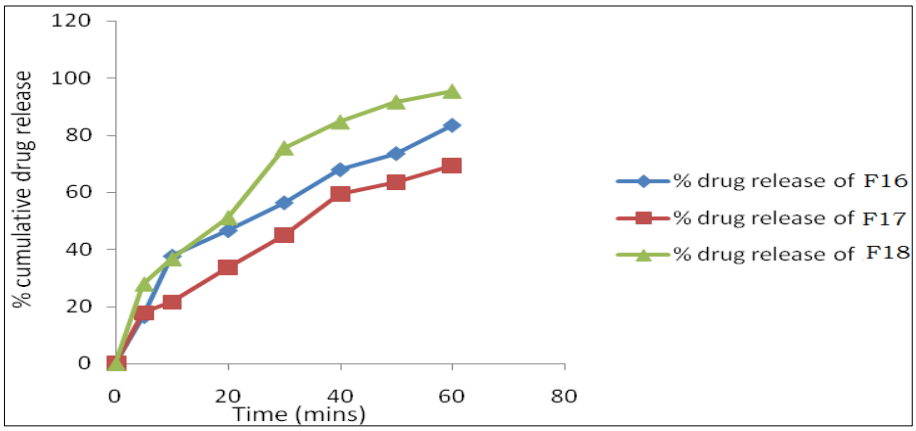

Fig 9: *In-vitro* Dissolution studies of f16,f17,f18.

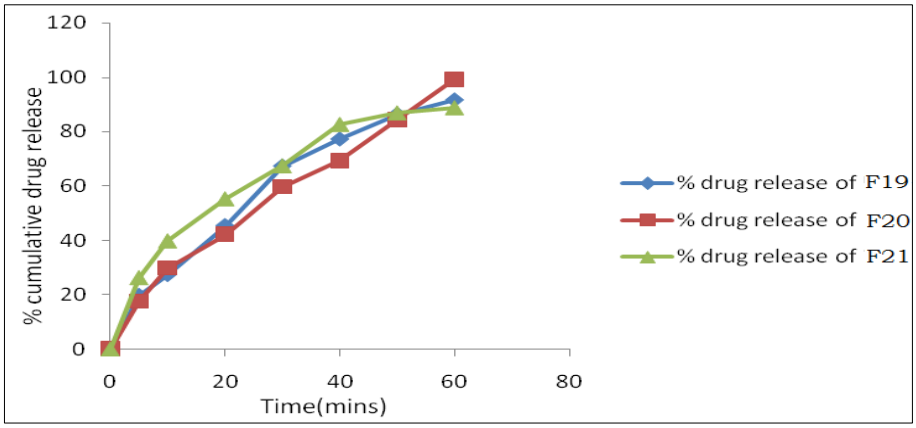

Fig 10: *In-vitro* Dissolution studies of f19, f20, f21

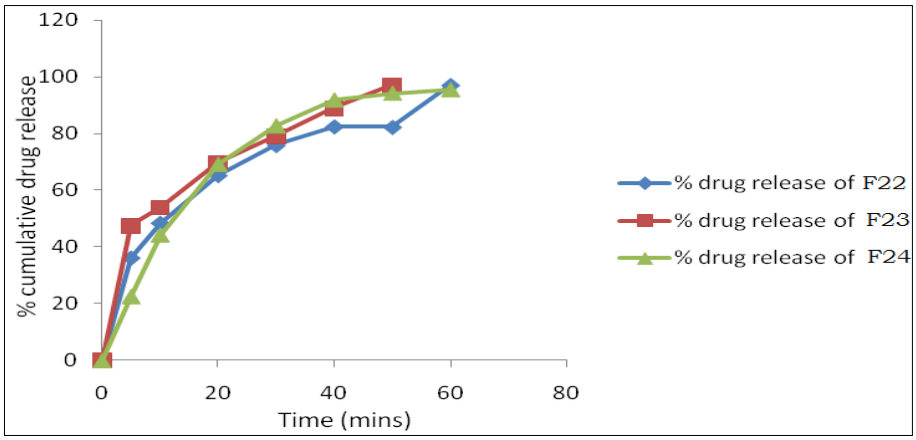

Fig 11: *In-vitro* Dissolution studies of f22, f23, f24

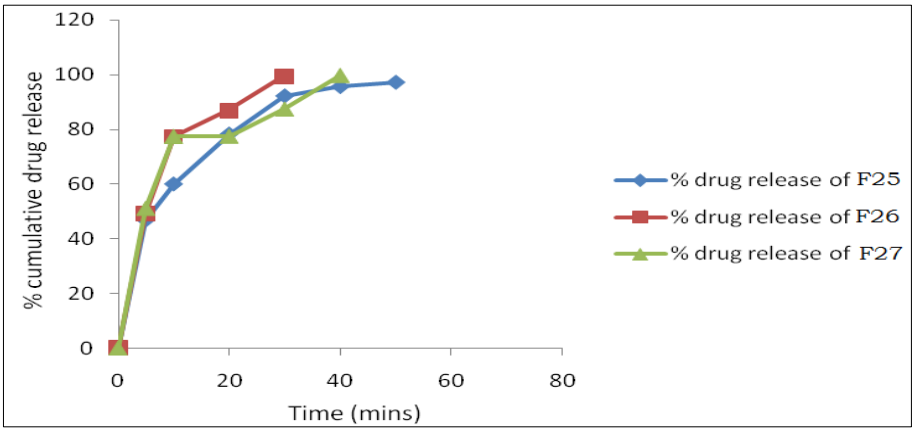

Fig 12: *In-vitro* Dissolution studies of f25, f26, f27

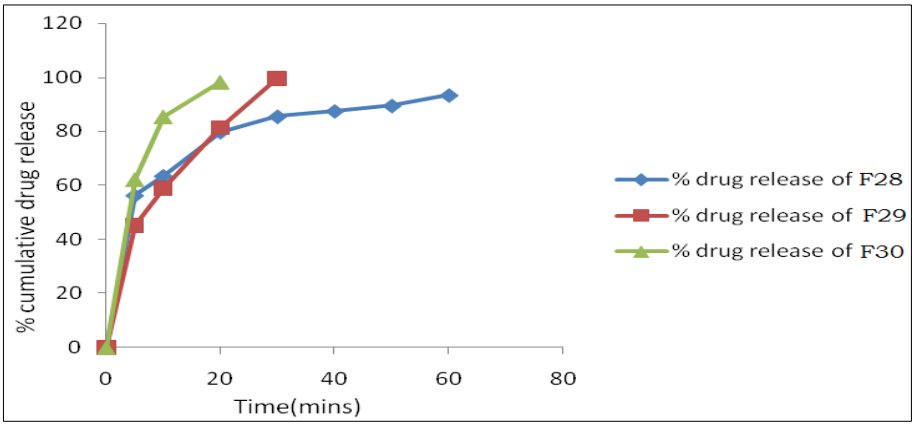

Fig 13: *In-vitro* Dissolution studies of f28, f29, f30

Powder X-ray diffraction studies

Polymorphic changes in the drug are important factor which might affect the dissolution rate of drug and in turn bioavailability. So that it is necessary to study the polymorphic changes of pure drug in liquisolid systems. The crystalline nature of drug was studied by the characteristic PXRD pattern which showed sharp peaks at 18o, 20o, 28o, and 30o positions. PXRD for pure drug, excipients and liquisolid systems.

Liquisolid powder x ray diffraction pattern showed absence of these characteristic peaks of drug, which indicated pure drug, was entirely converted into amorphous or solubilized from. The absence of crystalinity in the liquisolid formulation might be due to solubilization of drug in liquid vehicle that is possibly absorbed and adsorbed on the carrier and coating material. The amorphization or solubilization of pure drug may result in an enhancement of dissolution rate (Sanjeev Ragavendra Gubbi *et al*., 2010 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013).

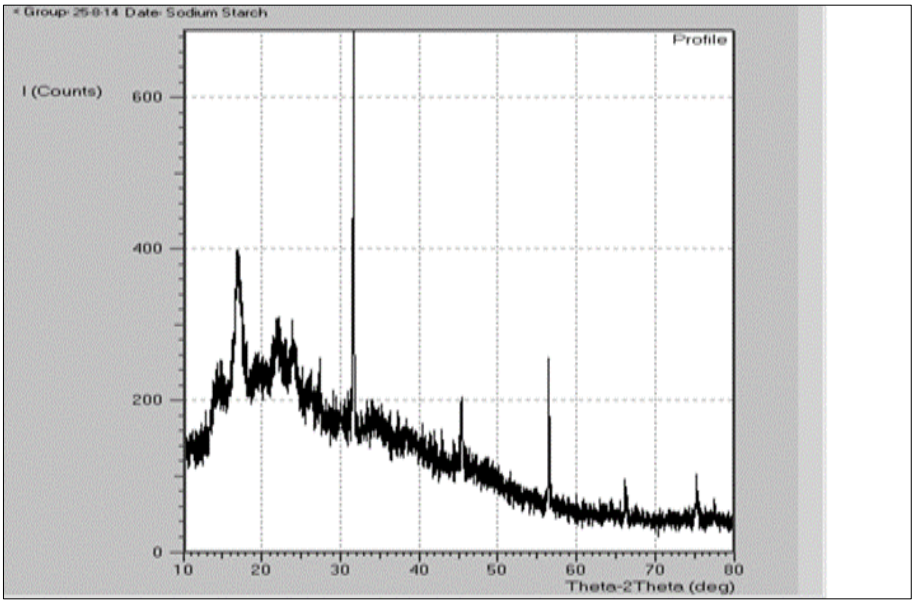

Fig 14: XRD of Ziprasidone

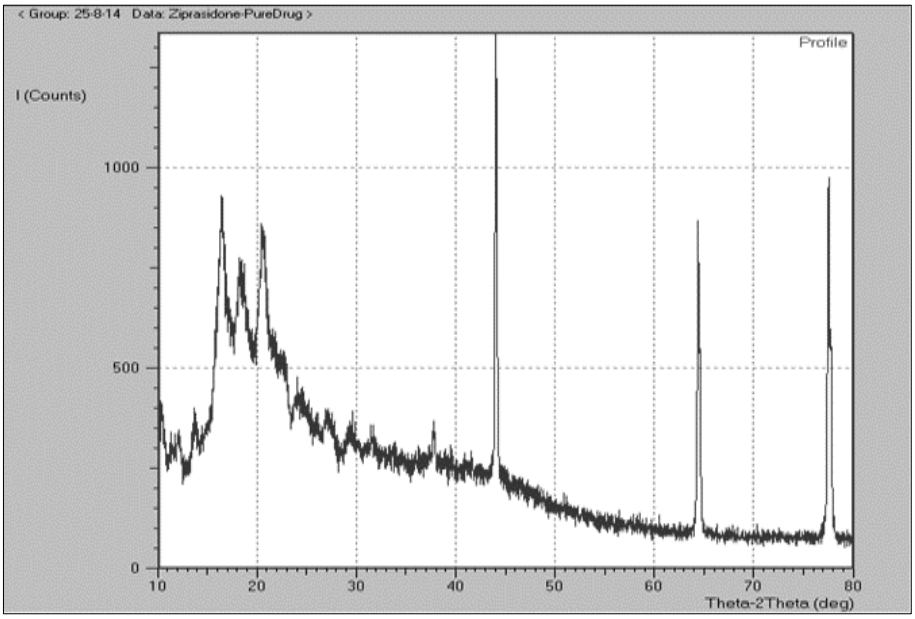

Fig 15: XRD of Excipients

Assessment and comparison of drug dissolution rates

The concentration of drug and Tween 80 is one of the main factors for the formulation of a liquisolid tablets and has considerable effect on the 10 min dissolution rate. Dissolution rate increased with an increase in the concentration of Tween 80 due to high molecular dispersion states of the drug in the formulations. The comparison of dissolution rate for pure drug, directly compressed tablets and liquisolid formulation.

Formulations F1, F2, F3, and F4 were prepared with 1:1, (ratio of drug and Propylene glycol) and R-value of 5,10,15 and 20 showed the dissolution rate of 100.60 µg/min, 97.70 µg/min, 120.48 µg/min, and 124..82 µg/min, respectively at 10 min.

Formulations F5, F6, F7, and F8 were prepared with 1:1, (ratio of drug and Polyethylene glycol-400) and R-value of 5,10,15 and 20 showed the dissolution rate of 127.27 µg/min, 135.24 µg/min, 120.48 µg/min, and 136.34 µg/min, respectively at 10 min.

Formulations F9, F10, F11, and F12 were prepared with 1:1, (ratio of drug and Tween 80) and R-value of 5,10,15 and 20 showed the dissolution rate of 114.41 µg/min, 127.91 µg/min, 153.00 µg/min, and 182.27 µg/min, respectively at 10 min. Among the Twelve formulations F12 showed maximum dissolution rate of 182.27 µg/min.

The dissolution rate of pure drug, directly compressed tablet and liquisolid formulation were showed 41.30 µg/min, 95.66µg/min and 182.27 µg/min respectively. As it clear from the figure 12, the liquisolid tablets displayed higher dissolution rate than those of directly compressed tablet and pure drug.

According to the classic dissolution equation:

$$DR = (D/h)\, S\, (CS - C)$$

The drug dissolution rate (*D*R) of a drug is directly proportional to its concentration gradient (*C*s–*C*) in the stagnant diffusion layer and its surface (*S*) available for dissolution. *C*s is the saturation solubility of the drug in the dissolution medium and, thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (*h*) of the stagnant diffusion layer and the diffusion coefficient (*D*) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of paliperidone from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed pioglitazone. In addition, the saturation solubility of the drug in the microenvironment (*C*s) might be increased in the liquisolid systems due to the presence of Tween 80. So, such an increase in *C*s, in a larger drug concentration gradient, increases the dissolution rate of pioglitazone according to the Noyes Whitney equation (Dinesh M. Pardhi *et al*., 2010 & Nokhodchi A. *et al*., 2005).

Comparison of dissolution rate of pure drug, conventional tablet and best formulation after 10 minutes

Table 2: Dissolution rate after 10minutes (µg/ml)

Pure drug	45.88
Conventional tablet	97.19
Best formulation	179.33

Table 3: Comparison of *in vitro* release profile for pure drug, conventional tablet and liquisolid tablet

Time in minutes	10	20	30	40	50	60
Pure drug	5.06±0.43	9.14±1.5	12.33±2.14	16.33±3.42	20.31±1.04	23.19±0.22
Conventional tablet	10.25±1.34	14.35±1.22	18.51±1.44	29.04±1.31	39.19±5.05	45.18±3.31
Liquisolid tablet	19.22±1.15	46.35±3.41	69.44±2.41	89.35±2.61	97.08±0.22	99.14±0.22

Cumulative percentage drug release ± SD*

Selection and evaluation of best formulation

From the above results of characterization F5 was selected as the best formulation.

1. Solubility of drug in Tween 80 – 14.124 (mg/10ml)
2. *In vitro* release studies - 98.66% at 60 min

1. Comparison of dissolution studies of best formulation with pure drug and directly compressed tablets

The *in vitro* dissolution studies of best formulation (F9) were compared with pure drug and directly compressed tablets. The cumulative percentage of drug in formulation was found to be 98.74% in 1 hour compared to the pure drug and directly compressed tablets whose cumulative percentage drug release was found to be 21.00% & 41.54% in 1 hour, respectively. Thus the formulation F9 showed higher drug release than the pure drug and directly compressed tablets.

2. Infrared spectroscopic studies

Infrared spectrum was performed for the liquisolid formulation, the major peaks of the drug still shown in the spectrum at 3521.31 cm-1, 3389.29 cm-1, 2919.21 cm-1,2324.61 cm-1,1625.81 cm-1, 1541.19 cm-1, 1241.08 cm-1, 1123.19 cm-1, 1012.41cm-1, 856.13 cm-1 indicated that there was no interaction between the drug and polymers in the preparation of liquisolid compacts.

FTIR Studies

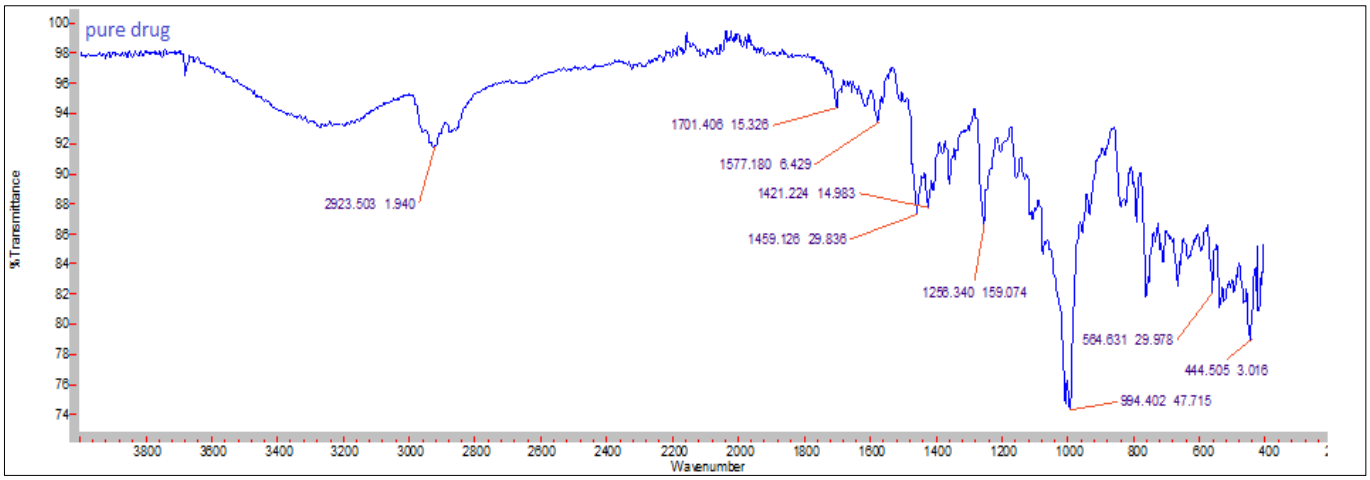

Fig 16: FTIR study of pure drug

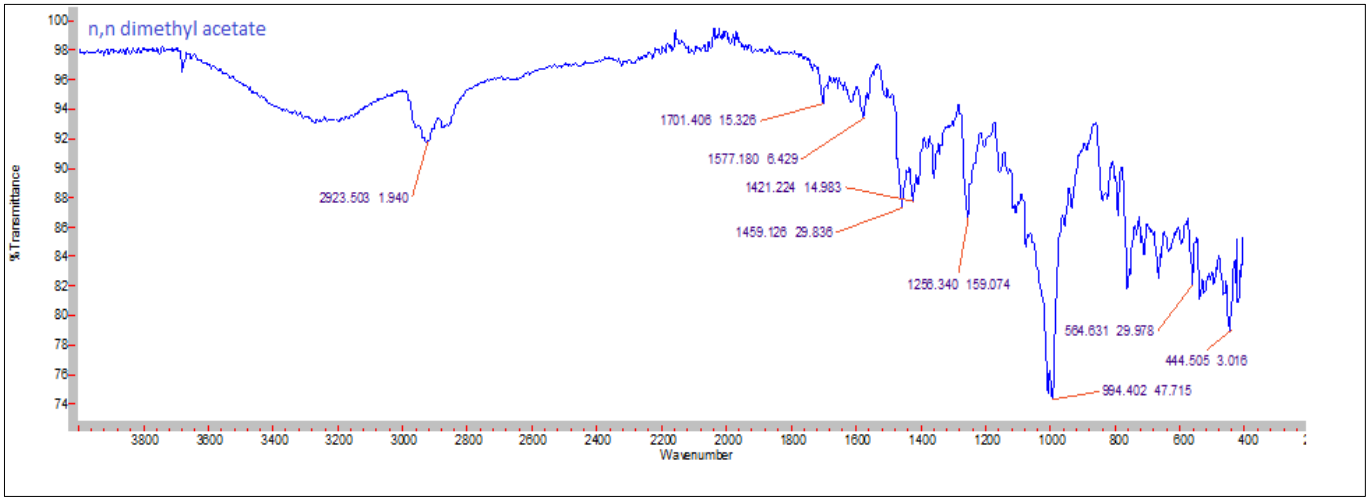

Fig 17: FTIR study of nn dimethylacetate

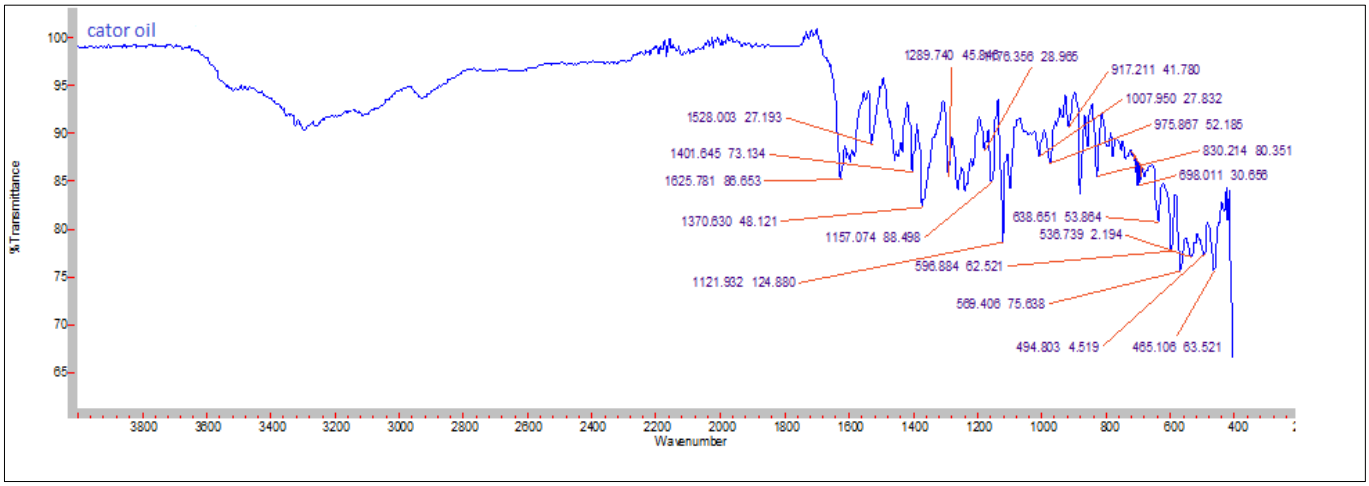

Fig 18: FTIR study of castor oil

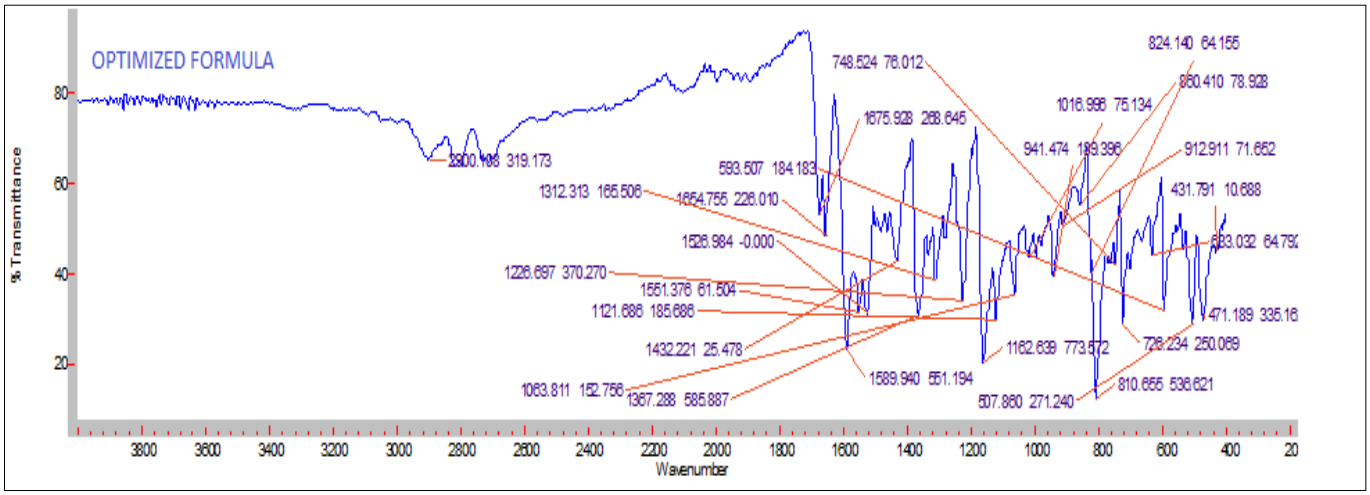

Fig 19: FTIR study of optimized formulation

3. Differential scanning colorimetric studies

The DSC thermogram of pure drug, excipients and final formulation, Pure Ziprasidone showed a sharp endothermic peak at 191.13°C corresponding to its melting temperature 180.14. Such sharp endothermic peak signifies that Ziprasidone used was in pure crystalline state. Microcrystalline cellulose showed sharp endothermic peak at 100.50 °C. The thermal behavior of aerosil 200 did not show any sharp endothermic peak and hence, the aerosil 200 was in an almost amorphous state.

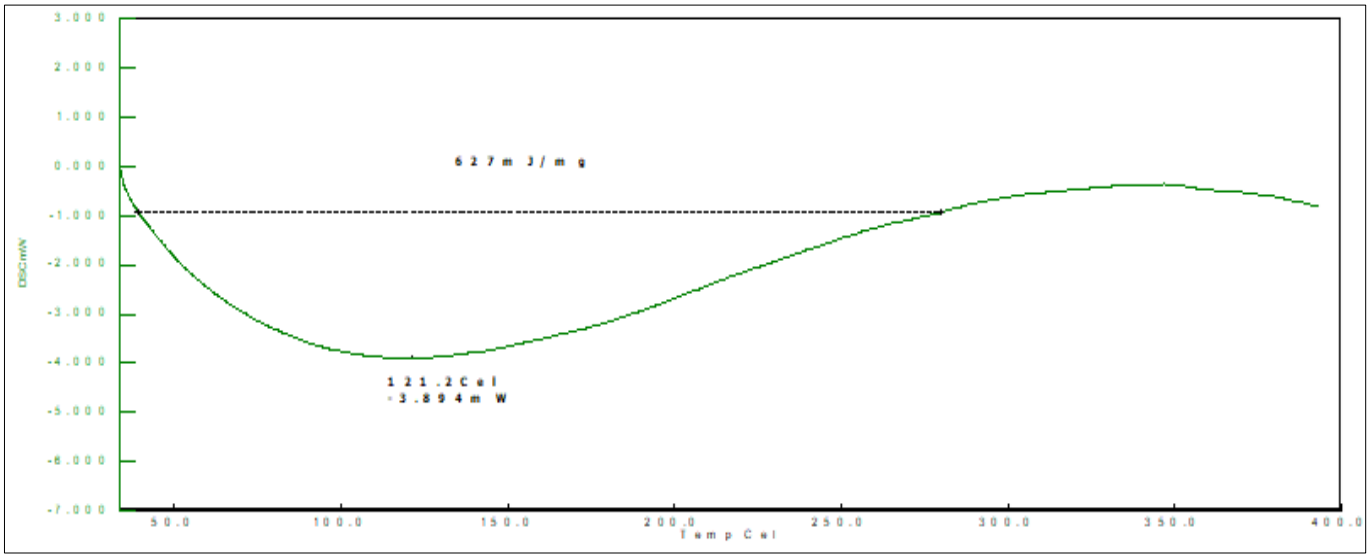

Fig 20: DSC thermogram of Ziprasidone

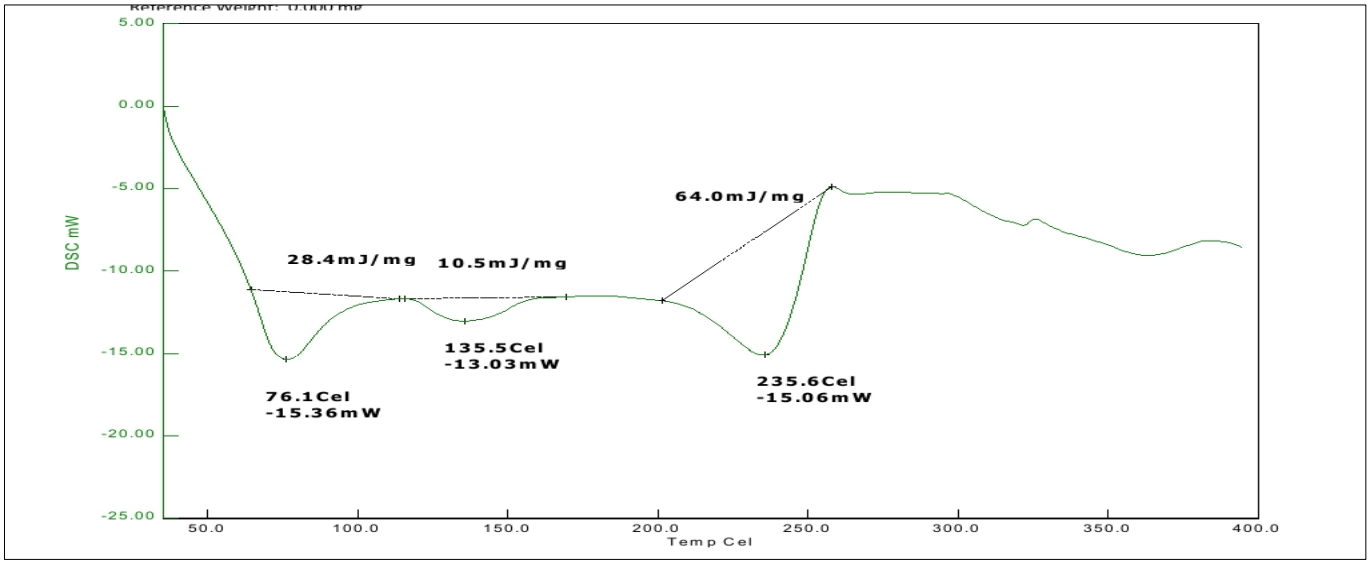

Fig 21: DSC thermogram of liquid solid formulation

4. Drug release kinetic model

In order to describe the kinetics of the release process of drug in all formulations, equations such as zero-order and first-order rate equations were used. Zero order rate equation describes the system where the release rate is independent of the concentrations of the dissolved species. While the first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. It is evident from that the drug release process is not zero order in nature. This indicates that the dissolution rate of the drug is not independent of the amount of drug available for dissolution and diffusion from the matrix. The dissolution data of all formulations when fitted in accordance with the first order equation it is evident that a linear relationship was obtained with 'r' (correlation coefficient) value close to unity and higher than 'r' obtained from zero order equation for all formulation (table), showing that the release is an apparent first order process. This indicates that the amount of drug released is dependent on the matrix.

The obtained from *in vitro* dissolution studies were fitted to zero –order, first-order and Korsmeyer Peppas equation. The first-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsmeyer Peppas equation:

$$Mt/m\infty = k\,t^{n}$$

where mt/m∞ is fraction of drug released, k is kinetic constant, t is release time and *n* is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism; when *n* =1, the release rate is independent of time (zero-order) (case II transport), *n* = 0.5 for Fickian diffusion and when 0.5 <*n* <1.0, diffusion and non-Fickian transport are implicated. Lastly, when *n* > 1.0 super case II transport is apparent. '*n*' is the slope value of log mt/m∞ versus log time curve**.** Slope values (*n* > 1.0) suggest that the release of cilnidipine from orodispersible tablets followed Supercase-II transport suggesting that more than one mechanism may be involved in the release kinetics.

Stability Study

The stability studies were investigated whether the physical chemical parameters and dissolution of liquisolid tablets is affected by storage under a 40° C ± 2°C and 75%± 5% RH. The best formulation of three batches is stored at 40° C ± 2°C and 75%± 5% RH for two months. The results showed no significant changes in physical appearance, hardness, thickness, drug content and dissolution test of aged tablets compared to the fresh liquisolid tablets. This indicates that the liquisolid tablets were stable under these storage conditions.

Table 4: Dissolution profile of best formulation (f5) at 40oc ± 2oc and 75% ± 5%

Time in minutes	Control	250c (room temperature)		400c / 75% rh	
		15th day	30th day	15th day	30th day
10	18.22 ± 1.01	18.36 ± 0.81	18.52 ± 1.05	18.19 ± 0.65	18.28 ± 0.61
20	42.21 ± 1.03	41.66 ± 0.34	43.13 ± 1.04	42.14 ± 0.41	42.19 ± 0.91
30	69.13 ± 1.18	67.12 ± 0.64	68.35 ± 0.16	68.14±0.61	69.38 ± 1.04
40	89.14 ± 0.83	89.32 ± 0.73	86.37 ± 0.91	89.44±0.31	89.35 ± 1.08
50	95.26 ± 0.28	9331 ± 0.83	96.85 ± 0.44	95.29±0.38	95.01 ± 0.61
60	99.14 ± 0.51	97.43 ± 1.03	97.31 ± 0.19	97.23±0.25	97.46 ± 0.19

***In-vivo* evaluation of liquisolid compacts of Ziprasidone Analysis by the high-performance liquid chromatography method**

Both haloperidol (IS) and Ziprasidone peaks were well resolved, with no interference from endogenous peaks. The retention times of haloperidol and Ziprasidone were found to be 10.23 and 21.336 min, respectively. The calibration curve from the standard samples was linear over the concentration range of 10–120 µg/ml. The squared correlation coefficient (r2) was over 0.9998. The average coefficient of variation (CV) for intraday and interday precision was found to be 4.84 and 9.61 respectively. According to ICH guidelines, the CV for the analytical method should be less than 20%. Hence, the HPLC method set for the estimation of Ziprasidone is reliable.

Table 5: Pharmacokinetic parameters of Ziprasidone

Pharmacokinetic parameters	Marketed formulation (Mean ± SD)	Optimized formulation (Mean ± SD)	Pure drug (Mean ± SD)
Cmax (µg/ml)	9.18 ± 1.25	11.09±1.25	8.11±1.16
tmax (h)	8.22±0.01	7.61±0.02	6.14±0.02
t1/2 (h)	6.19±0.02	6.98±0.03	5.91±0.01
Ke (h−1)	0.063 ± 0.01	0.061±0.01	0.059±0.01
AUC0–*t*(ng·h/mL)	101.31± 10.02	129.12±10.06	99.01±9.05
AUC0–∞ (µg h/ml)	143.28 ± 11.18	162.62±10.15	114.18±10.12
Ka	1.51±0.01	1.40±0.01	1.98±0.02
CL (L/h)	1.23± 0.01`	1.31±0.01	1.45±0.01

Data expressed as mean±SD. AUC, area under cure; Cmax, maximum peak concentration; Ka, absorption rate constant; Ke, elimination rate constant; t1/2, elimination half life; tmax, time to reach peak concentration. *Significantly different (*P*<0.05) from the marketed formulation and pure drug.

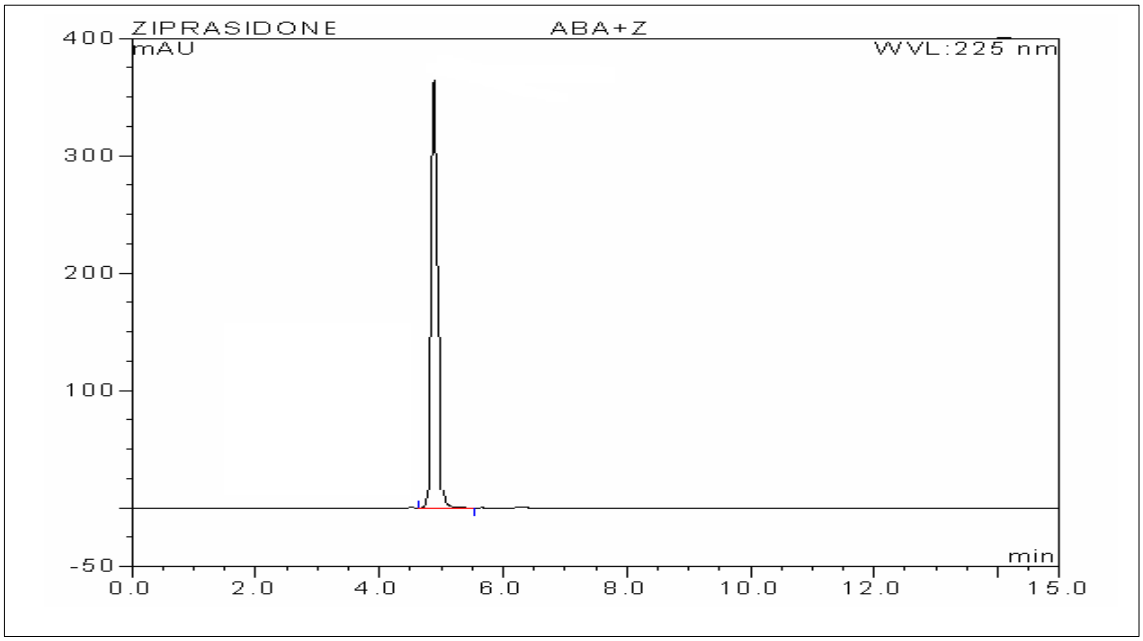

Fig 22: Sample chromatogram of the Ziprasidone (Z) spiked in rat plasma

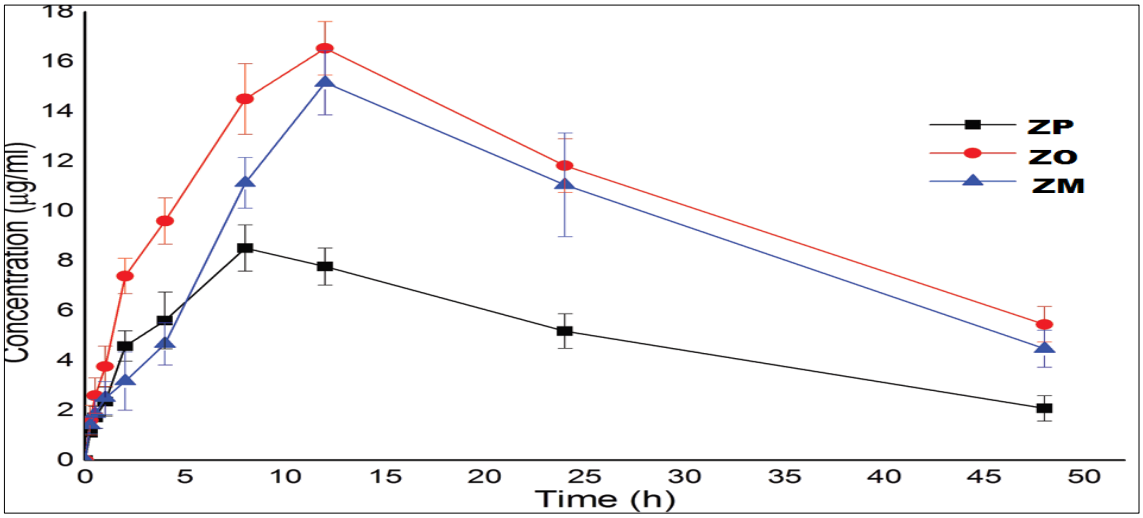

Fig 23: Pharmacokinetic profile of Ziprasidone following a single administration of pure drug (ZP), marketed formulation (ZM), and optimized formulation (ZO)

Pharmacokinetic analysis

The liquisolid tablets of Ziprasidone were evaluated for their *in-vivo* performance by comparing its pharmacokinetic parameters with the marketed product (immediaterelease Lercanidipine tablet). The mean plasma concentration–time curves following the oral administration of the marketed product, optimized liquisolid formulation and pure drug of Ziprasidone and the pharmacokinetic parameters. It is clear from the results of the pharmacokinetic study that the mean peak plasma concentration (Cmax) and the mean AUC0–∞ for an optimized liquisolid formulation were significantly higher (P<0.05) than those for the marketed formulation and pure drug. A 1.2-fold and 1.09-fold increase was found in AUC0–∞ and Cmax values of Ziprasidone from liquisolid compacts than the corresponding values of the marketed formulation.

The mean time to obtain the peak plasma concentration (tmax) for the optimized formulation is lower than the marketed formulation and higher than the pure drug. On the basis of these results, it can be concluded that the greater bioavailability can be obtained from optimized liquisolid formulation, with higher Cmax and tmax, which can be attributed to rapid and efficient
absorption of Ziprasidone.

Conclusion

Of the all liquisolid formulations of Ziprasidone prepared F5 was found to be optimized formulation as it showing desired release along with acceptable physical properties. Our main aim was to improve the dissolution behavior by improving the physical properties. F5 was showing 99.1% release hence it was considered as optimized formula. From the above discussions it can be concluded that F5 formulation having 50% drug concentration in Di-methyl lactamide, with R value 20 and Lf value 0.312 was showing 99.1% release.

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