INTRODUCTION

Oral Bioavailability Enhancement of Lovastatin

The therapeutic effectiveness of a drug depends upon the ability of the delivery system to make available the pharmacologically active moiety to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This feature of the delivery system is referred to as physiologic or biologic availability or still simply bioavailability. For a large number of drugs, a pharmacologic response can be related directly to the plasma levels.

Thus the term bioavailability is defined as “the rate and extent (amount) of absorption of unchanged drug from its dosage form”. It can also be defined as “the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action”.

Drug Solubility and Biopharmaceutics classification Scheme of Drugs

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for anticipated pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% new chemical entities (NCEs) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, and solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, its dose, site of absorption, its half life and required dosage form characteristics.

The Biopharmaceutics Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability.

A biopharmaceutics drug classification scheme for correlating in vitro drug product dissolution and in vivo bioavailability was proposed by Amidon et al., based on...
recognition that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. This analysis uses a transport model and human permeability results for estimating in vivo drug absorption to illustrate the primary importance of solubility and permeability on drug absorption.

On the basis of these solubility and permeability characteristics can be classified in one of the four possible categories, as indicated in Table 1.

**Table 1: The Biopharmaceutics classification scheme**

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Solubility</td>
<td>Low Solubility</td>
</tr>
<tr>
<td>High Permeability</td>
<td>High Permeability</td>
</tr>
<tr>
<td>Class III</td>
<td>Class IV</td>
</tr>
<tr>
<td>High Solubility</td>
<td>Low Solubility</td>
</tr>
<tr>
<td>Low Permeability</td>
<td>Low Permeability</td>
</tr>
</tbody>
</table>

**Bioavailability Enhancement of poorly water-soluble drugs**

Oral bioavailability enhancement of poorly water-soluble BCS class II drugs is considered as a difficult task in formulation development. As indicated by Table 1, these drugs have low solubility and high permeability.

Literature cites various methods to enhance the solubility of poorly water-soluble drugs. These are, Viz. Micronization, Micellar Solubilization, Salt formation, Soluble Prodrugs, Metastable polymorphs, Inclusion complexes, Solid dispersions, Nanosuspensions, Adsorbents, Microemulsions, Cosolvents, Spherical Agglomeration or Crystallization, Crosslinkage with polymers, etc.

Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs like Lovastatin; however the solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of these drugs.

Hence, the present study is planned to identify suitable techniques of solubility enhancement of a Cardiovascular drug i.e. Lovastatin as the key to ensure the goals of a good formulation like good oral bioavailability, reduced frequency of dosing and better patient compliance combined with a low cost of production.
The fact that dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release etc., will also impose constraints in the selection of suitable method and finally regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy etc., are also to be kept in mind before proceeding for research.

Establishment of *In Silico* Quantitative Structure Pharmacokinetic Relationships among Cardiovascular Drugs

The pharmaceutical industry has been late in recognizing that undesirable absorption, distribution, metabolism and excretion (ADME) of new drug candidates are the major cause(s) of many clinical phase trial failures. Identification of the fact has resulted in a refined and more scientific approach for launching drugs for patient needs. Accordingly, it has been an endeavor of the pharmaceutical scientists to design new drug molecules realistically predicting their pharmacokinetic and pharmacodynamic characteristics prior to their synthesis\(^5\).

It has been accepted by the research laboratories that the drug discovery and development using the conventional approaches of random screening have proved to be quite time consuming and expensive. This has resulted in a paradigm shift to identify such problems early during the drug discovery process. Apart from the scientific interest, there are economic considerations as well, as out of numerous compounds synthesized; only a few eventually reach the market as a new drug. A sizable proportion of drug candidates fail during clinical trials because of poor pharmacokinetic (i.e., ADME) properties. This is an economic disaster, as the failed drugs have been in pipeline for several years, with the large amounts of effort and money invested in their development. Hence, the focus of drug development has widely expanded to include procedures aimed at identifying potential failures as well as successes\(^5,6\).

More recently, *in silico* Quantitative Structure Pharmacokinetic Relationships (QSPkR) modelling has been investigated as a tool to optimize selection of the most suitable drug candidates for development. Being able to predict ADME properties quickly using computational means is of great importance, as experimental ADME testing is both expensive and arduous yielding low productivity. The use of computational models in the
prediction of ADME properties has been growing rapidly in drug discovery, as they provide immense benefits in throughput and early application of drug design\textsuperscript{5-7}.

The \textit{in vitro} approaches are widely practiced to investigate the ADME properties of new chemical entities. Most of such ADME properties are pictorially depicted in Fig 1.

![Fig. 1: Various ADME processes during drug sojourn in human body\textsuperscript{5}](image)

Cardiovascular drugs are very useful for therapeutic interventions to cure diseases affecting the physiology and anatomy of a normal heart. For the present study Cardiovascular drugs are selected for QSPkR investigations as this category of drugs consist of significant number of compounds for thorough investigation in their pharmacokinetic performance. Moreover, congeners of this class have many common pharmacokinetic characteristics, mechanism and degree of affinity with body tissues, etc. Also, important descriptors like experimental log P, melting point, molecular weight etc. of these drugs are known and are available in standard texts or journals\textsuperscript{5,6}.

In the light of above background, this study is undertaken to investigate suitability of some bioavailability enhancement techniques to enhance the bioavailability of a
cardiovascular drug i.e. Lovastatin and to find out *in silico* ADME predictions of cardiovascular drugs using quantitative structure pharmacokinetic relationships. This study will be very useful for future scientists as Lovastatin, being useful for the treatment of dyslipidemia and the prevention of cardiovascular diseases is clinically useful and by enhancing its Bioavailability, patient compliance can be improved and the total therapeutic dose of the drug can be reduced because due to enhanced dissolution profile, therapeutically appreciable amount of Lovastatin can be made available at the site of action from a lesser administered Lovastatin dose.

Secondly, from the Pharmacokinetic DATA of cardiovascular drugs that will be collected from literature, quantitative structure Pharmacokinetic relationships will be established so as to make some recommendations for the discovery of some novel cardiovascular compounds by pharmaceutical scientists in future.