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Research Article

Hepatoprotective Effect of Curcumin Microsponges against Paracetamol-Induced Liver Toxicity in Rats

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ABSTRACT

There are currently numerous pharmacological effects associated with curcumin, but its use in clinical settings is constrained by its poor bioavailability. In this research, we created a formulation for curcumin microsponges and assessed their ability to protect rats livers from damage brought on by paracetamol. Paracetamol (2 g/kg/day) was used to produce toxicity over the course of 10 days. Paracetamol causes marked hepatotoxicity in rats by raising the standard of ALT, AST, ALP, and total bilirubin, which are liver function indicators along with reducing total protein level. Animal were treated orally including Curcumin microsponges (100 mg/kg) and plain curcumin (P-CUR) (100 mg/kg) daily for 10 days. Rats were sacrificed on the last day of treatment and the liver was excised for histopathological analysis. According to our findings, microsponges have a greater hepatoprotective impact than regular plain curcumin. When curcumin microsponges were administered, paracetamol-induced liver damage was successfully reduced, as seen by a decrease in liver function indicators. Our study suggests that curcumin microsponges have strong potential hepatoprotective effects.

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INTRODUCTION

Liver is among the most crucial structures and is primarily responsible for the synthesis of protein, detoxification, the generation of variety of biochemical substances, and the control of the body's homeostasis [1]. It is constantly exposed to chemicals, alcohol and narcotics, which cause structural and functional alteration in the liver and lead to major complications for example hepatitis, cholestatic, hemochromatosis, and cirrhosis [2,3]. A common analgesic and antipyretic drug, paracetamol (PCM) is quite safe when used at prescribed dosages [4]. At a maximal dose of 4 g/day, PCM overdose may result in hepatotoxicity [5,6]. Due to their enormous frequency, hepatic disorders are the main cause of illness and mortality worldwide. In excess, PCM can harm the liver by producing N-acetyl-p-benzoquinone imine (NAPQI), a harmful result i.e., processed in the liver. NAPQI interacts with hepatic proteins and glutathione to cause lipid peroxidation, DNA breakage, free radical production, oxidative stress, then liver injury [7,8]. A wide range of ailments can be treated with several natural products. The biologically active polyphenolic substance known as curcumin (CUR) is originating from the plant Curcuma longa in the ginger family, Zingiberaceae. Reports revealed the protective effect of curcumin for the management of immune system illnesses [9], Degenerative diseases of the brain [10], coronary artery diseases [11], respiratory failures [12], gastrointestinal diseases [13], inflammation and joint discomfort [14], anticancer [15], Antioxidant treatment and hepatoprotective characteristics [16]. CUR consumption promotes liver detoxification by altering GSH activity [17], which also reduces structural alteration of the liver. It showed ameliorative activity in the treatment of liver cancer, liver fibrosis, and cholestasis [18]. It has a wide range of molecular targets that can interact with, including those implicated in inflammation [19]. Curcumins limitations application due to its limited absorption and poor water solubility as a medication to treat ailments [20,21]. To improve the absorption and pharmacological activity of curcumin, a novel preparation must be needed. In the present research curcumin microsponges are utilized because of their highly effective nature than the natural curcumin. Microsponges have particles that vary in size from 5 to 300 μm. highly stable, cross-linked, porous, and polymeric in nature [22]. Because of their sponge-like appearance, microsponges have unique compression and dissolving capabilities [23]. They exhibit less adverse reactions, nontoxic, do not cause mutations, and have higher levels of patient compliance [24]. Improving the substances rate of dissolution and adhesive properties ability was the goal of the present study. The microsponges were assessed using XRD, DSC, SEM, and FTIR techniques. A surface examiner was used to evaluate the gels mechanical strength inside the capsules, and the capsules were evaluated using a battery of pharmacological tests. The total drug content, manufacturing yield, average particle size, and entrapment efficiency were all calculated. The effectiveness of the prepared microsponges was evaluated for their hepatoprotective activity in experimental animals by using a paracetamol-induced liver toxicity animal model.

MATERIALS AND METHODS

Drugs and chemicals

Curcumin was obtained from Konark Herbal and Health Care, Mumbai, India as a gift sample. Ethylcellulose and polyvinyl alcohol (PVA) were purchased from Loba Chemical Pvt. Ltd., Mumbai. The other chemicals utilised were of an analytical grade.

Methods

Preparation of Microsponges

Oral microsponges are produced via quasi-emulsion solvent diffusion. This technique uses 1-

4% w/v ethyl cellulose in dichloromethane as the internal phase. Solution A was created by gradually adding the medication (200 mg) to the ethyl cellulose solution while continuously mixing at 500 rpm. Subsequently, PVA (0.3%w/v) was added to the aqueous phase to create solution B (Table 1). To create a clear solution, sonicate both solutions on the probe for fifteen minutes. After that, stir continuously for two hours while adding solution A to solution B dropwise at 1000 rpm. Microsponges were stirred for two hours, after which they were filtered and dried in an air-fitted container in a hot air oven [25].

Table 1: Formulation of Curcumin Microsponges

Sr.no	Formulation	Curcumin (mg)	Ethyl cellulose (mg)	Polyvinyl alcohol (mg)	Dichloromethane (ml)	Distilled water (ml)
1.	F1	200	100	300	25	150
2.	F2	200	200	300	25	150
3.	F3	200	300	300	25	150
4.	F4	200	400	300	25	150
5.	F5	200	500	300	25	150

Characterization of Microsponges

Particle size analysis, zeta potential and PDI

The particle size analysis is used for the analysis of the different sizes of particles present in the sample. The curcumin formulation was subjected to particle size, zeta potential and Polydispersity index (PDI) by using HORIBA SCIENTIFIC SZ-100.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR of ethylcellulose, curcumin, and curcumin microsponges sample was analyzed by the Fourier transform infrared spectrophotometer (Jasco-4100) between 400 and 4000 cm-1 in the range of values.

Differential Scanning Calorimetry (DSC) Analysis

Curcumin, ethylcellulose, and curcumin microsponges were conducted using DSC and heated between 30 and 400 °C at a rate of 10 °C per minute. (SETARAM KEP TECHNOLOGIES).

Entrapment Efficiency, Drug loading capacity and Practical yield

Take a weight of curcumin-loaded microsponges (10mg) dissolved in 10 mL methanol. then centrifuge the solution and take 1 ml supernatant from the centrifuge solution. The solution is diluted with a methanolic solution and takes absorbance by measuring with a blank employing a Shimadzu UV 1800 UV-visible spectrophotometer at 424 nm. using a methanolic solution. And the entrapment efficiency was calculated as follows:

Entrapment efficiency (EE)

Drug Entrapment Efficiency=(Total Drug Conc.– Supernatant Drug Conc)/(Total Drug Conc.) X 100

Drug Loading Capacity

Take a weight of curcumin-loaded microsponges as equivalent powder of curcumin (10mg) was dissolved in methanol (10ml). then make a dilution. And take absorbance by Employing a blank made of methanolic solution and a UV-visible spectrophotometer (Shimadzu, UV 1800) set at 424 nm. The following formulas were also used to determine the medication loading efficiency.

Drug Loading capacity=(Mact)/(Mms) X 100

Where Mact is the actual weight of curcumin in curcumin microsponges, Mms is the weight quantity of microsponges powder.

Practical Yield

Practical Yield=(Mass of obtained microsponges)/(Initial mass of polymer + Initial mass of polymer) X 100

Photomicroscopy

Photomicroscopy of curcumin microsponges was observed by using an optical microscope. On the surface of the slide, an aqueous micro-suspension drop was applied, and it was covered with a coverslip. And observed it under a 40X magnification lens.

Scanning Electron Microscopy (SEM)

The surface morphology of curcumin microsponges was studied using a scanning electron microscope. For analysis of surface morphology of formulation.

X-ray Diffraction Studies

Research on X-ray diffraction was carried out to find crystalline and amorphous characteristics. Curcumin, ethylcellulose and curcumin microsponges by using (LYNXEYE XE T (1D mode): PSD counter).

Stability Study

The stability of curcumin microsponges was taken at the accelerated condition as per the ICH Q1 guidelines. The preparation was placed in the stability chamber at 400C ± 20C and 75% ± 5% RH for 3 months. After the accelerated stability condition, microsponges were evaluated by their physical appearance and FTIR Study.

Hepatotoxicity study

Experimental Animals

Four sets of six male wistar rats each were created from healthy male rats. The rats were purchased by us from Wockhardt Ltd. in Aurangabad, India. The CCSEA's housing regulations were followed. The institution's IAEC approved the study's methodology, (SSDJ/IAEC/2022-23/03).

Experimental Protocol

Rats were divided into four groups of six rats each. The 10-day course of treatment began on the first day.

Group I:

Rats were treated with vehicle, and considered as normal control.

Group II:

Rats were given paracetamol (2g/kg/p.o./day) for 10 days and considered as disease control [26].

Group III:

Rats were given orally a single daily dose of both 2g/kg paracetamol and 100 mg/kg of plain curcumin (P-CUR group) for 10 days, dissolved in 1% Tween 80 [27].

Group IV:

Rats received a single daily dose of both 2g/kg paracetamol and curcumin microsponges (MS-CUR group) equivalent to curcumin 100 mg/kg orally for 10 days, dissolved in 1% Tween 80.

Curcumin microsponges were given three hours after paracetamol was given. The treatment course lasted for ten days. On the last day of the protocol, blood was drawn from the retroorbital nerve using a microcapillary under ether anesthesia, and the serum was separated using a high-speed centrifuge. Serum samples were used for a variety of biochemical calculations and were stored at -20 0C. Following the cervical dislocation method of rat sacrifice, the liver was removed, washed in cold physiological saline, and preserved in 10% formalin solution for histological analysis. Using an assay kit, the serum levels of total protein, total bilirubin, AST, ALP, and ALT were determined (Cloral Clinical System Pvt Ltd., Uttarakhand).

Histopathological Examination

A piece of 5 µm was produced. Hematoxylin and eosin (H&E) staining was applied to the sections, and images were taken at the Optimus Diagnostic Laboratory in Nashik. A light microscope (400x) was used to examine the sections for general morphological modifications.

Statistical Analysis

All variables were analyzed by Graph Pad Prism (version 5.0), and Dunnett's test was applied after doing an ANOVA. Data was mentioned in terms

of mean ± SEM (n=6). $p < 0.05$ was regarded as statistically significant for all variables evaluated.

Results

Particle size analysis, zeta potential and PDI

The particle size of the curcumin microsponges formulation was observed by zeta sizer, and the formulation shows ranges from 2.12 µm to 4.14 µm (Table 2). This particle size is affected by the concentration of ethyl cellulose and magnetic stirrer speed. And it was observed that the growth in the concentration of polymer and mixing speed of the formulation increases the production yield and entrapment efficiency (F4 formulation). And the addition of an excess amount of polymer into the formulation will form a cake. The F4 formulation shows good zeta potential and polydispersity index (Figure 1 and 2).

Table 2: Particle size analysis

Sr.no	Formulation code	Particle size (µm)	Entrapment efficiency (%)	Practical yield (%)	Drug loading capacity (%)
1.	F1	2.12	21.56	57	24.89
2.	F2	2.54	33	65	32.45
3.	F3	3.12	54.78	70	60.42
4.	F4	3.78	85	75	80.65
5.	F5	4.14	65.48	73	66.49

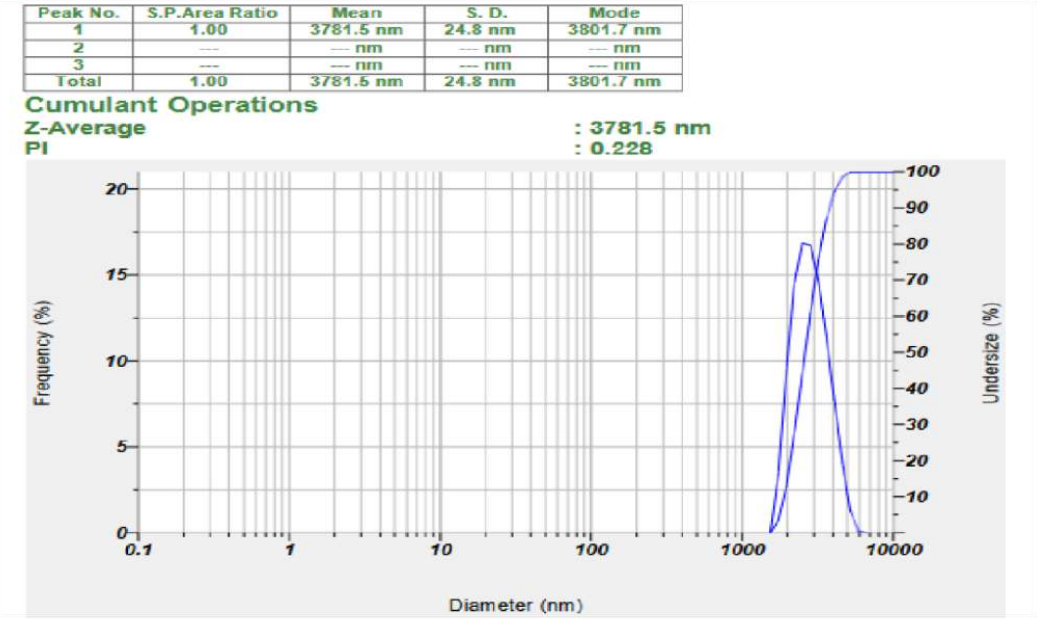


Figure 1: Particle size and PDI

Zeta Potential (Mean) : -15.8 mV
Electrophoretic Mobility Mean : -0.000230 cm²/Vs

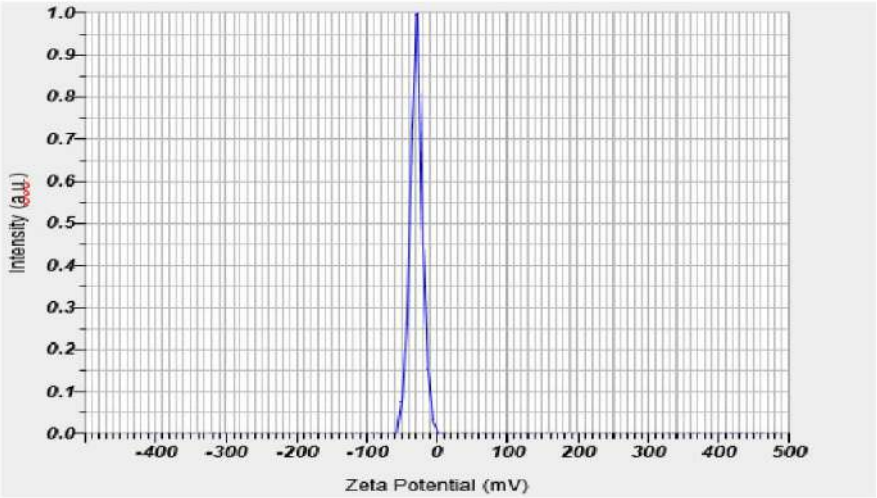
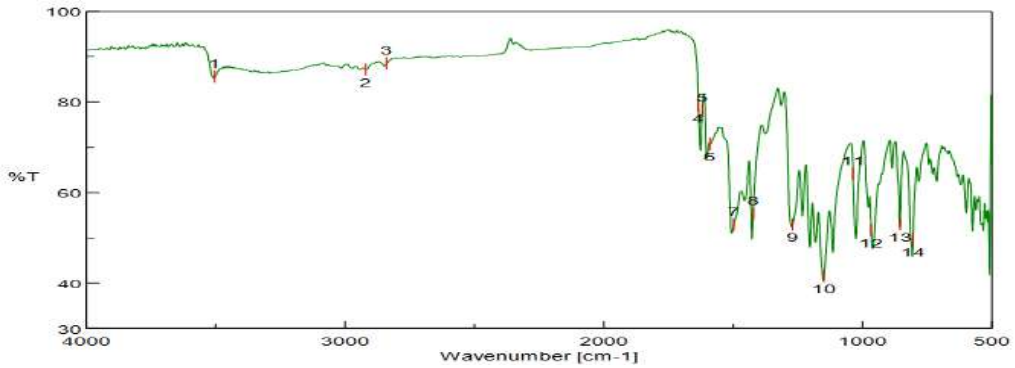


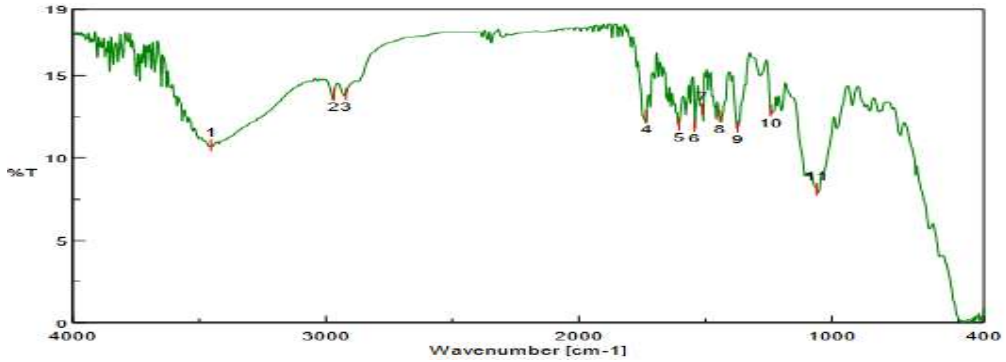
Figure 2: Zeta potential

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of curcumin, ethylcellulose, polyvinyl alcohol, and curcumin microsponges are shown in Figure 3. Curcumins spectra in Figure 3 (a) show a wide, sharp peak at 3504 cm-1, which is the O-H stretch of the phenolic hydroxyl group. The molecules aromatic ring vibrations have a peak at 1497 cm-1. peak at around 1618 cm-1, which is the beta-diketone functional groups C=O stretch. Peak 1269 cm-1 represents the phenolic hydroxyl groups C-O stretch. Peak 1036 cm-1, which represents the aromatic rings C-H bend. The curcumin microsponges formulations spectra in Figure 3(b) exhibit a large peak at around 3452 cm-1, which is indicative of the O-H stretch formed by the hydroxyl groups of ethyl cellulose and the phenolic hydroxyl group of curcumin. a peak at 1603 cm-1, which is the beta-diketone functional group of curcumin's C=O stretch. A peak located at 1732 cm-1 is indicative of the ester group's C=O stretch in ethyl cellulose. The aromatic ring vibrations of curcumin and the C-H bending vibrations of the ethyl cellulose backbone are represented by a series of peaks at 1541, 1510, and 1443. The C-O stretch of curcumins phenolic hydroxyl group and the C-O-C stretch of the ethyl cellulose ether bond are represented by a peak at about 1241 cm-1.



(a)



(b)

Figure 3: FTIR study of a) Plain Curcumin b) Curcumin Microsponges Formulation

Differential Scanning Calorimetry (DSC) Analysis

In Figure 4 shows, the DSC thermogram of curcumin, ethyl cellulose and curcumin microsponges. In Figure 4(a), curcumin shows a sharp peak at 182.678°C and ethyl cellulose is an amorphous substance it does not show a sharp endothermic peak which is shown in Figure 4(b). curcumin microsponges also show a 183.757°C sharp endothermic peak from this result we concluded that our formulation is stable (Figure 4c).

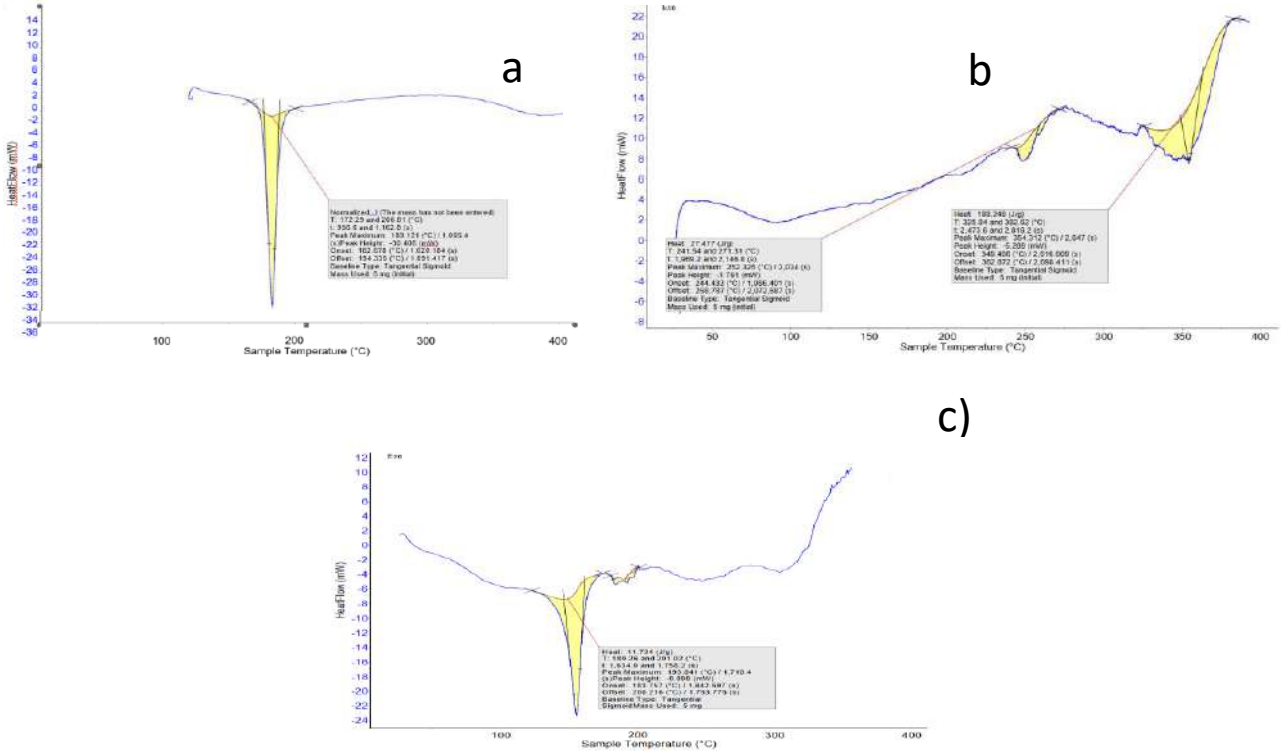


Figure 4: DSC curve for a) Plain curcumin b) Ethyl cellulose c) Curcumin Microsponges

Entrapment Efficiency, Drug loading capacity, and Practical yield

In Table 2 displays the entrapment efficiency, drug loading capacity, and practical yield of different formulation batches of curcumin microsponges. The Entrapment efficiency value ranges between 21.56 to 85. The drug loading capacity of different formulations of curcumin show values varied between 24.89 to 80.65. also, it shows the different practical yields from 57- 75%. When a particle size decreases with an increase in formulation speed.

The practical yield of the microsponges rises with an increase in the polymer content.

Table 2: Particle size analysis

Sr.no	Formulation code	Particle size (µm)	Entrapment efficiency (%)	Practical yield (%)	Drug loading capacity (%)
1.	F1	2.12	21.56	57	24.89
2.	F2	2.54	33	65	32.45
3.	F3	3.12	54.78	70	60.42
4.	F4	3.78	85	75	80.65
5.	F5	4.14	65.48	73	66.49

Photomicroscopy

Figure 5 shows, the Photomicroscopy images of the curcumin microsponges. In these images, the microsponges show a spherical shape

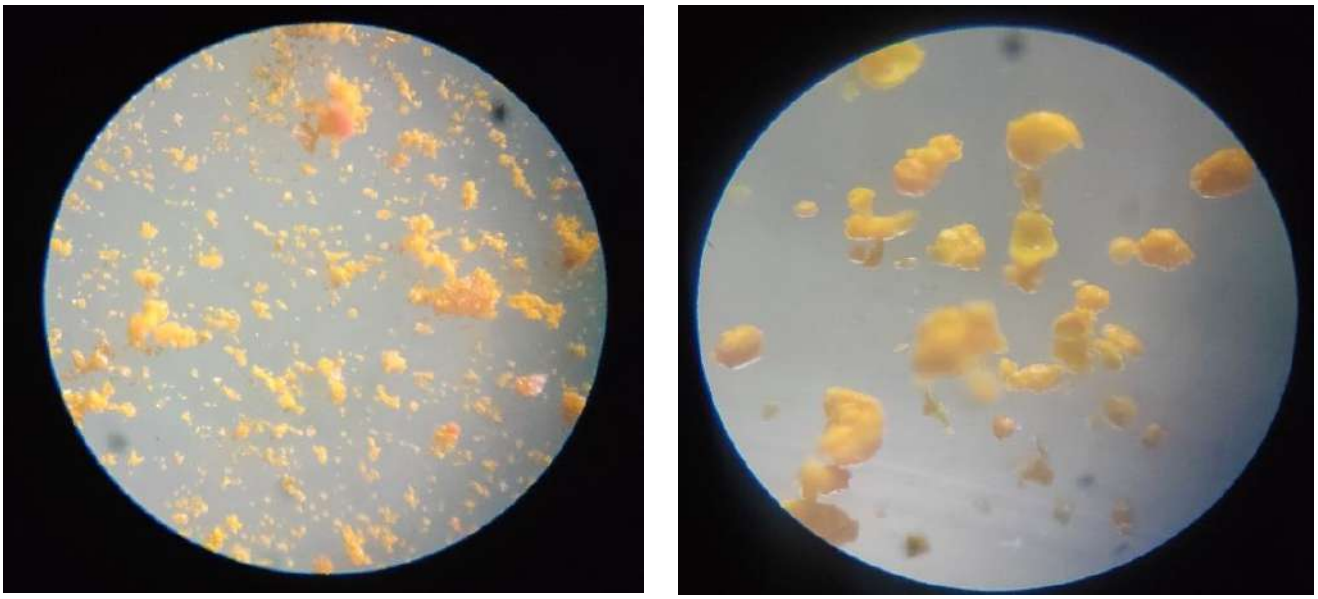


Figure 5: Photo microscopy images

Scanning Electron Microscopy (SEM)

Figure 6 indicates the outer structure images obtained by SEM of curcumin microsponges. The images show the micro sponges are formed in a spherical shape and curcumin crystals are not observed in these scanning electron microscopy images.

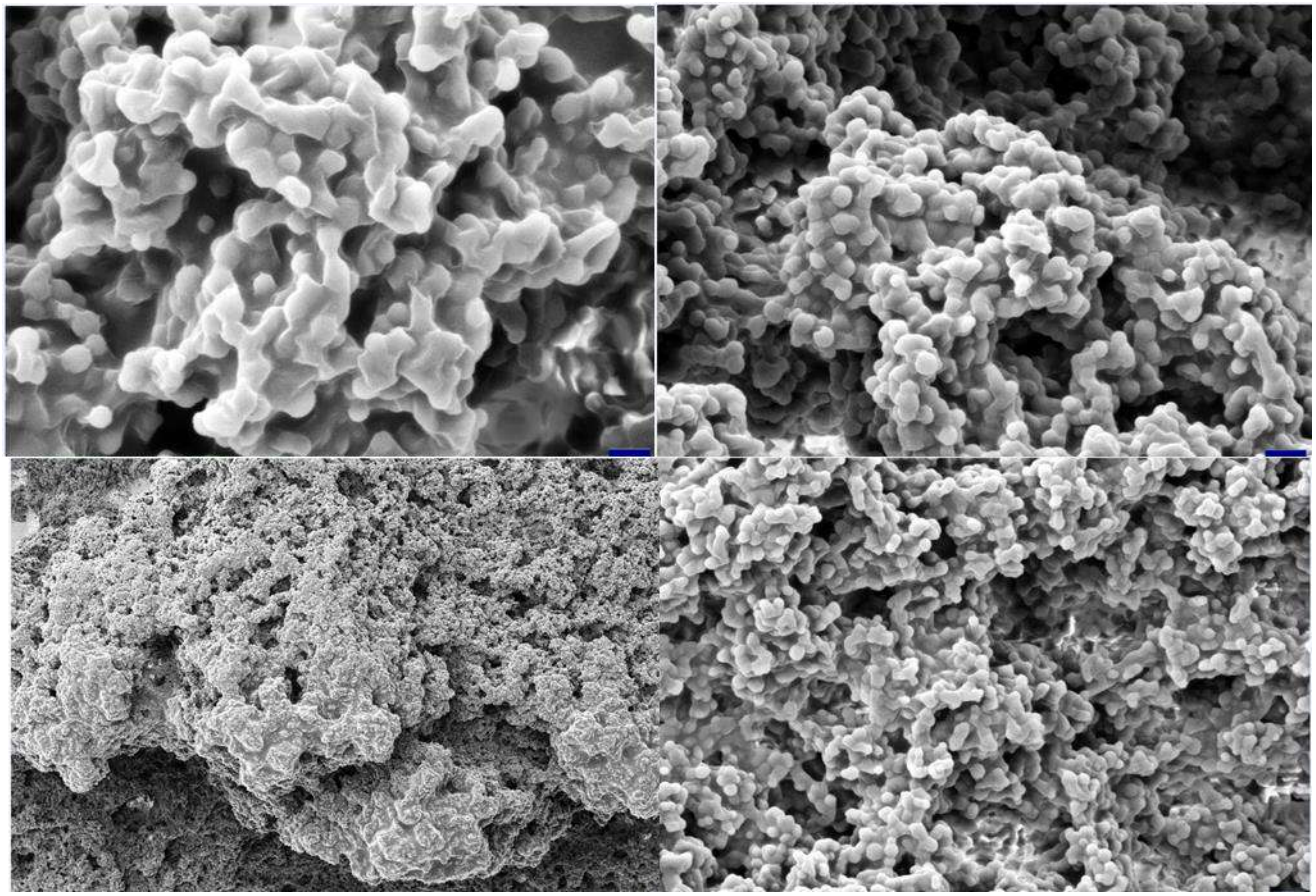
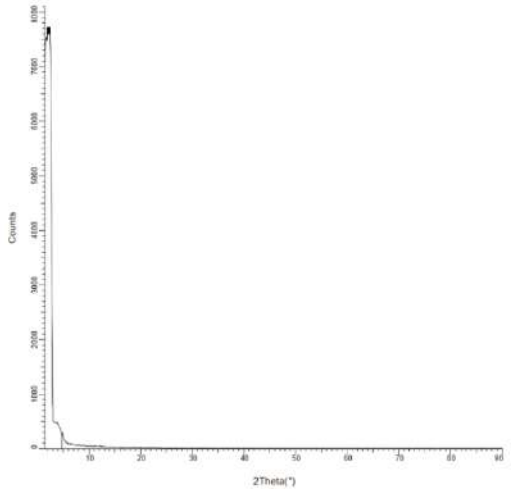


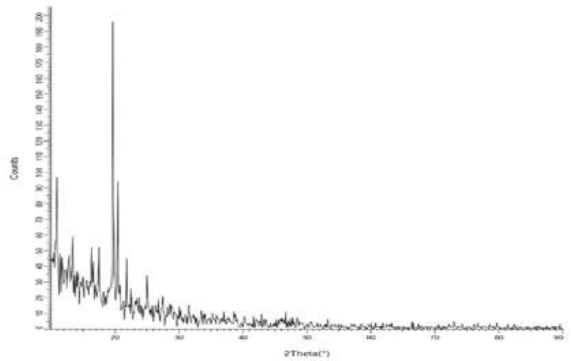
Figure 6: Scanning Electron Microscopy (SEM)

X-ray diffraction study

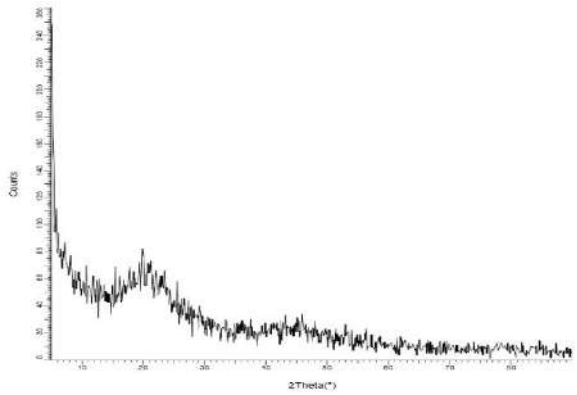
In Figure 7 shows, the Ethylcellulose, curcumin, and curcumin microsponges X-ray diffraction spectra. The X-ray diffractogram of EC has no distinct peaks, which are amorphous in nature. While the diffractogram of the curcumin microsponges exhibits strong peaks at 17°, 20°, 24°, and 28°, with reduced intensity, showing a decline in the crystalline character of the microsponges, which means the drug curcumin is encapsulated in the ethyl cellulose polymer., the spectra of curcumin show sharp peaks at 19°, 20°, 22°, and 25°, demonstrating the crystalline nature of curcumin.



(a)



(b)



(c)

Figure 7: XRD for a) Ethyl cellulose b) Plain curcumin c) Curcumin Microsponge

Stability Study

The formulation F4 was subjected to 3 months stability study conducted at accelerated conditions and was evaluated for physical appearances and FTIR spectroscopy. After the stability studies of 3 months, the formulation shows there are no changes in their appearances and FTIR study. And also, the FTIR study shows that there is no instability in the formulation. From these two parameters may have concluded that they may have good shelf life.

Effect of curcumin and curcumin microsponges on total protein in serum:

As shown in Figure 8, Rats treated with paracetamol only (Group I) displayed a marked decline ($p<0.01$) in serum level of total protein when compared to the normal rats. Rats administered with curcumin only indicated increase in the level of total protein but not significantly. Whereas rats treated with microsponges of curcumin revealed a substantial ($p<0.05$) rise in total protein levels as compared to the sick category

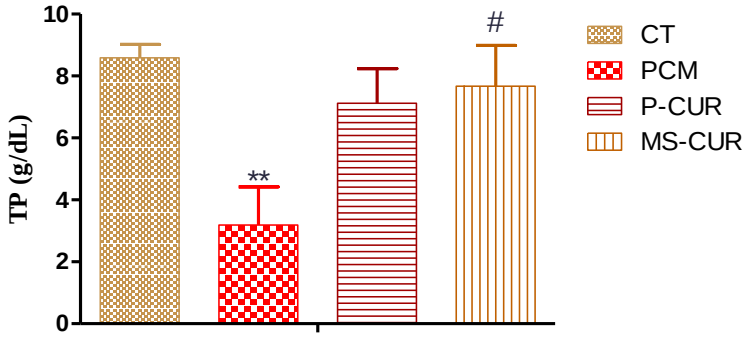


Figure 8: Effect of curcumin and curcumin microsponges on total protein in serum

Data was mentioned in terms of mean ± SEM n=6. ANOVA was applied with Dunnett 't' test for analysis.
*P<0.05, **P<0.01, ***P<0.001 compared to normal and #P<0.05, ##P<0.01, ###P<0.001 compared to PCM.

Effect of curcumin and curcumin microsponges on total bilirubin in serum:

When compared to a control group, rats given paracetamol showed a significant ($p<0.001$) increase in their blood level of total bilirubin. When rats treated with curcumin after being inebriated with paracetamol, their blood total bilirubin level significantly decreased ($p<0.05$).

When compared to the paracetamol group, rats treated with curcumin microsponges were able to significantly ($p<0.05$) lower these levels (Figure 9).

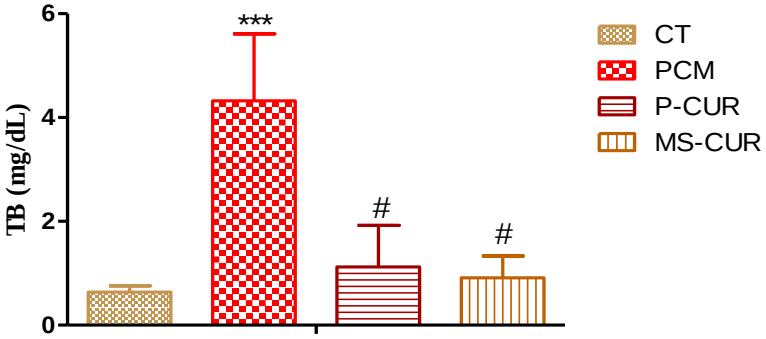


Figure 9: Effect of curcumin and curcumin microsponges on total bilirubin in serum

Data was mentioned in terms of mean ± SEM n=6. ANOVA was applied with Dunnett 't' test for analysis. *P<0.05, **P<0.01, ***P<0.001 compared to normal and #P<0.05, ##P<0.01, ###P<0.001 compared to PCM.

Effect of curcumin and curcumin microsponges on liver enzyme activities on paracetamol-treated rats in serum:

The level of liver enzyme activities in serum was monitored in all groups. There were significant changes observed in serum activities of ALT, AST, and ALP in diseased group when compared with normal group (Figure 10). Administration of curcumin to diseased rats displayed significant ($p<0.01$) declined in the level of liver activities. Whereas rats administered with curcumin microsponges displayed ($p<0.01$) powerful hepatoprotective activity by reducing level of ALT, AST, ALP as compared with diseased paracetamol groups.

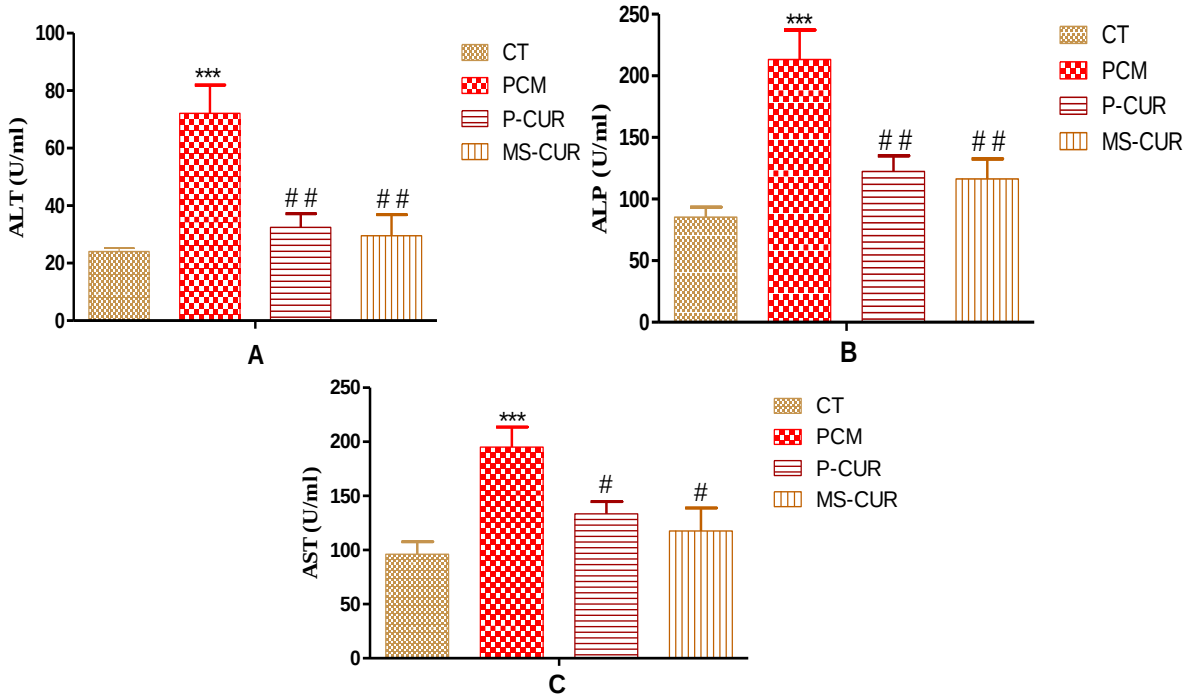


Figure 10: Effect of curcumin and curcumin microsponges on liver enzyme activities A) ALT, B) ALP and C) AST on paracetamol-treated rats in serum

Data was mentioned in terms of mean ± SEM n=6. ANOVA was applied with Dunnett 't' test for analysis. *P<0.05, **P<0.01, ***P<0.001 compared to normal and #P<0.05, ##P<0.01, ###P<0.001 compared to PCM.

Histopathological Examination:

Histopathological investigation is done as shown in the figure 11,

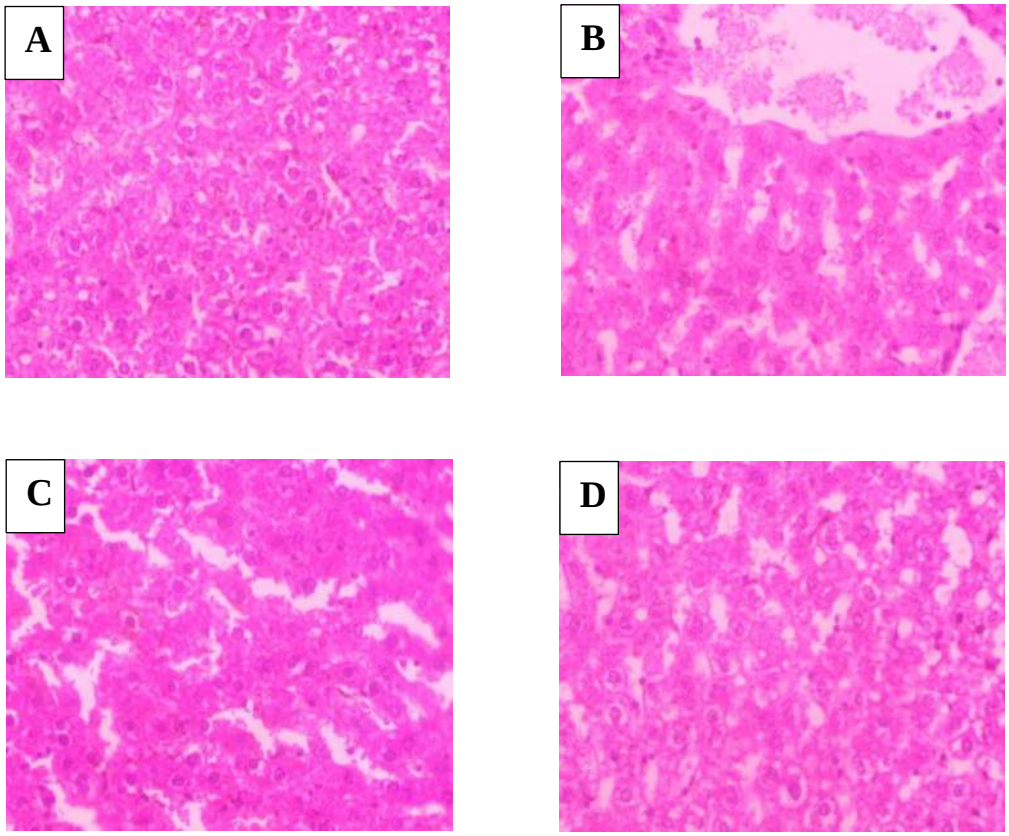


Figure 11: Histopathological analysis after PCM overdose and treatment with P-CUR or MS-CUR (H&E, 400) in the rat live

A: Group I- Hepatocytes in the control rats liver is normal, and there is some micro-vesiculation surrounding a moderately dilated central vein (CV).

B: Group II- Liver sections from the paracetamol-treated group exhibited extensive hepatocyte necrosis, the portal vein is severely enlarged and congested, inflammation, and fatty infiltration.

C: Group III- Curcumin treated group displayed moderate hepatocyte damage with less dilation and inflammation.

D: Group IV- Microsponges-curcumin-treated groups showed reduced hepatocyte damage, inflammation, and improved liver architecture.

DISCUSSION:

Clinicians have a huge difficulty when it comes to the treatment of drug-related liver injuries, due to its prevalence as a cause of liver failure. The most well-known, mechanistically well-studied, and clinically applicable model is the PCM-induced hepatotoxicity model [28]. Paracetamol has been utilised in numerous studies to cause liver injury [29]. Oxidative stress, inflammation, and cell death pathways all contribute to the toxicity of paracetamol in the liver. Several therapeutic approaches, including the use of organic substances like curcumin, have been researched to reduce the liver damage caused by paracetamol. The development of novel formulations for curcumin drug delivery is crucial, due to the

numerous positive effects of curcumin. According to studies, curcumin can neutralise reactive oxygen species, prevent lipid peroxidation, and alter different signaling pathways connected to liver damage. Due to its limited solubility, curcumin has poor absorption [30]. In this study, we successfully formulated curcumin microsponges that can increase curcumin's bioavailability. The benefits of using microsponges as a drug delivery system are prolonged release and higher bioavailability of curcumin, which may help to its improved efficacy in treating liver toxicity. In the present study, we evaluated the hepatoprotective qualities of CUR Microsponges against acute liver damage caused by PCM overdose, which in adult male albino rats may result in a variety of toxicological changes.

In the current investigation, adult male albino rats received 2g/kg of PCM, which caused a rise in ALT, AST, and ALP levels. It is widely established that the hepatocyte damage marker enzymes AST and ALT, as well as their high levels, are critical indicators of liver injury [31]. There were pathological changes in biliary flow that were seen in patients with liver disease who had elevated levels of ALP [32]. The histopathological investigation has verified that the elevated levels of ALT, AST, and ALP are indicative of hepatocellular damage. Our results were in accordance with previous studies, which found that the serum level of ALT, AST, and ALP was considerably more in the group treated with paracetamol than in the control group, remarking hepatotoxicity [33,34]. When compared to plain curcumin, our results demonstrated that CUR microsponges exhibited hepatoprotective effects against PCM-induced hepatotoxicity. This was shown by the fact that CUR microsponges dramatically lowered levels of AST, ALT, and ALP. PCM may have decreased the number of hepatocytes that are responsible for protein synthesis, which may have led to a decrease in serum total protein levels [35]. This may have occurred because of apoptosis and necrosis. Furthermore, the increase in serum total bilirubin was associated with hepatocyte activity and might be interpreted as an indication of red blood cell disintegration brought on by the hepatotoxicant [36]. These results were confirmed by the histopathologic hepatic architecture, which demonstrated significantly hydropic hepatocyte degeneration, inflated and swollen portal veins, and dilated portal bile ductules. These findings were also supported by the data stated above. When compared to simple curcumin, curcumin microsponges were able to counteract the altered hepatic cell shape that was brought about by PCM poisoning. Microsponges had a hepatoprotective effect that was much higher than that of simple curcumin when administered at the same dosage. Plain curcumin, administered at a dosage of 100 mg/kg, showed a slight improvement in the adverse effects that paracetamol would have generated in rats. When compared to curcumin, the microsponges at a dosage similar to 100 mg/kg of curcumin revealed greater healed liver damage in rats. The higher bioavailability of curcumin may be the source of the improved hepatoprotective activity of microsponges curcumin. In conclusion, our work indicated that curcumin microsponges greatly decreased acute hepatic damage in rats induced by paracetamol. The findings of this investigation suggested that simple curcumin and microsponges-curcumin are efficient at preventing the liver damage induced by paracetamol in rats. The remarkable improvement in liver function indicators and histological results revealed the protective advantages. The use of microsponges as a delivery mechanism for curcumin increases its therapeutic potential, enabling continuous release and focused delivery to the liver. Further investigations are warranted to explain the underlying mechanisms of curcumins hepatoprotective properties and refine the

composition of microsponges for better drug administration. Clinical investigations are essential to examine the translational potential of curcumin and microsponges-curcumin in human patients suffering from paracetamol-induced liver damage.

CONCLUSION:

Considering the present findings consequently, it may be said curcumin microsponges showed more hepatoprotective activity than plain curcumin against paracetamol-induced liver damage in experimental rats.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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