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).

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 organised 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 Felodipino, 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, lisinopril and
calcium channel blockers, verapamil, were also formulated in
mucoadhesive tablets aiming to increase their bioavailability.
Only those drugs related to infection and inflammation control,
like NSAIDs, antiseptics and antifungal, 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
administer 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.

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

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.

Several studies indicate that a maximum mucoadhesion occurs when the molecular size of the polymer lies within the range of $10^6$ to $4 \times 10^6$ 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

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**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.

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

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Classification</th>
<th>Charge</th>
<th>Mw (g/mol)</th>
<th>D (aqueous solution)</th>
<th>Water Solubility</th>
<th>pH (1% w/v aqueous solution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>Semisynthetic</td>
<td>Nonionic</td>
<td>Δ</td>
<td>-</td>
<td>N</td>
<td>1.12-1.14</td>
</tr>
<tr>
<td>MC</td>
<td>Semisynthetic</td>
<td>Nonionic</td>
<td>Δ</td>
<td>5–75000 cPs at 25°C (2% of Aq. Sol.)</td>
<td>Cold</td>
<td>0.25–0.7</td>
</tr>
<tr>
<td>CMC</td>
<td>Semisynthetic</td>
<td>Anionic</td>
<td>9 × 10³–7 × 10⁵</td>
<td>5–20000 cPs at 25°C (1% of Aq. Sol.)</td>
<td>Y</td>
<td>0.78</td>
</tr>
<tr>
<td>HEC</td>
<td>Semisynthetic</td>
<td>Nonionic</td>
<td>Δ</td>
<td>2–20000 cPs at 25°C (1% of Aq. Sol.)</td>
<td>Cold or hot</td>
<td>0.35–0.61</td>
</tr>
<tr>
<td>HPMC</td>
<td>Semisynthetic</td>
<td>Nonionic</td>
<td>Δ</td>
<td>100–80000 cPs at 20°C (2% of Aq. Sol.)</td>
<td>Y</td>
<td>0.25–0.7</td>
</tr>
<tr>
<td>Xanthan Gum</td>
<td>Natural</td>
<td>Anionic</td>
<td>~1 × 10⁶</td>
<td>1200–1600 cPs a 25°C (1% of Aq. Sol.)</td>
<td>Cold or hot</td>
<td>6.0–8.0</td>
</tr>
<tr>
<td>Tragacanth Gum</td>
<td>Natural</td>
<td>Anionic</td>
<td>8.4 × 10⁹</td>
<td>100–4000 cP a 20°C (1% of Aq. Sol.)</td>
<td>N</td>
<td>5.0–6.0</td>
</tr>
<tr>
<td>Guar Gum</td>
<td>Natural</td>
<td>Anionic</td>
<td>~2.2 × 10⁹</td>
<td>4860 cPs a 25°C (1% of Aq. Sol.)</td>
<td>Y</td>
<td>1.49</td>
</tr>
<tr>
<td>Alginate</td>
<td>Natural</td>
<td>Anionic</td>
<td>~2,1 × 10⁹</td>
<td>20 cP s a 20°C (0.5% of Aq. Sol.)</td>
<td>Y</td>
<td>1.60</td>
</tr>
<tr>
<td>Acrylates-Carbomers</td>
<td>Synthetic</td>
<td>Anionic</td>
<td>7 × 10⁵–4 × 10⁶</td>
<td>29.4–39.4 cPs a 25°C (0.5% of Aq. Sol.)</td>
<td>Y</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Semisynthetic</td>
<td>Cationic</td>
<td>1 × 10⁶–1 × 10⁹</td>
<td>-</td>
<td>N</td>
<td>1.35–1.4</td>
</tr>
</tbody>
</table>

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 (η); Density (ψ); 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-glycosidic 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 grade 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.

<table>
<thead>
<tr>
<th>Cellulose derivates</th>
<th>Natural Gums</th>
<th>Carboxymethylcellulose</th>
<th>Hydroxyethylcellulose</th>
<th>Hydroxypropylmethylcellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylcellulose</td>
<td>Xanthan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>Tragacanth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboxymethylcellulose</td>
<td>Guar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyethylcellulose</td>
<td>Alginate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

**Cellulose derivatives**

*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, Shradanan 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 not 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 glucose, 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 anhydroglucose 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 mucoadhesiveness 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 gumiﬁer Labillardiere’ 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 tragancanthe 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, tragancanthe produces L-arabinose, L-fucose, D-xylene, 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 Cytanopsis 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-mannuronic 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 $10^6$ 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/cm² 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 crustaceans’ 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 10^4-10^6 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/cm² for chitosan, high values in comparison to CMC of low, medium and high viscosity, with 1.8; 0.3 and 1.3 mN/cm² respectively, or 0 mN/cm² 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, mucousal 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 (Choppurapu 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, Salbutamol, 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 adhesives 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 (Velmiurugan, 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 mucosahesion. 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 mucosahhesive 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 mucosahesion (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 mucosahesion 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 mucosahesive 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 mucosahesive 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 mucosahesive 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 mucosahesive 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 mucosahesive 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.

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

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 mucus. 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 biodhesion 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 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 (Suja-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 dilution 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/cm²), 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/cm²) 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 different, 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. Therefore, 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 appropriate 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.

REFERENCES


Gavlighi HA. Tragacanth gum: structural composition, natural functionality and enzymatic conversion as source of potential prebiotic activity. Ph. D Thesis. DTU Chemical Engineering, Department of Chemical and Biochemical Engineering; 2013.


Sá LLF. Desenvolvimento tecnológico de comprimidos de Pilocarpina para tratamento da Xerostomia. Dissertação de Mestrado, Universidade Federal do Piauí, 2013.


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