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Review

Testing for drugs of abuse in saliva and sweat

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Abstract

The detection of marijuana, cocaine, opiates, amphetamines, benzodiazepines, barbiturates, PCP, alcohol and nicotine in saliva and sweat is reviewed, with emphasis on forensic applications. The short window of detection and lower levels of drugs present compared to levels found in urine limits the applications of sweat and saliva screening for drug use determination. However, these matrices may be applicable for use in driving while intoxicated and surveying populations for illicit drug use. Although not an illicit drug, the detection of ethanol is reviewed because of its importance in driving under the influence. Only with alcohol may saliva be used to estimate blood levels and the degree of impairment because of the problems with oral contamination and drug concentrations varying depending upon how the saliva is obtained. The detection of nicotine and cotinine (from smoking tobacco) is also covered because of its use in life insurance screening and surveying for passive exposure.

Keywords: Reviews; Sweat; Saliva; Drugs of abuse

Contents

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1. Introduction

Although the presence of drugs in sweat and saliva has been known for some time, the number of specimens tested is limited when compared to urine. The advantages and disadvantages of sweat, saliva and urine testing are outlined in Table 1. Two main limitations of sweat and saliva are apparent: (1) the amount of matrix collected is smaller when compared to urine and (2) the level of drugs in urine are higher than in either sweat or saliva, because drugs are concentrated by the kidneys [1]. The quantity of biological matrix that may be collected is especially important for forensic applications because preserving part of the specimen for an independent retest is crucial for acceptance of the testing process. For example, an aliquot of urine (usually >10 ml) is required to be kept frozen for an independent retest if the initial screen and confirmation are positive [2,3].

Analytical instrumentation has advanced since widespread urine testing was instituted in the late 1970s, although this increased sensitivity is not always trivial to maintain. Picogram quantities of drugs are now routinely detectable using mass spectrometry compared to the microgram quantities previously needed for detection by thin layer chromatography. Because of the developments of analytical instrumentation, all the requirements for forensic testing can be met with saliva and sweat testing that are being met with urinalysis. Nevertheless, no analytical laboratory wishes to test low levels of substances in complex matrices when higher levels are available in alternative matrices. More concentrated samples imply either an easier analytical scheme or a longer window of detection.

When is saliva and sweat testing justified? Generally, saliva or sweat testing is justified when the ease of collection as compared to the alternative matrices

Table 1
Advantages and disadvantages of sweat, saliva and urine testing (from [16])

	Sweat	Saliva	Urine
Sample collection	Noninvasive for skin wipes; invasive for patches and induced sweating	Noninvasive; possibility of low saliva flow with some drugs, such as alcohol	Privacy concerns; not easily field collected
Amount of sample normally available	Microliters of insensible sweat; 1–5 ml when induced by exercise	1–5 ml	>50 ml
Speed of collection	Seconds for wipes; hours to days for patches	Minutes	Minutes
Drug concentration	High for wipes; low for patches	Low	Moderate-to-high
Window of detection	Short, similar to blood	Short, similar to blood	Moderate, usually longer than blood
Determination of impairment	Correlation unlikely, except in induced sweating	Correlation with impairment in many cases	No correlation with impairment
Problems in interpretation	Limited sample for testing; environmental contamination	Limited sample for testing; contamination from previous ingestion; pH changes may affect saliva–plasma ratio	Possibility of adulteration by addition of substances; adulteration by gross physiological dilution

of urine, blood or hair outweighs the cost and technical difficulties in analysis. Due to commercial considerations rather than a substantial breakthrough in technology or knowledge, interest in both sweat and saliva testing has increased in recent years. An example of an interesting application of sweat testing, would be to predict a woman's fertile period by monitoring steroid secretions in sweat to either prevent pregnancy or promote it [4].

Several reviews have been written regarding the therapeutic monitoring of drugs in saliva [5–15]. Fewer reviews have been published on monitoring drugs of abuse [16–20]. Only two reviews have been published on monitoring drugs of abuse in sweat [21,22]. This review was written with a focus on forensic applications, such as monitoring individuals in drug treatment, drug use by prisoners/probationers, public safety of drivers [23,24], or drug use by employees. In these testing situations, the window of detection of drug use, the information sought, the invasiveness of the sample collection, and the sampling and testing cost must be weighed against obtaining the same information by collection of alternative matrices, such as urine, blood or hair. After a brief discussion of the collection of each matrix and the interpretation of results, this review summarizes the analytical results for each drug and drug class in tables. Critical comments are appended in each summary table rather than included in the body of the text. These comments highlight the results given in each paper as well as providing a brief discussion of the results. For alcohol, nicotine and barbiturates, only selected papers are included in the tables.

1.1. Mechanism of drug transport into saliva and sweat

A thin layer of epithelial cells separates the saliva ducts from the systemic circulation. The lipid membrane of these cells determines which molecules may be transferred from the plasma into the saliva [25]. Substances can be transported across biological membranes either by active transport (secretion), diffusion through pores in the membrane, or passive diffusion through the membrane across a concentration gradient. Some low-molecular-mass substances, such as lithium, are thought to be actively excreted into saliva. For these materials, the saliva concentration may be much higher than the plasma concentration. Molecules with molecular masses of less than 100 (i.e. ethanol) may diffuse through the water-filled pores in the membrane. However, for the majority of substances with molecular masses greater than 100 Da, passive diffusion across a concentration gradient is thought to be the major factor in transport. For passive diffusion through lipid membranes, the molecule must be in a lipid-soluble form [15]. For example, codeine-6-glucuronide is found in higher concentrations in plasma than is codeine. The glucuronide is too hydrophilic to transverse the membranes separating the saliva ducts from the blood capillaries. Thus, for these two similar compounds, codeine predominates in saliva because of its lipophilicity [26]. Likewise, cocaine predominates over benzoylecgonine in saliva and sweat because cocaine is more lipophilic and, thus, can be transported more easily [27]. The higher concentration of cocaine in saliva and sweat compared to benzoylecgonine is in contrast to blood or urine where benzoylecgonine is the predominant compound [28].

Saliva has little protein binding capacity compared to blood plasma. Once transported across the lipid membrane from the blood, the drug must have some water solubility to be retained in the saliva. For most compounds, ionization provides water solubility and, thus, prevents back diffusion from the saliva into the plasma. A schematic representation of this process is shown in Fig. 1.

When equilibrium is reached (for substances that can be transported across membranes), the saliva/plasma concentrations of drugs would only depend upon the pH of the saliva compared to plasma. The equations for calculation of saliva–plasma ratios may be derived from the Henderson–Hasselbalch [29,30] equation (Eq. (1)) and the equation for mass balance (Eq. (2)).

$$\mathrm{pH} = \mathrm{p}K_a + \log\frac{[A^-]}{[HA]} \quad (1)$$

$$[A] = [A^-] + [HA] \quad (2)$$

where [HA] is the concentration of the non-ionized form of the acidic drug,$[A^-]$ is the concentration of the anionic form, and[A] is the total concentration of drug in both forms.

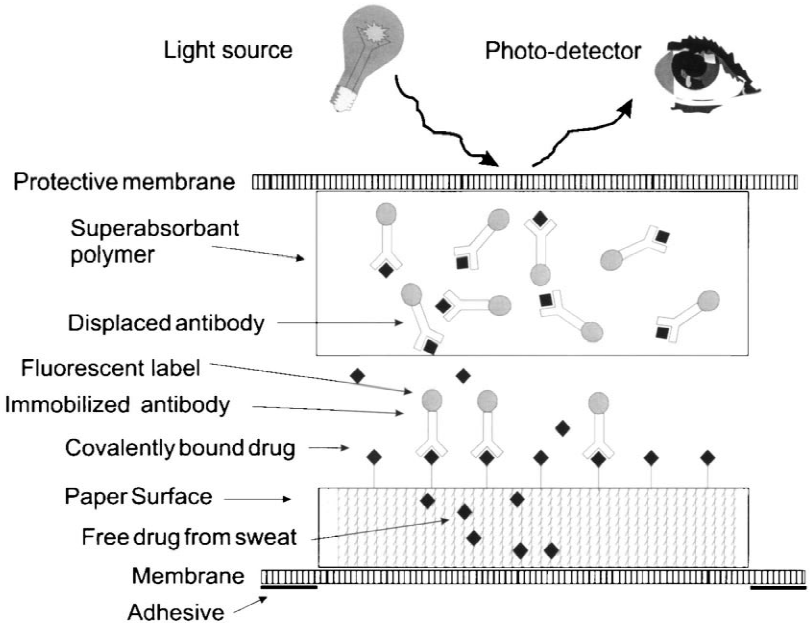

Fig. 1. Schematic diagram for transport of drugs into saliva or sweat.

Solving both equations for the total amount of drug in either form gives:

$$\frac{[A]}{[HA]} = 1 + 10^{(pH - pK_a)} \quad (3)$$

Because Eq. (3) applies to both saliva and plasma, the saliva/plasma ratio may be calculated by:

$$\frac{saliva}{plasma} = \frac{[A_{saliva}][HA_{plasma}]}{[A_{plasma}][HA_{saliva}]} = \frac{1 + 10^{(pH_{saliva} - pK_a)}}{1 + 10^{(pH_{plasma} - pK_a)}} \quad (4)$$

A modification must be made to Eq. (4) to take into account the binding of drugs to plasma and saliva proteins because only the free drug can cross the cellular membranes. Because of protein binding, the concentration of drugs in plasma (which drives the diffusion process) is reduced. Assuming that the [HA] must be the same in both saliva and plasma, because of equilibrium (HA is the species thought to be responsible for transport across the cellular membranes), Eq. (4) may be reduced to the standard equation, Eq. (5). A similar equation (Eq. (6)) can be derived for basic drugs if it is remembered that the un-ionized form of the drug is responsible for the transport across the saliva–plasma membrane:

$$\frac{saliva_{acidic\ drug}}{plasma_{acidic\ drug}} = \frac{1 + 10^{(pH_{saliva} - pK_a)}}{1 + 10^{(pH_{plasma} - pK_a)}} \times \frac{free_{plasma}}{free_{saliva}} \quad (5)$$

$$\frac{saliva_{basic\ drug}}{plasma_{basic\ drug}} = \frac{1 + 10^{(pH_a - pK_{saliva})}}{1 + 10^{(pK_a - pH_{plasma})}} \times \frac{free_{plasma}}{free_{saliva}} \quad (6)$$

The fraction of free drug (not bound to proteins) in saliva is assumed to be one, because of the much lower concentrations of protein in saliva compared to plasma. The plasma binding of drugs is usually measured by equilibrium dialysis, although proper care in the selection of buffers and protection from atmospheric carbon dioxide is not always taken [31]. Eqs. (5) and (6) predict that the concentrations of drugs in saliva will vary with the free fraction of drug in plasma rather than with the total level of drug. Since it is only the free form of the drug in plasma that is available to produce a pharmaco-

logical effect, saliva concentrations may be of greater therapeutic value than plasma levels. Because saliva is derived continuously from plasma, its pH is difficult to externally modify and, thereby, alter drug concentrations [32]. In contrast, urine pH may be influenced by ingestion of acids or bases, which may greatly change the rates of drug excretion [33].

Nearly identical considerations are thought to apply to the excretion of drugs in sweat as apply to excretion of drugs in saliva [34]. However, sweat has a lower average pH (pH ca. 5.8) [35] than does saliva (pH ca. 6.5) [36], which would affect the transport and retention of drugs in sweat.

1.2. Physiology of saliva secretion

Saliva is a colorless fluid excreted into the oral cavity from three principle glands: (1) the parotid gland, exiting at the top of the mouth, secretes saliva derived mainly from blood plasma (serous fluid). (2) the sublingual glands, exiting at the sides of the mouth, excrete both serous fluid and mucin and (3) the submandibular glands, exiting at the base of the tongue, also excrete both serous fluid and mucin. Several other minor glands are present. Saliva is approximately 99% water, 0.3% protein (mostly enzymes) and 0.3% mucin with the balance salts [36]. The mucin gives saliva its sticky character. The low protein concentration in saliva makes drug binding minimal compared to that observed in plasma. Between 500–1500 ml/day of saliva are produced [36]. Mixed saliva consists of submandibular excretions (71%), parotid secretions (25%), sublingual and other glands (4%) as well as epithelial cells, food debris and oral microorganisms [5]. Unstimulated saliva pH is in the range of 5.6–7 and increases with stimulation (to more approximate the pH of blood, i.e. 7.4) to a maximum of 8.0 [36]. Therefore, as discussed above, drug concentrations in saliva partially depend on the pH of the saliva and the degree of stimulation.

1.3. Collection of saliva

Limited amounts of mixed saliva may be collected by spitting. Larger amounts of saliva may be collected by stimulating saliva flow by chewing rubber bands, wax, Teflon tape or gum; sucking on pebbles, marbles or candy; by placing citric acid on the tongue; adsorption on cotton rolls or administration of pilocarpine. Selection of material for saliva simulation must be carefully chosen because lipophilic drugs may be adsorbed into the material. For identification purposes, adsorption (similar to solid-phase adsorption or solid-phase microextraction) could be employed to directly extract the drug from the saliva while inside the mouth [37,38]. Little research has been done in this area, as the sample size would be limited and the adsorption process variable (depending on the cooperation of the individual, i.e. the more sucking/chewing, the greater the adsorption). Some devices (OraSure) both stimulate saliva flow and collect the saliva on an absorbent pad [39–42]. Other devices have been developed to acquire saliva from selected glands [43]. In general, these devices acquire saliva by placing the end of the device over the gland and applying suction [44,45]. Although selected gland secretions have an advantage in reducing saliva/plasma ratios and minimizing oral contamination, most studies collect mixed saliva specimens because it is less invasive.

An ultrafiltration device (SalivaSac) has been developed to reduce the viscosity of saliva for easier analysis, and is similar to that collected by suction from the parotidal gland. It consists of a dialysis membrane enclosing sucrose crystals and is approximately 3.5 cm in diameter and a few millimeters thick [46–48]. The device is placed in the mouth and massaged with the tongue for a few minutes until all of the crystals are dissolved, collecting 1–2 ml of saliva ultrafiltrate. Both the sucking on the device and the sweet taste stimulate saliva production. The SalivaSac may also be externally coated with citric acid to stimulate saliva production. The dialysis membrane was chosen to exclude most higher-molecular-mass substances and, therefore, the mucopolysaccharides, food particles and bacteria are not collected. The SalivaSac may also have a handle for easier insertion and removal. In field studies, it has been our experience that some users do not leave the device in their mouth for long enough periods of time, such that all of the sucrose has not been dissolved and less saliva is collected. Also, the device leaves a moderately unpleasant sweet taste (without flavoring) after removal, which can be reduced by drinking fluids.

Two problems concerning the correlation of drug levels of the ultrafiltrate with saliva levels are apparent when quantitative information is needed. The sucrose in the SalivaSac takes up an appreciable amount of the molar volume of water inside the device. Therefore, measurement of the density of the fluid is necessary by careful weighing and a correction factor must be calculated [49]. Furthermore, diffusion through the dialysis membrane is related to molecular mass and, therefore, water is preferentially collected relative to drugs [49]. Thus, the concentration of drugs in the SalivaSac is lower than in the external saliva and this ratio may vary depending on how the user moves the device during the saliva collection. If one only wishes to have qualitative information on drug use, then these concerns are not applicable.

1.4. Interpretation of drug concentrations in saliva

If the pK_a of the drug is greater than 8.5 for basic drugs, less than 5.5 for acidic drugs, or if the drug is non-ionic, the pH of the saliva will have little effect on the concentration. Unfortunately, many drugs of abuse have pK_a values close to 8.5 and, therefore, their concentrations in saliva are influenced to some extent by the pH of the saliva. Therefore, the saliva must be collected under controlled conditions to allow estimation of blood levels of drugs from the saliva levels. However, for many forensic applications, the mere presence of drug has meaning. Impairment is difficult to establish even when the blood level of drug is known. For example, marijuana has been shown to only minimally affect driving ability, especially if compared to low levels of alcohol [50]. Therefore, pragmatically, many states (in the USA) have laws dictating a zero tolerance for drug levels in drivers. The presence of tetrahydrocannabinol (THC, the active substance in marijuana) in blood or metabolites in urine coupled with subjective measurements of impairment made in the field is often sufficient evidence to convict someone of driving under the influence of drugs. In such cases, the presence of drugs in saliva likewise would show recent ingestion of drugs and thus provide the same information as urine or blood (ingestion rather than impairment). However, saliva has the advantage of being easier to collect in the field than either blood or urine. The problem of relating impairment to blood levels also occurs with alcohol. In the case of alcohol, impairment of an individual is affected by experience with alcohol as well as the alcohol blood level. Alcohol is normally the major drug found in impaired drivers. Generally, if a drug of abuse is found, it is in conjunction with alcohol [51]. However, for truck drivers, marijuana and stimulants are more prevalent than alcohol [52].

If plasma levels of drugs are to be estimated so that impairment is inferred, careful attention to collection and pH must be made. Similarly, for therapeutic drugs where plasma levels must be carefully controlled, saliva should be taken under controlled conditions [53]. A major problem with correlation of drug levels with plasma levels is contamination of the saliva from the remains of orally ingested, smoked or internasally administered drugs. For alcohol, up to 30 min must have elapsed for the saliva levels to reflect the plasma levels. Likewise, for smoked or internasally administered cocaine, 4–8 h must pass before the contamination is removed.

The problem with oral contamination is illustrated in Fig. 2, which depicts the ethanol [54] and cocaine [55] concentrations in saliva and plasma. Ethanol, being a small neutral molecule, is absorbed and equilibrates with the blood plasma fairly rapidly, i.e. within 30 min. The saliva concentrations therefore parallel those in blood fairly closely (note the constant saliva/plasma ratio after 30 min). In contrast, cocaine readily contaminates the oral cavity so that the concentration in saliva, where cocaine is administered internasally or via smoking, does not reflect the plasma levels. Shown for comparison is the saliva/plasma ratio of cocaine where the cocaine was administered intravenously and no oral contamination could occur. The saliva/plasma ratios of the smoked cocaine and intravenously administered cocaine become similar only after 4 h and, at this time, the levels are low. If environmental contamination can be eliminated (for example, the subject did not recently bite his nails or place objects in his mouth), then the presence of drugs in saliva is a good indication that drugs are also present in plasma. Such information may have value for further forensic investigation.

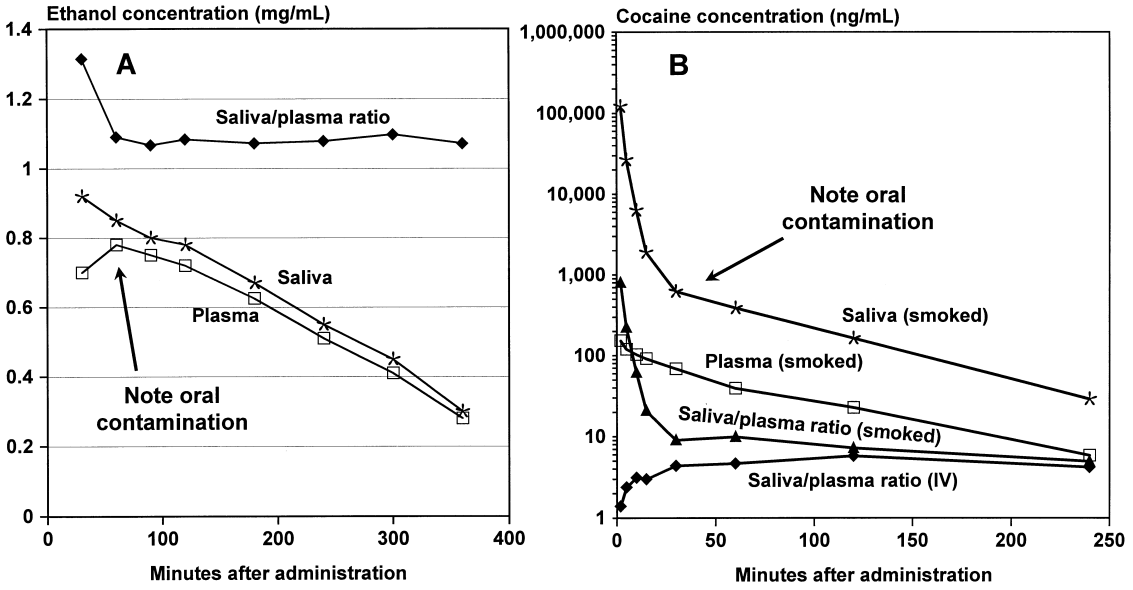

Fig. 2. (A) Concentrations of ethanol in saliva and plasma. From Jones [54]. (B) Concentrations of cocaine in saliva and plasma after smoking of 43 mg and ratio of plasma–saliva after intravenous administration of 40 mg of cocaine. Average of seven individuals. From Jenkins et al. [55].

1.5. Analysis of drugs in saliva

Tables 2–9 list the majority of the papers that analyze drugs of abuse in saliva. To reduce the length of the tables, most therapeutic drugs are excluded. Alcohol is listed because it is a major cause of traffic accidents and saliva alcohol levels are often used to establish blood alcohol levels. Nicotine is also listed because surveys for exposure to passive smoke and the linkage to disease are becoming increasingly common. Also, saliva is often used by the life insurance industry to verify the smoking status of an individual and, thereby, determine the insurance premiums to be collected.

1.6. Physiology of sweat

Moisture may be lost from the skin by either insensible sweat (sweat not visible), likely caused by diffusion through the skin, and sensible sweat, which is actively excreted during stress and exercise. Between 300–700 ml/day of insensible sweat is produced over the whole body, whereas 2–4 l/h of sensible sweat may be produced by extensive exercise [36].

Sweat glands are classified as being of two types: eccrine and apocrine. The apocrine glands are larger than the eccrine glands and secrete a more viscous substance. The apocrine glands are primarily located in the axillae, pubic and mammary areas. Besides opening directly onto the skin, sweat glands also develop in close association with hair and sometimes open inside hair follicles. In fact, sweat is thought to be a major contributor to drugs appearing in hair [56,57]. Besides aqueous secretion, the skin is also bathed with sebaceous secretions, especially on the face and scalp. The sebaceous secretions are primarily lipids that may transport and absorb many drugs. This method of transporting drugs to the skin surface has not been thoroughly examined. Sebum is excreted more on the scalp and forehead than on other areas of the body [58]. Therefore, different concentrations may be expected, depending upon the area of the body in which the sample is taken, because fat-soluble drugs may be sequestered or secreted in sebum. Almost all studies obtain mixed secretions of sweat and sebum, which is incorrectly

Table 2
Cannabinoids in saliva

Drug	Method of collection	Method of anslysls	LOD	Reference	Comment
THC	Not specified, expectoration likely	TLC, GC–MS of TLC extract	Not specified, poor	Just et al., 1974 [106]	THC likely due to sequestering of smoke. THC measurable 1–2 h after one low-dose marijuana cigarette
THC, 11-nor-Δ^9-THC-COOH	Not specified	Custom RIAs	Not specified	Gross and Soares 1978 [107]	THC possibly due to sequestering of smoke [108]. Washing of mouth did not eliminate drug. THC measurable for 5.5 h after three cannabis cigarettes. Both THC and metabolite claim to be detected. THC-COOH ca. 75% of THC. Confirmation not performed and presence of THC-COOH doubtful
CBN	Not specified	Fluorometric assay	1 ng/ml	Valentine and Psaltis 1979 [109]	CBN converted photolytically to a highly fluorescent compound and detectable in the saliva of a marijuana user
Delta-9-THC	Q-Tip or expectoration	Custom RIA	16 ng/ml	Gross et al. 1985 [110]	THC likely due to sequestering of smoke rather than measuring blood levels. THC measurable for 5 h after one–two cannabis cigarettes
Delta 9-THC	Not specified, expectoration likely	GC–ECD PFPA derivatization	ca. 0.5 ng/ml	Maseda et al. 1986 [111]	THC measurable for at least 4 h. One cigarettes with 10 mg of THC. Drinking decreased concentrations. Oral contamination likely
Deuterated CBD	Rinsing mouth with 10% ethanol	GC–MS	0.05 ng/ml	Ohlsson et al. 1986 [112]	Administered CBD both IV and smoking. Rinsed mouth to remove oral contamination. Very low CBD levels in saliva that do not reflect plasma levels
Delta 9-THC	Sour candy	HPLC, electrochemical detection	1 ng/ml	Thompson and Cone, 1987 [113]	Mostly methods paper. Smoking marijuana showed substantial oral contamination. THC detectable for up to 425 min
Delta 9-THC	Chewing gum stimulation; expectoration	GC–MS	ca. 1 ng/ml	Menkes et al., 1991 [114]	THC likely due to sequestering of smoke rather than measuring blood levels. THC measurable for 4 h after one cannabis cigarette
THC 11-nor-Δ^9-THC-COOH	Osmotic device, SalivaSac	LC–MS	ca. 1 ng/ml	Kidwell, 1990 [115] Kidwell, 1992 [116]	Direct injection of saliva from drug users. Presence of THC-COOH only preliminary and not confirmed with deuterated standards. Oral contamination not ruled out

For abbreviations, see Ref. [105].

referred to as sweat. In Tables 11–15, the mixed secretions are the matrix examined.

1.7. Collection of sweat

Sweating may be induced by exercise and several milliliters of sweat may be collected in conjunction with an occlusive wrapping or gloves [59,60]. Small amounts of sweat may be produced by electrical diffusion of pilocarpine into the skin [61,62] or by warming the area [63–65]. Devices have been developed using pilocarpine stimulation to take samples as a test for cystic fibrosis via chloride determination. Drugs may also be caused to diffuse into the skin under an electrical force [66,67], but this procedure has not been employed as a sampling technique for diffusion of drugs out of the skin.

Patches, similar to bandages, have been developed to wear for extended periods of time. Early patches were made of absorbent cotton pads sandwiched between a waterproof, polyurethane, outer layer and a porous inner layer that is placed against the skin [68–73]. To increase sweat production and uptake, the cotton pads were often saturated with sodium chloride solution. These patches had been successfully applied to the detection of ethanol in sweat [74,75]. Field testing of these patches showed variability in alcohol diffusion into the patch, possibly

Table 3
Cocaine in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Cocaine	Spitting	TLC, radiochemical detection	Not specified	Inaba et al., 1978 [117]	Radiolabeled cocaine given orally. Radioactivity detectable for at least 5 h in saliva.
Cocaine	Sour candy stimulation, spitting	CI-GC–MS	5 ng/ml	Thompson et al., 1987 [118]	Intravenous doses. Plasma lower than saliva. Detection up to 6 h
Cocaine	Mixed saliva, not specified	GC–NPD	5 ng/ml	Cone et al., 1988 [119]	Intravenous cocaine administration. Saliva levels paralleled blood levels. Physiological effects lasted for 60 min. Cocaine detectable for up to 6 h
Cocaine	Sour candy stimulation, spitting	RIA immunoassay; EI-GC–MS	0.5 ng/ml immunoassay; 5 ng/ml GC–MS	Cone and Weddington, 1989 [120]	Claims five–ten day detection after abstinence in heavy cocaine addicts. GC–MS confirmation only to one–two days. Urine levels>saliva levels
Cocaine, BE, EME, ecgonine	osmotic device, SalivaSac	LC–MS	ca. 1 ng/ml	Kidwell, 1990 [115]; Kidwell, 1992 [116]	Direct injection of saliva from drug users. All metabolites found. Cocaine in highest concentration. Concentrations generally much lower than in urine
Cocaine, BE, EME	Sour candy or non-stimulated	EI-GC–MS	Not specified	Kato et al., 1993 [27]	IV cocaine in five subjects. Stimulated and non-stimulated saliva. Unstimulated much higher concentrations. Cocaine, BE and EME found. Cocaine>BE±EME
Cocaine, BE	Osmotic device, SalivaSac	RIA, EI-GC–MS	0.3 ng/ml immunoassay; 10 ng/ml GC–MS	Schramm et al., 1993 [121]	Addicts in treatment with self-reported use. Cocaine approximates BE concentrations
Cocaine and metabolites	Sour candy	EI-GC–MS	1.6–3.1 ng/ml	Cone et al., 1994 [122]	Several metabolites and pyrolysis products of crack smoke examined. Only cocaine, BE and EME found. Observable for up to 6 h
Cocaine, BE, EME	Sour candy, spitting	BSTFA derivatization EI-GC–MS	1 ng/ml	Jenkins et al., 1995 [55]	Both IV and smoked cocaine administered. Comparison of two routes of administration show that smoked cocaine greatly contaminates saliva for up to 6 h

For abbreviations, see Ref. [105].

due to the subjects' behavior, temperature, or back-diffusion of the alcohol into the skin [76]. A patch was later developed that included a chemical binding layer in the absorbent pad to prevent back-diffusion of the drug through the skin [77,78]. This later design has been used to monitor theophylline in monkeys [79] and caffeine in infants [80].

Both of these early patches used aqueous media and an occlusive covering to stimulate sweat and prevent evaporation of the drug. A later device was developed that had a covering that allowed the passage of sweat from the skin through the device and prevented external water and other molecules from back-diffusing into the absorptive pad [81–83]. This device is being marketed as the PharmChek sweat patch [21]. A potential problem with the PharmChek patch is the absence of a layer between the skin and the absorptive pad, to prevent bacterial transfer into the pad and, therefore, the possibility of bacterial growth and drug degradation. Careful preparation of the skin prior to application of the patch should kill or remove bacteria and prevent these problems, although the absence of substantial moisture in the pad decreases the possibility of bacterial growth [63].

Even with these many devices, sweat is more

Table 4
Amphetamines in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Amphetamine	Chewing Teflon	*N*-Pentafluorobenzoyl *S*(−)-prolyl derivative CI, GC–MS	Not specified	Matin et al., 1977 [123] Wan et al., 1978 [124]	Saliva level closely follows plasma levels. Saliva ca. 2× plasma levels. D-Amphetamine excreted faster than L-amphetamine. Both detectable to 50 h
Amphetamine	Saliva stains	RIA	780 pg	Smith, 1981 [125]	Amphetamine detectable from saliva on cigarettes
Amphetamine, ephedrine, ampheprамone, prolintane	Non-stimulated spitting	TLC	Not specified	Vapaatalo et al., 1984 [126]	Five subjects. Oral administration. Amphetamine detectable for up to 12 h and urine to 24 h
Methamphetamine	Salivary glands in mouse	Immunohistochemical technique	Not specified	Kajitani et al., 1989 [127]	Immunohistological staining of sections of mouse saliva glands
Methamphetamine	Filter paper or gauze	TFAA, EI-GC–MS	20 pg of MA 100 pg of hydroxy-MA	Suzuki et al., 1989 [128]	Drug users studied. Only 3/25 low-level saliva samples were positive
Phentermine, phenylpropanolamine, ephedrine	Not specified	FPIA for amphetamines	Not specified <500 ng/ml	Turner et al., 1991 [129]	Mostly described assay. Limited data for saliva. Phentermine detectable for up to 72 h. Phenylpropanolamine was detectable to only 2 h

For abbreviations, see Ref. [105].

difficult to collect non-invasively than is saliva, due to the lower amounts/unit area secreted in a given time. In conjunction with the Jet Propulsion Laboratory, we have developed a system for the monitoring of parolees, probationers or pretrial individuals. This system both collects sweat and tests it remotely (Fig. 3) [84]. Such monitoring may be more invasive than that used in the general population because the individuals are under a court order to abstain from drug use. In one embodiment of this device, labeled antibodies are bound to an immobilized drug layer. Drugs in sweat displace a small amount of these antibodies that then are trapped in a superabsorbent polymer layer. An optical system then detects the presence of the label and the readout may be transferred to a remote location using cellular phone technology. The superabsorbent polymer layer allows absorption of substantial amounts of sweat before it becomes saturated, which improves the sensitivity of the device. Two polycarbonate membranes control fluid flow into and out of the sweat badge and improve user comfort. Like the polyurethane covering in the PharmChek system, the outer polycarbonate membrane prevents back-diffusion of liquid from the external environment, yet allows evaporation of moisture.

We have also investigated an alternative collection of 'sweat' by wiping the skin with a cotton pad moistened with alcohol [85,86]. This procedure allows rapid collection of drugs that may arise both from sweat evaporating on the surface of the skin and from external contamination. The exact fluid analyzed is not known because both the aqueous secretions (true sweat) as well as sebum are collected. Whether or not the presence of drugs on skin wipes indicates use only or use and exposure is unknown. Certainly, use of drugs implies exposure, but exposure does not imply use. In a survey of a university population, skin wipes detected more cocaine use/exposure than did hair analysis [87]. By selection of appropriate cut-off levels, both matrices agreed. Similarly, in a study of drugs users in rehabilitation, wipes detected about twice the number of individuals using/exposed to cocaine than did hair analysis [88]. Again, with the appropriate selection of cut-off levels, the matrices had a very high correlation [89].

1.8. Interpretation of drug concentrations in sweat

Quantitation of drugs in sweat is difficult because the amount of sweat collected is unknown. Early

Table 5
Opiates in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Methadone, morphine	Not specified	Spin immunoassay TLC	Not specified	Leute et al., 1972 [130]	Saliva not well correlated to urine. Urine detectable as easily as saliva
Heroin, dextromethorphen, morphine	Absorption on discs	RIA, FRAT, EMIT	22 ng/ml	Gorodetzky and Kullberg, 1974 [131]	Five subjects, single oral dose study. Drugs detectable for up to 12 h
Methadone	Unstimulated spitting	GC–FID	Not specified ca. 1 ng/ml	Lynn et al., 1975 [132]	Saliva levels cross over blood levels at about 2.5 h. Detection for up to 8 h. Administration by intramuscular injection of methadone
Methadone in rats	Infusion of pilocarpine	RIA	Not specified	DiGregorio et al., 1977 [133]	Acute and chronic doses studied. Excretion in chronic doses relatively constant for five weeks
Meperidine	Waxed films	GC	Not specified	Mucklow et al., 1978 [134]	Saliva–plasma ratios vary
Methadone	Spitting after mouth rinse	EI-GC–MS	20 ng/ml	Kang and Abbott, 1982 [135]	Oral methadone given to two patients and time-course of elimination measured for up to 24 h. Saliva–plasma ratio 0.51
Codeine	Parafilm stimulation, spitting	GC–NPD	<20 ng/ml	Sharp et al., 1983 [23]	Fourteen individuals, single oral dose of various drugs. Saliva–plasma ratio=3.3 (variable)
Hydromorphone	Parafilm stimulation, spitting	RIA	Not specified, <0.25 ng/ml	Ritschel et al., 1987 [136]	Eight subjects. Detectable for up to 10 h with 2–5 mg administered
Pholcodine	Parafilm stimulation, spitting	HPLC–fluorescent detection	1.5 ng/ml	Chen et al., 1988 [137]	20–60 mg pholcodine orally to six subjects. Saliva paralleled plasma. Detectable for up to 96 h (20 mg) and 168 h (60 mg)
Morphine, codeine	Sour candy stimulation, spitting	EI-GC–MS	0.6 ng/ml	Cone, 1990 [138]	Either morphine (10/20 mg) or codeine (60/120 mg) administered via intramuscular injection to two subjects. 36 h detection window
Codeine, morphine	Parafilm	HPLC	ca. 10 ng/ml	Chen et al., 1991 [26]	Saliva paralleled plasma. Glucuronides not observed in saliva, predominate in plasma
Heroin, MAM, morphine	Osmotic device, SalivaSac	LC–MS	ca. 1 ng/ml	Kidwell, 1990 [115] Kidwell, 1992 [116]	Direct injection of saliva from drug users. All metabolites found. MAM in highest concentration. Concentrations generally much lower than in urine
Heroin, MAM, morphine	Not specified	EI-GC–MS	1 ng/ml	Goldberger et al., 1993 [139]	Intranasal and intramuscular administration of heroin. Little saliva data given
Heroin and metabolites	Not specified	EI-GC–MS	5 ng/ml	Wang et al., 1994 [140]	12 mg heroin administered intravenously. Detectable for up to 6 h. Heroin, MAM and morphine detectable, ratios not constant
Heroin and metabolites	Sour candy, citric acid	EI-GC–MS	1 ng/ml	Jenkins et al., 1995 [122]	Both intravenous and smoked heroin administered. Comparison of two routes of administration show that smoked heroin greatly contaminates saliva. Heroin detectable for only 1 h

For abbreviations, see Ref. [105].

Table 6
Barbiturates/PCP in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Amobarbital	Glass marble stimulation, spitting	GC–FID	Not specified <200 ng/ml	Inaba and Kalow, 1975 [141]	pH of saliva measured. Linear correlation (0.993) between saliva and plasma. Serum levels were 3× saliva levels
Phenobarbital	Spitting and capillary	RIA	Not specified pg levels	Cook et al., 1975 [142]	Good correlation (0.98) between saliva and plasma levels, but not linear. Plasma levels ca. 4× saliva levels
Phenobarbital	Parafilm stimulation, spitting	EMIT and GC	Not specified, <100 ng/ml	McAuliffe et al., 1977 [143]	Good correlation (0.99) between predicted saliva and plasma levels. pH of saliva measured
Hexobarbital	Not specified	HPLC–UV	3 ng/ml	Tjaden et al., 1977 [144]	Mostly a methods paper with little clinical data
Phenobarbital	Parafilm stimulation, spitting	GC	Not specified	Mucklow et al., 1978 [134]	Good correlation (0.96) between saliva and plasma levels. Saliva–plasma ratio was 0.41
Phenobarbital	Unstimulated, spitting	UV	Not specified, ca. 500 ng/ml	Nishihara et al., 1979 [145]	Twenty-nine epileptic patients. Good correlation ($r=0.94$) between saliva and plasma levels. Saliva–plasma ratio = 0.63
Amobarbital, pentobarbital, phenobarbital	Not specified	2-Chloroethyl derivative GC–ECD	Not specified	Dilli and Pillai, 1980 [146]	Analysis method not optimal. Half-life measured. For pentobarbital, 17–19 h; amobarbital, 22–26 h
Phenobarbital	Unstimulated, spitting	RIA	1.2 ng/ml	Smith and Pomposini, 1981 [147]	Barbiturates detected in both free saliva and dried perspiration. Levels in perspiration very high
Phenobarbital	Unstimulated, spitting	EIA	Not specified	Friedman et al., 1981 [148]	Twenty saliva–serum pairs. Good correlation (0.97) between saliva and serum concentrations
Phenobarbital	Citric acid stimulation, spitting	GC–FID	Not specified	Mucklow et al. 1981 [149]	Small children studied. Saliva samples correlate well with plasma levels. Saliva used to adjust drug dosage
Phenobarbital	Mucous test tube, suction	GC–FID, EMIT	Not specified	Goldsmith and Ouvrier, 1981 [150]	Small children studied. Saliva levels correlate well with plasma levels ($r=0.94$)
Phenobarbital	Citric acid stimulation, spitting	GC–FID, EMIT	Not specified	Knott and Reynolds, 1984 [151]	Saliva pH measured. Saliva levels correlate well with plasma levels ($r=0.92$)
Phenobarbital	Not specified	EMIT	Not specified	Tokugawa et al., 1986 [152]	Saliva and serum levels measured in twenty children. Total serum levels were 2× saliva levels. Good correlations ($r=0.99$).
Hexobarbital	Parafilm stimulation, spitting	GC–NPD	Not specified	Van Der Graaff et al., 1986 [153]	Good correlation (0.92) between saliva and plasma concentrations. pH of saliva measured. Detectable for up to 12 h. Unacceptable variation among individuals in % plasma binding
Amobarbital	Not specified	HPLC–UV postcolumn derivatization	0.5–2.5 ng	Haginaka and Wakai, 1987 [154]	Mostly a methods paper. Only spiked samples analyzed
Methyl phenobarbital, phenobarbital	Non-stimulated, spitting	HPLC	Not specified	Herkes and Eadie, 1989 [155]; Herkes et al., 1989 [156]; Herkes and Eadie, 1990 [157]	Seizure frequency correlated with saliva levels. Poor correlation observed
PCP	Non-stimulated, spitting	HPLC with radiolabel detection	Not specified <0.1 ng/ml	Cook et al., 1982 [158]	Radiolabeled PCP given IV. Parent PCP found in saliva
PCP	Cotton swabs, then 70% ethanol	RIA	5 ng/ml	McCarron et al., 1984 [159]	100 emergency room patients. Correlation of saliva and serum concentrations moderate ($r=0.58$).

For abbreviations, see Ref. [105].

Table 7
Benzodiazepines in saliva

Drug	Method of collection	Method of analysis	LOD	Author	Comments
Diazepam	Chewing Teflon tape, spitting	GC	Not specified	Giles et al., 1977 [160]	Detectable for 24 h. Saliva–plasma ratio significantly time-dependent. Both diazepam and *N*-desmethyldiazapam detectable
Diazepam	Free-flowing saliva	RIA, GC–ECD	ca. 0.3 ng/ml	Dixon and Crews, 1978 [161]	Saliva paralleled blood after 2 h. Detectable to 24 h
Diazepam	Chewing Parafilm, spitting	GC–ECD	Not specified	DiGregorio et al., 1978 [162]	Nine subjects followed for 8 h after 10 mg oral dose. Mixed saliva and parotid saliva examined with similar results. Mixed saliva slightly lower concentrations
Diazepam, nitrazepam, oxazepam, chlorodiazepoxide	not specified	radioreceptor assay, and GC–ECD	0.14 ng/ml	Rosenblatt et al., 1979 [163]	Compared GC–NPD with a radioreceptor assay for eight samples from patients. Good correlations. No information on doses
Nitrazepam	Chewing Parafilm, spitting	GC–ECD	0.1 ng/ml	Kangas et al., 1979 [164]	Detectable to 70 h. Saliva–plasma ratio varies during elimination but about 1:10. Substantial oral contamination before 3 h
Chlorodiazepoxide	not specified mixed saliva	RIA	0.05 ng/ml	Lucek and Dixon, 1980 [165]	Three subjects studied. IV doses detectable for up to 30 h. Saliva half-lives of 12–20 h
Diazepam and *N*-desmethyldiazepam	chewing rubber band, spitting	GC–ECD	0.25 ng/ml	Hallstrom et al., 1980 [166]	Saliva levels detectable for up to 48 h from a single dose. Much drug bound to plasma. Saliva levels of diazepam 1.6% and of nordiazepam 2.6% of total plasma
Diazepam and metabolites	Not specified	HPLC–UV	0.2 ng/ml	Tjaden et al., 1980 [167]	Diazepam and metabolites detected. Varying ratios to parent compound
Diazepam and *N*-desmethyldiazepam	chewing Teflon, spitting	GC–ECD	0.2 ng/ml	de Gier et al., 1980 [168]	Single oral dose (10 mg). Saliva and plasma levels parallel well. Detectable to 9 h. Desmethyldiazepam metabolite appears slowly
Nitrazepam	Chewing Teflon, spitting	GC–ECD and GC–NPD	Not specified	t'Hart et al., 1987 [31]; t'Hart et al., 1988 [100]	Poor plasma–serum correlation. Many factors to consider in determining plasma binding discussed. Stability discussed
Desmethyldiazepam	Chewing Teflon, spitting	GC–ECD	<5 ng/ml	Giles et al., 1980 [169]	Levels of diazepam and *N*-desmethyldiazapam not well correlated to dose of diazepam. Only saliva measured

For abbreviations, see Ref. [105].

devices were occlusive so that the amount of sweat collected could be determined by the increase in weight of the device [69]. Most current devices are non-inclusive, to allow increased comfort to the wearer. Because they allow evaporation of the sweat, the amount of sweat collected is unknown. However, it could be estimated by ratioing the drug concentrations to either sodium or lactate concentration, both substances excreted relatively constantly in sweat. For the use of sodium, most extraction procedures would need to be modified because they employ buffers containing sodium.

The finding in skin wipes of unique metabolites of drugs that are not present in the environment would indicate use rather than exposure. The presence of cocaethylene or ecgonine methyl ester is thought to indicate the use of cocaine rather than exposure to it [90]. We have analyzed over 500 skin wipes for cocaine and its metabolites and mostly find cocaethylene and methylecgonine only when the cocaine levels are very high (Table 10). Based on the amount of cocaine present, it is very likely that these individuals are very heavy users of cocaine. Therefore, these minor amounts of unique metabolites may

Table 8
Alcohol in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Alcohol	Stimulated parotid saliva only, suction cup	GC–FID	Not specified	DiGregorio et al., 1978 [44]	Measured blood plasma levels. Excellent correlation with saliva levels. Oral contamination not observed
Alcohol	Unstimulated, spitting	Alcohol dehydrogenase detection	Not specified	Jones, 1979 [54,170]	Saliva and blood levels follow quite closely after 60 min
Alcohol	Parotid saliva via suction cup; citric acid stimulation	GC–FID	Not specified	McColl et al., 1979 [171]	Oral contamination present when time <20 min. Washing mouth did not remove oral contamination
Alcohol	Not specified	Dipstick	ca. 2 mg/dl	Tu et al., 1985 [172]	Described preparation of an alcohol dipstick. Compared urine, serum and saliva matrices
Alcohol	Dental cotton roll w/wo stimulation by citric acid	Enzymatic	Not specified	Haeckel and Bucklitsh, 1987 [173]	Ethanol concentration parallels the blood level in capillary blood closer than venous blood. Differences were slight for up to 6 h
Alcohol	Dipstick under the tongue	Alcoscreen saliva and dipstick	0.02 g/dl	Schwartz et al., 1989 [174]	Visual reading-only semi-quantitative. Compared saliva using dipstick to instrumental values for blood. Good correlations when alcohol >0.1 g/dl
Alcohol	Dipstick under the tongue	Alcoscan test strip instrumental reading	Not specified	Penttilla et al., 1990 [175]	Compared urine, saliva, blood and vitreous humor of 112 subjects
Alcohol	Not specified	Colorimetric dipstick	Not specified <4.3 mmol/l	Rodenberg et al., 1990 [176]	Patients in an emergency room. 12/67 (18%) false negative and 2/67 (1%) false positive results
Alcohol	Vacuum container	GC–FID, 2-butanol internal standard	Not specified	Kiesow et al., 1993 [177]	Blood and saliva levels compared. Correlation 0.97

For abbreviations, see Ref. [105].

require very sensitive techniques for detecting use versus exposure in infrequent drug users. The benzoylecgonine–cocaine ratio also varies widely. Why some subjects (cases 7 and 9) should have substantial amounts of benzoylecgonine with a high benzoylecgonine–cocaine ratio is unknown. Perhaps these individuals have active enzymes present on their skin or different excretory pathways for cocaine and its metabolites.

Since sweat patches or badges are sealed to the skin, they are thought to exclude environmental contamination. Fig. 4 shows the persistence of cocaine, benzoylecgonine (BE), THC and 11-nor-Δ^9-THC-COOH on human skin after application of 1 μg of the drugs. Normal hygiene was allowed. Cocaine and BE are more persistent than either THC or 11-nor-Δ^9-THC-COOH. Because drugs can remain detectable (Fig. 4) for up to three days [87], a simple cleaning of the skin with isopropanol may be insufficient to remove residual, previously deposited drug. The residual drug may then be transferred by sweat into the collection device and mimic use. In fact, in several controlled dose studies with the PharmChek patch, the zero point was positive for drugs [206]. In these studies, known cocaine users were recruited as subjects and, therefore, had likely contact with cocaine. Other authors have postulated storage of cocaine in the skin (not in contact with the blood circulation), which is detectable by radioimmunoassay [91]. However, confirmation via GC–MS produced a very poor correlation with the radioimmunoassay results, casting doubt on their conclusions. Alternatively, if the radioimmunoassay results are valid, they could be explained by a surface contamination by cocaine rather than storage of cocaine.

Table 9
Nicotine/cotinine in saliva

Drug	Method of collection	Method of analysis	LOD	Reference	Comments
Nicotine	Not specified	GC	Not specified	Feyerabend et al., 1982 [178]	Measurable levels of nicotine in non-smokers overlapped those of smokers. Saliva paralleled urine levels
Cotinine	Not specified	GC–NPD	1–5 ng/ml	Jarvis et al., 1987 [179]; Jarvis et al., 1985 [180]; Jarvis et al.,1988 [181] procedure, Jacob et al., 1981 [182]	Smokers>10 ng/ml cotinine. Measured thiocyanate, CO and carboxyhemoglobin. Cotinine best measure of smoking
Nicotine, cotinine	Not specified	GC	ca. 0.2 ng/ml	Curvall and Enzell, 1986 [183]	Cotinine has longer half-life (15.5 h) than does nicotine
Cotinine	Not specified	Paired-ion HPLC–UV	0.5 ng/ml	Machacek and Jiang, 1986 [184]	Cotinine levels in 31 passively exposed individuals, O–7.9 ng/ml. Cotinine detectable for up to 48 h after cessation of smoking
Cotinine	Non-stimulated, spitting	RIA	Not specified	Abrams et al., 1987 [185]	Mouth rinsed, then two samples taken. Smokers >10 ng/ml cotinine, which was detectable four–five days after cessation
Cotinine	Cotton dental rolls	GC–NPD	Not specified	McNeil et al., 1987 [186]; McNeil et al., 1989 [187]	Three year study. Saliva concentrations of nicotine increased in smoking girls. Stayed the same in daily smokers. Cut-off level for cotinine of >14.7 ng/ml. Classified most smokers from non-smokers
Cotinine	Non-stimulated, spitting	RIA	0.78 ng/ml	Coultas et al., 1987 [188]	Cotinine levels used to distinguish environmental exposure in children. Levels often overlap
Nicotine, cotinine	Not specified	GC	not specified	Wall et al. 1988 [189]	Cotinine levels in non-smokers overlapped the levels in smokers
Cotinine	Not specified	GC	Not specified	Jarvis et al., 1988 [190]	Oral ingestion of nicotine in five subjects. Cotinine half-live longer than that of nicotine
Cotinine	Chewing Teflon, spitting	RIA	Not specified	Van Vunakis et al., 1989 [191]	Used 25 ng/ml to indicate smoking status
Cotinine/nicotine	Mixed saliva, unstimulated; parotid saliva, suction	GC–NPD	0.1 ng/ml	Curvall et al., 1990 [192,193]	IV administration of cotinine in non-smokers. Saliva correlated to plasma ($r=0.93$) for 4 h.
Cotinine	Osmotic device, SalivaSac	HPLC	Nicotine (1 ng/ml), cotinine (3 ng/ml)	Schramm et al., 1992 [49]	Good correlation (r=0/96) between plasma and saliva levels. Saliva levels corrected for density of osmotic media and diffusion through membrane
Cotinine	OraSure device	EIA and GC–MS	Not specified	North et al., 1993 [40]	Mostly a sensitivity and specificity study. Few details given
Nicotine	Candy or Parafilm	GC	5–10 ng/ml	Rose et al., 1993 [194]	Transdermal nicotine administration in 25 subjects. Three methods of saliva stimulation
Cotinine	Not specified	Fluorescent polarization immunoassay-TDX	1.7 ng/ml	Colbert and Holmes, 1994 [195]	Modified assay sample size to increase sensitivity. Non-smokers showed passive inhalation

For abbreviations, see Ref. [105].

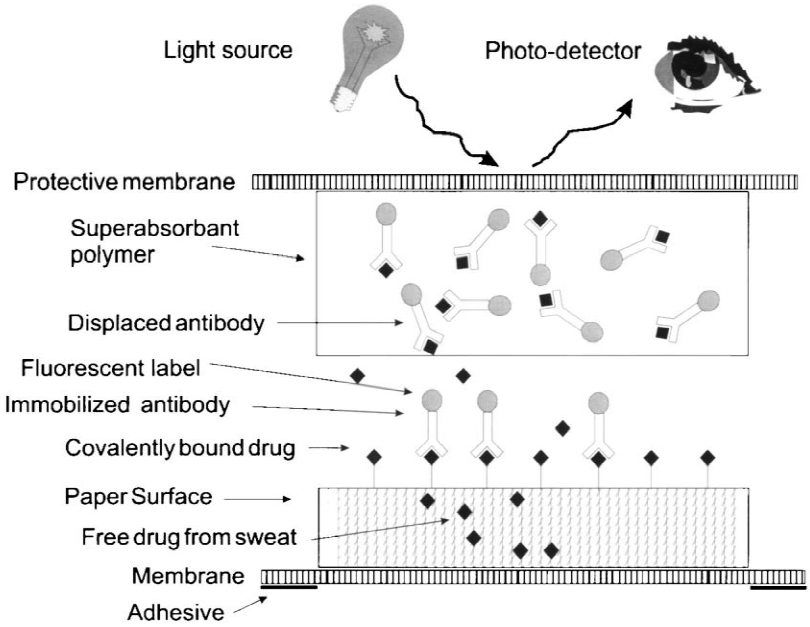

Fig. 3. Schematic diagram of the Naval Research Laboratory Sweat Monitoring Badge.

Although sweat may measure use and exposure, one hypothetical application of skin swab testing is in answering questions surrounding driving a motor vehicle while intoxicated. In one scenario, a police officer may observe a traffic violation. A roadside sobriety test may reveal alcohol present but below the legal limits where an arrest could be made. If additional information from a positive skin swab would be available, the officer could have sufficient/decisive evidence to arrest the driver, impound the

Table 10
Concentrations of cocaethylene and ecgonine methyl ester in sweat wipes from individuals in drug treatment. Out of 413 individual wipes, 183 were positive for cocaine (cut off >2 ng/wipe) and nine were positive for cocaethylene (cut-off >0.8 ng/wipe)

Subject ID	Cocaine (ng/wipe)	Benzoylecgonine (ng/wipe)	Cocaethylene (ng/wipe)	Ecgonine methyl ester (ng/wipe)	BE/Cocaine
1	43.3	2.30	1.93	Negative	0.05
2	45.9	5.87	Negative	Negative	0.12
3	310	31.3	Below cut-off	Negative	0.10
4	366	62.9	3.16	Negative	0.17
5	645	45.4	45.4	11.8	0.07
6	855	149	Below cut-off	Negative	0.17
7	989	621	11.5	Negative	0.63
8	1124	156	Below cut-off	Negative	0.14
9	1159	312	1.06	Negative	0.27
10	1482	137	7.85	17.8	0.09
11	1482	157	Below cut-off	Negative	0.11
12	1769	141	18.9	16.3	0.08
13	2281	386	1.26	Negative	0.17
14	3799	565	9.38	46.2	0.15

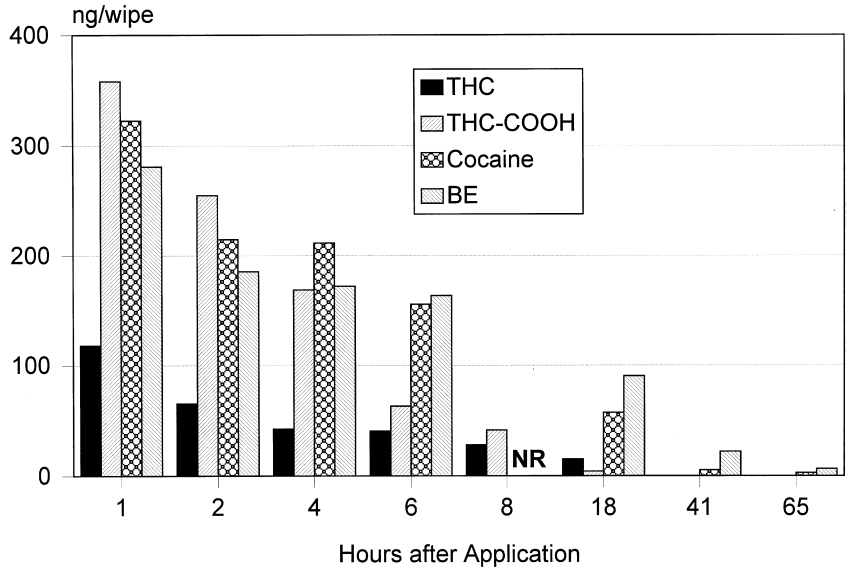

Fig. 4. Persistence of drugs on human skin. Solutions of drugs (1 μg) were placed on 10 cm^2 of skin and allowed to dry. For the 1–6 h samples with cocaine and BE, only 20 ng were applied. The recovered amounts were normalized to 1 ng applied. Samples were taken with a cotton ball wetted with isopropanol. Normal hygiene practices were followed and the skin remained uncovered. THC and THC-COOH were undetectable after 18 h. Time points are averages for three to four individuals.

car and preform additional tests for drugs. For use in such a scenario, information on the concentrations of cocaine on the skin of the general population must be known. Once this ''normal'' level is established, then amounts substantially above it would indicate recent use/exposure. This observation, coupled with the demeanour of the person, could provide probable cause. For road-side testing, either a portable immunoassay [92–95] or an instrumental test [96,97] could be used for screening, as a definitive result is not necessary to provide probable cause.

Ideally, an individual could be monitored for several days to a week by maintaining a sweat patch on his or her skin. If the patch was negative, that would be good evidence that the individual had not used drugs during this time. However, some designs for patches are too easily 'lost', damaged or tampered with by the individual. In a study monitoring prisoners, 30–50% refused to wear the PharmChek patch [21]. Of the remaining individuals, 12% lost the patch [21]. Even in compliant individuals where no sanctions were being applied for drug use, 11% lost or damaged the PharmChek patch [98]. In one case, one individual repeatedly could not wear the PharmChek patch, presumably because of adhesion problems [98]. For drug monitoring, lost patches would necessitate that a urine sample be taken. Furthermore, with the increased work necessary to test the sweat patches, it is not clear that this technique is cost-effective compared to more frequent urinalysis, urine testing being a highly automated procedure. Hopefully, a continuous, remote monitor will alleviate concerns about lost patches and the work necessary for testing.

1.9. Analysis of drugs in sweat

Much less is known about drugs in sweat than is known about drugs in saliva. For example, only one preliminary report on the detection of THC in sweat has appeared. Tables 11–15 list the majority of the papers that analyze drugs of abuse in sweat. Alcohol is listed to highlight early work on drug analysis in sweat rather than as a practical testing procedure.

1.10. Stability of drugs in sweat and saliva

The presence of metabolites is thought to distinguish passive exposure from active use. For cocaine, benzoylecgonine is the primary metabolite

Table 11
Cocaine in sweat

Drug	Method of collection	Extraction of the sample	Derivatization/ method of analysis	LOD	Reference	Comments
Cocaine	Various stains and hair	Buffer	RIA	0.5 ng/ml buffer	Smith and Liu, 1986 [196]	Observed on clothing, menstrual bloodstains, and with hair extracts. Cocaine cross- reacted in RIA. No confirmation performed
Cocaine	Pilocarpine stimulation; sweat stains	Extraction of sweat stains	RIA and GC–MS	Not specified	Balabanova and Schneider, 1990 [197]; Balabanova et al., 1990 [198]; Schneider and Balabanova, 1991 [199]; Balabanova et al., 1992 [200]	Mostly RIA detection from drug users or individuals in drug treatment
Cocaine	Pilocarpine stimulation, occluded filter paper	Distilled water	RIA, GC–MS	Not specified	Balabanova et al., 1992 [91]	Very poor correlation of RIA and GC–MS results. Results due to possible skin contamination rather than long-term skin storage
Cocaine, BE, EME	PharmChek patch	2.5 ml of 0.1% Triton -X-100 in 0.2 *M* acetate buffer	GC–MS	1 ng/patch	Cone et al., 1994 [206]	Cocaine administered. Cocaine, BE and EME found. Cocaine predominates. Mostly excreted within 24 h
Cocaine	PharmChek patch	0.1% Triton-X-100 in 0.2 *M* acetate buffer pH 5.0	RIA, selected samples by EI-GC–MS	Immunoassay; 2.5 ng/patch; 25 ng/patch GC–MS	Burns and Baselt, 1995 [98]	Followed up to seven days of wear. 10% of patches were lost or damaged. Drug reached maximum after 48 h. Urine much better than sweat for short-term determination of drug use
Cocaine and metabolites	Sweat wipes	0.1 *M* HCl	RIA and Cl, GC–MS	1 ng/wipe	Smith and Kidwell, 1996 [201]	Showed possibility of contamination of children living in an environment where cocaine used
Cocaine	PharmChek patch	2.5 ml of 0.2 *M* acetate buffer, pH 5.0, with methanol (25:75, v/v)	Enzyme immunoassay; GC–MS	1 ng/ml	Spiehler et al., 1996 [202]	Mostly confirmation of immunoassay procedure. Comparison made to GC–MS, but no data presented
Cocaine and metabolites	Sweat wipes	0.1 *M* HCl	CI, GC–MS	2 ng/wipe	Kidwell et al., 1997 [203]	Showed that sweat wipes detected as much or more use/exposure than did hair analysis

For abbreviations, see Ref. [105].

in urine and a secondary metabolite in sweat. Besides being in the environment, benzoylecgonine can also come from nonspecific hydrolysis of cocaine in the presence of base or by enzymatic action. Cone and Menchen [99] have shown that cocaine is relatively stable in mixed saliva when frozen and is more stable if the saliva is acidified. In contrast, other drugs, such as benzodiazepines, are relatively unstable [100]. Sweat contains nonspecific esterases [101,102] and other enzymes [103,104] that may allow for degradation of the drug on the surface of the skin. However, we have performed a number of experiments that show that cocaine is stable in contact with skin. For example, a solution of cocaine

Table 12
Opiates in sweat

Drug	Method of collection	Extraction of the sample	Derivatization/ method of analysis	LOD	Reference	Comments
Methadone	Exercise-induced sweating, 5–6 ml samples	Liquid–liquid extraction	GC–FID	Not specified	Henderson and Wilson, 1973 [204]	Methadone and its two metabolites found. Methadone higher than metabolites. Methadone in sweat higher than in urine in some patients
Morphine	Rubbing with cotton; dried on socks	Water extracted and freeze dried	EMIT	ca. 50 ng/ml	Ishiyama et al., 1979 [205]	10 mg oral doses of morphine
Morphine and methadone	Pilocarpine stimulation; sweat stains	Extraction of sweat stains	RIA and GC–MS	Not specified	Balabanova and Schneider, 1990 [197]; Balabanova et al., 1990 [198]; Schneider and Balabanova, 1991 [199]; Balabanova et al., 1992 [200]	Mostly RIA detection from drug users or individuals in drug treatment
Heroin, 6-MAM	PharmChek patch	2.5 ml of 0.1% Triton-X-100 in 0.2 *M* acetate buffer	BSTFA (1% TMCS) EI-GC–MS	1 ng/patch	Cone et al., 1994 [206]	Administered heroin and drug users tested. Heroin and 6-MAM found. 6-MAM likely due to hydrolysis. Morphine not detected. Excreted within 24 h
Morphine, codeine and 6-monoacetyl morphine	Clothing from fatalities	Extraction with phosphate buffer then solid-phase extraction	BSTFA (1% TMCS) EI-GC–MS	Not specified	Tracqui et al., 1995 [207]	T-shirt and underwear sampled but levels varied widely. No consistency in amounts of drugs and location of sampling
Methadone, EDDP, codeine, heroin, morphine, 6-MAM	PharmChek patch	Sorensen buffer (pH 7.4)	PFPA/PFP EI-GC–MS	ca. 1 ng/patch	Skopp et al., 1996 [83]	Individuals in drug treatment. Authors show that external molecules do not penetrate into the patch. Two–three days to reach maximum concentration even with chronic methadone administration
Codeine	PharmChek patch	0.2 *M* Methanol–sodium acetate buffer, pH 5.0, 3:1 (v/v)	BSTFA (1% TMCS) El-GC–MS	0.5 ng	Kintz et al., 1996 [208]	Single dose of codeine (90 mg). All excreted within 48 h. Patches remained on for six days. No morphine detected
Heroin, 6-MAM, codeine, buprenorphine	PharmChek patch	Methanol	BSTFA (1% TMCS) EI-GC–MS	Not specified	Kintz, 1996 [209,210]	Observes MAM>heroin>morphine. Patches longer detection window than urine because left on subject longer. Cost per test higher than urine
Opiates, THC and cocaine	Skin wipes	Direct immunoassay	Direct immunoassay	ca. 5 ng/wipe	Aberl et al., 1996 [211]	Field tasting of Securetoc immunoassays. Positive results useful for generating probable cause and making an arrest. Confirmation of drugs in urine or blood via GC–MS or HPLC

For abbreviations, see Ref. [105].

Table 13
Amphetamines in sweat

Drug	Method of collection	Extraction of the sample	Derivatization and method of analysis	LOD	Reference	Comments
Dimethylamphetamine	Exercise-induced	Not specified	GC and GC–MS	Not specified	Vree et al., 1972 [212]	Detection up to 30 h. Both dimethylamphetamine and methamphetamine observed. Parent drug predominates. Single oral dose of 20–25 mg
Amphetamine	Rubbing with cotton; dried on socks	Water extracted then solvent	GC–FID	ca. 50 ng/ml	Ishiyama et al., 1979 [205]	10 mg oral doses of amphetamine. Observed in sweat longer than in urine (up to five days)
Methamphetamine	Filter paper or gauze	Methanol	TFAA, EI-GC–MS	20 pg/ml MA; 100 pg/ml hydroxy MA	Suzuki et al., 1989 [213]	Drug users tested. Both methamphetamine and amphetamine found. Methamphetamine> amphetamine. Hydroxymethamphetamine was not found
Methamphetamine and amphetamine	PharmChek patch	0.2 *M* acetate buffer, pH 5, methanol (25:75, v/v)	Enzyme immunoassay; GC–MS (GC–MS)	3.69 ng/ml (EIA); 2 ng/ml	Fay et al., 1996 [214]	Mostly confirmation of immunoassay procedure. Comparison to GC–MS but no data presented

For abbreviations, see Ref. [105].

was placed on human skin and covered for several days with either an occlusive or non-occlusive patch. The layers of the sweat patch were analyzed for cocaine, benzoylecgonine and methylecgonine. Only cocaine was found. This implies that the enzymes are not sufficiently active for substantial cocaine hy-

Table 14
Miscellaneous drugs in sweat

Drug	Method of collection	Extraction of the sample	Derivatization and method of analysis	LOD	Reference	Comments
Diazepam and nordiazepam	PharmChek patch	Methanol	EI-GC–MS	Not specified <1 ng/patch	Kintz et al., 1996 [215]	Thirteen subjects, single oral dose of 30 mg. Peak concentration 48–72 h. Dose–response curve measured. Nordiazepam detected
Phenobarbital	Clothing stains	Buffer	RIA	1.2 ng/ml	Smith and Pomposini, 1981 [147]	Observed on wipes and clothing
Nicotine and cotinine	Pilocarpine stimulation; unstimulated	Buffer	RIA, GC–MS	Not specified	Balabanova et al., 1992 [216]; Balabanova and Krupienski, 1995 [217]	Mostly RIA detection. Apocrine levels higher than eccrine levels. Some GC–MS confirmation
THC	Apocrine sweat	Buffer	RIA	Not specified	Balabanova and Schneider, 1990 [197]	Mostly RIA detection

For abbreviations, see Ref. [105].

Table 15
Alcohol in sweat

Drug	Method of collection	Extraction of the sample	Derivatization and method of analysis	LOD	Reference	Comments
Alcohol	Custom sweat patch	None	Head-space GC	Not specified	Philips and McAloon, 1980 [74]	Occlusive sweat patch. Good correlation of sweat and blood alcohol levels. Left patch on for up to eight days
Alcohol	Custom sweat patch	None	Head-space portable sensor	Not specified	Phillips, 1982 [76]; Phillips, 1984 [75]	Occlusive sweat patch. Concentration in sweat and self-report. Left patch on for seven days. Poor correlation

For abbreviations, see Ref. [105].

drolysis. Nevertheless, the presence of some metabolites must be further studied to determine if they are markers of drug use or could arise from external contamination. The stability of other drugs, such as heroin or drug glucuronides, is unknown.

2. Conclusions

For monitoring of therapeutic drugs, increased usage of saliva testing has occurred whereas sweat has only been minimally explored. In contrast, urine is the primary matrix employed for the monitoring of drugs of abuse for forensic or deterrent purposes. Both sweat and saliva frequently require extraction steps from the collection devices before analysis. This increased handling, relative to urine, increases the cost of analysis. Furthermore, the concentrations of drugs are lower, the window of detection is often shorter than for urine, and few immunoassays exist that detect the unique drug profiles in saliva and sweat. All of these considerations reduce the enthusiasm for sweat and saliva testing in forensic applications. Nevertheless, sweat and saliva testing offer advantages over urine and blood in the ease of collection. Urine is impractical to collect under certain circumstances, such as in the monitoring of drivers, monitoring individuals in safety-related work, and surveying of drug use in the general population. In these limited areas, the ease of collection of sweat and saliva may outweigh the cost of testing and the poorer window of detection.

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