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Olanzapine Liquisolid Tablets Using Kolliphor EL with Improved Flowability and Bioavailability: *In vitro* and *In vivo* Characterization

Short Title in English: Liquisolid Tablets of Olanzapine

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Abstract
INTRODUCTION: Liquisolid tablet is an innovative approach to enhance dissolution rate and thereby, bioavailability of therapeutic agents with poor aqueous solubility.
METHODS: The objective of the current research was to compare the bioavailability of optimized formulation of olanzapine liquisolid tablet with marketed tablet by conducting pharmacokinetic and behavioural assessment studies. Ten formulations were designed using Kolliphor EL as a non-volatile solvent and the respective tablets were prepared by direct compression method.
RESULTS: Pre-compression studies of powders of all the formulations showed good/excellent flow property and compressibility. The drug release profiles of liquisolid tablets were determined and compared with marketed tablet. Based on the *in-vitro* results, K250 was considered as an optimized formulation, and it was selected for further *in-vivo* studies. The $AUC_{0-\infty}$ value of K250 formulation was found to be 357.2±35.5 ng.h.mL^{-1} which was higher than that of marketed tablet (258.4±29.9 ng.h.mL^{-1}). The reduction in locomotor activity was enhanced remarkably in K250 compared with marketed tablets at $p<0.05$. The time periods taken to fall in rotarod test were approximately equal in all the experimental groups which indicated the absence of extrapyramidal side effects. There was a remarkable decrease in the number of boxes covered in the open field test.
DISCUSSION AND CONCLUSION: Kolliphor EL was found to be a potential non-volatile solvent that can be used to produce liquisolid tablets of olanzapine with improved flow, compressibility, dissolution, and bioavailability properties.
Keywords: Liquisolid tablets, olanzapine, Kolliphor EL, pharmacokinetic study, behavioral assessments

INTRODUCTION

Oral route continues to be the major route of administration of drugs, as its advantages outweigh its major limitation, of low and varied bioavailability. The bioavailability depends on several factors, the most important being the drug's solubility and permeability. The drugs are categorized into four classes based upon their solubility in aqueous media and permeability through biological membranes.[1] The low bioavailability of drugs of classes II and IV of biopharmaceutical classification system (BCS) can be improved by solubility enhancement techniques. Chemical synthetic techniques and high-throughput analysis were used for drug targeting and reducing side effects, but this approach resulted in generating drug molecules with high lipophilicity.[2] Approximately 40 percent of currently marketed drugs and 70 percent of new drug molecules are poorly water soluble.[3] Poor water solubility is a crucial challenge for a formulation scientist. A number of pharmaceutical methods have been advanced to enhance the

drug's aqueous solubility, which include micronization,[4] solid dispersion,[5] cyclodextrin complexation[6] and liquisolid system.[7] Liquisolid method is a new means developed for improving the rate of dissolution and bioavailability of drugs having poor aqueous solubility.[8] It is the transformation of a liquid drug or a solid drug solubilised in a liquid vehicle into a dry powder which is non-tacky, free flowing and highly compressible.[9]

Olanzapine (OLZ) is a second-generation antipsychotic medication utilized in the therapy of bipolar disorder and schizophrenia. It is a member of Class II of biopharmaceutical classification system which comprises drugs having low aqueous solubility and high permeability. It is a yellow crystalline powder and is practically not soluble in aqueous media.[10] The oral bioavailability of olanzapine is 60%. It can be administered orally as a conventional tablet and an orally disintegrating tablet available in 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg dosages. Olanzapine can also be administered parenterally available in 5 $mg.mL^{-1}$ dosage. Plasma protein binding of OLZ is high (93%) and it undergoes extensive pre-systemic metabolism. The drug's poor water solubility and presystemic metabolism are responsible for its low oral bioavailability. The dissolution rate of OLZ is enhanced by solid dispersions,[11] inclusion complexes,[12] nanosuspensions[13], liquisolid tablets,[14,15] and self-nanoemulsifying drug delivery systems.[16] Natarajan *et al*.,[13] conducted pharmacokinetic studies of olanzapine nanosuspensions[13] using Albino Wistar rats. Shah Devarshi *et al*.[14] formulated liquisolid compacts of olanzapine using PEG 400 as non-volatile solvent, Neusilin as carrier material, Aerosil 200 as coating material. The effect of formulation parameters like drug:non-volatile solvent ratio and carrier:coating ratio was studied on angle of repose and percentage drug release was studied by 3^2 full factorial design. The prepared tablets were evaluated in-vitro quality control tests. Ramadevi *et al*.,[15] increased the dissolution rate of olanzapine by liquisolid technique employing Tween 80 and propylene glycol as non-volatile solvents. Although dissolution rate of the drug was increased, the flow property of the formulated pre-compression powder remained poor. Kolliphor EL is a non-ionic solubilizer used for solubility enhancement. The present work was aimed at formulation of liquisolid tablets employing Kolliphor EL as a non-volatile solvent with a view to improve bioavailability by conducting *in-vivo* studies. The bioavailability of the optimized formulation was compared with marketed tablet by pharmacokinetic and behavioural assessment methods. Till now no work was reported on the pharmacokinetic and behavioural assessment studies of olanzapine liquisolid tablets.

MATERIALS AND METHODS

Materials

The drug, olanzapine and non-volatile solvent, Kolliphor EL were obtained from Dr. Reddy's Laboratories, Hyderabad, India and Baden Aniline and Soda Factory (BASF), Mumbai, India respectively as gift samples. Starch and Avicel PH 102 were purchased from Yarrow Chem Products, Mumbai; Aerosil 200 was procured from Oxford Laboratory, Mumbai; Hydrochloric acid from Emplura, Mumbai; HPLC grade Methanol and Acetonitrile from Rankem, Haryana; Ketamine from local hospital. All other chemicals used were of analytical grade. Marketed tablet, Oleanz 10 (Sun Pharma, Gujarat) was obtained from a local pharmacy.

Determination of solubility of olanzapine in Kolliphor EL and distilled water

The drug's solubility was estimated in Kolliphor EL and distilled water. An excessive quantity of drug (30 mg) was put into each of the conical flask containing 10 mL of solvent. The flasks were shaken for 24 hours at 25 ± 2°C on a rotary shaker (Sisco).[17] The drug suspensions were centrifuged, and the clear supernatant liquids were collected. The liquids were appropriately diluted using 0.1 N HCl and the content of OLZ present in the supernatants was determined in ultraviolet-visible spectrophotometer (Elico, SL159) at 259 nm.[18]

Preparation of liquisolid tablets and directly compressible tablets (DCT)

Direct compression technique was used for preparing liquisolid tablets. Kolliphor EL was used as liquid vehicle and the composition of ten formulations are shown in Table 1. The required amounts of Avicel PH 102; used as a carrier material and Aerosil 200; used as a coating material were obtained from their flowable liquid retention potential (denoted as **φ**) values. Avicel PH102 and Aerosil 200 are having **φ** values of 0.27 and 0.9 respectively for Kolliphor EL.[19] The drug was mixed thoroughly using a glass rod in a preheated non-volatile solvent (Kolliphor EL) present in a beaker till a uniform solution was acquired. The carrier and coating materials were added to drug solution and transferred to a mortar. The mixing of liquid-powder contents was carried out according to three stage standard mixing process described Spireas.[20] In the first stage, it was blended using a spatula for one minute to disperse the liquid containing drug in the carrier and coating mixture evenly. As the second step, the drug in liquid/carrier and coating mixture was layered in the mortar for five minutes to permit drug permeation into powder particles. The last step involves scraping off powder from mortar and mixing with starch (5% w/w) for thirty seconds. A rotary tablet machine (Shakti, India) was used for compressing tablets from the uniform powder mixture. The number of tablets prepared in every batch were fifty.

Micromeritics of precompression powders

The micromeritic properties of precompression powder mixtures were evaluated by estimating Hausner ratio, Carr's Index, and angle of repose.[21] Bulk density and tapped density values were measured using bulk density apparatus (Excel Enterprises) and Hausner ratio and Carr's Index were determined using these values. The experiments were conducted in triplicate and the mean and standard deviation are calculated.

Characterization of liquisolid tablets

The hardness, friability, drug content and disintegration time were determined for the prepared liquisolid tablets. The drug release of liquisolid tablets was evaluated in distilled water (900 mL) using USP type II apparatus at 37±0.5ºC and operated at 50 rpm. The amount of OLZ released was estimated in a UV-vis spectrophotometer at 259 nm. The dissolution profiles of liquisolid tablets were compared with that of marketed tablets (MT), Oleanz 10 (Sun Pharma, Gujarat, India) containing 10 mg of drug. Fourier transform infrared (FTIR) spectroscophotometer (Bruker, Alpha-T) was used to determine drug-excipient compatibility. Solid state characterisation of OLZ and optimized liquisolid tablets was carried out by differential scanning calorimeter (Hitachi, STA-7300), x-ray diffractometer (PANalytical, X'Pert PRO) and scanning electron microscope (Jeol Asia PTE Ltd, JSM-6610LV). The hardness, drug content, disintegration time, dissolution studies were determined in triplicate and the mean and standard deviation are calculated.

In vivo bioavailability studies

These studies were conducted to quantify optimized liquisolid tablets after oral administration and to compare its bioavailability with marketed tablets. The studies were conducted according to Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) recommendations and after acquiring due approval from Institutional Animal Ethics Committee (IAEC), of Raghu College of Pharmacy, with number RCP/1549/PO/Re/5/11/21/06 dated 11/10/21.

Pharmacokinetic (PK) study

Male rabbits weighing 1.5 – 2.2 kg were assigned randomly to the two treatments (n = 6). The rabbits were abstained from food for 12 hours before starting the experiment and were fed 4 hours after dosing. Rabbits were given water as much as desired throughout the work.

Marketed and liquisolid tablets were powdered and dispersed in water. Two milliliters of suspensions containing OLZ equivalent to rabbit dose (1.0 mg) was administered orally. Rabbit equivalent dose was calculated based on average weight of rabbits (2 kg).[22,23] One milliliter of blood was taken through the marginal vein of the rabbit ear at specific hour intervals of 0, 1, 2, 3, 4, 6, 8, 12 and 24 and were transferred into eppendorf tubes containing ethylene diamine tetra acetic acid to avoid clotting of the blood sample. The blood samples were subjected to centrifugation using a cooling centrifuge (CM-12 plus, Remi) at 4000 rpm for a period of 10 minutes to obtain plasma. The samples containing plasma were kept at -20ºC in a deep freezer (Subzero, ULT80) till further evaluation was done. The proteins present in plasma were separated from drug by protein precipitation technique using acetonitrile as a protein precipitating agent. To 100 µL of plasma, one milliliter of acetonitrile was added and were centrifuged for 15 min at 4000 rpm. OLZ present in the clear supernatant was analyzed by a high- performance liquid chromatography (HPLC) (Shimadzu, Prominence) method with a UV detector which was developed and validated earlier. The HPLC conditions are column – Hypersil-BDS C18, mobile phase – mixture of 50 mM phosphate buffer (pH 5.5), acetonitrile and methanol (50:30:20 v/v/v), flow rate – 1.2 mL.min^{-1}, run time – 10 min, wavelength – 214 nm.

The pharmacokinetic parameters were calculated employing PK Solver 2 software. The peak height concentration, which is denoted by symbol as C_{max} and the time of peak height concentration, which is denoted by symbol as t_{max} were verified through the drug plasma level – time profile. K_E, the elimination rate constant was obtained by multiplying slope of the linear elimination phase with 2.303. $t_{1/2,}$ the biological half-life was obtained using $0.693/K_E$. Trapezoidal method was used to calculate area beneath the plasma level – time profile from zero to the last time point, which is denoted as AUC_{0-24}. The area under the curve from last time point to infinity ($AUC_{24-\infty}$) was obtained by dividing last measured concentration by K_E. The sum of both the areas gives total area beneath plasma level – time profile from zero to infinity ($AUC_{0-\infty}$). The pharmacokinetic parameters of two groups were compared for any significant differences using t test with probability value <0.05.

Behavioral assessments

Schizophrenia is a complex psychiatric disorder. The symptoms associated with the disorder are classified into positive symptoms, negative symptoms, and disorganized symptoms.[24] The potency of the drugs to exhibit pharmacological activity can be evaluated by animal models. Various animal models involve studies on rats, mice, and monkeys. Behavioral abnormalities are the symptoms of psychosis and can be studied by using different animal models.[25] In the present research work, spontaneous motor activity, rotarod test and open field test were used to evaluate the pharmacological response of the drug. Male Swiss albino mice were used for spontaneous motor activity and rotarod test[25], and male Wistar rats were used for open field test[24]. The open field test was done on rats

because it is easy to observe their movements. It is difficult to conduct the test on mice because of their fast movements and small size.

Spontaneous motor activity: Male Swiss albino mice, with an average weight of 25 grams, were selected and separated into three groups based on randomization, containing six animals in every group. The mice were given access to water and food as much as desired. The locomotor activity was determined by using a digital photoactometer (Indosati, CAT2002E). Normal mice will exhibit typical locomotor activity when placed in a photoactometer. The neurotransmitter dopamine regulates a wide array of physiological functions including locomotor activity in central nervous system. The pharmacological blockade of dopamine transmission inhibits locomotor activity.[26] Marketed and liquisolid tablets were powdered and dispersed in water. Volume of suspensions (0.1 mL) containing OLZ equivalent to mice dose (0.05 mg) was administered orally. Mice equivalent dose was calculated based on average weight of mice (25 g). The third group of mice received distilled water and considered as control. The animal to be tested was individually placed in the photoactometer for 10 minutes and the score on the digital photoactometer was recorded. The procedure was repeated every one hour for four hours. The percentage decrease in locomotor activity after administration of different formulations was calculated based on the locomotion exhibited by the animals in terms of the score given by the digital photoactometer.

Rotarod test: Male Swiss albino mice were placed into three groupings, with six mice in each group. The rotarod test was conducted according to method outlined by Dunham and Miya 1957.[27] The rotarod apparatus (Indosati, two compartment) is an electronic equipment containing rotating rod, speed knobs and a lever. The function of lever is to stop the timer when the mouse drops down from the rod. The mice to be tested were kept on the rotating rod[28] and their latency or time taken to fall was recorded. Drugs which alter neuromuscular coordination decrease the time taken by the animals to stay on the rod.[29]

Open field test: Male Wistar rats, having weight between 200 to 250 grams, were picked for the study. The rats were marked and were assigned to four different groups by randomization with six rats in all groups. The rats were given water and food as much as required. When ketamine is injected at sub anesthetic doses, it induces stereotypic behavior in animals.[24,30] The intensity of behavioral patterns increases, and this occurs due to disturbances in brain. These disturbances are like to those experienced by the patients suffering from schizophrenia. The effect of formulations in reversing the stereotypic behavior induced by ketamine was determined. The effect can be used to interpret the efficiency of formulations in controlling the symptoms of schizophrenia. The open field apparatus (Indosati) was used to observe behavioral changes in animals. The open field area was equally divided into squares. Marketed and liquisolid tablets were powdered and suspended in water. 0.5 mL of suspensions containing OLZ equivalent to rat dose (0.25 mg) was administered orally. Rat equivalent dose was calculated based on average weight of rat (250 g). Ketamine at a dosage of 30 $mg.kg^{-1}$ was injected 30 minutes after administration of formulations. The third group receives only ketamine, and the fourth group receives normal saline. The rats were positioned in the open field apparatus and the number of squares crossed was measured.

Statistical analysis

T test was used to compare the pharmacokinetic parameters. One way ANOVA was used to observe the remarkable differences between groups in behavioral assessment studies at $p<0.05$. Dunnett's test was performed to compare the optimized formulation with control group in spontaneous motor activity test, with ketamine group in open field test at $p<0.05$. Statistical analysis was done using Prism 5.0 software.

RESULTS AND DISCUSSION

Solubility analysis of olanzapine in Kolliphor EL and distilled water

The determination of solubility of OLZ in liquid vehicle is the first step in the design of liquisolid systems. Higher quantity of solubilised drug in liquid vehicle indicates higher solubility of drug, thereby improving its dissolution rate. OLZ is a BCS class II drug which is not freely soluble in water. The solubility of OLZ in distilled water was 0.044 $mg.mL^{-1}$ which agrees with the value given in literature.[31] The drug presented higher solubility in Kolliphor EL (3.63 $mg.mL^{-1}$).

Micromeritics of precompression powders

The uniform and reproducible powder flow from hopper to die cavity is highly essential to obtain tablets of constant weight and drug content. The nature of powder flow can be determined using Hausner ratio, Carr's Index, and angle of repose. Good (K210-K250) to excellent (K110-K150) flow properties were observed when liquisolid powders were prepared using Kolliphor EL as the liquid vehicle (Table 2). Liquisolid formulations containing higher drug concentration (K110-K150) exhibited good flow and compactability compared to liquisolid formulations containing lower drug concentrations (K210-K250). The results were analogous to the results reported by earlier workers.[32] The quantity of Avicel PH 102 has increased with increase in R value and thereby the flow properties of liquisolid powders improved with increase in R value. These findings can be attributed to the good flow properties of Avicel PH 102.[33]

Characterization of liquisolid tablets

The values of post compression parameters of liquisolid tablets are presented in Table 3 and were found to be within the limits. The findings of dissolution study of all the formulated tablets and marketed tablet are presented in Figures 1 & 2. The percentage released in 60 min was found to be 44.87 for marketed tablets and 90.21 to 100 for liquisolid tablets. The results clearly indicate that dissolution rate of liquisolid tablets is higher than MT. This is best described by Noyes-Whitney equation given in equation 1.

$$D_R = \frac{D}{h} S(C_s - C) \qquad \text{Equation 1}$$

where, D_R = rate of dissolution of the dissolved drug substances, D = diffusion coefficient of the dissolved drug substances, S = surface area of drug substances opens to dissolution vehicle, h = diffusion layer's thickness, C_S = maximum drug solubility in diffusion layer and C = drug's concentration in dissolution medium.

The dissolution medium is the same in all the studies; hence, there will be no change in values of D and h. S and $(C_s - C)$ were the variables left influencing dissolution rate. In the tablet prepared without any liquid vehicle, the surface area of drug open to dissolution vehicle is delimited because of drug's low aqueous solubility. In contrast, the drug substances in liquisolid tablets were dispersed in a non-volatile solvent, which enormously enhanced surface area of drug molecules. The drug's saturation solubility (C_s) is increased as the drug molecules are available in a state of molecular dispersion in liquisolid tablets. The quantity of non-volatile solvent used in formulation of liquisolid tablets is very small and it may not be ample to enhance the total saturation solubility of drug molecules in dissolution vehicle. But, at the junction between liquisolid particles and dissolution vehicle, the quantity of non-volatile solvent that diffuses with the drug substances is sufficient to augment the solubility of drug molecules. The non-volatile solvent acts as a cosolvent in the diffusion layer. Also, an increase in R value from 10:1 to 50:1 led to an increase in the dissolution of liquisolid tablets. The presence of high amount of Avicel PH 102 in liquisolid tablets with higher R values is responsible for improved imbibing, disintegration and deaggregation.[34] Liquisolid tablets, K210-K250 comprising 67.77% of Kolliphor EL exhibited larger drug release in contrast to formulations containing lower Kolliphor EL concentration (50% in K110 - 150). The calculated difference factors (f1) and similarity factors (f2) show a large difference in dissolution profiles of K250 and MT. The f1 and f2 for K250 and MT were 153.38 and 12.40. Formulation K250, formulated with Kolliphor EL as liquid vehicle, containing 67.77% of non-volatile solvent with carrier:coating ratio of 50, was the best formula selected considering the outcomes obtained from all the studies.

FTIR spectra of OLZ, Kolliphor EL and optimized liquisolid formulation with Kolliphor EL are given in Figure 3 and the values are given in Table 4. The distinct peaks of OLZ are observed at 2933 cm^{-1} (CH stretching), 1600-1500 cm^{-1} (double bonds attached partially to CH and NH bending deformation), 1500-1300 cm^{-1} (deformation of methyl, methylene and CH groups), 1300-1100 cm^{-1} (CC and CN stretching), 1009 cm^{-1} (deformation of piperazinyl group attached to methyl group) and 745 cm^{-1} (out of plane deformation of CH bonds belonging to the same group).[35] Any drug degradation or drug interaction with additives result in changes in its chemical structure which is reflected by the changes in FTIR spectra. FTIR spectra of liquisolid tablets exhibited the same distinct drug absorption peaks indicating the absence of drug liquid vehicle interaction.[36]

The DSC thermograms of OLZ and K250 are displayed in Figure 4 and the values are given in Table 5. A sharp endothermic peak at 194.25°C was observed in OLZ thermogram, which relates to the melting point of drug.[37] The thermogram of the liquisolid system showed a shift of the endothermic peak to lesser temperature indicating partial amorphization of the drug.[38]

Polymorphism of a drug is an important factor affecting its rate of dissolution and eventually, its bioavailability. Hence, it is essential to observe any changes in drug's polymorphism after formulating as liquisolid tablets. Sharp distinct peaks at 20.47°, 21.64° and 24.56° were observed in XRD pattern of pure drug (Figure 5, Table 5) indicating its high crystalline character.[39] X-ray diffraction pattern of optimized liquisolid formulation (Fig. 5) showed the disappearance or a lessening in intensity of drug's characteristic peaks which indicates that crystallinity of drug is reduced. This effect was also observed in the reports of earlier workers.[40,41]

Drug crystals of irregular shape were observed in the SEM photomicrograph of OLZ (Fig. 6)[12] and the inability to differentiate crystals of OLZ in the photomicrographs of K250 (Figure 6) indicates solid state transition in the drug.[42,43] The results of DSC, XRD and SEM indicate a reduction in crystallinity of the drug which would be another mechanism that explains the enhancement of dissolution in liquisolid tablets.

In vivo studies

Pharmacokinetic study

The plasma drug concentration versus time graphs of marketed formulation and optimized liquisolid formulation are presented in Figure 7 and the pharmacokinetic parameters obtained are given in Table 6**.** The peak plasma concentration obtained was higher for the optimized liquisolid tablets than for the marketed tablets. However, the

time taken to attain C_{max} was three hours, and it is similar in both the treatments. The $AUC_{0-\infty}$ which denotes the quantity of drug absorbed completely from zero to infinite time was higher for liquisolid tablets (357.2±35.5 $ng.h.mL^{-1}$) compared to marketed tablets (258.4±29.9 $ng.h.mL^{-1}$) and significant difference was observed at $p<0.05$ among the two groups. The higher $AUC_{0-\infty}$ and C_{max} values obtained for liquisolid tablet relative to the marketed tablet could be attributed to improved dissolution rate of OLZ from liquisolid tablets leading to higher absorption. The nonvolatile solvent, Kolliphor EL used in the formulation of liquisolid tablets has an inhibitory effect on P-glycoprotein.[44] P-glycoprotein is present in cell membrane and is responsible for efflux transportation of drugs and toxins. P-glycoprotein reduces absorption of many drugs through the intestine and thereby decreases drug plasma concentration. Thus, the inhibitory effect of Kolliphor EL on P-glycoprotein is an added benefit for enhancing the bioavailability of drug in the formulation.

Behavioral assessments

The results of locomotor activity are presented in Table 7. Liquisolid tablet formulation showed higher reduction in locomotor activity compared to marketed tablet. A remarkable difference at $p<0.05$ was observed in the photoactometer scores using one way ANOVA among the three groups. Dunnett's test was carried out to determine where the significant difference lay, i.e., whichever two among the three groups are significantly different. It was found that the effect of liquisolid tablet is significantly different from the control.

The results of rotarod test are given in Figure 8 and Table 8. The test was conducted to check for extrapyramidal side effects of optimized formulation because of increased bioavailability. The latency to fall after 3 hours after administration of distilled water for control was 236.83 seconds; for marketed tablet it was 223 seconds; and for K250 it was 220.35 seconds. There was no remarkable statistical difference among the three groups for the time taken to fall by the mice. The results indicate the absence of side effects for the optimized formulation.

The reversal of ketamine induced stereotypic behavior was determined by the number of boxes covered by rats in open field test apparatus (Figure 9, Table 9). The number of boxes covered was 44 by the control group, 82.5 by the ketamine administered group, 66.75 by the marketed tablet group and 61.17 by the K250 group. The liquisolid tablet showed a remarkable decrease in number of boxes covered. A remarkable statistical difference was noticed in the number of boxes covered among the four groups at $p<0.05$ using one way ANOVA. Dunnett's test showed that the effect produced by liquisolid tablet formulation is significantly different from the group that received only ketamine.

CONCLUSION

The dissolution rate and bioavailability of the optimized formulation was assessed by conducting relevant *in vitro* and *in vivo* experiments. The incorporation of Kolliphor EL in the formulation of the liquisolid tablets has produced remarkable improvement in the dissolution rate of OLZ. Precompression powders with improved flow properties were obtained. Formulation K250 prepared with OLZ:Kolliphor EL ratio 1:2 and Acicel PH 102:Aersosil 200 ratio of 50:1 showed the highest dissolution rate and thereby is the optimized formulation. A reduction in drug crystallinity is another reason for additional improvement in dissolution rate and it is distinctly observed in results of solid-state characterization. The pharmacokinetic and behavioural assessment study results clearly indicated the enhancement in bioavailability for the optimized formulation. Kolliphor EL was found to be a potential solubility enhancer for olanzapine liquisolid tablets.

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Conflict of Interest: The authors have no conflict of interest to declare.

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FIGURES

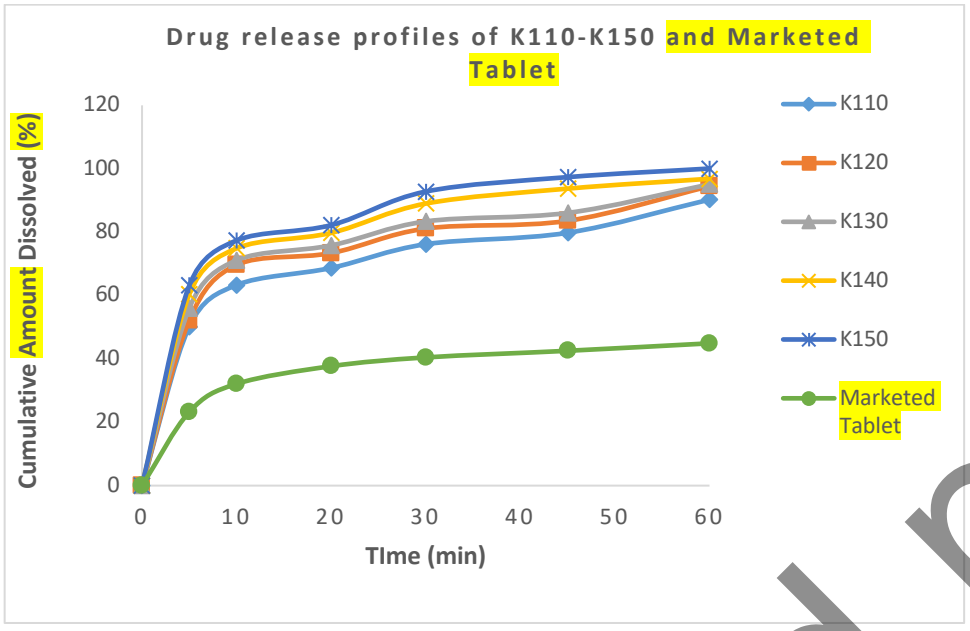

Figure 1. Drug release profiles of K110-K150 and Marketed Tablet

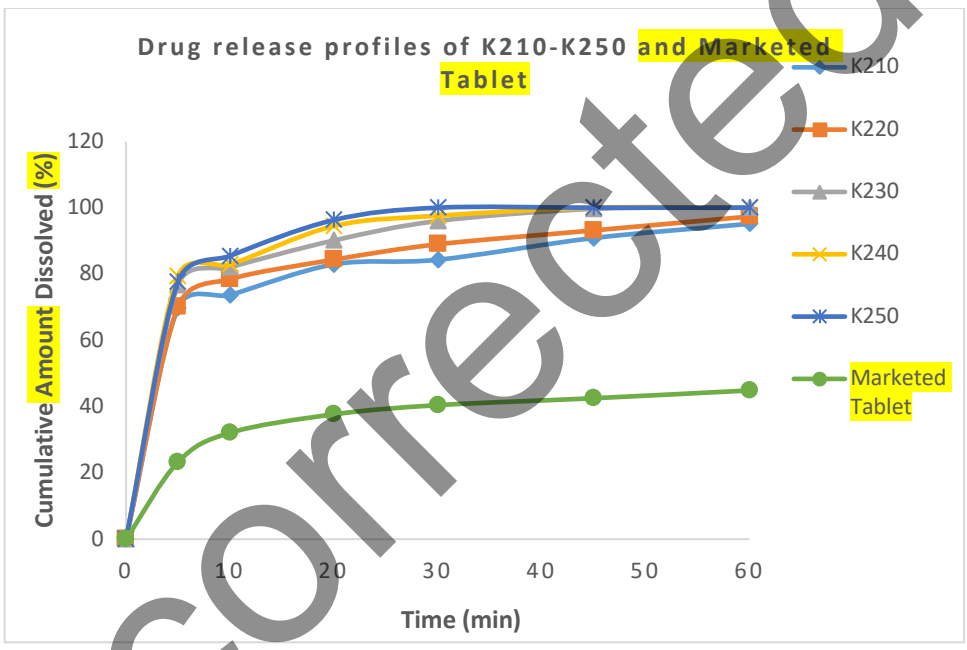

Figure 2. Drug release profiles of K210-K250 and Marketed Tablet

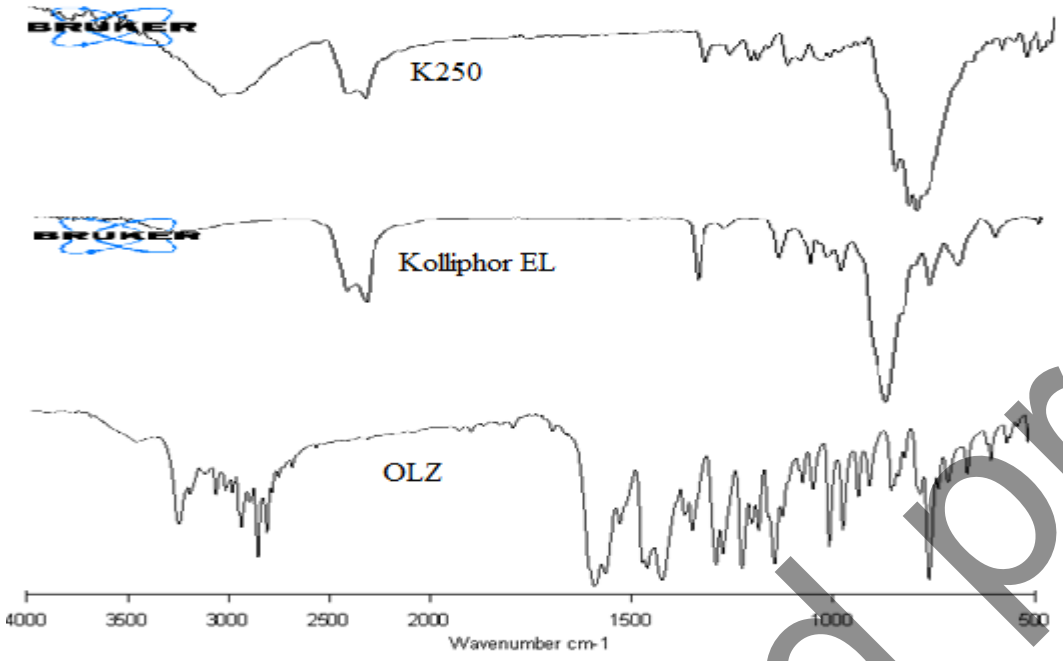

Figure 3. FTIR spectra of OLZ, Kolliphor EL and K250

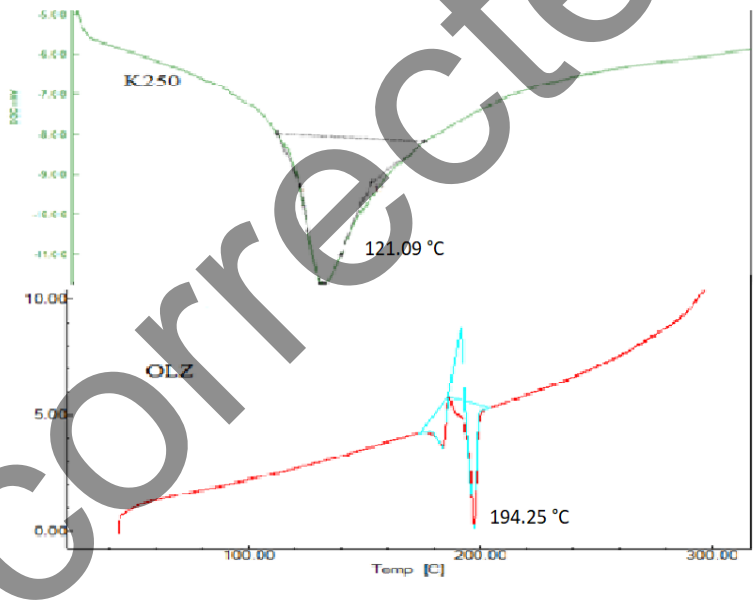

Figure 4. DSC of OLZ and K250

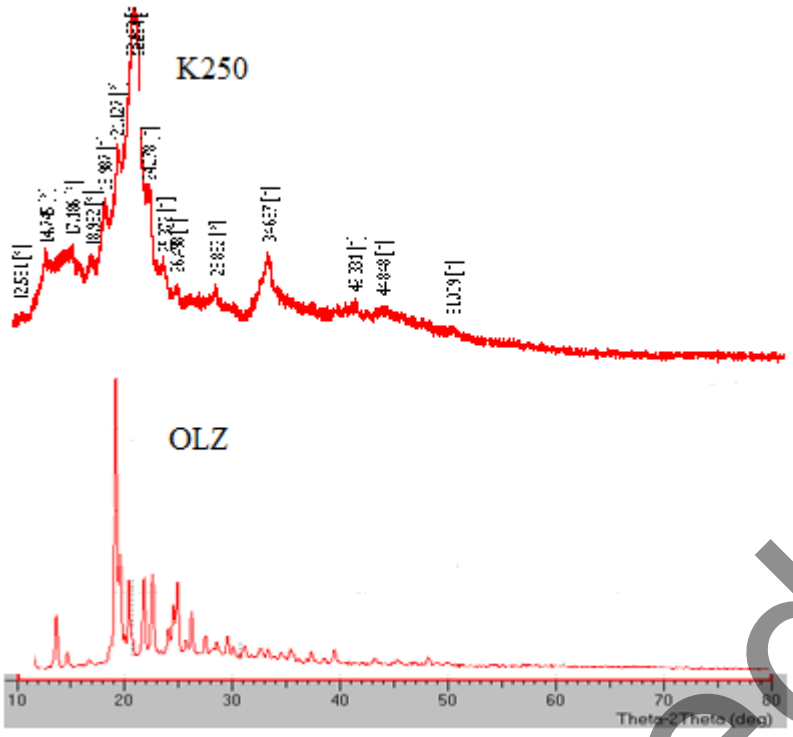

Figure 5. XRD of OLZ and K250

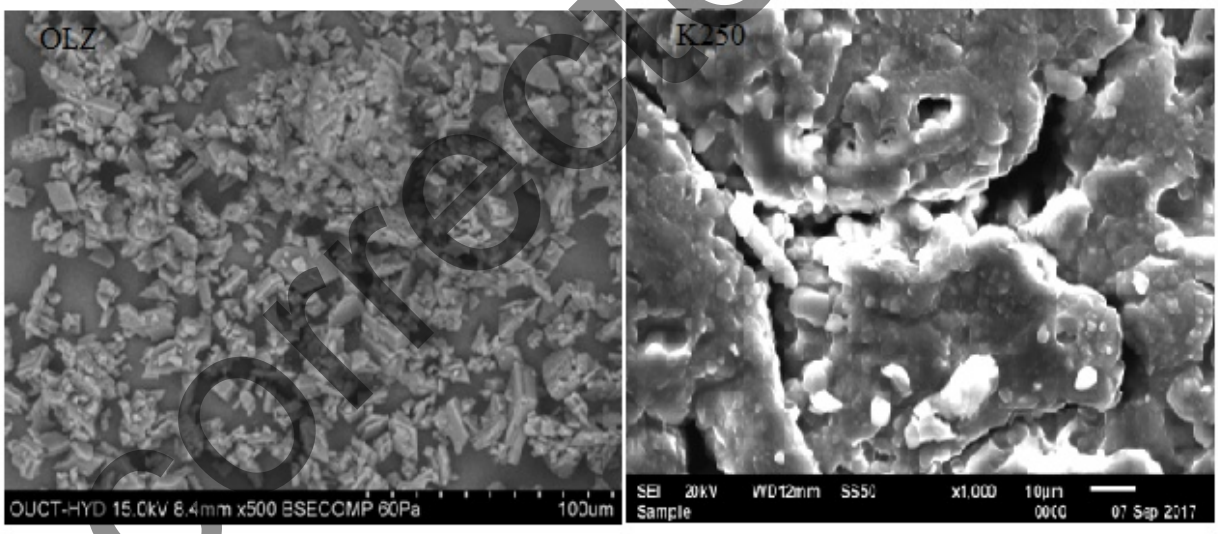

Figure 6. SEM of OLZ and K250

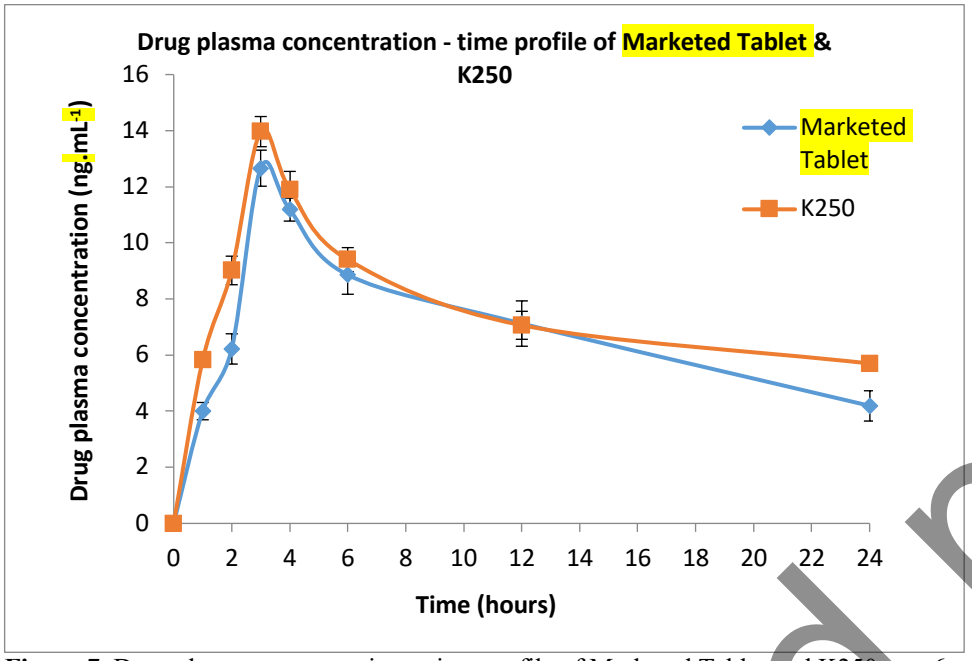

Figure 7. Drug plasma concentration – time profile of Marketed Tablet and K250, n = 6

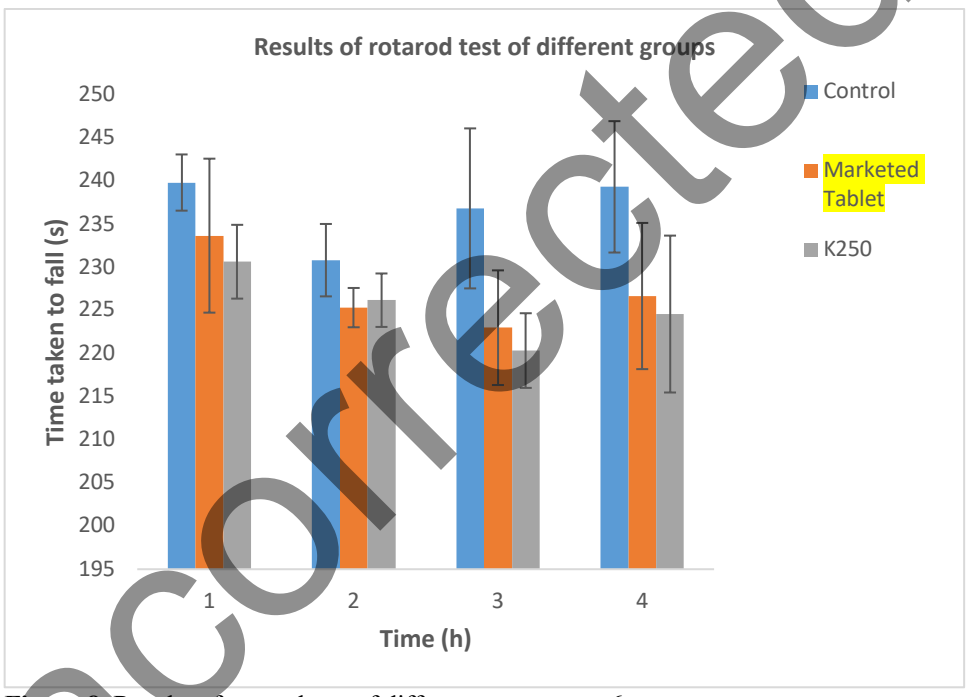

Figure 8. Results of rotarod test of different groups, n = 6

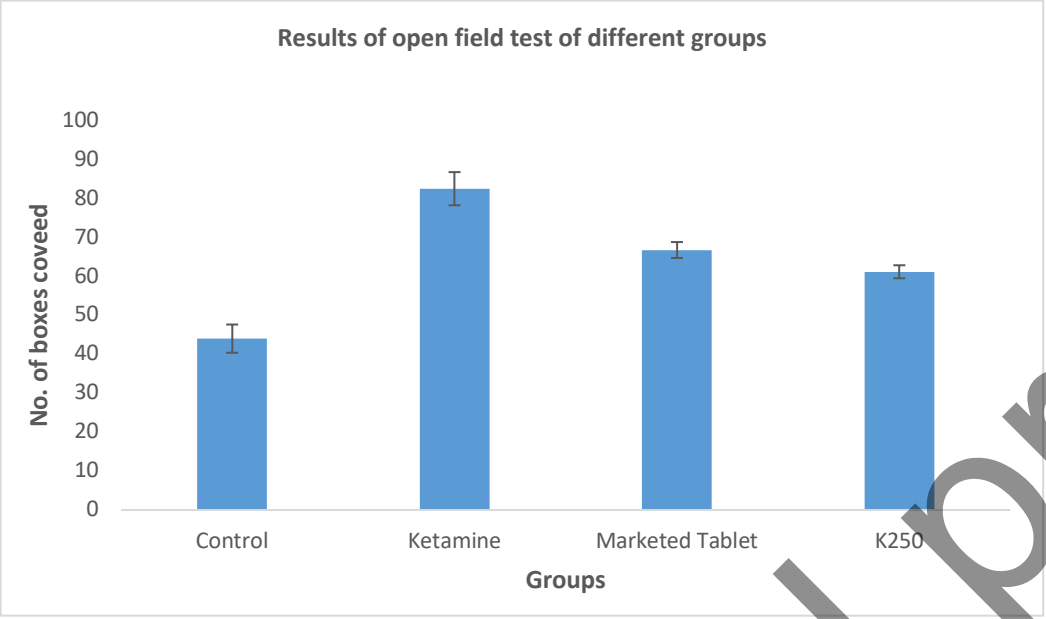

Figure 9. Results of open field test of different groups, n = 6

TABLES

Table 1. Formulation of OLZ liquisolid tablets

Formulations	Wt. of OLZ (mg)	Wt. of Kolliphor EL (mg)	Wt. of Avicel PH 102 (mg)	Wt. of Aerosil 200 (mg)	Wt. of starch (mg)	Total wt. (mg)	Carrier: coating ratio (R)	Liquid load factor (L_f)
K110	10	10	55.56	5.56	4.06	85.18	10	0.360
K120	10	10	63.49	3.17	4.33	90.99	20	0.315
K130	10	10	66.67	2.22	4.44	93.33	30	0.300
K140	10	10	68.26	1.71	4.50	94.47	40	0.293
K150	10	10	69.44	1.39	4.54	95.37	50	0.288
K210	10	20	83.33	8.33	6.08	127.74	10	0.360
K220	10	20	95.24	4.76	6.50	136.50	20	0.315

Formulations	Carr's Index (%)	Hausner ratio	Angle of repose (degrees)
K110	18.81±0.36	1.23±0.04	21.98±0.44
K120	16.67±0.21	1.20±0.02	21.47±0.63
K130	15.27±0.78	1.18±0.03	19.65±0.21
K140	14.32±0.55	1.16±0.03	18.97±0.28
K150	11.78±0.47	1.13±0.01	17.69±0.57
K210	28.57±0.19	1.40±0.02	24.74±0.17
K220	23.08±0.34	1.30±0.01	23.47±0.26
K230	22.25±0.26	1.29±0.05	23.04±0.31
K240	21.24±0.22	1.27±0.04	22.73±0.38
K250	16.72±0.57	1.20±0.02	22.04±0.54

K230	10	20	100.00	3.33	6.67	140.00	30	0.300
K240	10	20	102.39	2.56	6.75	141.70	40	0.293
K250	10	20	104.17	2.08	6.81	143.06	50	0.288

Wt.: Weight, OLZ: olanzapine,

Table 2. Flow parameters of precompression blends (mean ± SD, n: 3)

SD: Standard deviation

Table 3. Post compression parameters of liquisolid tablets (mean ± SD, n: 3)

Formulations	Hardness ($kg.cm^{-2}$)	Friability (%)	Drug content (%)	Disintegration time (seconds)
K110	2.98±0.37	0.980	97.26±1.62	125.62±2.40
K120	3.21±0.45	0.914	97.31±2.08	123.75±3.28
K130	3.54±0.28	0.790	99.26±2.74	120.39±2.60
K140	3.78±0.67	0.826	99.86±3.54	119.41±3.34
K150	3.89±0.31	0.880	101.65±3.62	118.47±2.35
K210	3.33±0.34	0.538	98.75±2.46	114.26±1.59
K220	3.81±0.26	0.612	99.29±1.98	113.64±1.56
K230	3.92±0.69	0.674	101.28±2.59	112.48±3.42
K240	4.12±0.62	0.706	101.67±3.62	112.23±3.45
K250	4.33±0.56	0.791	102.54±2.76	109.68±5.12

SD: Standard deviation

Table 4. FTIR peak values of OLZ and K250

	Wavenumber (cm^{-1})					
	CH stretching	NH bending	CH_3, CH_2, CH deformation	CC and CN deformation	Piperazinyl deformation	CH out of plane deformation
Literature values	2933	1600 - 1500	1500-1300	1300-1100	1009	745
OLZ	2926.62	1587.79	1468.23	1268.89	1004.83	746.91
K250	2925.15	1580.63	1463.66	1276.48	1007.35	743.28

Table 5. DSC and XRD peak values of OLZ and K250

	DSC peak values (°C)	XRD peak values (°2θ)		
OLZ	194.25	20.47	21.64	24.56
K250	121.09	19.31	Absent	23.98

Table 6. Pharmacokinetic parameters of Marketed Tablet and K250 (mean ± SD, n: 6)

Formulations	Pharmacokinetic parameters					
	C_{max} (ng.mL^{-1})	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng.h.mL^{-1})	$AUC_{0-\infty}$ (ng.h.mL^{-1})	K_E (h^{-1})
Marketed Tablet	12.663 ± 0.643	3.000 ± 0.000	15.238 ± 2.598	165.032 ± 7.218	258.482 ± 29.926	0.046 ± 0.007
K250	13.966 ± 0.538	3.000 ± 0.000	21.276 ± 4.141	182.705 ± 5.979	357.276 ± 35.598	0.034 ± 0.006

SD: Standard deviation

Table 7 Results of spontaneous motor activity of different groups (mean ± SD, n: 6)

Time (hours)	Photoactometer score		
	Control	Marketed Tablet	K250
1	591.83 ± 15.82	240.50 ± 6.70	224.17 ± 8.07
2	538.00 ± 14.51	183.00 ± 2.47	159.67 ± 4.86
3	551.83 ± 15.69	159.67 ± 4.86	100.17 ± 5.81
4	540.33 ± 10.43	121.00 ± 3.76	193.50 ± 3.35

SD: Standard deviation

Table 8. Results of rota rod test of different groups (mean ± SD, n: 6)

Time (hours)	Time taken to fall (seconds)		
	Control	Marketed Tablet	K250
1	239.83 ± 3.26	233.67 ± 8.93	230.65 ± 4.28
2	230.83 ± 4.20	225.33 ± 2.28	226.19 ± 3.10
3	236.83 ± 9.28	223.00 ± 6.65	220.35 ± 4.33
4	239.33 ± 7.62	226.67 ± 8.48	224.58 ± 9.10

Table 9. Results of open field test of different groups (mean ± SD, n: 6)

Groups	No. of boxes covered
Control	44.00 ± 3.63
Ketamine	82.50 ± 4.26
Marketed Tablet	66.75 ± 2.05
K250	61.17 ± 1.67