Chapter 2

Research Envisaged
RESEARCH ENVISAGED

Since the first scientific report by Regional Research Laboratory (CSIR), Jammu, India on the potential of piperine as bioavailability enhancer in late 70's, the institute has been doing extensive work on piperine. Though the molecule has been evaluated with more than 40 drugs belonging to diverse chemical and therapeutic categories, there are still large number of drugs which need particular attention for improving their bioavailability. Some of the prominent examples are prolonged therapy, highly toxic and/or very expensive drugs. Further, there is a very little information available on the mechanism of action of this compound while the work on its pharmacokinetics is patchy and inadequate.

In order to fill some of the gaps, it is planned to study the effect of piperine and its reported metabolites on gastrointestinal tract. The studies would include effect on gastric emptying and gastrointestinal transit in rats and mice. These physiological events play an important role in the bioavailability of drugs.

No HPLC method has so far been reported for the quantitative analysis of piperine in body fluids. Development of a new HPLC method would be tried for studying pharmacokinetics of piperine in rats. Comparative pharmacokinetic studies would be carried out on solution and suspension formulations of piperine for selection of the appropriate formulation.

It is also planned to study the metabolism of piperine and, if possible, see if any of the reported metabolites, particularly those reported in rat urine, possess bioavailability enhancement potential. It would be interesting to study the plasma profile of these metabolites and the sequence in which they are formed. The detailed study on metabolism of piperine in rats would also verify the reported differences in the metabolic pattern in humans and rats and whether the latter is
an appropriate model species to study the preclinical metabolism of piperine and its influence on bioavailability of drugs. For this purpose, plasma, urine and faecal samples would be analysed by HPLC for the presence of piperic acid, piperonylic acid, piperonal and vanillic acid. As vanillic acid has been suggested to be formed in-vivo from vanillin, it will also be included in the study. Once the metabolites are detected, they would be isolated in sufficient quantities and chemically characterised.

The second part of the investigations will deal with the influence of piperine and its metabolites on bioavailability of anticancer, antiviral and anti-infective drugs viz. 5-fluorouracil, azidothymidine and cefixime, respectively.

5-Fluorouracil as a candidate for bioavailability enhancement

This drug is selected due to its poor and variable oral bioavailability and recent interest in the development of modulators of its pharmacokinetics as well as anticancer activity. Though, the combination of piperine and 5-FU with an increased bioavailability has been patented, ironically the patent mentions the data generated directly in human volunteers.

It is planned to study the effect of piperine on the bioavailability of 5-FU in rats and to see if its metabolites have any influence on the bioavailability of 5-FU. In addition to the pharmacokinetic interaction of piperine with 5-FU in rats, its effect on in-vitro anticancer activity is also planned to be studied in this part of research work as there is no report on the influence of piperine on anticancer activity of 5-FU. The studies would also reveal if piperine has any anticancer activity.
Azidothymidine as a candidate for studying interaction with piperine

AZT is mainly metabolised by glucuronidation. Piperine has been reported to inhibit hepatic and intestinal UDP-glucuronyl transferases in-vitro. However, there is no report on inhibition or degree of inhibition of glucuronidation with reference to particular drug by piperine. Since AZT is one of the most widely used antiviral drug, it is planned to study the effect of piperine on its bioavailability.

Cefixime as a candidate for studying interaction with piperine

Piperine has been reported to influence absorption of molecules and increase their active as well as passive transport. It was found to stimulate \( \gamma \)-glutamyl transpeptidase and to increase the uptake of amino acids. Cefixime absorption from intestine is mediated partly by active transport (H\(^+\) dependent dipeptide transporter, PEPT1) and partly by paracellular route. Moreover, cefixime is not metabolised in body. Considering these characteristics of this drug, it is planned to study the effect of piperine on the bioavailability of cefixime to selectively deduce the effect of piperine on absorption processes.