Development and Characterization of Buccal Bilayer Tablets containing Microparticles with Ibuprofen


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Abstract The aim of this study was to develop and characterize buccal bilayer tablets containing ibuprofen microparticles, prepared through emulsion/chilling method, to obtain a sustained release. In this way, three formulations of bilayer tablets containing three bioadhesive polymers, namely Noveon® AA-1 Polycarbophil USP, Carbopol® 974 and Carbopol® 980 were prepared. Weight uniformity, friability, hardness and in vitro drug release studies, by two different methods, were evaluated in the manufactured tablets. The calculation of similarity factor (f2) was also carried out. In addition, three gels (0.5%, w/w) with the same polymers were prepared and textural analysis (firmness and adhesiveness) were assessed in comparison with the bioadhesive layer of tablets. Buccal bilayer tablets with suitable physical properties (weight uniformity, hardness and friability) were produced. In vitro dissolution tests, performed during 8 hours, have demonstrated a sustained release of ibuprofen (maximum drug released: 30.0 - 45.1%). According to f2, both dissolution methods and the three studied polymers showed similar dissolution profiles (f2 > 50). Tablets containing Carbopol® 974 showed higher values of firmness and adhesiveness after 6 h of hydration in phosphate buffer pH 7.4. On the other hand, it was not possible to verify a relationship between the textural parameters of the gels and the bioadhesive layer of tablets containing the same polymers.

Keywords: Buccal Bilayer Tablets, Bioadhesive Polymers, Microparticles, Ibuprofen, Sustained Release


1. Introduction

Bilayer compacting technology has gained more popularity in recent times, because bilayer tablets offer several advantages over conventional tablets [1]. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profiles may be modified by combining layers with various release patterns, or by combining slow-release with immediate-release layers [2]. Buccal drug delivery offers many advantages in comparison to oral delivery, such as, the avoidance of first-pass hepatic metabolism, leading to higher bioavailability and the drug withdrawal possibility [3,4].

Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s [5]. Several formulations have been developed earlier using mucoadhesive polymers like ointments [6], patches [7], films [8,9], tablets [10,11] and gels [12,13] containing different classes of drugs including antimicrobials (for example, metronidazole and miconazole nitrate), corticosteroids (for example, hydrocortisone acetate and triamcinolone acetonide), antiepileptics (for example, carbamazepine), local anesthetics (for example, lidocaine), etc. [4,5].

Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties [14]. Hydrogels are hydrophilic matrices that absorb water when placed in an aqueous media, and are composed of polymers such as polyacrylates (Carbopol and Polycarbophil), ethylene vinyl alcohol, polyethylene oxide, poly vinyl alcohol, poly(N-acryloylpyrrolidone), polyoxyethylene, self-cross linked gelatin, sodium alginate, natural gums like guar gum, karaya gum, xanthan gum, locust bean gum and cellulose ethers like methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, etc. [15].

Nano and microparticle carriers have important potential applications for the administration of therapeutic molecules [16]. Microparticles can have numerous advantages, as a good biocompatibility, low toxicity, high stability, and can improve efficacy, absorption, and bioavailability [16,17]. Some of the methods for production of lipid microparticles include: double-emulsion solvent evaporation, emulsion/chilling, fluid supercritical atomization and extrusion [17-25].

Ibuprofen (Figure 1) is an analgesic and anti-inflammatory drug (NSAID) used in the treatment of inflammatory diseases and for pain relief of oral mucositis,
and was used as a model drug of class II of Biopharmaceutical Classification System (BCS), characterized by high permeability but poor solubility [26]. Maximum ibuprofen plasma concentrations are achieved 1 to 2 hours after oral administration, but because of this drug’s short biological half-life (2 hours), the therapeutic plasma concentration can be maintained only if ibuprofen is administered frequently [27,28]. These characteristics make ibuprofen a suitable candidate for buccal administration by a sustained release mucoadhesive tablet.

The major objectives of this study were: (i) to prepare and to characterize lipid microparticles with ibuprofen; (ii) to develop and to characterize buccal bilayer tablets containing ibuprofen microparticles to obtain a sustained release with three hydrophilic polymers with high mucoadhesive properties, such as Noveon® AA-1 Polycarbophil USP, Carbopol® 974 and Carbopol® 980; (iii) to investigate the in vitro drug release; (iv) to evaluate firmness and adhesiveness of the bioadhesive layer of tablets and to compare these textural parameters with gels (0.5%, w/w) prepared with the same bioadhesive polymers.

2. Materials and Methods

2.1. Materials

Ibuprofen (Roig Farma, Spain), hydrogenated castor oil (Cutina® HR) (José M. Vaz Pereira SA, Portugal), monosodium phosphate (José M. Vaz Pereira SA, Portugal), disodium phosphate anhydrous (José M. Vaz Pereira SA, Portugal), propylene glycol (José M. Vaz Pereira SA, Portugal), Tween® 80 (Sigma-Aldrich, United States of America), chloroform (José M. Vaz Pereira SA, Portugal), Noveon® AA-1 Polycarbophil USP (Lubrizol, Brussels), Carbopol® 980 NF Polymer (Lubrizol, Brussels), and Carbopol® 974 NF Polymer (Lubrizol, Brussels) were used.

2.2. Preparation of Lipid Microparticles

Lipid microparticles of 1:2 ibuprofen/hydrogenated castor oil (Cutina® HR) ratio were prepared using the emulsion/chilling method [17]. The lipophilic excipient was melted on a hot plate (85-88°C) under stirring at 600 rpm and ibuprofen was added [17]. The oil phase was slowly added to a Tween® 80 solution (1.5%, w/w) at the same temperature, followed by the quick addition of a mixture of water:propylene glycol (75:25) at 0°C, maintaining the agitation at 600 rpm [17]. The obtained lipid microparticles were filtered and washed with water [17].

2.3. Determination of Drug Encapsulation Efficiency (EE%)

For the determination of ibuprofen content in lipid microparticles, 75 mg of sample was dissolved in chloroform (50 mL) and analyzed using a UV-VIS spectrophotometer (Jasco, model V-650, Japan) at 272 nm. Drug calibration curve was previously prepared (y = 0.989x + 0.029; R² = 0.999). EE% was calculated using the following equation:

\[
EE\% = \left(\frac{W_m}{W_i}\right) \times 100
\]

where \(W_m\) is the amount of ibuprofen in lipid microparticles and \(W_i\) is the amount of ibuprofen used.

2.4. Particle Size Analysis and Morphological Characteristics

Particle size measurements were determined using a laser diffraction particle size analyzer (Mastersizer 3000, Malvern Instruments, United Kingdom) with a range from 0.01 to 3500 µm. The determination was performed at room temperature using 1.6 for the refractive index, 0.1 for the absorption index, laser obscuration around 6% and scattering model mie. The dispersant was water with Tween® 80, and each sample was tested five times at 2000 rpm. The results were, respectively, expressed using volume distributions by the volume weighted mean (Dv [4,3]), surface weighted mean (Dv [3,2]), 10% percentile (Dv [10]), median (Dv [50]) and 90% percentile (Dv [90]).

The particle morphologies were also observed and captured by the inverted microscope (Motic®, model AE2000, China).

2.5. Manufacture of Tablets

Three types of bilayer tablets containing three bioadhesive polymers, namely Noveon® AA-1 Polycarbophil USP, Carbopol® 974 and Carbopol® 980 were prepared using a single-punch compression machine (Korsch 9048-71, Maschinenfabrik, Germany) with 13 mm diameter punches as follows: the first layer with a weight of 300 mg, responsible for the tablet retention on the mucosa, was obtained by compression of each one of the bioadhesive polymers; the second layer with a weight of 338 mg, responsible for buccal drug delivery, containing the lipid microparticles corresponding to 100 mg of ibuprofen, was then added to the first layer and tablets were obtained by compaction of the two layers.

2.6. Weight Uniformity, Friability and Hardness of Tablets

To study tablet weight uniformity, 20 tablets of each formulation were weighed using an analytical balance (Mettler Toledo, Mettler AE 200, Switzerland). For each formulation the hardness of 10 tablets was also evaluated using a tablet hardness tester (Erweka GmbH, Erweka TBH 28, Germany).
Friability was determined by submitting 10 previously weighed tablets to falling shocks for 4 min in a friabilator (Electrolab, EF-1W, India), set at 25 rpm/min. After 4 min, the tablets were reweighed and the percentage of friability was calculated.

2.7. In Vitro Release Studies

The in vitro drug release study was performed using a dissolution apparatus (Sotax, model AT7, Switzerland) according to the paddle method at 50 rpm. The dissolution medium consisted of 1000 mL of phosphate buffer pH 7.4 [29] at 37.0±0.5°C. The collection times were 30, 60, 120, 180, 240, 360, 480 minutes, and the volume of sample collected was 10.0 mL (without volume replacement and with the same adjustment in calculations).

The dissolution tests were performed by two different methods: A and B. In the method B the tablets were attached at a height of 7.0 cm to the inside of the dissolution vessel [30], and in method A, the tablets were positioned on the bottom of the dissolution vessel [31].

The samples, collected at established times, were filtered and the drug concentration was determined by a UV-VIS spectrophotometer (Jasco, model V-650, Japan). Drug calibration curve was previously prepared (λ \text{max} = 272.0 nm; y = 1.459x + 0.004; R^2 = 0.996). Dissolution studies were made in triplicate and results were registered as the average ± standard deviation (SD).

The dissolution profiles of tablets were compared using the $f_2$ similarity factor as follows [32,33]:

$$f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum_{j=1}^{n} \left( \frac{R_j - T_j}{R_j + T_j} \right)^2 \times 100 \right), \tag{2}$$

where $n$ is the number of time points, $R_j$ is the mean percent reference drug dissolved at time $j$ after initiation of the study, and $T_j$ is the mean percent test drug dissolved at time $j$ after initiation of the study.

2.8. Evaluation of Firmness and Adhesiveness of the Bioadhesive Layer of Tablets and Gels

Firmness and adhesiveness were assessed at 20°C in the bioadhesive layer of tablets after 6 h and 16 h of hydration in phosphate buffer pH 7.4 [29]. In addition, three gels (0.5%, w/w) were prepared with the same bioadhesive polymers and the same textural parameters were also evaluated.

Firmness and adhesiveness measurements were performed using a texture analyzer (Stable Micro Systems, TA-XT2i, United Kingdom) by carrying out a penetration test using a load cell of 5 Kg, a cylindrical probe (6 mm diameter for tablets and 25 mm in the case of gels), a penetration depth of 2 mm and velocities of 3 mm/s and a trigger force of 0.049 N. After penetrating the sample, the probe returned to a position 90 mm above the platform surface. The maximum force (firmness) and the negative area (adhesiveness) were obtained from the graphic force (N) versus distance (mm) [34]. All the measurements were performed in triplicate and data were statistically analyzed by one-way ANOVA followed by Tukey post hoc test (IBM® SPSS® Statistics, version 22). A value of $p < 0.05$ was considered significant.

3. Results

Lipid microparticles with ibuprofen, a BCS class II drug, through emulsion/chilling method were prepared (Figure 2). The result of the drug encapsulation efficiency was 87.4%.

The median size of lipid microparticles (Dv [50]) was 75.90 ± 0.55 μm. The particle size range can be represented as mean (Dv [10]) and mean (Dv [90]) which were, respectively, 6.30 ± 0.08 μm and 167.00 ± 1.26 μm. The volume weighted mean (D [4,3]) and the surface weighted mean (D [3,2]) were, respectively, 83.3 μm and 14.8 μm.

The buccal bilayer tablets presented suitable physical properties (Figure 3) and Table 1 shows the obtained results for weight uniformity, hardness and friability.

![Figure 2. Lipid microparticles with ibuprofen (A - macroscopic aspect, scale in millimeters; B - microscopic aspect, magnification of 40x)](image)

![Figure 3. Appearance of the buccal bilayer tablets before and after 16 h of hydration in phosphate buffer pH 7.4. (A - tablets with Carbopoli® 974; B - tablets with Polycarbophil; C - tablets with Carbopoli® 980; D - tablets with Carbopoli® 974 after 16 h of hydration; E - tablets with Polycarbophil after 16 h of hydration; F - tablets with Carbopoli® 980 after 16 h of hydration)](image)

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Weight (mg)</th>
<th>Hardness (N)</th>
<th>Friability (%)</th>
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<tbody>
<tr>
<td>Polycarbophil</td>
<td>652 ± 11</td>
<td>161 ± 34</td>
<td>0.88</td>
</tr>
<tr>
<td>Carbopoli® 974</td>
<td>635 ± 6</td>
<td>123 ± 15</td>
<td>0.55</td>
</tr>
<tr>
<td>Carbopoli® 980</td>
<td>622 ± 21</td>
<td>76 ± 25</td>
<td>0.91</td>
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Figure 4 shows the dissolution profiles of buccal bilayer tablets by two different methods: A and B. The results of firmness and adhesiveness of the bioadhesive layer of tablets, after 6 h and 16 h of hydration in phosphate buffer pH 7.4, and gels are illustrated in Figures 5 and 6, respectively.

**Figure 5.** Box plot of firmness and adhesiveness of bioadhesive layer of tablets after 6 h and 16 h of hydration in phosphate buffer pH 7.4. (TC974 - tablets with Carbopol® 974; TC980 - tablets with Carbopol® 980; TP - tablets with Polycarbophil)

**Figure 6.** Box plot of firmness and adhesiveness of gels. (G C974 - gel with Carbopol® 974; G C980 - gel with Carbopol® 980; G P - gel with Polycarbophil)

4. Discussion

Three types of bilayer tablets containing ibuprofen microparticles to obtain a sustained release with three bioadhesive polymers, Noveon® AA-1 Polycarbophil USP, Carbopol® 974 and Carbopol® 980, with uniform aspect and weight, friability < 1%, and suitable hardness were prepared.

The sizes of the lipid microparticles were all within the micrometer range, indicating that the emulsion/chilling method was able to achieve the intended objective. The EE% of ibuprofen in lipid microparticles was high (87.4%).

Many researches were devoted to the development and characterization of microparticles for the delivery of ibuprofen [17,35-40]. For instance, Zhang et al. [36] concluded that trehalose and glucose are effective cryoprotectants and mannitol and sucrose are not very good cryoprotectants for the ibuprofen-loaded solid lipid microparticles as they crystallize during the freeze-drying process.

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug [32]. In vitro dissolution tests (Figure 4), performed during 8 hours, have demonstrated a sustained release of ibuprofen (maximum drug released: 30.0 - 45.1%). Two different methods were followed in dissolution tests considering two possible tablet positions in the vessel [30,31]. An $f_2$ value between 50 and 100 suggests that the two dissolution profiles are similar [32]. According to the results of $f_2$, both dissolution methods (A and B) showed similar dissolution profiles ($f_2 > 50$) and the same results were obtained with the tablets containing the three types of polymers studied.

Several methods to study mucoadhesion of polymers and dosage forms were published in the last 30 years [41]. Nevertheless, a comparison of the results is hardly feasible, because of different experimental set-ups [41].

It can be observed in Figure 5 that tablets with Carbopol® 974 exhibit higher firmness (related to the maximum force) and adhesiveness (related to the negative area) than tablets with Carbopol® 980 and Noveon® AA-1 Polycarbophil USP, after 6 hours of hydration in phosphate buffer pH 7.4 [34]. On the other hand, the
adhesiveness and firmness of Carbopol® 980 and Noveon® AA-1 Polycarbophil USP were quite similar. A pronounced decrease of textural parameters was observed for all polymers after 16 hours of hydration. This fact may be due to dispersion of the polymer in the buffer solution and consequent erosion of the matrix resulting in the reduction of firmness and adhesiveness. The gel with Noveon® AA-1 Polycarbophil USP (Figure 6) showed values of firmness and adhesiveness significantly lower than those of the other polymers tested.

5. Conclusions

In this work, three formulations of buccal bilayer tablets containing ibuprofen microparticles with suitable physical properties (weight uniformity, hardness and friability) were prepared. In vitro dissolution tests have demonstrated a sustained release of ibuprofen. According to f2, both dissolution methods (A and B) and the three polymers studied showed similar dissolution profiles. As expected, a decrease in the adhesiveness and firmness of bioadhesive layers was observed with the increase of hydration time of tablets in phosphate buffer pH 7.4 (6 h versus 16 h). Tablets containing Carbopol® 974 showed higher values of firmness and adhesiveness after 6 h of hydration. This means that this polymer showed the best bioadhesive properties and is more suitable to be used in the formulation of buccal tablets. However, it was not possible to verify a relationship between the textural parameters of the gels and the bioadhesive layer of tablets containing the same polymers. For tablets with Carbopol® 980, firmness after 6 h of hydration was lower than tablets with Carbopol® 974, in opposition to what happened in the gels case in which firmness from both polymers was similar. The lower firmness in tablets with Carbopol® 980 after 6 h of hydration seemed to be related with the lower capacity of this polymer to compact originating more friable tablets with lower hardness.

Statement of Competing Interests

The authors have no competing interests.

References


