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COMPARATIVE BIOAVAILABILITY STUDY OF PALIPERIDONE PALMITATE NANOCAPSULE SUSPENSION WITH CONVENTIONAL SUSPENSION

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ABSTRACT

The bioavailability of a pharmaceutical compound is a critical parameter that directly influences its therapeutic efficacy and dosing regimen. This study aimed to assess the bioavailability of paliperidone palmitate nanocapsule a novel drug delivery system by animal study using albino rats. Following a single oral administration of paliperidone palmitate nanocapsule suspension, blood samples were collected at predetermined time points, and plasma concentrations were determined using HPLC analysis. Pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the curve (AUC), apparent volume of distribution (Vd) and mean residence time (MRT) were calculated. The results demonstrated that paliperidone palmitate nanocapsule suspension exhibited favourable bioavailability in comparison to conventional suspension of paliperidone palmitate. The calculated Tmax of 6 hr, Cmax and AUC values were 219 ng/ml and 2086.75ng*hr/L respectively, indicating efficient systemic exposure and sustained drug levels. The comparative bioavailability study of paliperidone palmitate nanocapsule suspension exhibit higher bioavailability compared with conventional paliperidone palmitate suspension. In conclusion, this bioavailability study provides valuable insights into the pharmacokinetic profile of paliperidone palmitate nanocapsule in animal study suggesting its potential as a promising drug candidate with efficient absorption and favourable systemic exposure.

KEY WORDS:
Nanocapsules, Bioavailability, Paliperidone palmitate,

INTRODUCTION: [1]

Nanocapsules are nanoscale drug delivery systems designed to encapsulate active pharmaceutical ingredients (APIs) or other bioactive compounds within a protective shell. They are part of a broader class of nanoparticles used in nanomedicine and are particularly valuable for their ability to improve drug delivery, enhance therapeutic efficacy, and reduce side effects.

The structure of a nanocapsule typically consists of the following components: [2]

1. Core: The core of the nanocapsule contains the drug or bioactive compound to be delivered. This core can be hydrophobic or hydrophilic, allowing for the encapsulation of a wide range of drugs with different properties.
2. Shell: The shell surrounds and protects the core, acting as a barrier that prevents premature drug release and degradation. The shell can be made from various materials, such as lipids, polymers, proteins, or a combination of these.

Key features and advantages of nanocapsules in drug delivery include:

1. Improved Solubility: Nanocapsules can improve the solubility of poorly soluble drugs, enhancing their bioavailability and therapeutic effectiveness.
2. Controlled Release: The design of the nanocapsule shell allows for controlled and sustained release of the drug over time, providing more predictable and targeted drug delivery.
3. Protection of the Drug: The protective shell helps shield the encapsulated drug from degradation, enzymatic activity, and other unfavourable conditions in the body, leading to increased stability and longer shelf life.
4. Targeted Delivery: Nanocapsules can be engineered to target specific tissues, cells, or organs in the body. Functionalization of the shell with ligands or antibodies allows for active targeting, increasing drug concentration at the desired site while reducing exposure to healthy tissues.
5. Reduced Side Effects: Targeted delivery and controlled release contribute to minimizing side effects and toxicity by reducing the drug's exposure to non-target tissues.
6. Versatility: Nanocapsules can accommodate a wide range of drugs, including small molecules, proteins, peptides, and genetic material like DNA or RNA.
7. Applications Beyond Drug Delivery: Nanocapsules have applications beyond drug delivery, including in diagnostics, imaging, and personalized medicine.

Overall, nanocapsules represent a promising platform for advancing drug delivery and nanomedicine, with the potential to revolutionize treatments for various diseases and medical conditions.

Nanocapsules can increase bioavailability compared to conventional drug formulations, leading to enhanced therapeutic efficacy. The increased bioavailability is primarily attributed to the unique properties of nanocapsules, which improve drug solubility, stability, and controlled release.

Nanocapsules can increase bioavailability by: [3]

1. Improved Solubility: Many drugs have poor solubility in aqueous environments, which can limit their absorption and bioavailability. Nanocapsules can encapsulate hydrophobic drugs within their core, effectively improving their solubility in biological fluids. This enhanced solubility allows for better drug absorption and subsequently increases bioavailability.
2. Protection from Degradation: Nanocapsules provide a protective shell around the drug, shielding it from enzymatic degradation and harsh physiological conditions in the body. This protection helps to maintain the drug's stability, preventing premature degradation and ensuring a higher fraction of the drug reaches the systemic circulation intact.
3. Controlled and Sustained Release: The nanocapsule shell can be engineered to release the drug in a controlled and sustained manner. This controlled release profile ensures a steady concentration of the drug over an extended period, which can lead to more effective therapy and better bioavailability.
4. Enhanced Cellular Uptake: Some nanocapsules can be functionalized with ligands or antibodies that enable active targeting to specific cells or tissues. This active targeting facilitates the cellular uptake of the nanocapsule, improving drug delivery to the target site and increasing bioavailability.
5. Reduced First-Pass Metabolism: When drugs are administered orally, they may undergo first-pass metabolism in the liver before reaching the systemic circulation. Nanocapsules can protect the drug from rapid metabolism during its passage through the liver, thereby increasing the fraction of the drug that becomes bioavailable.
6. Minimized Efflux Transporters: Efflux transporters in the gastrointestinal tract and other tissues can actively pump drugs out of cells, reducing their bioavailability. Nanocapsules can bypass or minimize the interaction with these transporters, allowing more drugs to be absorbed and remain available for therapeutic action.

The use of nanocapsules as drug delivery systems offers several advantages over conventional drug formulations. By overcoming challenges related to drug solubility, stability, and delivery, nanocapsules can significantly increase the bioavailability of drugs, leading to improved treatment outcomes and potentially reducing the required dosage and frequency of administration.

Paliperidone palmitate is an atypical antipsychotic medication used to treat schizophrenia and related mental disorders. Considering this information, it is plausible that researchers may have explored the possibility of formulating paliperidone palmitate into nanocapsules to enhance its pharmacokinetic properties.

MATERIALS AND METHODS

MATERIALS USED:

Paliperidone palmitate: Paliperidone palmitate, also known as 9-hydroxyrisperidone, is dopamine antagonist and 5-HT_2A antagonist of the atypical antipsychotic class of medications. Paliperidone is the primary active metabolite of the older antipsychotic risperidone.

Paliperidone palmitate was a gift sample from Leiutis pharmaceuticals. [4]

Polycaprolactone (PCL): Polycaprolactone (PCL) is biodegradable and biocompatible polyester that has gained significant attention in the field of biomaterials and drug delivery systems. The number "45000" refers to the molecular weight of the PCL, specifically polycaprolactone with a molecular weight of 45,000 g/mol. Polycaprolactone was purchased from yarrow chem. Products. [5]

Poloxamer 407: Poloxamer 407, also known as Pluronic® F127, is a non-ionic triblock copolymer composed of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) units. It is widely used in pharmaceutical, biomedical, and industrial applications due to its unique properties. Poloxamer 407 was purchased from chemdyes corporation.[6]

Castor oil: Castor oil can indeed be utilized in the preparation of nanocapsules, particularly in the oil-in-water (o/w) emulsion method. Nanocapsules are colloidal systems with a core-shell structure, where the core is typically filled with a hydrophobic payload, and the shell is composed of a polymeric material. Castor oil was purchased from Nice chemicals[6]

METHODOLOGY

Preparation of paliperidone palmitate nanocapsule: Formulation of paliperidone palmitate nanocapsule was optimized by response surface methodology. Depending on the study design, there is a test formulation (e.g., paliperidone palmitate nanocapsule suspension) and a reference formulation (e.g., conventional suspension of paliperidone palmitate).

Nanocapsule suspension preparation using the solvent evaporation method is a widely used technique in pharmaceutical research for encapsulating active pharmaceutical ingredients (APIs) or other bioactive compounds within nanocapsules. The process involves dissolving the drug and the material for the nanocapsule shell in a suitable organic solvent, followed by the evaporation of the solvent to obtain nanocapsules in suspension form.

Selection of Materials: The shell material is typically a biocompatible and biodegradable polymer, so polymer selected for the study was polycaprolactone.

Drug Dissolution: Dissolve the paliperidone palmitate in a castor oil to create a drug solution. The solubility of the drug in the oil is a critical factor in this step.

Polymer Dissolution: Dissolve the polycaprolactone in acetone to create a polymer solution. The polymer concentration and choice of solvent will influence the size and properties of the resulting nanocapsules.

Preparation of the Organic Phase: Combine the drug solution and the polymer solution to create the organic phase of the nanocapsule suspension.

Emulsification: Introduce the organic phase into an aqueous phase aqueous ie polaxomer solution to form an emulsion.

Solvent Evaporation: Stir or shake the emulsion to facilitate the evaporation of the organic solvents. As the solvent evaporates, the nanocapsules form within the aqueous phase, with the drug being encapsulated in the core. [6]

Preparation of paliperidone palmitate suspension

Measure the required quantity of the paliperidone palmitate using a balance, and also measure the suspension vehicle and suspending agent microcrystalline cellulose as per the formulation. If the drug particles are too large, they may settle quickly, leading to an unstable suspension. In such cases, reduce the particle size of paliperidone palmitate using a mortar and pestle or a mechanical mixer to improve suspension stability. Combine the paliperidone palmitate with a small amount of the suspension vehicle (about one-fourth of the total) in a clean container. Mix thoroughly to form a uniform, wetted mass. Gradually add the remaining suspension vehicle while continuing to mix. This process helps in uniform dispersion of the drug particles. Continue mixing until to obtain a homogeneous primary suspension. Depending on the desired consistency and ease of administration, adjust the viscosity of the suspension. This can be done by adding thickening agent methylcellulose, and mixing until the desired viscosity is achieved. Perform visual checks and, if possible, particle size analysis to ensure uniform distribution of the drug particles in the suspension.[7]

HPLC Analysis [8]

Analyze the plasma samples using validated analytical methods for paliperidone palmitate, such as high-performance liquid chromatography (HPLC), to measure the drug concentrations at different time points.

Creating a calibration curve for paliperidone palmitate using High Performance Liquid Chromatography (HPLC) involves analyzing a series of standard solutions containing known concentrations of the compound. The peak area obtained from each standard solution is then plotted against the corresponding concentrations to generate the calibration curve. This curve can later be used to quantify the amount of paliperidone palmitate in unknown samples based on their HPLC peak responses.

Here are the general steps to prepare and construct a calibration curve for paliperidone palmitate using HPLC:

Materials and Equipment

1. HPLC instrument with a suitable column (C18 column is commonly used).
2. Mobile phase (a suitable combination of solvents for HPLC separation).
3. Paliperidone palmitate reference standard (certified purity).
4. HPLC vials and syringes for sample preparation and injection.
5. Micropipettes or volumetric flasks for accurate dilutions.

Experimental Procedure:

10 mg of Paliperidone palmitate was accurately weighed and transferred into a 100 ml volumetric flask. The drug was dissolved in 20 ml of a 50:50 v/v mixture of ammonium acetate buffer and acetonitrile. The solution was sonicated for 15 minutes to ensure complete dissolution. The volume was made up to the mark with additional diluent to obtain a stock solution.

Preparation of Working Standard Solution:

0.1 ml of the stock solution was taken and transferred into a 10 ml volumetric flask. The volume was made up to the mark with diluent to obtain a working standard solution of Paliperidone with a concentration of 1 µg/ml. Further dilutions were prepared from the working standard solution in 10 mL volumetric flasks. The dilutions were prepared in the concentration range of 5-400 ng/mL of Paliperidone using the above diluent.

HPLC Analysis:

20 µL of each dilution was injected six times into the HPLC column. The HPLC was run at a flow rate of 0.8 ml/min. The chromatograms obtained were used to calculate the average peak area for each dilution.

A calibration graph was plotted by plotting the concentration of Paliperidone (ng/ml) on the x-axis and the average peak area on the y-axis. The regression equation for the calibration curve was computed, which allows the estimation of the amount of Paliperidone in formulation based on the peak area obtained from the HPLC analysis.

IN VIVO BIOAVAILABILITY STUDY

Study Design: Determine the objectives of the study, such as comparing different formulations on bioavailability. Designing a bioavailability study involves carefully planning the experimental setup to assess the extent and rate at which a drug becomes available in the systemic circulation after administration. [9],[10]

Animal used

Species	Strain	Sex	Body Weight range	Number of animal
Rat	Albino	Male	200-250gm	06 Per group

Table no 1: animals used for bioavailability study

Environmental Conditions: Air conditioned room with optimal air changes per hour, relative humidity, temperature and illumination cycle set to 12 h light and 12 h dark.

Accommodation: Groups housed in polypropylene cages with stainless steel grill top, facilities for food and water bottle and bedding of clean paddy husk.

Diet: Brand pelleted feed will be provided.

Water: U.V. Purified and filtered water will be provided in polypropylene bottles with stainless steel sipper tubes.

Group Treatment

Group I: Paliperidone palmitate Polymeric nanocapsule suspension.

Group II: Paliperidone palmitate oral suspension.

Administration of test substance [11]

The test substance will be administered by oral gavage to each animal as a single dose, using an intubation needle fitted on to a syringe of appropriate size.

The dose administered to individual animal will be calculated according to its body weight recorded on the day of test substance administration.

For oral administration, the paliperidone palmitate nanocapsule suspension and conventional paliperidone palmitate suspension equivalent to 3mg paliperidone was given to the rat through a gavage needle or by mixing it with a suitable vehicle to facilitate ingestion. This route mimics the human route of administration and is often used to study drug absorption through the gastrointestinal tract.

Ethical Considerations: The study is conducted in accordance with ethical guidelines and regulations for animal research. Obtained approval from the IAEC with Ref no:P.COL/62/2022/IAEC/VMCP.

Rats are valuable animal models in preclinical research as they are readily available, easy to handle, and have physiological and metabolic similarities to humans. However, it's important to recognize that animal models have limitations and may not fully represent the complexities of human physiology. Therefore, bioavailability studies in animal models serve as a critical step in drug development but must be followed by human clinical trials to fully assess the drug's behaviour and safety in humans.

Blood Sample Collection: The animals were fasted for 24 hrs before receiving the drug and have free access to water. 0.5ml of blood was taken at intervals of about 0.5, 2, 4, 8, 12, and 24 hrs from tail vein, and then transferred to glass tubes that had been heparinized with an anticoagulant (ammonium oxalate 1% solution).[12]

Plasma Separation and Sample Analysis: Process to obtain plasma and analyze them for drug concentrations using validated analytical methods (e.g., high-performance liquid chromatography).

In a bioavailability study, plasma sample separation from whole blood is a critical step to analyze drug concentrations in the plasma. The drug concentration in plasma reflects the bioavailable fraction of the administered drug in the systemic circulation. Here's a general overview of the process for plasma sample separation from blood:

Blood Collection: Collect blood samples from the rats at predetermined time points after drug administration.

Anticoagulant: Add an appropriate anticoagulant to the blood collection tubes. The anticoagulant prevents blood clotting and keeps the blood in a liquid state.

Centrifugation: Centrifuge the blood samples soon after collection to separate the plasma from the cellular components (red blood cells, white blood cells, and platelets). Centrifugation forces the denser cellular components to form a pellet at the bottom of the tube, while the plasma remains as the supernatant on top.

Plasma Transfer: Carefully transfer the plasma (the clear, straw-coloured liquid) to a new, labelled collection tube using a pipette or transfer pipette. Take care not to disturb the cellular pellet at the bottom of the tube.

Aliquot and Storage: Aliquot the plasma into smaller, pre-labelled tubes for individual analysis and storage. Store the aliquots at the appropriate temperature (usually -20°C or -80°C) to preserve the drug stability until analysis.

Quality Control: Include appropriate quality control measures to ensure the accuracy and reliability of the plasma samples for analysis. This can involve running control samples alongside the study samples and maintaining a log of sample handling and storage conditions.[13]

HPLC analysis of the blood sample:[8]

With the calibration curve and regression equation, the amount of Paliperidone sample can be estimated by analyzing their HPLC peak areas and applying the equation.

Pharmacokinetic Analysis: [14] Calculate pharmacokinetic parameters from the drug concentration-time data, including Tmax (time to maximum concentration), Cmax (maximum concentration), AUC (area under the curve) and others.

Pharmacokinetic analysis is a crucial step in a bioavailability study as it involves the mathematical evaluation of drug concentration-time data to understand how the drug is absorbed, distributed, metabolized, and eliminated from the body after administration. The pharmacokinetic parameters derived from the analysis provide valuable insights into the drug's behaviour, bioavailability, and potential therapeutic efficacy. Here's an overview of the key steps involved in pharmacokinetic analysis for a bioavailability study:

Data Preparation: Organize the drug concentration-time data obtained from plasma samples collected at different time points after drug administration. Ensure that the data is accurate and complete, and check for any outliers or inconsistencies.

Plotting Concentration-Time Profiles: Create concentration-time profiles by plotting drug concentration (usually in plasma) on the y-axis against time on the x-axis. This allows visual examination of the drug's absorption, distribution, and elimination phases.

Non-compartmental Analysis: Perform non-compartmental analysis to calculate the primary pharmacokinetic parameters, which include:

- Cmax: Maximum observed drug concentration.
- Tmax: Time to reach maximum drug concentration.
- AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration.
- AUC0-inf: Area under the concentration-time curve from time zero to infinity (extrapolated).
- Kel: Elimination rate constant.
- Vd: Volume of distribution.

Data Interpretation: Interpret the results to understand how the test formulation (e.g., nanocapsules) influences drug bioavailability compared to the reference formulation. Assess the implications of the findings in the context of the study objectives.[15]

RESULTS AND DISCUSSION

Paliperidone palmitate nancapsules were optimized by response surface methodology with Design expert software and the formulation is given below with characteristics of the nanocapsules.

OPTIMIZED FORMULATION			
Paliperidone palmitate (mg)	Polycaprolactone (mg)	Polaxomer 407 (mg)	Castor oil (mg)
50	**250**	**799.99**	**152.36**

Table no 2: Formula of optimized formulation

Calibration curve of paliperidone palmitate by HPLC

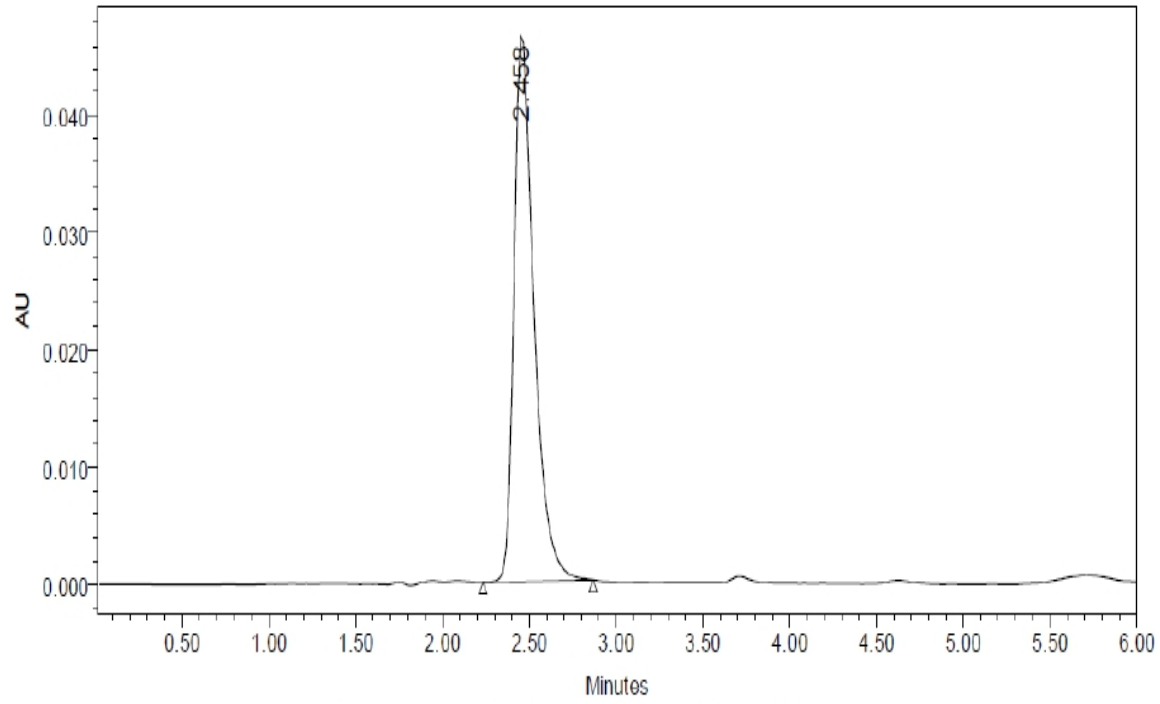

Figure no 1: HPLC of paliperidone palmitate

Concentration in ng/ml	Mean peak area
0	0
5	190
10	365
20	718
40	1368
60	2003
80	2578
100	3165
200	6300
300	9500
400	12800

Table no 3: Calibration curve data of Paliperidone palmitate

Different concentrations of paliperidone palmitate were prepared in the range from 5 ng to 400 ng. Calibration curve of paliperidone palmitate was obtained by plotting concentration of paliperidone palmitate on X axis and mean peak area on Y axis and the following calibration curve with r^2 value 0.999 was obtained.

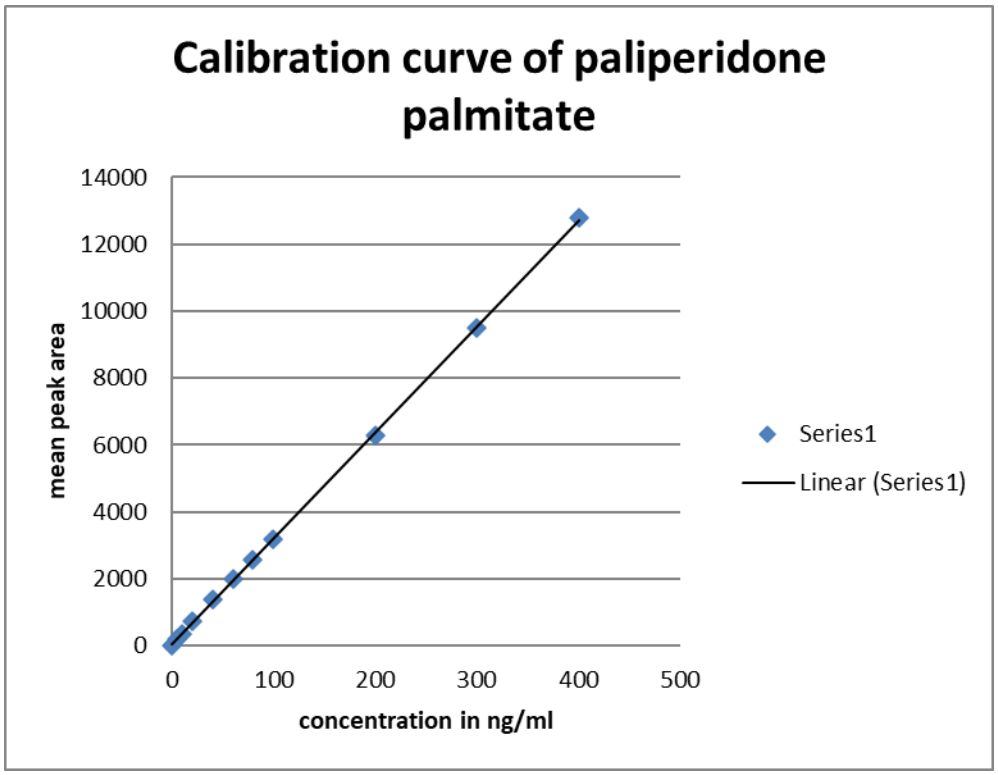

Figure no 2: calibration curve of paliperidone palmitate

In vivo bioavailability study of paliperidone palmitate nanocapsule suspension:

Blood samples were collected after the administration of prepared nanocapsule suspension to the group of rats. By HPLC analysis the following data was generated for sample collected for 24 hours.

Time in hrs	Mean peak area	Concentration ng/ml
0.25	410	11
0.50	757	22
1	1481	45
2	2205	68
4	5952	187
6	6959	219
8	4913	154
12	2835	88

16	1827	56
20	631	18
24	347	9

Table no 4: In vivo bioavailability study data of paliperidone palmitate nanocapsule

Pharmacokinetic Parameters- Nanocapsule Suspension

Time in hrs	Concentration ng/ml	ln concentration	Absorption Phase Concentration	Residual Concentration	ln residual concentration
0.25	11	2.39789527	1027.619231	1025.221	6.932664
0.5	22	3.09104245	1086.807719	1083.717	6.988152
1	45	3.80666249	1215.608411	1211.802	7.099864
2	68	4.21950771	1520.812453	1516.593	7.324222
4	187	5.23110862	2380.343252	2375.112	7.7728
6	219	5.38907173	3725.662547	3720.273	8.221552
8	154	5.0369526			
12	88	4.47733681			
16	56	4.02535169			
20	18	2.89037176			
24	9	2.19722458			

Table no 5: Pharmacokinetic parameter determination of nanocapsule suspension

From the concentration obtained from the blood sample collected from the rats were used for determining pharmacokinetic parameters. From the data natural logarithmic concentration of elimination phase ie, last linear phase was plotted against time in hours gives a straight line with r^2 value 0.976. From the slope we get the elimination rate constant (Ke) ie 0.181hr^{-1}.

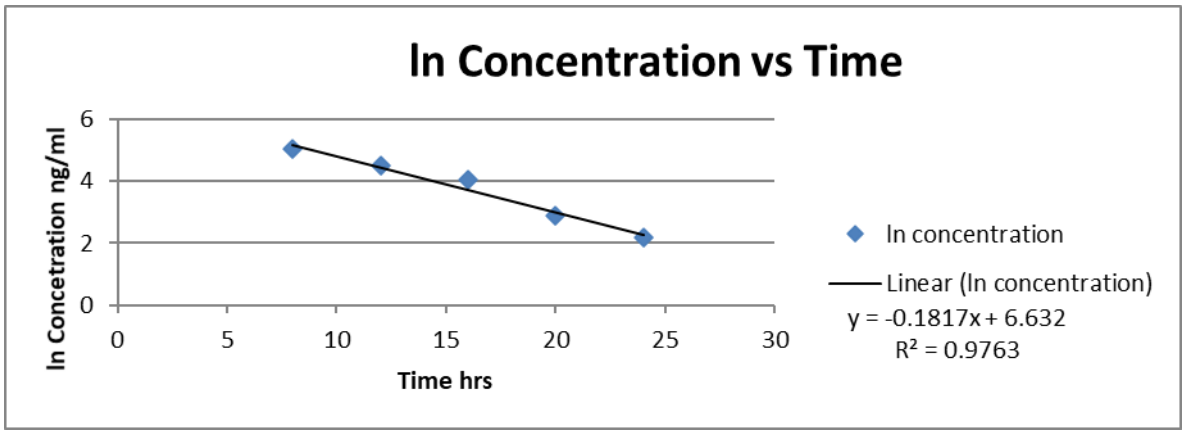

Figure no 3: Elimination rate constant determination of paliperidone palmitate nanocapsule.

For determining the absorption rate constant, residual concentrations of absorption phase was calculated. Residual concentration of absorption phase was plotted against the corresponding time gives a straight line with r^2 value 1 and from the slope we got the absorption rate constant (Ka) is 0.224 hr^{-1}.

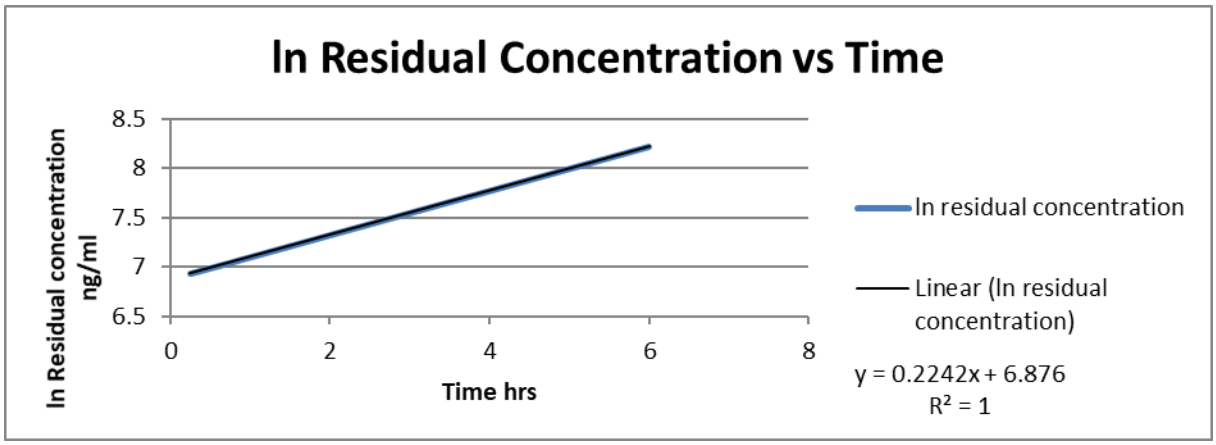

Figure no 4: Absorption rate constant determination of paliperidone palmitate nanocapsule.

From the two rate process such as absorption rate and elimination rate it shows that the rate of absorption rate 0.224 hr^{-1} of paliperidone palmitate from nanocapsule suspension was greater than that of the elimination rate of 0.181hr^{-1}.

Form the data obtained from the animal studies after administering paliperidone nanosuspension was used for determining the pharmacokinetic parameter AUC and AUMC for determining the bioavailability of the formulation. Drug concentrations at different time intervals are plotted against the time interval gives a graph as follows and the area under the curve (AUC) was determined by trapezoidal rule which directly related to the bioavailability of paliperidone palmitate from the nanocapsule suspension.

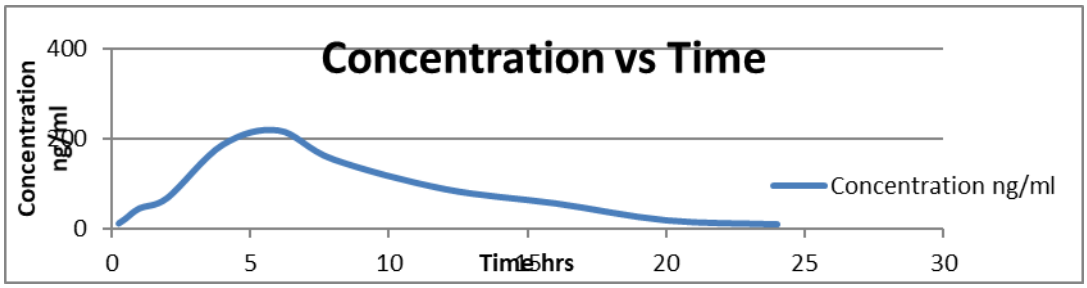

Figure no 5: AUC determination of paliperidone palmitate nanocapsule.

For determining the area under the first moment curve (AUMC) is determined by plotting a graph of concentration multiplied by time on Y axis and time in hours on X axis gives a graph. The area under this curve is determined by trapezoidal rule, gives the AUMC.

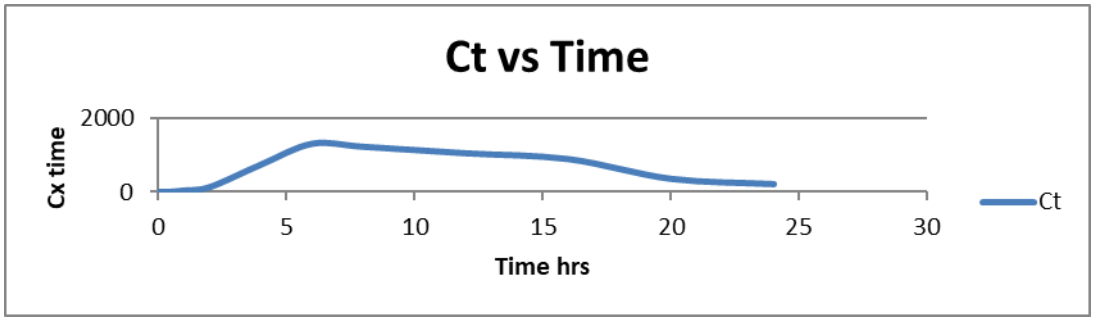

Figure no 6: AUMC determination of paliperidone palmitate nanocapsule.

DETRMINATION OF AUC AND AUMC - NANOSUSPENSION				
Time in hrs	Concentration ng/ml	AUC	Ct	AUMC
0	0	0	0	0
0.25	11	1.375	2.75	0.34375
0.5	22	4.125	11	1.71875
1	45	16.75	45	14
2	68	56.5	136	90.5
4	187	255	748	884
6	219	406	1314	2062
8	154	373	1232	2546
12	88	484	1056	4576
16	56	288	896	3904
20	18	148	360	2512
24	9	54	216	1152
	AUC	2086.75	AUMC	17742.56

Table no 6: AUC and AUMC determination of nanocapsule suspension

Mean residence time of paliperidone palmitate from nanosuspension was determined by the following equation

MRT= AUMC/AUC

= 17742/2086= 8.50 hr

Volume of distribution can be calculated by Vd= $\frac{FKaD0}{(Ka-Ke)A}$

PHARMACOKINETIC PARAMETERS	
Ke	0.181/Hr
Ka	0.224/hr
MRT	8.50249
CmaX	219 NG/ML
Tmax	6 hr
Vd	18.18L
AUC	2086.75 ng*hr/L

From the above data the following pharmaciokinetic parameters was determined and given in the table below

Table no 7: Pharmacokinetic parameters of nanocapsule suspension

Bioavailability study of paliperidone palmitate conventional suspension

For comparing the bioavailability of the nanosuspension with conventional suspension, paliperidone palmitate suspension equivalent to 3mg of paliperidone palmitate was administered to albino rats of second groups. Blood samples were collected from tail vein and analysed by HPLC and following data was generated.

Time in hrs	Mean peak area	Concentration ng/ml
0.25	99	1.1
0.50	180	3.7
1	300	7.5
2	631	18
4	1260	38
6	2457	76
8	3087	96
12	2047	63
16	820	24
20	335	8.6
24	162	3.11

Table no 8: In vivo bioavailability study data of conventional suspension of paliperidone palmitate

For the determination of pharmacokinetic parameters the generated data was used.

Time in hrs	Concentration ng/ml	ln conc	Absorption phase concentration	Residual	ln residual
0.25	1.1	0.09531018	1226.904884	1225.804884	7.111352956
0.5	3.7	1.30833282	1152.282368	1148.582368	7.046283738
1	7.5	2.014903021	1016.377305	1008.877305	6.916593413
2	18	2.890371758	790.7642815	772.7642815	6.649974062
4	38	3.63758616	478.6644944	440.6644944	6.088283802
6	76	4.33073334	289.7446224	213.7446224	5.364781949
8	96	4.564348191	175.3878702	79.38787024	4.374345589
12	63	4.143134726			
16	24	3.17805383			
20	8.6	2.151762203			
24	3.11	1.134622726			

Table no 9: pharmacokinetic parameters determination of conventional suspension of paliperidone palmitate

For determining the elimination rate constant of conventional suspension of paliperidone palmitate, a graph was plotted with natural logarithmic concentration of palieridone palmitate in different time interval collected blood sample of last linear elimination phase on Y axis and time in hours on X axis. The graph was a straight line with r^2 value of 0.999. From the slope of the line elimination rate constant Ke was calculated ie, 0.251hr^{-1}.

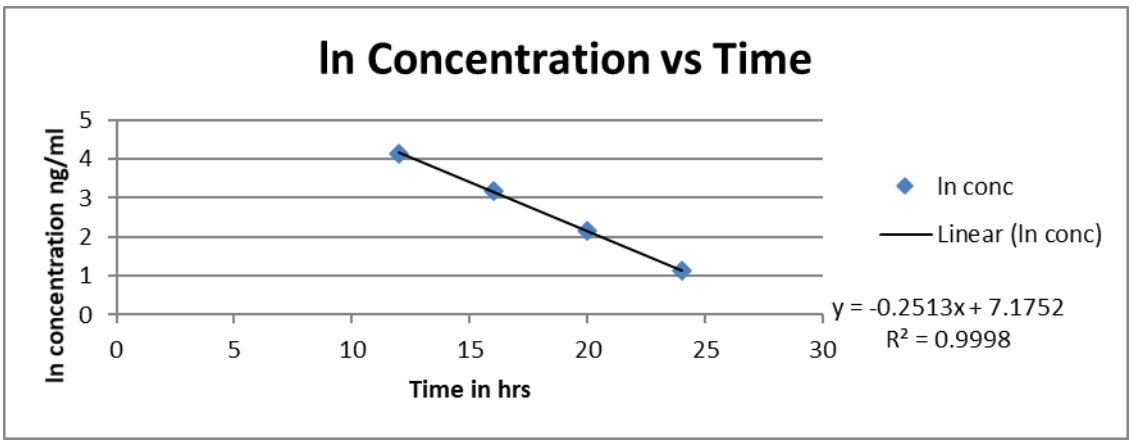

Figure no 7: Elimination rate constant determination of paliperidone palmitate conventional suspension

For determining the absorption rate constant Ka, a graph was plotted by residual concentration of paliperidone palmitate at the blood sample collected at the absorption phase against the time in hours. The graph was a straight line with r^2 value of 0.985. From the slope of the straight line absorption rate constant Ka was determined ie, 0.34 hr^{-1}.

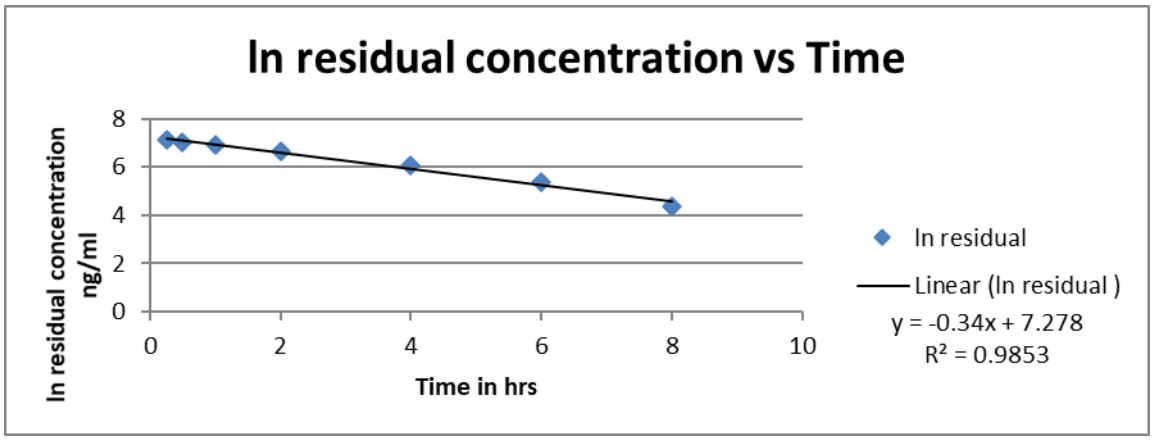

Figure no 8: Absorption rate constant determination of paliperidone palmitate conventional suspension

For determining the bioavailability of the conventional suspension of paliperidone palmitate we have to find out the AUC and AUMC. For AUC determination a graph was plotted by on Y axis concentration of paliperidone palmitate at different time interval and on X axis time interval in hours. From the curve obtained calculated the area under the curve by using trapezoidal rule ie 938.90 ng*hr/L. AUC is directly related to the extent of drug absorption.

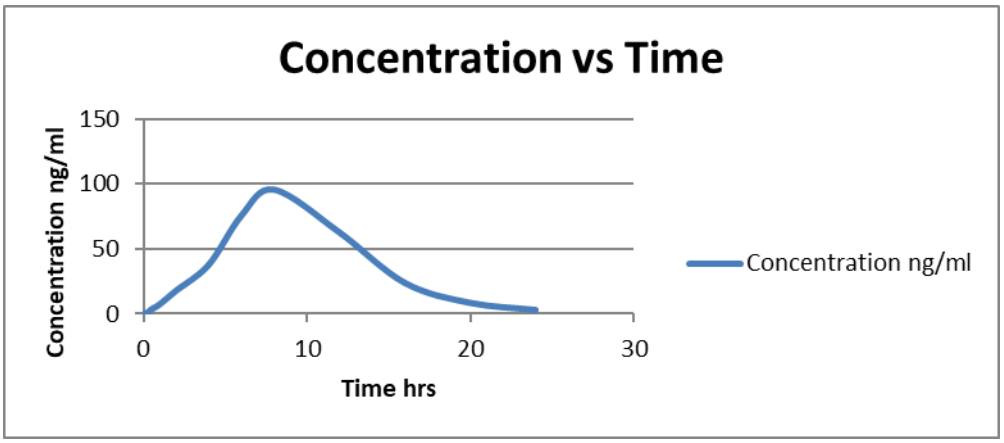

Figure no 9: AUC determination of paliperidone palmitate conventional suspension

For the determination of AUMC, a graph was plotted by on Y axis concentration of paliperidone palmitate at different time interval multiplied by time and time in hours on X axis gives a curve. The total area under the curve was calculated by trapezoidal rule. This calculated area gives the AUMC ie 8977.66 ng*hr/L.

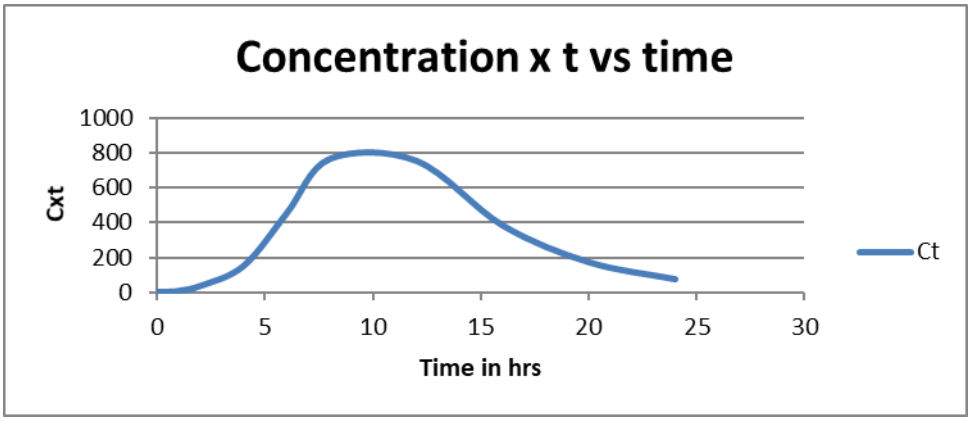

Figure no 10: AUMC determination of paliperidone palmitate conventional suspension

DETERMINATION OF AUC AND AUMC- CONVENSIONAL SUSPENSION				
Time in hrs	Concentration ng/ml	AUC	Ct	AUMC
0	0	0	0	0
0.25	1.1	0.1375	0.275	0.034375
0.5	3.7	0.6	1.85	0.265625
1	7.5	2.8	7.5	2.3375
2	18	12.75	36	21.75
4	38	56	152	188
6	76	114	456	608
8	96	172	768	1224
12	63	318	756	3048
16	24	174	384	2280
20	8.6	65.2	172	1112
24	3.11	23.42	74.64	493.28
		938.9075		8977.6675

Table no 10: AUC and AUMC determination of conventional suspension of paliperidone palmitate

From the values obtained for AUC and AUMC the mean residence time MRT was determined.

MRT= AUMC/AUC

= 8977/938= 9.56 hr

Volume of distribution can be calculated by Vd= $\frac{FKaD0}{(Ka-Ke)A}$

PHARMACOKINETIC PARAMETERS	
Ka	0.34/hr
Ke	0.251 /hr
Tmax	8hrs
Cmax	96ng/ml
AUC	938.9075 ng*hr/L
MRT	9.5618
Vd	8.2L

Table no 11: Pharmacokinetic parameters of conventional suspension of paliperidone palmitate

CONCLUSION

This bioavailability study has successfully investigated the extent and rate of absorption of the paliperidone palmitate nanocapsule suspension with conventional suspension. The results demonstrate the significant influence of nanocapsule formulation of paliperidone palmitate on the bioavailability of the compound. The comparative bioavailability study shows that AUC of nanocapsule suspension was 2086.75 ng*hr/L which is 2.22 times greater than that of the AUC of paliperidone conventional suspension ie 938.9075 ng*hr/L. Through careful experimentation and comprehensive data analysis, we have gained a deeper understanding of how the body processes and utilizes the compound after administration. This knowledge has important implications for drug development, clinical dosing, and therapeutic efficacy.

The study's findings emphasize the importance of tailoring drug delivery methods to optimize bioavailability, ultimately leading to more effective and efficient treatments. Furthermore, these insights contribute to the broader field of pharmacy by advancing our understanding of how different variables impact the bioavailability of pharmaceutical agents. It is worth noting that while this study provides valuable insights, there are potential limitations that should be acknowledged. Further research, including larger sample sizes, longer study durations, and additional comparative analyses, could refine our understanding and provide a more comprehensive picture of bioavailability dynamics.

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