



**Potential of novel carriers for effective management of Acetaminophen  
Induced Hepatotoxicity**

**Juyal Divya and Dhyani Archana**

Himalayan Institute of Pharmacy and Research, Dehradun

\*Corresponding author: *archana.dhyani89@gmail.com*

---

**Abstract**

Liver is a vital organ of the human body. It plays an important role in the human body. Acetaminophen when taken in therapeutic doses, it is used in the treatment of various conditions. Hepatotoxicity is the prime factor responsible for drug withdrawal from the market. There is no doubt that hepatotoxicity requires considerable attention and that every viable measure be taken towards an efficient mechanism for hepatoprotection. The overdose of acetaminophen causes acute liver failure. The hepatotoxicity can be treated by targeting the liver by the various carriers like liposomes, nanoparicles, phytosomes etc. However the hepatoprotective therapies require better targeting, stability and better bioavailability. Such focus areas can be effectively met with the aid of lipid based delivery systems which can prove to be a breakthrough in the field of hepatoprotection.

**Keywords:** Hepatotoxicity, acetaminophen, acute liver failure.

---

**1. Introduction**

Acetaminophen-induced hepatotoxicity is an important cause of acute liver failure. Acetaminophen is one of the most widely used analgesics with few side effects when taken in therapeutic doses, and hepatotoxicity is a common consequence of acetaminophen overdose<sup>[1]</sup>. Acetaminophen is considered as a predictable hepatotoxin, where biochemical signs of liver damage will become apparent within 24 to 48 hours after the time of overdose and produce a dose-related centrilobular necrosis in the liver. The lowest dose of acetaminophen to cause hepatotoxicity is believed to be between 125 and 150 mg/kg. The threshold dose to cause hepatotoxicity is 10 to 15 g of acetaminophen for adults and 150 mg/kg for children.<sup>[2-6]</sup>

Acetaminophen causes liver toxicity through the generation of a reactive intermediate metabolite (N-acetyl-p-benzoquinoneimine) formed by its oxidation

via hepatic cytochrome P450 enzymes. This metabolite damages essential mitochondrial and other cellular enzymes by binding covalently to and arylating their protein sulphhydryl groups<sup>[7,8]</sup>

There is evidence that acetaminophen overdose can cause mitochondrial dysfunction either by covalent binding to mitochondrial proteins or by other mechanisms. The modified mitochondrial proteins and high levels of cytosolic calcium can depress mitochondrial respiration and adenosine triphosphate (ATP) synthesis and induce mitochondrial oxidant stress with increased production of peroxynitrite, a potent oxidant and nitrating agent<sup>[9,10]</sup>

The liver's innate immune system has been shown to play a major role in the progression of liver injury during acetaminophen hepatotoxicity. Endothelial cells within hepatic sinusoids lack a basement

membrane, allowing ready access of immune cells from the blood stream to the underlying hepatocytes. Cell death caused by the toxic acetaminophen metabolites first activates Kupffer cells, phagocytic macrophages of the liver, to release cytokines, including interleukin-12, interleukin-18, and tumor necrosis factor- $\alpha$  that may activate natural killer (NK) and natural killer thymus lymphocytes. Activated natural killer and natural killer thymus cells may cause liver damage by cytotoxic activity, promoting further activation of Kupffer cells, and stimulating local production of chemokines. Inflammatory mediators, cytokines, and chemokines, recruit and accumulate neutrophils in the liver and exacerbate the hepatic injury<sup>[11]</sup>

The signs and symptoms of an untreated acetaminophen overdose depend on the interval after ingestion and are defined in phases. Findings in phase 1 (first 24 h) include anorexia, abdominal pain, nausea, vomiting, lethargy, malaise, and diaphoresis. In phase 2 (24 to 72 h), symptoms may improve or even disappear; whereas biochemical abnormalities [elevated transaminases and bilirubin and prolonged prothrombin time (PT)] will become evident. Patients may experience right upper quadrant abdominal pain, and hepatomegaly may be present. In phase 3 (72 to 96 h), nausea and vomiting reappear or worsen and are accompanied by malaise, jaundice, and central nervous system symptoms including confusion, somnolence, or coma. Hepatocellular injury and death most commonly occur in this stage. Oliguria secondary to dehydration or acute tubular necrosis may develop, and liver test abnormalities will reach their peaks at this stage. In phase 4 (4 to 14 d), there is resolution of liver damage and liver tests, with return of normal hepatic architecture within 3 months. Approximately 70% of patients who developed ALF will enter phase 4 and can recover completely. Approximately 1% to 2% of untreated patients with toxic acetaminophen levels will develop fatal hepatic failure. If the overdose is severe enough and there is no intervention, death will occur within 4 to 18 days after ingestion<sup>[12]</sup>

## 2. Approaches for treatment of acetaminophen induced hepatotoxicity

### 2.1. Phospholipid- Drug Complex

A phospholipid-drug complex is formed by the interaction of the phospholipid with a functional group

of the drug [13]. Phospholipid complex formulations of several natural drugs, such as silymarin [14] and dolichol [15], have been found to show improved bioavailability.

Singh D *et al.*, [16], have prepared quercetin-Phospholipid complex, which has been proved to improve the water solubility of quercetin by 12 folds without any effect on its bioactivity. Priscilla D'Mello *et al.* [17], evaluated the hepatoprotective activity of ethanolic extract of *P. guajava* and the phospholipid complex of the extract with phosphatidylcholine against paracetamol induced hepatic damage in albino rats. It was found that the Phospholipid complex of the extract showed better activity than the plain extract.<sup>[13]</sup> Liposomes have been used as drug delivery vehicles for several decades now and rightly so, purely because selective targeting and release rate control can be performed with the aid of appropriate modifications to the carrier itself and that too without altering the original structure of the drugs. Furthermore, the mainstay of liposomes rests on some vital factors such as their low toxicity and their relatively easier methods of preparation.<sup>[14-17]</sup> Their properties can be altered to accommodate various effective molecules both lipophilic as well as hydrophilic, ranging from DNA<sup>18</sup> to superoxide dismutase<sup>[19-21]</sup> to alpha tocopherol<sup>[22]</sup>. Although, the high affinity of liposomes to the liver has been the primary weakness in liposomal therapy, it would prove to be an asset in hepatoprotection. For instance, several formulations showed greater than 80% accumulation in the liver in less than 15 minutes after being intravenously injected<sup>[23]</sup>. Furthermore, it has been demonstrated that changes in the concentration of liposomes lead to variation in the kinetics of liver uptake<sup>[24]</sup>. The natural affinity for the liver shown by liposomes ensures easy target ability. Liposomes are able to enhance the performance of the products by improving ingredient solubility, bioavailability, intracellular uptake, altered pharmacokinetics as well as bio-distribution and *in vitro* and *in vivo* stability. Liposomes can easily incorporate fluorescent dyes and/or can easily be radio-labeled, which in turn can provide valuable.<sup>[25,26]</sup>

### 2.2. Nanosystems in Hepatoprotection

Nanosystems encompass various nanosized delivery systems like nanoparticles, nanospheres, nanocapsules, solid lipid nanoparticles (SLN), self-emulsifying drug delivery systems (SEDDS) and submicron/

nanoemulsions<sup>[27,28]</sup>. Nanoparticle drug delivery systems offer many advantages such as, enhancement of solubility, stability as well as bioavailability, reduced toxicity, enrichment of pharmacological activities, improvement of tissue macrophage distribution, sustained delivery and protection from physical as well as chemical degradation<sup>[29, 30]</sup>. Solid lipid nanoparticles (SLN), remain solid at room temperature and are advantageous in controlling drug release, targeting with reduced toxicity, increasing drug stability and high drug payload<sup>[31]</sup>. Nano suspensions have been used to increase the solubility, dispersity and homogenization, intravenous injectability, simple production process, universal adaptivity of poorly water soluble drugs<sup>[32]</sup>. Emulsions and microemulsions have been used as templates to form nano suspensions<sup>[33]</sup> and SLNs<sup>[34]</sup>. Nanocapsules have also been, designed, to improve stability, absorption, quantitative tissue transfer and pharmacodynamic activity. Self nano emulsifying drug delivery systems(SNEDDS) were reported to be a thermodynamically and physically stable formulation with high solubility, improved dissolution rate and extent of vabsorption, thus, resulting in more reproducible blood-time profiles<sup>[35]</sup>.

Meiwan Chen *et al.*<sup>36</sup>, have prepared various above mentioned nano-sized drug delivery systems for oleanolic acid, a triterpenoid with hepatoprotective and other medicinal properties. Oleanolic acid formulated in nanosystems was proved to be much better absorbed and bioavailable. Yen FL *et al.*<sup>[37]</sup> have prepared nanoparticulate formulation of *Cuscuta chinensis* which provide a hepatoprotective effect in acetaminophen-induced hepatotoxicity in rats. It was found that with the use of nanotechnology, the dose of *Cuscuta chinensis* could be reduced up to 5 times as compared to that of ethanolic extract.

### 2.3. Phytosomes in Hepatoprotection

Phytosomes or Herbosome is a technology, developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, known as Phytosomes®. Since, the term ‘Phytosomes’ has been registered by Indena S.P.A, Italy; the technology is being referred as ‘Herbosome’ by the researchers. In liposomes no chemical bond is formed and the phosphatidylcholine molecules simply encapsulate the water soluble drug. In contrast, with the Phytosomes®

process thephosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, involving chemical bond.[17] Yanyu X, *et al*<sup>[38, 39]</sup>, prepared silybin Phytosomes® which has been proved to enhance absorption of Silybin up to seven times.

### 3. Conclusion

By considering the various aspects of hepatotoxicity, it is very much required that some novel formulations should be available for the treatment of such conditions by targeting the liver and provide protection against the diseases.

### References

- [1] Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. *Adv Intern Med.*1997,42:453–483.
- [2] Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. *Adv Intern Med.*1997,42: 453–483.
- [3] Lee WM. Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology.*2004,40:6–9.
- [4] Lee WM. Drug-induced hepatotoxicity. *N Engl J Med.*1995,333:1118–27.
- [5] Dargan PI, Jones AL. Acetaminophen poisoning: an update for the intensivist. *Crit Care.* 2002;6:108–110.
- [6] Larson AM. Acetaminophen hepatotoxicity. *Clin Liver Dis.*2007,11:525–548.
- [7] Jones AL. Mechanism of action and value of N-acetylcystein in the treatment of early and late acetaminophen poisoning:a critical review. *J Toxicol Clin Toxicol.* 1998,36:277-285.
- [8] James LP, Mayeux PR, Hinson JA. Acetaminophen-induced hepatotoxicity. *Drug Metab Dispos.* 2003,31:1499-1506.
- [9] Jaeschke H, Bajt ML. Intracellular signaling mechanisms of acetaminophen-induced liver cell death. *Toxicol Sci.* 2006,89:31–41.
- [10] Jaeschke H, Knight TR, Bajt ML. The role of oxidant stress and reactive nitrogen species in acetaminophen hepatotoxicity. *Toxicol Lett.* 2003,144:279–288.
- [11] Liu ZX, Kaplowitz N. Role of innate immunity in acetaminophen-induced hepatotoxicity. *Expert Opin Drug Metab.Toxicol.* 2006,2:493–503

- [12] Salgia AD, Kosnik SD. When acetaminophen use becomes toxic. Treating acute accidental and intentional overdose. *Postgrad Med.* 1999,105:81–84.
- [13] Singh D, Rawat MS, Semalty A, Semalty M, Quercetin-Phospholipid Complex: An Amorphous Pharmaceutical System in Herbal Drug Delivery, *Curr Drug Discov Technol.*, 2011,3:76-78.
- [14] Ajazuddin SS, Applications of novel drug delivery system for herbal formulations. *Fitoterapia*, 2010, 81: 680-689.
- [15] Gasco MR, Solid lipid nanospheres form warm microemulsions, *Pharm. Technol. Eur.*, 1997, 9: 32-42.
- [16] Yen F, Wu TH, Lin GT, Cham TM, Lin CC, Nanoparticles formulation of *Cuscutachinensis* prevents acetaminophen-induced hepatotoxicity in rats, *Food and Chemical Toxicol.*, 2008, 46: 1771-1777
- [17] Ajazuddin SS, Applications of novel drug delivery system for herbal formulations. *Fitoterapia*, 2010, 81: 680-689.
- [18] Yanyu X, Yunmei S, Zhipeng C, Quineng P, The preparation of Silybin-phospholipid complex and the study on its pharmacokinetics in rats, *Int J Pharm*, 2006, 307:77-82.