Review on Drug Excretion via Non Renal Route: Through Sweat and Saliva

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Abstract: Despite the fact that many different medications have been found in sweat little is known about the properties of drug excretion in sweat during regulated dosage. A sweat patch was used to collect sweat, and because it could be worn for several days to several weeks at a time, the patch accumulated medicine over time. On other hand Saliva's constituents serve as a gauge of the body's health. Biomarkers from serum, gingival crevicular fluid, and mucosal transudate are found in saliva. Saliva is a diagnostic tool that benefits patients, researchers, and medical professionals. Saliva testing can be utilised in public health initiatives since it is non-invasive, affordable, secure, and takes less time. Since one of the roles of the salivary gland is the excretion of medications, it aids in not only detecting various disorders but also determining the excretion of various pharmaceuticals. Details regarding drug excretion in sweat and saliva are provided in this review article.

Keyword: Drug Excretion, Renal Route, Non Renal Route, Sweat Excretion, Salivary Excretion

I. INTRODUCTION

Drug excretion refers to the processes that remove a drug from the body, either unaltered or in the form of biotransformation products. The urine and bile are the primary pathways for medication excretion. Renal excretion is critical in the elimination of unmodified medicines or their metabolites into urine [1]. The fact that chemicals discharged in urine are polar and it is an important feature (e. g., ionized). Hydrophobic medications require prior metabolism (phase I and/or phase II biotransformation processes) to improve kidney excretion. Drugs may also be expelled through the lungs (volatile drugs or metabolites) and sweat in some situations. Drugs may be expelled through milk, tears, sperm, hair, and saliva, even if these are not "planned" routes. In the administration of single doses of some drugs to human participants, a number of clinical trials were created to ascertain the identity, concentration, time course, dose dependence, and variability of drug and metabolite excretion in sweat [2-4].

II. EXCRETION OF DRUGS VIA SWEAT

Sweat glands: Sweat glands are cutaneous appendages like hair follicles. Sweat glands are small tubular structure of the skin that produces sweat. Sweat glands are type of exocrine gland, which are glands that produce and secrete substances onto an epithelial surface by way of a duct. Sweat is initially formed in the coil of both apocrine and eccrine sweat glands, where it is isotonic with the blood plasma. When sweating rates are low, salt is conserved and reabsorbed by the gland's duct; when sweating rates are high, salt reabsorption is reduced and more water is allowed to evaporate on the skin (through osmosis) to improve evaporative cooling [5]. Sweat glands are classified into two categories based on their structure, function, secretory product, excretion mechanism, anatomic distribution, and species distribution [6].

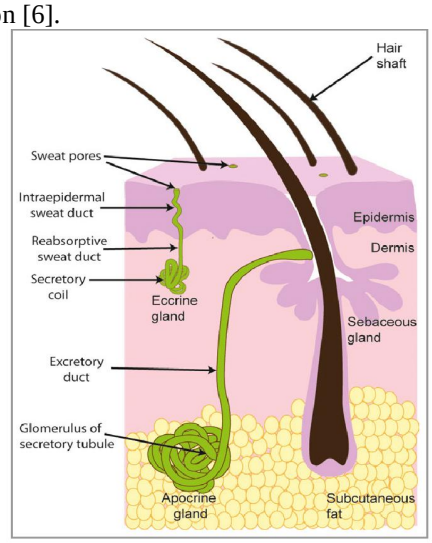

Fig. 1- Structure of sweat gland

Sweat glands secrete either apocrine (secretion occurs via pinch off of outer cell parts) or eccrine (secretion is released from the cell as a liquid without disintegration) [5].

Types of Sweat Glands:

There are three types of sweat gland in the human:
Eccrine
Apocrine
Apoeccrine

Eccrine gland- The eccrine glands release a hypotonic solution into the plasma, including varied concentrations of electrolytes, primarily sodium, chloride, and potassium, as well as other substances in very minute levels, such as lactate, urea, ammonia, proteins, and peptides [6,7]. Eccrine sweat glands are present at birth and can be found everywhere over the body, with the exception of the lips and the penis glands. Sweat glands (1.6-5 million) are found throughout the body, with an average density of 200 sweat glands per square centimetre. The eccrine sweat gland is made up of a simple tubular epithelium and the reabsorptive sweat duct (RSD) and secretory coil [9].

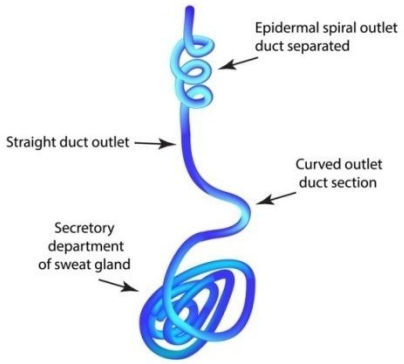

Fig. 2- Structure of eccrine sweat gland

The secretory coil is having three types of cells: clear (secretory) cell, myoepithelial cell and dark cell. The clear cell of the secretory coil is characterised by the presence of basal membrane in foldings (the reported site of Na - K ATPase), membrane villi, intercellular canaliculi which open into the lumen, and abundant mitochondria located near the basolateral membrane (BLM), which indicates that the clear cell is involved in the active secretion of electrolytes and water [8]. The myoepithelial cells are located near the BLM of the secretory coil, and are filled with dense myofilaments, which contract in response to cholinergic, but not adrenergic, stimulation. The function of the myoepithelial cells is believed to be structural in providing mechanical support for the secretory coil wall against the increase in luminal hydrostatic pressure during sweating, rather than the pumping out of preformed sweat [10-11]

Apocrine sweat glands- Apocrine glands already exist at birth but do not become active until puberty. Apocrine glands are restricted to hairy body areas, as they open and secrete into the hair canal. For this reason, apocrine glands can only be found in the axilla, mammary, perineal and genital region. Apocrine glands open to the hair canal. Apocrine and apoeccrine glands generally produce secretions which are richer in fats, proteins and salts, and which evaporate at a slower rate than eccrine secretions, and thus reduce the rate of heat loss [12,13].

In humans, apocrine glands are mainly restricted to the face and hands, but are also located with apoeccrine glands in the mammary, axillary, anal and genital areas, whereas eccrine glands are distributed widely over the body surface,

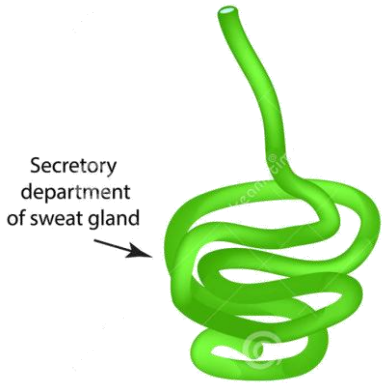

Fig. 3- Structure of apocrine sweat gland

The apocrine gland coil with an outer diameter of about 800 Im is bigger than the eccrine coil. The outer diameter of the apocrine gland tubule is about 120-200 lm, whereas the inner diameter is around 80-100 Im. The apocrine duct is quite short and can be located near the hair follicle. The secretory coil is made up of two types of cells: secretory and myoepithelial cells. Emotional cues such as worry, pain, or sexual excitement cause apocrine sweat glands to respond. Apocrine secretion occurs as apical branching out from luminal cells and is controlled by the adrenergic system via adrenaline and noradrenaline [14].

Type of sweating:

Thermal sweating- Thermal (thermoregulatory) sweating is controlled directly by the hypothalamus and involves both eccrine and apocrine sweat glands. Internal body temperature and mean skin temperature both increase thermal sweating. Eccrine sweat glands are stimulated by acetylcholine, which binds to the gland's muscarinic receptors [15, 16].

Emotional sweating- Stress, anxiety, fear, and pain all cause emotional sweating, which is independent of ambient temperature. To create perspiration, acetylcholine acts on the eccrine glands while adrenaline operates on both the eccrine and apocrine glands. Emotional sweating can happen anywhere, although it is particularly noticeable on the palms, soles of the feet, and axillary areas. Sweating on the palms and soles is hypothesised to have originated in animals as a flight response: it increases friction and avoids sliding while running or climbing in stressful conditions [17, 18].

Gustatory sweating- Gustatory sweating is thermal sweating caused by food consumption. Ingestion causes an increase in metabolism, which raises body temperature and causes thermal perspiration. Hot and spicy foods also cause modest gustatory perspiration in the face, scalp, and neck because capsaicin (the chemical that gives spicy foods its "hot" flavour) attaches to oral receptors that detect temperature. The stimulation of these receptors causes a thermoregulatory response [19, 20].

Drugs excreted through skin via sweat:

Passive excretion of drugs and their metabolites through skin is responsible to some extent for urticaria and dermatitis and other hypersensitivity reactions. Compounds such as benzoic acid, salicylic acid, alcohol and antipyrine and heavy metals like lead, mercury and arsenic are excreted in sweat [21].

III. BUCCAL ABSORPTION AND SALIVARY EXCRETION OF DRUG

Absorption process developed in biological system for getting required organic and inorganic chemicals (nutrients) into systemic circulation to maintain life. Absorption of drug in buccal cavity by buccal mucosa is known as buccal absorption Drugs nutrients absorb by same pathway and we also know the fact that majority of drug taken orally [22-24].

Drugs in the buccal route is classified into three categories

(i) Sublingual delivery: systemic delivery of drugs through the mucosal membranes lining the floor of the mouth,

(ii) Buccal delivery: drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

(iii) Local delivery which is drug delivery into the oral cavity.The Buccal mucosa has a rich blood supply and it is relatively permeable [23]

Advantages of Buccal Drug Delivery System:

Drug administration via buccal mucosa have number of advantages:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
3. Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.
4. Advantage for number of drugs as because they have more contact time with the mucosa.
5. High patient acceptance as compared to other non-oral drug administration modalities.
6. Tolerance to possible sensitizers (in comparison to nasal mucosa and skin).
7. Longer residency duration paired with restricted API release may result in less frequent administration.
8. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
9. Because of adhesion and intimate contact, the formulation remains at the delivery site longer, boosting API bioavailability and allowing lower API concentrations to be used for disease therapy.
10. Harsh environmental variables that exist in oral medicine delivery are avoided by buccal drug delivery.
11. Unlike the rectal or transdermal routes, the presence of saliva assures a relatively substantial volume of water for drug dissolution.
12. Offers an alternate route for the administration of hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents, and other medications.
13. It enables local tissue permeability modification, protease inhibition, and immunogenic response decrease. Thus, medicinal substances such as peptides, proteins, and ionised species can be conveniently delivered [21-23].

Anatomy & physiology of buccal mucosa

The oral mucosa is made up of a layer of stratified squamous epithelium on the outside. Below this is a basement membrane, followed by a lamina propria and, finally, the submucosa as the innermost layer. The epithelium is comparable to the rest of the body's stratified squamous epithelia in that it has a mitotically active basal cell layer that advances through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the epithelium's surface. The buccal mucosa epithelium is 40-50 cell layers thick, whereas the sublingual epithelium is slightly thinner. As they progress from the basal to the superficial layers, epithelial cells grow larger and flatter. The buccal epithelium has a turnover time of 5-6 days, which is probably indicative of the oral mucosa as a whole. The thickness of the oral mucosa varies depending on the site: the buccal mucosa measures 500-800 um, whereas the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingiva measure 100-200 um. The makeup of the epithelium changes according to the location in the oral cavity. The mucosa of mechanically stressed places (the gingivae and hard palate) keratinizes similarly to the skin. The mucosae of the soft palate, sublingual, and buccal regions, on the other hand, are not keratinized [24-25].

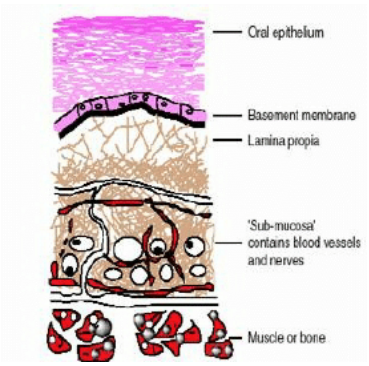

Fig. 4- Structure of oral mucosa

Permeability- In general, the oral mucosa is a leaky epithelia midway between the epidermis and the intestinal mucosa. The permeability of the buccal mucosa is estimated to be 4000 times greater than that of the skin. In general, oral mucosa permeability

decreases in the sequence of sublingual greater than buccal and buccal greater than palatal. This ranking is determined by the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal being thicker and non-keratinized, and the palatal being intermediate in thickness but keratinized [25]. The permeability barrier in the oral mucosa is thought to be caused by intercellular material generated from so-called' membrane coating granules' (MCG). When cells differentiate, MCGS begin to develop and fuse with the plasma membrane at the apical cell surfaces, releasing their contents into the intercellular spaces of the upper one-third of the epithelium. This barrier lies in the superficial layer's outermost 200m. Permeation investigations have been conducted employing a variety of tracers with extremely high molecular weights, such as horseradish peroxidase and lanthanum nitrate [26].

Composition-

Mucus- The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. This matrix may play a function in cell adhesion in addition to acting as a lubricant, allowing cells to move relative to one another. Similarly, mucus is thought to have a function in the bioadhesion of mucoadhesive drug delivery systems. The small salivary glands contribute up to 70% of the total mucin contained in saliva. The mucus network has a negative charge at physiological pH (owing to sialic acid and sulphate residues), which may play a role in muco adhesion. At this pH, mucus can form a very cohesive gel structure that forms a gelatinous coating on the epithelial cell surface [27-28].

Saliva- The presence of saliva produced by the salivary glands is another feature of the oral cavity environment. Saliva is the protective fluid for all oral cavity tissues. It shields the soft tissues against abrasion caused by harsh materials and chemicals. It promotes the continual mineralisation of tooth enamel following eruption and aids in the remineralisation of enamel in the early stages of dental caries. Saliva is aqueous fluid that contains 1% organic and inorganic elements. Depending on the flow rate, the salivary pH ranges from 5.5 to 7. At high flow rates, salt and bicarbonate concentrations rise, causing the pH to rise. The daily salivary volume ranges from 0.5 to 2 litres, and this amount of fluid is available to hydrate oral mucosal dosage forms. The water-rich environment of the oral cavity is a major factor for the use of hydrophilic polymeric matrices as vehicles for oral transmucosal medication delivery systems [24,29].

IV. MINOR PATHWAY OF EXCRETION

Major pathways are urinary excretion and biotransformation. Minor pathways sometime contribute a significant elimination of drug such as pulmonary excretion of general anaesthetics. Various factors influencing the excretion of drug via saliva, such as lipid solubility, pka, plasma protein binding, pH of saliva.

pH of saliva is about 6.2-8.0 (average ph is 6.5) because of lower pH of saliva from plasma saliva free drugs are less than unity for weak acids and more than for weak bases. Drugs are transferred into saliva mainly by passive diffusion Lipid soluble unionized form of drug diffuses into saliva from plasma Saliva is free of proteins so drug level in saliva are free drug level or reflects free drug level in plasma.

$$\text{Saliva/plasma conc. Ratio} = Cs/Cp \qquad \text{Eq.1}$$

For weak acid- $Cs/Cp=1+10(pHs-pKa)*fup/1+10(pHp-pka)*fus$

For weak base- $Cs/Cp=1+10(pKa-pHs)*fup/1+10(pKa-pHp)*fus$

Where- Cs- Drug concentration in saliva

Cp- Drug concentration in plasma

pHs- saliva pH

php- plasmapH

fup- fraction of unbound drug in plasma

fus- fraction of unbound drug in saliva

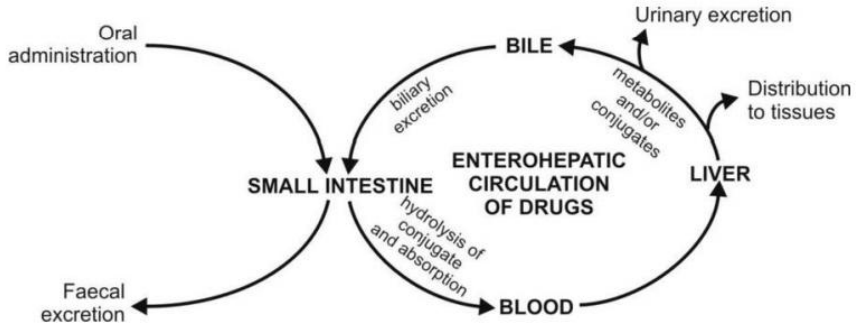

Fig. 5- Salivary-GIT cycling of drug given by various route of administration

70% of saliva entering mouth originates by submandibular gland 25% of saliva entering mouth originates by parotid gland and 5% of saliva entering mouth originates by sublingual gland. Composition of saliva depends upon stimulation provide production reach upto 7ml/min at mean time. Therefore, considerable amounts of drugs reach oral cavity and then pass into GIT from which it can be reabsorbed leading to the cycling of drugs ex Antibiotics and Clonidine. Salivary excretion of antibiotics drug is considered to be responsible for lingua nigra (black hairy tongue), gingival hyperplasia in epileptic patient mainly induced by phenytoin. Bitter taste after administration is also due to salivary excretion of drug [25,28].

Drug absorption- There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Paracellular means transport between cells and transcellular means transport across the cells as illustrated in figure 5. Transcellular is the primary route mainly fairly lipophilic drug diffuses through cell membrane and water soluble drugs

diffuse through aqueous spaces in between. While drugs uses paracellular route are mainly water soluble drugs and having low partition coefficient.

Permeates can employ both pathways at the same time, although depending on the physicochemical qualities of the diffusant, one is usually chosen over the other. Lipophilic substances would be insoluble in this environment due to the hydrophilic nature of the intercellular gaps and cytoplasm. The cell membrane, on the other hand, is lipophilic in nature, and hydrophilic solutes will have difficulties entering it due to a low partition coefficient. As a result, the intercellular gaps act as the primary barrier to the penetration of lipophilic chemicals, whereas the cell membrane serves as the primary transport barrier for hydrophilic compounds. Due to the stratification of the oral epithelium, solute penetration may involve a combination of these two routes [24, 25].

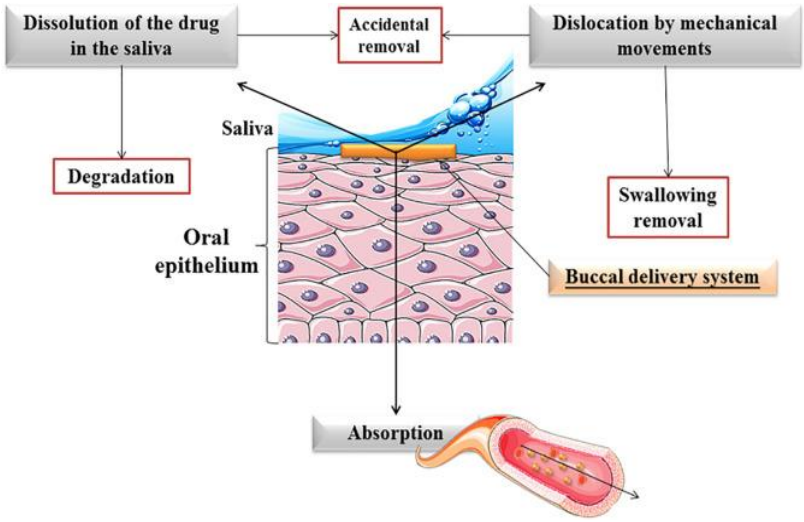

Fig. 6- Diagram for Buccal drug absorption

Buccal Mucosa as a Site for Drug Delivery-

There are three types of medication administration within the mouth cavity (i.e., sublingual, buccal, and local drug delivery). The choice is primarily based on anatomical and permeability differences between the various oral mucosal locations. The sublingual mucosa is relatively permeable, allowing for quick absorption and adequate bioavailability of many medications, as well as being handy, accessible, and widely accepted. Because the buccal mucosa is far less permeable than the sublingual area, it cannot achieve the quick absorption and high bioavailability found with sublingual dosing. Local administration to oral cavity tissues offers a variety of applications, including the treatment of toothaches, periodontal disease-related, bacterial and fungal infections, aphthous and dental stomatitis, and tooth movement using prostaglandins. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is regularly cleaned by a significant amount of saliva, making device implantation challenging. Because of its high permeability and abundant blood flow, the sublingual route can produce a rapid beginning of effect, making it suitable for medications with short delivery periods and occasional dosage regimens [29, 30].

Table 1- Various buccal dosage forms

Dosage forms	Structures	Release	Effect	Active ingredients
Matrix tablets	Monolithic matrix,	Sustained or Bidirectional	Local or systemic	Local administration: metronidazole
	Coating matrix (coated on the outer side or on all but one faces)	Monodirectional	Systemic	Systemic administration: propanolol, timolol, metoclopramide, morphine sulphate, nitroglycerin, codein,
	Two-layer matrix,	Bidirectional	Local (mainly)	insulin, calcitonin, glucagone-like peptide
	Two layer matrix coated with impermeable layer	Monodirectional	Systemic	
Patches	Laminated film with coating	Monodirectional	Local or systemic	Local administration: diclofenac, tannic acid, boric acid. Systemic administration: thyrotropin releasing hormone, octreotide, oxytocin, buserelin, calcitonin, leuenkephalin

Lipophilic gels	Cubic and lamellar liquid crystalline phases of glycerylmonooleate	-	Systemic	Systemic administration: (D-Ala2, D-Leu5) Enkephalin
Transfersomes	Phospholipids deformable vesicles	-	Systemic	Systemic administration: insulin

Buccal Tablets- They softens, adheres to the mucous and retained in position untl dissolution and/or release is complete

Active ingredient	**Polymer**
Baclofen	NaMC, Na alginate and Methood KISM
Carvedilol	HPMC K4M and CP 934P

Boccal patches- Buccal patches are described as laminates which comprise of an impermeable backing layer and drug reservoir.

Active ingredient	**Polymer**
Aceclofenac	Gelatin, Poly Na CMC and PVA
Atenolol	CP 934P, HPMC and NaCMC

Buccal films- buccal films are preferable because they ensure more accurate drug dosing and longer residence time

Active ingredient	**Polymer**
Atenolol	Na alginate, CP 934P and EC
Carvedilol	HPMC K15,Eudragit RL100, CP-934P, NaCMC and PVP

Buccal gels and ointments- semisolid dosage forms having easy dispersion but there is problem of poor retention of gels at the application site.

Active ingredient	**Polymer**
Insulin	Pluronic F-127gel, oleic acid, eicosapentaenoic acid and docosahexaenoic acid
Itraconazole	2-ethylmethyl-2 pyrrolidone, Polaxamer 188 and CP 934

Saliva is secreted mostly by three major glands: parotid, submandibular, and sublingual, as well as several tiny salivary glands, and serves the primary tasks of lubrication, taste, speech, and digestion. These glands' secretions are intermingled with nasal and bronchial secretions, gingival crevicular fluid, blood constituents from bleeding gums, bacteria, virus, fungi, exfoliated epithelial cells, and food debris. These materials aid in the diagnosis of many disorders. Saliva also plays an important part in drug excretion, therefore it can be used to detect drug excretion utilising a drug monitoring system [31].

V. CONCLUSION

The main benefits of employing sweat and saliva are that it is non-invasive, affordable, safe, and takes less time. It can also be utilised in public health initiatives. For many years, it has served as a diagnostic tool. It aids in not only identifying various ailments but also locating drug excretion. The use of oral fluid has been discovered to play a crucial role in the non-invasive detection of drug usage. Drug abuse can also be diagnosed by employing a drug monitoring device, which also makes it simple to identify drug excretion through saliva.

VI. ACKNOWLEDGMENT

The authors are thankful to the Danteswari College of Pharmacy, Borpadar, Raipur road, Jagdalpur, Bastar, Chhattisgarh for the infrastructural facilities.

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