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Paradigm Shift in Drug Development for the New Millennium: From *In Vitro* to *In Silico*.

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As the demand for new high-quality pharmaceutical surges, conventional methodology used in drug discovery and development is becoming increasingly restrictive due to the high costs and risks involved. The average cost (cash and capital) for development of one successful drug is reported to be $802 mil. Per new chemical entity (NCE), pre-clinical costs average $336 mil (42%) and clinical costs average 466 mil (58%), while the average drug development time is 12 years. In 2000, the FDA approved 27 new drugs, or one drug per every $950 million in R&D spending by the pharmaceutical industry. Further, there is tremendous pressure on pharmaceutical companies to meet growth expectations of shareholders and large pharmaceutical companies must deliver multiple new drugs per year in order to meet those expectations. However, financial pressure (profitability) also limits R&D expenses available to support NCE discovery and development of drug candidates. Discovery and development must, therefore, become more rapid and more cost effective. Already many companies have begun to intensify their goals for drug development. For example, Bristol-Myers Squibb (BMS) aims to have 10 drugs in full development on an ongoing basis and to launch 3 drugs per year starting in 2003. Survival rate for their compounds in development has improved from 8% to 15%. BMS intends to reduce time from first synthesis to market launch from 8 years to 5 years and to advance 20 NCE to development candidate status per year.

In the past, many big products were discovered by serendipity (e.g. penicillin, aspartame, viagra) and tested for proof of concept extensively using both in vitro and in vivo models. The problem of this traditional approach is that it is very empirical, labor intensive and relies heavily on luck. It leads to significant delays in product development with major cost implications. Further, there is no guarantee of successful development, even after high R&D expenditure in money and time. However, these problems may be reduced substantially by the following approaches:

- More rational design of drug molecules using better computer modeling for receptor sites
- Combinatorial chemistry

- HTP screening and HTP bio-assay
- In silico prediction of biopharmaceutical properties, ADME and toxicities
- Development of sensitive biomarkers for toxicity and disease ("eomics"),
- Development of femtogram sensitive assay for a sub-clinical dose study in humans
- Establishment of PK/PD relationship in the early discovery stage

It has been estimated that almost half of all drug candidates fail as a result of undesirable properties of absorption, distribution, metabolism, excretion and toxicity (ADME/T). To solve these problems, many companies are developing tools that help evaluate these ADME/T characteristics at an early stage of drug development, allowing pharmaceutical companies to be more selective in choosing candidates. Examples are QMPRPlus™ and ACD for prediction of biopharmaceutical properties, GastroPlus™, Cyprotex, IDEA, Absorption Systems and Camitro for ADME prediction, and TOPCAT and DEREK for toxicity prediction. The focus of this presentation will be on the use of in silico predictions in drug development and awareness of their prediction power.

Identifying potential ADME/T issues early is critical to reducing late-stage attrition and to speeding the time from "hit" to "lead". The most important parameters for drug absorption are solubility and permeability. The solubility at different pHs as well as log P and pKa values can be predicted reasonably well without any experimental data using the QMPRPlus™ (Fig 1) or ACD programs. Using the predicted solubility together with permeability measurements from an in vitro system (e.g., Caco-2, MDCK, diffusion chamber) and a clearance value obtained from an allometric scaling method or in vitro metabolism methods (V_{max}/K_m, $T_{1/2}$ method), human plasma concentration – time curves and bioavailability can be predicted. Figure 2 shows predicted and observed plasma concentrations in humans after oral administration of a selective aldosterone blocker, eplerenone, an anti-arrhythmic drug, disopyramide and a COX-2 inhibitor celecoxib using the GastrPlus program. The following parameters were used to predict plasma concentrations:

Compound	Solubility (mg/mL)	LogD	Caco-2 Papp (10^{-6} cm/sec)	Vmax/Km	CL (mL/min/kg)	V1 (L/kg)
Eplerenone	0.5	1	29.3	0.00956	10.8	0.68
Disopyramide	100	-0.79	2.61	NA	12.39	0.7
Celecoxib	5	4	4	NA	18.8	0.7

As can be seen in these figures, plasma concentrations can be predicted reasonably well with input of simple biopharmaceutical parameters and pharmacokinetic parameters obtained from either in vitro metabolism or extrapolated values.

Camitro is another program which has built models of drug absorption, intestinal absorption, solubility, blood-brain barrier permeation and serum albumin binding. However, this program has focused on metabolism, in particular, the CYP450 systems. Camitro is able to predict the likelihood that metabolism will occur at specific positions (Figure 3) in a molecule by using 3-D depiction of predicted regioselectivity and lability of selected sites and classifications of metabolic lability of sites of metabolism (labile, moderately labile, moderately stable and stable) for CYP isozymes (e.g. 3A4, 2C9, 2D6). Predictability of CYP3A4, 2C9 and 2D6 is reported to be approximately 80% or greater. Since the vast majority of the drugs are metabolised by CYP450 enzymes this is also useful tool for drug discovery and development.

In summary, with input of simple biopharmaceutical properties and clearance values, reasonable plasma concentration-time curves for many drugs in humans could be predicted using the commercially available computer programs. Furthermore important CYP450 3A, 2C9 and 2D6 metabolism for many compounds can also be predicted. These predictive tools to evaluate ADME/T properties of drug candidates allows pharmaceutical companies to decrease time and cost in drug discovery.

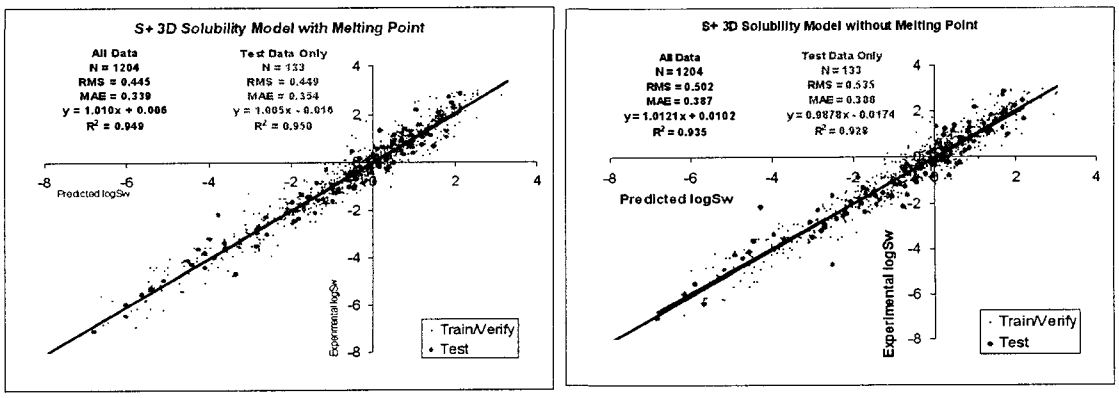

Figure 1. Prediction of solubility with and without melting points using QMPRPlus

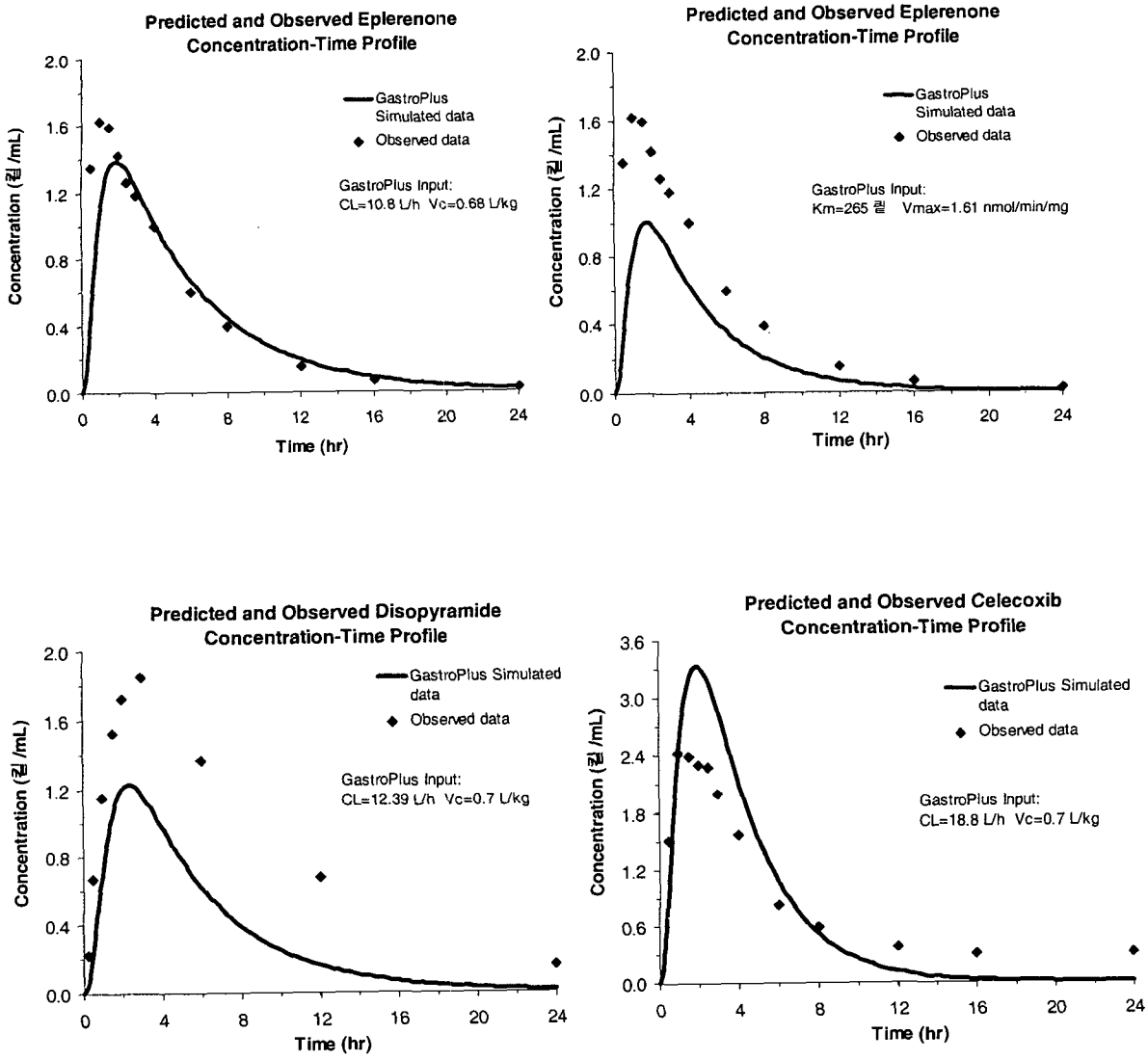

Figure 2. Predicted and observed plasma concentrations of eplerenone (top 2 panels), disopyramide (bottom left panel) and celecoxib (Bottom left panel)

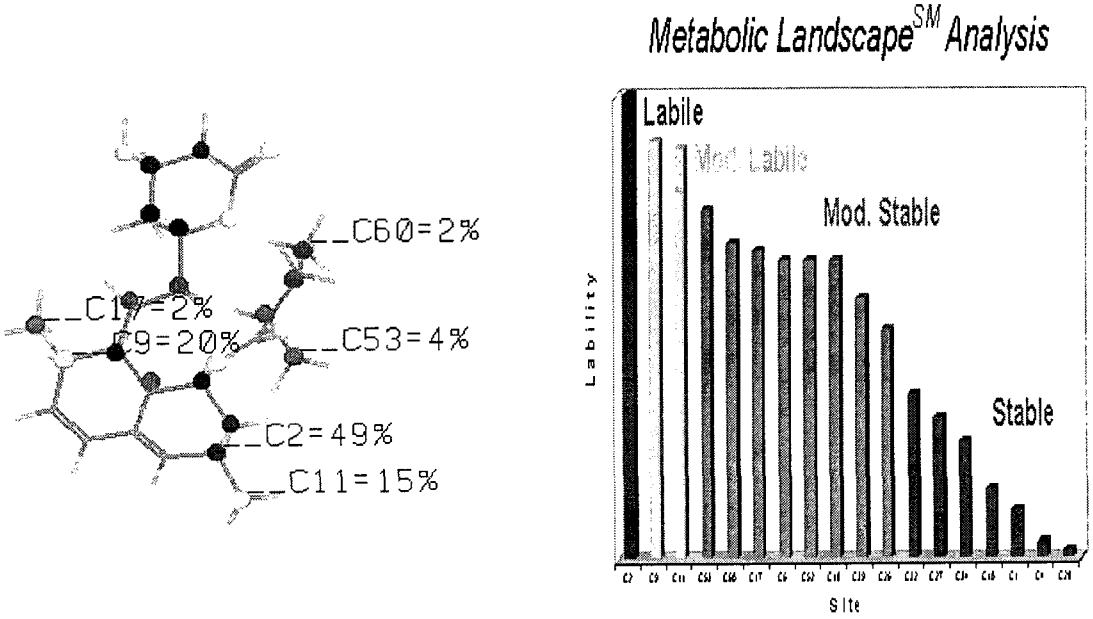

Figure 3. Prediction of metabolic sites using Camitro