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Invited Review

Absorption of drugs from the human oral cavity

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Summary

The rate and extent of drug loss from the human oral cavity can be measured using several different methods. These include the buccal absorption test (Beckett and Triggs, 1967), disc methods (Kaaber, 1974; Schurr and Ziegler, 1983; Pimlott and Addy, 1985) and perfusion cells (Barsuhn et al., 1988; Rathbone, 1990). These methods have provided information on the mechanisms by which drugs are transported across oral cavity membranes and suggest that passive diffusion (Beckett and Triggs, 1967; Beckett and Moffat, 1968, 1969a,b) or carrier-mediated transport systems (Manning and Evered, 1976; Sadoogh-Abasian and Evered, 1979; Evered et al., 1980; Evered and Mallett, 1983; Hunjan and Evered, 1985) may be involved. An appropriate kinetic model to describe the transfer of drugs across oral cavity membranes is problematic (Beckett et al., 1968; Beckett and Moffat, 1970; Beckett and Pickup, 1975; Dearden and Tomlinson, 1971a; Schurmann and Turner, 1978). This is most likely due to the inherent disadvantages associated with the techniques used. Mathematical models describing drug loss from the oral cavity during a buccal absorption test appear equally successful (Ho et al., 1971; Lien et al., 1971; Vora et al., 1972; Wagner and Sedman, 1973). This is despite marked contrast in the underlying assumptions. The object of this review is to evaluate critically the methods available for studying drug loss from the human oral cavity. In addition we review studies which aimed to elucidate the mechanism of drug transfer across human oral cavity mucosa. The review considers literature that has been published since 1967 and highlights areas that appear worthy of further investigations.

Introduction

The different mucosa that line the oral cavity offer advantages as both sites of drug administration and as model biological membranes upon which to perform fundamental drug absorption studies. Recently there has been much interest expressed in the use of oral cavity membranes as sites of drug administration (Livingstone and Livingstone, 1989). Both the buccal and sublingual sites have advantages compared with other routes. These include rapid onset of action, high blood levels, avoidance of first-pass effect and the drug is not exposed to the fluids of the gastrointestinal tract (Moffat, 1971). Also, there is excellent accessibility and the drug can be applied, localised and removed easily (Garren and Repta, 1988; Gu et al., 1988). In addition the buccal membrane is a potential platform for prolonged drug delivery (Garren and Repta, 1988; Gu et al., 1988; Tucker, 1988). The rational design of drug delivery systems for use on oral cavity membranes requires

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amongst other things information on, and an understanding of, the incorporated drug's ability to permeate the oral cavity membrane that it must cross to reach the systemic circulation. Such information might also provide the investigator with an insight into those factors which influence, control and govern the permeability of drugs across biological membranes. The readily accessible, relatively large areas of flat membranes associated with the oral cavity make them ideal candidates upon which to perform these fundamental investigations.

Oral Mucosa Structure

The oral cavity may be divided into two regions, the outer oral vestibule, bounded by the lips and cheeks and the oral cavity itself, the borders being formed by the hard and soft palates, the floor of the mouth and the pillars of the fauces and tonsils (Squier et al., 1976a). The mucosa that line the oral cavity may be divided into three types classified according to their function. These are (1) masticatory mucosa, which includes the mucosa around the teeth and on the hard palate, (2) lining mucosa which covers the lips, cheeks, fornix, alveolar process, base of the oral cavity, lower part of the tongue and the soft palate and (3) specialised mucosa covering the dorsum of the tongue (Squier et al., 1976a). The oral mucosa in these regions can be structurally viewed as a laminate of layers, the epithelial layer, a highly cellular layer composed stratified squamous epithelium and the lamina propria, a relatively acellular connective tissue layer consisting of dense connective and fibrous tissue. These two layers are separated by a basement membrane, a layer about 1–2 μm in thickness which frequently appears as an undulating boundary. In some parts of the oral cavity such as the cheek, lips and parts of the hard palate a further layer exists, the submucosa, whose structure is variable. This layer comprises a loose fatty or granular connective tissue and contains the major blood vessels and nerves that supply the mucosa and is present between the mucosa proper and underlying muscle or bone. The outer layers of the oral mucosa epithelia form a protective surface which is mechanically tough and resistant to physical insult and penetration by foreign substances. The protective surface layers originate from cells in the basal region of the epithelium which divide and differentiate. The process of differentiation is not identical in the various regions of the oral mucosa and, as a consequence, two distinct types of surface layers are recognised and referred to as keratinised and non-keratinised. In keratinised tissue the outer layer comprises up to 20 rows of flattened, hexagonal shaped cells termed squames which are filled with a dense crystalline protein called keratin, arranged in interconnecting fibres through the cell. Keratinised tissue may be subdivided into ortho- and para-keratinised. In orthokeratinised cells a predominant granular layer is present which is not readily present in parakeratinised tissue cells. Non-keratinised tissue contains no keratinised squames (Squier et al., 1976a).

In the adult human, the mucosa lining the oral cavity covers an area of approximately 200 cm^2 (Collins and Dawes, 1987). The thickness of human oral mucosa varies according to its site. For example, epithelial thickness of buccal mucosa (non-keratinised) is approximately 500 μm (Meyer and Gerson, 1964; Landau and Schroeder, 1977), palatal epithelium 270 μm, which includes a keratin layer thickness of 32 μm (Meyer and Gerson, 1964), and gingival epithelium approximately 250 μm (Squier et al., 1976b). In general, non-keratinised tissue is considerably thicker than keratinised tissue, however, the floor of the mouth (non-keratinised) is very thin (approximately 100 μm) (Squier et al., 1976b).

Methods for Estimating Drug Loss from the Oral Cavity

Buccal absorption test

General methodology

The buccal absorption test was introduced by Beckett and Triggs (1967). The test represents a simple, non-invasive method for estimating the rate and extent of drug loss from the oral cavity.

The method involved swirling a buffered drug solution of known concentration around the mouth by movement of the cheeks and tongue some 60 times per minute. After a known period of time the solution was expelled and the subjects rinsed their mouth with an aliquot of either distilled water or an appropriately buffered solution. The drug solution and rinse were then combined, adjusted to volume and analysed for drug content. The difference between the amount of drug contained in the original buffered drug solution and the amount recovered was assumed to be the amount of drug lost into the oral cavity mucosa during the test interval. Drug loss was usually expressed as a percentage of the original amount entered. To provide information on the relative permeability properties of drugs under different conditions percentage loss during a fixed time period was measured (Beckett and Triggs, 1967; Beckett and Moffat, 1968, 1969a,b, 1971; Dearden and Tomlinson, 1971b; Hicks, 1973; Schurmann and Turner, 1977; Temple and Schesmer, 1978; Chan, 1979). To provide kinetic information percentage loss for the same drug would be measured at different time points (Beckett et al., 1968, Beckett and Moffat, 1970; Sutherland et al., 1974; Beckett and Pickup, 1975; Kates, 1977; Tucker, 1988).

Drug solution volume

There appears to be little variation between authors in the buffered drug solution volume used in a buccal absorption test. Authors employed either a 20 ml (Temple and Schesmer, 1978; Henry et al., 1980; McElnay and Temple, 1982; Blackett et al., 1983; Randhawa et al., 1986; Randhawa and Turner, 1988) or 25 ml volume (Beckett and Triggs, 1967; Bickel and Weder, 1969; Dearden and Tomlinson, 1971a; Odumosu and Wilson, 1971; Manning and Evered, 1976; Mathison and Morgan, 1976; Pickup et al., 1977; Chan, 1979; Edwards et al., 1981; Kaminsky et al., 1987). One author used a 10 ml volume (Kates, 1977). There appears to be little rationale in choosing a buffered drug solution volume other than 20 or 25 ml since these volumes are not too large to cause subject discomfort, allow homogeneous mixing of contents during a test and provide an adequate volume in which to dissolve the drug.

Contact time

Test duration periods vary in the literature dependent on study conditions employed. In the case where investigators determined the kinetics of drug loss from the oral cavity, buffered drug solutions containing the same amount of drug remained in contact with the oral mucosa for different time periods before expulsion. A plot of percentage drug loss versus time provided information on the kinetics of drug loss. A characteristic profile was observed when contact time (test duration period) was varied during a buccal absorption test. In general there was an initial fast disappearance of drug up to about 5 min, followed by a slower, progressive loss. In the second case investigators used a fixed test duration period to compare the absorptive properties of different drugs, or the same drug subjected to different conditions. In these studies the test duration period was chosen to correspond to the end of the initial fast disappearance. Beckett and Triggs (1967) showed that the initial fast disappearance of some amphetamine compounds had occurred within 5 min of swirling. From these observations Beckett and his co-workers, and the majority of other investigators used a 5 min contact time when relative studies were performed, without first performing preliminary studies to determine when the initial fast disappearance period had occurred for the particular drug or class of drugs used in their studies. Clearly this time period will be dependent upon the physicochemical properties of the drug and it is interesting to note that those authors who performed preliminary studies used contact times of 3 min (Pickup et al., 1977), 4 min (Arbab and Turner, 1971; Kaminsky et al., 1987) and 6 min (Chan, 1979). Contact times of 15 min have been reported (Taraszka, 1970; Henry et al., 1980; Tucker, 1988). Taraszka (1970) suggested that such extended time periods were inappropriate to use in a buccal absorption test due to subject discomfort and the inevitable swallowing of a portion of the drug solution. Henry et al. (1980) and more recently Tucker (1988) report no such

problems. The latter authors do report large volumes of secreted saliva (up to 10 ml) and significant differences between the initial and final pH values of the drug solution (Henry et al., 1980; Tucker, 1988).

Non-absorbable marker compounds

A number of authors expressed concern over non-absorbable losses that might occur due to swallowing of drug during a buccal absorption test (Arbab and Turner, 1971; Meyer et al., 1974; Manning and Evered, 1976; Schurmann and Turner, 1977, 1978; Past et al., 1979). These investigators added non-absorbable marker compounds to the buffered drug solution and determined the amounts of these compounds before and after a buccal absorption test. Inulin (Manning and Evered, 1976), ^{125}I-labelled polyvinylpyrrolidone (Past et al., 1979), polyethylene glycol (Meyer et al., 1974) and phenol red (Schurmann and Turner, 1978; Henry et al., 1980; Tucker, 1988) have been used to assess the extent of drug loss arising from non-absorbable sources during a 5 min buccal absorption test. In each case no significant losses were observed. Independent studies by Arbab and Turner (1971) and Schurmann and Turner (1977) using polyethylene glycol and phenol red, respectively, showed that marker loss was minimal around pH 8 ($1 \pm 1.8\%$) but increased with acidity of the buffered drug solution to $14 \pm 7\%$ at pH 5. In general the high and consistent amounts of non-absorbable marker compounds recovered after a buccal absorption test confirm the assumption that negligible drug losses arise from non-absorbable sources.

Pre-test modifications

Pre-test washout In order to cleanse mouth and adjust pH prior to a buccal absorption test McElnay and Temple (1982) performed a 30 s swilling using 20 ml of a pH 9.5 buffer solution without drug. Tucker (1988) followed a similar procedure using a few millilitres of distilled water. Randhawa and Turner (1988) rinsed the mouth for 10 s prior to a buccal absorption test with 20 ml of the buffer used in the test.

Equilibration of buffered drug solution to 37 °C Evered and his co-workers pre-equilibrated the buffered drug solution to 37 °C immediately prior to a buccal absorption test in order to reduce pH changes with temperature (Manning and Evered, 1976). Evered considered this necessary with the physiological buffers employed in their studies. Such a protocol was deemed unnecessary by Beckett and Moffat (1968) who employed buffers which had a large pH–temperature coefficient and for which standard tables were available that documented change of pH with temperature.

Post-test modifications

Nominal volume for froth The rapid movement of the buffered drug solution around the oral cavity in the presence of salivary secretions promotes the formation of froth. After expulsion, the exact volume of the expelled solution is difficult to determine because of the presence of large amounts of froth. In order to overcome this problem one of three methods has been adopted. In the first the froth is allowed to subside (Beckett and Moffat, 1968). This method suffers from the disadvantage that this may take a considerable length of time. In the second, a nominal volume of buffer solution is added to the expelled solution to account for the volume occupied by the froth. Nominal volumes of 0.5 ml (Beckett and Moffat, 1968) and 0.3 ml (Schurmann and Turner, 1978) have been suggested. In the third method volumes are adjusted by weight (Tucker, 1988).

Post-test rinsing Immediately after a buccal absorption test subjects rinsed their mouth with an aliquot of fresh, drug free buffer or distilled water for a short period of time to remove any unabsorbed drug that may still be present in the oral cavity. It was soon recognised that such a procedure may encourage 'absorbed' drug to return back into the oral cavity from the membrane (Beckett and Moffat, 1968). Beckett and Triggs (1967) employed a 10 ml, 10 s rinse. Others used a 10 ml, 5 s rinse (Manning and Evered, 1976), 20 ml, 10 s rinse (Henry et al., 1980; Randhawa and Turner, 1988), a 20 ml, 30 s rinse (Randhawa et al., 1986), a 10 ml, 5 s rinse (Sadoogh-Abasian and Evered, 1979; Evered et al., 1980) and a 5 ml, 3 s rinse (Beckett and Pickup, 1975). It is clear that the post-test swilling period, although re-

quired, should involve small volumes and be restricted to short periods of time. This is particularly important with drugs that can readily return to the oral cavity from the membranes.

Recovery after buccal partitioning It was recognised early in the historical development of the buccal absorption test protocol that 'absorbed' drug could return back into the oral cavity given an appropriate concentration gradient. Initially this led Beckett and Moffat (1968) to caution investigators to keep swilling periods to a minimum. Later, repeated post-test rinsing was employed to recover drugs from the oral cavity membranes after a buccal absorption test. For some amphetamine compounds approximately 50% of 'absorbed' drug could be returned to the oral cavity after repeated post-test rinsing with freshly introduced buffer solutions (Beckett and Triggs, 1968). Little return from the oral mucosa back into the oral cavity was observed for some carboxylic acids after a buccal absorption test (Beckett and Moffat, 1970). For testosterone and progesterone 33% and 14%, respectively, of 'absorbed' drug were recovered from the oral mucosa (Beckett and Pickup, 1975). About 70% of fomocaine was 'absorbed' by the oral mucosa during a 5 min buccal absorption test, repeated post-test swillings initiated immediately after a test returned most of the 'absorbed' drug back into the oral cavity and 1 h after cessation of a buccal absorption test, 30% of the absorbed fomocaine could still be recovered from the oral mucosa (Temple and Schesmer, 1978). The return of verapamil into the buccal cavity after a buccal absorption test was dependent on the pH of the post-test rinse solution (Davis and Johnston, 1979). A technique for repeated recovery in which the kinetic profile for drug recovery could be drawn was reported by Henry and his coworkers (Henry and Ohashi, 1979; Henry et al., 1980). Recovery involved the introduction of 20 ml of fresh buffer solution into the oral cavity and circulated in the manner as for absorption, for 115 s. 5 s were allowed for expulsion of the buffer and the introduction of a further 20 ml of fresh buffer of the same pH. This procedure was repeated twelve times, the duration of recovery being 24 min (Henry et al., 1980). Results showed that large amounts of propranolol were recoverable from the oral mucosa; recovery was biexponential and the amount recovered was dependent upon the time allowed for absorption (percentage recovery decreased with increasing contact time of buccal absorption test), pH (percentage recovery increased as percentage ionised species in fresh buffer increased) and recovery time (percentage recovery increased with time of recovery) (Henry et al., 1980). The basic method of the 2 min repeated recovery procedure has been used by others (McElnay and Temple, 1982; McElnay et al., 1982; Blackett et al., 1983). The recovery of acetylsalicylic acid was less than 1% at pH 5 or 8, while that of indalpine was 19% and 13% at pH 5 and 8, respectively, the difference in recovery being explained in terms of a difference in their distribution in the oral mucosa dependent upon their lipid solubilities (Blackett et al., 1983). These observations underline the fact that drug loss from the oral cavity during a buccal absorption test and systemic absorption are not synonymous (Henry et al., 1980). It does not follow that disappearance of drug from the oral cavity results in its appearance in the systemic circulation. The term 'buccal absorption' may thus be an inaccurate description of the processes that occur during a buccal absorption test (Henry et al., 1980; Blackett et al., 1983; Sadoogh-Abasian and Evered, 1979; Evered et al., 1980).

Time between repeats

An implicit assumption of the buccal absorption test is that tests are performed upon oral cavity membranes which are void of drug content. Thus, if investigators are to perform repeat experiments upon the same person they must ensure sufficient time has elapsed between repeats. Dearden and Tomlinson (1971a) found the minimal period between successive tests, for satisfactory repeat values to be obtained, was about 15 min after a 5 min contact time, and 50 min after a 10 min contact time. A waiting time of 30 min after a buccal absorption test of 5 or 6 min was considered of sufficient length by a number of authors (Beckett and Moffat, 1968; Arbab and Turner, 1971; Chan, 1979; Evered and Vadgama, 1983). Other authors preferred waiting times be-

tween repeats of 2 h (Edwards et al., 1981; McElnay and Temple, 1982), 5 h (Tucker, 1988) or 24 h (Randhawa et al., 1986). There is little agreement in the length of time allowed to elapse between repeats. Time periods will be dependent on the buccal absorption test duration period and on the physicochemical properties of the drug. Longer lapses of time must be allowed when longer buccal absorption test contact times are used (Henry et al., 1980) or when very lipid soluble drugs are investigated (Temple and Schesmer, 1978).

Intra- and inter-subject variation

Surprisingly small intra- and inter-subject variation is observed during a buccal absorption test. Beckett and Triggs (1967) demonstrated that intra-subject variations of drug loss from the oral cavity of some amphetamines for one man on different days were small and that inter-subject variation was also not great. Experiments performed on two subjects who had never participated in a test before also showed small variations in drug loss and compared favourably with results obtained from trained subjects. These observations were verified using a variety of different drug structures including benzphetamine (Taraszka, 1970), thiamine (Evered and Mallett, 1983), ascorbic acid (Sadoogh-Abasian and Evered, 1979), indomethacin (Garnham et al., 1977), mexiletine (Kaye et al., 1977), β-adrenoreceptor blocker drugs (Schurmann and Turner, 1977, 1978; McElnay and Temple, 1982), medifoxamine (Randhawa et al., 1986), *p*-substituted acetanilides (Dearden and Tomlinson, 1971b), fomocaine (Temple and Schesmer, 1978), imipramine (Bickel and Weder, 1969) and ergotamine (Sutherland et al., 1974). A comparison of untrained and trained subjects was performed by Schurmann and Turner (1978) using propranolol. Fifteen untrained subjects gave the same profile as a single subject, however, each point was associated with wide scatter and lower mean readings which were similar to those associated with inter-subject variation. Intra- and inter-subject variations were reported by Schurmann and Turner (1978) to increase at points of high absorption. Other authors demonstrated that little or no variation in reproducibility occurred at different pH values or extents of absorption (Garnham et al., 1977; Kaye et al., 1977; Temple and Schesmer, 1978; Randhawa et al., 1986). Intra-subject variation was always smaller than inter-subject variation. As a consequence kinetic studies were usually performed upon a single subject (Dearden and Tomlinson, 1971a; Hicks, 1973; Schurmann and Turner, 1978).

Subject populations appear to have received little attention when subjects were chosen for a buccal absorption test. Odumosu and Wilson (1971, 1977) reported that ascorbic acid loss during a buccal absorption test was greater in males than females, an observation supported by Temple and Schesmer (1978) using fomocaine. Several authors report no significant difference in drug loss between male and female subjects (Bickel and Weder, 1969; Sutherland et al., 1974; Sadoogh-Abasian and Evered, 1979; Evered and Vadgama, 1983; Hunjan and Evered, 1985).

Inter-author variation

A comparison of the percentage loss for propranolol during a 5 min buccal absorption test performed by five independent authors shows good agreement. At pH 9.5 the following percentage losses for propranolol were reported: 79.0 (Henry et al., 1980), 77.0 (Hicks, 1973), 90.5 (McElnay and Temple, 1982) and 80.0 (McElnay and Mooney, 1983). Schurmann and Turner (1977) reported values of 76.9 and 89.0 percentage loss of propranolol at pH 9.0 and 10.0, respectively. Independent studies by Beckett and Triggs (1967) and Taraszka (1970) using benzphetamine in a 5 min buccal absorption test produced results in close agreement with each other. These results confirm the reproducible nature of the buccal absorption test.

Multiple sampling

In order to estimate the transfer kinetics of a given drug the buccal absorption test requires repeated swillings over different time periods up to a maximum of 15 min – a process which can take days for the mapping of a drug's kinetic profile (Tucker, 1988). In this respect Tucker (1988) reported a technique which enables kinetic data to be collected in a single 15 min trial. The

method involved multiple samples being withdrawn from the mouth throughout the duration of a buccal absorption test. The method was validated using verapamil.

Monitoring of drug appearance in blood

Drug loss from the oral cavity during a buccal absorption test is often referred to as 'drug absorption'. Drug absorption implies, by definition, passage across a membrane into the systemic circulation (Wagner, 1968). It is evident from repeated recovery of drug after a buccal absorption test has been performed that drug loss from the oral cavity and entry into the systemic circulation are not synonymous (Davis and Johnston, 1979; Henry and Ohashi, 1979; Henry et al., 1980; Blackett et al., 1983). Studies measuring drug loss from the oral cavity and appearance in the blood are sparse in the literature. Pickup et al. (1977) used a 3 min buccal absorption test to investigate the absorption of ICI 74917 (6-*n*-butyl-2,8-dicarboxy-4,10-dioxo-1,4,7,10-tetra-hydro 1,7-phenanthroline, disodium salt). Blood samples collected up to 4 h and urine samples up to 36 h after expulsion were void of drug content. This was attributed to the lack of a specific transport mechanism for the drug in the oral mucosa and the high degree of ionisation of the drug at the chosen pH of the study. Kates (1977) investigated the buccal absorption of propranolol with a 10 ml buffered drug solution containing 10 mg of drug and a 5 min contact time. Blood samples were collected following administration. The half-life for appearance in the blood was about three times the half-life for disappearance from the oral cavity indicating the rate-limiting step to be transfer of propranolol out of the membrane into the blood.

Concluding remarks

The buccal absorption test provides a simple, non-invasive method for measuring the rate and extent of drug loss from the oral cavity from solutions. The method has been used extensively by authors in a variety of scientific disciplines. However, the technique has several disadvantages. Firstly, as drug absorption has taken place over all mucosa surfaces, the technique cannot provide information on the relative permeabilities of different regions of the oral cavity. In addition each oral cavity membrane differs in its anatomy and composition. Secondly, there is no control over the area across which transfer can take place. Due to biological variability different subjects will have different areas and will expose the various areas of oral cavity membranes to differing degrees throughout the duration of a test. Thirdly, there is a continual and erratic secretion of saliva throughout the duration of a test. The saliva will continually change drug solution pH and volume, and can potentially interact with drug leading to possible interference with assay procedures and problems in the interpretation of buccal absorption test data. Finally, only a tentative estimate of the impelled aqueous drug solution boundary layer conditions can be postulated. It should be remembered that this test only measures disappearance from the oral cavity, which in the absence of information on pharmacological effects or systemic levels, may not necessarily reflect complete transfer across the mucosa into the blood.

Disc methods

Historical development

Kaaber (1974) developed a quantitative method for investigating the transport of water and ions through known regions of the oral mucosa. The author used an airtight sampling chamber comprising a standardised disc of dry, ash-free filter paper overlaid with a disc of porous membrane material. The filter paper was then protected from evaporation by an airtight sampling chamber comprising a disc adhered to a piece of surgical tape. Schurr and Ziegler (1983) used a polytef disc with a diameter of approximately 3.5 cm^2 and height of 1 cm. The disc had a central circular depression depth of 4 mm, leaving an elevated rim. A previously water-soaked filter paper disc was placed in the depression and 20 mg of crystalline protirelin spread onto the filter paper which dissolved immediately. Subsequently the device was placed in contact with the buccal mucosa. Pimlott and Addy (1985) modified the method of Kaaber (1974) to study steroid absorp-

tion across keratinised and non-keratinised oral mucosa sites. The vehicle for drug delivery was a three disc thickness of Whatman Ashless 42 filter paper 1 cm in diameter. Discs were impregnated with an aqueous solution (1.25 mg/100 μl) of prednisolone sodium phosphate and placed on three different mucosa sites. Lip and sublingual areas were isolated with cotton wool and saliva ejectors and the discs allowed to lie on the mucosa but not in contact with the isolation materials for a period of 5 min. The palate discs were held gently against the mucosa with tweezers while the subject was in the supine position (Schurr and Ziegler, 1983). A non-impregnated disc of filter paper was used to wipe the oral mucosa immediately after disc removal and the concentration of drug in each of the 4 discs was determined. Percentage drug losses from the discs at the different sites were shown to be significantly different from each other at 65.4%, 24.1% and 9.9% for sublingual, buccal and palatal sites, respectively.

Concluding remarks

Disc techniques allow investigators to study drug loss across a fixed area of defined oral cavity membrane. The technique might also lend itself to the estimation of kinetic rates of transfer through repeated application and sampling of identically prepared discs resting in contact with the oral mucosa for different lengths of time. However, such studies do not appear in the literature probably due to the inherent difficulties of the technique which include adherence of disc to membrane, leakage of drug from the disc and interference from salival secretions.

Perfusion cells

Barsuhn

Barsuhn et al. (1988) devised a closed-perfusion cell apparatus to study the transport of flurbiprofen across a fixed (1.8 cm^2) area of human buccal membrane. The cell was constructed of a hydrophilic polymer and was pliable to allow a comfortable fit when placed against the buccal mucosa. Two internal posts were moulded into the cell to provide adequate turbulence within the perfusion cell and to prevent the buccal membrane from collapsing into the cell void. The design also incorporated a sealing lip to prevent fluid leaks. Aqueous solutions (8.0 ml total volume) of flurbiprofen (0.28 mg/ml) were maintained at 37 °C and recirculated through the perfusion apparatus at 10 ml/min for a total perfusion time of 42 min. Samples (0.05 ml) were removed from a stirred reservoir at the start of perfusion and at 7 min intervals during the course of an experiment. Removed samples were analysed for drug content and apparent first-order rate constants calculated. No irritation was apparent at the perfusion site and all subjects tolerated the perfusion procedure without difficulty (Barsuhn et al., 1988). The closed-perfusion cell apparatus is a significant improvement over both the buccal absorption test and disc methods for estimating kinetic rate constants for disappearance across a specified oral cavity membrane; however, Barsuhn et al. (1988) reported problems of perfusion circuit leakage. Also inter-subject variation was large, rate constants for disappearance varied from 2.88×10^{-5} s^{-1} to 8.07×10^{-5} s^{-1} (mean $\pm$ SD = $5.88 \pm 1.85 \times 10^{-5}$ s^{-1}, $n = 8$ subjects) for flurbiprofen at pH 5.5.

Rathbone

Recently Rathbone (1991) reported on an improved buccal perfusion cell design in which cell leakage was not a problem, perfusion circuit pressure maintained low and both intra- and inter-subject variations were small. The buccal perfusion cell was circular with an internal diameter of 1 cm, internal depth of 0.5 cm and allowed 3.14 cm^2 area of buccal membrane to be perfused. Small bore Teflon circulation tubing (0.08 cm internal diameter) led from the inside of the cell to permit connection into a perfusion circuit. 27.5 ml of buffered aqueous donor phase containing a model drug, butyl *para*-hydroxybenzoate and maintained at 37 °C was continually circulated across a subject's buccal membrane at 10 ml/min for the duration of an experiment (40–60 min). Drug concentrations were continuously monitored as a function of time by pumping the drug solution through a flow-cell in a spectrophotome-

ter. An apparent first-order rate constant for drug disappearance was calculated from knowledge of the change in drug concentration with time. It was shown that intra-subject variation of drug transfer was small, with inter-subject variation only slightly larger (Rathbone, 1991). No significant difference in drug transfer kinetics was observed between a subject's left and right buccal membranes or between male and female subjects (Rathbone, 1991). Subjects can tolerate extended periods of perfusion (up to 2 h) and the method is sensitive enough to detect differences in transfer rate constants between closely related members of a homologous series and to allow the effect of pH upon drug transfer to be studied (Rathbone, 1990). Recently, the method has been successfully used to simultaneously monitor disappearance of propranolol from the buccal perfusion cell and its appearance in the blood (Rathbone et al., 1990).

Concluding remarks

Buccal perfusion cells of the type depicted above offer fixed (known) interfacial areas over which transfer can take place into a defined oral cavity membrane. The isolation of the area over which transfer occurs prevents interference from salivary secretions, thus aqueous phase volumes, pH and temperature of the perfusant remain constant throughout the duration of an experiment (Rathbone, 1991). Buccal perfusion cells may provide an investigator with a technique suitable to quantify those factors which influence, control and govern drug permeability across oral cavity membranes and the authors believe that such studies will proliferate in the literature.

Mechanisms of Drug Transfer

Evidence for passive drug transfer

The early works of Beckett and his co-workers (pre-1971) have been extensively reviewed (Beckett and Hossie, 1971; Moffat, 1971; Muzaffar, 1975; Spiers, 1977). Beckett's studies indicated that loss of drugs from the oral cavity occurred by the process of passive diffusion of the non-ionised form from an aqueous phase into one which was essentially lipid in nature. Evidence for this include: (1) a linear relationship between percentage loss and initial drug concentration for a fixed test duration period (Beckett and Triggs, 1967); (2) disappearance of drug from the solution exposed to the oral cavity increased with time of contact (Beckett and Triggs, 1967; Beckett et al., 1968; Beckett and Moffat, 1968, 1970); (3) with multicomponent mixtures percentage loss was the same as when each drug was administered separately (Beckett and Triggs, 1967; Beckett and Moffat, 1968; (4) percentage loss increases with an increase in non-ionised drug species (Beckett and Triggs, 1967; Beckett and Moffat, 1968; (5) the shapes of the percent loss versus pH curves varied with variation in the pK_a values of the drugs (Beckett and Triggs, 1967; Beckett and Moffat, 1968, 1969a, 1971; Beckett et al., 1968); (6) percentage loss increased with increasing lipid solubility of the drug (as expressed by the oil: water partition coefficient) (Beckett and Triggs, 1967; Beckett and Moffat, 1968, 1969a,b, 1971; Beckett et al., 1968); and (7) optical isomers were absorbed to the same extent at a given pH and test duration period (Beckett and Triggs, 1967). Tables 1 and 2 summarise work performed by various authors using the buccal absorption test of Beckett and Moffat (1967) from 1971 to date. It is clear from Tables 1 and 2 that most drugs are lost from the oral cavity throughout the duration of a buccal absorption test by the process of passive diffusion of the non-ionised species in accord with the pH–partition hypothesis.

Evidence for carrier-mediated transport systems

Manning and Evered (1976) studied the uptake of certain hexoses into the oral mucosa using a modified buccal absorption test. Loss from the oral cavity of D-glucose, D-fructose, D-galactose and 3-O-methyl-D-glucose showed a non-linear dependence of concentration upon uptake (Manning and Evered, 1976). Metabolic losses were shown to be negligible and led the authors to conclude that transport of these sugars across the oral mucosa was by a specialised transport system capable of saturation. A stereospecific effect was

TABLE 1

Literature evidence to suggest that the non-ionised form of a drug is lost from the oral cavity during a buccal absorption test

Experimental variable	Drug(s) investigated		Observation
pH of buffered drug solution in oral cavity	Pethidine [a]	Norpethidine [a]	% drug loss from the oral cavity varied according to the extent of ionisation. Ionised species remained confined to the oral cavity while non-ionised species were observed to transfer across the oral epithelia
	Pethidine *n*-oxide [a]	Acebutolol [b]	
	Propranolol [c,d,e,f,g,h,i]	Practolol [c,h]	
	Pindolol [c]	Verapamil [j]	
	Oxprenolol [h]	Cycloserine [k]	
	Lignocaine [l]	Fomocaine [m]	
	Procainamide [n]	Ergotamine [o]	
	4-/3-Indolyl-2-ethyl/piperidine [p]	Acetylsalicylic acid [q]	
	Indalpine [q]	Indomethacin [r]	
	Imipramine derivatives ($n = 10$) [s]	Isoprenaline [h]	
	8-Substituted decahydroisoquinoline derivatives ($n = 21$) [t]	Salbutamol [h]	
		Diethylcarbamazine [u]	
	Thymoxamine HCl [v]	Mexiletine [l]	
	Zipeprol and its *n*-alkylated derivatives ($n = 10$) [w,x]		

[a] Chan, 1979; [b] Kaye and Long, 1976; [c] Hicks, 1973; [d] Schurmann and Turner, 1977; [e] Schurmann and Turner, 1978; [f] Henry et al., 1980; [g] Henry and Ohashi, 1979; [h] Ohashi and Turner, 1980; [i] Davis and Turner, 1979; [j] Davis and Johnston, 1979; [k] Sprake and Evered, 1979; [l] Kaye et al., 1977; [m] Temple and Schesmer, 1978; [n] Meyer et al., 1974; [o] Sutherland et al., 1974; [p] Kaspi et al., 1979; [q] Blackett et al., 1983; [r] Garnham et al., 1977; [s] Bickel and Weder, 1969; [t] Mathison and Morgan, 1976; [u] Edwards et al., 1981; [v] Arbab and Turner, 1971; [w] Achari and Beckett, 1982; [x] Beckett and Chidomere, 1977.

demonstrated by D- and L-glucose and by the pentose isomers D- and L-arabinose (Manning and Evered, 1976). Removal of Na^+ ions from the drug solution during a buccal absorption test resulted in a 30% inhibition of D-glucose and D-galactose transport and a 40% inhibition of 3-O-methyl-D-glucose transport (Manning and Evered, 1976). Uptake of D-glucose was also shown to be inhibited in the presence of large concentrations of galactose and 3-O-methyl-D-glucose suggesting that these sugars are transported by a carrier-mediated system and share a common transport system (Manning and Evered, 1976). McMullan et al. (1977) examined the effect of Ca^{2+} and Mg^{2+} ions on the transport of various hexoses across the oral mucosa. Mg^{2+} ions produced no significant increase in uptake of any of the sugars tested whereas Ca^{2+} ions significantly increased the uptake of certain hexoses but had no effect upon the others tested (McMullan et al., 1977). Their results supported the results of Manning and Evered (1976) that certain sugars are transported across the human oral mucosa by a carrier-mediated process. Evered and Offer (1981) showed that absorption of glucose was inhibited by the presence of aspirin providing further evidence for the presence of a Na^+ dependent carrier-mediated transport system for D-glucose. Certain vitamins are transported across the oral mucosa by a carrier-mediated process. These include L-ascorbic acid (Sadoogh and Evered, 1979), nicotinic acid (Evered et al., 1980) and thiamine (Evered and Mallett, 1983). Glutathione is transported by a non-energy requiring sodium-independent carrier-mediated diffusion process (Hunjan and Evered, 1985), homocitrulline by a sodium-dependent carrier-mediated process (Evered and Vadgama, 1981) and nicotinic acid by facilitated diffusion (Evered et al., 1980).

These studies suggest that the human buccal mucosa possesses carrier-mediated transport sys-

TABLE II

Literature evidence to suggest that the lipid soluble form of a drug is lost from the oral cavity during a buccal absorption test by the process of passive diffusion

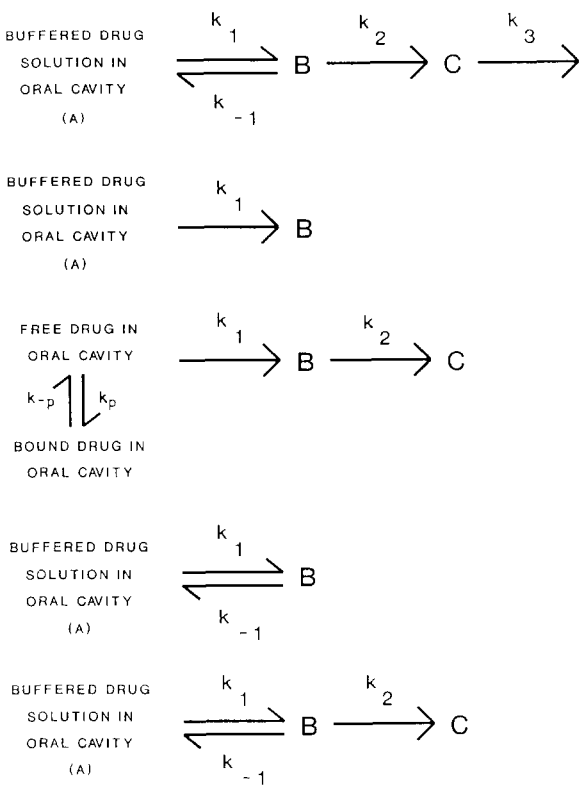
Experimental variable	Drug(s) investigated		Observation
Affinity of drug for membrane (as measured by the oil/water partition coefficient)	Pethidine derivatives [a] ($n = 3$)	*p*-Substituted acetanilide derivatives [b] ($n = 16$)	For a given series as the affinity of the analogue for the epithelial membrane increased (as measured by the oil/water partition coefficient) the greater was the observed % loss from the oral cavity
	β-Adrenoceptor blocking drugs [c] ($n = 3$)	Steroid derivatives [d] ($n = 15$)	
	Amphetamine derivatives [e,f] ($n = 4$)	Imipramine derivatives [g] ($n = 10$)	
	8-Substituted decahydroisoquinoline derivatives [h] ($n = 21$)	Zipeprol and its *n*-dealkylated derivatives [i,j] ($n = 10$)	
Stereospecificity	D-Cycloserine [k,l]		No difference observed in the % loss from the oral cavity
	L-Cycloserine		
Initial concentration of buffered drug solution	Fomocaine [m]	Ergotamine [n]	Linear relationship observed between initial concentration and % loss from the oral cavity
	Atenolol [o]	Propranolol [o]	
	Lactulose [p]	Cycloserine [k]	
	Ascorbic acid [q]	Nicotinic acid [r]	
	Nicotinamide [r]		

[a] Chan, 1979; [b] Dearden and Tomlinson, 1971b; [c] Hicks, 1973; [d] Beckett and Pickup, 1975; [e] Beckett and Triggs, 1967; [f] Beckett et al., 1975; [g] Bickel and Weder, 1969; [h] Mathison and Morgan, 1976; [i] Achari and Beckett, 1982; [j] Beckett and Chidomere, 1977; [k] Sprake and Evered, 1979; [l] Evered, 1972; [m] Temple and Schesmer, 1978; [n] Sutherland et al., 1974; [o] Schurmann and Turner, 1978; [p] Evered and Sadoogh-Abasian, 1979; [q] Sadoogh-Abasian and Evered, 1979; [r] Evered et al., 1980.

tems for certain compounds which exhibit apparent saturation kinetics, mutual inhibition and partial sodium dependency.

Kinetic Models of Drug Transfer

A number of schematic models for drug transfer from the oral cavity have been described in the literature. Beckett et al. (1968) proposed a kinetic model to describe the loss of amphetamine compounds from the oral cavity (Scheme 1) where k_1 and k_{-1} represent the forward and reverse rate constants for transfer between the oral cavity (A) and mucosa membranes (B), respectively, k_2 refers to the transfer rate constant between the mucosa membranes and blood (C) and k_3 represents a rate constant required to account for the slight absorption which occurred between 5 and 10 min contact times. Transfer of drug between compartments A and B (Scheme 1) was considered to be a reversible process since immediately after a buccal absorption test approximately 50% of 'absorbed' drug could be returned to the oral cavity by successive rinsing of the mouth with a pH 4.0 buffer. There was good agreement between analogue computer predicted amounts of the drug in compartment A and the experimental data points. Later, Beckett and Moffat (1970) suggested Scheme 2 to be a simpler and more useful compartmental model for oral cavity mucosa absorption. This model predicted a linear relationship between ln (absorption) and time, however, a linear relationship was not observed for any of 10 carboxylic acids studied (Beckett and Moffat, 1970). Return of acid from the oral cavity mucosa after a test was negligible, thus a reversible transfer step between compartments A and B could not explain the poor fit. Results were explained by volume and



Schemes 1–5.

pH changes which occurred during the test. Beckett and Moffat (1970) suggested that this simpler model (Scheme 2) may have given a good fit for the amphetamine data measured previously (Beckett et al., 1968), however, complete data analysis was not possible since the authors had neglected to measure volume and pH changes.

Dearden and Tomlinson (1971a) proposed a kinetic scheme for oral mucosa absorption which involved reversible protein-binding in the oral cavity (Scheme 3) where k_p and k_{-p} are the corresponding forward and reverse rate constants for protein-binding, respectively. Dearden and Tomlinson validated the model (Scheme 3) using a number of *p*-substituted acetanilides and suggested that the apparent return of drug from the oral cavity mucosa after a buccal absorption test was due to dissociation of protein-bound drug. Beckett and Pickup (1975) criticised the model of Dearden et al. (1971a) after studying the oral mucosa absorption of some steroids. Their data were satisfactorily explained by Scheme 1 (Beckett and Pickup, 1975). In contrast Temple and Schesmer (1978) used the scheme (Scheme 3) of Dearden and Tomlinson (1971a) to describe the buccal absorption of fomocaine.

Schumann and Turner (1978) examined the models of Dearden and Tomlinson (1971a) and Beckett and Pickup (1975) and their application to the oral mucosa absorption of propranolol. The authors pointed out that, although the models differed in their anatomical implications, drug disappearance from the oral cavity in both models could be described in terms of a biexponential function. In other words the disappearance functions derived from both Schemes 1 and 3 were identical, but the definitions of the parameters distinguished the models and the choice of which model was appropriate, based upon anatomical considerations.

Recently Scheme 4 has been used to describe successfully the disappearance kinetics of verapamil from the oral cavity during a buccal absorption test (Tucker, 1988).

Authors employing perfusion cell apparatus of the type depicted by Barsuhn et al. (1988) and Rathbone (1991) assume that drug transfer is unidirectional and there is negligible transfer between the buccal membrane and drug solution in the perfusion cell. Rates of drug loss from the buccal perfusion cells into the human buccal mucosa should therefore follow first-order kinetics. Excellent linearity of plots of ln(transferable concentration) versus time attested to the validity of these assumptions (Rathbone, 1991). Recently Rathbone (1990), using the buccal perfusion cell, has observed that disappearance of triprolidine hydrochloride could be described in terms of a biexponential function (Scheme 5) while a simpler scheme (Scheme 4) appeared to describe adequately the disappearance kinetics of propranolol.

Quantitative Analysis of Drug Transfer

Several attempts have been made in the literature to interpret quantitatively buccal absorption data reported by Beckett and Moffat (Beckett

and Moffat, 1968, 1969a,b, 1971). Lien et al. (1971) used regression equations to correlate buccal absorption data with partition coefficients. Ho and co-workers (Ho and Higuchi, 1971; Vora et al., 1972) used the physical model approach while Wagner and Sedman (1973) derived equations based on extraction theory.

Lien et al. (1971) correlated the buccal absorption test data of 31 acids and 10 bases (Beckett and Moffat, 1968, 1969a,b; 1971) with the log Pc, where Pc is the octanol/water partition coefficient of the drug. The authors demonstrated that loss from the oral cavity of these compounds was parabolically dependent on log Pc. The most important parameter in determining the loss of these compounds was their log Pc value. The extent of ionisation of the drug was also shown to play a role and results suggested that only non-ionised species transferred through the membrane. The ideal lipophilic character (log Pc) for maximum loss from the oral cavity was in the range 4.2–5.5 (Lien et al., 1971).

Ho and Higuchi applied the physical model approach (Suzuki et al., 1970a,b) to interpret the loss from the oral cavity of *n*-alkanoic acid derivatives (Ho and Higuchi, 1971) and *p-n*-alkyl phenylacetic, *p*-halogen phenylacetic and toluic acids (Vora et al., 1972) at various buffer pH values. The major assumption used by the authors was that the stagnant aqueous diffusion layer on the oral cavity side of the membrane was the rate-limiting step in transfer. Using a series of mathematical approximations the theory was successfully applied to buccal absorption test data with good agreement between experimentally observed values and theoretical predictions for the dependence of the apparent first-order rate constant for drug loss from the oral cavity, k_{obs}, on buffer pH. The theory attributed the greater rates of loss of the higher molecular weight acids exclusively to the higher partition coefficient of the acids. The shift to the right of the profiles for the homologous series relative to the dissociation curve were ascribed not only to the increase in lipid solubility but also to the presence of an aqueous diffusion layer on the oral cavity side of the lipoidal barrier (Ho and Higuchi, 1971).

Wagner and Sedman (1973) derived equations which described the rate of drug loss from the oral cavity of acidic and basic drugs as a function of pH and time based on extraction theory. In contrast to Ho and co-workers' theories (Ho and Higuchi, 1971; Vora et al., 1972) the equation was derived assuming the rate of transfer of non-ionised drug out of the membrane into the blood was the rate-limiting step in transfer. The equation successfully predicted k_{obs} versus buffer pH profiles for *ortho-*, *meta-* and *para*-toluic acids during a buccal absorption test. The authors also considered the case where not only non-ionised but also ionised drug species could partition into, through and out of the membrane (Wagner and Sedman, 1973). This resulted in a second equation which provided a better prediction for k_{obs} versus buffer pH profiles for a series of alkanoic acid derivatives during a buccal absorption test. The equation of Wagner and Sedman (1973) quantified the pH–partition hypothesis and has been shown to account for experimentally observed rates of drug loss from the oral cavity, the observed pH shifts and the limiting k_{obs} value for drug loss in a homologous series as the series is ascended. The analysis suggested that drug absorption during a buccal absorption test is rate-limited by the transfer of drug out of the membrane.

A comparison of these two models shows that both appear to be equally successful in quantifying the buccal absorption data of Beckett and Moffat, despite marked contrast in the underlying assumptions inherent in the models. The equal success does not mean that one theory is correct and the other incorrect, rather that the appropriate model cannot be chosen on the basis of the type of data which had been collected. Although we may obtain some information about the transport of non-ionised drug molecules across the oral cavity membranes by the use of regression equations as suggested by Lien et al. (1971), this method only provides a one point comparison at any one particular pH. The models of Ho and co-workers (Ho and Higuchi, 1971; Vora et al., 1972) and Wagner and Sedman (1973) offer the advantage that drug loss profiles for each of the drugs for the entire experimental buffer pH range studied may be generated.

Concluding Remarks

The buccal absorption test of Beckett and Triggs (1967) may provide a simple and reliable method for estimating drug loss from the oral cavity, however, because of the limitations of the technique, investigations can only provide qualitative information on the relationship between drug structure and membrane permeability. The recent introduction of perfusion cells (Barsuhn et al., 1988; Rathbone, 1990) that allow drug transfer kinetics to be reliably estimated across known areas of defined oral cavity membranes may provide investigators with a means of quantifying the complex interrelationships between these variables. Clearly some fundamental research in this area is still required.

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