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Buccal films: A review of therapy possibilities, treatment plans and appropriate evaluation techniques

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ABSTRACT

Due to apparent greater patient acceptance compared to buccal tablets and enormous therapeutic opportunities compared to traditional oral drug delivery methods, particularly for those who suffer from dysphagia, the potential of the mucoadhesive film technology is difficult to ignore. Despite this, there are currently no authorised mucoadhesive buccal films, and the translation of published literature into the commercial market is essentially non-existent. In order to help this patient-centred dosage form become more widely used, this review aims to give an overview of mucoadhesive buccal film technology and highlight crucial areas on which to concentrate scientific efforts. While discussing the patient-related aspects influencing the utilisation of various dosage forms, a number of indications and development potential were noted. A technical description of the processes used to create these films, including solvent casting, hot melt extrusion, inkjet printing, and three-dimensional printing, was also offered. The utilisation of more than thirty mucoadhesive polymers in film formulations was found, and information about their mucoadhesive properties as well as their inclusion with other essential formulation ingredients was supplied.

Keywords: *Mucoadhesive films; Buccal film; Buccal drug delivery; Oral physiology; In-vitro evaluation; Patient-centric formulation development; Physiological relevance.*

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INTRODUCTION

In recent years, the scientific community has begun to recognise the importance of the patients themselves in the drug development process giving rise to the term 'patient-centricity' [1]. In pharmaceutics this can be enhanced through the re-formulation of medicinal products, which presents an attractive strategy to drug developers due to lower costs, shorter development durations, and decreased incidences of product failure, as authorised drugs have proven safety in pre-clinical models and human trials [1]. For example, the re-formulation of orally administered tablets into buccal drug delivery systems for patients who suffer from dysphagia. Buccal drug delivery refers to the administration of drugs to the buccal mucosa, located on the inside of the cheek within the mouth, and is capable of facilitating both local and systemic drug delivery [2]. This route avoids first-pass metabolism, enzymatic drug degradation, and it provides effective therapy to patient groups unable to swallow or with swallowing difficulties [3]. Of the limited dosage forms in this area, buccal tablets have the greatest presence within the commercial marketplace. However, mucoadhesive buccal films are believed to be the favoured dosage form amongst patients when compared to buccal tablets, owing to their superior flexibility which enhances comfort, in addition to a customizable size [2]. Such films are comprised of multiple layers and are predominantly indicated for prolonged drug release within the oral cavity [4].

Despite the therapeutic potential of the buccal route of administration it is underutilised, evidenced by the lack of translation from published work into the commercial marketplace. Though there is no direct correlation between published work and the commercial arena, the scarcity of commercially available buccally administered formulations is thought to be due to the lack of compendial and physiologically relevant evaluative methodologies to properly characterise developed dosage forms in vitro [5,6].

Therapeutic opportunities for mucoadhesive buccal films

Due to the wide-ranging applicability of mucoadhesive buccal films, there are many therapeutic and clinical opportunities whereby the mucoadhesive buccal film technology can be utilised to deliver quality, efficacious and safe therapy. Figure 1 illustrates the different therapeutic areas and diseases for which mucoadhesive buccal films have been developed in the literature [7–9]. Following (Figure 1) clockwise, it can be seen that mucoadhesive films are preferentially indicated for use in cardiovascular and inflammatory diseases, potentially to overcome the low oral bioavailability of beta-blockers such as propranolol hydrochloride and carvedilol as a result of extensive hepatic first-pass metabolism [10,11]. Although it is also possible that the authors cited here, are simply demonstrating the feasibility of the mucoadhesive buccal film technology, without such consideration for the therapeutic area that the active agent corresponds to.

Mucoadhesive buccal films and special patient populations

Mucoadhesive buccal films represent a clear therapeutic advantage in special patient populations (paediatric and geriatric age groups), due to the prevalence of dysphagia and instances of swallowing difficulties [12]. In the paediatric population, this has been associated with respiratory disorders, cardiac disorders, gastrointestinal disorders, neurological disorders, congenital abnormalities, maternal and perinatal issues, iatrogenic complications, and caustic injuries [13]. Swallowing difficulties in this population are also a consequence of the developmental process [14], resulting in the use of different dosing aids e.g. oral syringe [15]. Ostrom, Meltzer, and Welch demonstrated that a vast majority of children aged between 6 and 11 years old were able to swallow a small oral tablet [16], while Bracken et al. demonstrated that most children aged 4–8years successfully swallowed tablets upon attempting to do so [17].

Mucoadhesive buccal films and personalised medicine

Conventional mass-produced dosage forms, such as tablets and capsules are beginning to be recognised as sub-optimal in terms of their effectiveness in treatment. This is due to the inherent differences between patients, inflexible dose strengths and the problematic nature of adjusting drug doses within oral-solid dosage forms (i.e., tablet splitting) [18]. This leaves the present 'one size fits all' approach to treatment inefficient, echoed by a UK National Health Service report published in 2016, which stated that personalised medicine (tailored treatment to match an individual patients' therapeutic needs) is the future of medicine [19]. Figure 2 illustrates the differences between conventional and personalised therapy.

Opportunities for developing countries

Access to medicines is a much-discussed topic within the literature and is a concern for approximately 33% of all people globally [20]. The World Health Organisation has published a list of essential medicines for children up to 12 years old (350 total) and for individuals above (479 total) to shape the acquisition and supply of essential medicines at both the national and local levels around the world [21,22]. However only 2 out of the 829 products mentioned in this published information are indicated for buccal administration and both are oro-mucosal solutions of midazolam [23,24].

Patient-related factors influencing mucoadhesive film development

The therapeutic needs of patients should be prioritised when developing medicines. Although this is often the case, there are typically more confounding factors that influences the performance of drug products that developers may be aware of or are willing to thoroughly explore during the development process. It is therefore necessary to design effective, quality and safe dosage forms with patient physiology, and the various factors that may influence physiological characteristics in mind. In addition to the effects of concomitant medications and/or drivers of patient acceptability in order to increase the likelihood of positive therapeutic outcomes.

Oral physiology influencing buccal drug delivery

Thorough consideration of oral physiology can be used to inform the development process of the dosage forms that reside in the mouth, and aid in overall dosage form knowledge which may be passed down to patients via their healthcare professionals or included in patient information leaflets. The fundamental outline of oral anatomy and oral physiology has been reviewed extensively [25], therefore only the physiological characteristics that have been adjudged to underpin buccal drug delivery and the factors influencing these characteristics will be discussed here.

Pathological influences on buccal drug delivery

As mucoadhesive buccal films reside in the oral cavity, it follows that diseases affecting the oral cavity will also influence the effectiveness of mucoadhesive buccal films. One example of this being oral mucositis whereby a low salivary flow rate was believed to be a risk factor in patients targeted to receive 5-fluorouracil indicated for chemotherapy [26]. Additionally, complications relating to the jugular vein would likely influence the systemic absorption of drugs administered buccally. Slow blood flow was shown to be majorly caused by internal jugular valve incompetence, whereas increased turbulent flow was

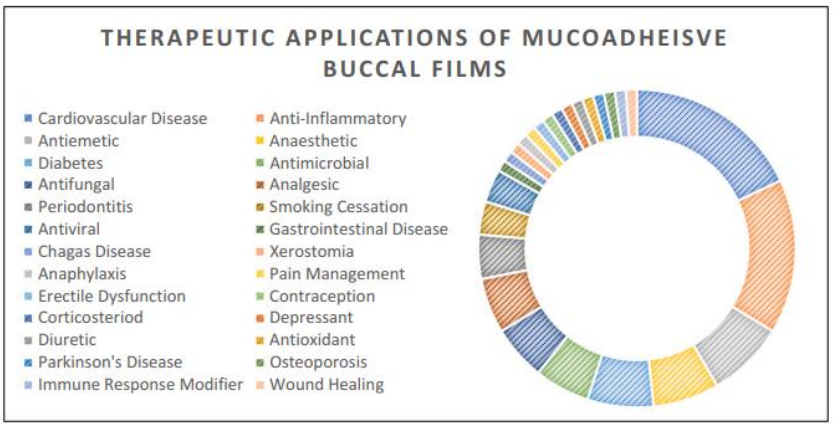

Figure 1: Diagram Illustrating the Therapeutic Areas and Diseases where the use of Mucoadhesive Buccal Films have been demonstrated [17–19].

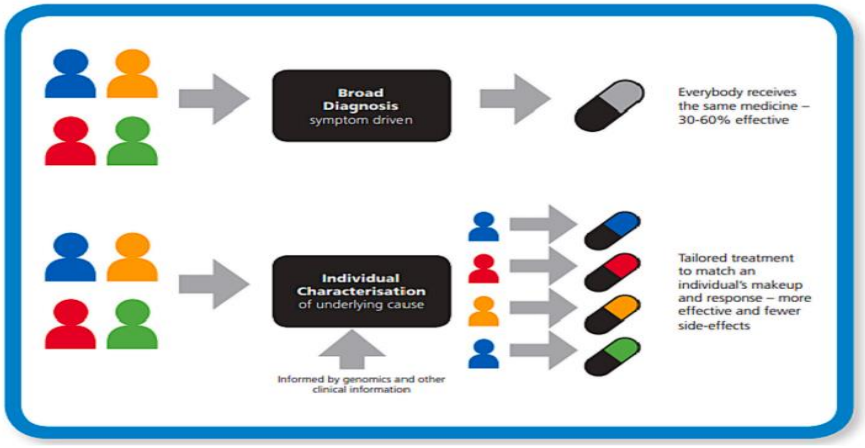

Figure 2: Diagram illustrating the differences between conventional therapy and personalised therapy [24].

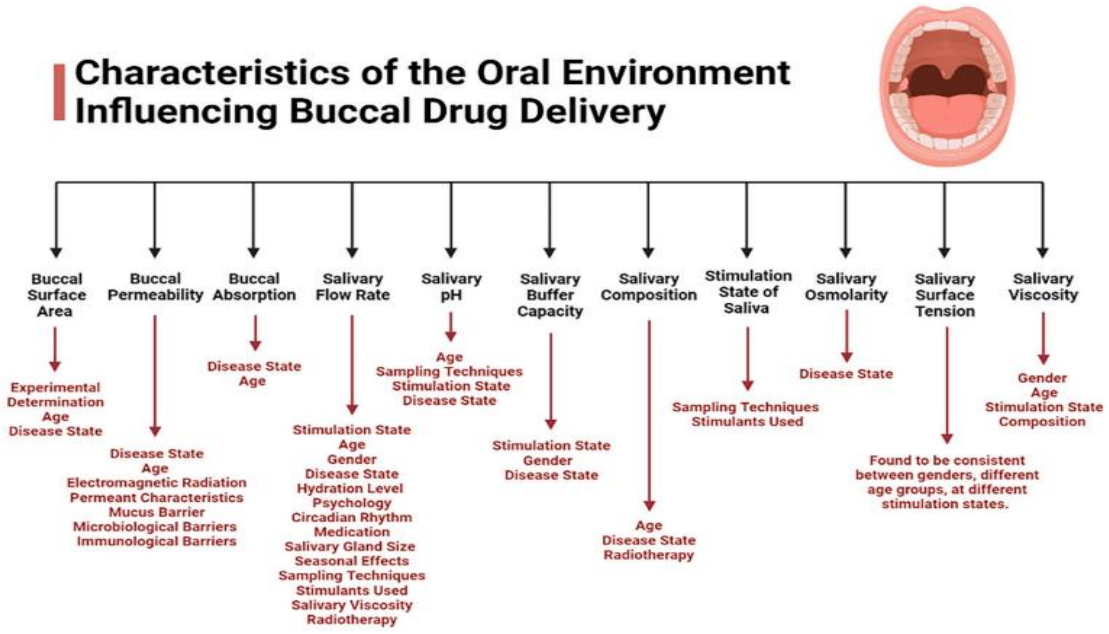

Figure 3: Overview of the characteristics of the oral environment relevant to buccal drug delivery (black) and the factors that influence them (red) [29,30].

found in patients with hyperthyroidism as well as women during pregnancy [27]. The causes for pulsatile turbulent jugular venous flow have been attributed to arteriovenous malformation and carotid-cavernous fistula [28].

The influence of concomitant medications and instances of polypharmacy

It may be tempting to consider one therapeutic intervention, such as a mucoadhesive buccal film, in

Table 1: Theories of Mucoadhesion

Theory	Brief Description
Wetting	Adhesion is instigated by material penetration into the surface irregularities of mucus. Material hardening then occurs yielding adhesive connections. This theory is applicable to mucoadhesive materials of low viscosity.
Electrostatic	At the interface between mucus and the mucoadhesive material, electron transfer occurs, resulting in an electrical double layer at the interface with attractive forces maintaining adhesion.
Diffusion	Mucoadhesive polymeric chains interact with glycoprotein mucin chains, and as a result of penetration (diffusion), leads to the formation of a semi-permanent bond which maintains adhesion.
Adsorption	After the contact stage of mucoadhesion, adhesion is due to surface forces on the materials in question. Adhesion is therefore maintained by intermolecular forces (hydrophobic bonding, hydrogen bonding and van der Waal's forces).
Fracture	This theory can be thought of as the amount of force that is required to separate two adhered surfaces. This theory provides the rationale for the *in vitro* analysis of mucoadhesive strength with a texture analyser.

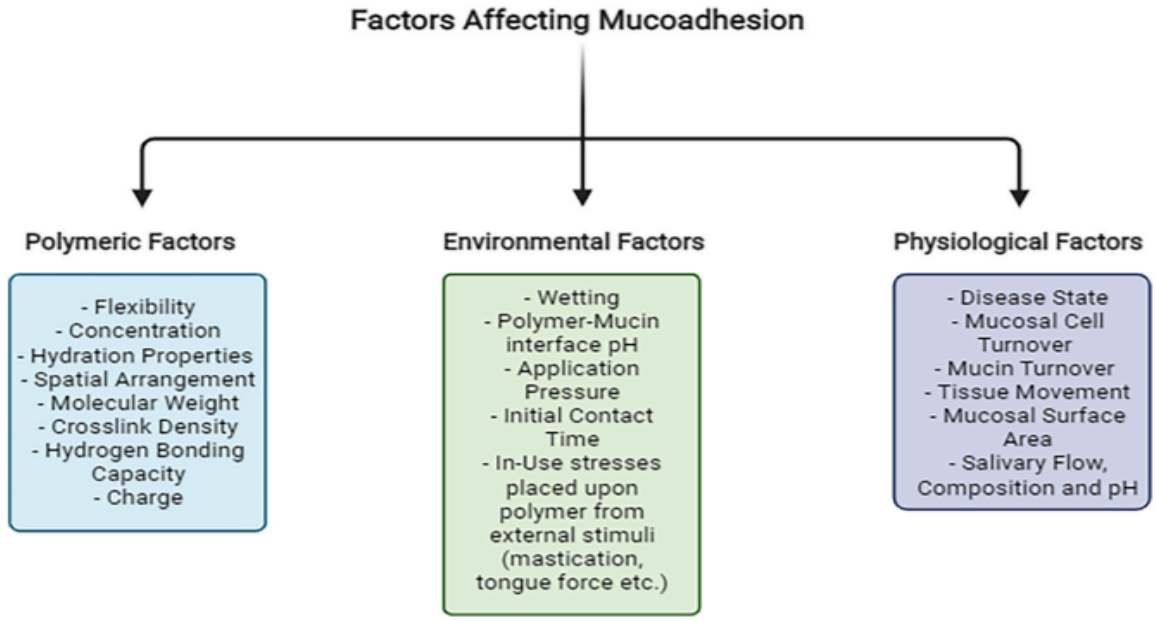

Figure 4: Diagram illustrating the polymeric, physiological and environmental factors affecting mucoadhesion [48].

isolation and envisage a treatment regimen whereby patients take this single medication. However, this is seldom the case. In an NHS Health Survey conducted between 2015 and 2016, 24% of adults were found to be concomitantly taking at least three or more medicines [31]. There is also a widely accepted correlation between increasing age and the number of medications administered, with 48% of adults shown to be administering at least one prescribed medicine (not including contraception or nicotine replacement therapy) over the course of a week. This increased from 19% of young adults aged 16 to 24 to more than 90% of those aged 75 and over [32]. It has been seen that ageing can alter both the quantity and quality of saliva, denoted by its ion/protein composition [33]. This is potentially a result of the larger number of drugs administered by individuals in this age group and the likelihood of polypharmacy compared to younger age groups, evidenced by the NHS Health Survey [34].

Drivers of patient acceptability for mucoadhesive buccal films

Patient acceptability is a well-discussed concept within pharmaceutics. However, there is often a disconnection between what developers perceive to be drivers of patient acceptability of a particular dosage form and what actually drives acceptability. Robust and reproducible acceptability studies should be carried out when developing dosage forms to characterise the key acceptability determinants within a targeted patient population, as the drivers of

acceptability are not consistent throughout all patient populations. For example, in the paediatric population maximising taste, smell and palatability are critical acceptability parameters [35].

An overview of the mucoadhesive film technology

As discussed, mucoadhesive buccal films are multi-layered systems designed for prolonged drug release into the oral cavity [36]. Mucoadhesive buccal films, which adhere to the buccal mucosa, are often bundled in to include mucoadhesive films which adhere to different areas of the oral cavity, like the sublingual or gingival mucosa. It may be more appropriate to define mucoadhesive films of this nature by the area of mucosa to which they adhere, such as sublingual films [37] or gingival films [38], respectfully. Additionally, orodispersible films are another type of film formulation that is applied to the oral cavity [39], and is designed for rapid release and subsequent absorption primarily in the gastrointestinal tract [40].

Mucus and mucoadhesion

Mucus, or at least the salivary mucus of interest here, is secreted by the major and minor salivary glands and acts as a protective coating on epithelial surfaces [41]. This protective layer is comprised of water, enzymes, electrolytes, glycoproteins and mucins [42]. Mucins are a collection of glycosylated proteins and are the primary gel forming components of mucus, responsible for its viscoelasticity [43]. Mucins are made up of basic units (approximately 400–500 kDa) linked together forming an extended 3D network [44]. At the physiological pH level, this network carries a net negative charge, forming a cohesive gel which binds to the buccal epithelial surface [45]. It is this gelatinous nature that is believed to facilitate the adhesion of mucoadhesive drug delivery systems, and subsequent delivery of drugs across the buccal membrane [6].

The formulation of mucoadhesive buccal films

Research carried out for this review identified 88 mucoadhesive buccal film formulations in the literature [46,47], which were captured according to the mucoadhesive polymers used, the chemical characteristics that provided their mucoadhesive functionality, their commercial availability, their use alongside other key film formulation constituents, and details of their effect on *in-vitro* drug release properties.

CONCLUSION

This review has sought to bring attention to the development of mucoadhesive buccal films, given their patient-centric nature and the significant therapeutic opportunities that may come from wider adoption of the technology. It is clear that patients themselves, and their individualised characteristics should be at the forefront of drug development decisions, and the information discussed here should aid in the development of mucoadhesive buccal films with patients in mind. Progress with regards to enhancing the physiological relevance of *in-vitro* methodologies to evaluate mucoadhesive films in the areas of drug dissolution, mucoadhesion and drug permeability represent significant achievements, which are underpinned by consideration, characterisation and understanding of the complexity of biological fluids such as saliva, as well as the innate complexity of human biological membranes and their properties. This information may lead to better translation from in vitro evaluation to in vivo studies and human clinical trials for mucoadhesive buccal films and other buccal drug delivery systems which may lead to a greater presence within the commercial marketplace.

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