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In Vitro Release Profile and *In-Vivo* Pharmacokinetic Parameters of Ziprasidone Hydrochloride Bilayer Tablet for Schizophrenia Treatment

[1*] Devendra Singh Lodhi, [2] Aakash Singh Panwar
[1][2] Institute of Pharmaceutical Sciences, SAGE University Kailod-Kartal Indore by Road Indore (MP) 452027

*Corresponding author. Devendra Singh Lodhi
Email-devendralodhi86@gmail.com

Abstract :- Psychosis is a prominent symptom of schizophrenia and other psychotic illnesses, as well as a common but variable component of mood and substance use disorders and a somewhat common symptom of many developmental, acquired, and degenerative neurological and medical conditions. People with these disorders often struggle because psychosis makes it difficult for them to function in everyday life. As a result, neurologists and psychiatrists frequently assess and treat patients for psychosis as part of their care. In the present study, we developed a bilayer tablet of Ziprasidone and evaluated it for *in vitro*drug release and pharmacokinetic analysis. The *in vitro* drug release study was conducted in Dissolution Apparatus Type II at pH 7.4, and the release kinetics were calculated for Zero order release rate, Korsmeyer-Pepas model, Hixson Crowell's cube root curve, and First-order release curve. Moreover, the pharmacokinetic profile was conducted in Wistar rats weighing 260 to 280 gm. The *in vitro* drug release of the optimized batch shows 96.8 ± 6.78 % releases at 660 minutes. However, the pharmacokinetic parameters are found to be satisfactory. Thus, the outcomes of the study revealed that the prepared Ziprasidone bilayer tablet shows sustained release behaviour with better therapeutic outcomes.
Keywords: Psychosis, Bilayer tablet, Ziprasidone, In vitro release, Pharmacokinetic

1. Introduction

Most people who suffer from psychotic illnesses, according to the reports available, lack insight. It appears that these individuals are unaware of, unwilling to accept, or unable to acknowledge that they are experiencing mental health issues [1]. Conceptual difficulties inherent to the term "insight" and the lack of a commonly used standardized test have made the research of insight in psychiatric diseases challenging [2]. However, there is also a growing body of research that demonstrates a lack of insight may significantly impact the development and management of psychotic diseases, particularly schizophrenia. Developments in neuropathology and psychoanalysis changed the original meaning of the term "neurosis," leading to a corresponding shift in the meaning of "psychosis" [3]. In the second half of the 19th century, the idea of neurosis became increasingly limited to exclusively psychogenic disorders as a result of advancements in neuropathology and the discovery of new somatic pathological causes of disease. This time frame saw the discovery and description of diseases like Binswanger's dementia, Pick's and Alzheimer's disease, multiple sclerosis, neurosyphilis, and thyroid disorders. Neurologists and other internal medicine specialists have largely abandoned the use of terms like "vasomotor," "trophic," "traumatic," "epileptic," and "tetanic" neurosis [4]. Pharmacological interventions for schizophrenia and associated illnesses are diverse. Several 'new' chemicals called 'atypical antipsychotics' have been introduced in the last 20 years, and they are more effective and have a lower side effect profile than first-generation neuroleptics [5]. Ziprasidone (ZIP) is one of them that is currently popular due to its efficacy as an adjunctive treatment for bipolar illness. The antipsychotic ZIP is a newer "atypical" or "second-generation" medication [6]. The Food and Drug Administration (FDA) of the United States has approved ZIP hydrochloride, orally administered, for the treatment of schizophrenia and acute mania or mixed episodes associated with bipolar illness (with or without psychotic symptoms). Acute agitation in schizophrenia patients may be treated with intramuscular ZIP (ZIP mesylate), which has Food and Drug Administration approval [7].

When it comes to alleviating the negative symptoms of schizophrenia, oral ZIP appears effective and has been demonstrated to have some limited therapeutic advantages over chlorpromazine and haloperidol.The combination of improved delivery methods, patient compliance, and combination therapy has led to the widespread use of therapeutic regimens based on oral delivery of bilayer (and multilayer) tablets. Formulation design, tablet press monitoring and control, and other difficulties must be surmounted for the successful production of these more sophisticated systems [8].Drug release refers to the process by which a drug exits a drug product and undergoes ADME to become available for pharmacological activity in the body. Several terms are used to describe the release of a drug. Drugs can dissolve in immediate-release pharmaceuticals without any attempt to slow or lengthen the process of drug absorption [9]. Both delayed- and extended-release pharmaceuticals fall under the umbrella term "modified release." When a medicine is administered and then slowly released over time, it is said to have a delayed release. Products with prolonged release are designed to gradually release the medicine in the body over time. Extended release and pulsatile release products round out controlled release [10]. The term "pulsatile release" refers to a method by which a drug product is designed to release a set amount of drug at regular intervals. The value of in vitro dissolution testing has been acknowledged in the pharmaceutical industry [11]. It can stand in for the real thing during bioequivalence testing under specific conditions. Drug dissolution from both immediate and modified release dose forms is described by a number of different theories and kinetic models. Different models can be used to depict the time-dependent profiles of drug dissolution from a pharmaceutical dosage form, where the dissolution rate, ft, is a function of time, t. Using a general equation that quantitatively translates the dissolution curve as a function of some other parameters linked with the pharmaceutical dosage forms allows for the quantitative interpretation of the values acquired in the dissolution assay [12]. Theoretical investigation of the process, as in zero-order kinetics, can sometimes lead to the derivation of that equation. Tablets, capsules, coated forms, and prolonged release forms typically lack this theoretical foundation, necessitating the application of empirical equations. The rate of drug release from a pharmaceutical dosage form can be affected by a number of factors, including the drug's kind, polymorphic form, crystallinity, particle size, solubility, and quantity. Diffusion is the primary mechanism for the release of a water-soluble medication from a matrix, while self-erosion is the primary mechanism for the release of a low water-soluble drug [13].To determine how a drug in a bilayer tablet is absorbed, distributed, metabolised, and excreted from the body, a pharmacokinetic research must be conducted. Bilayer tablets are a special dosage form because they have two layers, each of which might contain a different medication formulation for controlled release or combined treatment. The results of this research are essential for optimising dosing schedules and ensuring the tablet's therapeutic efficacy in humans. The findings from these research help improve clinical practise and aid in the creation of new, more potent and less dangerous drug compositions [14]. The rational of this work is to provide in vitro drug release pattern and in vivo pharmacokinetic estimation of ZIP bilayer tablet for sustained release behaviour with better therapeutic outcomes.

2. Materials and Methods

2.1. Materials

Ziprasidone Hydrochloride procured as a gift sample from Ziprasidone HCl was obtained as a gift sample from (Dr Reddy’s lab Pvt Ltd.Animals were purchased from were procured from market although all the chemicals and reagents used in the study were of analytical grade.

2.2. Methods

2.2.1. *In vitro* Dissolution Study:

The analysis of ZIP HCl was performed at a speed of 50 rpm using a USP dissolution device of type II (Paddle) (Electro lab Pvt. Ltd). pH 7.4 buffered 1% SLS dissolving medium.

2.2.2. Procedure for in vitro release of Ziprasidone HCl tablets

A Dissolution Apparatus Type II of USP (Paddle) was used to measure the rate of release of ZIP HCl at 50 revolutions per minute. Concisely, 900 mL of a phosphate buffer solution (pH 7.4) containing 1% SLS was used in the dissolution test. A constant 37 ± 0.5 °C was maintained. At 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, and 150 minutes, 5 mL of the sample was removed, filtered through Whatmann filter paper, and then reintroduced with an equivalent volume of dissolving media. In order to detect ZIP, samples were

properly diluted. The amount of HCl by analyzing the spectra [15]. The percentage of ZIP HCl release was calculated.

2.2.3. Animal Study

2.2.3.1. *In-vivo* Pharmacokinetic Analysis

In vivo studies were conducted on adult male Wistar albino rats weighing 230-250 g. The animals were provided with regular laboratory feed and water in polypropylene cages. All in-vivo experiments complied with the regulations set forth by the institution's animal ethics committee All in-vivo experiments complied with the regulations set forth by the institution's animal ethics committee **IAEC/918/CPCSEA/004**.Rats (n = 6) were split into two groups. Both groups were given ZIP; Group I received a placebo and Group II received a ZIP bilayer tablet at a dose of 12.0 mg/kg orally. The pill was orally delivered via a catheter in a rat by means of surgical forceps and 1 mL of water. The blood was obtained at set intervals of up to 24 hours. An anticoagulant (sodium EDTA)-treated blood sample weighing about 0.5 ml was taken from the retro-orbital plexus. After separating plasma from whole blood by centrifuging at 3000 rpm for 30 minutes, the samples were frozen at -18°C. After letting the sample thaw at room temperature, it was ready for analysis. To extract the medication, 0.2 ml of plasma was added to 1.8 ml of Acetonitrile in a test tube and the two were shaken for 5 minutes. High-performance liquid chromatography (HPLC) was performed on the supernatant after centrifuging the tube for 30 minutes at 3000 rpm [16].

Non-compartment pharmacokinetic analysis was used to determine the maximum plasma concentration (Cmax), the time to reach Cmax (tmax), and the area under the plasma concentration-time curve ($AUC_{0\rightarrow\infty}$) for both ZIP and ZIP-bilayer at various time points. Cmax and tmax were obtained by extrapolating the linear relationship between time and plasma concentration of ZIP and ZIP-bilayer. The trapezoidal rule was used to determine the AUC. By using regression analysis to determine the line's slope, we were able to get the elimination rate constant (Ke), and by dividing 0.693 by Ke, we acquired the half-life ($t_{1/2}$). Through the use of the formula, the steady-state plasma concentration of the drug may be determined. A t-test was used to determine whether or not there was a statistically significant difference between the two approaches. To be statistically significant, a difference has to be smaller than the $p < 0.05$ threshold. MS Excel 2007 (Microsoft Corporation, USA) was used to determine all pharmacokinetic parameters [16].

3. Results and discussion

3.1. Drug content, Dissolution, and disintegration time of sustain release bilayer tablet of Ziprasidone

The drug content, solubility, and pharmacokinetics of ZIP sustained-release bilayer tablets can be analyzed in the following ways:

First, analytical technologies like high-performance liquid chromatography (HPLC) can be used to determine the tablet's medication content. By comparing the extracted material to a standard calibration curve, the concentration of ZIP may be calculated. Dissolution testing is used to assess ZIP tablet release (fig 1). Tablets are dissolved in a controlled setting (dissolution medium, temperature, and agitation) using USP equipment or a comparable device. Taking samples at regular times and studying them allows one to estimate the drug release profile. The disintegration time of a tablet is the amount of time it takes for the tablet to completely dissolve in a specific medium. Submerging a tablet in a medium and watching how rapidly it dissolves while being stirred by a basket or paddle assembly is how disintegration testing machines determine this. The time it takes for everything to completely fall apart has been measured. The composition, dissolving profile, and disintegration time of the ZIP sustained-release bilayer tablet will be revealed by these analyses, which will aid in establishing the drug's efficacy and quality (table 1).

Table. 1. Estimation of Drug content, Dissolution, and Disintegration time

S.No	Formulation	Drug content mg/tab	Dissolution	Thickness (mm) n=10	Disintegration time
1	Z1	19±0.05	33%	2.1±0.2	5minutes
2	Z2	20±0.1	29%	2.2±0.04	25minutes
3	Z3	39±0.01	96.8%	2.2±0.10	1 hours
4	Z4	12±0.32	95.0	2.08±0.3	58minutes
5	Z5	14±0.32	33.19%	2.66±0.01	10minutes

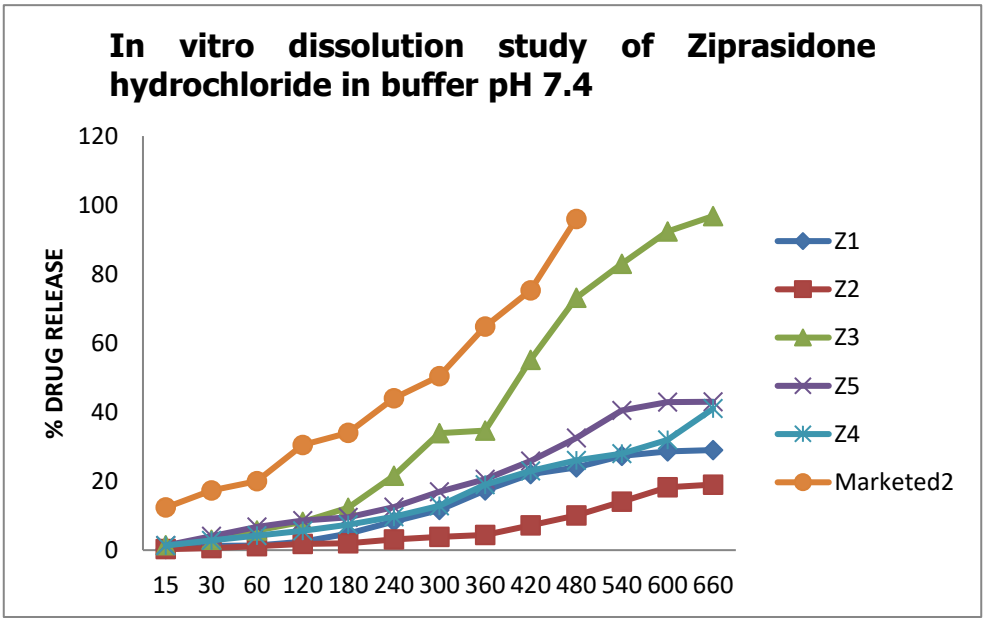

Fig. 1.*In vitro* dissolution study of ZIP hydrochloride bilayer sustain release formulation

Therefore, we selected the Z3 Formulation to further investigate the release rate profile and compare it to commercially available products of varying concentrations (table 2 and fig 2).

Table. 2. *In vitro* release profile of the final batch

S.No	Time	Log time	Cube root	Square root	Log % release	% Release
1	15	15	0.25	3.872	4.05	1.46±0.01
2	30	30	0.78	5.447	5.7	3.03±0.25
3	45	45	0.80	6.708	7.4	4.5±0.21
4	60	60	0.90	7.745	8.2	5.7±0.31
5	90	90	0.96	9.486	9.5	7.4±0.03
6	120	120	1.02	10.954	11	8.2±0.35
7	150	150	1.03	12.247	12.3	9.5±0.35
8	180	180	1.07	13.416	18	11.0±0.36
9	240	240	1.10	15.491	21.6	12.3±0.035
10	300	300	1.13	17.320	22.6	18.0±0.36
11	360	360	1.23	18.973	28.6	21.6±0.31
12	420	420	1.24	20.237	33.9	22.6±0.32
13	480	480	1.28	21.237	34.6	28.2±0.36

14	540	540	1.29	24.494	47.2	33.9±0.35
15	600	600	1.31	25.690	55.2	34.6±0.52
16	660	660	1.34	26.832	65.2	47.2±0.32

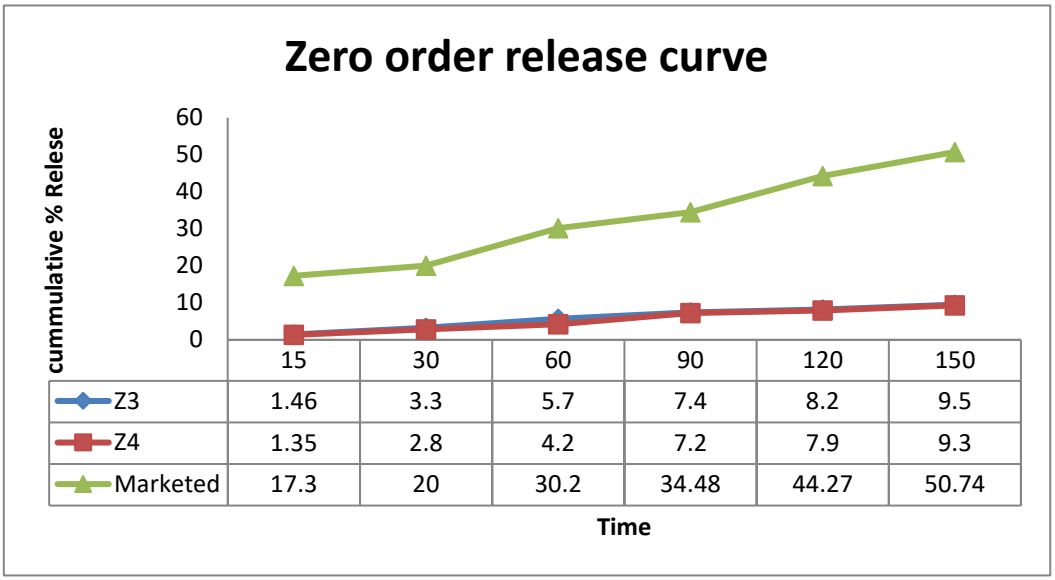

Fig. 2. Zero order release rate of the final batch

3.2. Korsmeyer-Pepas model

Korsmeyer-Peppas modeling is used to calculate drug release kinetics from pharmaceutical formulations. It is based on the Fickian diffusion theory, which is used to calculate the release mechanism and kinetics. This model employs the release rate constant (k) and the release exponent (n) from the Korsmeyer-Peppas equation. Different drug release mechanisms are described by the release exponent, such as Fickian diffusion ($n < 0.45$), non-Fickian or anomalous transport ($0.45 < n < 0.89$), and case-II transport ($n = 0.89$). By using the Korsmeyer-Peppas model to fit experimental data, researchers can get a deeper understanding of drug-release behavior and create more potent sustained-release formulations (fig 3).

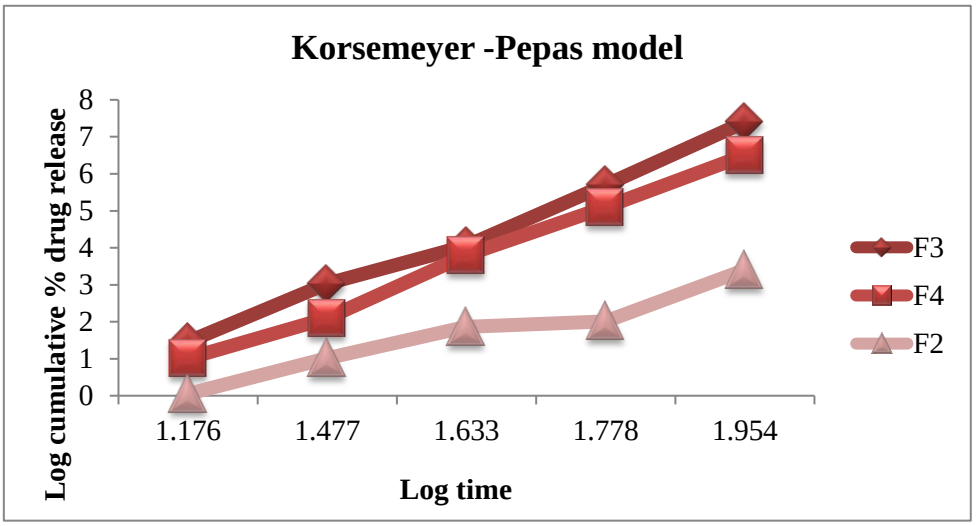

Fig. 3. Korsmeyer-Pepas model

3.3. Hixson Crowell's cube root curve

The Hixson-Crowell cube root curve is a mathematical model of how drugs dissolve in the body. The rate of dissolution is found to be proportional to the cube root of the residual drug mass, assuming geometric erosion and an ever-increasing surface area. Analyzing and forecasting dissolution kinetics for solid dosage forms aids in formulation optimization and controlled-release product development (fig 4).

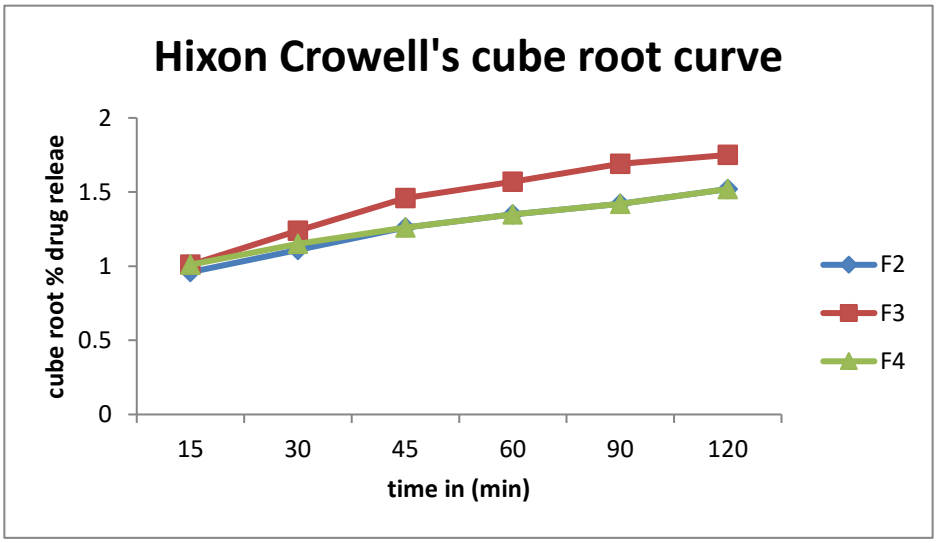

Fig. 4. Hixson Crowell's cube root curve

3.4. First-order release curve

In modeling the kinetics of drug release from pharmacological dosage forms, the first-order release curve is commonly used. It assumes that the remaining drug content in the dose form is proportional to the drug's rate of release. It is expected that the rate of release decreases exponentially over time. A linear relationship between time and the natural logarithm of the remaining drug mass characterizes the first-order release curve. The discharge rate is proportional to the slope of the line, which can be expressed as a constant (k). The first-order release model is commonly used in the pharmaceutical industry to assess and anticipate drug release behavior across a variety of dose forms, which in turn aids in formulation optimization and controlled-release product design (table 3 and fig 5).

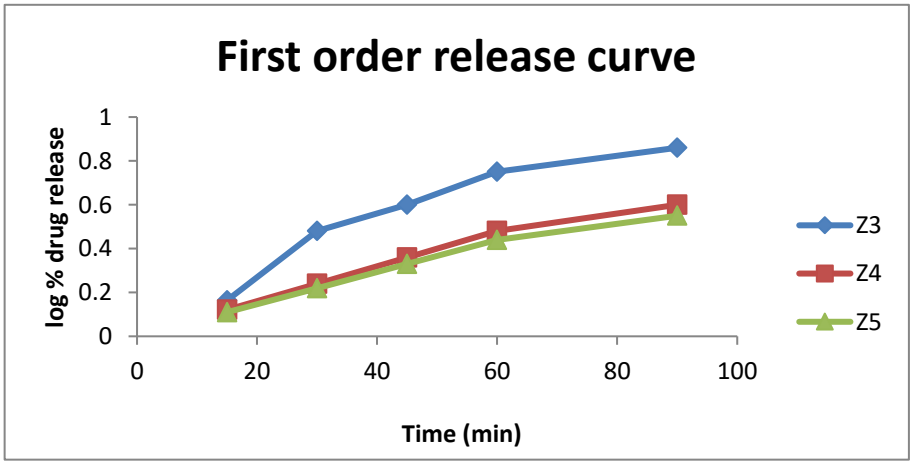

Fig.5. First order release curve

Table. 3. First order and zero order release profile of formulation (ZF3-ZF5)

S. No	Time (min)	Hixon Crowell	Zero-order release	Korsemeyer Peppas model	First order release
1	15	1.01	5.7	1.46	0.164
2	30	1.24	7.4	3.3	0.48
3	45	1.46	8.2	5.7	0.6
4	60	1.57	9.5	7.4	0.75
5	90	1.69	11	8.2	0.86
6	120	1.75	12.3	9.5	0.91
7	150	1.83	18	8.2	1.04
8	180	1.98	21.6	11	1.08
9	240	2.02	22.6	18	1.25
10	300	2.25	28.6	22.6	1.33
11	360	2.46	33.9	33.9	1.45
12	420	2.59	34.6	47.2	1.67
13	480	2.79	47.2	65.3	1.92
14	540	2.8	91.2	84.1	1.95
15	600	3.01	96.8	96.8	1.96

3.5. Pharmacokinetic Analysis

The results were calculated by non-compartmental analysis. Group I received ZIP orally; Group II received ZIP-bilayer. The Prepared bilayer tablet was given to the rat and the drug plasma concentrations were monitored for 18 h.The mean of ZIP and ZIP-bilayer pharmacokinetic parameters for control and test were summarized in Table 4. The drug plasma concentrations of ZIP and ZIP-bilayer are shown in Fig 6.*In-vivo* results of ZIP and ZIP-bilayer clearly show that the bilayer tablet was significantly more rapidly absorbed than the conventional formulation.

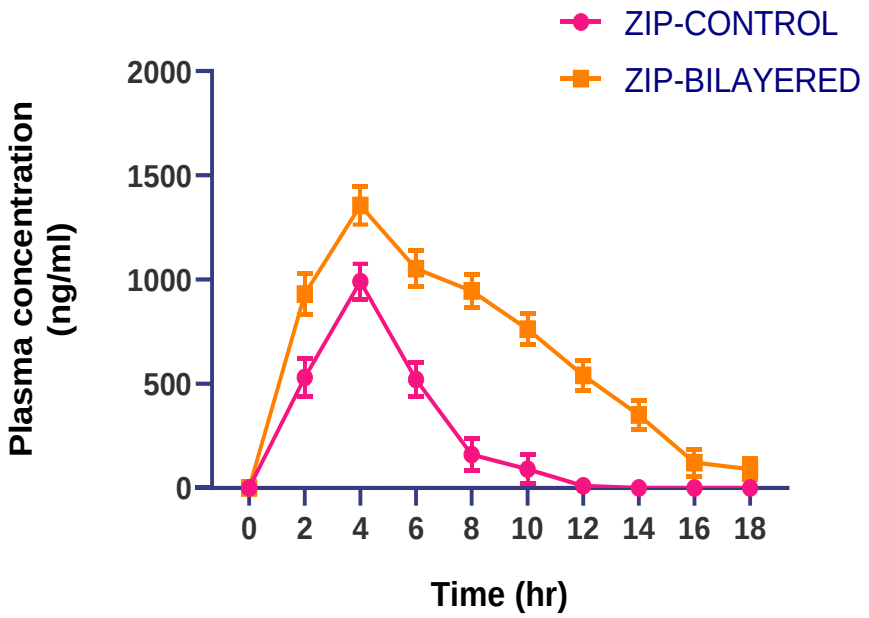

Fig.6. Pharmacokinetic parameter of ZIP HCl

Table.4. Result of Pharmacokinetic Parameters of ZIP control and ZIP bilayer tablet

Parameter	Unit	ZIP-Control	ZIP-BILAYER
T ½	h	0.41± 0.05	2.01 ± 1.32
Tmax	h	2.12 ± 0.14	3.46 ± 1.76
Cmax	ng/ml	783.19 ± 12.39	579.17 ± 13.59
AUC 0-t	ng*h/ml	3978.06 ± 453.17	4786.07 ± 389.13
AUC 0-∞	ng*h/ml	4135.67 ± 523.14	7456.98 ± 612.39
Ke	1/h	0.48 ± 0.05	1.23 ± 0.03

4. Conclusion

In the current research, we performed in vitro release and pharmacokinetic analysis of ZIP-control and ZIP-bilayer tablets. The optimised batch had a medication release rate of 96.8 ± 6.78 % after 660 minutes in vitro. Nonetheless, the pharmacokinetic characteristics are considered to be adequate. The results of the study suggest the sustained release behaviour and improved therapeutic outcomes of the manufactured Ziprasidone bilayer tablet.

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