Can we predict saliva penetration of drugs?: a systematic review

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INTRODUCTION

- Saliva is an emerging matrix for therapeutic drug monitoring (TDM).
- Saliva-based TDM offers a simple, less-invasive and patient-friendly alternative to current blood-based approach.

OBJECTIVE

To determine the physicochemical properties that influence the penetration of drugs from plasma to saliva.

METHODS

Data collection

- **Medline** and **Web of Science** (1980−2023) were searched for human clinical studies, which determined drug pharmacokinetics in both saliva and blood.
- **Inclusion criteria: N ≥ 10 subjects** and **≥ 5 paired saliva-blood concentrations** per subject
- Screening was managed using Covidence [1].
- For each study, the **ratio of the area under the concentration-time curve** between saliva and total (protein-bound and unbound) blood was determined (**Fig. 1**)

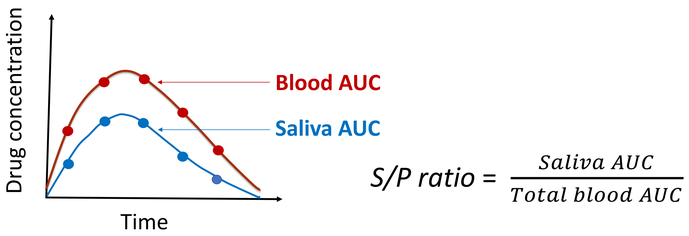

Fig.1 Drug penetration into saliva (saliva to plasma ratio)

- **Physicochemical properties** of each drug were obtained from **PubChem** and **Drugbank:**
  - pKa
  - Lipophilicity (logP)
  - Molecular weight
  - Physiological charge
  - Hydrogen-bond donor
  - Hydrogen-bond acceptor
  - Polar surface area
  - Rotatable bond counts
  - Fraction of drug unbound to plasma protein

Data analysis

- Drugs were categorized by their ionizability.
- S/P ratios were predicted after adjustment for protein binding and physiological pH using the Henderson-Hassenbach equation [2].
- Spearman rank correlation analyses were performed for each category to identify factors predicting saliva penetration (α = 5%).
- Study quality assessed by the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool [3].
- Data were analyzed using R [4].

RESULTS

- 48 studies including 44 drugs (e.g., antipsychotics, antimicrobials, immunosuppressants, anticancer, and cardiac drugs) included.
- S/P ratios were similar for drugs in the amphoteric, basic, and acidic groups and lowest for drugs in the neutral group (**Table 1**).
- The acidic and a half of the basic groups followed Henderson-Hassenbach principle, but the amphoteric group did not (**Fig. 2**).

Table 1 Observed S/P per group

Group	S/P, median (IQR)
Acidic (n=6)	0.43 (0.17–0.68)
Basic (n=22)	0.50 (0.29–1.13)
Amphoteric (n=10)	0.59 (0.10–1.20)
Neutral (n=6)	0.16 (0.08–0.24)

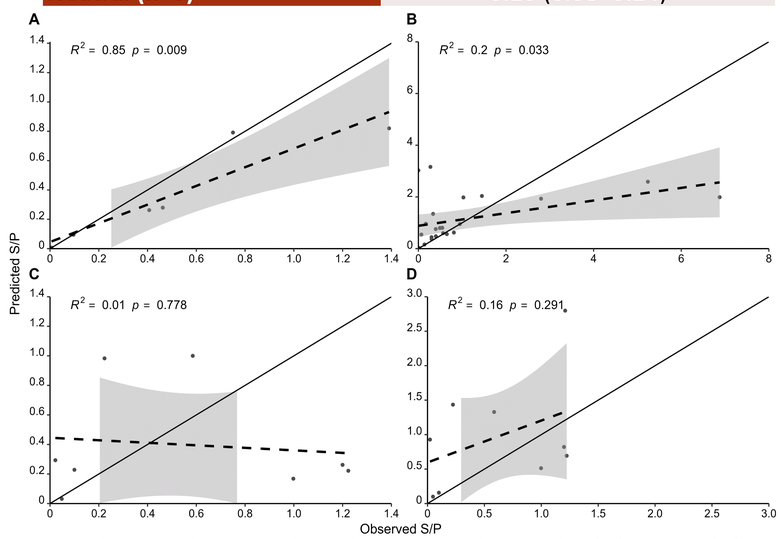

Fig.2 Observed vs. predicted S/P ratio for acidic (A), basic (B), amphoteric-acid (C) and amphoteric-base (D) drugs.

- There was weak-to-moderate evidence that physicochemical properties can predict saliva penetration (0.01 < P ≤ 0.05) (**Table 2**).

Table 2 Spearman correlation analysis to investigate physicochemical factors influencing the penetration of drugs into saliva (only significant factors shown)

S/P of \ Factor	pKa	logP	Rotatable bond count	Polar surface area	H-bond donor
Acidic		R = -0.89 P = 0.03	R = -0.82 P = 0.04		
Basic*	R = 0.69 P = 0.02				
Amphoteric				R = -0.69 P = 0.03	R = -0.76 P = 0.01
Neutral			R = 0.95 P = 0.05		R = 0.95 P = 0.05

R: Spearman correlation coefficient; *log transformed

- All studies had a low-to-moderate risk of bias.

CONCLUSIONS

- Many commonly used drugs penetrate saliva.
- Physicochemical properties can partly predict saliva penetration.
- Further research is required to evaluate the contribution of drug transporters and physiological factors influencing saliva penetration of drugs.

ACKNOWLEDGEMENTS

- Thi A. Nguyen was supported by the Ph.D. scholarship "The University of Sydney, Faculty of Medicine and Health Executive Dean Scholarship in Personalized Medicine".
- We thank Prof Paul W. Groundwater (Univ of Sydney, Australia) for assistance with methodology and Tri Phuoc Nguyen (HCMC Univ of Technology, Vietnam) with data visualization.

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