Usefulness of Saliva for Measurement of 3,4-Methylenedioxymethamphetamine and Its Metabolites: Correlation with Plasma Drug Concentrations and Effect of Salivary pH

Mònica Navarro,1 Simona Pichini,2 Magí Farré,1,3 Jordi Ortuño,1 Pere N. Roset,1 Jordi Segura,1,4 and Rafael de la Torre1,3*

Background: Saliva is an alternative biologic matrix for drugs-of-abuse testing that offers the advantages of noninvasive, rapid, and easy sampling. We studied the excretion profile of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in both saliva and plasma, as well the effect of the drug on salivary pH.

Methods: Saliva and plasma samples were obtained from eight healthy MDMA consumers after ingestion of a single 100-mg dose of the drug. Concentrations of MDMA and its main metabolites, 3,4-methylenedioxyamphetamine (MDA) and 4-hydroxy-3-methoxymethamphetamine (HMMA), in saliva and plasma were measured by gas chromatography–mass spectrometry. Apparent pharmacokinetic parameters for MDMA in saliva were estimated, and the salivato-plasma ratio at each time interval was calculated and correlated with salivary pH.

Results: MDMA, MDA, and HMMA were detected in saliva. Salivary concentrations of MDMA were 1728.9–6510.6 µg/L and peaked at 1.5 h after drug intake. This was followed by a progressive decrease, with a mean concentration of 126.2 µg/L at 24 h. The salivato-plasma ratio was 32.3–1.2, with a peak of 18.1 at 1.5 h after drug administration. Salivary pH seemed to be affected by MDMA administration; pH values decreased by 0.6 units (mean pH values of 6.9 and 6.8 at 1.5 and 4 h after drug administration vs predose pH of 7.4).

Conclusions: Measurement of MDMA in saliva is a valuable alternative to determination of plasma drug concentrations in both clinical and toxicologic studies. On-site testing is also facilitated by noninvasive and rapid collection of salivary specimens.

Alternative biologic matrices to urine and plasma have recently been introduced for drug monitoring (1, 2). Analysis of certain matrices, such as tears, cerebrospinal fluid, and bronchial secretions, may reveal the presence of a drug at the site of action, whereas others, such as amniotic fluid, cord blood, or breast milk, are useful for determining fetal and perinatal exposure to drugs (3–7). An individual’s past history of medication, compliance, or drug abuse can be obtained from drug testing of hair and nails (8–11), whereas data on the current status of drug use might be also provided by sweat and saliva analysis (12).

In fact, saliva is the only fluid that has successfully been used as an alternative to blood in several pharmacokinetic and pharmacotoxicologic studies (13–16), and there is evidence that when a given drug is detected in salivary specimens, there is a high likelihood that the individual tested is under the pharmacologic effects of the drug. Previous studies on drugs in saliva (17) have shown that weak bases, such as cocaine, opiates, benzodiazepines, or nicotine, tend to concentrate in saliva because its pH is slightly acidic compared with that of plasma (12, 17–19). Although some metabolites have been detected, the parent drug is usually the main analyte found in saliva (2). Saliva has the advantage of noninvasive sampling, which is particularly convenient in any situation in which samples must be collected with minimum

1 Department of Pharmacology, Institut Municipal d’Investigació Mèdica (IMIM), E-08003 Barcelona, Spain.
2 Clinical Biochemistry Department, Istituto Superiore di Sanità, 00161 Roma, Italy.
3 Universitat Autònoma de Barcelona, E-08193 Barcelona, Spain.
4 Universitat Pompeu Fabra, E-08003 Barcelona, Spain.
*Address correspondence to this author at: Drug Research Unit, Depart-ment of Pharmacology, Institut Municipal d’Investigació Mèdica (IMIM), C/Doctor Aiguader 80, E-08003 Barcelona, Spain. Fax 34-93-2213237; e-mail rtorre@imim.es.

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controlled administration of amphetamines and related compounds in saliva after the administration of 100 mg of MDMA. Obtained from individuals participating in a clinical trial, saliva and plasma samples were used to determine the effect of salivary pH on the MDMA saliva-to-plasma (S/P) ratio. Saliva and plasma samples were used to assess the eventual correlation between salivary and plasma MDMA concentrations; and (c) to determine the effect of salivary pH on the MDMA saliva-to-plasma (S/P) ratio. Saliva and plasma samples were obtained from individuals participating in a clinical trial involving the controlled administration of 100 mg of MDMA.

**Materials and Methods**

**Participants and Study Design**

Eight males were included in the study. Eligibility criteria required the required use of MDMA on at least five occasions. Each participant underwent a general physical examination, routine laboratory tests, urinalysis, and a 12-lead electrocardiogram. The mean age of the participants was 24.4 years (range, 21–33 years), the mean weight was 72.7 kg (range, 60.6–86.5 kg), and the mean height was 177.3 cm (range, 167.5–190 cm). All participants were declared MDMA consumers (mean number of times drug had been consumed, 24; range, 5–100). We phenotyped participants for CYP2D6 activity, using dextromethorphan as a drug probe. The dextromethorphan/dextromethorphan ratio was used to classify participants as poor or extensive metabolizers (27). All participants were extensive metabolizers.

All participants gave written informed consent before inclusion in the study and received financial compensation for inconveniences caused by their participation in the study. The study was conducted in accordance with the Declaration of Helsinki, approved by the local Ethical Committee (CEIC-IMAS), and authorized by the Agencia Española del Medicamento (reference AEM 98/532) of the Spanish Ministry of Health.

The study design was double blind, randomized, crossover, and controlled. The volunteers participated as outpatients in two different randomly assigned 10-h experimental sessions in which they were given single 100-mg doses of MDMA or placebo by the oral route. The volunteers were requested to abstain from consumption of any drug of abuse during the study period, and urine drug testing was performed before each experimental session for opiates, cocaine, cannabinoids, and amphetamines. For all four groups of substances tested, all volunteers were negative before each experimental session. MDMA and placebo were prepared by the Pharmacy Service of Hospital del Mar (Barcelona, Spain) as white soft-gelatin capsules (two capsules each time) and administered in a fasting state with 100 mL of tap water.

**CHEMICALS**

MDMA, MDA, HMMA, and the internal standards MDMA-d5, MDA-d5, and pholedrine were purchased from Cerilliant (formerly Radian Analytical Products). N-Methylbis(trifluoroacetamide) (MBTFA; gas chromatography grade) was supplied by Macherey-Nagel. Potassium dihydrogen phosphate, potassium hydroxide, ethyl acetate, and ammonia solution were from Merck. Ultra-pure water was obtained using a MilliQ purification system (Millipore). All other reagents were of analytical grade.

**COLLECTION OF SALIVA AND BLOOD SAMPLES**

Samples of mixed saliva (saliva secreted by the different salivary glands) (12) were obtained without any stimulation over a 5-min period at 0, 1.5, 4, 6, 10, and 24 h after drug administration. Samples were collected in polypropylene tubes. The salivary pH was recorded at the time of collection, and the samples were immediately stored at −20 °C until analysis. Blood samples were centrifuged, and the plasma obtained was immediately frozen at −20 °C. Blood and saliva from a placebo group that tested negative for the presence of MDMA were used as drug-free blank samples.

The collection times selected in the present experiment...
were based on previous experience from more extensive pharmacokinetic studies (28, 29).

DETERMINATION OF SALIVARY AND PLASMA MDMA, MDA, AND HMMA
Frozen saliva and plasma were allowed to thaw at room temperature. Before analysis, saliva was centrifuged to remove the mucous part that accumulated at the bottom. To 1 mL of plasma or saliva, we added 200 ng each of MDMA-d₅, MDA-d₅, and pholedrine; we then extracted the drugs from the samples by solid-liquid extraction using mixed cation-exchange/hydrophobic interaction columns (Bond-Elut Certify®, Hewlett Packard). The compounds were separated on a quadrupole mass spectrometer (Agilent, formerly Hewlett Packard). This method has previously been validated for plasma samples, and it was reapplied for saliva and plasma samples in this present study.

We adjusted the pH of the samples to 6 by adding 1 mL of 0.1 mol/L phosphate buffer, pH 6, and passed the samples through the columns, which had previously been conditioned by sequential passage of 2 mL of methanol and 2 mL of 0.1 mol/L phosphate buffer, pH 6. Columns were washed consecutively with 1 mL of 1 mol/L acetic acid and 6 mL of methanol. MDMA and its metabolites were eluted with 2 mL of ethyl acetate containing 20 g/L ammonium hydroxide. After the addition of 20 μL of MBTFA to prevent drugs losses, the eluates were evaporated to dryness at 40 °C under a nitrogen stream. Residues were reconstituted and derivatized with 50 μL of MBTFA at 70 °C for 45 min to obtain trifluoroacetyl derivatives of the analytes (30).

The MDMA concentration in saliva was determined on a HP6890 gas chromatograph coupled to a Model HP5973 quadrupole mass spectrometer (Agilent, formerly Hewlett Packard). The compounds were separated on a cross-linked 5% phenyl-methylsilicone capillary column [Ultra-2; 12 m × 0.2 mm (i.d.); 0.33-μm film thickness; Hewlett-Packard]. The samples were injected in splitless mode, and helium gas was used as carrier at a flow rate of 1.2 mL/min (measured at 180 °C). The mass spectrometer was operated in the electron impact ionization and selected-ion monitoring acquisition mode. The ions m/z 154 for MDMA, HMMA, and pholedrine; m/z 162 for MDA; m/z 158 for MDMA-d₅; and m/z 167 for MDA-d₅ were selected for quantification (31). This method has previously been validated for plasma samples, and it was reapplied for saliva and plasma samples in this present study (28, 31).

Calibration curves were prepared in drug-free saliva and plasma by adding appropriate volumes of working methanolic solutions of the analytes under investigation. Peak-area ratios between each compound and the internal standard (MDMA-d₅ for MDMA, MDA-d₅ for MDA, pholedrine for HMMA) were used for calculations. Curves were linear at 25–400 μg/L for MDMA and HMMA and 2.5–40 μg/L for MDA. Samples containing concentrations above the working ranges were reanalyzed after appropriate dilution with phosphate buffer.

Analytical recoveries were calculated by comparing the peak areas obtained for calibration samples, prepared by adding the reference substances and the internal standards to blank plasma or saliva, before or after the above-mentioned extraction procedure. The mean analytical recovery for MDMA was 90% in both saliva and plasma; recoveries for MDA and HMMA were 92% and 74%, respectively.

Four replicate analyses were performed with a plasma and saliva supplemented with 25 μg/L MDMA and HMMA and 2.5 μg/L MDA. The standard deviation of the quantitative values was used as a measure of the noise to calculate the limit of quantification (10 SD). The limits of quantification were 5.7 μg/L for MDMA, 1 μg/L for MDA, and 2.9 μg/L for HMMA in both biologic fluids.

To determine intraassay imprecision and accuracy, we analyzed three replicates each of blank plasma and saliva containing three different concentrations of MDMA, MDA, and HMMA (25, 100, and 400 μg/L for MDMA and HMMA; 2.5, 10, and 40 μg/L for MDA); for interday imprecision and accuracy, we measured the above-mentioned replicates on three different days.

Intraday imprecision (expressed as CV for specific added target concentrations) and accuracy (expressed as percentage error of concentration found compared with added target concentrations) were always <6.5% for all analytes under investigation. Similarly, the interday CV and error were <8.5%.

pH MEASUREMENTS OF SALIVARY SAMPLES
The pH of salivary samples from the eight volunteers in the MDMA or placebo groups was measured at all time intervals with a pH indicator stick (Riedel-de Haën) with a pH range of 6.4–8 (increments of 0.2 pH units). Results were recorded by two independent observers, who were unaware of treatment conditions.

PHARMACOKINETICS AND STATISTICAL ANALYSIS
With regard to saliva and plasma concentrations of MDMA, the following parameters were determined: peak concentration (c max); time taken to reach c max (t max), area under the concentration–time curve from 0 to 24 h (AUC₀–₂₄); elimination half-life (t ½d) in plasma and disappearance half-life (t ½d) in saliva; elimination constant (k e) in plasma; and disappearance constant (k d) in saliva. First-order constant kinetics are usually described as elimination constants for either plasma or saliva. Because drugs are not properly eliminated from saliva, but rather what is observed is a disappearance rate, we preferred to use the term disappearance constant to describe this kinetic parameter (32).

The AUC for each drug was calculated by the linear trapezoidal rule, and the elimination and disappearance constants were calculated by log-linear regression of the three last points with concentrations above the quantification limit. Correlations between different variables were analyzed by regression analysis. The Wilcoxon test for nonparametric data was used to assess differences in salivary pH values between treatment and placebo. Differences associated with P values <0.05 were considered statistically significant.
Results

CONCENTRATION–TIME PROFILES AND PHARMACOKINETICS OF MDMA IN SALIVA AND PLASMA

The time courses of the MDMA concentrations in saliva and plasma for each of the eight volunteers are shown in Fig. 1. At 1.5 h after administration of MDMA, concentrations appeared to be the highest in both saliva (range, 1728.9–6510.6 μg/L) and plasma (range, 134.9–223.0 μg/L). It should be noted that two of the eight volunteers had peak MDMA concentrations in saliva more than twofold higher than the mean c_{max} in the remaining six participants. These two individuals were also the ones showing the highest plasma c_{max}. After the absorption phase, saliva and plasma MDMA concentrations decreased to mean concentrations (SD) at 24 h of 126.2 (101.8) μg/L and 13.5 (18.6) μg/L, respectively. The mean concentration–time curves for MDMA in saliva and plasma are shown in Fig. 2. The MDMA concentrations in saliva were one order of magnitude higher than those observed in plasma. The pharmacokinetic parameters for MDMA in saliva and plasma are presented in Table 1. It is important to point out that these are only “apparent” parameters because of the few concentration–time data points for saliva and plasma evaluated in this study. Nonetheless, the apparent pharmacokinetic parameters for MDMA in plasma were in accordance with those reported by our group in a previous study (30). The t_{max} was attained at 1.5 h in both saliva and plasma. The t_{1/2d} and k_{d} values for saliva were greater than the t_{1/2e} and k_{e} values for plasma.

MDA AND HMMA IN SALIVA

HMMA, the major metabolite of MDMA, was detected in the nonconjugated form in trace amounts, but quantification was not possible. MDA was also excreted in saliva, with concentrations representing ~4–5% of the concentration of salivary MDMA (AUC comparisons), as was also observed in plasma (Fig. 2). The highest salivary concentrations of MDA occurred between 1.5 and 4 h after drug administration, whereas in plasma, the highest concentrations were between 4 and 6 h.

MEASUREMENTS OF pH IN SALIVARY SAMPLES

The 24-h profiles for mean salivary pH in both the placebo group and MDMA samples are shown in Fig. 3. The mean predose salivary pH was 7.4 and 7.3 in the MDMA and placebo samples, respectively. At 1.5 h after drug administration, which corresponds to the MDMA t_{max}, the salivary pH in the MDMA group showed a mean (SD)
A statistical decrease to 6.9 (0.2) compared with 7.3 (0.2) for the placebo group (Wilcoxon test, P < 0.001). The decrease in pH values was homogeneous; all participants treated with MDMA showed lower values than those observed for the placebo group. At 4 h after treatment (1 h after a light meal given to participants), minimum mean (SD) pH values of 6.8 (0.4) and 7.1 (0.3) were obtained in the MDMA and placebo samples, respectively. The two mean values were not statistically different. In fact, six of the eight participants showed the same pattern; in one participant, no changes were observed, and in another, the pH value in the placebo condition was higher than that during MDMA treatment. Finally, pH returned to predose values between 6 and 24 h after treatment in both the MDMA and placebo groups.

S/P ratio for MDMA
The time-course curve for the S/P ratio during the 24 h after drug administration is presented in Fig. 4. The S/P ratio exhibited a mean (SD) maximum value of 18.1 (7.9) at 1.5 h, corresponding to the MDMA t_{max}. The high variability observed (CV = 43%) was attributable to the two individuals with the highest MDMA salivary c_{max}, who had S/P ratios of 26.6 and 32.3, whereas the remaining volunteers had values between 10.3 and 16.9. In the postabsorption phase, the S/P ratio decreased to reach values of ~7.3 and 6.4 at 10 and 24 h after drug administration, respectively. S/P ratios showed a strong correlation with salivary MDMA concentrations (r = 0.96; P < 0.001) as well as a lower but significant correlation with salivary pH values (r = 0.62; P < 0.002) and plasma MDMA concentrations (r = 0.69; P < 0.001; Fig. 5). In any case, regardless of the variation of S/P ratio during the time course of MDMA administration, salivary concentrations were correlated to plasma concentrations (r = 0.81; P < 0.001).

**Discussion**
Overall, the patterns of salivary and plasma MDMA concentration–time profiles for different participants agreed well, but certain interindividual variations were evident for salivary MDMA concentrations. Data obtained for plasma samples were more homogeneous and were in agreement with previously reported findings after the administration of the same MDMA dose to eight different individuals (31).

MDMA appeared in saliva in concentrations remarkably higher than those in plasma (Fig. 2). This is not surprising and may be attributable to several causes. Drugs are generally incorporated into saliva by passive diffusion because of a concentration gradient in which only the free fraction of the drug (not bound to proteins) diffuses through lipidic membranes from plasma to saliva. It should be noted that saliva has little protein-binding capacity compared with plasma. There are no specific data on the fraction of MDMA bound to plasma proteins, but from what is known for amphetamine and methamphetamine (33), it should be ~20%. In practice, such low binding means that the MDMA available in plasma may diffuse into the saliva. In addition, the passage across cells membranes is favored for low-molec-

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**Table 1. Apparent pharmacokinetic parameters for MDMA in saliva and plasma.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saliva</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>CV, %</strong></td>
</tr>
<tr>
<td>AUC_{0–24 h}, μg/L · h</td>
<td>20 843.1</td>
<td>12 656.6</td>
</tr>
<tr>
<td>t_{max}, h</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>c_{max}, μg/L</td>
<td>3375.6</td>
<td>1812.8</td>
</tr>
<tr>
<td>k_{u}, h^{-1}</td>
<td>0.1279</td>
<td>0.0231</td>
</tr>
<tr>
<td>t_{1/2,a} h</td>
<td>5.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

For plasma, k_{u} and t_{1/2,a}.  

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**Fig. 3.** Time profile of salivary pH during treatment administration.  
○, placebo; ●, MDMA. ●, P < 0.001.  

**Fig. 4.** Time profile of MDMA S/P ratio.
ular weight molecules, such as MDMA. Furthermore, MDMA is a basic drug with a \( pK_a \) of 9.9 [data derived from methamphetamine], and because under typical conditions (absence of salivary flow stimulation) saliva is more acidic than blood, MDMA is converted to its ionized form, which cannot diffuse back into plasma and thus accumulates in saliva.

The theoretical S/P ratio for MDMA should be \(~3.9\) as calculated with the Henderson–Hasselbalch equation. In our study, the mean S/P ratio was 18.1 at peak MDMA concentrations and 6.4 at 24 h after drug administration. However, it must be noted that there were two individuals who had S/P ratios that were exceedingly high. Mean S/P ratios increased to a 20-fold difference between plasma and salivary concentrations at \( t_{\text{max}} \), when most probably this difference may be closer to 10-fold (mean value for six participants, excluding outliers). In any case, it is apparent that excretion of MDMA in saliva occurs to a greater extent than expected. Interindividual variations in the MDMA S/P ratio, as well as in salivary MDMA concentrations, could be partly explained by the fact that the saliva was collected without flow stimulation. It is known that stimulation of saliva secretion increases the pH to values approaching plasma pH. In the case of basic drugs, such as MDMA or cocaine, this reduces the salivary drug concentration, and the variability in S/P ratios is narrowed.

In this study, the saliva collected was nonstimulated to measure true saliva pH. This approach allowed the observation of eventual pH changes produced by MDMA. In addition, most volunteers receiving MDMA experienced jaw clenching, and the production of stimulated saliva by conventional methods, such as chewing, seemed inadequate for this drug. Salivary pH appeared to be affected by MDMA concentration in saliva after drug administration. In volunteers receiving MDMA, the salivary pH was lowered, attaining a maximal effect at MDMA \( t_{\text{max}} \). Most probably this contributed to the accumulation of the drug in the salivary fluid. In the two cases where S/P ratios were extremely high, a poor correlation with salivary pH was observed (Fig. 4), so that other mechanisms may operate in the diffusion to saliva. Changes in salivary pH observed at 4 h after drug administration represented the combined effect of MDMA and the ingestion of a light breakfast 3 h after drug administration. In the hours following maximum MDMA concentrations, S/P ratios decreased and reached almost constant values, but were still higher than the theoretical value from the Henderson–Hasselbalch equation. Because MDMA acts on serotonergic neurotransmission, with resulting vasoconstriction and significant changes in hemodynamics, a reduction in saliva production probably occurs, which concentrates this fluid. In fact, individuals receiving MDMA usually exhibit dry mouth. Presumably MDMA also impairs salivary flow through its sympathomimetic effects, producing a sympathetic constriction of the salivary bed. Consequently, buffering capacity, which is maximal in conditions of flow stimulation, can be reduced, and the pH of mixed saliva obtained from the oral cavity (the one measured) may not be the same as the pH at the site of saliva secretion. Hence, a dynamic concentration gradient takes place, which probably produces MDMA S/P ratios higher than those calculated with the Henderson–Hasselbalch equation. Unfortunately, one limitation of this study was that it was not possible to measure salivary flow during collection, a variable that could have explained apparent deviations from theoretic values.

S/P ratios exceeding theoretical values were also found by Samyn and Van Haeren, who measured MDMA in saliva and plasma in individuals who admitted recent drug abuse. Similar results were also reported by...
Cook et al. (37), who compared methamphetamine concentrations in the saliva and plasma of volunteers receiving the drug by smoking and intravenous routes. Both authors always found S/P ratios exceeding theoretical values and attributed the circumstance to buccal contamination by tablets or smoked drugs, at least for the first hours after drug administration. However, this is not the case of the present study, where MDMA was administered as capsules. Moreover, if buccal contamination can be hypothesized for the first 2 h after drug administration, this event had to be excluded in the following hours because the light meal (snack and juice) given to the volunteers 3 h after the start of treatment should have eliminated this contamination. Indeed, S/P ratios exceeding theoretical values were also found when methamphetamine was administered intravenously (37).

MDMA was the principal analyte detected in saliva. In fact, MDA was found in the saliva in minute abundance relative to MDMA, as it is in plasma (28). Regarding HMMA, only trace amounts could be found in saliva because it is mainly present in plasma in its glucuronically-conjugated form (38), which does not diffuse through the lipid barrier dividing salivary ducts from the systemic circulation. The evidence that MDMA was the major analyte found in saliva was in agreement with results reported by Cone (17) for cocaine and methamphetamine, as well as with those reported by Kintz (26) for N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine. Therefore, it can also be stated for MDMA that the parent drug is the target compound to be detected in saliva to assess consumption.

The apparent pharmacokinetic parameters calculated for plasma and saliva showed that MDMA disappears more rapidly from saliva than from plasma. This apparent discordance in the disposition of MDMA in the body may most probably be related to the changes in salivary pH discussed above during the first 4 h of MDMA kinetics. Despite the faster disappearance of the drug from saliva, because MDMA concentrations are one order of magnitude higher in saliva than those observed in plasma, salivary concentrations showed an average value of ~100 μg/L at 24 h. In contrast, it was not always possible to detect the drug in plasma at that same time.

Regarding the possible correlation between salivary concentrations of MDMA and cardiovascular effects, results from previous investigations showed a good agreement between MDMA concentrations in saliva and changes in blood pressure, heart rate, and pupillary diameter (28). Indeed, the pharmacologic effects rose and fell with a profile similar to that of salivary MDMA, presenting peak effects statistically different from placebo treatment between 1 and 2 h after MDMA administration. Similar results may be obtained when comparing the time course of MDMA in saliva and subjective feelings of intoxication (29). Subjective effects reach their maximum between 1.5 and 2 h and return to basal values ~4 h after drug treatment.

In conclusion, the measurement of MDMA in saliva appears to be a suitable alternative to plasma analysis in clinical and toxicologic situations where detection of recent abuse is requested. Despite changes in the S/P ratio during the time course for MDMA in saliva and plasma, the correlation between MDMA concentration in the two biologic fluids indicates that salivary concentrations of this drug may be a predictor of plasma concentrations. It should be acknowledged, nevertheless, that the results were obtained under controlled conditions where several factors that may modify salivary concentrations and that are difficult to ascertain in drug users were not considered: fasting state, dehydration, buccal contamination, and others. Because of the higher concentrations encountered, saliva exhibits a larger time window for detection of MDMA consumption. This may help establish whether individuals are under the influence of the drug in a much less invasive way than with plasma and without specific requirements for sample collection, thus facilitating onsite sample collection and drug testing.

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