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ORIGINAL ARTICLE

Comparative assessment of saliva and plasma for drug bioavailability and bioequivalence studies in humans

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KEYWORDS

SECS;
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Abstract *Aims:* To study the pharmacokinetics of selected drugs in plasma and saliva matrixes in healthy human volunteers, and to suggest using non-invasive saliva sampling instead of plasma as a surrogate in bioavailability and bioequivalence (BA/BE) studies.

Methods: Four different pilot BA/BE studies were done in 12–18 healthy humans. Saliva and plasma samples were collected for 3–5 half life values of metformin, tolterodine, rosuvastatin, and paracetamol after oral dosing. Saliva and plasma samples were assayed using LC-MSMS, and then pharmacokinetic parameters were calculated by non-compartmental analysis using Kinetica program. Effective intestinal permeability (P_{eff}) values were also optimized to predict the actual average plasma profile of each drug by Nelder-Mead algorithm of the Parameter Estimation module using SimCYP program.

Results: All studied drugs showed salivary excretion with strong correlation coefficients between saliva and plasma concentrations. The optimized P_{eff} ranged 1.44–68.3 $\times 10^{-4}$ cm/s for the drugs under investigation. Saliva/plasma concentrations ratios ranged 0.17–1.5. Inter and intra individual variability of primary pharmacokinetic parameters in saliva matrix was either close to or higher than plasma matrix. This requires larger sample size in saliva studies for some drugs.

Conclusion: Our results suggest that there is a potential in BA/BE studies for saliva to be considered as a surrogate for plasma concentration, which goes along with drug regulations. The use of saliva instead of plasma in such studies makes them non-invasive, easy and with a lower clinical burden.

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1. Introduction

Salivary excretion of some drugs has been reported previously as a good indicator for drug bioavailability, therapeutic drug monitoring, pharmacokinetics and also drug abuse. Saliva sampling offers simple, non-invasive and cheap method as

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compared with plasma sampling with no contamination risk (Gorodischer and Koren, 1992; Ruiz et al., 2010). The rules of drug protein binding and membrane permeability on salivary excretion were previously investigated for several drugs, where a Salivary Excretion Classification System (SECS) was proposed as shown in Table 1 (Idkaidek and Arafat, 2012). High intestinal permeability corresponds to fraction absorption $F_a > 0.9$ and high protein binding corresponds to low fraction unbound fu of < 0.1 (Amidon et al., 1995; Sunil and Philip, 2009). According to SECS classification Class I drugs of high intestinal permeability and low protein binding, such as paracetamol, are subjected to salivary excretion. Class II drugs of low permeability and low protein binding, such as metformin, are subjected to salivary excretion since low permeability is counterbalanced by low protein binding. Class III drugs of high intestinal permeability and high protein binding, such as tolterodine, are subjected to salivary excretion since high protein binding is counterbalanced by high permeability. Class IV drugs of low intestinal permeability and high protein binding, such as montelukast, are not subjected to salivary excretion (Idkaidek and Arafat, 2012).

Four pilot studies were previously done in our laboratory on SECS class I drugs: paracetamol and tolterodine, SECS class II drug: metformin and SECS class III drug: rosuvastatin. Results were promising and have demonstrated high saliva-plasma correlations with relatively higher variability in saliva parameters (Idkaidek and Arafat, 2014a, 2014b, 2015, 2016).

Table 1 Salivary Excretion Classification System (SECS) according to drug permeability (P_{eff}) and fraction unbound to plasma proteins (fu).

Class	Parameter		
	P_{eff}	fu	Salivary excretion
Class I	High	High	Yes
Class II	Low	High	Yes
Class III	High	Low	Yes
Class IV	Low	Low	No

2. Objective

The objective of this review was to further investigate the robustness of using non-invasive saliva sampling method instead of plasma sampling method as a surrogate for bioavailability and bioequivalence studies of SECS classes I, II and III drugs that are excreted in saliva.

3. Experimental

Saliva BA/BE under fasted state, in 12–18 healthy human volunteers after signing informed consent, was compared to plasma pharmacokinetics in crossover or parallel design studies. Medical history, vital signs, physical examination, and laboratory safety test results showed no evidence of clinically significant deviation from normal medical condition as evaluated by the clinical investigator. The pilot bioavailability study was conducted as per the ICH, GCP, and Helsinki declaration guidelines after IRB of International Pharmaceutical Research Center and Jordan FDA approvals. Single oral doses of study drugs were administered after 10 h overnight fasting without dietary restrictions. Then resting saliva (without stimulation) and plasma samples were collected at specific time intervals up to 3–5 half lives. Thorough rinsing of the mouth was done after dosing to avoid contamination of saliva samples with any drug residues. Sensitive and accurate LC-MS/MS methods were developed and validated for the determination of study drugs in human plasma and saliva (Idkaidek and Arafat, 2014a, 2014b, 2015, 2016).

4. Data analysis

4.1. Pharmacokinetic analysis

Individual pharmacokinetic parameters for drug concentration in both saliva and plasma samples were calculated by non-compartmental analysis (NCA) using Kinetica program V5. Investigated pharmacokinetic parameters were area under the concentration curves to last collection time (AUC_t), maximum measured concentration (C_{max}) and time to maximum concentration (T_{max}).

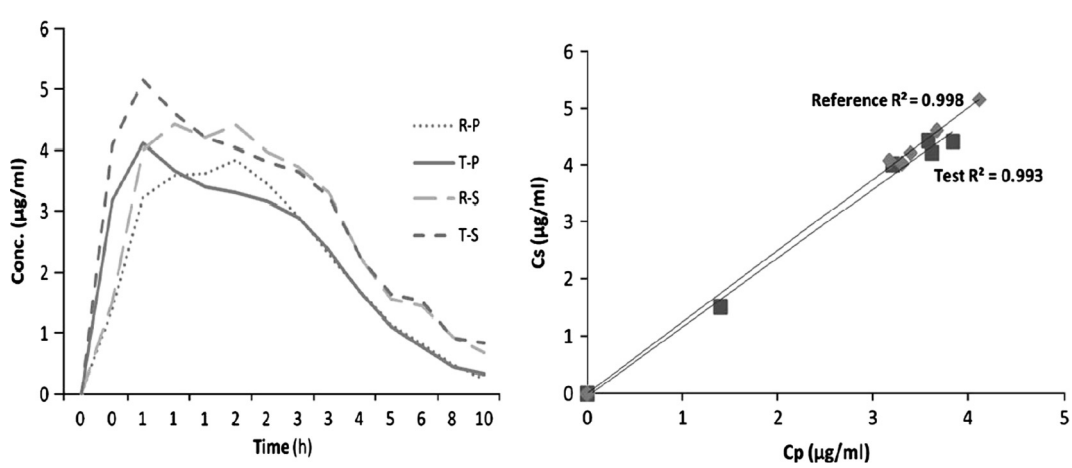

Figure 1 Paracetamol plasma and saliva mean profiles & correlations.

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