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Design of buccal mucoadhesive tablets: understanding and development

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ABSTRACT

Mucoadhesive tablets for administration in buccal mucosa are unconventional formulations with many technological attractions. However there is no standardization of information for its formulation. The present article aims to evaluate, by means of a systematic review with meta-analysis, the data related to the final quality of this technology. The development of oral tablets with 100 to 150 mg, including soluble drugs and sustained release for 6 hours or more, is a consensus. The most frequent polymers used are those derived from cellulose, Carbopol (CBM), Chitosan (CS), and Gums, alone or blended, with adhesive strength in the order: CBM > Alginates > cellulose derivatives > Gums. Among other results, this article demonstrates that this technology depends on a detailed analysis between the polymer, the physical characteristics of the tablet, the physicochemical characteristics of the drug to be incorporated and the buccal region in which it will remain in contact.

INTRODUCTION

Mucoadhesive tablets are unconventional formulations with a few number of products registered by regulatory agencies such as FDA and ANVISA, and available to the population. However, there are a high number of patents and articles using this pharmaceutical form as an alternative to the oral administration. These formulations can be applied in areas with low vascularization, aiming local administration, or with high vascularization, when systemic absorption is desired; in opposition to the oral tablets, whose pharmacological efficacy depends necessarily on the absorption and systemic distribution (Mansuri, 2016). The main advantages of these formulations are: drug targeting, sustained release, increased permanence time in the buccal mucosa, increased bioavailability, and decreased potential adverse effects (Reddy, 2015).

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The buccal mucosa is an alternative for the oral route avoiding mainly the first-pass metabolism and the excessive degradation by the gastrointestinal environment. In addition, it allows interruptions at any time in the case of toxicity or adverse effects. It is also possible to administrate drugs to patients who have difficulties in swallowing, a common situation in patients undergoing oncology therapy (Shirsand, 2012; Acholu, 2014). There are four effective regions for drug administration into the oral cavity: cheek, palate, sublingual and gingival. Buccal administration refers to the release of drugs into or through the buccal mucosa, in which the formulation sits between the cheek and the gum, providing local and/or systemic effects (Reddy, 2015).

Despite being a formulation of increasing interest in the pharmaceutical industry, introduced since 1947, with the development of oral gel from the mixture of gum tragacanth and dental adhesive powders for the application of penicillin to the oral mucosa, it is still minimally regulated (Kaundal et al., 2015). Information about quality control is obtained

almost exclusively from scientific articles. Therefore, the disadvantage resides in the fact that this information is neither standardized, nor synchronized.

Among other factors, mucoadhesive tablets should guarantee compatibility with the mucosa in which will remain in contact, as well as good adhesive behavior, to remain adhered until the tablets' dissolution. Besides these characteristics, adhesive polymers are characterized by the presence of a molecular mesh that increases their pores gradually according to the swelling capacity of each polymer, resulting in a sustained drug release. Therefore, these formulations have variable drug release profiles, which relates to the composition of the formulation and chemical characteristics of the drug. The easier diffusion of the drug from the polymer matrix to the external medium is proportional to its solubility in the medium, ionization capacity within the formulation, modifying its interaction with the polymer mesh; among other variables less described (Kaundal et al., 2015).

Given the importance and the complexity of this technology, the present article aims to evaluate and standardize, from a systematic review with meta-analysis, the tests of physicochemical characterization, and specifications for this technology applied to the surface of the buccal mucosa.

MATERIALS AND METHODS

It was conducted a systematic review study with meta-analysis using databases: PubMed, Scopus and Web of Science. The Cochraine database was also evaluated to confirm if any review article with the same topic had been already performed. It was also used the descriptors, 'Mucoadhesive tablets', 'buccal', 'mucoadhesion' found in the titles of the articles. As inclusion criteria, it was selected articles with oral mucosal formulations published since 2013, which were grouped by polymer composition, tablets' size and shape, for a detailed analysis of their properties, such as hardness, surface pH, time and mucoadhesion strength, and time required to release 40% and 60% of the drug.

RESULTS AND DISCUSSION

Using the terms 'mucoadhesion', 'tablets', and 'buccal' in the databases Pubmed, Web of Science and Scopus, were found 42, 131 and 74 articles, respectively. Of these, 68 provided experimental data consistent with the statistical analysis proposed in this paper, the remaining are review articles. The experimental articles included the development of mucoadhesive tablets containing drugs complexed with cyclodextrins or nanoparticles, considered to be more complex variations of the mucoadhesive pharmaceutical form, influencing the quality control, mainly regarding the drug release profile. Thus, only 52 articles that discussed the development of mucoadhesive tablets exclusively with the inclusion of polymers, or mixtures of them, and active substances were analysed and organized in Table 1.

The majority of the research found in the articles, aimed a systemic absorption to prevent the first pass effect resulted from oral administration. Thus, from the articles analysed, 30% were for the administration of antihypertensive, 10% antihistaminic, and 60% for administration of less frequent classes of drugs (Figure 1). The use of the buccal cavity for the administration of formulations containing antihypertensive drugs is a common scenario. Examples of such drugs are carvedilol, a β-adrenergic antagonist whose bioavailability after oral administration does not exceed 35% (Elbary *et al*. 2015), and Felodipno, a calcium channel blocker which in spite of being readily absorbed after oral administration, undergoes extensive first-pass hepatic effect, influencing the final bioavailability, that does not exceeding 15% (Reddy *et al*., 2015). As such, other β-blockers, nadolol, nebivolol, atenolol, propranolol, metoprolol, labetalol, angiotensin receptors antagonists, losartan and candesartan, ACE (Angiotensin-converting enzyme) inhibitors, lisinipril and calcium channel blockers, verapamil, were also formulated in mucoadhesive tablets aiming to increase their bioavailability. Only those drugs related to inftion and inflammation control, like NSAIDs, antiseptics and antfungal, or even for anaesthetic effects, were produced to obtain local action, not exceeding 5 articles in total.

The articles that comprise local administration, however, justify its application by relating it to lesser adverse effects when compared to the oral formulations, precisely because they present lower systemic absorption. This apparent ambiguity, related to the greater bioavailability offered by the oral cavity and the lower occurrence of adverse effects, does not occur simultaneously. It is related to the physiology of the different regions of the mouth, whose vascularization determines whether the administration will be primarily systemic or not (topical or buccal).

There are four effective regions for drugs administration into the oral cavity, including cheek, palate, sublingual and gingival (Reddy *et al*., 2015). The most common administration found in the articles were sublingual (the pharmaceutical form remains in the floor of the mouth for a systemic administration due to the high vascularization of the region), buccal (internal region of the cheek, known as oral mucosa, lesser vascularized when compared to the sublingual region and used for local and/or systemic administration) or local, which intends to obtain a pharmacological action in the mouth (Khairnar and Sayyad, 2010; Patel *et al*., 2012; Reddy *et al*., 2015; Kaundal *et al*., 2015).

In buccal administration, the solid pharmaceutical forms usually remain between the gum and the cheek (known as the lateral or buccal sulcus) to remain fixed, preventing possible displacement due the natural movements of the oral cavity, as shown in Figure 3.

Therefore, it is an administration route in which the drug will be absorbed in an intermediate proportion, when compared to the sublingual route – that provides a greater absorption, and topical administration – that results in a lesser absorption, making it ideal for slow and prolonged drug release, aiming to maintain pharmacological effects by long periods without the need to administrate a second dosage. Therefore, the oral cavity is a route of administration with wide technological applications, justifying the diversity of drugs found in these articles.

In this sense, the specifications for mucoadhesive tablets will be dependent, therefore, on the objectives proposed with the developed formulation. All 52 articles analyzed were grouped according to the polymers used and incorporated active ingredients, separated by type of administration, whether for systemic or local absorption.

Table 1. Composition of mucoadhesive tablets developed from 2012 to 2016.

Administration route	Polymeric composition	Drug	References
Buccal mucosa (systemic action)	Jackfruit mucilage, CBM e Marigold mucilage, Xanthan gum, HPM	Chlorfeniramine	Sabale *et al*., 2012; Sabale *et al*., 2014
	HPMC, CBM, CMC, pectin, alginates	Losartan	Velmurugan *et al*., 2013b
	CMC, CBM	Promethazine	Chopparapu *et al*., 2012
	CMC, CBM, HPMC, Alginate, EC	Nebivolol	Shirsand *et al*., 2013
	Xanthan gum, Tamarid gum, Gellan Gum and CS	Rosuvastatin	Panchal *et al*., 2012
	CBM, Guar Gum, CS, HEC	Furosemide	Umarji *et al*., 2012
	CBM, HPMC e EC	Atenolol	Shirsand *et al*., 2012
	Guar Gum e EC	Terbutaline	Kulkarnila *et al*., 2013
	Quitoasana, Xantan Gum, Gelatine e HPMC	Ondansetron	Azhar *et al*., 2012
	Xanthan Gum, EC	Salbutamol	Kulkarni *et al*., 2012
	CMC, CBM, EC	Carvedilol	Elbary *et al*., 2015
	CBM, HPMC, Alginate	Nitroglycerin	Kumar *et al*., 2014
	CS/Gelatina (microparticles)	Propanolol	Abruzzo *et al*., 2015
	Alginate e HPMC	Domperidona	Pandey *et al*., 2014
	HPMC, CMC, CS	Lisinopril	Hussein *et al*., 2013
	CBM, HPMC, CS	Glimepiride	Bhanja *et al*., 2013a; Bhanja *et al*., 2013b
	Badam Gum	Metoprolol	Mylangam, 2016
	CBM, CMC, HPMC, Alginate, Guar Gum, HEC	Felodipino	Acholu *et al*., 2014 Reddy *et al*., 2015b
	CMC and *Momordica charantia* extract	Glicazide	Saravanakumar *et al*., 2014
	CBM, CS, Guar Gum, HPMC e Alginate	Glipizide	Reddy *et al*., 2015a Velmurugan, *et al*., 2013a
	CBM, CS, Guar Gum, Casein, HPMC	Carvedilol	Fathima *et al*., 2015, Chaudhari *et al.* 2012
	CBM, HPMC, CMC, Xanthan Gum	Tromethamine	Shukr *et al*., 2014; Rao *et al*., 2014
	CBM, HPMC, Alginate	Nitroglycerin	Kumar *et al*, 2014
	CBM, CMC, HPMC	Candesartana	Vinay *et al*., 2015
	Xanthan Gum, Tamarind Gum, Gellan Gum, CS, HPMC, Guar Gum, Karaya Gum	Rosuvastatina	Panchal *et al*., 2012; Krishnarajan *et al*., 2012
	Xanthan Gum, CBM, HPMC, CS, Alginate	Zolmitriptan	Khazaal *et al*., 2012
	CS, HPMC	Timolol	Sheikh *et al*., 2012
	Alginate, Guar Gum	Labetolol	Shabaraya *et al*., 2012
	HPMC, CBM, CMC	Candesartana	Vinay *et al*., 2015
	Goma de Almondega	Tizanidine	Harikrishnan *et al*., 2015
	Polycarbophil Thiolate	Selegiline	Wasnik *et al*., 2014
	CBM, CS, CMC	Nadolol	Sandhyarani *et al*., 2014
	CBM, Alginate	Metoclopramide	Pawar *et al*., 2012; Pawar *et al*., 2015
	CBM, HPMC, HEC, CMC.	Verapamil	Aboutaleb *et al*., 2013
	CBM, HPMC	Sinvastatin	Chikate *et al*., 2014
	HPMC, CBM, MC	Quetiapine	Potu *et al*., 2012
	CBM, HPMC	Esomeprazole	Othman *et al*., 2013
	CBM, HPMC, Alginate	Prochlorperazine	Jain *et al*., 2016
	CBM, Alginate, CS, EC	Tapentadol	Reddy *et al*., 2013

Buccal mucosa (local action)	Milk proteins e Hypromellose	Miconazole	Vazquez *et al*., 2012
	CBM, Xanthan Gum, EC	Indomethacin	Ikeuchi-Takahashi *et al*., 2013a; Ikeuchi-Takahashi *et al*., 2013b
	HPMC, Cordia mucilage	Chlorhexidine	Moghimipour *et al*., 2012
	HPMC, CMC, EC and CBM	Fluconazole	Singh *et al*., 2013
	CBM, HPMC, EC	Itraconazole	Sayeed *et al*., 2014
	CBM, HPMC	Clotrimazole	Reza e Sara, 2014

Abbreviations: Carbomer (CBM); Chitosan (CS); Carboxymethylcellulose (CMC), Ethylcellulose (EC), Hydroxyethylcellulose (HEC), Hydroxypropylmethylcellulose (HPMC).

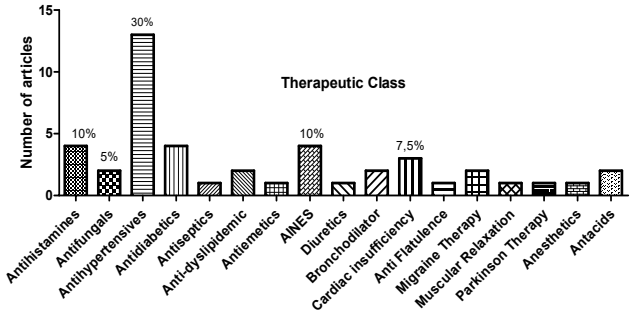


Fig. 1: Number of articles per therapeutic class of drugs inserted into buccal mucoadhesive tablets.

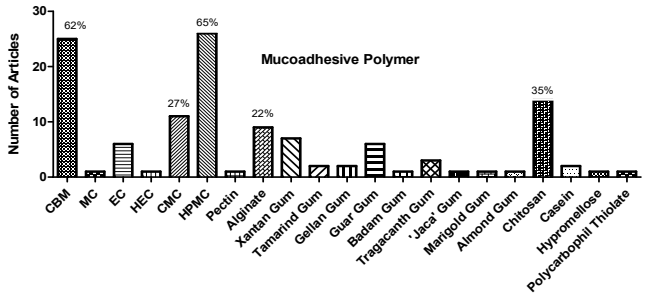
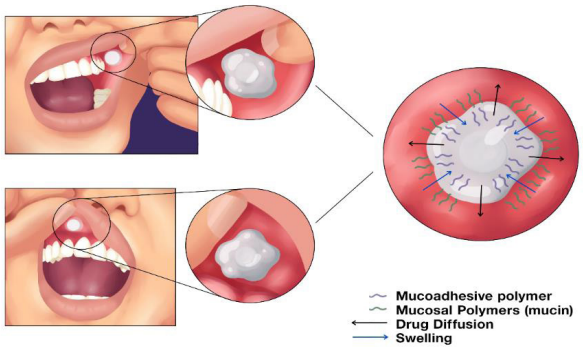


Fig. 2: Proportion of the most used polymers for buccal mucoadhesive tablets.

The mucoadhesive polymers used included some unconventional, natural or artificial, such as, milk proteins and hypromellose, mucilage of jackfruit, marigold and cordia, tamarind gum, thiolated polycarbophil (Wasnik *et al*., 2014), as well as chemical alterations of chitosan with addition of thiol groups (Boatend & Ayensu, 2014). These polymers, not conventionally applied for mucoadhesive purposes, were found in isolated articles, which make it impossible to compare them with other papers. The polymers most cited in the articles are organized in Figure 2. It is highlighted, therefore, cellulose derivatives, Ethylcellulose (EC), Methylcellulose (MC), Carboxymethylcellulose (CMC), Hydroxyethylcellulose (HEC), Hydroxypropylmethylcellulose (HPMC), Gums (Xanthan, Badam, Gellan, Guar and Alginate), Acrylates and Chitosan.

Some of the structural features required for bioadhesive polymers include the presence of groups able to form hydrogen bonds, strong anionic or cationic charges, high molecular weight, chain flexibility and surface energy properties that favour their interpenetration in the mucus layer (Salamat-Miller *et al*., 2005) ; Figueiras and Veiga, 2009).

It is worth mentioning that mucoadhesive interactions in the oral cavity occur between the polymers and the substances present in the oral surface. This surface is covered by a layer of mucus, which consists mainly of water (95%), but also salts, lipids, phospholipids, cholesterol, proteins with defensive function, such as lysozyme, immunoglobulins, etc. However, the main component responsible for its viscoelastic properties is the glycoprotein mucin (Sogias *et al*., 2012). Mucins are large extracellular glycoproteins with molecular weights ranging from 0.5 to 20 MDa, highly glycosylated consisting of 80% carbohydrates, mainly N-acetylgalactosamine, N-acetylglucosamine, fructose, galactose, sialic acid (N-acetylneuraminic acid), mannose and sulphate traces (Bansil *et al*., 2006). The main mucoadhesive interactions are established between the polymers and the carbohydrates constituent of the mucin.



Mucoadhesive polymer	General Tablets Characteristics	Mucosa	Drug
Solubility/pKa	Average weight/Content	Mucosal pH	Solubility
Molecular size/Chain Flexibility	Hardness/Friability	Time to renew mucine	pKa

Footnote: Polymer, general tablets properties and mucosa characteristics are important factors to be considered in order to have a good mucoadhesion behavior; all these factors added to drug characteristics will determinate the release profile

Fig. 3: Factors related to influencing the mucoadhesion tablets behavior and their release profile.

Several studies indicate that a maximum mucoadhesion occurs when the molecular size of the polymer lies within the range of 10^4 to 4×10^6 g/mol. As for the flexibility of the polymer chain, it is desirable the presence of equal charges in its units, allowing repulsion between them and thus facilitating the opening of the

chain and the release of the drug incorporated during the swelling process (Salamat-Miller *et al*., 2005; Figueiras and Veiga, 2009). This process can be better illustrated in Figure 3.

Thus, it is important to evaluate the polymers' physicochemical characteristics to choose the most suitable one for the administration surface. Being the saliva characterized as an aqueous buffer with normal pH values between 6.2–7.6 (Baliga *et al*., 2013), the physicochemical characteristics of the polymers were sought for solubility, viscosity and pH in water, data grouped in Table 2. Their chemical structures can be visualized in Table 3, in order to better understand Table 2.

Table 2: Physicochemical characteristics of the most used mucoadhesive polymers for buccal formulations.

Polymer	Physicochemical characteristics						
	Classification	Charge	Mw (g/mol)	Ɒ (aqueous solution)	Water Solubility	ƥ (g/cm³)	pH (1% w/v aqueous solution)
EC	Semisynthetic	Nonionic	Δ	-	N	1.12-1.14	x
MC	Semisynthetic	Nonionic	Δ	5–75000 cPs at 25°C (2% of Aq. Sol.)	Cold	0.25–0.7	5.0–8.0
CMC	Semisynthetic	Anionic	9×10^4–7×10^5	5–2000 cPs at 25°C (1% of Aq. Sol.)	Y	0.78	6.5–8.5
HEC	Semisynthetic	Nonionic	Δ	2–20000 cPs at 25°C (1% of Aq. Sol.)	Cold or hot	0.35–0.61	5.5–8.5
HPMC	Semisynthetic	Nonionic	Δ	100–80000 cPs at 20°C (2% of Aq. Sol.)	Y	0.25–0.70	5.0–7.5
Xanthan Gum	Natural	Anionic	~1×10^6	1200–1600 cPs a 25°C (1% of Aq. Sol.)	Cold or hot	-	6.0–8.0
Tragacanth Gum	Natural	Anionic	$8{,}4 \times 10^5$	100–4000 cP a 20°C (1% of Aq. Sol.)	N	-	5.0-6.0
Guar Gum	Natural	Anionic	~$2{,}2 \times 10^5$	4860 cPs a 25°C (1% of Aq. Sol.)	Y	1.49	5.5–7.5
Alginate	Natural	Anionic	~$2{,}1 \times 10^5$	20 cP s a 20°C (0,5% of Aq. Sol.)	Y	1.60	1.5–3.5 (3% w/v)
Acrylates-Carbomers	Synthetic	Anionic	7×10^5–4×10^9	29.4–39.4 cPs a 25°C (0.5% of Aq. Sol.)	Y	0.2–0.4	2.5–3.0
Chitosan	Semisynthetic	Cationic	1×10^4–1×10^6	-	N	1.35–1.4	4.0–6.0

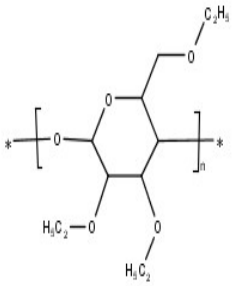
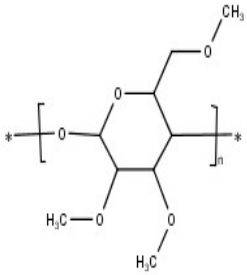
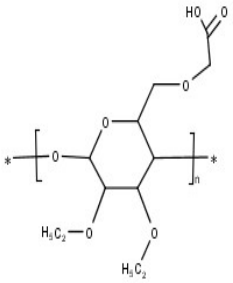
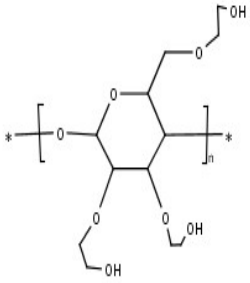
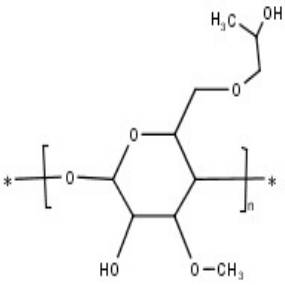
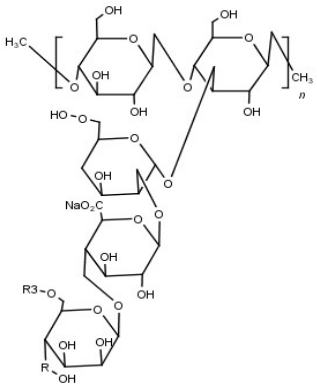
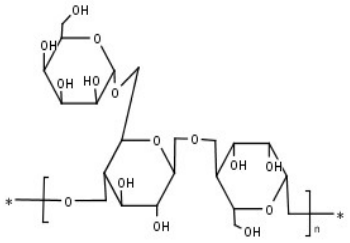
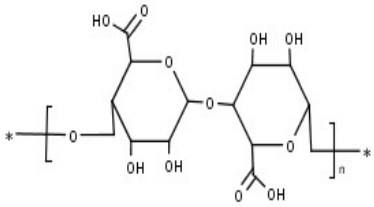
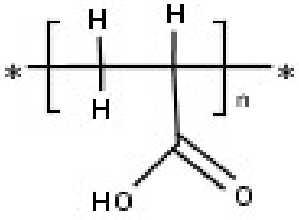
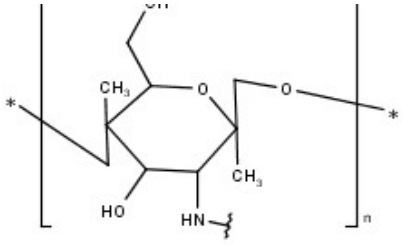
Source: Rowe *et al*., 2009; Russo *et al*., 2016; Sogias *et al*., 2012; Figueiras e Veiga, 2009.
Abbreviations: Ethylcellulose (EC); Methylcellulose (MC), Carboxymethylcellulose (CMC); Hydroxyethylcellulose (HEC); Hydroxypropylmethylcellulose (HPMC); Viscosity (ŋ); Density (ƥ); Molecular weight (Mw); Yes (Y); Not (y); Variation (Δ); Information not found (-).

Physicochemical characteristics of mucoadhesive polymers

These polymers are polysaccharides, characterized by the presence of monosaccharides residues joined by O-glyosidic linkages. The great diversity of monosaccharides as well as the different possibilities for them to bond dictates the unique functional properties exhibited by each polymer. They are also called as hydrocolloids or gums and occurs in nature as storage materials, cell wall components, exudates and extracellular substances from plants (like cellulose and pectin), animal (chitin and chitosan), or microorganisms (like alginates and agar obtained by seaweed or even Xantan and Gellan gum, obtained by microbial polysaccharides). Over the years the demand for natural products has increased. Gums for example, which was seen in the articles as one of the most used polymers to compose buccal mucoadhesive formulations, have both the appeal of being a natural product, as well having a more affordable cost, justifying its prevalence in the articles analyzed. Some of the advantages of these materials over synthetic ones are that they are potentially biodegradable and widely available (Avachat *et al*., 2011). However, chemical modification provides additional sources of gums with improved functionality (Izydorczyk, Cui & Wang, 2005).

They are frequently classified according to their original source, as mentioned previously. However, as mucoadhesive polymers, to better understand these properties, they were organized in this study according to their physical and chemical characteristics as natural or synthetics, ionic or non-ionic, or even uniformity grade of monosaccharides. Thus, we selected cellulose derivatives as a group with grate uniformity in monosaccharides units, others natural gums without this characteristic, acrylates as synthetic and ionic polymer, and chitosan, as a semisynthetic and cationic polymer, included in Tables 2 and 3.

Table 3: Molecular structure of the repeating units of the described polymers.

Cellulose derivates				
Ethylcellulose	Methylcellulose	Carboxymethylcellulose	Hydroxyethylcellulose	Hydroxypropylmethylcellulose
				
Natural Gums				
Xanthan	Tragacanth	Guar		Alginate
	-			
Carbomers				**Chitosan**
				

Abbreviations: - (Molecule with very large repeating units, best described in the text).

Cellulose derivates

Ethylcellulose is a non-ionic polymer, insoluble in water, formed by acetal bonds between units of β-anhydroglucose and with considerable variations among suppliers, influenced by the amount of units and amount of ethoxylic groups present in the molecule. It is therefore related to the increase in the degree of ethoxylation with its more viscous behaviour (Rowe *et al*., 2006). However, such a value was not established for aqueous solutions, being widely quoted in technical reports from suppliers the viscosity of 10cPs in toluene: ethanol (80:20) solution for the polymer with degree of ethoxylation of 48-49%. In addition to this parameter, pH was also not identified in aqueous solutions, since it is an insoluble polymer (Figueiras and Veiga, 2009; Rowe *et al*., 2009).

Methylcellulose (MC), also a non-ionic polymer, despite being insoluble in water, is considered capable of forming a clear or opalescent colloidal dispersion by slow dispersion in cold water (Rowe *et al*., 2009). It also shows variations in molecular weight between 10000 and 220000 g/mol, influencing the wide ranges found for pH, viscosity and density (Rowe *et al*., 2009).

Carboxymethylcellulose (CMC) exhibits water solubility at any temperature and a pH range closer to neutrality, similar to buccal cavity (Figueiras and Veiga, 2009). It is the

first ionic polymer described until then, with potential of ionic interactions with the buccal coating. *Hydroxyethylcellulose* (HEC) and *hydroxypropylmethylcellulose* (HPMC) are also water soluble, being the hydroxyethylcellulose solubility in water limited to hot or cold solution. Hydroxypropylmethylcellulose presents hydroxypropyl and/or methyl radicals in the hydroxyls of cellulose, in which the degree of substitutions will determine whether the polymer will be more or less viscous, however, all considered water soluble. It is an agent with higher viscosity and more acidic pH ranges (Rowe *et al*., 2009).

The polymers derived from cellulose are characterized by a wide molecular weight range described in the literature and, therefore, different materials are offered by chemical suppliers (Eagle CMC, Sigma-Aldrich, Shradanand Building, etc.). This variation directly influences the other parameters mentioned in table 2. However, it is worth noting that HPMC and MC are those related to greater viscosity, following the order: CMC <HEC <MC <HPMC. EC, the only one that is nor soluble in the buccal medium, does not have described in the consulted literature the values of its viscosity in water.

Such behaviour is related, among other factors, to the molecular size, the solubilization of the material in water, and the surface energy properties that favours the polymer chain opening. It is thus justified the high viscosity of HPMC, high molecular weight non-ionic polymer and with high intermolecular interactions that hampers the chain opening. Also, the low viscosity for the only ionic polymer derived from cellulose, CMC, with high solubility due to its high capacity to promote electrostatic and hydrogen interactions with water, facilitating the opening of the chain.

Another noteworthy observation is that the radicals associated with cellulose confer ionic bonding power, hydrogen interaction, or hydrophobic interactions with the mouth residues of mucin in different degrees. In a theoretical model, methyl and ethyl radicals confer hydrophobic interactions, having the ethyl greater intensity due to its chain size. Hydroxypropyl and hydroxyethyl are capable of interacting with hydrophobic or hydrogen bonds. Carboxymethyl is the only radical with the possibility to form ionic, hydrophobic and hydrogen interactions, conferring to it high adhesive capacity. Theoretically, it can be established an increase relation relative to the interactions strength with mucin: CM <EC <HEC <HPMC <CMC (Russo *et al*., 2016).

Among the preference in the described articles, cellulose derivatives are widely used, especially HPMC, present in 65% and CMC in 27% (Figure 2).

Other Gums

As explained previously, in this group, their great structural variation may result in less predictable interactions between mucous membrane and the drug to be released. However, their large availability in nature makes them a very useful alternative for mucoadhesive oral application.

Xanthan gum is an anionic polymer, water soluble and has a high molecular weight. Each repeating unit contains 5 sugar residues: 2 glucoses, 2 mannoses and 1 glucuronic acid. The backbone of the polymer is formed by β-D-glucose units attached at the positions 1 and 4, similar to the cellulose structure. Trisaccharides in the side chains, alternating anhydrous glucose chains, distinguish this gum from cellulose. This trisaccharide comprises a residue of glucuronic acid, which confers anionic properties to the polymer, between 2 units of mannose (Rowe *et al*., 2009). It is described as a polymer of moderate mucoadhesion due to its high swelling power. In addition, it is described as an excellent hydrophilic matrix for sustained release of drugs, with release profile close to zero order (Park and Munday, 2004).

Gum Tragacanth is a natural gum obtained from the *Astragalus gummifer* Labillardie`re and other species of Astragalus grown in Western Asia. It has in its composition a mixture of soluble and insoluble polysaccharides, which confers it emulsifying properties. Bassorin, or tragacanthic acid constitutes 60-70% of the gum, represents the main water-insoluble quantum, and with high-gelling capacity, while the rest of the gum is composed by a water-soluble and neutral material, tragacanthine. Upon hydrolysis, tragacanthin produces L-arabinose, L-fucose, D-xylose, D-galactose and D-galacturonic acid (Gavlighi, 2012). It is a polymer with a high viscosity, inferior to those of the cellulose derivatives, and pH range just below the buccal cavity.

Guar gum consists of linear chains of (1,4)-b-D-mannopyranosyl units with α-D-galactopyranosyl units attached by bonds (1,6). The ratio of D-galactose to D-mannose is between 1:1.4 and 1:2. This gum is obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L.) (Rowe *et al*., 2009; Kumar *et al*., 2012). It presents a high viscosity and pH range close to neutrality; in addition, it has a slight sweet taste, unlike the other polymers described which may be attractive for buccal applications (Rowe *et al*., 2009).

Alginic acid or *alginate* is an anionic polysaccharide, also called algin and obtained on the cell walls of brown algae. Its composition is given by a mixture of polyuronic acids composed of residues of D-manuronic acid and L-glucuronic acid. Sodium alginate is slightly soluble in water and insoluble in ethanol and ether, with low viscosity and very acidic pH values when compared to the oral physiology, however, it is one of the most used polymers in the analyzed articles, being cited in 22% of these. Despite the low viscosity, it is able to absorb 200-300 times its own weight in water, being reported its use in mucoadhesive formulations, delaying the release of ketoprofen in about 8 h (Kumar *et al*., 2012).

Acrylates

Also known as Carbomers, are synthetic polymers with high molecular weight derived from polyacrylic acid, with acrylic acid repeat units cross linked with allyl sucrose or allyl ethers of pentaerythritol (Russo *et al*., 2016). Their molecular weight can range from 10^5 to 10^9 g/mol, distinguishing the brands commercially available, among them, 237 600 g/mol for Carbopol 941 and 104 400 g/mol for Carbopol 940. In general, the carbomers with lower viscosity and lower stiffness will have higher molecular mass values (Rowe *et al*., 2009).

Due to its excellent mucoadhesive properties, with mucoadhesion strength of around 17,6 N/cm^2 for polymer films, this polymer plays as a reference for mucoadhesiveness (Lehr *et al*., 1992). In tablet formulations, comparing the polymeric compositions of CMC, HPMC, Pectin and Chitosan, Carbomers 934 and 940 presented values 4x, 10x, 10x and 7x higher than these, respectively. However, it is a polymer with very acidic pH range in aqueous solution, resulting in tablets with low pH, which

is a limiting aspect when the pharmaceutical form will remain in contact with mucous membranes for long hours (Nafee *et al*., 2004).

Chitosan

Chitosan is a linear copolymer obtained from the deacetylation of chitin, a polymer obtained mainly from crustacean's shells. It presents β-(1,4) glycosidic bonds between 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose, varying in commercially available types, with molecular weight between 10^4-10^5 Da, and consequent varying the degree of deacetylation and the viscosity. The viscosity of the polymer was not found for aqueous solutions, only for acid solutions, in which the polymer is able to solubilize (e.g. 260 cPs at 25°C in acetic acid solution 1%) (Rowe *et al*., 2009; Sogias *et al*., 2012).

The amine radicals determine the unique cationic characteristic possessed by this polymer, standing out among the mucoadhesive polymers as the one with the greatest adhesion force. Several polymers were evaluated regarding their mucoadhesion strength in the form of polymeric films, being obtained values of 6,6 mN/cm^2 for chitosan, high values in comparison to CMC of low, medium and high viscosity, with 1,8; 0,3 and 1,3 mN/cm^2 respectively, or 0 mN/cm^2 for pectin or xanthan gum (Lehr *et al*., 1992).

Some generalizations on the bioadhesive polymer load were made previously, where non-ionic polymers appeared to exhibit an inferior degree of adhesion in comparison to anionic polymers (Salamat-Miller *et al*., 2005). In addition, cationic polymers readily interact with the sialic acid presents in mucin, a reaction demonstrated exactly for chitosan (Sogias *et al*., 2012). It is therefore justified that this polymer, of high molecular weight, natural origin, biocompatible, with cationic charge, and high attraction to mucosal surfaces, presents highly acceptance among mucoadhesive polymers.

Mucoadhesive tablets development

All those studied articles show some important factors to be considered in mucoadhesive tablets development, including besides the polymer choice, the general tablets characteristics, mucosal behavior and physical and chemical drug characteristics, as shown in Figure 3.

Specifically for buccal mucosa, this tablet must be compatible with mucosal pH, within normal values between 6.2–7.6 (Baliga *et al*., 2013), must also be adhered to the mucosa with strength and time sufficient to resist the process of salivation and allows the drug to be released in the proposed time, whether for local or systemic action. In this way, it is extremely important to find a relation between hardness, polymer chosen, tablet composition and drug physicochemical characteristics to obtain a formulation with optimal mucoadhesion profile, including time and strength, and optimal release profile (Ford, 2014). Therefore, quality control applied to mucoadhesive tablets include basically average weight, thickness, hardness, friability and release profile further on specific tests like mucoadhesive time and strength, swelling degree or percentage and surface pH.

In spite of so many variables to be considered in mucoadhesive tablets development, the articles analyzed do not consider them as a whole, being common to fix only some of these. The majority prioritize the polymer composition as the only interfering factor in the quality of the adhesive tablet. Furthermore, most of the articles selected do not analyses formulations with isolated polymers, but only with associations of them. The articles focus mainly on pharmacological suitability, aiming to improve the administration of an active principle, either to reduce adverse effects or the effect of first pass metabolism, without worrying about the influence of each one of the polymers. This demonstrates that in the name of the larger goal of developing an appropriate formulation as quickly as possible, the articles developed until now, leave out the nuances of the technology itself, making it difficult for researchers who want to start developing this technology.

Promethazine tablets, for example, were developed with a polymer mixture between CMC and CBM, without any analysis of formulations with the isolated polymers (Chopparapu *et al*., 2012). Chlorpheniramine was incorporated into a polymer blend in order to specifically evaluate the quality of the mucilage of jackfruit and marigold mixed with synthetic polymers derived from cellulose (Sabale *et al*., 2014). Nebivolol, also for systemic absorption, was incorporated into EC mixtures with CMC or Alginate, never isolated (Shirsand, 2013). Rosuvastatin was incorporated into EC tablets associated with natural gums, including Xanthan, Tamarind and Gellan (Panchal *et al*., 2012). Furosemide mucoadhesive tablets were made with mixtures of CBM 934, HEC, CS and Guar Gum. In these, it is mentioned that formulations containing CBM associated to CS or HEC present greater adhesion, strength and time, in addition to a higher percentage of swelling (Umarji *et al*., 2012).

In addition to these studies, some articles present EC as a fixed polymer, varying its constitution in relation to other polymers, this is the case of the studies developed with Atenolol, Terbutaline, Salabutamol, Carvedilol and Quetiapine (Shisand *et al*., 2012; Kulkarni *et al*. 2012; Potu *et al*., 2012; Elbary *et al*., 2015). A justification for this choice is because EC is the only water insoluble polymer mixed with hydrophilic polymers, which may result in a delay in the swelling process. Another possibility is the unidirectional drugs release. In such a case, each surface of the tablet, except the one in contact with the buccal mucosa, may be coated with water impermeable materials such as EC, hydrogenated castor oil, etc., using multicompression or spray coating (Spray Drier) (Salamat-Miller *et al*., 2005; Panchal *et al*., 2012).

Another frequent association is between CBM and other hydrophilic polymers, this is the case of the studies developed with Candesartan, Nitroglycerin, Trometamine, Glimepiride, etc. Such justification is given by the high adhesive capacity of CBM, improving the association with other polymers with lower adhesive power. For Losartan mucoadhesive tablets the order of mucoadhesion strength found was CBM 940 > Alginate > Pectin > HPMC > CMC sodium (Velmurugan, 2013). Another justification is that it is an acid polymer, at values below the physiological pH of the mouth, however, in association with polymers closer to neutrality, the surface pH of the formulation becomes adequate.

Despite these variations, this work aimed to find some relation between these parameters. The search for specifications was conducted regarding parameters that influence in mucoadhesive profile and release profile. Thus, from the few

studies that developed tablets with isolated polymers, were collected information about average weight, hardness, surface pH, time and strength of mucoadhesion, % of swelling after 6 h of analysis, drug content and their pKa and solubility, and release profile after 4 h and 6 h of analysis, seeking relations between these parameters and mucoadhesion profile and release profile, data shown in Table 4.

Mucoadhesive profile

As previously spoken, the polymer composition and tablet characteristics are determinant to establish a strong mucoadhesion. About general tablets characteristics, Table 4 shows that for the same polymer several hardness values were found. The developed tablets include other hardness imparting excipients, such as microcrystalline cellulose, pharmaceutical talc, lactose, mannitol, polyvinylpyrrolidone, etc., justifying the variations found. These, together with the omission of results or non-execution of tests, made it impossible to correlate the values of the general tablets characteristics with the mucoadhesive behavior.

For the polymer, factors such as solubility, molecular size, chain flexibility and pKa can influence the adhesiveness. The molecular sizes of the polymers described in Table 2 are similar, around 10^5 to 10^6 g/mol, referenced as ideal for mucoadhesion (Figueiras and Veiga, 2009). Among those described, only ethylcellulose is insoluble in water, and none of the papers this polymer was used alone. The pKa, at last, is one of the most important parameters in bioadhesion. Depending on the pH of the medium, this parameter will influence the degree of ionization of the molecule, the flexibility of the chain, and therefore the mucoadhesion strength and time (Park and Robinson, 1985).

Polymer pKa and tablet surface pH

The normal pH range of saliva is 6.2-7.6 with an average value of 6.7. The resting pH of the mouth does not fall below 6.3. In the oral cavity, pH is maintained close to neutrality (6.7-7.3) by saliva (Baliga *et al*., 2013). The surface contact of a tablet containing mucoadhesive polymers with acid or basic pH values will influence the degree of mucin ionization and will be related to the degree of bioadhesion, which is justified by the electronic bioadhesion theory (Patel *et al*., 2012; Kaundal *et al*., 2015). According to this theory, the adhesive material and the biological target have different electronic structures and when they come into contact, a double layer of electronic charge is formed at the interface, responsible for the creation of attractive forces and therefore bioadhesion (Salamat-Miller *et al*., 2005; Figueiras and Veiga, 2009).

If the local pH is above or below the polymer pKa, the polymer will be largely ionized. This ionization influences two aspects, first the interaction with mucin and second the ease of opening of the polymer mesh and, therefore, it's swelling ability (Ching *et al*., 1985; Park and Robinson, 1985).

The estimated pKa for the polycarbophilic polymer family, for example, is between 4 and 5. The maximum adhesive strength occurs when the medium has pH of 4-5. This adhesiveness gradually decreases in pH above 6. The explanation for this fact is because at a high pH value, the polymer chain ionization tends to facilitate repulsion between the units, facilitating its opening during the swelling process, and reducing adhesiveness. At pH below the polymer pKa, the non-ionized form is predominant and the adhesive strength decreases too (Ching *et al*., 1984; Park and Robinson, 1985; Patel *et al*., 2012).

Anionic polymers also possess mucoadhesive properties due to the establishment of hydrogen bonds with the mucus layer. While cationic polymers form ionic bonds with negatively charged mucin chains, anionic polymers with more negative charges tend to have greater adhesion due to interaction by hydrogen bonds with high range of mucosal aminoacids (Lee *et al*., 2016).

Despite being important for the bioadhesion process, ionic, acidic or basic polymers, which causes changes in the ionization degree of the mucin and remain for a long time in contact with the oral mucosa can produce irritation, causing damage to its normal structure (Nafee *et al*., 2004). Therefore, the articles analyzed assume the specification of the surface pH within normal values of the physiological pH, from 6.2 to 7.6. In Table 4, all the analyzed papers presented formulations with pH within the described range.

The incorporation of Losartan into mucoadhesive tablets, for example, was made using Pectin, Alginate, CMC, CBM and HPMC. The tablets had besides the polymers, addition of microcrystalline cellulose, pharmaceutical talc and magnesium stearate. Thus, although with polymers of different pKa's, the formulations developed had surface pH in the range of 6 to 7, which, according to the author, is compatible with the buccal mucosa (Velmurugan, 2013).

Although, in most of the studies the tablets were produced by inserting, in addition to the active principle and the mucoadhesive polymer, other excipients, such as microcrystalline cellulose, lactose, pharmaceutical talc, magnesium stearate and saccharin, or other sweetener. In other hand, the tablets developed with simvastatin (Chikate *et al*., 2014), were constituted almost exclusively by the CBM polymer (70% of the formulation), which justifies being the only one to report a surface pH value below to 6, compatible with the pH value in aqueous solution for the polymer described.

In Table 4 it is possible to observe that the strength and time of mucoadhesion suffer many variations for the same polymer in different articles. Comparing literature data with the variable numbers of the analyzed articles it was not possible to establish a real order between composition and force/strength of mucoadhesion. However, the uniformity of results for Alginates, CBM and Chitosan, in order, CBM > Alginate > CS, stands out.

The acidity conferred by CBM and Alginate is related to the establishment of strong hydrogen interactions with the mucosa. It had already been described the superiority of anionic polymers in mucoadhesion in relation to cationic or non-ionic (Nafee *et al*., 2004). For CBM, practically all Carbopol® commercially available are completely ionized at pH 6.8, making it easy to produce a swelling matrix due to the repulsion described previously, however, unlike that described for polycarbophil, it has high interaction ability by formation of hydrogen bonds, justifying its high adhesive value even at buccal pH (Russo *et al*., 2016).

In an attempt to elucidate the mucoadhesive mechanism of alginates, the role of molecular weight and chain flexibility to determine the extent of mucin interaction has recently been

demonstrated. In fact, the interaction between mucin and low molecular weight alginate does not affect the conformation of the protein, once its molecules are too rigid to produce significant contraction in the mucin. In contrast, high molecular weight alginate molecules are more flexible and capable of binding distant mucin sites causing protein contraction (Russo *et al*., 2016).

Table 4. Mean results of quality control for mucoadhesive tablets of 100-200 mg, per type of polymer and drug inserted.

Polymeric Composition		Quality Control								
		Average weight (mg)	Hardness (Kg/cm²)	% of swelling (6 h)	Surface pH	Mucoadhesion time (h)	Mucoadhesion strength (N)	Drug	pKa/§	FR 4 h–6 h
Anionic	CMC	150	-	35%	6,50	8	0,11	Losartan	5,5/S	20–40%
		130	12,5	332%	6,00	-	0,416	Lisinopril	2,5/S	50–80%
		150	4,5	-	6,13	6,63	0,137	Felodipino	5,39/S	40–60%
		150	4,5	-	-	7,5	-	Glicazida	4,07/S	40–60%
Nonionic	HPMC K15M	150	-	38%	6,50	3	0,1	Losartan	5,5/S	80–100%
		150	-	-	6,72	4,22	-	Carvedilol	14/S	20–30%
		130	13,5	268%	5,2	-	0,343	Lisinopril	2,5/S	20–40%
		150	3,6	100%	7,16	4,83	0,24	Glimepirida	4,3/S	80–90%
		150	5,8	-	6,28	7,45	0,11	Felodipino	5,39/S	34–54%
		100	6,8	-	6,80	> 8	0,154	Glipizide	4,3/S	40–50%
		120	4	-	-	-	-	Glipizide	4,3/S	65–87%
		150	4,41	46%	7,24	3	0,284	Itraconazole	3,9/S	84–94%
Anionic	Xanthan Gum	150	3,6	33,10%	6,4	-	0,082	Rosuvastatin	4/S	80–100%
		110	1,7	1105%	-	> 8	0,215	Rosuvastatin		18–25%
Anionic	Guar Gum	120	5	-	-	-	-	Glipizide	4,3/S	74–99%
		100	7,4	54%	-	-	0,076	Carvedilol	14/S	87–92%
		110	1,7	426%	-	> 8	0,196	Rosuvastatin	4/S	10–20%
		200	3	69%	6	-	0,296	Labetolol	8/S	42–64%
Anionic	Alginate	150	-	38%	6–7	4	1,2	Losartan	5,5/S	60–70%
		100	7,1	-	7,1	> 8	1,43	Glipizide	4,3/S	30–40%
		200	3,98	67%	6,38	-	2,8	Labetolol	8/S	48–71%
		120	4,1	300%	5–6	15	1,118	Sinvastatin	14,9/S	60–75%
Anionic	CBM 940/ CBM 934	150	-	12%	6–7	6	1,4	Losartan	5,5/S	50–70%
		150	5,1	-	6,23	6,27	1,05	Felodipino	5,39/S	34–60%
		120	4,4	450%	6–7	20	2,02	Sinvastatin	14,9/S	50–60%
		120	4,5	51%	6,8	6,5	3,8	Glipizida	4,3/S	56–78%
		100	6,6	-	6,6	> 8	2,36	Glipizida		40–50%
		150	4,71	51,17%	6,17	> 12	3,01	Itraconazole	3,9/S	37–69%
Cationic	Chitosan	150	-	-	6,52	3,92	-	Carvedilol	14/S	40–50%
		150	3,2	106%	7,22	5,25	0,162	Glimepiride	4,3/S	70–90%
		120	4,3	-	-	-	-	Glipizide	4,3/S	66–88%
		100	6,7	Tablet breaks	-	-	0,856	Carvedilol	14/S	90–93%
		100	6,7	Tablet breaks	-	-	0,83	Carvedilol		77–93%
		150	3,6	26,22%	7,1	-	0,42	Rosuvastatin	4/S	100% em 1h

Abbreviations: Ethylcellulose (EC); Methylcellulose (MC), carboxymethylcellulose (CMC); Hydroxyethylcellulose (HEC); Hydroxypropylmethylcellulose (HPMC); Time to release 100% of the drug (FR); solubility in water (§); Soluble (S).

Chitosan is the third polymer with the highest adhesion values reported, corroborating the association between cationic polymers and anionic mucins. However, the molecular mass, conformation and overall flexibility of chitosan (determined by the charge density, e.g., the degree of acetylation) also play a significant role (Sogias *et al*., 2012; Salamat-Miller *et al*., 2005; Russo *et al*., 2016).

HPMC and CMC have similar characteristics regarding mucoadhesion. Some articles describe HPMC as being more adhesive than CMC, others state the opposite. By the electronic bioadhesion theory, CMC would have greater adhesive strength due to the possibility to form hydrogen bonds from its carboxylic radicals. The non-ionic polymer, HPMC, is characterized by moderate adhesion strength, and reduced ability to form hydrogen bonds with mucus (Russo *et al*., 2016). The relatively low adhesion strength for HPMC can therefore be attributed to the absence of proton donor carboxyl groups, which reduces its ability to form hydrogen interactions (Nafee *et al*., 2004).

Among the others studied gums, the strength-time relationship of mucoadhesion was described as Xanthan gum > Guar gum. They are polymers with greater variations within the repeating unit compared to the polymers previously described, and whose adhesion mechanism is more related to the high swelling capacity conferred by them (Park and Munday, 2004). In Table 4, analyzing two different articles with the proposition to develop tablets with Xanthan Gum and the same drug, rosuvastatin, allows to infer that the formulation with less hardness and greater swelling is related to greater adhesive strength, despite the absence of enough data for statistical analysis.

To corroborate what was found until now, a specific analysis of the mucoadhesion strength between CMC, CBM (71G) and Xanthan Gum polymers was performed between tablets constituted only by the isolated polymers described. This study, performed in a buffer solution with pH similar to the buccal pH (6.8), the order CBM (71G) > CMC > Xanthan Gum was obtained (Figueiras and Veiga, 2009), corroborating with the information described.

Drug release profile

The drug release is a phenomenon known to be a complex process of interaction between dissolution, diffusion and erosion mechanisms (Huanbutta *et al*., 2013). For hydrophilic matrices, the characteristics of the drug, such as solubility and pKa, are determinant for diffusion to occur. The polymer, when in contact with the aqueous medium, gradually initiates to swell from the periphery to the center, forming a gelatinous mass that controls the drug diffusion through the polymer matrix, or is subjected to a relaxation process, resulting in a slow erosion of the hydrated polymer (Figure 3). As these mechanisms can operate simultaneously, each one contributes to the overall rate of drug release. In particular, a careful balance between the mechanisms of diffusion, swelling and erosion is required to obtain an ideal drug release from a polymeric matrix (Sujja-Areevath *et al*., 1998).

The swelling characteristics for each polymer, dependent on chain flexibility, solubility in the medium, molecular size, pKa, etc. (Figure 3) influence the drug release in a more easily perceivable way. As for the flexibility of the polymer chain, it is desirable the presence of equal charges in its units, allowing repulsion between them and thus facilitating the opening of the chain and the release of the drug incorporated during the swelling process (Salamat-Miller *et al*., 2005; Figueiras and Veiga, 2009).

The release from hydrophilic matrix discs depends on the formation of a viscous layer hydrated around the discs, which acts as a barrier to drug displacement, due to an opposing gradient of liquid uptake. The hydrophilic polymers hydration behavior and the subsequent dilation properties of the viscous hydrated layer can have a critical impact on drug release (Sriamornsak *et al*., 2007).

All drugs incorporated into the polymeric matrices described (Table 4) are water soluble, which facilitate the release by the diffusion process. However, all the described polymers were able to maintain a sustained release for 4 to 6 hours, demonstrating the balance of the other two factors (swelling and erosion). Commercially available mucoadhesive tablets are characterized by the slow release and maintenance of the therapeutic concentration in the patient's bloodstream for long periods of time, for example, 1 to 2 h for Buccastem® and 8 h or more for Striant® (Guilhotra *et al*., 2014).

In 6 h of analysis, all the polymers described present formulations possible to release less than 40%, except chitosan, related to release profile higher than 40% in less than 4 h of analysis. Therefore, a greater release velocity for soluble drugs. The relation between the other polymers cannot be assessed by the lack of uniformity.

For the same polymer there is much variation regarding the amount of drug released in a given time, corroborating the theory of other parameters interference besides the type of polymer chosen. For a detailed analysis of these parameters, tablets with CBM and Xanthan Gum were analyzed, because they were the only ones developed by more than 1 article, with the same drug incorporated, and with all the quality control parameters, mentioned in table 4. With Xanthan Gum for Rosuvastatin release, there is a relation between the lower hardness (1.7 kg/cm^2), greater swelling (1105%) and lower drug release (18-25%), prevailing a diffusion behavior hampered by the gelatinous matrix formed. A reverse relation, however, was obtained with CBM 934 used to incorporate Glipizide. The formulation with the lower hardness value (4.5 kg/cm^2) had an easier release in the analyzed period of 4 to 6 hours (56-78%).

Evaluating the physical characteristics of tablets to understand this effect, in table 2 is mentioned that the others gums, including Xanthan, are dense polymers, related to a lesser capacity of compaction, which results in tablets with inferior hardness. With this characteristic, gums have in their swelling facility its mechanism of release, which is determinant to maintain the drugs inside the matrix for a longer period of time. Carbomers, however, are cited as lower density polymers, related to higher compaction, which justify the higher hardness values for tablets developed with them (Table 4). Thus, with the fast swell of Xanthan the gelatinous matrix exercises a control by decreasing the speed of drug release.

For CBM tablets, there is a delay in the formation of the matrix which should retard even more the release process meantime it does not occurs. Trying to explain this behavior were evaluated physicochemical characteristics of the drugs, both soluble and

with close pKa values, 4 for Rosuvastatin and 4.3 for Glicazide. However, the pKa values of the polymers are differents, resulting in different surface pH for the developed tablets (Table 2). CBM matrix with higher release is an anionic polymer with pKa close to 4, in buccal medium, pH 6.8, and incorporating a drug with pKa close to 4. Both polymer and the drug will be ionized, leading to repulsion between them, which can have some influence in the diffusion process. Thereby, even when occurs delay in the matrix formation, the similar pKa of the polymer and drug, added to high buccal pH values would accelerate the release process.

Therefore, it is corroborated the importance of taking into account not only the type of polymer, but also the drug to be incorporated, and the physical characteristics of the tablets to be developed, aiming to obtain tablets with appropriated release time for each effective treatment.

CONCLUSION

As an important pharmaceutical technology, mucoadhesive tablets should be produced taking into account many variables. However, the lack of consolidated information, impairs the process of constructing concrete association between these parameters, being common to consider only the polymer chosen as the main important factor in mucoadhesive tablets development. Among other results, this article demonstrates that this technology depends not only on a detailed analysis of the polymer, but also the physical characteristics of the tablet, the physicochemical characteristics of the drug to be incorporated and the buccal region in which it will remain in contact.

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