HIGHLIGHTS

ADME

Pressures in the pipeline

Poor pharmacokinetic properties, such as low oral absorption, have been associated with ~40% of drug failures, and so understanding how these properties are affected by physiochemical properties of potential drugs, such as molecular weight (MW), is of great importance in reducing the costs of drug development. A recent comparison of physiochemical properties of marketed oral drugs with those in different development phases, which is reported in the *Journal of Medicinal Chemistry*, provides some intriguing insights into the influence of these properties on the likelihood of progression through the drug development process.

Wenlock and colleagues took ~600 oral drugs marketed in the United States and ~600 potential oral drugs from all phases of clinical development — both those still in trials and those for which trials had been discontinued — and calculated various physiochemical properties for each. Several trends emerged. Particularly notable was that the mean MW of orally administered drugs in development decreases on passing through each phase, and seems to converge towards the mean MW of the marketed drugs. Moreover, the mean MW of the compounds discontinued from a particular phase is greater than the mean MW of the compounds in the next phase. A similarly clear trend was apparent in the data for log P — a measure of lipophilicity — with the most lipophilic compounds being discontinued at each phase, consistent with the common finding that high lipophilicity frequently leads to compounds that are rapidly metabolized and that have low solubility and poor absorption.

Previous analyses of the physiochemical properties of orally available drugs have had a considerable impact on the type of compounds thought to be 'drug-like'. For example, Lipinski and colleagues' analysis of the World Drug Index lead to the formulation of the famous "Rule of 5", which suggests (among other things) that compounds with MW >500 and log P >5 are less likely to be orally bioavailable, and which is now widely used to filter out compounds likely to have poor pharmacokinetic properties early on in drug discovery. The study by Wenlock *et al.* adds further support to the idea that there are limiting values for the MW and lipophilicity of a candidate oral drug that are reflected in the physiochemical properties of marketed oral drugs.

Another interesting issue that is highlighted by the authors is the possible influence of high-throughput screening (HTS) on the type of compound now coming through the pipeline. Looking at the properties of compounds in Phase I, which were presumably in early-stage discovery in the early 1990s when HTS began to be implemented widely, the authors note that there is a significant increase (86 Da) in the mean MW compared with marketed drugs. Bearing in mind that optimization of HTS hits often increases MW and lipophilicity, and the apparent upper limits on MW and lipophilicity for oral drugs, the findings of this study also support the idea that screening libraries for HTS need to be more 'lead-like' — that is, have lower MW and lipophilicity than marketed drugs.

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References and links

ORIGINAL RESEARCH PAPER Wenlock, M. C. *et al*. A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* **46**, 1250–1256 (2003)

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