Can we predict saliva penetration of drugs? A systematic review (Part 1) Nguyen TA[1,2,3], Chen RH[1,4], Hawkins BA[1,5], Hibbs DE[1], Kim HY[1,3,6], Wheate NJ[1], Groundwater PW[1], Stocker SL[1,2,3,,7], Alffenaar JWC[1,2,3,]; [1]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; [2]Westmead Hospital, Sydney, NSW, Australia; [3]Sydney Institute for Infectious Diseases, The University of Sydney, Sydney, NSW, Australia; [4]Department of Pharmacy, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [5]Antimicrobial Discovery Center, Department of Biology, Northeastern University, Boston, MA, USA; [6]Department of Pharmacy, Westmead Hospital, Sydney, NSW, Australia; [7]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia

Background and Objectives. Saliva is a patient-friendly matrix for therapeutic drug monitoring (TDM) but is infrequently used in routine care. This is due to the uncertainty of saliva-based TDM results to inform dosing. This study aimed to determine the physicochemical properties that influence the penetration of drugs from plasma to saliva to facilitate accelerated translation into practice.

Methods. Medline, Web of Science, and Embase (1974−2023) were searched for human clinical studies, which determined drug pharmacokinetics in both saliva and plasma. Studies with at least 10 subjects and 5 paired saliva-plasma concentrations per subject were included. For each study, the ratio of the area under the concentration-time curve between saliva and plasma was determined to assess penetration into saliva. Physicochemical properties of each drug (pKa, lipophilicity, molecular weight, physiological charge, number of hydrogen-bond donor and hydrogen-bond acceptor groups, polar surface area, rotatable bonds, and fraction of drug unbound to plasma proteins were obtained from PubChem and Drugbank. Drugs were categorised by their ionisability, after which saliva-to-plasma ratios were predicted with adjustment for protein binding and physiological pH via the Henderson-Hasselbalch equation. Spearman correlation analyses were performed for each drug category to identify factors predicting saliva penetration (α = 5%). Study quality was assessed by the Risk Of Bias In Non-randomised Studies–of Interventions tool.

Results. Overall, 42 studies including 40 drugs (antipsychotics, antimicrobials, immunosuppressants, antithrombotic, anticancer, and cardiac drugs) were included. The median saliva-to-plasma ratios were similar for drugs in the amphoteric (0.59), basic (0.43), and acidic (0.41) groups and lowest for drugs in the neutral group (0.21). Higher penetration of acidic drugs (n = 5; e.g., amoxicillin, phenytoin, and 5-fluoro uracil) into saliva was associated with lower ionisation and protein binding (correlation between predicted vs. observed saliva-to-plasma ratios: $R^2 = 0.85$, $p = 0.02$). For basic drugs (n = 21; e.g., indinavir, clonazepam, and lamotrigine), pKa predicted saliva penetration (Spearman correlation coefficient: $R = 0.53$, $p = 0.02$). For amphoteric drugs (n = 10; e.g., moxifloxacin, tenofovir, and voriconazole), hydrogen-bond donor ($R = -0.76$, $p = 0.01$) and polar surface area ($R = -0.69$, $p = 0.02$) were predictors. For neutral drugs (n = 10; e.g., carbamazepine, oxazepam, and tacrolimus), protein binding ($R = 0.84$, $p = 0.004$), lipophilicity ($R = -0.65$, $p = 0.04$) and hydrogen-bond donor count ($R = -0.68$, $p = 0.03$) were predictors. Included studies had a low-to-moderate risk of bias.

Conclusion. Many commonly used drugs penetrate saliva and this penetration can be partly predicted by a drug's ionisation state, protein binding, lipophilicity, hydrogen-bond donor count and polar surface area. Further research is required to evaluate the contribution of drug transporters and other physiological factors that may influence the saliva penetration of drugs.

Keywords. Drug monitoring, physicochemical properties, saliva, oral fluid, penetration