Oral films: Current status and future perspectives

Ana Filipa Borges, Cláudia Silva, Jorge F.J. Coelho, Sérgio Simões

PII: S0168-3659(15)00153-4
DOI: doi: 10.1016/j.jconrel.2015.03.006
Reference: COREL 7591

To appear in: *Journal of Controlled Release*

Received date: 29 November 2014
Revised date: 28 February 2015
Accepted date: 2 March 2015

Please cite this article as: Ana Filipa Borges, Cláudia Silva, Jorge F.J. Coelho, Sérgio Simões, Oral films: Current status and future perspectives, *Journal of Controlled Release* (2015), doi: 10.1016/j.jconrel.2015.03.006

Oral films: current status and future perspectives

I - Galenical development and quality attributes

Ana Filipa Borges[1,2], Cláudia Silva[1], Jorge F. J. Coelho[3], Sérgio Simões[1,2]
[1] Bluepharma, Indústria Farmacêutica, S.A.
[2] Faculty of Pharmacy, University of Coimbra
[3] CIEPQPF - Faculty of Sciences and Technology, University of Coimbra

Contents

1 Introduction

A thin film that readily dissolves in the oral cavity is commonly referred as orodispersible film by the European Medicines Agency (EMA) [1] or simply soluble film by the FDA [2]. Although, oral films initially appeared as innovative breath freshening formulations, it rapidly evolved to give response to different market needs, namely an easy-to-carry and easy-to-swallow drug delivery system.

The oral films are essentially complex polymeric matrices that may be used efficiently as drug release platforms. These polymeric matrices may be composed by several components in order to achieve well-designed drug-delivery platforms, but usually hydrophilic polymers are its main core. The polymers early entered into the pharmaceutical and biomedical industries as essential components of the formulations and their range of applicability easily spread to several areas, from packaging material to the most sophisticated drug delivery systems and devices. The basic understanding of the role of polymers as excipients, meaning as ingredients in drug products, is critical for formulation development and quality control. Additionally, the knowledge of polymers' basic concepts, as chemistry, properties and types may be critical to develop new or improve conventional drug delivery systems.

Both natural and synthetic polymers can be used in orodispersible dosage forms. The oral films are basically a polymeric matrix which may vary on its composition in order to achieve the desired final product properties. There are several characteristics, such as mucoadhesiveness, disintegration time, % of drug load, mechanical / handling properties (among others) which may be fine-tuned by adjusting the type, amount or grade of the polymers. Additionally, other components may be added in order design the final product according to the target product profile, depending on the drug substance and therapeutic indication. Some of these substances include plasticizers, sweeteners, flavors, colorants, stabilizers, fillers, saliva stimulating agents, buffer systems and others.

Oral films emerged as a very promising and prominent pharmaceutical dosage form in a field subdued to tablets and capsules. The state of the art was also diffused and restrained about the matter until Dixit et al. in 2009 pledge us with a comprehensive overview of the subject, which may probably functioned as a catalyst for several research works. Currently, several original works and patents can be found in literature, but considerable efforts still need to be carried out to optimize the performance of the films [3-5]. Regarding the pharmaceutical field, there is still a considerable lack of guidance for the manufacture, characterization and quality control of the oral films.

This review highlights the essential points of oral films development from their appearance through their market growth and formulation key points. To facilitate the readers understanding, the review is divided in two distinct parts. The first part is focused in the galenical development and quality attributes of the oral films whereas the second part covers technological platforms, Intellectual Property protection and a market outlook.

2 Miscellaneous terms

Thin-film, oral film, wafer, oral strip, orodispersible film, oral thin film, oral soluble film, dissofilms, buccal soluble film, mucoadhesive film, buccal film, transmucosal film, are some of the innumerous terms that can be found in literature. Although, the terms seem to be easily differentiated, their meaning can sometimes be misinterpreted and misunderstood.

The oral films were recently introduced in the “Oromucosal Preparations” monograph of the European Pharmacopeia (Ph. Eur. 7.4) with the subchapter “Orodispersible films” whereas the mucoadhesive buccal films are included in the “Mucoadhesive preparations” [1]. These terms and designations should be carefully read and interpreted to avoid possible misinterpretations.

Orodispersible films should not be confused with buccal films, which should not also be narrowed to the mucoadhesive films designation.

2.1 Orodispersible films

Non-adhesive fast dissolving films are normally composed by low molecular weight (Mw) (approx. between 1.000 to 9.000 Da) hydrophilic polymers. The majority of the orodispersible films are not necessarily designed to be mucoadhesive, but they may exhibitsome degree of mucoadhesiveness, due to the inherent characteristics of the polymers used. This mucoadhesion may also vary depending on the chemical properties and Mw of the film-forming polymer used, as discussed later in this review. However, the Mw of the most common polymers used for this formulation type is usually below 200,000 Da [6]. Additionally, these films are intended to exhibit a fast disintegration in the oral cavity, be swallowed and absorbed to the systemic circulation in the gastro-intestinal tract. Actually, this is somehow explicit in both official definitions: “single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly” (Ph. Eur. 7.4, “Orodispersible films”) and a “thin layer or coating which is susceptible to being dissolved when in contact with a liquid” (FDA, dosage form) [1, 2]. Clearly, the high exposition of the drug substance in the oral cavity may influence its absorption through the oral mucosa, but certainly this fact is not the main purpose of the fast dissolving oral films. Indeed, this aspect may lead to another controversial issue, the urgent need of new regulations for oral films, aiming to establish adequately the product differentiation and to eliminate the idea that oral films compete directly with

the generics. Additionally, according with the previous, being develop as a generic would not be an easy task due to the interference in the Bioavailability and Bioequivalence Studies (BDBE) related with a possible super-bioavailability and consequently, the failure of these tests. In this case the higher bioavailability may be related with the fast availability of the drug and consequently some oral adsorption. However, if the reference product is already an orodispersible formulation, as the orodispersible tablets, this issue is easily surpassed, being the recent marketed generic oral films good examples.

2.2 Buccal films

The buccal films are intended to deliver drug substances through the oral mucosa. This goal might be more complex than it seems, since a higher residence time in mouth is far from being the only determining factor. The oral mucosa drug saturation should also be considered, and the one-way absorption should be kept in mind to avoid minimize inter and intra –individual variability. Consequently, multilayer films also appear as a new designation for the buccal films. The advantages of this drug delivery system are very significant. The oral cavity presents many advantages to drug delivery beyond its good acceptably by the patients. The oral mucosa, generally divided in sublingual, gingival, buccal and soft palatal mucosa, is relatively permeable allowing systemic transmucosal drug delivery (Figure 1). For instance drugs that can be rapidly absorbed via buccal delivery do not pass the gastrointestinal tract, which may subject the drug to degradation from stomach acid, bile and other first pass metabolism. As a result, these thin films have the potential to fasten the drug onset of action, to lower the drug strength and enhance the efficacy and safety profile of some drugs. Curiously, the European and USA definition is more consensual regarding these pharmaceutical dosage form - buccal films. In the European Pharmacopeia they are included in the mucoadhesive preparations, referred as buccal films and defined as “single-or multilayer sheets that adhere to the buccal mucosa and may dissolve” (Figure 2). FDA does not have so clear definition or designation for these films, but buccal soluble film or buccal film, may be acceptable designations if Onsolis® submission is taken as an example.

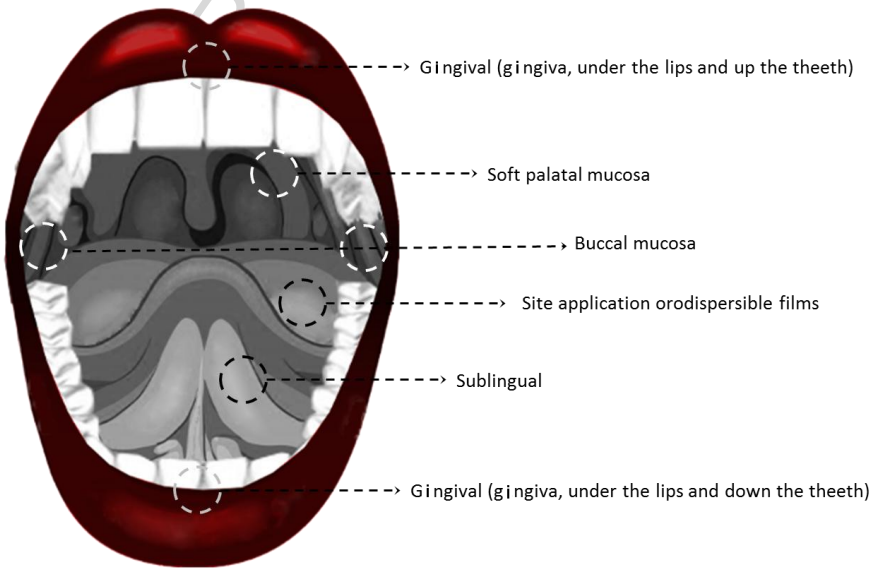

Figure 1 – Different local application sites of the oral films. Depending on the type of film the site of application may vary.

Finally, it is important to consider that additional designations may be used to specify and differentiate the oral film platform technology developed by each company. For example there are also references of some double- or multi- layer orodispersible films and sublingual orodispersible films [6, 7].

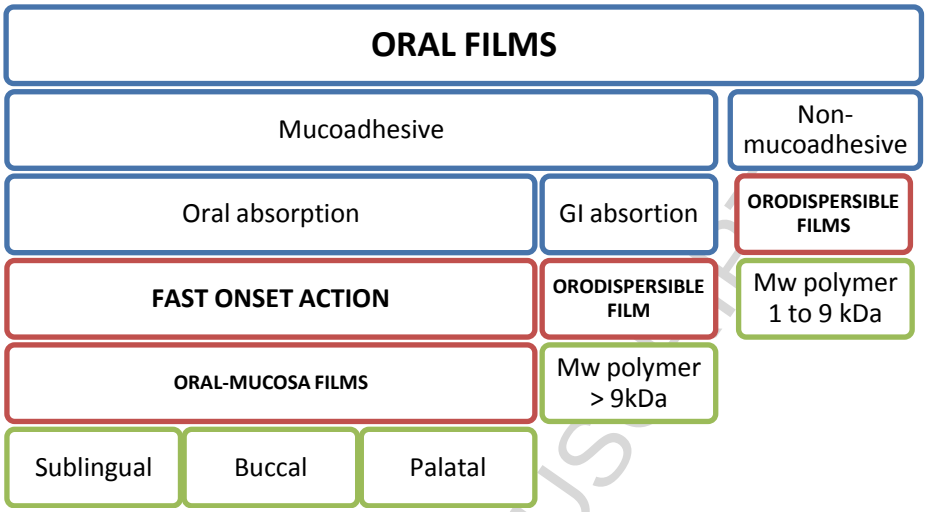

Figure 2 – Simplified scheme with the different terminologies.

3 Why oral films? Particular features for patients and companies

The design of an oral formulation is generally based on two critical factors, drug therapy and the target population. However, the choice of the type of pharmaceutical dosage form may become very difficult when specific target groups include very young children, from birth to 8 - 10 years of age, and geriatric population. Regarding the pediatric segment the major challenge involves the development of a specific type of dosage form suitable for children of all ages. Additionally, for both population groups the size of the dosage form can also be a challenge, essentially due to swallowing issues. The swallowing process involves synchronized actions of several nerves and muscles. It is assumed that a safe swallowing is an ability developed since the 12 years-old [8, 9]. Generally, the swallowing function underlay an aging process, then, some malfunctions may be age-related, normally called as presbyphagia, but also may be due to pathological conditions, usually referred as dysphagia [9]. These conditions are directly related with patients' drug therapy adherence which had led to the huge concern in the development of patient-centered formulations. Therefore, liquid or orally disintegrating dosage forms have been the most preferred and exploited for these population segments. Hence, the oral films appeared as a suitable alternative to patients with swallowing difficulties and also as a more suitable and convenient dosage form when compared to the conventional oral dosage forms.

3.1 Advantages for patients

In fact, orodispersible films promote patient compliance due to its appellative form and inherent ease administration [10]. These overall characteristics are especially important for young and elderly patients when proper and complete dosing can be difficult. Additionally, the drug delivery for these groups sometimes needs to be individualized / patient-tailored and may require special delivery devices. Nevertheless, this dosage form can also be beneficial for drugs with small therapeutic windows and for those that need precise dose adaptation in phases of initial dose monitoring; allowing the development of tailored therapeutic drug targets that otherwise may not be possible in conventional formulations. Furthermore, the oral films can be useful for bedridden and non-cooperative patients since they are easily administrated and hardly spited out.

3.2 Advantages over other oral dosage forms

There are also other advantages of the oral films when compared with conventional oral delivery forms. The orodispersible films are a fast dissolving dosage form more stable and resistant in comparison to some orodispersible tablets (ODTs), which are fragile and brittle. Oral films tend to be flexible and portable, whereas

ODTs demand special package for transportation. On the other hand, liquid dosage forms are considered very flexible and an alternative to overcome swallowing issues but they are usually associated to some limitations. Generally, liquids should be accurately measured by the care-giver and carefully shaken before administration. The amount of volume is also an important consideration since small amounts may lead to inaccurate measures whereas large amounts may contribute to diminish the adherence of the patients. On contrary, oral films enable improved dosing accuracy once every strip is manufactured to contain a precise amount of the drug. Additionally, depending on the package device is also possible to achieve high dose flexibility, as an electronic tape dispenser can be used that allows to dispense individual strips with adjustable doses simply by controlling an electronic system with a display [11]. As previously referred, oral films are an easy portable dosage form in contrast to the large liquid bottles and measuring devices that are inconvenient to transport. Besides that, it is also important to consider the poor stability of the liquid formulations, especially the aqueous-based mixtures, that in opposition to the majority of the oral films formulations require the addition of several substance to extend their shelf-life [1].

3.3 Market advantages

From the market perspective new drug delivery technologies offer the opportunity to extend revenue life cycles for pharmaceutical companies whose drug patent is about to expire and will soon be vulnerable to generic competition. Moreover, the grant of marketing exclusivity to the new dosage form would help to enlarge the revenue. This type of formulation may also be designed to discourage common methods of tampering associated with misuse and abuse of some prescription drugs [12].

Considering oral films as novel dosage form for drugs already in the market, with a different pharmacokinetic profile, the approval process should be a New Drug Application (NDA) 505(b)(2) for FDA approval, or an Abridged Application, Directive 2001/83/EC, for European Marketing Authorization approval. In this case, especially for the USA market clinical studies would be essential for the FDA granting three marketing exclusivity (3-5 years) [10, 13].

3.4 Clinical advantages

From the clinical point of view, some oral films may improve the oral bioavailability of drugs with extensive first pass metabolism, by promoting the absorption of the drug substance through the oral mucosa reducing the dose necessary to achieve the therapeutic action, which may contribute also to a reduction of the side effects [10]. Nevertheless, this absorption route may also be advantageous in drug therapies where a fast onset action is essential.

3.5 Major limitations

The most common limitations of the oral films are related to their instability in environments with high relative humidity, and the small drug dose that can be incorporated, essentially due to its small size, low weight and thin form. However, some companies had managed to develop oral film technology platforms that can incorporate more than 50% of drug substance (DS) per film weight (GAS-X Strips ®). There are also some types of drugs that should not be selected to incorporate in this pharmaceutical form, such as drugs that are unstable at buccal pH and that may irritate the oral mucosa [10].

Another critical issue is taste-masking since the dosage form is in direct contact with the oral mucosa and may remain in the mouth for long periods of time.

4 Polymers in oral films: the key component

Orodispersible films are basically a polymeric matrix which may be composed by one or more polymers with different physicochemical and functional properties. There are several characteristics that may be controlled depending on the type or grade of polymers: mucoadhesiveness, disintegration time, drug loading capacity, mechanical strength, elasticity, handling properties and others.

The selection of the polymer (or mixtures) for the development of oral film matrices is a critical step and may vary taking into account the desired target product profile. Hydrophilic polymers have been extensively studied and tested for this application.

Table 1, presents a summary of the most widely used polymers in the oral films preparation. Some chemical critical aspects that should be taken in consideration during formulation are revised hereinafter.

4.1 Celluloses

Celluloses, namely cellulose derivatives are widely used. Among those, hydroxypropyl methylcellulose (HPMC) is one of the most used. HPMC is a partly O-methylated and O-(2-hydroxypropylated) cellulose which is available in several grades that differ on their Mw and the amount of substituent groups on the anhydroglucose units [14]. The average number of methoxyl and hydroxypropyl groups attached to the ring, usually designated by degree of substitution (DS), influences greatly the oral film properties. There are some references that highlight how these structural and chemical differences may contribute to the final product properties, especially concerning the drug substance release and mechanical and thermal properties. Briefly, hydroxypropyl group, -$OCH_2CH(OH)CH_3$ is relatively hydrophilic group contributing to the rate of hydration, whereas the methoxyl group is more hydrophobic. Therefore, polymeric matrices with high hydroxypropoxyl / methoxyl ratio may easily establish a gel barrier [15]. This characteristic in polymeric film matrices was found important in the dissolution profile and drug substance release. HPMC grades with higher hydroxypropoxyl / methoxyl ratio were found to delay the release of the DS from the oral film matrix due to the formation of a thick matrix gel upon contact with the dissolution or biologic media [16]. Regarding the mechanical properties of the polymeric matrices it is described that methoxyl substitution degree along with the HPMC grade intrinsic viscosity has a remarkable influence. In general, HPMC grades with high viscosity and methoxyl content tend to produce more resistant, stiff and extensible polymeric matrices. High viscosity is possibly associated to higher branching and /or higher Mw related with physical entanglement due to longer chains. This phenomenon may increase the input strength required to disrupt the primary chain interactions (higher tensile strength). In turn, higher methoxyl substitution degrees may lead to an anchoring effect on HPMC chains provided by their larger dimensions compared to the original hydroxyl groups that may also contribute to high tensile strength. The Young's modulus seems not to be significantly affected by methoxyl substitution degree. Concerning the thermal characteristics of the HPMC films, the polarity of the polymer chains conferred by the methoxyl content apparently affects the glass transition temperature (Tg). HPMC grades with lower amount of methoxyl groups present lower polarity that contributes to the reduction of the free space between the polymer chains. The increasing proximity of the polymeric chains will strengthen the secondary interactions between them, which increases the energy required for chain mobility [17].

Additionally, the rearrangement of the methoxyl groups during the film formation could also diminish the polymer inter- and intra-chain hydrogen interactions, thereby suppressing possible hydrophilic hydroxypropyl group actions, which may affect the final product characteristics [18].

There are several HPMC grades available and as discussed above their selection should not be random, but evaluated according to the desired product profile. Essentially, there are 2 types of HPMC that are widely used in the oral films formulation, which according to Dow Chemicals grade classification are HPMC type K and E. The HPMC type K contains 22% methoxyl, or a methoxyl DS of 1.4, and 8.1% hydroxypropyl, or a hydroxypropyl DS of 0.21, whereas HPMC type E has 29% methoxyl, or a methoxyl DS of 1.9, and 8.9% hydroxypropyl, or a hydroxypropyl DS of 0.23 [15, 19]. The HPMC K is often used as polymeric matrix but mainly for controlled and /

or delayed release of the drug substance [16, 20-22], whereas HPMC type E is amply described in literature as film-forming polymer. The E3, E5 and E15 are referred, tested and used intensively, essentially due to their low viscosity and optimal Tg for suitable oral film matrices, 160^{o}C, 170^{o}C and 175^{o}C, respectively. The major difference between these grades are the polymer chain length, which together with the increasing number of their designation is associated with the increase in the HPMC's Mw (e.g. Mw HPMC E3 < Mw HPMC E5< Mw HPMC E15< Mw HPMC 50). It is reported that low concentration's solutions of E3 and E5 may lead to thin, brittle and non-peelable films. These properties can be ameliorated with the increase of these polymers' concentration, but the films are still referred as tacky [23]. Therefore, combinations of the different grades are preferred, especially mixtures with higher HPMCs' Mw [24]. Mixtures with other polymers are also described. HPMC E15 is found to have suitable film former properties when mixed with synthetic polymers, as polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP). Also, good film former properties can be achieved when HPMC is blended with microcrystalline cellulose and plasticizers, such as PEG 400 and glycerol [25]. HPMC was also blended with a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate (Eudragit® E PO), contributing to the formation of films with better clarity and flexibility [26]. On the other hand, HPMC - Maltodextrin blends, with higher Maltodextrins' concentration, allowed to obtain thin, fast-disintegrating, sweeter and tastier films [27].

It is demonstrated that HPMC origins films with optimal properties depending on its concentration and different blends. This fact is probably the reason why different authors are not consensual regarding the most suitable HPMC to obtain thin films with optimal characteristics. Additionally, it was shown that the drug substance may also have an important impact in the final film properties; some found that HPMC E3 was the most suitable grade to the manufacture cetirizine films [28], whereas others preferred the E5 to prepare triclosan films [29]. It is also described that the mechanical properties of the polymeric matrices are greatly affected by the different grades, and generally, the maximum puncture strength increase with Mw, E3 < E5 < E15 < E50 [30].

Hydroxypropyl Cellulose (HPC) is another cellulose derivative where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming $–OCH_2CH(OH)CH_3$ groups [14]. HPC has been used as film former due to its good properties to origin films with proper mechanical properties [31, 32]. HPC films have good carrying capacity, reasonable clarity and moderate bioadhesive properties associated with HPC's swelling capacity [30, 32]. An evident advantage of the use of this cellulose is the wide range of solubility [14], which allows a flexible selection of the solvent according to the drug solubility [33]. Interestingly, it is reported that when a combination of HPCs (Klucels EF - Mw 80.000, and KlucelX GF - Mw 300.000) is used to replace synthetic polymers (PVA and PVP) or HPMC in a polymer matrix with modified starch (Maltrin M100, Maltrin M180, Maltrin's QD M550, and Maltrin's QD M600 or Pure-Cote B792) the solubility properties of the films tend to improve [34].

Carboxymethylcellulose (CMC) is another cellulose derivative that in opposition to the previous non-ionic polymers is an anionic linear polysaccharide, produced by reacting cellulose with sodium monochloroacetate under controlled conditions [35]. CMC, also known as cellulose gum, is an important industrial polymer with a wide range of applications, essentially due to its low cost. In the pharmaceutical field it has a prominent value as thickener and it is ideal for applications requiring a fast dissolving base. It is commercially available with a wide DS range, between 0.4 and 1.5. The DS value of CMC has an important impact on the film-forming solutions properties, since higher DS values are directly related with a decrease in the interchain interactions due to the increase substitution of the hydroxyl sites [35]. CMC had proven to be useful for the preparation of optimal polymeric matrices, produces films with excellent clarity and with the ability of carrying a wide range of active components. CMC oral films with optimal characteristics to be used in oral health biotherapy had also been prepared [36]. In the preparation of buccal mucoadhesive films it was shown that sodium CMC improved the residence time of HPC and sodium alginate films [37]. It is also reported that CMC has a good compatibility with starch forming single-phase of polymeric matrix films with improved mechanical and barrier properties [38, 39]. However, some authors showed that HPMC based films are tougher, more elastic and bioadhesive *in vivo* than sodium CMC based films [40].

4.2 Starch

Among all natural biopolymers, starch was always considered one of the most promising polymers for this application, due to its wide availability, biodegradability and low cost [41, 42]. However, pure starch films are usually brittle and tacky. Native starch generally contains 75% of amylopectin and 25% of amylose, a combination that for this application is associated with a lack of strength, water resistibility, thermal stability and processability difficulties [41, 43]. Therefore, to obtain oral film matrices with optimal properties native starch should be blended with other polymers. The process issues are essentially related with the difficulty of dissolving native starch in water, due to its high molecular size and strong hydrogen bonding. In fact, to dissolve starch, low concentrations and high temperatures need to be used, which is not economically favorable. Thus, in order to overcome this disadvantage and also improve the product performance, several starch derivatives have been developed and are currently available on the market. Examples of modified starches applied to oral films are hydrolyzed starches, such as Maltodextrins (MDX) (e.g. MALTRIN®, from Grain Processing Corporation), hydroxypropyl starches (e.g. Lycoat ®, from Roquette), pre-gelatinized starches (e.g. INSTANT PURE-COTE® by Grain Processing Corporation (GPC)) and others, such as Pullulan.

In fact, Maltodextrins have been used blended with other polymers to improve the overall properties of the film, as already discussed, but also as sole film forming polymer [4, 44-46]. Chemically, MDX is a mixture of polymers that consists in D-glucose units, with a dextrose equivalent (DE) lower than 20, and are prepared by the partial hydrolysis of a food-grade starch [14]. MDX origins good quality films [47] with fast disintegration and low dissolution time (<45 seconds) [44, 46]. Low DE MDXs offer higher viscosity and better film formation than higher DE MDXs. It is also referred that low DE MDXs present an improvement on flexibility and reduced cracking compared to modified starch-based films [48]. In turn, when blended with microcrystalline cellulose (MC) tends to form non-sticky and smooth polymeric matrices [4].

Similarly, Lycoat® can also be used as sole film forming polymer with excellent functionality. Although, it is easily dispersed in cold water, it is suggested the treatment at 70°C in order to improve its film forming ability. In addition, by contrast with native starch solutions, Lycoat® cooked solutions can be immediately cooled down, since the gelation and retrogradation would not be probable to happen due to the high stability of the hydroxypropylated starch molecules [49]. Compared with HPMC, hydroxyethylcellulose and polyvinyl alcohol, Lycoat® showed faster dissolution time, moderate moisture uptake and satisfactory mechanical properties [50].

The pre-gelatinized starch is a chemically and/or mechanically processed starch, commercially available in fully or partially pre-gelatinized grades. The first is easily soluble in cold water, whereas partial pre-gelatinization produces a starch with soluble (gelatinized) but also insoluble fractions [14, 51]. The knowledge of these differences is critical to obtain formulations with the desired disintegration times.

INSTANT PURE-COTE® is a pre-gelatinized starch, marketed by GPC, with good film-forming capabilities. This polymer origins clear, strong and flexible films using a 15 to 20% solution by solvent-casting process [52]. GPC offers a broad range of modified starches for pharmaceutical applications including also the PURE-COTE® a corn starch specifically modified to produce clear, flexible, fast drying and tasteless oral polymer matrices [53-55].

Pullulan, is a modified starch composed by glucose units in maltotriose units connected by α(1→4) glycosidic bonds whereas the consecutive maltotriose units are linked by α(1→6) glycosidic bonds. Pullulan have both suitable processing and film-forming properties that turn it into one of the preferred polymers to be used in the preparation of oral polymeric matrices. It is easily soluble in hot or cold water, and forms a clear and viscous solution that origins smooth, transparent and stable films. Pullulan is obtained from a fermentation process of yeast, the *Aureobasidium pullulans*, thus, its low availability results in a high cost product [56]. Therefore, Pullulan is usually blended with other compatible polymers that are more abundant and less expensive. For example, other modified starches may be used in combination with Pullulan, to decrease the overall cost. In fact, 50 to 80% of Pullulan can be replaced by starch or modified starch without the loss of its required properties as a good film-former [10]. Sodium alginate and CMC, can also be used with the same purpose since they are compatible. In fact, the formation of hydrogen bonds between the COO groups of alginate and CMC with the –OH groups of Pullulan may synergistically enhance the material properties of the resulting film [30,

57]. In addition, it is also reported that Pullulan – HPMC blends, with a HPMC content above 50%, a miscible composition is obtain, and the final polymeric matrix presents improved thermal and mechanical properties [58].
The mechanical properties of Pullulan films prepared at various temperatures were also studied. Generally, films prepared at low temperatures are stiffer and more flexible than films prepared at higher temperatures that are brittle and do not have a clear plastic deformation. The Pullulan based films usually present a fast disintegration time. [59]

4.3 Semi-synthetic, synthetic and others

There are others natural or semi-synthetic polymers that have been tested as polymeric matrices for drug delivery application, such as: rosin and rosin derivatives, gelatin, sodium alginate, pectin and others [60, 61]. Gelatin has excellent properties as film former, but the high viscosity during the processing difficults the handling and limits its applicability in films formulations. On the other hand, the pectin usage limitation is more related with the final product characteristics rather than the manufacturing process. Pectin is a natural polymer obtained from citrus fruits and apples, with a good film forming capacity. Pectin based films have optimal capacity to carry drug substances [61], but tend to dissolve slowly. This is related with pectin's strong mucoadhesive properties, which is not very useful for fast dissolving films. Thus, modified pectins had also been produced and tested to obtain films with fast dissolution rates [62].
The synthetic polymers have been also intensively explored as film-formers, but the majority converge to PVA, PVP [63] and methacrylate polymers [25].
PVA is a water soluble polymer prepared by partial or complete hydrolysis of polyvinyl acetate that has been successfully used as main film-former polymer [64, 65]. It is also available a polyvinyl alcohol-g-polyethylene glycol copolymer (PVA–g-PEG), Kollicoat® IR, composed by 75% PVA and 25% PEG units. There are considerable advantages of this copolymer compared to pristine PVA. Regarding the manufacturing process, it is important to consider that PVA is only completely solubilized in hot water and the increase of the PVA hydrolysis is directly proportional to the temperature needed to PVA complete dissolution. In opposition, Kollicoat® IR is freely soluble in water and the presence of the PEG spares the addition of plasticizers to the formulation, simplifying the processability. Additionally, it was shown that the higher ability of Kollicoat® IR to form very flexible films with higher elongation at break values when compared with cellulose derivatives based films. This is probably due to the PVA moiety, combined to the plasticizing and surfactant properties of the PEG moiety [66, 67].
PVP or Povidone is a polymer with linear 1-vinyl-2-pyrrolidinone groups that is available with different molecular weights [14]. In general, PVP is described as a good film former [32, 50, 68-70], but some authors described PVP as a polymer with very poor film forming capacity, which may be improved to an average film former polymer when blended with PVA or HPMC, resulting in transparent and fast disintegration films [71]. This discrepancy may be due to the different PVP's Mw used in the different studies. PVP has been widely explored as film former because it is an edible polymer that rapidly dissolves in mouth. It is sufficiently soluble in both water and organic solvents enabling the use of the most appropriate solvent during the process and manufacture depending on the drug substance. However, PVP exhibits higher hygroscopicity than HPC, which justify the preference of some authors for this cellulosic derivative polymer [68]. It is reported that PVP K90 (about Mw 750.000) blended with Ethyl Cellulose and HPC origins films with increased flexibility and softer and tougher properties. It was also verified that the PVP addition, contributes to an increase of the film's swelling rate and extent which results in higher barrier effects that decrease the drug substance diffusion. It is also described that PVP may augment significantly the bioadhesive strength probably due to hydrogen bonding and Van der Wall forces [32]. PVP K90 based films may also present fast disintegration time depending on the formulation composition. However, it is reported that HPMC-PVP K90 based films, when compared with HPMC-MDX and HPMC-PVA blends, had lower dissolution rate, probably due to the viscoelastic properties of PVP K90 [50]. It is also demonstrated that different ratios of PVP - alginate blends can be used to control the drug release: higher amount of PVP

contributes to smaller dissolution times whereas higher Mw PVP origins films with increased drug release lags [70].

Polyethylene Oxide (PEO) is another synthetic polymer that has been used as main film forming polymer for the preparation of oral films due to its peculiar characteristics [72-75]. PEO is a nonionic hydrophilic PEG with high molecular weight that is commercially known by POLYOX™. Interestingly, PEO can be used as self-plasticizing polymer matrix, due to its low Tg, about -67°C [30], especially for Mw ranging from ~100kDa (Polyox WSR N-10) to ~4,000kDa (Polyox WSR 301). This feature eliminates the need of an additional plasticizer in the oral films formulation, allowing a higher drug load due to the smaller number of excipients (56% by weight of the film) [74]. PEOs with higher Mw, as Polyox WSR Coagulant or WSR 303, may be preferentially used to increase the mucoadhesiveness of the films [14, 74].

PEO based films are described as films with good resistance to tearing, minimal or no curling, and fast dissolution rate [76]. Additionally, it is reported the dissolution time for different POLYOX grades, as expected, increases with the Mw: N-10 (Mw=100kDa) < N-80 (Mw=200kDa) < N-750 (Mw=300 kDa) < WSR 205 (Mw=600 kDa). In fact, POLYOX N-10, N-80 present disintegration times lower than Pullulan films, whereas POLYOX WSR 205 and N-750 have dissolution times similar to the Pullulan films. The same authors also reported that PEO based films have a pleasant mouth feel, without a sticky feeling or formation of a highly viscous gel in the mouth. However, the puncture strength of POLYOX N-750 is reported to be 3,000 kg/m^2, slightly lower when compared with some available commercial Pullulan based films (about 10,000 kg/m^2) [72]. The desirable characteristics of the resulting oral film can be designed by using different PEOs' grades and concentrations. On this matter, it is possible to balance the tear resistance, dissolution rate, and adhesion tendencies of film compositions combining low Mw PEO from 50% to 75%, with a higher Mw PEO and / or with a cellulosic polymer, as HPC or HPMC [76].

There are several polymers that are continuously being explored to develop these matrices for drug delivery. The innumerous types of polymers, the different polymer grades, and the several possible polymer-polymer blend ratios result in an exponential number of possible formulations and a wide range of final product characteristics. Therefore, it is crucial to have a deep understanding of the system under development to avoid undesired and unexpected product profiles.

Although, polymers are the main oral films component, additional excipients may be required in order tailor the target product profile. These excipients include plasticizers, sweeteners, flavor, colorants, stabilizers, fillers, saliva stimulating agents, buffer systems and others.

Table 1 - Most widely used polymers in oral films formulations.

Class Polymer	Polymer ID	Chemical features to consider	Formulation Impact		Examples	Characteristics	Application	
Celluloses								[14-18]
	HPMC	• Several Mw • Diverse substituent groups on the anhydroglucose units • average number of methoxyl and hydroxypropyl groups attached to the ring	• high hydroxypropoxyl / methoxyl ratio	• easily establish a gel barrier • delay the release of the DS	type K	• 22% methoxyl or DS of 1.4, • 8.1% hydroxypropyl, or DS of 0.21 • mainly for controlled and / or delayed release of the drug substance		[15-22]
			• high viscosity and methoxyl content (lower hydroxypropoxyl / methoxyl ratio)	• more resistant, stiff and extensible polymeric matrices • suppression possible hydrophilic hydroxypropyl group actions	type E	• 29% methoxyl → DS of 1.9 • 8.9% hydroxypropyl → DS of 0.23 • low viscosity and optimal Tg for suitable oral film matrices • the maximum puncture strength increase with Mw, E3 < E5 < E15 < E50 • E3, E5 and E15 Tg for suitable oral film matrices,	• E3 and E5 may lead to thin, brittle and non-peelable films • HPMC E15 has suitable film former properties mixed with PVA PVP • good film former blended with microcrystalline cellulose, Eudragit® E PO or Maltodextrins • good film former with plasticizers PEG 400 or glycerol	[15, 19, 23-30]

		160°C, 170°C and 175°C

Class Polymer	Polymer ID	Chemical features to consider	Formulation Impact		Examples	Characteristics	Application	
Celluloses	HPC	• Several Mw • Degree of substitution	• good drug loading capacity		Klucels EF KlucelX GF		• used to replace synthetic polymers or HPMC in a polymer matrix with modified starch to improve solubility	[14, 31-34]
			• swelling properties	• moderate bioadhesiveness				
			• wide range of solubility	• allows a flexible selection of the solvent according to the drug solubility • simplified processability				
	CMC	• DS range, between 0.4 and 1.5	• higher DS values	• decrease in the interchain interactions due to the increase substitution of the hydroxyl sites				[35, 36]
			• Swelling properties	• mucoadhesive preparations	NaCMC	• films with excellent clarity and with the ability of carrying a wide range of DS	• sodium CMC improved the residence time of HPC and sodium alginate films • good compatibility with starch forming single-phase polymeric matrix films with improved mechanical and barrier properties	[37-40]

Class Polymer	Polymer ID	Chemical features to consider	Formulation Impact		Examples	Characteristics	Application	
Starch	Native starch	• generally contains 75% of amylopectin and 25% of amylose • high molecular size • strong hydrogen bonding		• lack of strength, water resistibility, thermal stability and processability difficulties				[41-43]
	Maltodextrins	• D-glucose units, with a dextrose equivalent (DE)	• Low DE MDXs	• higher viscosity • better film formation	MALTRIN®		• fast disintegration • blended with microcrystalline cellulose (MC) tends to form non-sticky and smooth polymeric matrices	[4, 44-48]
	Hydrolyzed substituted starches	• Hydrolysis degree • Substituent type • Substitution degree	• hydroxypropylated starch molecules	• high stability	Lycoat® (hydroxypropylated pea starch)	• fast dissolution time • moderate moisture uptake • satisfactory mechanical properties		[49, 50]
	pre-gelatinized	• fully or partially pre-	• partially pre-gelatinized grades	• insoluble fractions	INSTANT PURE-COTE®	• clear, strong and flexible		[14, 51-

	starch	gelatinized grades		• critical to produce formulations with the desired disintegration time		films	55]
					PURE-COTE®	• clear, flexible, fast drying and tasteless oral polymer matrices	
	Pullulan		• Too expensive	• 50 to 80% of Pullulan can be replaced by starch or modified starch		• smooth, transparent and stable films • films with fast disintegration	• Blended with Sodium alginate and / or CMC, may synergistically enhance the properties of the film • Pullulan – HPMC films, have improved thermal and mechanical properties	[10, 30, 57-59]
			• films prepared at low temperatures	• stiffer and more flexible				
			• higher temperatures	• brittle and do not have a clear plastic deformation				

Class Polymer	Polymer ID	Chemical features to consider	Formulation Impact		Examples	Characteristics	Application	
Pectin			• Swelling properties	• strong mucoadhesiveness • not very useful for fast dissolving films		• good film forming capacity • optimal capacity to carry drug substances • dissolve slowly	• modified pectins tested to obtain films with fast dissolution rates	[61, 62]
PVA		• Hydrolysis degree	• Fully hydrolyzed	• Not soluble in cold water • Not useful for fast dissolving films				[64, 65]
			• partially hydrolyzed	• soluble in cold water • application in fast dissolving films				
	PVA–g-PEG		• PEG incorporated	• spares the addition of plasticizers • simplified processability	Kollicoat® IR	• very flexible films • higher elongation at break values		[66, 67]
PVP		• Molecular weights	• wide range of solubility	• flexible solvent selection according to the drug solubility • simplified processability			• improved to an average film former polymer when blended with PVA or HPMC • blended with EC and HPC origins films with increased flexibility, softer and tougher properties. • different ratios of PVP - alginate blends can be used to design drug controlled release	[32, 50, 68-70]
			• swelling rate and extent	• higher barrier effects → decrease the drug substance diffusion				
PEO		molecular weight	• low Tg	• self-plasticizing		• films with good	• balance the tear	[14, 30,

			polymer matrix • higher drug load due to the smaller number of excipients • simplified processability		resistance to tearing, minimal or no curling, • fast dissolution rate • pleasant mouth feel, no sticky feeling or highly viscous gel formation	resistance, dissolution rate, and adhesion tendencies of film compositions combining low Mw PEO, with a higher Mw PEO and / or with a celluloses	72-76]
		• high Mw	• mucoadhesive films • dissolution time increase				

5 Mucoadhesion: a polymeric inner property?

Although the mucoadhesion concept appeared early during the eighties, it was only ten years later that improved mucoadhesive polymers were introduced in the pharmaceutical field [77]. There are several theories that may explain the bioadhesion process, but none is able to explain the overall mechanism. The wetting theory is one of the oldest theories and involves notions of thermodynamic work and contact angle. Briefly, the bioadhesion in this theory is defined as the surface tension of the two adherent phases subtracted by their apparent interfacial tensions. On the other hand, the diffusion theory is related with the possible relation between the polymeric chains with the glycoprotein mucin chains. According to this theory depending on the depth of the contact, semi-permanent bonds, between the substrate and polymer adhesive chains, may occur. Therefore, the diffusion coefficient may be influenced by the polymer's Mw and cross-link density. Other theories are associated with attractive forces mediated by electrons transference (electrostatic theory) or by chemisorption due to the formation of van der Waal's, hydrogen and hydrophobic bonding (adsorption theory) and / or fracture strength (fracture theory). Nevertheless, the polymers may be categorized according to the binding type to the mucosa [77].

5.1 Ionic polymers

The bioadhesive polymers tend to adhere to the biological substrates mostly by interpenetration followed by secondary non-covalent bonding. These secondary interactions are usually hydrogen bonds between the charged polymers' chains with the oligosaccharide side chains of the mucus proteins. Some of the most effective anionic polymers are the polyacrylates (Carbopols) and carboxymethylcelluloses (CMC) [77-79]. Carbopols are synthetic high-molecular-weight polymer cross-linked with either allyl sucrose or allyl ethers of pentaerythritol, which present a rapid, high, and stable swelling and good mucoadhesive properties. The NaCMC is also used but normally in combination with other polymers to increase the bioadhesive performance of the oral films. Hydroxyethyl cellulose (HEC) based films generally present high swelling properties and rapid erosion but exhibit poor mucoadhesive properties, therefore NaCMC can be added to enhance this property. The referred mucoadhesive polymers are included in the so called first-generation and have been intensively used. Their bioadhesion properties come essentially from the H-bonds with their carboxyl functional groups. In addition, the sulfate groups are also characterized by their bioadhesion due to anionic non-covalent and H-bonds. These functional groups are characteristic of the Carragenans, a gum polymer widely used. There are several types of carrageenan but Carrageenan k, is the most mentioned for the oral films development. This is a strongly gelling polymer with small but stable swelling characteristics and moderate mucoadhesive properties [77-81] (Figure 3). Additionally, cationic polymers can naturally be used as bioadhesive materials since they tend to interact with the anionic substructures present in the mucus, such as sialic acid groups. Chitosan is among all cationic polymers one of the most widely used and tested for biomedical and pharmaceutical applications [82, 83]. Chitosan is a natural polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine presenting a high to moderate swelling and mucoadhesive properties [14, 77, 84] (Figure 3).

Regarding amphiphilic polymers, non-covalent bonds can also be established. The cationic structures adhere to the mucosa by interacting with negatively charged substructures of the mucus, whereas the anionic parts interact with the oral mucosa essentially through hydrogen bonds.

5.2 Neutral polymers

Non-ionic polymers can also present bioadhesive properties through non-covalent interactions with the surrounding fluids. For instance, the mucoadhesiveness of PEO and Polycarbophil polymers would be promoted by the high entanglement level of their polymer chains followed by possible hydrogen bonds formation [85] (Figure 3).

The concept of chain entanglement emerged early during the nineties in attempt to explain the mechanical properties of amorphous polymers above the Tg. The evidence of its existence is mainly based in the mechanical properties behavior of the materials. The entangling interactions might be simply resumed as an ability of the molecules to slip to different equilibrium positions promoting somehow temporary links of physical interlocking, distinct from the permanent chemical linkages [86].

The length and flexibility nature of the polymeric chains may allow the rearrangement through loops that might offer high resistance to deformation for a while, but would eventually slip or be removed and reformed by random thermal motion. Additionally, most prominent effects were observed at high polymer concentrations and Mw, with low crosslink densities and large primary chain lengths [86].

After the polymer matrix-substrate contact the interpenetration of the polymer chains with the mucus glycoproteins may induce the chain interlocking or physical entanglement, which would be associated with possible conformational changes and followed by secondary chemical interactions.

The mucoadhesiveness measured by rheology comparing different non-ionic polymers, showed that, although weak, the HPMC adhesiveness was superior to the MC. The same authors also reported that PEO with low Mw, inferior to 4000kDa, do not present significant mucoadhesiveness [87].

PEO are polymers with long linear chains in which their length is directly related with de Mw. Low Mw PEOs may not be so favorable to form entanglement conformations able to promote mucoadhesion. Regarding the celluloses, it is also valid the unfavorable conformation for entanglement that is probably more related with the stiffness of their backbone as a result of their inherent chemical nature. The cellulosic anhydroglucose ring is empirically more rigid than the long linear chains of ethylene oxide oligomers (PEO). Furthermore, despite the physical interlocking of the chains, secondary chemical bonds (as hydrogen bonds) may be formed and would contribute to strengthen the links. Therefore, between the celluloses, the high density of available hydrogen bonding groups may contribute to stronger interactions of the polymer chains with the mucin glycoproteins. Nevertheless, the celluloses tested by the authors have significant different viscosities (MC with 4000 cp and HPMC 80000–120000cP, 2% solutions [19]) indicative of very distinct Mw, which may turn this mucoadhesiveness comparison unreliable regarding the different type of cellulose.

Other assays with neutral polymers, dextran and PEO, reforced that mucoadhesion could be increased by the polymer concentration, is hardly affected by the pH and may be reduced by the molecular branching and short linear polymer chains [88, 89].

These studies highlight the existence of physical chain entanglement between the polymer chains and glycoproteins and their relevance in the mucoadhesion.

Furthermore, it is important to consider that besides the importance of this mechanism to explain the mucoadhesiveness of the neutral polymers, it may also be relevant in the ionic polymers [87]. In fact, the chain entanglement is also described for charged polymers, as poly (acrylic acids). Depending on the polymer chain lengths the entanglement may also favor the chemical reactions between ionic polymers and the mucin proteins as well as to other secondary chemical bonds.

Moreover, the high Mw Poly(methacrylate) with effective entanglement chains exhibit a very poor bioadhesive properties in its non-ionic form, which may only be mitigated when its salt form is used [90]. Though, the non-covalent adhesive bonds of non-ionic polymers are usually weaker than the non-covalent bonds established by charged polymers (anionic or cationic).

5.3 Thiomers

The majority of the polymers referred are essentially water-soluble and their bioadhesiveness to the mucous membrane arises from their non-covalent bonds after hydration. This property has been widely explored in pharmaceutical technology for several years, but only during the 90s real ‘pharmaceutical glue’ excipients had been developed. In fact, a clear distinction can be found in literature, a first generation including the mucous-non-covalent-bond polymers and a second generation comprising mucous-covalent-bond polymers. These

polymers commonly called thiomers are capable of forming covalent bonds, mainly based on thiol /disulfide exchange reactions. The thiol groups of the polymers bond covalently to the cysteine-rich subdomains of the mucus layer by the formation of disulfide bonds (Figure 3). There are several anionic and cationic thiolated polymers that have already been synthesized: polycarbophil-cysteine, poly(acrylic acid)-cysteine, alginate-cysteine, chitosan-4-thio-butylamidine, chitosan-thioglycolic acid, chitosan-2-mercaptoethylamine [77, 78, 91].
It is reported that these thioled polymers present improved mucoadhesion characteristics compared to the unmodified counterparts. In addition, a new type of thiomers has been recently developed, the preactivated thiomers, which have better mucoadhesive properties and higher stability: chitosan-thioglycolic acid mercaptonicotin amide, pectin-cysteine-mercaptonicotinic acid and chitosan-4-thiobutylamidine-mercaptonicotinamide.
Generally, these second generation mucoadhesive polymers are usually less sensitive to ionic and pH changes and the disulfide bonds may facilitate controlled drug diffusion due to the higher rigidity and cross-linking. Therefore, these polymers may be preferred to develop modified profile release drug delivery systems whereas the first-generation polymers are preferable to fast onset drug release [77, 78, 91].
Although many researches have been performed in this area, the application of thiomers in oral films has not been explored to the best of our knowledge. In table 2 it is summarized some of the research work performed with thiomers. There is a wide range of drug delivery systems developed and studied but for buccal or oral delivery, but it is mainly related to tablets. Regarding the first generation thiomers, their usage in the oral films development may also be challenging due to their inherent instability. Thiomers are unstable in aqueous solutions with pH ≥ 5 due to the oxidation of the thiol groups. It is also advisable the production and storage under inert conditions, light and oxygen protection, to avoid thiomer formulations instability. However, the second generation thiomers are more stable in solutions and in a broader pH range [92, 93]. Nevertheless, the inclusion of these components in pharmaceutical dosage forms may be still restricted to some applications due to regulatory (e.g. safety assays, registration) and process-production scale-up issues [93]. Currently, there are only clinical trials for ocular application of chitosan-N-acetylcysteine conjugate [92-95] and hyaluronic thiomer [96].
Additionally, the inclusion of these compounds in the oral films, especially in buccal films, may also be used as permeation enhancers and protein /peptides stabilizers as already explored by others [97-100].

Table 2 – Summary of some of the research work performed with the thiomers.

		Drug Delivery type	Dosage form	Drug substance	Reference
Thiomers	Polycarbophil-cysteine	Buccal	Patch; four layered films		[101]
		Buccal	tablets	rifampicin	[102]
	poly(acrylic acid)-cysteine	Oral	Liposomes		[103]
		Ocular	Inserts	diclofenac salts	[104]
		Ocular	microparticles	bromelain	[105]
			Tablets		[106, 107]
	alginate-cysteine	Ocular	bilayer inserts	Gatifloxacin	[108]
		Oral	Tablets		[109]
		Oral	Tablets	tramadol hydrochloride	[110]
	chitosan-4-thio-	Oral	Tablet		[111]

	butylamidine		in situ gel-forming system	Protein	[112]
		Oral	Tablets	peptide	[113]
preactivated thiomers	chitosan-N-acetylcysteine conjugate	Ocular	Lacrimera® eye drops	dry eye syndrome	[92, 93]
	pectin-cysteine-mercaptonicotinic acid	Oral	Minitablets	rosuvastatin	[114]
		Buccal	Gel delivery	calcium lidocaine	[115]

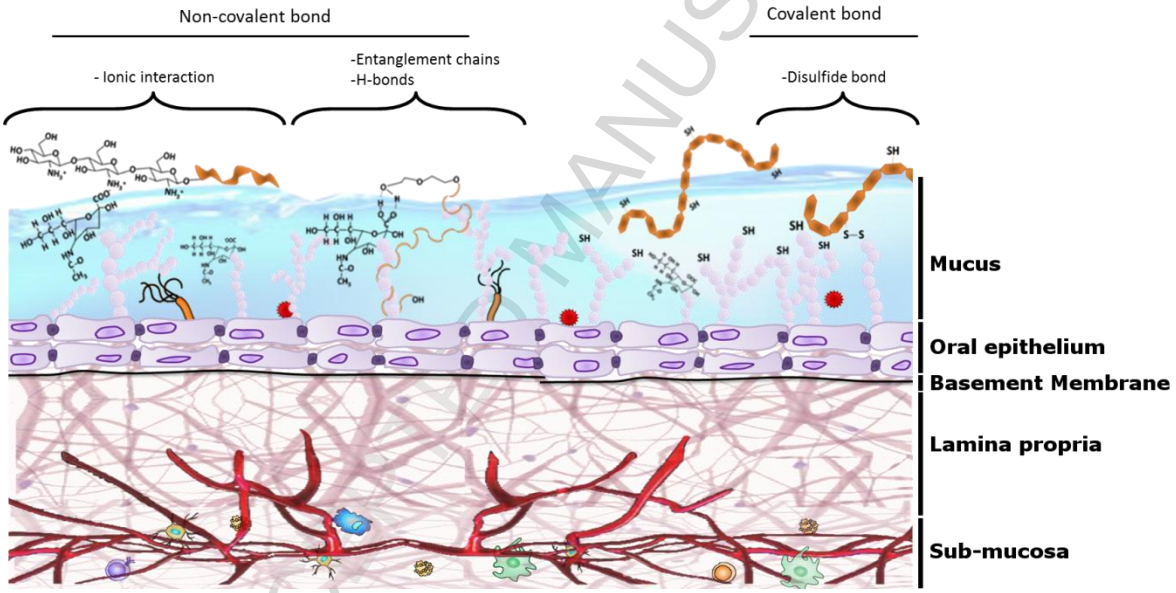

Figure 3 – Bioadhesive interactions. Simplified oral mucosa representation: sub-mucosa with nerves and blood vessels, lamina propria, essentially with connective tissue and with some blood vessels, basement membrane usually a single cell layer lying in the interface of the epithelium and lamina propria; a simplified oral epithelium only for representative purposes; and a mucus layer with mucin and glycoproteins. The mucoadhesiveness of the polymers to the oral mucosa may be explained by the non-covalent and covalent bonds, depending on the polymers' functional groups.

In general, any polymer is capable of establishing electrostatic interactions presenting some degree of bioadhesive properties. Additionally, the majority of polymers used to prepare oral film matrices are rich in hydroxyl groups, which can easily interact with the biological subtracts through H-bonds. This is associated with the natural mucoadhesion of the majority of the hydrophilic polymers used to prepare these platforms. Furthermore, some of these polymers can also be used as adjuvants or modifiers to improve or diminish film's mucoadhesive characteristics. Polymers with small but stable swelling properties characterized by very poor mucoadhesion, such as Agar (hydrophilic colloidal polysaccharide) or Acacia (complex and loose aggregate of sugars and hemicelluloses) can be used to decrease matrices bioadhesion. Another example is the Poly-D,L (lactide-co-glycolide) (PLGA), a synthetic copolymer of lactide and glycolide PLGA, that can be added to the polymeric matrix to confer hydrophobicity to diminish the swelling of other polymers and / or to obtain a prolonged drug release [116-121].

6 Polymer selection

As discussed on previous sections, the polymer selection during the formulation development of polymeric matrices may be critical and some points should be considered. Several examples were given related the ability of the polymer to affect the mechanical and texture properties of the films and also their influence on the drug release. On the other hand, the inclusion of the drug substance in the polymer matrix may also affect significantly the mechanical properties of the film. Depending on the chemical structure of the DS and the % of drug load the DS may easily interpose between the polymer chains, interfering with the polymer intermolecular bonds. This effect may allow the polymer to move more freely, resulting in matrices with higher flexibility due to a reduction on the elastic modulus and tensile strength parameters [32]. In fact, depending on the drug, the effects may be different, for example, chlorpheniramine maleate has a higher plasticizer effect on HPC based films than indomethacin. Nevertheless this plasticizing effect may also have direct impact in the oral film manufacture, due to chemical modifications of the mixture properties, such as reducing the softening temperature [122].

Aesthetic and performance characteristics should also be considered during the selection of the polymer. This dosage form is for oral administration and may have some residence time in the oral mucosa. Therefore, polymers that may become unpleasant should be avoided. Therefore some aspects as taste masking, physical appearance and mouth feel should be considered. The hydrophilic polymers are the major choice for the preparation of oral film matrix so the film may smoothly and softly dissolve in the oral cavity. Polymers or combinations that tend to form pastes should be avoided since it may become unpleasant. Regarding the manufacturing process, properties such as good wetting, spreadability, sufficient peel, shear and tensile strengths, should also be taken in consideration.

The mechanical properties of the polymeric matrix are also critical. An ideal oral film should be flexible, elastic and robust enough to resist to handling, transportation and the stress from mouth activities. Generally, low-molecular-weight polymers dissolve quicker, but polymers with higher molecular mass origin films with better mechanical properties. Additionally, the polymer should be preferentially ready-to-use, not toxic or irritant to the oral mucosa and ideally not very expensive. Therefore, a mixture of polymers is preferable used, instead of a one-polymer-based- film, in attempt to improve and optimize the final polymeric matrix characteristics.

7 Critical quality attributes (CQA)

There are general critical quality attributes of the oral films that should be considered during their development. These properties are obviously inherent to the formulation but also significantly influenced by the manufacturing process. Hereinafter, are described briefly some of the most common quality attributes that should be considered during the oral film development.

7.1 Physical strength

Appropriate physical strength, is one of the most evident CQA of the oral films. The product should have suitable mechanical properties so it can be easily manufactured, packaged and handled without damage or break. However, there are no guidelines with the description of the most adequate properties, methods and ranges that should be studied. However, in literature there is a general consensus about the main properties that should be tested: elongation at break, young's modulus and tensile strength [10, 123, 124]. The literature review highlighted the difficulty of stablishing strict ranges for these parameters [123] and a wide variation may be appropriate depending on the polymeric matrix under development. In fact, the appropriate value for the mechanical strength may vary significantly depending on the polymeric matrix and method of manufacture [125].

An appropriate balance should be found between these properties. The oral film should be malleable so it can be handled without break but not too flexible that extends easily and deforms during cutting or packaging processes. It should present enough tension so it can be pulled out from the pouch, rolled up after casting, pealed from the release liner, but not too much that may difficult the cutting process. Nevertheless, the mechanical evaluation is particularly important during the product life-time but also for up-scale manufacturing process, since all the process from coiling to the packaging demands robustness [81].

7.2 Stability

It is important that the product has the ability to maintain its suitable properties over time, so physical and chemical stability are assured. These characteristics depend on the polymeric matrix and possibly on the manufacturing process. Thus, suitable stability and screening tests should be planned and performed during the development stage. However, proper approaches that may also guarantee the product stability are well-controlled manufacturing conditions, and the selection of an adequate packaging material in an early-development-stage.

Regarding the chemical stability, it is important to consider the polymeric matrix characteristics. The complexity of these matrices is sometimes underestimated and careful attention should be taken during its development. Although the majority of the reaction / interactions need high temperatures to take place, it is found in literature hypothesis of some reactions that may occur at room temperature in polymeric film matrices [126, 127]. Nevertheless, there are excipients that may inadvertently function as reaction catalyzers, compromising the product stability.

Importantly, it is also to assure the drug substance stability incorporated in the polymeric matrix. Although the stability of some drug substances is well known, the change of the pharmaceutical form may interfere with it. The Suboxone® sublingual film is a good example, in which Naloxone may be more easily oxidized in the film compared to the sublingual tablets available. Therefore, the shelf-life is limited to 12 months if the storage temperature is reduced from 30^{o}C to 25^{o}C [128].

The thermal stability of the product should also be considered since it may influence its long term stability, its storage conditions and possible restrictions.

7.3 Appearance

The appearance of the films is another relevant CQA. The size and the shape should be carefully studied and selected depending on the strength and application site. This has special importance for sublingual formulations which have a small available area to adhere. Moreover, the buccal films, which generally tend to be placed in the mouth for long periods of time, should also have suitable dimensions to be comfortable for the patient.

7.4 Drug release profile

The target drug release profile delivery should be defined early in the development based on the target product profile. The most reliable tests available to this evaluation are the disintegration time and the dissolution profile. Depending on the product, it may be intended to have a bioequivalent oral dosage form or other specific drug-delivery type (e.g. extended or fast release, mucosa or gastrointestinal absorption).

It is also important to consider that according to the FDA guidance a fast disintegration time *in vitro* should be less than 30s [129].

7.5 Residual water content

The residual water content of the films is critical and should also be strictly defined for each specific formulation, since it may influence significantly any of the properties described. It is also crucial to monitor and control the

room conditions during production (temperature and relative humidity), and an appropriate primary packaging material should be provided to avoid water transferences between the product and the surrounding room.

An excess or deficit of water content may affect the mechanical properties of the polymeric matrix. The water molecules may interpose in the polymer chains functioning as a plasticizer, so the loss of water content, may contribute for brittle polymeric matrices. In turn, an excess of water absorption by the polymeric matrix may originate sticky films that may adhere to the patient fingers and / or packaging material.

Moreover, the interposition of the water molecules in the polymeric chains may also influence the disintegration / dissolution of the films. The loss of water molecules would contribute to thigh the polymeric chain links, turning difficult the water penetration and therefore the disintegration time.

Furthermore, the free water in the film may also interfere with the stability of the drug substance incorporated and / or with the excipients.

7.6 Organoleptic characteristics

The oral films have a relatively high surface area in contact with the oral mucosa, which makes important to focus some of the development efforts in the formulation of a pleasant and palatable system. Generally, the disagreeable taste is related with the drug substance characteristics (bitterness, particle size / shape, solubility, ionization) and strength in the oral film [130]. Therefore, depending on these properties is important to define an efficient strategy to assure an agreeable taste, aftertaste and mouthfeel.

Another important point to consider is the target market, since there may be regional and / or aged group preferences. Different consumers have different preferences and should be captivated by different and independent ways. From the formulation point of view it is important to consider the regional and aged group tastes. For example, children generally prefer fruit and / or sweetener flavors, while adults tend to prefer slightly acid flavors and older people frequently prefer mint or wine flavored products. Even so, it is important to notice that even flavors' children preferences may vary from country to country and may depend on social and cultural factors [131-133]. Curiously, even for animals' medicine market is important to record that the choice of the flavor and color may have impact in the acceptance of the medicine. Actually, these animals' preferences can be surprising. Regarding colors, it is known that iguanas and emus are attracted to red and yellow, respectively. About the flavors, horses may prefer banana instead of apple or molasses, some ferrets may be fond of bubblegum and rabbits and guinea pigs may prefer pina-colada flavor [134]. Despite that, the appropriate choice of flavor is mainly affected by the taste sensation conferred by the drug substance, and the flavors or their combination should mask any bitterness, providing a good balance of acid, salty or sour taste, and covering any unpleasant aftertaste.

7.7 Dose uniformity

The individual weight of the films and the dosage uniformity must be also controlled during the process. It is also important to have a deep knowledge of the process and the product so slightly adjustments may be performed during manufacturing if necessary.

7.8 Others

Additional attributes may also be considered depending on the type of the oral film to develop. For example, adhesion or mucoadhesion tests, for buccal and / or sublingual films and pH values measurements, when the drug absorption or stability depends on it. Moreover the pH assays may also be important to predict possible mucosa irritation, since acidic or alkaline pH may cause some discomfort, and the surface pH should be ideally close to neutral [135].

The CQA must be defined in the beginning of the development according to the target product profile. Moreover, due to the sensitivity / complexity of the product other properties / process parameters involved in the oral films formulation and manufacturing must not be discarded (release liner and packaging material properties). A helpful way to define efficiently the quality attributes of the oral film under development is to consider the quality target product profile and (if possible) previous knowledge of the product and manufacturing process. This should be followed by an appropriate quality risk management to evaluate and highlight the critical and potential attributes that would affect the quality of the drug product [136].

8 Manufacturing processes overview: from the conventional to the innovative

The two main techniques used to prepare oral films are solvent casting [45, 50, 135, 137-141] and hot melt extrusion [4, 46, 122] (Figure 4). However, during the past few years some developments and innovative techniques have emerged. Some variants of these manufacturing methods of casting and extrusion have also been described and used alone or in combination, such as semisolid casting and solid-dispersion extrusion [142]. Inventive manufacturing processes as the rolling [142] or printing [81].methods have also been described. The first involves essentially the preparation of a pre-mix with a further addition of the drug substance, and the resulting matrix is passed through a metering roller. The printing method consists literally in printing the drug substance on a placebo oral film with specific techniques [81].

8.1 Conventional methods

The solvent-casting method consists essentially in an aqueous or hydro-alcoholic mixture of excipients and drug substance(s) that is casted onto a surface, dried, and cut into a desirable size. On the other hand, hot-melt extrusion consists simply in shaping an adequate mixture of polymer(s), other excipients and drug substance(s) into a film by melting all the components [143]. Both techniques allow the preparation of films with good characteristics, but generally the solvent casting method is the most widely used, probably due to the special equipment required and high costs associated to the hot melt extrusion method [10].

Regarding the variant methods referred previously, the semisolid casting consists in a gel mass casted using heat controlled drums and obtained by the addition of an acid insoluble polymer to the main liquid mixture in a preferential ratio of 1:4. In turn, the solid dispersion extrusion consists essentially in the dispersion of a drug substance dissolved in an appropriate solvent and its incorporation into polyethylene glycol (PEG) melted. However, the drug substance or the solvent used to dissolve it should be insoluble in polyethylene glycol.

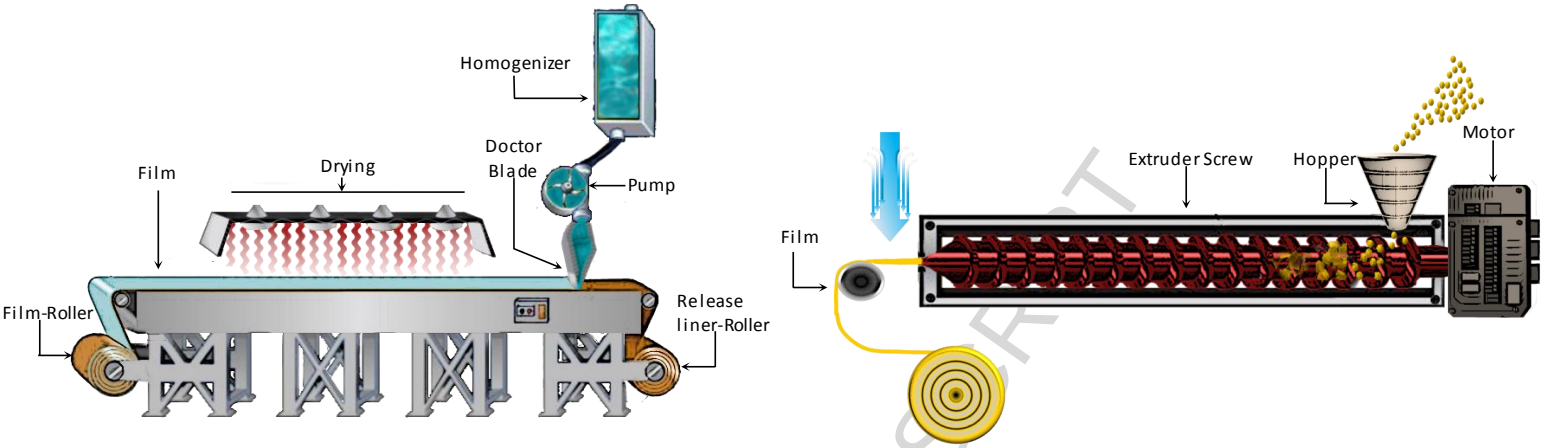

Figure 4 – Most common techniques to prepare oral films. Solvent casting technique (left) and Hot-melt-extursion method (right).

8.2 Innovative methods

An inventive manufacturing processes is the rolling method which involves the preparation of a pre-mix with a further addition of the drug substance, and the resulting matrix is passed through a metering roller [142].
Another, are the drug printing technologies methods, that seemed to be highly flexible and cost-effective [81] (Figure 5).
Printing technologies are widely used in the pharmaceutical industry to identify or label the pharmaceutical dosage forms, especially for personalization purposes to be readily identified and to avoid counterfeit production. However, instead of merely printing some identification characters, this technology early started to be adapted to the drug load of pharmaceutical dosage forms. During the 80's, Anhauser, Klein and Nick et al. used screen printing and pad printing to load transdermal patches with drug substances [144] (Figure 5 C, D). Nevertheless, for large production scale, these methods are essentially limited by the low speed production. Later, the inkjet printing started to be explored as a safe and accurate method to produce dosage forms with potent or low-dose drugs. GlaxoSmithKlein (GSK) has a GMP Pilot machine since 2005, based on this innovative technology, the Liquid Dispensing Technology, used as a new tablet-manufacturing process that delivers microgram doses with unparalleled precision. GSK is the owner of all intellectual property for this technology until 2028, which was also rewarded in 2012 with a Health and Safety Award by IChmE [145, 146]. The application of this technology to oral films is not yet much explored. Nevertheless, during 2011, based on printable medicines and with the idea of printing a drug substance onto a carrier (such as a paper strip that can be then inserted into a capsule for an easy administration), a revolutionary concept was established: personalized medicines [147]. Although, some references to this concept have emerged in the last years [148, 149], there is still no reference to the industrial application of these methods for the production of oral films.
GSK technology may achieve a medium output of 20,000 tablets per hour. However, it has no direct correlation with oral films manufacturing production, and some authors consider that inkjet printing is still not suitable for high-throughput industrial production (Figure 5B). Therefore, another printing technology is suggested to be more feasible for oral films industrial production, the flexographic printing technology [144] (Figure 5A). The flexographic printing is a rotary printing process in which the ink (drug substance solution or suspension) is metered by an anilox roller then transferred to printing cylinder that prints the drug-free-film after unrolling the daughter roll. On the other hand, the drop deposition of the DS solution or suspension with the ink-jet printing may be challenging considering that it is important to avoid the film disintegration or rupturing and simultaneously maintaining the oral film's fast dissolving properties [144].

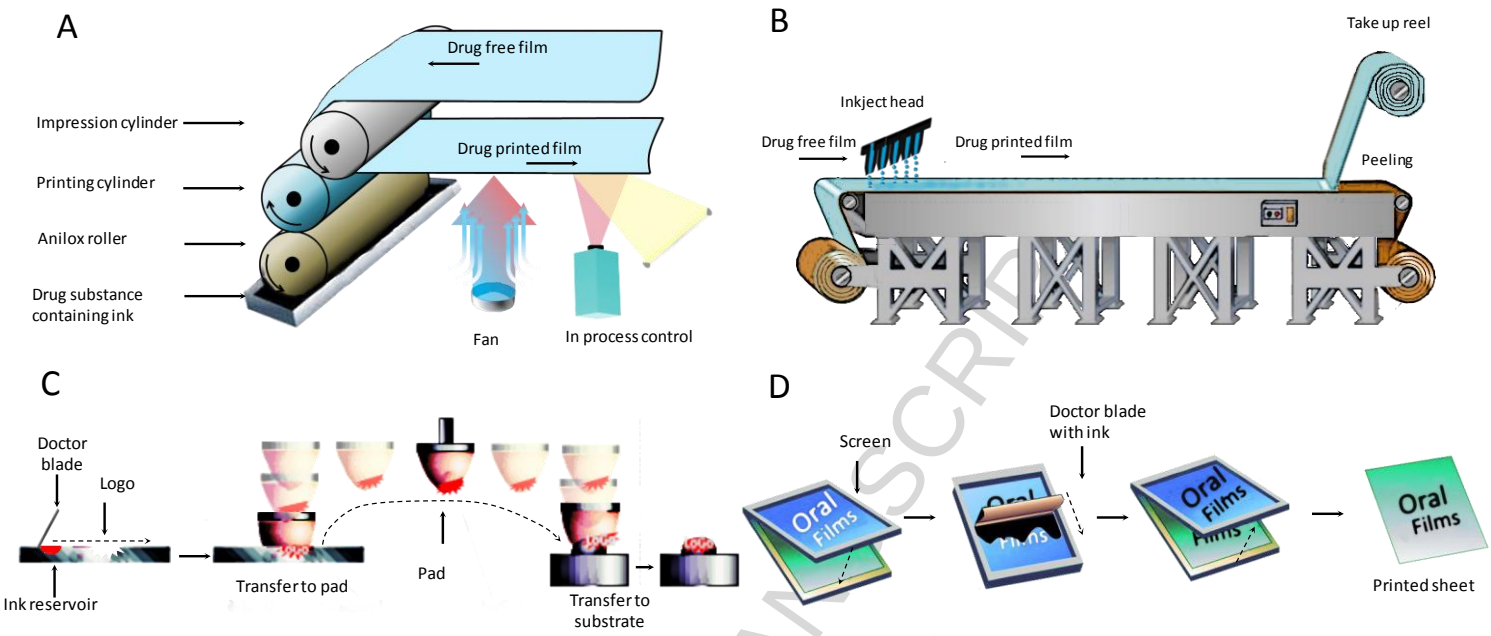

Figure 5 – Printing techniques. Representation of the 4 main printing techniques used in oral films preparation. The two top figures are simplified schemes of possible printing industrial techniques applied to the oral films, flexoprinting (A) and inkjet (B) printing. The two bottom pictures represent two simpler printing methods the pad (C) and screen printing (D).

In theory, any of the printing methods mentioned above would contribute to a more homogeneous distribution and accurate dosage of the drug substance within the film, which by the conventional methods is very challenging. Moreover, dose accuracy and uniform distribution of the drug substance in the films normally depends on the coating mass properties, like viscosity or density, which in turn are affected by the characteristics and amount of the processed drug substances. On this matter, with the conventional methods the formulations have often to be adjusted for each drug substance and dosage strength [144]. Hence, the application of these technologies could streamline all the manufacturing process and shorten the time to the market.

In summary, printing drug substances on dosage forms are nowadays a reality and its application in oral films has opened a new world of opportunities when referring to personalized and individualized medicines.

9 Characterization methods

Several efforts have been made to develop suitable techniques for oral films evaluation and characterization, considering their particular characteristics. There are critical parameters that should be evaluated for the quality control of the films. Despite the lack of guidance, the European Pharmacopeia refers the need of a “suitable mechanical strength to resist handling without being damaged” and an appropriate dissolution method “to demonstrate the appropriate release of the active substance”. However, it is advisable to evaluate other critical properties, usually also referred as critical quality attributes that are referred hereinafter.

9.1 Mechanical properties

The variety of dimensions of commercially available oral films difficult the standardization of specific evaluation techniques. The most referred is the determination of mechanical properties based on ASTM or DIN-ISO guidelines, namely DIN EN ISO 527 for foil materials and ASTM D882-01 for tensile properties of thin plastic sheeting. This method consists in the fixation of the sample between two clamps and pull until breaking [123]. The main limitations of this approach is the unresponsiveness of the apparatus and the preferential use of bone shapes samples to assure that the forces are centered in the middle of the specimen, which does not match the

common small rectangular format (about 2 to 8 cm^2) of the oral films [150]. More suitable methods were developed as the puncture test with a cylindrical probe with a plane flat-faced surface using Texture Analyzer equipment. The probe with the flat face surface allows retrieving the area directly affected by the strain [123].

9.2 Dissolution

The dissolution method is also critical, especially concerning the apparatus and media selection. Despite the simple orientation of the Pharmacopeia description, it is important to consider that this assay should be representative and an approach to predict the *in vivo* behavior.

The majority of the methods described do not mimic the physiological conditions satisfactorily, regarding the dissolution method conditions and apparatus [150, 151]. Another point to consider is the type of oral film to test, which may include different challenges and limitations. Briefly, the major restrictions in the oral films dissolution methods are the *in vivo* small volume dissolution, the short residence time in mouth (specially fast dissolving films), mucosal absorption (buccal films), composition (e.g. adhesive compounds) and incomplete dissolution (sometimes a complete disintegration is preferred instead of a complete dissolution).

Generally, the apparatus selection would be based on two different assumptions: orodispersible dosage forms (e.g. orodispersible tablets) or transdermal dosage forms, which commonly uses accessories to lock the dosage form in the bottom of the vessel. The paddle apparatus (USP type II) is more used [44, 135, 140, 152-156] than the basket apparatus (USP type I) [23, 45, 50, 157]. But, due to the limitations of both methods, many researchers have suggested the use of modified apparatus [3, 150, 151]. The majority of the modifications consisted in dissolution media volume reduction (usually including the vessel type modification), stirring accessory modifications [3, 26, 151] and type of dissolution medium, such as simulated artificial saliva [153-155].

Additionally, Gursuch et al. presented a fiber-optic sensor system to overcome the shorter intervals sampling collection (lower than 30s) and the filters clog in apparatus with modified sample withdraw [150]. In fact, fast orodispersible films usually exhibit a rapid disintegration / dissolution, becoming sometimes hard to obtain suitable dissolution profiles with the conventional (manual or automated) sampling collection. Although the online measurement may surge as a suitable alternative for fast dissolvable dosage forms, some points should be considered. The majority of the online fiber optic sensor systems currently available usually use UV spectroscopy, which becomes unviable if there is similar absorption spectrum between drug substance and any other compound of the formulation.

The selection of the correct apparatus and possible adaptive accessories should also be carefully chosen. One-layer fast dissolving films should have both surfaces in contact with the dissolution media, but in multi-layer films this choice may not be the most appropriate. Furthermore, the adhesion of some components of the formulation may also origin trapped disintegrated masses on the accessory / sinker / basket used, resulting in irreproducible dissolution profiles.

Another approach is the usage of the paddle over disk apparatus (USP type V). This dissolution apparatus was used in the development of Zuplenz® along with a gastric pH dissolution media. This may be justified since the primary objective of this fast dissolving film is to disintegrate fast in the mouth to be readily swallowed with the saliva [158].

Finally, there are many critical points to consider in the development of the dissolution method and many options are available due to the nonspecific or inexistence of pharmacopeia guidance. However, the method choice should be well grounded and justified.

Table 3 – Summary of the dissolution methods currently used to test oral films

Apparatus	Method				Reference
	Dissolution Media	Stirring	Sampling	Details	

USP type V	900 mL 0.1N HCl 37.0°C ± 0.5°C	50 rpm	10 minute intervals		[159]
JP15 paddle apparatus	900 mL of phosphate solution (pH 1.2) 37.0°C ± 0.5°C 50 rpm		Ten-milliliter aliquot from 2 min to 60 min		[152]
USP type I	400 ml freshly distilled water, 37±0.5°C 100 rpm		2, 4, 6, 8, and 10 min		[50]
JP15 paddle apparatus	900 mL of phosphate solution (pH 1.2), 37 ± 0.5 C	50 rpm	10 mL from 2 min to 120 min		[140]
USP type II	300 mL freshly deionized water, 37±1°C	50 rpm			[44]
USP type II	300 ml distilled water or simulated saliva (pH 6.8) or 900 mL of simulated gastric fluid (pH 1.2) 37°C ± 0.5°C	50 rpm	5 ml 0-, 1-, 2-, 3-, 5-, 10-, and 20-minute	simulated saliva:12 mM KH2PO4, 40 mM NaCl, 1.5 mM CaCl2 and NaOH to pH 6.8)	[153]
USP type II	simulated saliva (phosphate buffer pH 6.4) 37±0.5°C.				[154]
USP type I	300 ml simulated saliva (phosphate buffer pH 6.8) or 900 ml of simulated gastric fluid (0.1N HCl) 37 ± 0.5°C	50 rpm.	5 mL		[23]
USP type II (?)	900 mL phosphate buffer pH 6.6 37±0.5°C	50 rpm	1 to 30 min		[135]
USP type II	simulated saliva (phosphate buffer pH 6.8) 900 ml phosphate buffer saline (pH6.8) 37°C,	50 rpm	1, 2, 3, 4, 5, 10, 15, 20 and 30 minute	Each film is attached to a glass slide (with glue) that remains in the bottom of the vessel Simulated saliva: 2.38 g Na2HPO4, 0.19 g KH2PO4, and 8.00 g NaCl per liter adjusted with phosphoric acid to pH 6.8).	[155]
USP type II	900 mL 0.1 M HCl 37.0±0.5°C	50 rpm	3 mL 1, 3, 5, 10, 20 and 30 min	reposition	[156]
USP type I	500 mL deionized water 37 ±1°C	25 rpm			[45]
USP type I	900 ml buffer pH 6.8 37°C ± 1°C		5 ml	Media reposition	[157]

Modified USP-XXIII type1 apparatus	20 ml phosphate buffer pH 6.4	100 rpm	4 ml 7, 14, 21, 28, 35 and 42 min	Media reposition, film was placed with the help of forceps in a 50 ml glass beaker Without the basket attached with a shaft.	[3]
Modified USP XXIII apparatus (paddle over disk)	1000 ml distilled water 37.0±0.5°C	100 rpm	5 ml		[26]
Third method apparatus Chinese Pharmacopeia (CP 2010, appendix XD modified	100 ml Distilled water	30rpm 50 rpm 100 rpm.	Autosampling	Film samples were sandwiched between two pieces of a sieve mesh and fixed in the right and vertical position	[151]

9.3 Mucoadhesiveness

There are no mucoadhesion methods described in any Pharmacopeia. Also, it is complex to define an appropriate method considering the numerous approaches available in literature, the lack of correlation between *in vivo* and *in vitro* tests and the challenge to found intact and fresh buccal mucosa [81, 125]. Nair et al. recently compiled the most used in vitro techniques to evaluate the buccal films with a short but relevant section of mucoadhesive studies [125].

10 Conclusion

The flexibility of this dissolvable film technology platform offers future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets. It also provides an opportunity to extend revenue life cycles for existing drugs whose patent is expiring and will soon be vulnerable to generic competition. In other words, oral films allow the lifecycle management of the products. Additionally, the majority of the manufacturing approaches used are well understood and easily controlled, prompting a robust and efficient development from bench to market.

There are some important issues that should be taken in consideration regarding the oral films development, manufacturing and marketing. During the development the critical quality attributes should be well-stablished to prevent unfortunate and uncontrolled events. Despite the complexity of the formulation and process, a deep knowledge of the system may be sufficient to control and surpass some inevitable and unpredictable proceedings.

Finally, it is important that the combination of thin film technology with the selected drug substance gain wide consumer acceptance and pave the way for other medicines to move to this portable, exceptionally convenient pharmaceutical form.

11 Acknowledgements

POPH PROGRAMA OPERACIONAL POTENCIAL HUMANO
QREN QUADRO DE REFERÊNCIA ESTRATÉGICO NACIONAL PORTUGAL 2007.2013
Governo da República Portuguesa
UNIÃO EUROPEIA Fundo Social Europeu

Funded by FCT grant, reference SFRH / BDE / 51271 / 2010 and by QREN SI-I&DT Empresa Individual Project No.18472

12 References

[1] E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Advances in orodispersible films for drug delivery, Expert opinion on drug delivery, 8 (2011) 299-316.
[2] FDA, Dosage Form, in, Development & Approval Process (Drugs).
[3] A. Dinge, M. Nagarsenker, Formulation and Evaluation of Fast Dissolving Films for Delivery of Triclosan to the Oral Cavity, AAPS PharmSciTech, 9 (2008) 349-356.
[4] F. Cilurzo, I.E. Cupone, P. Minghetti, F. Selmin, L. Montanari, Fast dissolving films made of maltodextrins, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 70 (2008) 895-900.
[5] H.G. Zerbe, J.H. Guo, A. Serino, Water soluble film for oral administration with instant wettability, in, Google Patents, 2003.
[6] G.L. Myers, E. Dadey, Sublingual and buccal film compositions, in, Google Patents, 2014.
[7] A. Breitenbach, S. BRAUN, R. Schliephacke, Orodispersible films for the manufacturing of individualised medicine or for large scale production, in, Google Patents, 2014.
[8] A. Zajicek, M.J. Fossler, J.S. Barrett, J.H. Worthington, R. Ternik, G. Charkoftaki, S. Lum, J. Breitkreutz, M. Baltezor, P. Macheras, M. Khan, S. Agharkar, D.D. MacLaren, A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms, The AAPS journal, 15 (2013) 1072-1081.
[9] S. Stegemann, M. Gosch, J. Breitkreutz, Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy, Int J Pharm, 430 (2012) 197-206.
[10] R.P. Dixit, S.P. Puthli, Oral strip technology: overview and future potential, Journal of controlled release : official journal of the Controlled Release Society, 139 (2009) 94-107.
[11] B.J. Wening K, Review: Oral drug delivery in personalized medicine: Unmet needs and novel approches, International Journal of Pharmaceutics, 404 (2010) 1-9.
[12] IBISWorld, Thin Film Drug Manufacturing in the US: Market Research Report, in, http://www.ibisworld.com/industry/thin-film-drug-manufacturing.html, 2015.
[13] C.L.P. Fereshteh Barei, Steven Simoens, The generic pharmaceutical industry: moving beyond incremental innovation towards re-innovation, Generics and Biosimilars Initiative Journal, 2 (2013) 13.
[14] S.P. Rowe R, Equinn M, Handbook of Pharmaceutical Excipients, Pharmaceutical Press and American Pharmacists Association, London and Whashington, 2009.
[15] T.D.C. Company, Using Dow Excipients for Controlled Release of Drugs in Hydrophilic Matrix Systems, in, 2006.
[16] A. ElMeshad, A. El Hagrasy, Characterization and Optimization of Orodispersible Mosapride Film Formulations, AAPS PharmSciTech, 12 (2011) 1384-1392.
[17] C.G. Otoni, M.V. Lorevice, M.R.d. Moura, L.H.C. Mattoso, Effect of hydroxyl substitution and viscosity on thermal and mechanical properties of hydroxypropyl methylcellulose films, in: XIV Latin American Symposium on Polymers, XII Ibero American Congress on Polymers, 2014.
[18] C. Gustafsson, M.C. Bonferoni, C. Caramella, H. Lennholm, C. Nystrom, Characterisation of particle properties and compaction behaviour of hydroxypropyl methylcellulose with different degrees of methoxy/hydroxypropyl substitution, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 9 (1999) 171-184.
[19] T.D.C. Company, METHOCEL Cellulose Ethers - Technical Handbook, in, 2002.
[20] H. Wen, K. Park, Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, Wiley, 2011.
[21] R. Kumria, V. Gupta, S. Bansal, J. Wadhwa, A.B. Nair, Oral buccoadhesive films of ondansetron: Development and evaluation, International journal of pharmaceutical investigation, 3 (2013) 112-118.

[22] M.A. Repka, K. Gutta, S. Prodduturi, M. Munjal, S.P. Stodghill, Characterization of cellulosic hot-melt extruded films containing lidocaine, European Journal of Pharmaceutics and Biopharmaceutics, 59 (2005) 189-196.
[23] S.N. Mahesh A, Sadanandam M, Development of Taste Masked Fast Disintegrating Films of Levocetirizine Dihydrochloride for Oral Use, Current Drug Delivery, 7 (2010) 21-27.
[24] A.M. Schobel, S.S.K.S. Vangala, Solid dosage form containing a taste masked active agent, in, Google Patents, 2010.
[25] D.H. Kulkarni AS, Mane M, Ghadge D, Exploration of different polymers for use in the formulation of oral fast dissolving strips, Journal of Current Pharmaceutical Research, 2 (2010) 33-35.
[26] P.R. Sharma R, Gohel M, Soniwala M, Development of taste masked film of Valdecoxib for oral use, Indian J. Pharm. Sci., 69 (2007) 318-320.
[27] T.P. Kunte S, Fast dissolving strips: A novel approach for the delivery of verapamil, Journal of Pharmacy and Bioallied Sciences, 2 (2010) 325–328.
[28] A.A. Mishra R, Formulation Development of taste rapidly dissolving films of cetirizine hydrochloride, in: PharmTech.com - Advancing development and manufacturing, PharmTech.com, PharmTech.com, 2009.
[29] N.M. Dinge A, Formulation and Evaluation of fast dissolving films for delivery of triclosan to the oral cavity, AAPS PharmSciTech., 9 (2008).
[30] S.S. Dahiya M, Shahiwala A, A Review on Mouth Dissolving Films, Current Drug Delivery, 6 (2009) 469-476.
[31] W.L. Bunnelle, R.M. Hume, L.C. Jannusch, Thermoplastic films and methods for making, in, Google Patents, 2005.
[32] F.K. Alanazi, A.A.A. Rahman, G.M. Mahrous, I.A. Alsarra, Formulation and physicochemical characterisation of buccoadhesive films containing ketorolac, J. Drug Deliv. Sci. Technol., 17 (2007) 183-192.
[33] K. Yasuda, T. Okubo, Y. Sawai, Rapidly soluble film-shaped preparation, in, Google Patents, 2011.
[34] H.G. Zerbe, F. Al-Khalil, Rapidly disintegrating flavored film for precooked foods, in, Google Patents, 2003.
[35] E.A. Baldwin, R. Hagenmaier, J. Bai, J.M. Krochta, Edible Coatings and Films to Improve Food Quality, Taylor & Francis, 1994.
[36] S. Saha, C. Tomaro-Duchesneau, J.T. Daoud, M. Tabrizian, S. Prakash, Novel probiotic dissolvable carboxymethyl cellulose films as oral health biotherapeutics: in vitro preparation and characterization, Expert opinion on drug delivery, 10 (2013) 1471-1482.
[37] M. Nappinnai, R. Chandanbala, R. Balaijirajan, Formulation and evaluation of nitrendipine buccal films, Indian journal of pharmaceutical sciences, 70 (2008) 631-635.
[38] W. Tongdeesoontorn, L.J. Mauer, S. Wongruong, P. Sriburi, P. Rachtanapun, Effect of carboxymethyl cellulose concentration on physical properties of biodegradable cassava starch-based films, Chem Cent J. 2011;5(1)-6, 2011.
[39] D.R. Lu, C.M. Xiao, S.J. Xu, Starch-based completely biodegradable polymer materials, Express Polym. Lett., 3 (2009) 366-375.
[40] K.K. Peh, C.F. Wong, Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties, J Pharm Pharm Sci, 2 (1999) 53-61.
[41] F. Xie, P.J. Halley, L. Averous, Rheology to understand and optimize processibility, structures and properties of starch polymeric materials, Progress in Polymer Science, 37 (2012) 595-623.
[42] G.M. Mali S, Yamashita F, Starch films: production, properties and potential of utilization (Review), Semina: Ciências Agrárias, (2010) 137-156.
[43] G.T. Koch K, Stading M, Andersson R, Mechanical and structural properties of solution-cast high amylose maize starch films, International Journal of Biological Macromulecules, 46 (2009) 13-19.
[44] F. Cilurzo, I.E. Cupone, P. Minghetti, S. Buratti, F. Selmin, C.G. Gennari, L. Montanari, Nicotine fast dissolving films made of maltodextrins: a feasibility study, AAPS PharmSciTech, 11 (2010) 1511-1517.

[45] F. Cilurzo, I.E. Cupone, P. Minghetti, S. Buratti, C.G. Gennari, L. Montanari, Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system, Drug development and industrial pharmacy, 37 (2011) 252-259.
[46] F. Cilurzo, P. Minghetti, L. Montanari, Self-supporting films for pharmaceutical and food use, in, Google Patents, 2012.
[47] S. Shamekh, P. Myllärinen, K. Poutanen, P. Forssell, Film Formation Properties of Potato Starch Hydrolysates, Starch - Stärke, 54 (2002) 20-24.
[48] A.H. Chapdelaine, M.J. Dzija, D. Zyck, Improved edible film formulations containing maltodextrin, in, Google Patents, 2003.
[49] J.A. Parissaux X, Francois A, Lefevre P, Evaluation of a Novel Modified Starch Polymer in an Easy to formulate thin-film drug delivery system and comparation with some marketed formulations, Poster AAPS, (2007).
[50] D.A. El-Setouhy, N.S. Abd El-Malak, Formulation of a novel tianeptine sodium orodispersible film, AAPS PharmSciTech, 11 (2010) 1018-1025.
[51] C.R. Cunningham, Starch Contrastcs, in: Formulation - Excipient Focus, https://www.colorcon.com/literature/marketing/ex/Starch%201500/pfq_starch.pdf.
[52] B. Wire, BioDelivery Sciences and Meda Announce European Approval of BEMA Fentanyl (BREAKYL), in, http://www.businesswire.com/news/home/20101020005551/en/BioDelivery-Sciences-Meda-Announce-European-Approval-BEMA#.Uv36r3cacbE, 2010.
[53] GPC, Quick dissolve films, in: Pharmaceutical - Quick Dissolve Films, Grain Processing Corporation, http://www.grainprocessing.com/pharmaceutical-nutraceutical/quick-dissolve-films.html, 2014.
[54] N. Kulkarni, L. Kumar, A. Sorg, Fast dissolving orally consumable films containing sucralose as a sweetener, in, Google Patents, 2006.
[55] D.J. Fadden, N.M. Kulkarni, A.F. Sorg, Fast dissolving orally consumable films containing a modified starch for improved heat and moisture resistance, in, Google Patents, 2006.
[56] V.D. Prajapati, G.K. Jani, S.M. Khanda, Pullulan: An exopolysaccharide and its various applications, Carbohydr. Polym., 95 (2013) 540-549.
[57] X.Q. Tong Q, Lim L, Preparation and properties of pullulan–alginate–carboxymethylcellulose blend films, Food Research International, 41 (2008) 1007-1014.
[58] G.G. Prasad P, Shivakumar H,Rai K, Miscibility, Thermal, and Mechanical Studies of Hydroxypropyl Methylcellulose/Pullulan Blends, Journal of Applied Polymer Science, 110 (2008) 444–452.
[59] M.K. Kawahara M, Suzuki S, Kitamura S, Fukada H, Yui T, Ogawa K, Dependence of the mechanical properties of a pullulan film on the preparation temperature, Bioscience, Biotechnology, and Biochemistry, 67 (2003) 893-895.
[60] S.P. Fulzele S, Dorle A, Polymerized rosin: novel film forming polymer for drug delivery, International Journal of Pharmaceutics, 249 (2002) 175-184.
[61] U.C. Galgatte, S.S. Khanchandani, Y.G. Jadhav, P.D. Chaudhari, Investigation Of Different Polymers, Plasticizers and Superdisintegrating Agents Alone And In Combination For Use In The Formulation Of Fast Dissolving Oral Films, PharmTech, 5 (2013) 1465-1472.
[62] R. Puri, R.G. Zielinski, Dissolvable film, in, Google Patents, 2007.
[63] R.A. Alanazi F, Mahrous G, Alsarra I, Formulation and physicochemical characterization of buccoadhesive films containing ketorolac, Journal Drug Del. Sci., 17 (2007) 183-192.
[64] C. Leichs, A. Breitenbach, I. Lehrke, P. Galfetti, Non-mucoadhesive film dosage forms, in, Google Patents, 2008.
[65] M. Horstmann, W. Laux, Individually dosed foil-form presentation which decomposes rapidly on contact with liquid and contains an active substance, in particular an aromatic substance, in, Google Patents, 2004.

[66] C.G. Mura P, Cirri M, Maestrelli F, Mennini N, Bragagni M, Development of Mucoadhesive Films for Buccal Administration of Flufenamic Acid: Effect of Cyclodextrin Complexation, Journal of Pharmaceutical sciences, 99 (2010) 3019-3029.
[67] J. Bougaret, D.S.I. Ribeiro, M. Sournac, Rapid-disintegration monolayer film for the oral administration of active substances, in, Google Patents, 2009.
[68] D. Asari, M. Hori, T. Shishido, Film-form preparation, in, Google Patents, 2011.
[69] C.f.D. Control, Prevention, Prevalence and Most Common Causes of Disability Among Adults --- United States, 2005, MMWR Morb Mortal Wkly Rep, 58 (2009) 421 - 426.
[70] C.K. Chu, J.P. Ryoo, Z. Wang, Dosage form for insertion into the mouth, in, Google Patents, 2012.
[71] D.H. Kulkarni AS, Mane M, Ghadge D, Exploration of different polymers for use in the formulation of oral fast dissolving strips, Journal of the Current Pharmaceutical Research, 2 (2010) 33-35.
[72] T.G. Chen M, Schmitt R, Chien C, Dualeh A, Film-Forming Polymers in Fast-Dissolve Oral Films, in: Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists, San Antonio, Texas, USA, 2006, pp. Poster.
[73] G.L. Myers, S.D. Hilbert, B.J. Boone, B.A. Bogue, P. Sanghvi, M. Hariharan, Sublingual and buccal film compositions, in, Google Patents, 2011.
[74] G.L. Myers, High dose film compositions and methods of preparation, in, Google Patents, 2008.
[75] C. Bruce, M. Manning, Melt extruded nicotine thin strips, in, Google Patents, 2011.
[76] R.K. Yang, R.C. Fuisz, G.L. Myers, J.M. Fuisz, Polyethylene oxide-based films and drug delivery systems made therefrom, in, Google Patents, 2006.
[77] F. Laffleur, Mucoadhesive polymers for buccal drug delivery, Drug development and industrial pharmacy, 40 (2014) 591-598.
[78] G.P. Andrews, T.P. Laverty, D.S. Jones, Mucoadhesive polymeric platforms for controlled drug delivery, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 71 (2009) 505-518.
[79] J.O. Morales, J.T. McConville, Manufacture and characterization of mucoadhesive buccal films, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 77 (2011) 187-199.
[80] C. Woertz, M. Preis, J. Breitkreutz, P. Kleinebudde, Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview, European Journal of Pharmaceutics and Biopharmaceutics, 85 (2013) 843-853.
[81] M. Preis, C. Woertz, P. Kleinebudde, J. Breitkreutz, Oromucosal film preparations: classification and characterization methods, Expert opinion on drug delivery, 10 (2013) 1303-1317.
[82] R. Jayakumar, D. Menon, K. Manzoor, S.V. Nair, H. Tamura, Biomedical applications of chitin and chitosan based nanomaterials—A short review, Carbohydr. Polym., 82 (2010) 227-232.
[83] M. Dash, F. Chiellini, R.M. Ottenbrite, E. Chiellini, Chitosan—A versatile semi-synthetic polymer in biomedical applications, Progress in Polymer Science, 36 (2011) 981-1014.
[84] M.J. Morales J, Manufacture and characterization of mucoadhesive buccal films, European Journal of Pharmaceutics and Biopharmaceutics, 77 (2011) 187–199.
[85] Z. Zhu, Y. Zhai, N. Zhang, D. Leng, P. Ding, The development of polycarbophil as a bioadhesive material in pharmacy, Asian Journal of Pharmaceutical Sciences, 8 (2013) 218-227.
[86] W. Graessley, The entanglement concept in polymer rheology, in: The Entanglement Concept in Polymer Rheology, Springer Berlin Heidelberg, 1974, pp. 1-179.
[87] F. Madsen, K. Eberth, J.D. Smart, A rheological examination of the mucoadhesive/mucus interaction: the effect of mucoadhesive type and concentration, Journal of controlled Release, 50 (1998) 167-178.
[88] E. Hassan, J. Gallo, A Simple Rheological Method for the in Vitro Assessment of Mucin-Polymer Bioadhesive Bond Strength, Pharmaceutical research, 7 (1990) 491-495.

[89] F. Nakamura, R. Ohta, Y. Machida, T. Nagai, In vitro and in vivo nasal mucoadhesion of some water-soluble polymers, International Journal of Pharmaceutics, 134 (1996) 173-181.
[90] F. Cilurzo, P. Minghetti, F. Selmin, A. Casiraghi, L. Montanari, Polymethacrylate salts as new low-swellable mucoadhesive materials, Journal of controlled release : official journal of the Controlled Release Society, 88 (2003) 43-53.
[91] A. Bernkop-Schnurch, S. Steininger, Synthesis and characterisation of mucoadhesive thiolated polymers, Int J Pharm, 194 (2000) 239-247.
[92] S. Bonengel, A. Bernkop-Schnurch, Thiomers--from bench to market, Journal of controlled release : official journal of the Controlled Release Society, 195 (2014) 120-129.
[93] M. Ijaz, A. Bernkop-Schnürch, Preactivated thiomers: their role in drug delivery, Expert opinion on drug delivery, 0 1-13.
[94] G. Garhofer, Evaluation of the Corneal Residence Time of Chitosan-N-acetylcysteine Eye Drops in Patients With Dry Eye Syndrome After Single and Multiple Instillation, in: Medical University of Vienna, ClinicalTrials.gov 2012.
[95] M.U.o.V. Gerhard Garhofer, Local Tolerability of Chitosan-N-acetylcysteine Eye Drops in Healthy Young Volunteers, in, ClinicalTrials.gov 2010.
[96] C.-P. GmbH, Safety of Hyaluronan Thiomer i.o. Implant During Combined Phacoemulsification - Non Penetrating Deep Sclerectomy, in, ClinicalTrials.gov 2013.
[97] V.M. Leitner, D. Guggi, A. Bernkop-Schnürch, Thiomers in noninvasive polypeptide delivery: In vitro and in vivo characterization of a polycarbophil-cysteine/glutathione gel formulation for human growth hormone, Journal of Pharmaceutical Sciences, 93 (2004) 1682-1691.
[98] M.D. Hornof, A. Bernkop-Schnürch, In vitro evaluation of the permeation enhancing effect of polycarbophil–cysteine conjugates on the cornea of rabbits, Journal of Pharmaceutical Sciences, 91 (2002) 2588-2592.
[99] C. Kast, D. Guggi, N. Langoth, A. Bernkop-Schnürch, Development and in Vivo Evaluation of an Oral Delivery System for Low Molecular Weight Heparin Based on Thiolated Polycarbophil, Pharmaceutical research, 20 (2003) 931-936.
[100] A. Bernkop-Schnurch, S.C. Thaler, Polycarbophil-cysteine conjugates as platforms for oral polypeptide delivery systems, J Pharm Sci, 89 (2000) 901-909.
[101] H. Hoyer, M. Greindl, A. Bernkop-Schnurch, Design and in vivo evaluation of a patch system based on thiolated polymers, J Pharm Sci, 98 (2009) 620-627.
[102] A. Bernkop-Schnurch, S. Scholler, R.G. Biebel, Development of controlled drug release systems based on thiolated polymers, Journal of controlled release : official journal of the Controlled Release Society, 66 (2000) 39-48.
[103] M. Werle, K. Hironaka, H. Takeuchi, H. Hoyer, Development and In Vitro Characterization of Liposomes Coated with Thiolated Poly(Acrylic Acid) for Oral Drug Delivery, Drug development and industrial pharmacy, 35 (2009) 209-215.
[104] M. Hornof, W. Weyenberg, A. Ludwig, A. Bernkop-Schnürch, Mucoadhesive ocular insert based on thiolated poly(acrylic acid): development and in vivo evaluation in humans, Journal of controlled Release, 89 (2003) 419-428.
[105] A. Bernkop-Schnurch, C. Egger, M. Elhassan Imam, A.H. Krauland, Preparation and in vitro characterization of poly(acrylic acid)-cysteine microparticles, Journal of controlled release : official journal of the Controlled Release Society, 93 (2003) 29-38.
[106] V.M. Leitner, M.K. Marschutz, A. Bernkop-Schnurch, Mucoadhesive and cohesive properties of poly(acrylic acid)-cysteine conjugates with regard to their molecular mass, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 18 (2003) 89-96.
[107] D. Guggi, M.K. Marschutz, A. Bernkop-Schnurch, Matrix tablets based on thiolated poly(acrylic acid): pH-dependent variation in disintegration and mucoadhesion, Int J Pharm, 274 (2004) 97-105.

[108] N.D. Aher, H.A. Nair, Bilayered Films Based on Novel Polymer Derivative for Improved Ocular Therapy of Gatifloxacin, The Scientific World Journal, 2014 (2014) 9.
[109] A. Bernkop-Schnurch, C.E. Kast, M.F. Richter, Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine, Journal of controlled release : official journal of the Controlled Release Society, 71 (2001) 277-285.
[110] J.A. B, W.M. N, N. HA., Synthesis of thiolated alginate and evaluation of mucoadhesiveness, cytotoxicity and release retardant properties. , Indian journal of pharmaceutical sciences, 72 (2010) 766-774.
[111] M. Roldo, M. Hornof, P. Caliceti, A. Bernkop-Schnurch, Mucoadhesive thiolated chitosans as platforms for oral controlled drug delivery: synthesis and in vitro evaluation, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 57 (2004) 115-121.
[112] X. Liu, Y. Chen, Q. Huang, W. He, Q. Feng, B. Yu, A novel thermo-sensitive hydrogel based on thiolated chitosan/hydroxyapatite/beta-glycerophosphate, Carbohydr Polym, 110 (2014) 62-69.
[113] A. Bernkop-Schnurch, Y. Pinter, D. Guggi, H. Kahlbacher, G. Schoffmann, M. Schuh, I. Schmerold, M.D. Del Curto, M. D'Antonio, P. Esposito, C. Huck, The use of thiolated polymers as carrier matrix in oral peptide delivery--proof of concept, Journal of controlled release : official journal of the Controlled Release Society, 106 (2005) 26-33.
[114] S. Hauptstein, C. Muller, S. Dunnhaupt, F. Laffleur, A. Bernkop-Schnurch, Preactivated thiomers: evaluation of gastroretentive minitablets, Int J Pharm, 456 (2013) 473-479.
[115] S. Hauptstein, F. Hintzen, C. Müller, M. Ohm, A. Bernkop-Schnürch, Development and in vitro evaluation of a buccal drug delivery system based on preactivated thiolated pectin, Drug development and industrial pharmacy, 40 (2014) 1530-1537.
[116] G.I. Perugini P, Conti B, Modena T, Pavanetto F, Periodontal delivery of ipriflavone: new chitosan/PLGA film delivery system for a lipophilic drug, International Journal of Pharmaceutics, 252 (2003) 1–9.
[117] E. Jones, E. Ojewole, R. Kalhapure, T. Govender, In vitro comparative evaluation of monolayered multipolymeric films embedded with didanosine-loaded solid lipid nanoparticles: a potential buccal drug delivery system for ARV therapy, Drug development and industrial pharmacy, 40 (2014) 669-679.
[118] C. Shen, B. Shen, H. Xu, J. Bai, L. Dai, Q. Lv, J. Han, H. Yuan, Formulation and optimization of a novel oral fast dissolving film containing drug nanoparticles by Box-Behnken design-response surface methodology, Drug development and industrial pharmacy, 40 (2014) 649-656.
[119] P. Rana, R.S. Murthy, Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: a potential approach for delivery of drugs having high first-pass metabolism, Drug Deliv, 20 (2013) 224-235.
[120] C. Dott, C. Tyagi, L.K. Tomar, Y.E. Choonara, P. Kumar, L.C. du Toit, V. Pillay, A Mucoadhesive Electrospun Nanofibrous Matrix for Rapid Oramucosal Drug Delivery, Journal of Nanomaterials, 2013 (2013) 19.
[121] C. Cavallari, A. Fini, F. Ospitali, Mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 83 (2013) 405-414.
[122] A.Q. Low, J. Parmentier, Y.M. Khong, C.C. Chai, T.Y. Tun, J.E. Berania, X. Liu, R. Gokhale, S.Y. Chan, Effect of type and ratio of solubilising polymer on characteristics of hot-melt extruded orodispersible films, Int J Pharm, 455 (2013) 138-147.
[123] M. Preis, K. Knop, J. Breitkreutz, Mechanical strength test for orodispersible and buccal films, Int J Pharm, 461 (2014) 22-29.
[124] N. Cao, X. Yang, Y. Fu, Effects of various plasticizers on mechanical and water vapor barrier properties of gelatin films, Food Hydrocolloids, 23 (2009) 729-735.
[125] A.B. Nair, R. Kumria, S. Harsha, M. Attimarad, B.E. Al-Dhubiab, I.A. Alhaider, In vitro techniques to evaluate buccal films, Journal of controlled release : official journal of the Controlled Release Society, 166 (2013) 10-21.

[126] R. Ortega-Toro, A. Jimenez, P. Talens, A. Chiralt, Properties of starch-hydroxypropyl methylcellulose based films obtained by compression molding, Carbohydr Polym, 109 (2014) 155-165.
[127] O.M. Koo, J.D. Fiske, H. Yang, F. Nikfar, A. Thakur, B. Scheer, M.L. Adams, Investigation into stability of poly(vinyl alcohol)-based Opadry(R) II films, AAPS PharmSciTech, 12 (2011) 746-754.
[128] A. Government, D.o. Health, T.G. Administration, Australian Public Assessment Report for Buprenorphine/Naloxone, in: A.P.A. Report (Ed.), https://www.tga.gov.au/auspar/auspar-buprenorphine-naloxone, 2011.
[129] U.S.D.o.H.a.H. Services, F.a.D. Administration, C.f.D.E.a.R. (CDER), Guidance for Industry

Orally Disintegrating Tablets, in: Chemistry, Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf, 2008.
[130] U. Gala, Taste Masking Techniques in the Pharmaceutical Industry, in: Articles, CompareNetworks, American Pharmaceutical Review 2014.
[131] K.A.w. John F Marriott, Christopher A langley and Dawn Blecher, Pharmaceutical Compounding and Dispensing, in: P. Press (Ed.), Pharmaceutical Press, google books, 2010, pp. 288.
[132] A.J.T.a.R.S.T. Linforth, Food Flavour Technology, John Wiley & Sons, Ltd., 2010.
[133] W.E.C.o.S.f.P. Preparations, Development of Paediatric Medicines: Points to Consider in Formulation, in: W.T.R. Series (Ed.), WHO, WHO Technical Report Series, 2012, pp. 29.
[134] Slade, Flavouring, in, Slade, http://www.slade.net.au/flavouring-animal-medications/, 2012.
[135] S. Kunte, P. Tandale, Fast dissolving strips: A novel approach for the delivery of verapamil, Journal of pharmacy & bioallied sciences, 2 (2010) 325-328.
[136] F.a.D. Administration, Q8(R2) Pharmaceutical Development, in: Guidance for Industry, Food and Drug Administration, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, 2009.
[137] R.C. Mashru, V.B. Sutariya, M.G. Sankalia, P.P. Parikh, Development and evaluation of fast-dissolving film of salbutamol sulphate, Drug development and industrial pharmacy, 31 (2005) 25-34.
[138] V. Garsuch, J. Breitkreutz, Comparative investigations on different polymers for the preparation of fast-dissolving oral films, The Journal of pharmacy and pharmacology, 62 (2010) 539-545.
[139] P. Mura, G. Corti, M. Cirri, F. Maestrelli, N. Mennini, M. Bragagni, Development of mucoadhesive films for buccal administration of flufenamic acid: Effect of cyclodextrin complexation, J Pharm Sci, 99 (2010) 3019-3029.
[140] M. Nishimura, K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, T. Sugiyama, Y. Itoh, In vitro and in vivo characteristics of prochlorperazine oral disintegrating film, Int J Pharm, 368 (2009) 98-102.
[141] V.A. Perumal, D. Lutchman, I. Mackraj, T. Govender, Formulation of monolayered films with drug and polymers of opposing solubilities, Int J Pharm, 358 (2008) 184-191.
[142] T. Nagaraju, R. Gowthami, M. Rajashekar, S. Sandeep, M. Mallesham, D. Sathish, Y.S. Kumar, Comprehensive review on oral disintegrating films, Curr Drug Deliv, 10 (2013) 96-108.
[143] A.A. Renuka Mishra, Manufacturing Techniques of Orally Dissolving Films, in, Pharmaceutical Technology, Jan 2, 2011, pp. 70-73.
[144] E.M. Janssen, R. Schliephacke, A. Breitenbach, J. Breitkreutz, Drug-printing by flexographic printing technology--a new manufacturing process for orodispersible films, Int J Pharm, 441 (2013) 818-825.
[145] I.A.c.e. worldwide, GlaxoSmithKline wins top prize at IChemE Awards, in, http://www.icheme.org/media_centre/news/2012/glaxosmithkline%20wins%20top%20prize%20at%20icheme%20awards.aspx#.Uv3Xp3cacbE, 2012.
[146] M.R.M. Wilson, Liquid Dispensing Technology (LDT) – Summary Presentation, in, GlaxoSmithKline, 2013.
[147] A.Z. Johannes G. Khinast, Guenter Brenn, Wolfgang Bauer, Bernhard Eitzinger, Daniela Strohmeier, Nina Schroedl, Michael M. Gruber, Christine Voura, Printable medicines: a microdosing device for producing personalised medicines, in: PharmaTech, 2011, pp. 32-36.

[148] A.M. Niklas Sandler, Petri Ihalainen, Leif Kronberg, Axel Meierjohann, Tapani Viitala, Jouko Peltonen, Inkjet printing of drug substances and use of porous substrates-towards individualized dosing, Journal of Pharmaceutical Sciences, 100 (2011) 3386-3395.
[149] A.B. Buanz, M.H. Saunders, A.W. Basit, S. Gaisford, Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing, Pharmaceutical research, 28 (2011) 2386-2392.
[150] V. Garsuch, J. Breitkreutz, Novel analytical methods for the characterization of oral wafers, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 73 (2009) 195-201.
[151] Y. Xia, F. Chen, H. Zhang, C. Luo, A new method for evaluating the dissolution of orodispersible films, Pharmaceutical Development and Technology, 0 1-5.
[152] H. Shimoda, K. Taniguchi, M. Nishimura, K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, K. Hirano, M. Yamamoto, Y. Kinosada, Y. Itoh, Preparation of a fast dissolving oral thin film containing dexamethasone: a possible application to antiemesis during cancer chemotherapy, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 73 (2009) 361-365.
[153] M.C. Gohel, R.K. Parikh, P.Y. Aghara, S.A. Nagori, R.R. Delvadia, M.R. Dabhi, Application of simplex lattice design and desirability function for the formulation development of mouth dissolving film of salbutamol sulphate, Curr Drug Deliv, 6 (2009) 486-494.
[154] A.C. Arun Arya, Vijay Sharma and Kamla Pathak, Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form, PharmTech, 2 (2010) 576-583.
[155] Gupta M.M, P.M. G, K. M., Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with β-cyclodextrine, Journal of Applied Pharmaceutical Science, 1 (2011) 150-153.
[156] K. Liew, Y. Tan, K. Peh, Characterization of Oral Disintegrating Film Containing Donepezil for Alzheimer Disease, AAPS PharmSciTech, 13 (2012) 134-142.
[157] K.V. Sri, P. Rohini, G.K. Reddy, Montelukast sodium oral thin films: Formulation and invitro evaluation, Asian Journal of Pharmaceutical and Clinical Research, 5 (2012).
[158] N. Warren, and Balerna, MonoSol Rx Announces FDA Approval of Zuplenz® Oral Soluble Film for Treatment of Nausea and Vomiting, in: Press Release, MonosolRx.com, 2010.
[159] I. Par Pharmaceutical, ZUPLENZ (ondansetron) oral soluble film, 4 mg and 8 mg, in: D.A.a.d. bases (Ed.) Clinical Pharmacology Biopharmaceutics Review(s) Food and Drug Administration website, 2010.

Graphical abstract