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Review article

Buccal films: A review of therapeutic opportunities, formulations & relevant evaluation approaches

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ABSTRACT

The potential of the mucoadhesive film technology is hard to ignore, owing to perceived superior patient acceptability *versus* buccal tablets, and significant therapeutic opportunities compared to conventional oral drug delivery systems, especially for those who suffer from dysphagia. In spite of this, current translation from published literature into the commercial marketplace is virtually non-existent, with no authorised mucoadhesive buccal films available in the UK and very few available in the USA. This review seeks to provide an overview of the mucoadhesive buccal film technology and identify key areas upon which to focus scientific efforts to facilitate the wider adoption of this patient-centric dosage form. Several indications and opportunities for development were identified, while discussing the patient-related factors influencing the use of these dosage forms. In addition, an overview of the technologies behind the manufacturing of these films was provided, highlighting manufacturing methods like solvent casting, hot melt extrusion, inkjet printing and three-dimensional printing. Over thirty mucoadhesive polymers were identified as being used in film formulations, with details surrounding their mucoadhesive capabilities as well as their inclusion alongside other key formulation constituents provided. Lastly, the importance of physiologically relevant *in vitro* evaluation methodologies was emphasised, which seek to improve *in vivo* correlations, potentially leading to better translation of mucoadhesive buccal films from the literature into the commercial marketplac.

1. 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]. The development of such methodologies is reliant on thorough understanding of the physiological environment where buccally administered dosage forms reside, as well as the various factors that may influence physiological characteristics. Biological fluids such as saliva have innumerable characteristics which may not be fully understood and are not considered in the majority of *in vitro* dissolution

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analyses of buccal dosage forms. In addition, the complexity of human biological membranes such as the buccal mucosa are poorly represented within *in vitro* mucoadhesion and permeation evaluations. The heterogeneity between patients, from the very young to the old-aged who are affected by variable disease status and multi-morbidities, renders it a big ask to develop a singular 'one size fits all' *in vitro* methodology for the characterisation and evaluation of buccal delivery systems. However, the availability of alternative dosage forms (solutions, syrups *etc.*) specifically indicated within special populations, may also be contributory to the lack of commercial realisation of the mucoadhesive film technology.

This review was centred on mucoadhesive buccal films, and discusses the patient-related physiological, pathological and pharmacotherapeutic factors which underpin their development. The formulation, manufacturing, and *in vitro* evaluation of mucoadhesive films was also considered, focusing on *in vitro* mucoadhesion, permeability, and dissolution evaluations, and the attempts to enhance their physiological relevance.

2. 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. Fig. 1 illustrates the different therapeutic areas and diseases for which mucoadhesive buccal films have been developed in the literature [7–94]. Following Fig. 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 [95,96]. 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.

2.1. 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 [97]. 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 [98]. Swallowing difficulties in this population are also a consequence of the developmental process [98], resulting in the use of different dosing aids *e.g.* oral syringe [99]. 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 [100], while Bracken et al. demonstrated that most children aged 4–8 years successfully swallowed tablets upon attempting to do so [101]. These results, however, are based on individual populations of children and are subject to variability, which makes the definition of an age from where children can definitively swallow tablets problematic. Difficulty in swallowing may be a prominent issue in geriatric patients who are >65 years old, which emphasises the requirement for alternative routes of administration, such as the buccal route. Dysphagia in this population has been referred to as a distinct geriatric syndrome, due to increased incidences of multimorbidity and polypharmacy [102], which may also induce dry mouth [103]. Therefore, the development of buccal delivery systems requires special consideration in this age group. Both the geriatric and paediatric populations are thought of as heterogeneous age groups, where marked differences in the chronological ageing process can be seen amongst people due to their lifestyle, genetic make-up, and overall health [104]. Heterogeneity is more prominent in the older population as a result of this [105]. This heterogeneity amongst individuals within these age populations suggests there is a need for the personalisation of treatment regimens, which is thought can be achieved through 3D printing technologies [106].

Situational swallowing related difficulties can occur in the form of hyperactivity and unconsciousness, whereby mucoadhesive buccal films can be deployed to illicit effective therapy in these situations. This is evidenced by the development of a rapidly dissolving mucoadhesive buccal films containing diazepam, indicated for the treatment of seizures, currently pending FDA approval [107]. Additionally, being advantageous with respect to the administration of injectable formulations in instances whereby seizures occur in environments away from trained healthcare professionals in terms of safety.

2.2. 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

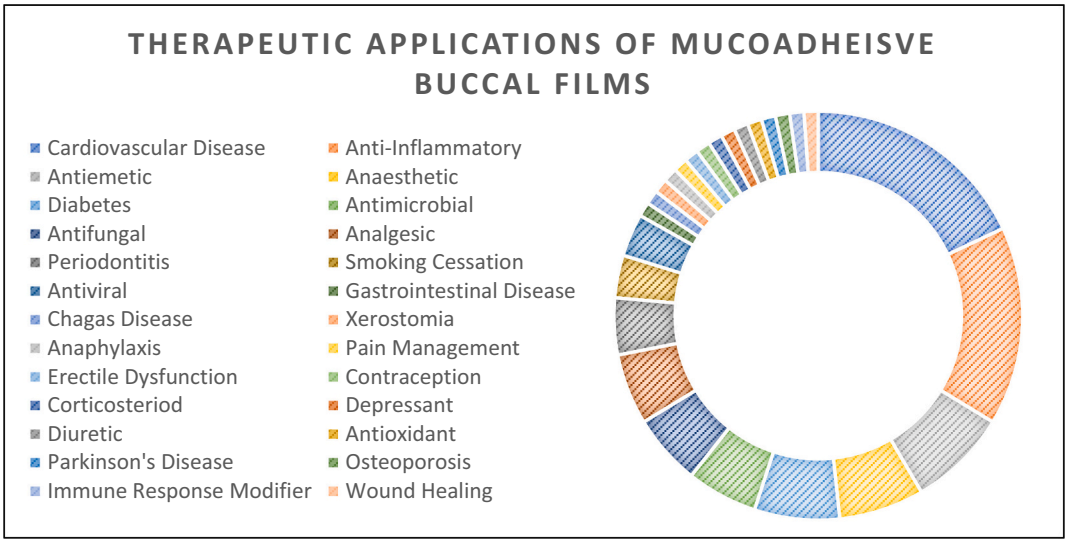

Fig. 1. Diagram Illustrating the Therapeutic Areas and Diseases where the use of Mucoadhesive Buccal Films have been demonstrated [7–94].

adjusting drug doses within oral-solid dosage forms (*i.e.*, tablet splitting) [108]. 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 [109]. Fig. 2 illustrates the differences between conventional and personalised therapy.

As a result of this, the use of three-dimensional (3D) printing in pharmaceutics has become a hot topic in recent years. In the not-so-distant future, there are expectations that benchtop 3D printers could become commonplace in clinical environments such as pharmacies and/or hospitals in order to dispense medicinal products based on individual patient needs [106]. This technology has also found use in the production of mucoadhesive buccal films, enabling dosage form personalisation, which will be discussed later [106].

2.3. 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 [110]. 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 [111,112]. 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 [111,112].

Not only is rice the most popular staple food in the world, yielding in excess of 500 million tonnes per year, rice starch has been used to produce mucoadhesive films [113]. There are over 240,000 registered varieties of rice in the world and due to different country or region-specific growth environments, this results in many varieties of rice starch with unique characteristics [113]. A higher ratio of amylose to amylopectin within the rice starch is thought to produce films with superior mechanical properties [113]. Owing to the abundance of rice in developing countries, local governmental initiatives to encourage the development of mucoadhesive films utilising rice starch can be proposed, which may translate to improved medicines access for patients in these countries. Additionally representing an environmental and economic advantage over the production of plastics [113].

Despite helpful governmental initiatives, the challenge of medicine and healthcare access remains multi-factorial. Peters et al. summarised four key access-related considerations which were as follows: a) geographic accessibility, b) the availability of appropriate care and interventions for those who need it, c) financial accessibility, and d) how expectations of services are satisfied by healthcare providers [114]. For a further elaboration of this summary, readers are directed to Peters et al. [114]. Innovation in this area has taken the shape of partnerships, intellectual property, and pricing stimuli to improve equity in access [110]. Stevens and Huys state that stakeholders should prioritise engaging in partnerships which facilitate the promotion of knowledge and technology transfer across the manufacturing, authorisation and subsequent distribution of medicines at affordable prices in appropriate conditions [110].

3. 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.

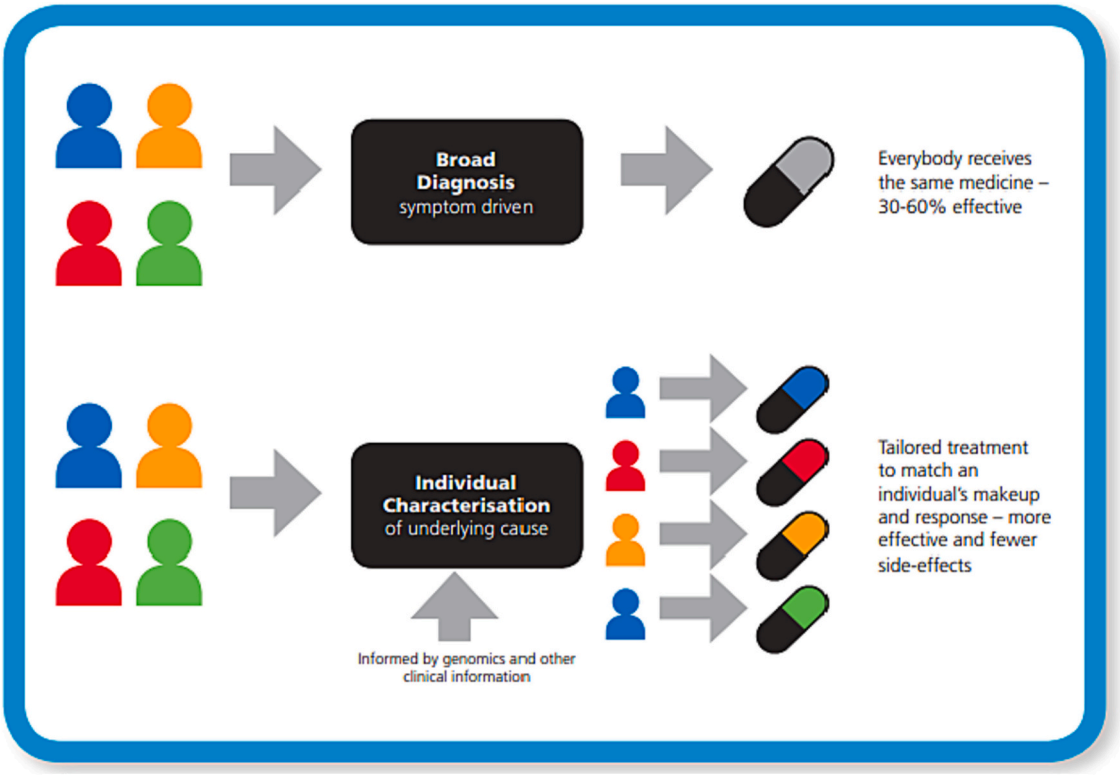

Fig. 2. Diagram illustrating the differences between conventional therapy and personalised therapy [109].

3.1. 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 [6,115–118], therefore only the physiological characteristics that have been adjudged to underpin buccal drug delivery and the factors influencing these characteristics will be discussed here.

Human saliva is comprised of approximately 99% water, in addition to various enzymes, mucins, inorganic ions, electrolytes, and other small molecules [119,120]. The composition of saliva is important to drug delivery as salivary components may influence drug dissolution and absorption [120]. The pH of human saliva is known to be variable. Should the pH of saliva fall outside the physiologically typical range, it is an indicator of poor oral health [121]. When developing buccal drug delivery systems, attention should be paid to the salivary pH, as alterations and variations in salivary pH may induce drug ionisation [122]. Salivary buffer capacity not only ensures the maintenance of salivary pH, but also plays a role in overall oral health through bacterial growth reduction and aiding in dental remineralization [123]. Saliva is buffered by four key systems: 1) the protein system, 2) the phosphate system, 3) the urea system, and 4) the bicarbonate system [124].

The drug dissolution and absorption from mucoadhesive buccal films is facilitated by the continuous flow of saliva over the dosage form surface [122,125]. A mouth that is dry could ultimately reduce the amount of drug that ends up in the systemic circulation, and *vice versa* [122]. Olfactory, gustatory, and mechanical stimulation of saliva can occur, affecting salivary characteristics such as the pH, buffer capacity, and obviously salivary flow rate [5]. Therefore, the stimulation state of saliva is an important physiological characteristic that can influence buccal drug delivery [5]. Salivary osmolarity refers to the concentration of electrolytes per litre of saliva and is believed to play a role in hydration status [126]. The surface tension of saliva is thought to affect the dissolution rate of dosage forms that are administered to the oral cavity, with a high interfacial tension reducing the wettability of drug particles and consequently reducing the drug dissolution rate [120]. An increased salivary viscosity could increase the boundary layer thickness and decrease the diffusion coefficient of the drug molecule when compared to a medium of lower viscosity [120]. Hence, decreasing the rate of drug dissolution [120].

The surface area of the buccal mucosa plays an important role in buccal drug delivery as it influences the area available for delivery systems to be applied to and consequently for drug absorption. Buccal surface area has historically been determined using an aluminium foil technique developed by Dawes and Collins who determined the total surface area of adult oral mucosa to be 214.7 cm^2, and by Dawes and Watanabe who determined a group of 5-year-old children's total oral mucosal surface area to be 117.6 cm^2 on average [127,128]. In addition, Dawes and Collins also estimated the salivary film covering the buccal mucosa to be between 70 and 100 μm thick, based on available volumes of saliva before and after swallowing [127]. It has been shown that the main barrier to drug permeation across the oral mucosa are the superficial epithelial cells, when compared to that of the submucosal space [129]. Nevertheless, it is believed that the buccal epithelium is 4-4000 times more permeable than the skin [130]. Small, lipophilic molecules are able to permeate paracellularly, while small hydrophilic molecules permeate transcellularly [131]. The tight junctions present within the buccal epithelium and enzymatic action of the mucus layer coating the epithelium represent barriers to large macromolecules such as proteins and/or peptides [132]. For drug molecules to be able to travel through the oral mucosa, the drug must initially diffuse through the lipophilic cell membrane, and subsequently pass through the hydrophilic interior of the oral epithelial cells [132]. It can be said that lipophilic compounds exhibit superior permeability coefficients than hydrophilic compounds, but inferior aqueous solubility [132]. Therefore, the amount of a lipophilic drug that is absorbed may not be as high as expected due to high hydrophobicity [132]. Systemic absorption of buccally administered formulations is facilitated by the distribution of drug molecules throughout the body into the systemic circulation *via* the jugular vein thus avoiding hepatic first pass metabolism [133].

It is worth noting that a lot of the parameters discussed here have knock on effects amongst each other. For example, the use of salivary stimulants increases salivary flow rate, decreases the ionic concentration of saliva, increases salivary pH, and decreases the viscosity of saliva. Fig. 3 displays the discussed physiological characteristics of the oral cavity relevant to buccal drug delivery (black) and the various factors which may affect them (red) and hence, influence the buccal administration of medicinal products. This review has not included the normal and abnormal ranges of the aforementioned physiological characteristics, and the readers are directed to Wolmer et al. who have conducted an extensive literature review of 357 paediatric studies and 195 adult studies relating to oral and gastrointestinal physiology relevant to drug absorption [119]. Wolmer et al. also proposed ranges for basal and stimulated salivary pH, salivary flow rate, and highlight the lack of data available within the new-born, infant, and toddler paediatric age groups with regards to oral physiology [119]. No such characterisation was found for the geriatric population.

3.2. 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 [142]. 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 found in patients with hyperthyroidism as well as women during pregnancy [143]. The causes for pulsatile turbulent jugular venous flow have been attributed to arteriovenous malformation and carotid-cavernous fistula [143].

In the paediatric population, Wollmer et al. described how diseases such as asthma, caries, cerebral palsy, congenital heart disease, cystic fibrosis, diabetes mellitus, down syndrome, juvenile idiopathic arthritis, malnutrition, moebius syndrome and obesity affect salivary properties such as pH, buffer capacity, flow rate, composition osmolarity as well as oral transit time despite most of these disorders being non-specific to the oral environment [119]. However, within the geriatric population the most relevant issue is xerostomia (dry mouth). Xerostomia is thought to affect 1 in 4 people and is related to salivary gland hypofunction owing to anxiety, infection, low hydration, drug effects, birth defects, Sjögren's syndrome, HIV/AIDS and radiotherapy, amongst other causes [144]. Xerostomia is seen as a confounding factor in the development of orospecific pathologies such as dental caries, periodontal disease, candidiasis, ulceration, and even dysphagia [134]. Although, the major cause of xerostomia is widely considered to be the administration of xerogenic drugs [103]. It is therefore difficult to ascertain whether it is the diseases themselves, or the medications indicated to treat the diseases that promote xerostomia and alter salivary properties in the geriatric population.

3.3. 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 isolation and envisage a treatment regimen whereby patients take this single medication. However, this is

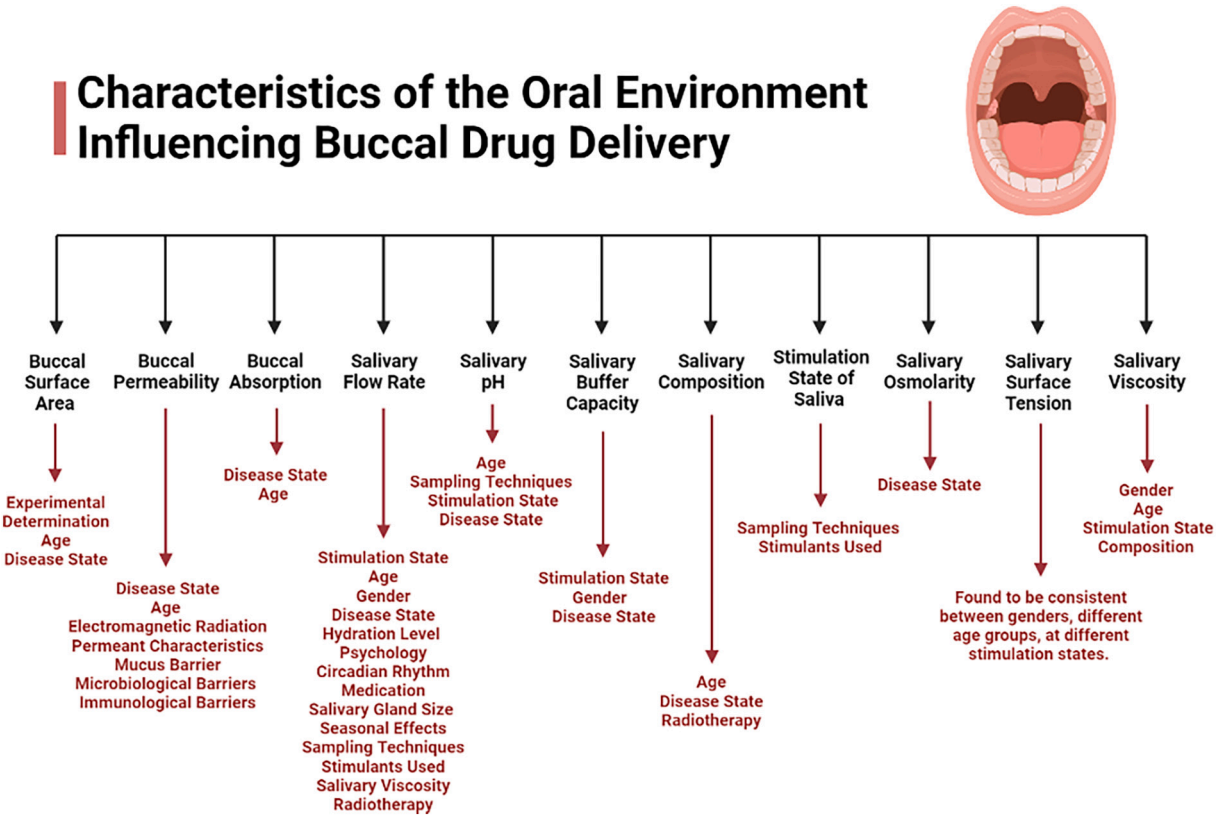

Fig. 3. Overview of the characteristics of the oral environment relevant to buccal drug delivery (black) and the factors that influence them (red) [119,120,134–141]. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 [145]. 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 [145]. It has been seen that ageing can alter both the quantity and quality of saliva, denoted by its ion/protein composition [134]. 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 [145,146].

There is an extensive list of drugs that have been shown to induce dry mouth, therefore polypharmacy may not be the sole cause – it may just be that instances of polypharmacy increase the likelihood of administering a xerogenic medication. Schwartz and Sreebny have identified over 400 xerogenic drugs in 42 therapeutic categories and 56 subcategories [147]. This information was compiled primarily using the 1996 Physicians' Desk Reference (PDR) which is a compilation of pharmaceutical manufacturers' drug package inserts derived from the results of phase three clinical trials, however they acknowledge that the PDR does not contain information surrounding the salivary flow rates of affected individuals therefore the xerogenic effect of listed drugs is unable to be quantified [147].

3.4. *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 [105]. Whereas, for older or geriatric patients the ability to safely swallow medicine is crucial to guard against an inherent fear of choking [105]. Therefore, it can be said that mucoadhesive films are more attuned to geriatric patient preferences in addition to their therapeutic needs. Despite this, a cursory understanding of age-group associated preferences alone is not sufficient to characterise patient acceptability which requires robust evaluation in distinct patient populations in order to inform dosage form development.

Published literature on the acceptability of mucoadhesive buccal films is scarce [148], and so, some of the drivers of acceptability of mucoadhesive buccal films discussed here will be based on perceived logic and inferences from literature, rather than from a definitive study regarding the acceptability of mucoadhesive buccal films in targeted patient populations. Mucoadhesive buccal films represent a clear perceived advantage over buccal tablets, owing to superior flexibility [2]. Consideration should also be given to the pH at the film surface, which should not differ from the physiological pH of the oral mucosal surface too significantly as to minimise irritation [149]. As mucoadhesive buccal films are typically indicated for prolonged drug release, consideration should also be given to the duration of treatment, and the perceived invasiveness of the adhered film which is a problem not encountered in fast-dissolving orodispersible films [150] or typically faster dissolving sublingual films [151]. Another important factor to consider is the patient perception of the dosage form, regarding safety concerns with respect to normal food and drink intake and the potential of detachment and subsequent choking. Mucoadhesive buccal films are able to be produced *via* 3D printing, however one study has shown that

older patients have doubts surrounding the novel technology when compared to established dosage form manufacturing techniques [152]. Key points of scepticism were appearance, physiological processes such as swallowing, product handling, process knowledge, and pre-conceptions surrounding the technology [152]. The dosage forms evaluated here were tablets, in a sample size of 8, so this data alone is not sufficient to characterise acceptability of the 3D printing technology as a whole, and only bears slight relevance to acceptability in mucoadhesive buccal films [152]. Other points worth considering are the administration convenience in comparison to tablets, the ease of dosage form application and subsequent removal if the mucoadhesive film is not biodegradable, the film dimensions which may influence dosage form perception, and the in-mouth feel of the film which will likely be a new experience for a prospective patient that may require acclimation to.

4. 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 [4]. 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 [151] or gingival films [153], respectfully. Additionally, orodispersible films are another type of film formulation that is applied to the oral cavity [150,154], and is designed for rapid release and subsequent absorption primarily in the gastrointestinal tract [4].

4.1. 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 [155]. This protective layer is comprised of water, enzymes, electrolytes, glycoproteins and mucins [156]. Mucins are a collection of glycosylated proteins and are the primary gel forming components of mucus, responsible for its viscoelasticity [157]. Mucins are made up of basic units (approximately 400–500 kDa) linked together forming an extended 3D network [158]. At the physiological pH level, this network carries a net negative charge, forming a cohesive gel which binds to the buccal epithelial surface [6]. 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].

Mucoadhesion refers to an instance whereby two materials, one of these being mucus, are held together by interfacial forces of attraction [159]. The other material is usually a polymeric material with mucoadhesive capabilities. The mucoadhesion process occurs in two stages – contact and consolidation [160]. The ‘contact’ stage is where the mucoadhesive substance first meets the mucus covered membrane [160]. Here, mucus wets the material then ‘consolidation’ occurs [161]. This is where the mucoadhesive substance is joined to the mucus membrane due to physicochemical forces of attraction resulting in mucoadhesion [160]. There are various theories regarding the phenomenon of mucoadhesion, and such theories are outlined in Table 1. The mucoadhesion process is also dependent on a combination of polymeric, environmental and physiological factors which are outlined in Fig. 4. It is worth noting that a combination of theoretic modes of adhesion are seen in practice, with neither theory acting alone, something often overlooked in the literature.

Table 1
Theories of Mucoadhesion [159,162].

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.

4.2. The formulation of mucoadhesive buccal films

Research carried out for this review identified 88 mucoadhesive buccal film formulations in the literature [7–94], 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. This data is available in Table 2 and emphasises the potential of the mucoadhesive film technology for buccal drug delivery, which is not limited to the number of film formulations identified.

Mucoadhesive polymers are natural or synthetic polymeric substances that facilitate the adherence of a buccal drug delivery system to the buccal mucosa enabling the delivery of an API. Such polymers usually possess functional groups with hydrogen bonding capability, sufficient anionic or cationic charge potential, high molecular weight, sufficient flexibility of the polymer chain, and characteristics that enable wetting of mucus, plus other desired attributes of pharmaceutical polymers (*i.e.*, non-toxic, readily available, and cost-effective) [162]. The theories of mucoadhesion discussed earlier are directly related to the properties and functionalities of mucoadhesive polymers. For example, cationic chitosan, owing to its positive charge is believed to adhere to mucus membranes through electrostatic interaction between the opposing charges on the mucus [162]. While non-ionic mucoadhesive polymers such as poly (vinyl) alcohol, adhere to the mucus by penetrating into the mucus gel, in line with the diffusion theory of mucoadhesion [162]. Thiolated polymers or thiomers on the other hand, facilitate mucoadhesion through the formation of covalent disulphide bridges between cysteine rich domains of mucin subunits [162].

It is rare to find a single mucoadhesive polymer used within a mucoadhesive buccal film formulation. More often, a polymer blend is typically utilised to illicit not only favourable mucoadhesive properties but also a favourable drug release profile, desired mechanical properties, and other physicochemical properties [163]. For example, Kumria et al. utilised hydroxypropyl methylcellulose (HPMC) K15M, Carbopol 940, and Eudragit NE 40D as a polymer blend when developing mucoadhesive films loaded with prednisolone [81]. They found that altering the polymer content was able to control drug release by altering the amount of Carbopol used [81]. Kumria et al. surmised that the retardation of drug release from the increase in concentration of Carbopol was due to increased swelling capabilities of these hydrophilic polymers, creating a cohesive gel barrier to drug diffusion [81]. Additionally, Al-Dhubiab et al. formulated a mucoadhesive buccal film loaded with almotriptan, indicated for the treatment of migraines, using Proloc™ 15 (waxy maize starch (85% *w*/w), carbomer (15% w/w)) and Eudragit RL100 as the mucoadhesive polymeric blend [85]. In terms of *in vitro* drug release, rapid release was demonstrated by formulations with lower Eudragit RL100 concentrations and higher Proloc™ 15 concentrations, due to the hydrophilicity of Proloc™ 15 compared to the water insoluble Eudragit RL100 [85].

Mucoadhesive polymers and their concentrations within a

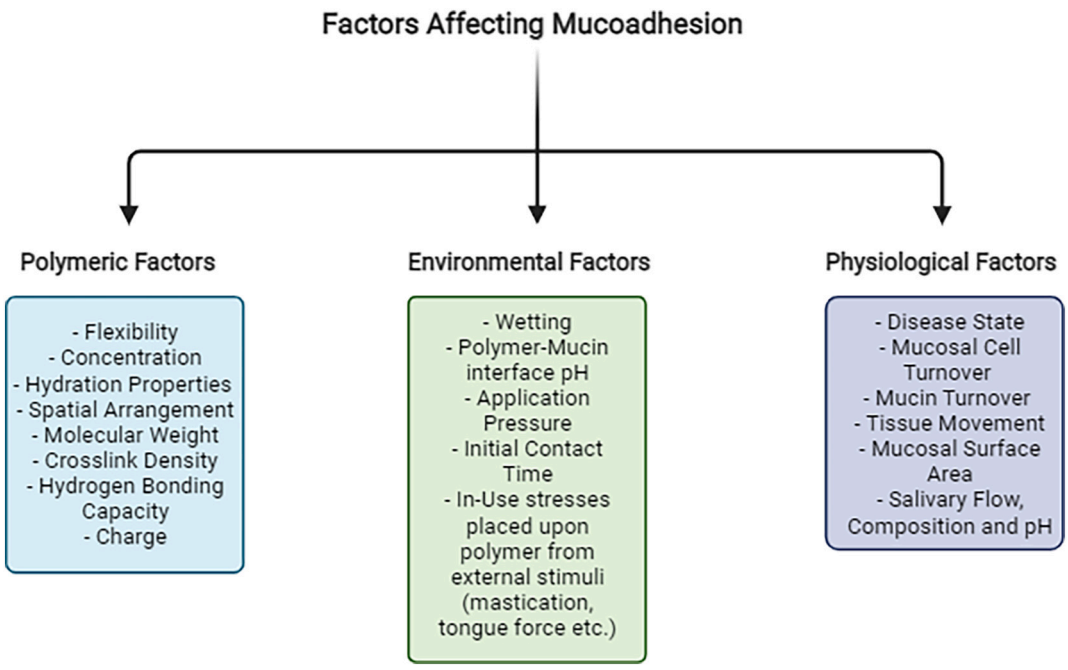

Fig. 4. Diagram illustrating the polymeric, physiological and environmental factors affecting mucoadhesion [159].

mucoadhesive film formulation can directly influence the *in vitro* evaluation parameters of produced films such as mucoadhesive strength, buccal residence time and drug release [91]. Due to the high glass transition temperatures of mucoadhesive polymers, plasticisers are included in mucoadhesive film formulations to improve the mechanical properties of the dosage form, namely; folding capacity, tensile strength, toughness, hardness and elastic modulus [164]. Goh et al. found that the interactions between the API and plasticiser had a considerable impact on the mechanical properties of rice starch films [71]. Plasticisers improve the film flexibility and as a result the patient acceptability, by improving the in-mouth feel of the device through movement which is consistent with the natural movements of the human mouth [9]. From the data collected in Table 2, it can be seen that glycerol was the most popular plasticiser used in mucoadhesive buccal film formulations (39.77%), ahead of propylene glycol (35.23%), with 18.18% of the film formulations either not stating the plasticiser used or not needing one to achieve sufficient properties for desired function [7–94]. Polyethylene glycol with different molecular weights (PEG-200 (1.14%), PEG-400 (13.64%), PEG-600 (3.41%), PEG-800 (1.14%), PEG-3350 (2.27%)) have been used in mucoadhesive film formulations and combine to take up approximately 22% of the total [7–94]. The remainder of films were plasticised with sorbitol (2.27%), castor oil (1.14%), dibutylphtalate (1.14%), triethanolamine (1.14%) and triethyl citrate (1.14%) respectively [7–94]. The inclusion of polyethylene oxide in the mucoadhesive films decreases the use of plasticisers, owing to its low glass transition temperature and increased drug loading ability [91]. Interestingly, polyols are osmotically positive compounds, which may result in an increased uptake of water from saliva if used in excess, consequently causing xerostomia and increasing salivary viscosity [72].

Backing membranes, which are impermeable to the API and saliva are necessary in buccal drug delivery systems in order to control the direction of drug release from the dosage form towards the buccal mucosa, as shown by Govindasamy, Kesavan, and Narasimha when developing a carbamazepine buccal patch [165]. Dosage forms with no backing layer will release drug in all directions - into the buccal mucosa, to the sides of the device, and back towards the tongue [165]. Backing membranes are typically made of ethyl cellulose alone [41,84,87,166,167] or in combination with hydroxypropyl methyl cellulose [168]. In addition to the impermeability of ethyl cellulose to drug molecules and biological fluids, it has good film forming properties and modest flexibility [169], making ethyl cellulose an ideal backing membrane.

Other excipients that can be found in mucoadhesive film formulations include enzyme inhibitors to aid in the delivery of protein and peptide-based drugs, permeation enhancers to improve the permeability of large macromolecules or molecules with significant hydrophilicity, saliva stimulations to increase the dissolution rate, in addition to flavouring and colouring agents to improve patient acceptability [2,170].

4.3. *The manufacture of mucoadhesive buccal films*

Several techniques have been employed/investigated for the manufacturing of mucoadhesive buccal films, including solvent casting, hot melt extrusion, inkjet printing and 3D printing. These approaches offer several advantages and disadvantages as shown in Table 3. Stability of products after manufacturing is very crucial. Packaging not only represents a critical barrier to light, moisture and oxygen, but provides mechanical protection for film formulations. This can protect children from unintended ingestion/administration of such medicinal products [163]. In the case of mucoadhesive buccal films, aluminium foils which offer light and moisture protection and lidding foil which can offer tamper-proof packaging are common [163]. Packaging of films in this manner offers economic, handling, and ease of production advantages [163]. Commercialised films that have been produced using the PharmFilm® technology for example, are packaged within hermetically sealed child-resistant foil wrappers in order to stop films from sticking to the packaging. Such packaging also gives produced films high portability, increasing convenience to patients [171].

4.3.1. *Solvent casting*

Solvent casting is the most widely used manufacturing process for making buccal films [178], due to the low cost and simplicity of the processes [178]. The ‘casting solution’ is prepared by dissolving water soluble ingredients like polymers to form homogenous viscous solution and then subsequently dissolving the API and other excipients [179]. Once the solution is dried, films are cut in specified dimensions as to contain the required amount of the drug [179]. Solvent casting has been used to produce an extensive list of buccal films, containing Furosemide

Table 2
Mucoadhesive Polymers used in Mucoadhesive Buccal Film formulations identified in the literature, their mucoadhesive functionality, commercial availability, inclusion alongside other key film formulation constituents and details of their effect on *in vitro* drug release properties [7–94,159,162].

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
Methyl Cellulose (MC)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Low Substitution MC, MC viscosity 4000 cP	BDH Lab Supplies (England), Sigma Aldrich (UK and India), S.D. Fine Chemicals (Mumbai)	Propylene glycol, PEG-400	Cetylpyridinium chloride [7], Carvedilol [8], Omeprazole [9], Nebivolol [82]	5 h to 12 h
Ethyl Cellulose (EC)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	EC viscosity 9.9 cP - 20 cP, Ethocel® Standard 10 Premium	Sigma Aldrich (Germany), Colorcon (Italy and India), S.D. Fine Chemicals (Gujarat), ICN Biomedicals, Inc. (USA), Dow Chemical (Netherlands)	PEG-400, Triethyl Citrate, Propylene glycol, PEG-800, PEG-600, Castor Oil, Glycerol, Dibutylphthalate	Allantoin [10], Fluticasone Propionate [11], Propranolol Hydrochloride [12], Ketorolac Tromethamine [13], Resveratrol [14], Propranolol Hydrochloride & Nifedipine [15]	6 h to 24 h
Hydroxypropyl Methyl Cellulose (HPMC)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	HPMC (K15M, K4M, E5, E15, K100M, F4M), Methocel® (E4M, K15M, K4M PREMIUM EP®, K100 Premium LV), HPMC (viscosity 5 cP - 5600 cP), Pharmacoat® 603, HPMC (MW 250 kDa, methoxyl content 19–24%, hydroxypropyl content 7–12%), HPMC (HME Grade), Hypromellose acetate succinate 716, METOLOSE (90SH-15000SR HPMC2208 type),	Fluka Biochemica (Switzerland), Glenmark Generics Ltd. (India), Sigma Aldrich (Mumbai, UK, Germany, USA), Colorcon (Italy, England, Brazil, USA, India), S.D. Fine Chemicals (India), Dow Chemical Company (USA, India), KP Labs (India), Shin Etsu Chemical Co. (Japan), Dr. Reddy's Laboratories (India), Lab Chemicals (India), M/S Max India Ltd. (India), Rama Production Co., Ltd. (Thailand), Eigenmann & Veronelli. (Italy), Medical Union Pharmaceuticals (Egypt), Central Drug House (India), Ind Swift Ltd., (India), Norsk Medisinaldepot AS, (Norway)	Propylene glycol, PEG-400 Triethyl Citrate, PEG-800, PEG-600, Castor Oil Glycerol, PEG-3350, TriethanolamineSorbitol, PEG-200	Cetylpyridinium chloride [7], Carvedilol [8,90], Omeprazole [9], Allantoin [10], Fluticasone Propionate [11], Propranolol Hydrochloride [12,25], Ketorolac Tromethamine [13], Enalapril Maleate [16], Glibenclamide [17], Cetirizine Dihydrochloride [19], Glimepiride [20], Nitrendipine [21], Clotrimazole [22], Lidocaine Hydrochloride [23,73], Ibuprofen [24], Ondansetron Hydrochloride [26], Meloxicam [27], Prednisolone [81], Rizatriptan Benzoate [87,91], Lycopene [76], Risedronate Sodium [84], Clinidipine [80], Furosemide [70], Domperidone [86], Catechin [93], Lidocaine Hydrochloride & Benzydamine Hydrochloride & *N*-acetyl-L-cysteine [72], Nebivolol [82], Nicotine [18,75], Piroxicam [74], Glipizide [92]	30 mins to 24 h
Hydroxypropyl Cellulose (HPC)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	HPC (average MW 100,000 Da), Klucel™ (HXF Pharm, GF), HPC (low viscosity), HPC (M, EF-P, EF), HPC (viscosity 150-400 cP)	Winlab Co. (UK), Hercules Incorporated (USA), Lab Chemicals, (India), M/S Ranbaxy Labs Ltd. (India), Egyptian International Pharmaceutical Company (Egypt), Shin Etsu Chemical	Propylene Glycol, PEG-400, Glycerol, PEG-3350	Ketorolac Tromethamine [13], Resveratrol [14], Nitrendipine [21], Clotrimazole [22], Lidocaine Hydrochloride [23,29], Diltiazem Hydrochloride [28], Indomethacin [30], Lycopene [76]	90 mins to 24 h

(*continued on next page*)

Table 2 (*continued*)

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
				Co., Ltd. (Japan), Wako Pure Chemical Industries (Japan)			
Hydroxyethyl Cellulose (HEC)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	HEC (average Mw 90.000 Da), HEC (viscosity 10 cP), HEC (medium viscosity)	Fluka Biochemica, (Switzerland, UK), Sigma-Aldrich (Germany, USA), S.D. Fine Chem. (India), Medical Union Pharmaceuticals (Egypt), Thermo Fisher Scientific (UK)	PEG-400, Triethyl Citrate, PEG-600, Castor Oil, Glycerol Propylene Glycol	Cetylpyridinium chloride [7], Allantoin [10], Propranolol Hydrochloride [12], Meloxicam [27], Moxifloxacin Hydrochloride & Clove Oil [31], Acyclovir [32], Hyaluronic Acid [33], Nebivolol [82]	90 mins to 48 Hours
Carboxymethyl Cellulose (CMC, SCMC)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	SCMC (Low-High Viscosity), SCMC (viscosity 8000-10,000 cP)	Sigma-Aldrich (Germany, USA, Egypt), Oxford Laboratory Reagents (India), BDH Co. (UK), S. D. Fine Chem. Ltd. (India), El Nasr Pharmaceutical Chemicals Co. (Egypt), FMC Biopolymer (N/A) Noveon Inc. (N/A), Central Drug House (India), CP Kelco (Brazil)	PEG-400, Triethyl Citrate, Propylene glycol, PEG-800, Glycerol, Triethanolamine, Sorbitol	Allantoin [10], Fluticasone Propionate [11], Ketorolac Tromethamine [13], Enalapril Maleate [16], Nitrendipine [21], Ibuprofen [24], Meloxicam [27], Diltiazem Hydrochloride [28], Lysozyme [34], Rizatriptan Benzoate [35], Ciprofloxacin [36], Glipizide [37,92], Carvedilol [90], Lycopene [76], Lidocaine hydrochloride & Benzydamine hydrochloride & *N*-acetyl-L-cysteine [72], Simvastatin [77], Lysozyme & Epidermal Growth Factor [89], Imiquimod [88]	1 h to 12 h
Xyloglucan (XYL)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Tamarind Seed	Arihant Industries (India)	Glycerol	Rizatriptan Benzoate [35]	2 h
Polycarbophil (PCP)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus	Diffusion	Noveon AA1®	Noveon, Inc. (USA), Lubrizol Company (USA), Namsiang Co., Ltd. (Thailand)	Glycerol, PEG-3350, Triethanolamine, Propylene Glycol	Lidocaine Hydrochloride [23], Ibuprofen [24], Propranolol Hydrochloride [25]	5 h to 24 h
Poly-ethylene Oxide (PEO)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	PolyOx™ (N80, WSR 301 ≈ 4000 kDa, N80 LEO NF), PEO (MW 35000 Da)	Dow Chemical Company (USA), Colorcon Ltd. (UK, USA), Merck Chemical Company (Germany), Aldrich Chemical Company (USA)	PEG-3350, Glycerol	Lidocaine Hydrochloride [23,73], Streptomycin & Diclofenac [38], Rizatriptan Benzoate [91], Domperidone [86]	70 mins to 72 h
Poloxamer (POL)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Pluronic® F68, Poloxamer 407	Sigma-Aldrich (USA, UK)	Propylene Glycol, PEG-600, Glycerol	Glimepiride [20], Ibuprofen [39], Methylene Blue [40]	2 h to 12 h
Polyacrylic Acid (PAA)	Anionic carboxylic acid groups enabling hydrogen bond formation	Adsorption	Carbopol® (940, 971P NF, 934P, 974P, 971 NF, 934, Ultrez-21)	Lubrizol Advanced Materials (India, Italy), Sorgan Co. (Germany), S. D. Fine	Propylene glycol, PEG-800, Glycerol, Triethanolamine, PEG-400	Carvedilol [8,90], Fluticasone Propionate [11], Ketorolac	90 mins to 12 h

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Table 2 (*continued*)

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
	with oligosaccharide component of mucin.			Chem. Ltd. (India), M/S Ranbaxy Labs Ltd. (India) M/S Max India Ltd. (India), Galeno. (Italy), Noveon Inc. (USA), B. F. Goodrich (N/A) Ind Swift Ltd. (India) Central Drug House (India), Corel Pharma Chem. (India)		Tromethamine [13], Glimepiride [20], Nitrendipine [21], Clotrimazole [22], Ibuprofen [24], Rizatriptan Benzoate [35], Atenolol [41], Prednisolone [81], Lycopene [76], Piroxicam [74], Glipizide [92]	
Polymethacrylic Acid (PMA)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	Eudragit® (RSPO, RL100, RLPM, NE30D, NE40D, E100, RLPO, RS100)	Evonik Industries (Germany), Rohm GmbH & Co., (Germany), Ind Swift Ltd. (India), Central Drug House (India)	Propylene glycol, Triethanolamine, PEG-400, PEG-200	Carvedilol [8], Glibenclamide [17], Glimepiride [20], Clotrimazole [22], Ibuprofen [24], Acyclovir [32], Penciclovir [42], Almotriptan [85], Prednisolone [81], Glipizide [92], Rizatriptan Benzoate [87]	3 h to 12 h
Chitosan (CHT)	Cationic amine groups enable interaction with negatively charged mucin molecules.	Electrostatic Interaction	CHT (MW 50-500 KDa, 75% - 97% deacetylation), CHT Glutamate (viscosity <20 cP)	Sigma Aldrich (Germany, USA, UK), Aldrich Chemical Co. (USA), Zhejiang Chemicals Import and Export Cooperation (China), Pronova Laboratories (Norway), Seafresh Chitosan Lab Co. Ltd. (Thailand), Fluka (Italy) CIFD, (India), M/S Panacea Biotech (N/A) GTC Union Group Ltd. (China), Heppe Medical CS GmbH (Germany), Indian Institute of Fisheries (India)	Propylene glycol, PEG-800, Glycerol, Dibutylphthalate, PEG-400, Sorbitol	Cetylpyridinium chloride [7], Fluticasone Propionate [11], Propranolol Hydrochloride & Nifedipine [15], Propranolol Hydrochloride [25,47], Ondansetron hydrochloride [26,43], Tenoxicam [44], Tramadol [45], Progesterone [46], Insulin [48,79], Lidocaine Hydrochloride [49], Clotrimazole [50], Paracetamol [51], Metronidazole [52], Miconazole Nitrate [53], Risedronate Sodium [84], Lidocaine Hydrochloride & Benzydamine Hydrochloride & *N*-acetyl-L-cysteine [72], Ropinirole Hydrochloride [83], Piroxicam [74]	30 mins to 15 days
Polyvinyl Alcohol (PVA)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	PVA (Average DOP 1700), PVA (MM = 44.05 g/mol), PVA (MW 10-124 kDa)	Sigma Aldrich (USA, Germany), Hayashi Pure Chemical Industries Ltd. (Japan), S.D. Fine Chem. Ltd. (India), Arabic Laboratory Equipment Co. (Egypt), Neon (Brazil), VETEC (Brazil), VWR® International (USA), Central Drug House (India)	Glycerol, PEG-400, Propylene Glycol, Sorbitol	Cetylpyridinium chloride [7], Nitrendipine [21], Meloxicam [27], Methylene Blue [40], Benznidazole [54], Dexamethasone [55], Paracetamol [71], Rizatriptan Benzoate [91], Carvedilol [90], Propranolol Hydrochloride [94]	30 mins to 48 h
	Non-Ionic hydrophilicity	Diffusion		BASF (Germany, USA), S.D. Fine	PEG-400, Triethyl Citrate, PEG-600, Castor Oil,	Allantoin [10], Propranolol	90 mins to 24 h

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Table 2 (*continued*)

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
Polyvinyl Pyrrolidone (PVP)	enabling diffusion and formation of interpenetration layer with mucus.		PVP (K90, K30, K70, K25, K40), PVP (MM 111.14 g/mol)	Chemicals (India), Sigma Aldrich (USA), Sigma Chemical Co. (Germany), Central Drug House (India), ISP (USA), Spectrum Chemicals (USA), Serva GmbH & Co. (Germany), Labsynth (Brazil), Ozone international (India), HiMedia (India)	Glycerol, Triethanolamine, Propylene Glycol.	Hydrochloride [12,94], Ketorolac Tromethamine [13], Enalapril Maleate [16], Nitrendipine [21], Ibuprofen [24], Methylene Blue [40], Penciclovir [42], Ondansetron hydrochloride [43], Tenoxicam [44], Tramadol [45], Progesterone [46], Lysine Clonixinate [56], Carvedilol [90], Lycopene [76], Simvastatin [77], Ropinirole Hydrochloride [83], Epidermal Growth Factor & Lysozyme [89], Imiquimod [88]	
Gelatin (GEL)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption & Electrostatic Interaction	Type B (MW 50 kDa, ~225 Bloom, iso. Point pH 4.5–5.5), Type A (~300 g Bloom), GEL (160 bloom)	Sigma-Aldrich (Italy, USA), HiMedia (India), PB Gelatins (Belgium)	Glycerol	Ondansetron Hydrochloride [26], Lysozyme [34], Progesterone [46], Propranolol Hydrochloride [47,57,94], Lidocaine Hydrochloride [58]	30 h to 8 h
Sodium Alginate (SA)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	SA (10,000 - 600,000 g/mol), Protonal® LF 240 D, Manugel® DMF	The General Chemical and Pharmaceutical Co Ltd. (UK), FMC BioPolymer (N/A), AppliChem GmbH (Germany), S. D. Fine Chem. Ltd. (India), Sigma Aldrich (USA, UK), ISP Thailand Ltd. (Thailand), Central Drug House (India)	PEG- 400, Glycerol, Propylene Glycol	Cetylpyridinium chloride [7], Omeprazole [9], Cetirizine Dihydrochloride [19], Nitrendipine [21], Ciprofloxacin [36], Atenolol [41], Nicotine [59,75], Carvedilol [90], Lycopene [76]	2 h to 6 h
Gellan Gum (GLG)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	KELCOGEL® CG-LA, Gelzan™ CM	Sigma Aldrich (USA) CP Kelco Inc. (Brazil)	Glycerol, Propylene Glycol	Moxifloxacin Hydrochloride & Clove Oil [31], Triamcinolone, Acetonide [60], Fluconazole [61]	20 mins to 48 h
Guar Gum (GUG)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Not Specified	Cosmopolita Drugstore (Mexico), Sigma-Aldrich (China, Germany)	Propylene Glycol, Glycerol	Lysine Clonixinate [56], Zolmitriptan Succinate [62], α-casozepine [63]	70 mins to 12 h
Xanthan Gum (XG)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	Not Specified	Panacea Biotech Ltd. (India)	Not Stated	Domperidone [64]	8 h
Carrageenan (CRG)	Anionic sulphur containing groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	Gelcarin® (GP 812 NF, NF 911, 812, NF379), CRG (λ-, K-, L-)	IMCD Ltd. (UK), BASF (UK), FMC BioPolymer (USA), Sigma Aldrich (Germany)	PEG-400, Glycerol, PEG-600, Propylene Glycol	Omeprazole [9], Streptomycin & Diclofenac [38], Ibuprofen [39], Miconazole Nitrate [53], Artemether [65]	90 mins to 72 h

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Table 2 (*continued*)

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
Pectin (PCT)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	PCT (GENU®, (USP–H, USP-B), PCT (Low-High Methoxyl), PCT (Apple)	Sigma Aldrich (Germany, China), CP Kelco Inc. (USA, Brazil), Herbstreith & Fox KG (Germany)	PEG-400, Glycerol Propylene Glycol	Meloxicam [27], Clotrimazole [50], Paracetamol [51], Metronidazole [52], Triamcinolone Acetonide [60]	30 mins to 24 h
Hyaluronic Acid (HA)	Anionic carboxylic acid groups enabling hydrogen bond formation with oligosaccharide component of mucin.	Adsorption	Sodium HA (MW 400–2300 kDa)	ACEF (Italy), Orchadia Pharmaceutical ind. (Egypt), Kadıoğlu Medikal (Turkey)	PEG-400, Glycerol	Ondansetron Hydrochloride [26], Hyaluronic Acid [33], Benzydamine Hydrochloride [66]	1 h to 8 h
Rice Starch (RS)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Thai glutinous rice of Niaw San-Pah-Tawng, Thai non-glutinous Saohai Rice (2013), Thai glutinous Niaw Sanpatong Rice (2013)	Khon Kaen rice seed centre (Thailand), Sekinchan, Sabak Bernam (Malaysia)	Glycerol, PEG-400, Propylene Glycol, Sorbitol	Lidocaine Hydrochloride [49], Diclofenac Sodium [67], Paracetamol [71]	30 mins to 6 h
Tapioca Starch (TS)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Not Specified	Thaiwah (Thailand)	Glycerol	Lidocaine Hydrochloride [58]	8 h
Arrowroot Starch (AS)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Amylose 46.8%, Amylopectin 53.2%	Local Market (India)	Glycerol	Glipizide [37]	4 h
Agarose (AGR)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Not Specified	Ultrapure™ (USA)	Glycerol	Zolmitriptan Succinate [62]	70 mins
Pullulan (PLL)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	MW = 150 kDa	TCI Europe (N/A), Hayashibara Biochemical Laboratory Inc. (Japan), Xi'an Sonwu Biotech (China)	Glycerol, Propylene Glycol	Enalapril Maleate [69], Yonkenafil [68], Methylene Blue [78]	8 mins to 9 h
Proloc™ Bioadhesive (PRO)	Non-Ionic (hydrophilicity) and Anionic (Carboxylic Acid Groups) Characteristics Facilitating Mucoadhesion	Adsorption / Diffusion	PRO 15	Henkel Corporation (USA)	PEG-400, Propylene Glycol, PEG-200	Almotriptan [85], Rizatriptan Benzoate [87]	3 h to 6 h
Maltodextrin (MAL)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Dextrose between 13 and 17	Sigma Aldrich (USA)	Propylene Glycol	Methylene Blue [78]	N/A
Soluplus™ (SOL)	Non-Ionic hydrophilicity enabling diffusion and formation of interpenetration layer with mucus.	Diffusion	Not Specified	BASF (Germany)	Glycerol	Furosemide [70]	30 mins
Lyocoat™ (Pea Starch) (LYO)	Non-Ionic hydrophilicity enabling diffusion and formation of	Diffusion	LYO RS720	Roquette Pharma (France)	Glycerol	Furosemide [70]	30 mins

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Table 2 (*continued*)

Polymer Name	Chemical Characteristics		Commercial Availability		Application in Mucoadhesive Buccal Films		
	Mucoadhesive Functionality	Mucoadhesive Theory	Brand Name / Grade	Supplier(s) (Country)	Plasticiser(s)	API(s)	*In Vitro* Drug Release
	interpenetration layer with mucus.						

Table 3
Brief overview of the manufacturing techniques used to produce mucoadhesive buccal films [148,163,172,173,174–177]. Created with BioRender.com.

Solvent casting	Hot Melt Extrusion
Advantages	Advantages
• Simple, reproducible, and established process • Industrial solvent casting offers better control over film thickness & polymer concentrations	• Solventless, continuous process, with fewer operations and better content uniformity than solvent casting • Ability to incorporate poorly soluble drugs
Disadvantages	Disadvantages
• Drug re-crystallisation after production • Changes in film mechanical properties due to plasticising small molecules • Difficult to achieve dose uniformity • Potential for entrapped air bubbles • Lack of control over film thickness & polymer concentration	• Drug re-crystallisation after production • Swelling of film after leaving the die • Limited and specialist excipients required • Agglomeration of ingredients • Weight variations due to improper flow • Problems with chemical stability • Not suitable for thermosensitive drugs
Inkjet Printing	3D Printing
Advantages	Advantages
• Recrystallisation prevented by depositing API onto the film, rather than building the API in • Mechanical properties of drug free film retained • Able to precisely deposit small volumes of liquids • Ability to personalise treatment	• Continuous process capability, with personalised treatment • Compartmentalisation can prevent incompatible excipient interactions • Increases precision of manufacture • In SSE, thermosensitive drugs can be used with high loading capacity
Disadvantages	Disadvantages
• Requires another process to make the film to then deposit drug substances onto • Primarily applicable where a low dose of active substance is required • Nozzle blockage may lead to inaccurate printed dosages	• FDM filaments production by HME have the same challenges • Drying in SSE may alter dimensions of printed objects • Only small scale, non-reproducible manufacture possible • Barriers to clinical adoption for this emerging technology

[70], Ondansetron [26], and Cilnidipine [80], but has its limitations. For example, it has been difficult thus far to achieve dose uniformity within produced films [178]. This is thought to be caused by the material of the trays or moulds onto which the films are casted. Recently, work has been undertaken in reducing dose variability within buccal films, by proposing a different mould material to conventional Teflon-coated Perspex trays [180]. This silicone-moulded tray has been shown to improve dose uniformity and reduce the variability in mucoadhesive strength, drug release, and film thickness, when compared to Teflon-coated Perspex moulds [180].

Industrial standard solvent casting, however, is not reliant on the casting of films into moulds. Instead, the API and other key formulation constituents (plasticisers, flavouring agents *etc.*) are suspended or dissolved within volatile solvents and therein represent the 'film dope' [163,181]. The film dope is then spread over a continuous roll of 'release media', which resembles plastic-impregnated paper [163,181]. The resultant media is then dried, facilitating the evaporation of volatile solvents used initially, cut, and packaged [163,181]. This provides better control over film thickness and drug content than benchtop solvent casting [163,181]. However, the toxicity and environmental impact with respect to the use of solvents is a limitation of the technology [172]. An additional limitation here, is due to film storage prior to cutting in the roller [163,181]. This leaves films exposed for undefined time periods, which may impact on film stability [163,181]. Other critical quality attributes also represent a challenge to this process; however, such attributes must be considered for all large-scale manufacturing processes involving pharmaceutical dosage forms. Here, the rheology of the material from the hopper, the drying temperature and the removal of air, represent process factors to optimise [163,181]. This industrial apparatus enables this simple and economically viable manufacturing process to be scaled significantly and represents the most promising platform for the large-scale manufacture of mucoadhesive films in addition to hot melt extrusion.

4.3.2. Hot melt extrusion

Hot Melt Extrusion (HME) is a continuous and reproducible process, capable of automation, and therefore has a range of applications across pharmaceutical production [172]. In HME, a molten blend of pharmaceutical ingredients is forced through an orifice to produce a more homogeneous material and subsequently customisable pharmaceutical dosage forms, one of which being mucoadhesive films [178]. Unlike solvent casting, HME operates without solvents. Which, due to the volatility and toxicity of organic solvents, is an advantage of HME over solvent casting [172]. It is also possible that residual amounts of solvents can remain within produced films even after drying, which could cause harmful effects to prospective patients [172]. Additionally, upon disposing of production waste, such solvents can negatively impact the environment [172]. However, due to the temperatures and shear stresses involved in the HME process, there are limitations with regards to the class of API's and excipients that can be used here [173]. Despite this, many buccal films have been produced by HME to date [86,182,183]. HME is also a common method of filament production for the fused deposition modelling 3D printing technology discussed later [184,185].

4.3.3. Inkjet printing

Inkjet printing is the printing technology most alike to the conventional printing that will be familiar to most. However, the 'inks' involved are different pharmaceutical formulations. To create a pharmaceutical ink, the API is dissolved or dispersed in a liquid substance and loaded into the printer [186]. Once the ink is loaded into the printer, it is deposited in a droplet fashion through a nozzle [186]. This droplet-based printing technique is combined with either the heating of the liquid above its boiling point (thermal inkjet printing) or the application of a voltage to a piezoelectric transducer, which leads to vibration of the material (piezoelectric inkjet printing) [186]. Inkjet printing is used in combination with other buccal film fabrication techniques (solvent casting, HME, 3D printing), and is used to deposit the API onto a substrate, rather than building the API within a substrate [173,187]. The advantages of inkjet printing over solvent casting and/or HME, are the improved mechanical properties of produced films, better long-term stability, and the opportunities for personalised medicine [148,173]. A novel application of the inkjet printing technology is to deposit the API onto a substrate in the form of a readable QR code which could help to reduce medicines counterfeiting [148,188]. The main challenges of the inkjet printing technology are that nozzle blockage may occur leading to

inaccurate dosing, the API must be soluble and stable within the ink, and that only potent drugs can be used currently [148].

4.3.4. Three-dimensional (3D) printing

3D printing has the potential to solve formulation obstacles within the production of buccal films. At present, buccal dosage forms are typically exclusive to potent drugs due to low drug loading capacity [2]. 3D printing could solve this issue through the depositing of formulation layers on top of each other, incorporating more active substance per unit area of a mucoadhesive film for example, while also tackling the issue of limited mucosal surface area for drug absorption [148,189]. This layered approach, could also provide a potential solution to issues regarding incompatible ingredients, through the compartmentalisation of buccal film layers [2], and a platform for controlled drug release over longer periods of time resulting in a reduced frequency of administration [148].

Fused deposition modelling (FDM) is one of the most popular techniques in 3D printing. In FDM, the printed object is formed through the layering of either melted or softened thermoplastic filaments which are extruded through a nozzle to produce a pre-defined geometry in combination with computer automated design (CAD) [190]. Inside the head of the printer the material is heated to just above its melting point, and upon deposition, the material rapidly solidifies to form a 3D object [190]. FDM has been used to produce mucoadhesive buccal films containing diclofenac sodium [191], lidocaine [73], and has been used in combination with inkjet printing to produce another buccal film containing lidocaine [187].

Semi-solid Extrusion (SSE) 3D printing involves layer-by-layer deposition of semi-solid materials through a syringe-based tool-head [190]. Such materials are formulated by mixing polymeric substances and appropriate solvent(s) to produce a material with the appropriate viscosity for printing [190]. The key differences to the FDM process are in the properties of the starting materials (semi solid *vs* heated thermoplastic filament), the temperatures required for printing (room temperature *vs* 180 degrees Celsius for polylactic acid filament), and the mechanical properties of the printed object (solid, but 'wet' *vs* rapidly solid, hard and dry) [192,193]. As printed objects produced by SSE are still 'wet', they require additional processing and solidification in the form of post-printing drying [193]. During the drying process, the semi-solid nature of the starting materials may cause unintended changes to the printed object in terms of shrinkage, deformation or collapse owing to insufficient hardness [193]. Gajdziok et al. modified an SSE 3D printer to include an in-process drying step and demonstrated the feasibility of this apparatus through the production of multi-layered benzydamine hydrochloride orodispersible films [194]. Produced films were dried prior to the printing of subsequent layers which is believed to not only shorten the development time but improve the mechanical properties and drug uniformity of films also [194]. This in-step drying development may alleviate concerns surrounding the post printing processes in SSE 3D printing. SSE has been used recently to produce a mucoadhesive prolonged-release buccal film loaded with propranolol hydrochloride, a drug that undergoes extensive hepatic first pass metabolism [94]. Additionally, Tagami et al. utilised a 3D bioprinter to produce mucoadhesive films loaded with catechin, indicated for the treatment of mouth ulcers [93]. Personalised treatment was considered here, due to the individual nature of the size and shape of mouth ulcers, therefore films of different sizes and shapes were developed [93].

The rheological considerations of semi-solid inks used in the development of mucoadhesive buccal films *via* the SSE technology are often overlooked. Such parameters provide an indication of process parameters that will need to be optimised during formulation development such as the printing speed, extrusion pressure, nozzle diameter *etc.* [195]. Rheological properties that require characterisation include the material viscosity, deformation behaviour, thixotropy, yield stress, as well as storage and loss moduli [196]. It is possible to formulate mucoadhesive films without such in-depth characterisation, however total process knowledge and understanding can only aid in formulation development and the wider adoption of both the mucoadhesive film technology and the SSE 3D printing technology. For a more in-depth discussion of material processing and process models relating to SSE 3D printing, readers are directed to Rahman and Quodbach [197].

Translation of the 3D printing technology into clinical settings, thought to be the primary application of the technology, still has some way to go. Barriers to the wider adoption of the technology include the trial-and-error approach to producing dosage forms due to undeveloped process knowledge and understanding as well as the lack of established compendial methodology to evaluate printed dosage forms on demand in clinical settings [174]. According to O'Reilly et al., the introduction of machine learning into the production of orodisperable films by 3D printing in combination with real-time non-destructive evaluation *via* Near Infrared Spectroscopy can aid in process knowledge and understanding as well as remove some of the trial-and-error concerns relating to 3D printed formulations. This will enable the development of safe, quality, and efficacious medicines on demand in time-sensitive clinical settings [174]. In order to facilitate the wider adoption of the technology, the dosage form design parameters deemed to be clinically relevant must be clearly identified, with acceptable ranges for such parameters stated across the wide-ranging variety of pharmaceutical dosage forms that can be produced *via* 3D printing, including mucoadhesive buccal films [175]. Although, this may be problematic given the multitude of different 3D printing platforms, each with their own individual requirements.

5. The evaluation of mucoadhesive films

Despite the apparent success of buccal drug delivery formulations (including mucoadhesive films) in the literature there has been little translation into the commercial marketplace. This could be due, in part to the lack of compendial *in vitro* evaluative methods for film dosage forms [5,6]. The more common evaluation techniques for mucoadhesive films have already been reviewed previously [2,164,198]. Here, however, we will discuss *in vitro* dissolution, mucoadhesion, and permeation in more detail.

5.1. In vitro dissolution evaluation

The dissolution of mucoadhesive buccal films is facilitated by the continuous flow of saliva over the dosage form [122]. The *in vitro* determination of the dissolution behaviour of mucoadhesive films lacks established compendial methodology. Although, a preferred apparatus has been suggested by the United States Pharmacopeia (USP 5 - Paddle over Disc) [199], varied experimental set ups are seen in the literature with no consensus surrounding the volume and composition of the dissolution medium that is to be used in such evaluations [200].

5.1.1. Dissolution apparatus

Speer et al. reviewed four different dissolution set-ups for the evaluation of mucoadhesive buccal films and orodispersible films, which had been modified from solid dosage form dissolution evaluations [4]. These were as follows: 1) the basket method (USP 1), 2) the paddle over disc method (USP 5), 3) the flow-through cell method (USP 4) with modified sample holders, and 4) the punch and filter method [4]. Speer et al. found that all methods were adequate in determining drug release from film dosage forms, but with a note that these methods were not suitable for all film types [4]. It is worth noting that this review specifically discusses and evaluates orodispersible films in detail, with only partial consideration given to mucoadhesive films [4]. The USP 5 Paddle over Disc apparatus was deemed suitable to evaluate the dissolution behaviour of multi-layered films, as such appropriate for testing mucoadhesive buccal films [4].

Zhang et al. upon review of the various *in vitro* dissolution evaluation methods employed for film dosage forms, described the dissolution

testing that the commercially available mucoadhesive buccal films authorised by the FDA underwent [201]. Details of these evaluations are shown in Table 4.

There are other experimental set ups seen across the literature, such as the use of a conical flask with a simulated salivary media, and a shaking tool such as an Orbital Shaker or a Thermostatic Horizontal Shaker to evaluate the dissolution behaviour of mucoadhesive films loaded with propranolol hydrochloride and tenoxicam [44,94]. Films were stuck to the bottom of the flasks with double-sided tape to enable unidirectional release, temperature was fixed at 37 °C, with a shaker speed of 50 rpm [44,94]. In addition, a vertical Franz-Cell set up has also been seen to evaluate HPMC-based oral thin films [202].

One novel set up was the use of a millifluidic device (Fig. 5) to evaluate mucoadhesive film dissolution, whereby films are placed on the bottom plate of a horizontal plexiglass cell, and the dissolution media maintained at 37 ± 1 °C, was channelled through the cell *via* a volumetric pump with varying flow rates (between 2 mL/min and 20 mL/min) [203]. Physiological relevance was enhanced through: A) flow rates consistent with normal salivary production, B) low hold up volumes not seen in USP 1 or USP 2 dissolution apparatus, and C) laminar tangential solvent flow consistent with normal salivary flow dynamics [203]. However, the simulated salivary media used (phosphate buffer saline, pH 6.75), fails to account for a large portion of actual salivary characteristics, namely: viscosity, composition, as well as accurately modelling how changes in stimulation state (and therefore flow rate and pH) may affect the dissolution of film dosage forms [203]. In addition, Adrover et al. states that upon wetting of the film, dosage forms adhere rapidly to the walls of the device, which alleviates concerns surrounding unpredictable detachments or flotations that have been witnessed during other dissolution analyses [203]. However, this is not the case *in vivo*, as films are designed to adhere to mucous membranes.

5.1.2. Dissolution media

The importance of media volume in dissolution evaluations has been stated, but the composition of artificial saliva formulations is a much-debated topic in the scientific literature, with a consensus on the composition of such salivary media yet to be achieved. This could be due to the inherent interpatient variability of human saliva which is not conducive to developing a model to accurately produce and characterise a singular artificial salivary medium. Physiological properties of saliva relevant to buccal drug delivery were presented in Fig. 3, so it should come as no surprise that many of these characteristics should also be considered when developing an artificial salivary media for physiologically relevant dissolution experiments. Current literature shows that research groups who conducted *in vitro* dissolution analyses for the oral cavity prefer to select simple media such as phosphate buffered saline which sparingly considers the pH and buffer capacity of saliva in analyses [120]. The reason for this is potentially multi-factorial. Firstly, it could be a matter of cost, as phosphate buffer saline (PBS) is cheap to acquire and is far cheaper than attempting to create a novel simulated salivary media. Secondly, a lack of understanding surrounding the characteristics of human saliva could point researchers in the direction of a simpler and cheaper alternative in PBS.

Table 4
In Vitro Dissolution Evaluation of Commercially Authorised Mucoadhesive Buccal Films in the USA [200].

Brand Name	Dissolution Apparatus	Dissolution Media	Media Volume
Onsolis™	USP 1	Phosphate Buffer (25 mM) at pH 6.4	100 mL and 60 mL
Belbuca™	USP 1	0.05 M Monobasic Sodium Phosphate (Phosphate Buffer) at pH 4.5	60 mL
Bunavil™	USP 1	Sodium phosphate buffer at pH 4.5	500 mL
Suboxone™	USP 5	Acetate Buffer at pH 4.0	900 mL

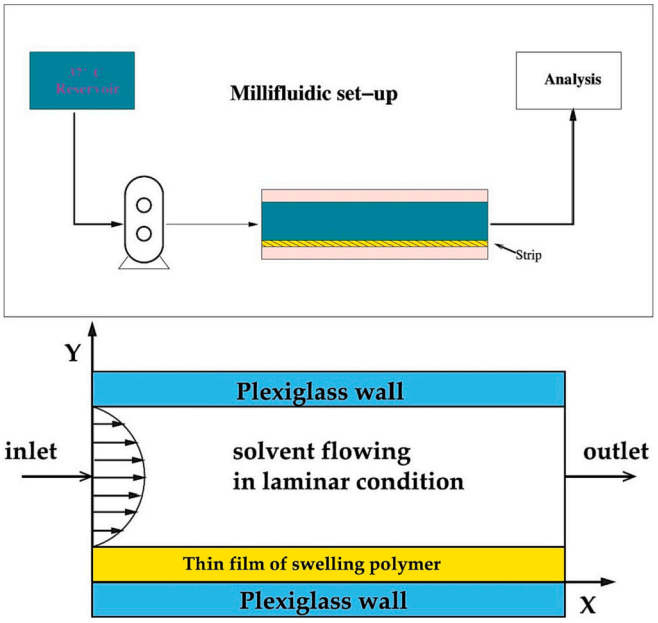

Fig. 5. Schematic Representation of a Milifluidic Flow through Cell developed by Adrover et al. [203]. Reposted with permission from Elsevier.

Kirsanov et al. conducted a study on three different novel artificial saliva formulations and evaluated the dissolution behaviour of two model tablets (quinine hydrochloride dihydrate and ibuprofen sodium dihydrate) in these developed dissolution media [204]. The salivary media were gradually modified to encompass more characteristics of human saliva and the composition of these three medias are detailed in Table 5 [204]. The fastest API release was seen in water for both quinine and ibuprofen tablets [204]. Significantly slower dissolution was registered in the third protein-laden artificial saliva formulation for the quinine tablets which was not consistent with its effect on the ibuprofen formulation [204]. Finally, the most retarded dissolution rates were observed for both tablet types in the first and second artificial salivary media [204].

Gershkovic et al. have also developed a novel simulated salivary media considering the salivary stimulation state for dissolution studies and evaluated the effectiveness of this media on three model compounds (sildenafil citrate, efavirenz, and caffeine), and found a comparable dissolution profile *versus* human saliva [5]. Details of the two formulations can also be found in Table 5. Animal mucin proteins are added to such formulations to produce comparable *in vitro* salivary media to that of human saliva [5]. In the study by Gershkovic et al., for example, it was determined that a simulated salivary fluid containing Tween 20 and Xanthan Gum alone did not yield a comparable dissolution profile with human saliva [5]. Therefore, porcine gastric mucin (PGM) was added [5]. Here, PGM was used owing to batch-to-batch variability with bovine submaxillary mucin (BSM) not seen in PGM [5]. PGM is also cheaper, contains lower amounts of sialic acid and has a similar mucin structure to that of human salivary mucins. However, Madsen et al. surmised that BSM is more elastic and less viscous than PGM, which offers favourable lubricative properties [205].

Both studies utilise xanthan gum, porcine gastric mucin and amylase in their artificial media [5,204]. Differences arise between Gershkovic et al. and Kirsanov et al. when considering the stimulation state and surface tension of saliva, and the ionic composition of saliva respectively [5,204]. In any case, the development of a universal simulated salivary medium seems far from reality, with significant inter-patient variability in salivary characteristics reducing the likelihood of a ‘one size fits all’ scenario. Efforts thus far by Gershkovic et al. and Kirsanov et al. have

Table 5
Composition of artificial salivary media developed by Kirsanov et al. and Gershkovic et al. and the physiological characteristics of human saliva that were considered (5204).

Kirsanov *et al*			Gershkovic *et al*		
Media	Composition	Aspects of Human Saliva Considered	Media	Composition	Aspects of Human Saliva Considered
1	KH2PO4 (25 mM), xanthan gum 200 mesh (0.75 g/L)	pH, buffer capacity and viscosity	1 (US*)	pH 7.0 buffer (6.211 mL), Tween 20 (5.6 μL), Xanthan Gum (0.05% *w/v*), Porcine Gastric Mucin (10 mg/mL), Porcine pancreatic alpha-amylase (1.0 mg/mL)	pH, buffer capacity, surface tension, viscosity, protein composition, stimulation state
2	KH2PO4 (25 mM), KCl (9.55 mM), NaCl (6.88 mM), CaCl2 x 2H2O, xanthan gum (0.75 g/L)	pH, buffer capacity, viscosity, and inorganic ionic composition	2 (SS**)	pH 7.4 buffer (6.892 mL), Tween 20 (5.6 μL), Xanthan Gum (0.05% *w/v*),	
3	KH2PO4 (25 mM), KCl (9.55 mM), NaCl (6.88 mM), CaCl2·2H2O (1.42 mM), NaN3 (0.08 mM), porcine gastric mucin (1.8 g/L), α-amylase (1 g/L)	pH, buffer capacity, viscosity, inorganic ions, and protein composition		Porcine Gastric Mucin (10 mg/mL), Porcine pancreatic alpha-amylase (1.0 mg/mL	

* US = Unstimulated Saliva.
** SS = Stimulated Saliva.

made great strides in the understanding of the various factors to consider when developing a simulated salivary medium, and it can be seen from the data presented that the developed media by both groups offers a better option than simple PBS media for *in vitro* dissolution analyses which may lead to a better *in vivo* correlation [5,204].

5.2. *In vitro/ex vivo mucoadhesion evaluation*

Mucoadhesion is of significant importance to dosage forms that are designed to be mucoadhesive. This is even more important for dosage forms indicated for prolonged drug release, whereby the strength of adherence (mucoadhesive strength), and the time taken for detachment (retention time) should be sufficient to facilitate drug release over a prolonged period. To evaluate mucoadhesion *in vitro*, several methods have been developed, however, only few are relevant to mucoadhesive films, with the rest being outside the scope of this review, such as rheological analyses for semi-solid preparations [206], as well as atomic force microscopy [207].

5.2.1. *Mucoadhesive strength*

Besides the simple thumb test – that is, placing one's thumb on the surface of a mucoadhesive buccal film and qualitatively measuring the difficulty of removal [164], the mucoadhesive strength of film formulations can be determined using a texture analyser. This is the most widely used apparatus found in the literature, potentially owing to its simplicity and use on extensive list of mucoadhesive films [32,33,35,72,81,208]. The experiment typically consists of the lowering of a cylindrical probe at a defined speed until it reaches the mucoadhesive film surface with a predesigned contact force [209]. Contact between the probe which has a form of mucus or mucus-like substrate such as porcine gastric mucin attached *via* double sided tape and the mucoadhesive film formulation are to be kept in contact for a predetermined time, prior to probe withdrawal at a defined rate until complete detachment is observed between mucoadhesive film and substrate [209]. Two parameters are calculated: a) the detachment force and b) the work of adhesion, where the detachment force represents the force required to separate the mucin from the film formulation denoted by the peak of a force *vs* time curve, and the work of adhesion represents the energy required to separate two phases from each other and is denoted by the area under a force *vs* time curve [208]. The primary limitations of the technique are the differences between experimental set up amongst different research groups with variations in method selection, including differences amongst substrates, owing to the lack of compendial evaluation techniques for mucoadhesion [210].

Biomimetics refer to a class of materials, synthetic systems or equipment that possess characteristics which facilitate the mimicry of biological processes and/or functions [211]. Cook and Khutoryanskiy reviewed the topic of biomimetics relating to the evaluation of mucoadhesion *in vitro* using a texture analyser, with consideration given to hydrogels produced by Hall et al. [212] and Cook et al. [213] that demonstrated similar mucoadhesive properties to porcine buccal mucosa with respect to detachment force and retention time [211]. An unpublished study (1998-2008) of 348 papers on mucoadhesion conducted at the University of Reading found that in 2/3 articles, laboratory animals were sacrificed specifically for their mucosal tissue [213]. Efforts from researchers in the development of biomimetic materials for mucoadhesion evaluations may reduce the needless sacrifice of animals for no additional physiological relevance.

While a texture analyser works vertically *i.e.*, the removal of the cylindrical probe in the vertical plane from a substrate or mucoadhesive dosage form, other methods of mucoadhesion can be used to characterise the detachment force in different directions. For example, McCarron et al. demonstrated the ability of a texture analyser to measure the peel strength of mucoadhesive films indicated for the treatment of vulval lesions [214]. The experimental set up can be seen in Fig. 6.

5.2.2. *Residence time*

There are two perspectives to the evaluation of mucoadhesion. For example, mucoadhesion can be thought of as the force required to separate a mucoadhesive material, such as a mucoadhesive film from a mucus or mucus-like material, which is described above. However, mucoadhesion can also be thought of as the duration of time that a mucoadhesive material remains adhered to a mucous substrate (retention time). In the literature, usually one method of mucoadhesion evaluation is chosen, such as the measurement of detachment force, while retention time is neglected. One such method to characterise the retention time of mucoadhesive dosage forms is through the use of modified pharmaceutical disintegration apparatus, which has been used to evaluate mucoadhesive buccal films containing nebivolol [82], simvastatin [77], and ropinirole hydrochloride [83].

Jacobsen et al. have developed an *ex vivo* liquid flow through apparatus to evaluate the retention time of metformin microparticles that were spray dried with the mucoadhesive polymer chitosan [215]. The proposed apparatus has the potential to be modified in order to evaluate the mucoadhesive properties of mucoadhesive buccal films,

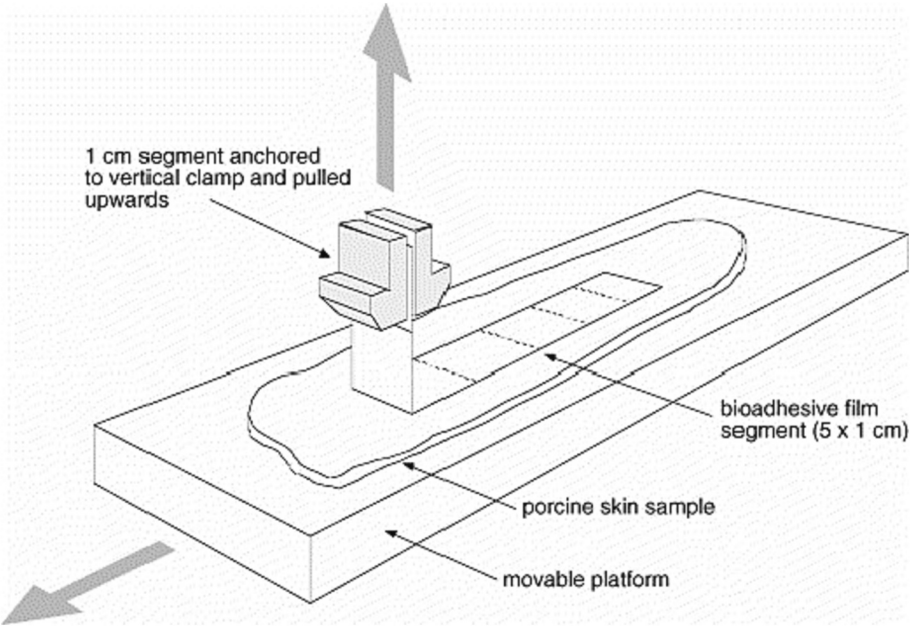

Fig. 6. Mucoadhesive Peel Strength Determination by McCarron et al. [214]. Reposed with permission from Elsevier.

shown in Fig. 7. Here, Jacobsen et al. utilised an 'irrigation media', which was run over the dosage form in question [215]. Four types of irrigation media were chosen in this physiologically relevant study and were all designed to replicate human saliva; phosphate buffer, xanthan gum loaded electrolyte solution (0.075% *w/v*), porcine gastric mucin loaded electrolyte solution (2.5% w/v), and commercially available Saliva Orthana® [215]. The media were then compared to human whole saliva that was collected [215]. It was concluded that the retention profiles of Saliva Orthana® and porcine gastric mucin loaded electrolyte solution (2.5% w/v) displayed the highest similarity to human whole saliva [215]. Additionally, the porcine gastric mucin solution also displayed comparable physicochemical properties to collected human saliva [215]. Hence, porcine gastric mucin loaded electrolyte solution (2.5% w/v) and Saliva Orthana® were considered the most physiologically relevant irrigation media for future analyses of this nature [215].

Goniometry can also be used in mucoadhesive studies to evaluate the mucoadhesion properties of buccal films, namely those containing poly-acrylic acid and polyethylene glycol *co*-polymers [216]. Given the polarity of poly-acrylic acid, the resulting interfacial energy serves to hinder wetting onto a mucous membrane and as a result mucoadhesion [216]. The addition of poly-ethylene glycol was shown to decrease the polarity of polyacrylic acid hence lowering the interfacial energy and improving mucoadhesive performance [216]. While the above examples correspond to the fracture theory of mucoadhesion, the use of goniometry relies on the wetting theory of mucoadhesion which is thought to favour low viscosity polymers. In such evaluations, desired parameters are that the spreading coefficient of the mucoadhesive polymers must be positive and the contact angle between polymer and substrate must be close to zero [217].

To translate the *in vitro* mucoadhesion assessments to *in vivo* performances of the films, techniques which evaluate not only the mucoadhesive strength, but also the retention time should be used in combination during *in vitro* evaluations to fully characterise the mucoadhesive properties of film formulations.

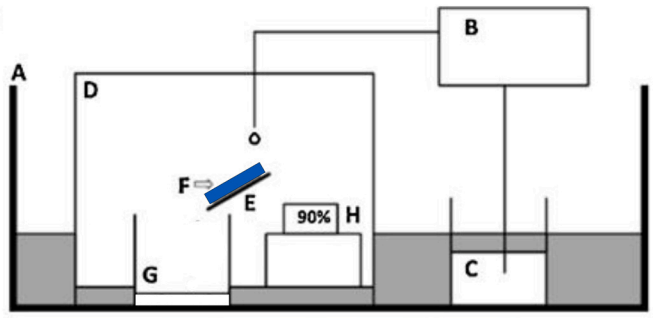

Fig. 7. Schematic diagram of a flow through apparatus for mucoadhesive film retention time evaluation, modified from Jacobsen et al. Where: (A) Temperature Controlled Water Bath (37 °C), (B) Peristaltic Pump, (C) Irrigation Media, (D) Temperature Controlled Hydration Chamber (33 °C), (E) Fixed Mucosa Substrate, (F) Mucoadheisve Buccal Film, (G) Collection Vessel, and (H) Hygrometer [215].

5.3. *In vitro/ex vivo permeation evaluation*

In the context of buccal drug delivery, permeability refers to the ability of drug molecules to pass through the buccal mucosa. To replicate the *in vivo* scenario of buccal drug permeation, *in vitro/ex vivo* techniques have been developed. The first method is perhaps the most widely used in the literature, consisting of the use of a Franz Diffusion Cell [164], and has been used to evaluate an extensive list of mucoadhesive buccal films in addition to dosage forms indicated for other routes of administration [25,74,87,92]. The advantages of the Franz Cell are its simplicity, reduced tissue handling, low frequency sampling, and high drug sensitivity [218]. Animal mucosa has been derived from multiple sources to evaluate buccal permeability in this manner, however porcine mucosa remains the most widely studied due to its similarities with human mucosa [219]. Other species of animal utilised in buccal permeability evaluation are; bovine [220], canine [221], hamster [88], rabbit [85], sheep [222], monkey [223] and goat [91]. In recent times it can be seen that animal free models are of growing interest to pharmaceutical development, and strides have been made in replacing the animal mucosal component for drug permeation studies [224]. The development of animal free models to evaluate drug permeation is an area that requires further work from scientists if it is to replace the conventional *ex vivo* models described above. It has been stated that the outermost layer of the buccal mucosa (buccal epithelium) represents the largest barrier to drug delivery [129]. However, there is also a salivary mucus layer which coats the buccal epithelium that is believed to be

approximately between 70 and 100 μm thick [127,225]. The environmental sensitivity of the mucus network coating animal mucosa means that it is lost upon excision, which is a limitation of the use of excised animal mucosa in such analyses.

Due to the ethical issues surrounding the use of animal mucosa, *in vitro* cell cultures have been developed. However, the cells used are derived from human subjects. This removes the interspecies variation between humans and animals, which can result in a better prediction of the *in vivo* fate of developed formulations. Two primary assays exist for such cell cultures: a) permeation/diffusion, and b) transendothelial/transepithelial electrical resistance [226]. The first assay provides an indication of the flux across the cell barrier, while the second assay correlates with the tightness of the monolayer *i.e.*, the resistance to permeation of small organic/ionic species [226]. It is recommended that these two techniques be used in conjunction to characterise the properties of the cultured cell layer [226].

The cell cultures used to evaluate buccal drug delivery systems can be derived from cancer cells [129]. The TR146 cell line, which was first established from a biopsy of squamous cell carcinoma of the buccal mucosa of a 67-year-old female patient in 1985, has since been established as the most widely used cell line for modelling buccal permeation since first grown on filter inserts in 1995 [227]. TR146 has been used to evaluate the buccal delivery of metformin [228], salbutamol [229], nicotine [230], mannitol [223], ten β-adrenoceptor antagonists [223], testosterone [223], polydopamine nanoparticles [55], and many more drug substances. A novel development including the TR146 cell line was created by Teubl et al., who produced a porcine gastric mucin containing film with glycerol as a plasticiser and deposited this film on top of a TR146 culture [219]. The mucin layer maintained cell viability for 48 h, and demonstrated that a combination of epithelial cells or epithelial mimics and an accompanying salivary mucus layer represent a barrier to the permeation of drug molecules, in this case carboxyl polystyrene nanoparticles [219]. The carcinogenic nature of these cells means they do not show differentiation, which is in direct contrast to the highly differentiated nature of the oral mucosa [231]. Additionally, the permeation of several drug substances has been reported to be higher in the TR146 cell model than seen in human subjects [129,198,223].

Traditionally, cell culture models are two dimensional, grown as a monolayer onto a flat surface using one cell type [232]. Three dimensional and organotypic cell culture models have been developed with considerable advantages over two dimensional models, specifically in terms of physiological relevance [232,233]. Owing to this method of culture, it can be seen that the 3D tissue culture models contain cells which are completely exposed to their neighbouring cell, something that is also observed *in vivo*, but not in the 2D tissue culture models [232]. This limits the value of such models in predicting the fate of buccally administered drugs *in vivo* [232,233]. Additionally, the culture conditions are directly linked to the barrier function of the developed tissue [129]. The composition of 3D oral mucosal systems thus far involves the use of stratified epithelial cell sheets, cultured on scaffold-embedded fibroblasts which mimic cellular structures below the epithelium, such as the submucosa [129]. The inclusion of fibroblasts in structures of this nature is believed to be crucial in the development of squamous epithelia *via* the proliferation and differentiation of keratinocytes [231]]. Such models have been used to evaluate the permeation of nano-titanium dioxide [234], nanometer polymersomes [235], and nano-hydroxyapatite [236]. A commercial product that is seen in the literature is EpiOral™, which consists of normal, human-derived oral epithelial cells which have been cultured to form multi-layered, highly differentiated models of the human buccal phenotypes [224]. EpiOral™ has been used to evaluate mucoadhesive buccal films loaded with insulin [79], nicotine [75], Epidermal Growth Factor and lysozyme [89], plus evaluate the permeation of caffeine after pre-treatment with ethanol or Listerine™ mouthwash [237]. EpiOral™ can be used to study drug permeability *via* placing the tissues in diffusion chambers such as the Franz Cell, or drugs can be added directly to cell inserts, and inserts can be transferred between wells filled with fluid [224]. However, the EpiOral™ model and other 3D organotypic models of this nature lack vascularity and immune system constituents which play roles in epithelial barrier function [234]. Again, such models also neglect the salivary mucus layer on the epithelial surface. Something of note, 3D bioprinting has been used to print cellular materials and tissue constructs and is a hot topic of pharmaceutical research currently [232,238]. 3D bioprinting has also been used to produce mucoadhesive films, so this versatile equipment could be used to both produce and evaluate mucoadhesive films in terms of their buccal permeability [93].

In the context of buccal permeation, a commercial biomimetic (Permeapad™) has been developed which can be used in a conventional Franz Cell apparatus to measure drug permeability [239]. The use of Permeapad™ has been used in the literature to evaluate the permeation of several compounds and showed a good correlation between other *in vitro* methods (Parallel Artificial Membrane Permeation Assay, Caco-2, TR146 cell layers, porcine buccal mucosa) and an *in vivo* method (Göttingen minipigs) [239,240]. An *in vitro-in vivo* correlation of $R^2 = 0.98$ was seen when comparing the buccal permeability of metoprolol in minipigs [240]. It can be seen from this data that the Permeapad™ offers a simple and effective alternative to conventional *in vitro* permeation studies for buccally administered formulation. It is worth noting, however, that the published work that is referenced here in relation to Permeapad™ was authored by the co-inventors of the technology.

6. Conclusions

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.

Data availability

All the resources used for this study have been included in the reference list.

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