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Sub-Chronic Toxicity Test of Solid Self Nanoemulsifying Drug Delivery System (S-Snedds) Hydrochlorothiazide in Male Rats

Asep Nurrahman Yulianto[1], Wahyu Widyaningsih[2], Iis Wahyuningsih[3], Ilham Fadilah[4], Tatang Tajudin[5]
[1,4,5] Faculty of Pharmacy, Science and Technology, Universitas Al-Irsyad Cilacap, Indonesia
[2,3] Faculty of Pharmacy, Universitas Ahmad Dahlan Yogyakarta, Indonesia
Email: widyaningsihwahyu@yahoo.com

ABSTRACT

Hydrochlorothiazide (HCT) is a diuretic thiazide that is commonly used in the treatment of hypertension, although it exhibits has low bioavailability. The development of the Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) is expected to be able to increase the solubility and bioavailability orally administered of HCT. This study aims to evaluate the sub-chronic toxicity of S-SNEDDS HCT formulations by examining biochemical parameters (SGOT, SGPT, BUN, and creatinine), and histopathological analysis of liver, kidney, and heart in male Wistar strain rats. An experimental design with five distinct treatment groups was utilized: negative control (CMC-Na 0,5%), S-SNEDDS base (aerosil), positive control (pure HCT 25 mg/kg BW), S-SNEDDS HCT (25 mg/kg BW), and satellite group (S-SNEDDS HCT 50 mg/kg BW). The treatment spanned for 28-days, followed by a 14-days observation period with no treatment for the satellite group. The results showed that SGPT, BUN, and creatinine remained normal across all groups, suggesting the absence of liver or kidney damage. Histopathology analysis shows structural changes in the form of degeneration, necrosis, and infiltration of inflammatory cells mainly in the pure HCT and S-SNEDDS HCT groups, however in the satellite group the damage may return to normal when administration is stopped.

***Key words**: Hydrochlorothiazide, S-SNEDDS, Sub-chronic Toxicity Test*

INTRODUCTION

Hypertension is often referred to as the silent killer because it generally does not show specific symptoms or complaints, so many sufferers are unaware that they have this condition (Ministry of Health, 2023). According to Salmah Arafah et., al., (2024) in his journal it was stated that hypertension is still a serious health problem in Indonesia, with a prevalence rate of 31.7% in the adult population. This figure is relatively high when compared to neighboring countries such as Singapore (27.3%), Thailand (22.7%), and Malaysia (20%). The number of people with hypertension worldwide continues to increase from around 639 million cases in 2000, expected to jump to 1.15 billion cases by 2025. Among adults, the prevalence of hypertension ranges from 6 to 15%, and alarmingly, about half of them are unaware that they have this condition. In Indonesia alone, hypertension is the third most common cause of death in all age groups, accounting for around 6.83% of total deaths.

Treatment of hypertension can be done with several therapy options including the Diuretic group. One of the diuretics is hydrochlorothiazide (HCT). The drug works by increasing the excretion of water and sodium through the kidneys, which ultimately reduces cardiac output and lowers blood pressure. Although effective, the use of HCT as an antihypertensive has a drawback, namely its relatively low bioavailability, around 65-70% (Farahiyah & Syaifullah, 2021). One of the solutions that can be pursued is to develop HCT in the form of Solid Self Nano Emulsifying Drug Delivery System (S-SNEDDS) preparations.

In recent years, solid Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS) have attracted a lot of attention due to their significant success in improving the oral bioavailability

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of low-solubility drugs. Various techniques have been developed to convert conventional liquid SNEDDS into solid form, one of which is dispersion to solid carriers (Nasr *et al.,* 2016). The high concentrations contained in Solid-SNEDDS preparations often cause some toxic effects. Toxicity measurements are complex because the severity can vary between organs and is influenced by factors such as age, genetics, gender, diet and individual health status (Irianti & Sugiyanto, 2017).

Toxicity tests are performed to evaluate the potential risks that may be posed by a chemical or toxic substance. The resulting data provides information on the level of danger of the substances being tested in the event of human exposure, so that the dosage of use can be determined to ensure safety.

MATERIALS AND METHODS

Equipment and Materials

The tools used in this study include test animal cages, oral probes, syringes, glass tools (pyrex), sonicators, vortex mixers (VM - 300), capillary tubes, hematocrit blood tubes, scalpels, surgical scissors, organ pots, tweezers and analytical balances. The ingredients used in this study include Hydrochlorothiazide (HCT) PT Kimia Farma Plant Banjaran, Labrasol, PEG 400 (Brataco®), Tween 80 (Brataco®), NaCL, HCL Concentrate, aquadest (Brataco®), formalin buffer, phosphate buffer, haemotoxin eosin, male Wistar rats.

Method

The method used in this study uses an experimental method. Preparation of test animals using wistar strain rats. The preparation was given orally to rats for 28-days and continued for 14-days without treatment for the satellite group, then tested for SGOT, SGPT, BUN and Creatinine levels, weight observation and histopathology in rats. The observation data was analyzed using one-way ANOVA.

Preparation of SNEDDS

SNEDDS HCT preparations are made by mixing Labrasol (oil phase), Tween 80 (Surfactant), and PEG 400 (Co-surfactant) with 25 mg of HCT. The mixture is stirred using a vortex for 15 minutes until evenly distributed, then processed using an ultrasonicator to remove air bubbles. The resulting SNEDDS HCT has a concentration of 25 mg of HCT in 1 mL of SNEDDS.
The formulation of SNEDDS HCT can be seen in the Table 1.

Table 1. Composition of SNEDDS HCT Formulation

Vehicle	Function in SNEDDS	Composition (% v/v)
Labrasol	Oil phase	16,67
Tween 80	Surfactant	59,97
PEG 400	Co-surfactant	23,36
HCT	Drug	25mg

Percent Transmittance

The transmittance test is carried out by measuring the level of clarity of the preparation. A transmittance value of almost 100% indicates that the SNEDDS formula produces a clear preparation with a droplet size estimated to reach the SNEDDS scale with a percent transmittance value of more than 90%. Measurements were made using a UV-VIS

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spectrophotometer at a wavelength of 650 nm, the transmittant value was calculated to ensure the level of clarity of the formed nanoemulsion system (Huda & Wahyuningsih, 2018).

Formulation of S-SNEDDS HCT

Solid SNEDDS HCT is made using the adsorption to solid carrier method. In this process, 1 mL of SNEDDS HCT (25mg/kg BW) preparation is dried by gradually mixing it with 500 mg of aerosil until the mixture becomes homogeneous and dry.
The formulation of S-SNEDDS HCT can be seen in the Table 2.

Table 2. Composition of S-SNEDDS HCT Formulation

Vehicle	Composition (% v/v)
SNEDDS HCT (25mg/1mL SNEDDS)	1 mL
Aerosil	500mg

Ethical Clearance

Ethical clearance for the animal test has been approved by the Komisi Etik Penelitian Kesehatan (KEPK-UMP) of Universitas Muhammadiyah Purwokerto, with number KEPK/UMP/195/I/2025.

Sub-chronic Toxicity Testing Treatment

Rats were obtained from the "Iman Saliman" mouse farm located in South Purwokerto, Banyumas. The test animals were divided into 5 groups placed in cages with each group containing 5 rates. Administration is given orally with the following doses:

a. Group I was given drinking water, standard feed during the study, and 0.5% Na-CMC suspension (Negative control)
b. Group II was given drinking water, standard feed during the study, and aerosil (base S-SNEDDS) in 0.5% Na-CMC
c. Group III was given drinking water, standard feed during the study, and HCT suspension in 0.5% Na-CMC (Dose 25mg/kg Bw)
d. Group IV was given drinking water, standard feed during the study, and S-SNEDDS suspension in 0.5% Na-CMC (Dose 25mg/kg Bw)
e. Group V (satellite group) was given drinking water, standard feed during the study, and S-SNEDDS HCT with a dose of 50mg/kg BW then the test animal was left with an additional time of 14 days without treatment.

The test animals that will be used in this study are male rats of the wistar strain that have previously passed the acclimatization period. The test animals amounted to 25 rats which were divided into 5 test groups where each group contained 5 test animals. The provision will be done once in the afternoon and carried out daily during the research period. Provision will be made by administering preparations to each group of Negative, Positive, Base S-SNEDDS, S-SNEDDS HCT and satellite groups via peroral route for a period of 28 days and an additional 14 days will be given to the satellite group without administering preparations, with the aim of seeing the effect of the preparations on test animals.

SGOT, SGPT, BUN and Creatinine Levels Analysis

Blood sampling was carried out from the corner of the rat's eye after oral treatment on day 28. Before ingestion, the rats were first anesthetized using ether. Blood is drawn from the

orbital sinuses (corners of the eye) using capillary tubes inserted in a circular motion. The blood that comes out is then collected into the tube and stored in a cooler box to maintain the stability of the sample (Budiyanto *et., al*., 2022).

Examination of the weight of the target organs

Examination of the weight of the target organs is carried out as soon as the test animal is sacrificed. Target organs such as liver, kidneys and heart before weighing must first be dried with absorbent paper and then immediately weighed to obtain the absolute weight of the organs. The relative weight of the organs can be found using the following formula:

$$\text{Relative Weight of Organs} = \frac{\text{absolute organs weight}}{\text{Rats Body Weight}}$$

Histopathological examination of the target organs

Extraction of target organs in the form of liver, kidneys and heart is carried out at the end of the treatment period and after blood collection. Furthermore, the rats were sacrificed by giving ether, their liver, kidneys and heart organs were taken. The organ is stored in a 10% formalin solution to be prepared for histopathology.

Data collection and analysis

Data collection was obtained from tests that have been carried out, such as blood clinic chemistry test data which included SGOT, SGPT, BUN and Creatinine levels after treatment, Organs Weight after research, Weight of rats during the study and assessment of the results of histopathological tests on target organs. Where then the data will be presented in the form of a table for further data analysis. The results of the experiment from the administration of Solid-Self Nano Emulsifying Drug System (S-SNEDDS) HCT were analyzed by analyzing quantitative data of toxicity tests on rats conducted statistically using the One-Way ANOVA test which was then followed by the LSD (Lease Significant Different) test.

RESULTS AND DISCUSSION

SGOT and SGPT Rate Test

To find out the damage caused by the drug Hydrochlorothiazide in the form of Solid SNEDDS preparation, a study was carried out in the form of comparison and different doses, where the S-SNEDDS group was given with a concentration of 25mg/1ml of SNEDDS into 500mg aerosil, and a satellite group with a concentration of 1 ml SNEDDS HCT into 1g of aerosil, besides that for comparisons there was also a positive group with pure HCT powder, the negative group that was only given Na-CMC and also the base group that was given only the Aerosil (S-SNEDDS base).

The results of the measurement of SGOT and SGPT levels can be seen in the following table.

Table 3. Table of SGOT and SGPT Measurement Results

Group	SGOT (U/L)	SGPT (U/L)
Negative	37.67 ± 7.51	15.00 ± 2.00
Positive	45.33 ± 3.06	18.00 ± 1.00
S-SNEDDS Base	33.33 ± 5.51	18.00 ± 1.00
S-SNEDDS HCT 25mg/kg BW	45.00 ± 8.89	23.33 ± 2.31
Satellite S-SNEDDS HCT 50mg/kg BW	37.33 ± 0.58	15.33 ± 1.15

Normal values for SGOT and SGPT levels are 45-100 U/L and 10-50 U/L (BPOM, 2021). The results of the study for SGOT and SGPT levels showed that for the negative, base

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and satellite groups, values in the normal range tended to be low, while for SGOT and SGPT levels for the positive test group and S-SNEDDS HCT preparations, the values were higher than the other groups, but still within the normal range. This shows that HCT preparations both in the state of pure powder and those that have been formed into S-SNEDDS preparations do not show toxic effects on the liver organs as shown that the levels of SGOT and SGPT in blood serum are still at normal values. Increased levels of SGOT and SGPT enzymes in liver damage occur due to damage to liver cells (hepatocytes), especially in the cell membrane. This damage causes these enzymes to leave the hepatocyte cells and enter the bloodstream (Sukohar *et al*., 2019). The satellite group was further observations where the test animals were left for 14 days to monitor the effects of improvement experienced by the test animals. In accordance with the results of the study for the satellite group, after being left for 14 days, results were obtained with lower values than the S-SNEDDS HCT group. This indicates that the effects of the administration of S-SNEDDS HCT preparations are not permanent or permanent, but may return to normal after administration is stopped.

BUN and Creatinine Levels Test

The results of BUN and Creatinine levels measurement can be seen in the following table.

Table 4. BUN and Creatinine Test Results

Group	Creatinine (mg/dl)	BUN (mg/dl)
Negative	0.80 ± 0.00	10.73 ± 1.61
Positive	0.87 ± 0.06	17.50 ± 0.72
S-SNEDDS Base	0.60 ± 0.10	13.00 ± 1.67
S-SNEDDS HCT 25mg/kg BW	0.73 ± 0.06	13.70 ± 3.12
Satellite S-SNEDDS HCT 50mg/kg BW	0.57 ± 0.06	12.73 ± 1.60

The normal value for creatinine levels in rat blood ranges from 0.5 to 0.8 mg/dl, while for urea nitrogen levels in the blood ranges from 10-16 mg/dl in male rats and 10-19 mg/dl in female rats (Kurniawati, 2016). According to the data, the results of the study showed that the values of creatinine and BUN in the positive group were slightly higher than the normal limit, while in the other group it was still in the normal limit range. Looking at the data from the results of the study in each group, it does not show a significant increase. This shows that HCT preparations both in their pure state and after conversion to S-SNEDDS preparations do not cause toxic effects on blood serum for kidney damage parameters.

Target Organs Weight Examination

The results of the calculation of the relative weight of the targets organ can be seen in the following table.

Table 5. Results of Calculation of Relative Weight of Target Organs

Group	Relative Organ Weight		
	Heart	Liver	Kidney
Negative	0.77 ± 0.0036	6.495 ± 0.0305	1.37 ± 0.0064
Positive	0.71 ± 0.0033	5.285 ± 0.0248	1.24 ± 0.0058

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Group	Relative Organ Weight		
	Heart	Liver	Kidney
S-SNEDDS Base	0.745 ± 0.0040	7.09 ± 0.0379	1.37 ± 0.0073
S-SNEDDS HCT 25mg/kg BW	0.61 ± 0.0037	7.615 ± 0.0460	1.495 ± 0.0092
Satellite S-SNEDDS HCT 50mg/kg BW	0.74 ± 0.0038	6.4 ± 0.0324	1.755 ± 0.0088
one-way Anova (Sig.)	0.661	0.192	0.522

The results of the analysis using one-way anova showed that in all organs the significance value of p>0.05, this shows that from each test group there was no significant difference between the test groups, so that the administration of S-SNEDDS HCT preparations with doses of 25mg/ml did not affect the weight of liver, kidney and heart organs in the test animals. According to research conducted by Putra *et., al* (2023), organ index cannot be used as the only parameter to assess the toxic effects of test preparations on organs. This is due to the possibility of a mismatch between the weight of the organs and the body weight of each test animal. Therefore, further studies through histopathological examination are needed to observe the cell structure and tissue of the organ in detail, so that the effect of the toxicity of the test preparation on the organ can be known.

Histopathology Analysis

Extraction of target organs in the form of liver, kidneys and heart is carried out at the end of the treatment period and after blood collection. Furthermore, the rats were sacrificed by giving ether, their liver, kidneys and heart organs were taken. The organs is stored in a 10% formalin solution to be prepared for histopathology.

Figure 1. Histopathological Cross-Section of Heart

Based on the results of histopathological testing on the target organs, results were obtained in the form of cross-sectional images of the target organ with the heart organ showing the presence of hemorrhage marked by a white arrow, degeneration marked by a green arrow

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and necrosis marked with a black arrow in negative group samples, positive, S-SNEDDS base, and satellite, while in the S-SNEDDS HCT group, only hemorrhoids and degeneration were found.

Table 6. Scoring of histopathological results of the heart organs.

Test Group	Average Heart Damage Score
Negative	2
Positive	2
S-SNEDDS Base	1
S-SNEDDS HCT 25mg/kg BW	2
Satellite S-SNEDDS HCT 50mg/kg BW	1

Based on the scoring results of the histopathological test carried out, it shows that all categories show minor damage which is shown with a scoring value of 1-2 only. In the Negative, Positive, and S-SNEDDS HCT showed a score of 2 where this showed minor damage to the heart with a percentage of damage ranging from 25%-50%. Meanwhile, in the S-SNEEDS Base and Satellite group, it showed scoring at a value of 1 with a percentage of damage below 25%. The results of histopathological tests on the heart organ can be concluded that in this study there was minor damage in all test groups, so it is necessary to ensure that the damage occurred either from the effect of giving the preparation or from the condition of the rats themselves.

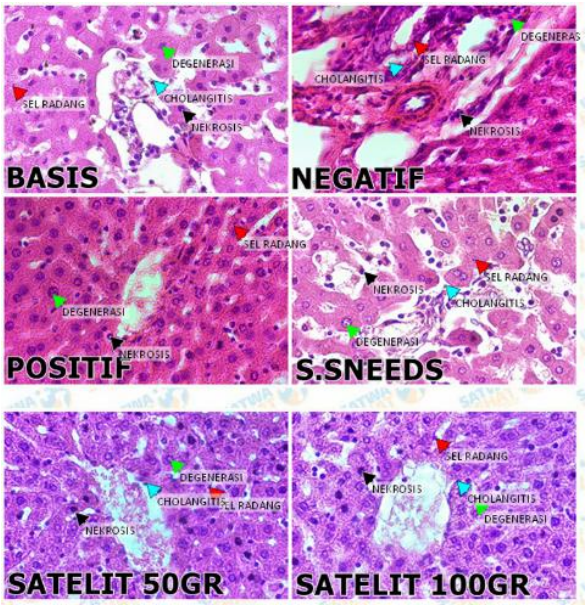

Figure 2. Histopathological Cross-Section of Liver

Histopathological results in liver organs showed the presence of inflammatory cells marked with red arrows, cholangitis marked with blue arrows, degeneration marked with green arrows, and necrosis marked by black arrows found in the cross-section of the organs in the negative group, S-SNEDDS HCT base, and satellite. Meanwhile, in the positive test group, only inflammatory, degenerative and necrosis cells were found without cholangitis.

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Table 7. Scoring Histopathological Results of the Liver Organ

Test Group	Necrosis	Degeneration	Inflammation	Cholangitis
Base S-SNEDDS	1	2	1	1
Negative	2	2	2	0
Positive	3	2	2	1
S-SNEDDS HCT 25mg/kg BW	4	3	3	1
Satellite S-SNEDDS HCT 50mg/kg BW	3	2	2	2

The results of the liver histopathology test showed varying levels of tissue damage between groups. The negative control group and the S-SNEDDS base group showed low scores, indicating relatively normal liver condition and minimal damage. The positive control group experienced mild damage, characterized by an increased score of necrosis and cholangitis. The group given S-SNEDDS HCT showed the highest score on all parameters, indicating the presence of severe liver damage due to the toxicity of the active ingredient. Meanwhile, the satellite groups showed lower scores than the full S-SNEDDS HCT group, indicating the likelihood of recovery of liver tissue after discontinuation of treatment.

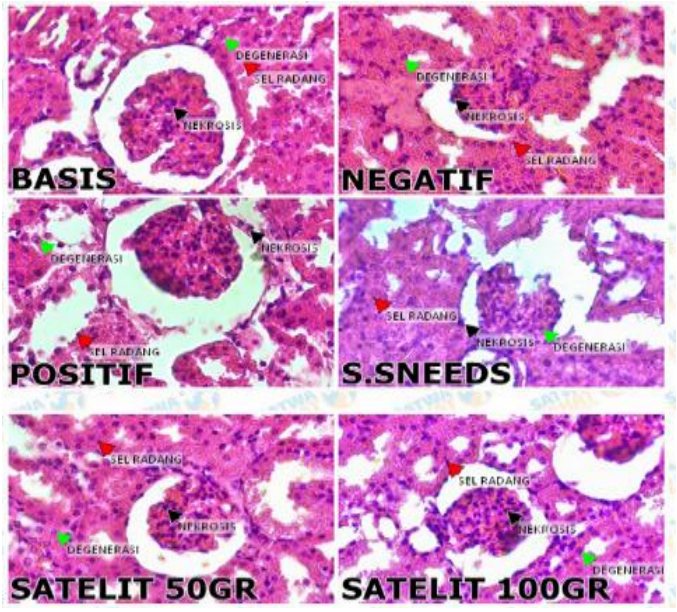

Figure 3. Histopathological Cross-Section of Renal

Histopathological examination of the renal organs showed the presence of inflammatory cells marked with red arrows, degeneration marked with green arrows, and necrosis marked with black arrows found in all test groups.

Table 8. Scoring Histopathological Results of Renal Organs

Test Group	Tubule Epithelial Cell Degeneration	Necrosis of tubule epithelial cells	Inflammatory Cell Infiltration (Interstitial)
Basic S-SNEDDS	2	4	1
Negative	2	4	2
Positive	3	4	2

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Test Group	Tubule Epithelial Cell Degeneration	Necrosis of tubule epithelial cells	Inflammatory Cell Infiltration (Interstitial)
S-SNEDDS HCT 25mg/kg BW	3	4	3
Satellite S-SNEDDS HCT 50mg/kg BW	2	6	3

Renal histopathology tests evaluate three main parameters: tubule epithelial cell degeneration, necrosis, and inflammatory cell infiltration. The negative control group and the S-SNEDDS base showed mild damage with a low score, indicating relatively normal kidney condition. The S-SNEDDS HCT group showed an increase in scores, especially in degeneration (score 3) and infiltration (score 3), which reflected the presence of more significant inflammation and tissue damage. The satellite groups showed a high necrosis score (score 6), but still classified as mild damage. Despite the increased damage, the data showed that kidney tissue had the potential to recover after discontinuation of preparation, especially seen in the satellite group.

Data Analysis of SGOT, SGPT, BUN and Creatinine Serum Test Results

Table 9. Normality Test Results Data

Parameters	Group	Shapiro-Wilk (Sig-)
SGOT	Negative	0.637
	Positive	0.174
	S-SNEDDS Base	0.433
	S-SNEDDS HCT 25mg/kg BW	0.363
	Satellite S-SNEDDS HCT 50mg/kg BW	0.567
SGPT	Negative	1.000
	Positive	1.000
	S-SNEDDS Base	1.000
	S-SNEDDS HCT 25mg/kg BW	0.637
	Satellite S-SNEDDS HCT 50mg/kg BW	1.000
BUN	Negative	0.298
	Positive	0.537
	S-SNEDDS Base	0.702
	S-SNEDDS HCT 25mg/kg BW	0.787
	Satellite S-SNEDDS HCT 50mg/kg BW	0.931
Creatinine	Negative	1.000
	Positive	0.637
	S-SNEDDS Base	1.000
	S-SNEDDS HCT 25mg/kg BW	0.637
	Satellite S-SNEDDS HCT 50mg/kg BW	0.637

S-SNEDDS HCT preparations through analysis of blood parameters (SGOT, SGPT, BUN, and creatinine) using Shapiro-Wilk, ANOVA, and LSD assays. All data were distributed normally ($p > 0.05$) and the ANOVA test showed significant differences between groups ($p < 0.05$). The LSD test revealed that SGPT levels experienced significant differences mainly in

the S-SNEDDS HCT group compared to other groups, but were still within normal limits, indicating no significant liver damage. SGOT levels did not show a significant difference, although there was an upward trend.

In renal parameters, creatinine levels showed significant differences between groups, but remained within the normal range (0.2–0.8 mg/dL). BUN levels increased significantly in the positive control group, while the S-SNEDDS HCT and satellite groups showed lower values and did not differ significantly from the controls, indicating the possibility of milder renal toxicity. Overall, despite the improvement in some parameters, the values were still within normal physiological limits, indicating that S-SNEDDS HCT preparations were relatively safe for liver and kidney function.

CONCLUSION

Based on the results of the blood serum test, it showed that the HCT and S-SNEDDS HCT showed an increase in each parameter, where the highest levels for SGOT and SGPT parameters occurred in the S-SNEDDS group with values of 45.00 ± 8.89U/L and 23.33 ± 2.31U/L. The highest levels of Creatinine and BUN occurred in the positive group where the values were consecutively at 0.87 ± 0.06mg/dL and 17.50 ± 0.72mg/dL. In the S-SNEDDS satellite group, there was a counter-effect by showing a decrease in blood serum levels from all parameters after administration was stopped for 14 days. The data show that S-SNEDDS preparations can cause non-persistent hepatotoxicity damage as evidenced by decreased levels after discontinuation of use. Meanwhile, in the positive group, it can cause kidney dysfunction due to the administration of pure HCT.

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