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Evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption: a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan

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ABSTRACT

Background and the purpose of the study: Partition coefficients (log *D* and log *P*) and molecular surface area (PSA) are potential predictors of the intestinal permeability of drugs. The aim of this investigation was to evaluate and compare these intestinal permeability indicators.
Methods: Aqueous solubility data were obtained from literature or calculated using ACD/Labs and ALOGPS. Permeability data were predicted based on log *P*, log *D* at pH 6.0 (log $D_{6.0}$), and PSA.
Results: Metoprolol's log *P*, log $D_{6.0}$ and a PSA of <65 Å correctly predicted 55.9%, 50.8% and 54.2% of permeability classes, respectively. Labetalol's log *P*, log $D_{6.0}$, and PSA correctly predicted 54.2%, 64.4% and 61% of permeability classes, respectively. Log $D_{6.0}$ correlated well (81%) with Caco-2 permeability (P_{app}). Of the list of national essential medicines, 135 orally administered drugs were classified into biopharmaceutical classification system (BCS). Of these, 57 (42.2%), 28 (20.7%), 44 (32.6%), and 6 (4.4%) were class I, II, III and IV respectively.
Conclusion: Log $D_{6.0}$ showed better prediction capability than log *P*. Metoprolol as permeability internal standard was more conservative than labetalol.

Keywords: Biopharmaceutical classification system, Permeability, log *P*, log *D*, PSA.

INTRODUCTION

Systemic bioavailability of an orally administered drug is largely dependent on its physicochemical properties and dosage formulation factors (1). Sophisticated modeling of the kinetics and dynamics of drug processes in the gastrointestinal tract subsequently led to the advent of the biopharmaceutical classification system (BCS) (2). According to the biowaiver, any possible variation in the bioavailability of a rapidly dissolving and highly soluble drug is attributed to physiological conditions rather than formulation and hence there is no logic in conducting a bioequivalence testing for such formulation (2). BCS offers a framework for development of pharmaceutical formulations. It has been estimated that the pharmaceutical industry can save $35 million annually through the applications of BCS (3). Assignment of the solubility and permeability classes of a drug is a laborious task. Lately, computational models to predict aqueous solubility and permeability through biological membranes have received considerable attention. The use of physicochemical properties in predicting in vivo behavior of drugs has many advantages including cost reduction; better control over protocol, reproducibility and avoidance of risk presented to human volunteers usually encountered in the bioequivalence studies (4). Molecular surface properties and partition coefficients have been used actively in construction of quantitative structure activity relationship (QSAR) models to predict intestinal permeability (2, 5-6).

This study reports for the first time an evaluation and comparison of pH-dependent and pH-independent n-octanol/water partition coefficients (log *D* and log *P*) and polar surface area (PSA) in prediction of intestinal permeability of drugs. The log *D* at physiologically relevant pH of 6.0 (log $D_{6.0}$) was used to provisionally classify the orally administered drugs on the list of national essential medicines (NEML) of Pakistan into BCS.

MATERIAL AND METHODS

The present revision of the NEML contains 335 medicines of different pharmacological classes (7). The highest dose of drug products available in oral dosage forms, i.e. oral tablets and capsules, were used.

Solubility

The dose number (Do) was calculated using equation 1:

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