1 INTRODUCTION

1.1 ADME/PK in drug discovery

The need to carry out ADME/PK (Absorption-Distribution-Metabolism-Excretion/Pharmacokinetics) studies prior to start of drug development has recently become widely accepted. The very high failure rate of drug development has been well known for a long time, but the key publication highlighted that a significant proportion of the failures (39%) for the seven major United Kingdom pharmaceutical companies could be attributed to “inappropriate pharmacokinetics” (Prentis et al., 1988). In a later report (McAuslane, 1999), the failure rate attributed to the same cause was 25%. Whether this apparent improvement is due to the variability in the reporting system or a very rapid change due to the incorporation of DMPK (Drug Metabolism Pharmacokinetics) into discovery is not clear. However, it is often very difficult to attribute a failure to a single cause; is the failure due to the toxicity of the compound or to poor PK, which leads to excessive exposures at the peak concentrations that are necessary to achieve the required pharmacological effect over the whole dosing period. The timing of pharmacokinetic and metabolic studies in pharmaceutical research and development has changed dramatically in the last decades. Traditionally, industrial Drug Metabolism Departments have performed fairly standardized studies required for dmg registration, including so-called ADME/PK and bioanalytical studies. In addition to this traditional role, a great deal of emphasis has recently been put on integrating some of these studies in the early stages of the research and development process.

The incorporation of ADME/PK into the discovery process has required a complete re-evaluation of approach to the science. Drug discovery can be seen as a cyclical process (Figure 1.1), with chemists making compounds that are screened for biological activity. The biological data are fed back to the chemists who use it to improve the design of the next compounds, which are then used to initiate the next revolution of the cycle. The incorporation of ADME/PK into drug discovery means that there is now a second, often orthogonal, test cycle. For this cycle to be productive it is essential for it to operate at the same rate as the biological testing, otherwise the chemistry will have moved on, and the ADME/PK data will have been generated on compounds that are no longer of interest.
The major reason for this trend is the fact that, in the pharmaceutical industry, the most successful drug is quite often not the most potent one but rather the one that has the optimum balance of suitable potency, safety, pharmacokinetics, formulation, drug-drug interactions, and manufacturing cost. Some years ago, the traditional process for discovering a new drug was that research chemists and pharmacologists would combine forces to identify the most potent molecule in the chosen pharmacological model, which was predicted to have some relevance to the disease in humans. Little attention was paid to the study of drug delivery, pharmacokinetics, duration of action, metabolism, solubility, and formulation. The project was passed over to another Division, quite often based on another site or another country, whose objective was to 'develop' the compound. This process design inevitably produced many pharmacologically active compounds which could never become drugs due to insurmountable 'developability' problems, typically poor oral bioavailability, high clearance, low solubility, or formulation difficulties.

Nonetheless, it is now generally accepted that it is worthwhile “front-loading” projects with ADME/PK and toxicology information in order to improve the chance of compounds achieving registration and becoming “best in class”.

Pharmaceutical companies accepted that the attrition rate of compounds was high, but whilst sales profits were high and competition was low, this was not a particular problem. A number of years ago, several factors started to cause a rapid change in this.
situation. Government spending on national health and particularly on drugs was cut world-wide; registration authorities became much stricter in authorizing drugs with no significant improvement on existing medications or with significant drug-drug interactions. This and the rapidly increasing cost of new technology needed to remain competitive and overhead costs, started to eat away at pharmaceutical companies' profits. Clearly, in this environment, the high attrition rate was no longer acceptable, and companies started looking harder at when and why drugs were failing to make it to the market. Many surveys were performed, and it became evident that poor human pharmacokinetics was a major reason for failure.

The overall costs of bringing a new medicine to the market lie between £100 and £300 million (Halliday et al., 1997), and because the attrition rate is so high, much more money is spent on compounds that fail to make it compared to those that do. In addition, the more advanced the development stage of the compound is, the more money is spent, thus any method capable of identifying high-risk projects early on in the process allows to fail quickly and cheaply and hence enables the dedication of the always limited resources to lower-risk, higher-return projects.

1.2 The need for prediction

As pharmacokinetics has been recognized as being one of the major factors for project failure, there has been a huge drive to perform these studies much earlier in the process and, more importantly, before the drug candidate is selected (in the lead-optimization phase) so that only compounds with high potency and good pharmacokinetic properties are chosen for development (Singh et al., 1996). Development of in vitro models to study individual disposition parameters has been fundamental in helping to identify the crucial physiological factors affecting drug disposition.

The major driving force (Rodrigues, 1997) behind the rapidly increasing amount of pharmacokinetic information has been the development of high-throughput screening and combinatorial chemistry, which have enabled pharmaceutical companies to multiply the probability of rapidly selecting a large number of potential drug candidates. Clearly, these technologies would not serve the purpose if the compounds selected could not be rapidly screened for developable pharmacokinetic parameters and the best-balanced compound(s) selected. Therefore, companies have also been
investing heavily in developing high-throughput *in vitro* ADME screens and *in vivo* screens. *In vivo* studies provide information about the complete complex system which, by its nature, does not lend itself to aiding drug design, because the effect of chemical structure on individual processes cannot be ascertained. For example, it is not easy to derive relationships between chemical structure and oral bioavailability, as a number of processes like solubility, stability, permeability, and intestinal and hepatic metabolism, combine together to produce the overall result. Studying those individual physiological parameters *in vivo* can be done in most cases, but requires considerable expertise in animal surgery and cannot be considered for a large number of compounds due to ethical aspects. Therefore, there has been considerable drive in the areas of metabolism and intestinal permeability (Tarbit and Berman, 1998) to set up high-throughput *in vitro* screens. Compounds can be selected on the basis of their properties in these screens and also to rapidly increase corporate databases so that algorithms linking physicochemical properties and chemical structure to the physiological process can be developed. This enables prediction of these properties.

The rate of absorption (permeation) is, in turn, determined by the physicochemical properties of the drug molecule, the specificity of the drug for the intestinal transport systems, and the environmental, anatomical and physiological state of gastrointestinal (GI) tract. In order to predict the absorption of a drug (e.g., permeation through the intestinal epithelium) and to distinguish between the different mechanisms for absorption, several *in vitro* models have been developed, one of which is the immobilized artificial membrane (IAM) chromatography. Currently, the fraction of a drug dose absorbed by humans is frequently predicted using capacity factor ($k'_{IAM}$) obtained from IAM chromatography (Yoon et al., 2004; Yen et al., 2005). This system is regarded as reasonably reliable tool in the area of drug discovery. However, several issues limit the performance of IAM and further research is essential to increase the predictive ability of this *in vitro* system.

Another approach to improve the physiological basis of this *in vitro* system for oral absorption/permeability screening is the inclusion of physicochemical descriptors. The application of molecular weight (MW), molar volume, polar surface area (PSA) and hydrogen bonding had been described in the literature (Pidgeon et al., 1995; Stewart et al., 1998; Genty et al., 2001; Yoon et al., 2004; Chan et al., 2005; Yen et al., 2005), but also in this case more systematic studies had not been performed.
In conclusion, the new challenges are to rapidly improve productivity in producing \textit{in vivo} pharmacokinetic information, to develop high-throughput \textit{in vitro} ADME screens to obtain information on discrete drug-disposition processes, and, more recently, to interpret and apply these data as well as to predict what effect chemical structure has on individual pharmacokinetic parameters in order to allow the medicinal chemist to design a better pharmacokinetic profile into the molecules \textit{(in silico modeling)}.

1.3 References


