Formulation and in vitro assessment of sustained release matrix tablets of atenolol containing Kollidon SR and carnauba wax

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The goal of this study was to evaluate the possibility of using Kollidon SR and carnauba wax in sustained release matrix tablets of atenolol obtained by direct compression. The compatibility between atenolol and excipients (microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, Kollidon SR, and carnauba wax) was demonstrated by differential scanning calorimetry. 100 mg atenolol tablets were prepared by direct compression, using varying amounts of Kollidon SR (20 or 40%) and carnauba wax (5 or 10%), according to a 2^2 factorial design, resulting in four formulations. The response studied was the dissolution efficiency in 8 h (DE%8h). Dissolution tests were performed with the paddle method, 50 rpm, 900 ml phosphate buffer, pH 6.8, 37°C. The mathematical model derived from the experimental design indicated that concentrations of Kollidon SR and carnauba wax negatively affected the DE%8h, while the interaction between thereof had a positive effect. The Korsmeyer-Peppas kinetic model described the dissolution curves and evidenced that drug release occurred by Super Case II transport, mostly controlled by erosion of the matrix, for all formulations. In general, the mechanical strength of the tablets was satisfactory (except for one formulation, which had high friability). Our results indicated that matrices combining Kollidon SR and carnauba wax by direct compression are promising for the sustained release of atenolol.

Key words: Matrix tablets, direct compression, Kollidon SR, carnauba wax, atenolol, sustained release.

INTRODUCTION

Atenolol is a β-adrenergic blocker antihypertensive drug, included in class III of the biopharmaceutical classification system, that is, has high aqueous solubility but low gastrointestinal permeability, resulting in low oral bioavailability (Lindenberg et al., 2004). The oral bioavailability and biological half-life of atenolol are 50% and 6 to 8 h, respectively (Dey et al., 2012; 2014).

An ideal drug release system provides the proper amount of the active substance for the time required, thus optimizing the therapeutic action of the drug. Drugs having short biological half-life, when present in conventional formulations, require multiple daily doses to
produce the desired therapeutic effect, and a strategy to overcome this problem is the development of a sustained release system (Sarwar and Hossain, 2012).

The oral dose of atenolol in antihypertensive treatment for adults is 50 mg in conventional release systems, twice daily. However, fluctuations may occur in the plasma concentration of the drug, resulting in adverse effects. This combined with the short biological half-life of atenolol make it a suitable drug for the development of sustained release formulations (Dey et al., 2012; 2014).

A commonly employed method to obtain sustained drug release systems is the production of matrix tablets by direct compression, with the main advantages of having few processing variables, the ease and low cost of production (Sakr et al., 2011).

Polymer blending is an alternative approach to obtain new materials with desirable properties based on commercially available polymers rather than to design and synthesize completely new polymers. Polymer blending is designed to generate materials with optimized chemical, structural, mechanical, morphological and biological properties (El-Bagory et al., 2012).

Kollidon SR is an excipient obtained from the association between the polymers polyvinyl acetate and povidone, used to obtain sustained release matrices by direct compression. Polyvinyl acetate is insoluble in water, while povidone is water soluble. When the matrix tablet comes in contact with the aqueous environment of the gastrointestinal tract, povidone is solubilized, forming pores in the matrix, through which the drug is slowly released by diffusion (Sarwar and Hossain, 2012).

Carnauba wax is an ester wax of vegetable origin, which is extracted from the leaves of the Brazilian carnauba palm (Copernica cerifera). It has been suggested as an erodible matrix material for sustained-release tablets (Emås and Nyqvist, 2000; Kanokpanont et al., 2013). Waxy materials control the release of drug from matrix systems through pore diffusion and erosion (Reza et al., 2003).

Previous works have described the preparation of matrix tablets from Kollidon SR, containing propranolol hydrochloride (Strübing et al., 2008; Mulani et al., 2011), labetalol hydrochloride (Jain et al., 2011), albuterol sulfate (Sakr et al., 2011), losartan potassium (Sarwar and Hossain, 2012), atenolol (Bhowmik et al., 2013), among others. The association of Kollidon SR and carnauba wax was used in matrix tablets containing diltiazem hydrochloride (Islam et al., 2008), theophylline (El-Bagory et al., 2012), among others. There were no studies in the literature that employ the association of Kollidon SR and carnauba wax in matrix tablets of atenolol. These insoluble materials were chosen to modulate the release in this study because the high water solubility of atenolol hinders its formulation in hydrophilic matrices.

The aim of this study was to evaluate the possibility of successfully using Kollidon SR and carnauba wax in sustained release matrix tablets of atenolol obtained by direct compression. To this end, four formulations of matrix tablets of atenolol were prepared to study (1) the compatibility of the drug and excipients; (2) mechanical strength of the tablets; (3) effects of concentrations of Kollidon SR and carnauba on drug dissolution and (5) the drug release mechanism.

**MATERIALS AND METHODS**

Atenolol (Fagron, São Paulo, Brazil); Kollidon SR (BASF, Ludwigshafen, Germany); carnauba wax (All Chemistry, São Paulo, Brazil); microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate (Hennfarma, São Paulo, Brazil). All other reagents were analytical reagent grade.

**Experimental design**

A $2^2$ factorial design was adopted to study the dissolution profile of atenolol from sustained release matrix tablets. The concentrations of Kollidon SR ($X_1$) and carnauba wax ($X_2$) in the formulations were the independent variables, and dissolution efficiency in 8 h ($DE_{8h}$) was the dependent variable. These factors were studied in two levels (encoded as -1 and +1), as shown in Table 1. The Design Expert software 9 (Stat-Ease Inc., Minneapolis, USA) was used to run the multiple regression analysis, analysis of variance (ANOVA) and statistical optimization. A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2$, including polynomial and interactive terms were used to test the effects of independent variables on the response, where $Y$ is the response, $b_0$ is the intercept, $b_1$ and $b_2$ are the regression coefficients, $X_1$ and $X_2$ are individual effects, and $X_1X_2$ is the interaction effect. The estimate of

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>40.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>q.s.</td>
</tr>
<tr>
<td>Kollidon SR ($X_1$)</td>
<td>20.0 (level -1) 40.0 (level +1) 20.0 (level -1) 40.0 (level +1)</td>
</tr>
<tr>
<td>Carnauba wax ($X_2$)</td>
<td>5.0 (level -1) 5.0 (level -1) 10.0 (level +1) 10.0 (level +1)</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>0.5 0.5 0.5 0.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0 1.0 1.0 1.0</td>
</tr>
</tbody>
</table>

---

*Table 1. Formulations 1 to 4 of sustained release matrix tablets of atenol (100 mg) obtained according to a $2^2$ factorial design.*
the significance of the model was performed by ANOVA (P<0.05).

**Differential scanning calorimetry (DSC)**

Atenolol, excipients, binary mixtures (1:1) between the drug and each excipient, and a multicomponent mixture (equivalent to the formulation 3) were subjected to DSC analysis (DSC Q20 TA Instruments, New Castle, USA). Samples of approximately 5 mg were sealed in aluminum crucibles and analyzed between 30 and 300°C, under a nitrogen gas flow (50 ml/min) at a heating rate of 10°C/min. DSC was carried out for just one formulation (formulation 3), which represents the others, since the developed analysis was qualitative and all formulations had the same qualitative composition.

**Preparation of matrix tablets**

The direct compression method was used to prepare four formulations of matrix tablets containing 100 mg of atenolol (Table 1). The components were weighed, passed through a 1 mm sieve and mixed. The mixture was compressed in a hydraulic press (Protécni, Araraquara, Brazil), adapted for a die and punch of 9 mm in diameter. The compression force used was 0.5 tons for 5 s.

**Hardness and friability tests**

Hardness of tablets was determined in quintuplicate using a 298-DGP digital hardness tester (Ethik Technology, Vargem Grande Paulista, Brazil). Friability was determined with five tablets in a friability tester (Nova Ética, Vargem Grande Paulista, Brazil) at a speed of 20 rpm for 5 min.

**Dissolution study**

*In vitro* dissolution tests were performed using the paddle method at 50 rpm (Nova Ética 299/6, São Paulo, Brazil). The dissolution medium was 900 ml potassium phosphate buffer, pH 6.8, at 37°C. At predefined times, aliquots were collected and centrifuged at 3,000 rpm for 10 min (Nova Técnica NT 812, Piracicaba, Brazil). Drug in solution was quantified by absorption spectrophotometry at 274 nm (spectrophotometer Shimadzu 1601 PC, Kyoto, Japan). Tests were run in triplicate. The cumulative percentage of drug released was plotted against time to determine the release profile.

**Drug release kinetics**

The software KinetDS (Mendyk et al., 2012) was adopted to analyze the mechanism of drug release from matrix tablets. The results of release were fitted to kinetic models of zero- and first-order (Equations 1 and 2), Higuchi (Equation 3), Korsmeyer-Peppas (Equation 4) and Hixson-Crowell (Equation 5). The choice of model that best described the dissolution curve was based on the best fit, from the coefficient of determination ($R^2$).

\[
Q = k \cdot t + Q_0 \quad (1)
\]

\[
\frac{1}{Q} = k \cdot t + \frac{1}{Q_0} \quad (2)
\]

\[
Q = k \cdot t^{n} \quad (3)
\]

\[
Q = k \cdot t + Q_0^{1/3} \quad (5)
\]

where $Q$ is the amount of drug released (%) in the time $t$, $Q_0$ is the initial amount of drug, $t$ is time, $k$ is a constant and $n$ is the diffusion exponent.

The software also calculated the dissolution efficiency (DE%) (Equation 6), defined as the area under the curve in a given time interval, expressed as a percentage of the rectangle area described by 100% dissolution in that time (Costa and Lobo, 2001).

\[
DE\% = \frac{\int_0^t Q dt}{Q_{max} \times t} \times 100 \quad (6)
\]

where $Q_{max}$ is the maximum amount of drug released or 100%.

**RESULTS AND DISCUSSION**

**Differential scanning calorimetry (DSC)**

DSC was employed in this study to investigate the compatibility between the drug and excipients used in the formulations. An interaction can be viewed as a change in melting point, shape and area of peaks, or as a transition, appearance or disappearance of peaks compared with the drug alone, after a binary or multicomponent mixture with the excipients. Small changes in the transition temperature, shape and area of peaks can occur due to the presence of excipients, however, without the occurrence of harmful interactions that characterize incompatibility (Oliveira et al., 2011).

DSC curve of atenolol alone (Figure 1A) showed a single endothermic peak at 155.54°C ($\Delta H = 174.0$ J/g), corresponding to the melting of the drug, which characterized its crystallinity.

DSC curves of binary mixtures of atenolol with excipients and of the multicomponent mixture (formulation 3) showed the melting event of atenolol without significant change in shape, in the same temperature range observed for the drug alone (Figure 1B). Also, additional peaks were found only in DSC curves of the formulation 3 and binary mixtures of the drug with carnauba wax, magnesium stearate and Kollidon SR, which correspond to melting (carnauba wax or magnesium stearate) or glass transition (Kollidon SR) events observed for these excipients, when analyzed separately. Thus, the thermal curve of each binary mixture can be considered as a superposition of the atenolol curve and the curve of the corresponding excipient, evidencing the compatibility between the drug and microcrystalline cellulose, Kollidon SR, carnauba wax, colloidal silicon dioxide and magnesium stearate.
Table 2. Hardness, friability and dissolution efficiency in 8 h ($DE\%_{8h}$) of formulations of sustained release matrix tablets of atenolol (100 mg).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kgf)</th>
<th>Friability (%)</th>
<th>$DE%_{8h}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.6 ± 1.6</td>
<td>9.6</td>
<td>63.4 ± 3.6</td>
</tr>
<tr>
<td>2</td>
<td>9.3 ± 0.6</td>
<td>0.3</td>
<td>36.2 ± 2.0</td>
</tr>
<tr>
<td>3</td>
<td>7.2 ± 0.6</td>
<td>0.3</td>
<td>46.9 ± 2.5</td>
</tr>
<tr>
<td>4</td>
<td>7.2 ± 1.2</td>
<td>0.2</td>
<td>33.3 ± 1.1</td>
</tr>
</tbody>
</table>

Results of hardness and $DE\%_{8h}$ are expressed as mean ± standard deviation.

Table 3. Analysis of variance of values of dissolution efficiency in 8 h ($DE\%_{8h}$) for formulations of sustained release matrix tablets of atenolol (100 mg).

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>Degrees of freedom</th>
<th>Mean square</th>
<th>F-value</th>
<th>p-value; Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>3469.64</td>
<td>3</td>
<td>1156.55</td>
<td>152.46</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>$X_1$</td>
<td>2649.24</td>
<td>1</td>
<td>2649.24</td>
<td>349.24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>$X_2$</td>
<td>521.40</td>
<td>1</td>
<td>521.40</td>
<td>68.73</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>$X_1X_2$</td>
<td>299.00</td>
<td>1</td>
<td>299.00</td>
<td>39.42</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pure error</td>
<td>60.69</td>
<td>8</td>
<td>7.59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>3530.33</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$X_1$ - Kollidon SR concentration; $X_2$ - carnauba wax concentration.

Hardness and friability of tablets

Results of hardness and friability obtained for formulations 1 to 4 of sustained release matrix tablets of atenolol are listed in Table 2. Formulations 2 to 4 exhibited hardness above 7 Kgf and met the criterion of a mass loss <1% (w/w) according to USP 36 (2013) for friability test, showing a satisfactory mechanical strength. Although formulation 1 had adequate hardness (> 7 Kgf), friability was quite high, indicating low mechanical resistance to abrasion.

Dissolution study

Dissolution profiles of the formulations of sustained release matrix tablets of atenolol are illustrated in Figure 2. The differences detected in performance of formulations in the dissolution study (Figure 2) are due to the influence of Kollidon SR and carnauba wax on the drug release. To better understand this, formulations were based on a $2^2$ factorial design, varying concentrations of Kollidon SR ($X_1$) and carnauba wax ($X_2$), and checking the effects of these variations on $DE\%_{8h}$. The results are presented in Table 3.

Considering the analysis of variance of the regression (Table 3) and the hierarchy criterion, the model is highly significant ($p<0.0001$). The adjusted coefficient of determination ($R^2 = 0.98$) indicates a good mathematical representation of the process, that is, 98% of the total variation around the mean is explained by the model and the remaining 2% is residual. The obtained model to describe the $DE\%_{8h}$ of atenolol from sustained-release matrix tablets is expressed as shown in Equation 7.

$$DE\%_{8h} = +44.94 - 10.19X_1 - 4.87X_2 + 3.41X_1X_2$$  (7)

The concentration of Kollidon SR ($X_1$), the concentration of carnauba wax ($X_2$) and their interaction ($X_1X_2$) are significant terms in Equation 7, since F values are higher than critical values, with $p<0.001$ for a confidence level of 95%. In this way, the null hypothesis $H_0$ is rejected and the alternative hypothesis that the concentrations of the two components used (Kollidon SR and carnauba wax) significantly influence drug release from matrix tablets of atenolol was taken as true.

Equation 7 indicates that the effects of concentrations of Kollidon SR and carnauba wax are negative on $DE\%_{8h}$, that is, the increase in the concentration of each component in the formulation decreases the release of the drug. Thus, formulation 1, which had lower levels of both $X_1$ and $X_2$, showed the highest $DE\%_{8h}$ ($p<0.001$). The model also indicated a positive effect of the interaction between factors ($X_1X_2$), while modifying simultaneously the contribution of each factor for drug
release. The magnitude of the effect of concentration of Kollidon SR is greater than that of carnauba wax, and thus the contribution of Kollidon SR for the synergistic effect is greater in modulating the release of atenolol. Thus, due to the main effects modulated by the interaction, formulation 4, with higher levels of both factors, showed $DE_{8h}$ lower than observed for formulations 1 and 3 ($p<0.01$). The formulation 2 showed a similar value of $DE_{8h}$ compared with formulation 4 ($p>0.05$), because of the interaction between the factors, although the main effects, when taken in isolation, suggest that the $DE_{8h}$ of the formulation 2 would exceed that of the formulation 4.

Negative effects of concentrations of Kollidon SR and carnauba wax on drug release were expected, since other studies have reported decreased drug release rates resulting from higher polymer contents (Reza et al., 2003; Strübing et al., 2008; Sarwar and Hossain, 2012) or higher wax contents (Qiu et al., 1997).

To understand the mechanism of release of atenolol from the matrix tablets developed, the results were fitted to models describing drug dissolution. As indicated by the $R^2$ values, shown in Table 4, all the formulations did not follow a pattern of release of zero order, first order, Hixson-Crowell or Higuchi. The kinetic model that best described the dissolution curves of all formulations was the Korsmeyer-Peppas model, with $R^2$ equal to or higher than 0.9964.

The Korsmeyer-Peppas model allows characterizing the mechanism involved in drug release from the diffusion exponent $n$ (Ritger and Peppas, 1987). For cylindrical dosage forms like tablets, $n = 0.45$ means Fickian diffusion, corresponding to the case I transport, in which drug release is controlled by diffusion. Values of $0.45 < n < 0.89$ correspond to non-Fickian release (anomalous transport), including first-order kinetics, where drug release depends simultaneously on mechanisms of swelling and diffusion. A value of $n = 0.89$ indicates case II transport (kinetic of zero order release), where the drug release is controlled by the swelling of the polymer (Ritger and Peppas, 1987; Costa and Lobo, 2001; Maderuelo et al., 2011). Values of $n > 0.89$ indicate super case II transport, involving the relaxation of polymer chains and the erosion of the matrix (Costa and Lobo, 2001; Asghar et al., 2009).

Poly(vinyl acetate), the main component of Kollidon SR, forms a non-disintegrating matrix, which will only swell to a limited amount when placed in an aqueous environment (Strübing et al., 2008) and carnauba wax is not a swellable material (Rojas et al., 2013). Therefore, in this study, values of $0.45 < n < 0.89$ were not expected, because they are usually obtained for systems in which swelling is involved in drug release. In fact, the values of $n$ of formulations 1 to 4 were superior to 0.89 (Table 4), indicating that the release of atenolol occurred by super case II transport, and in this way erosion was the predominant mechanism.

Strübing et al. (2008) stated that hydrophilic drug will be released due to dissolution and diffusion of the drug through water filled capillaries present in Kollidon SR-based matrix systems. Siepmann et al. (2010) concluded that drug diffusion is the dominant mass transport mechanism in Kollidon SR-based matrix tablets containing diprophylline, as a model drug. Sarwar and Hossain (2012) reported that diffusion is the dominating drug release mechanism from Kollidon SR matrix tablets containing losartan potassium. So, it is believed that matrices in the present study have erosion-controlled release and not diffusion-controlled release due to the presence of carnauba wax, which is an erodible material. It seems that the combination of carnauba wax and Kollidon SR provided a very hydrophobic character to the formulations, inhibiting the entry of water, hindering the diffusion, making erosion the dominant mechanism of drug release.

Formulation 3 had $DE_{8h}$ lower than that of formulation 1 (both with 20% Kollidon SR) due to the higher concentration of carnauba wax, which results in increased erosion and, consequently, higher drug release.

In turn, formulations 2 and 4, with 40% Kollidon SR, showed reduced concentration of carnauba wax than formulation 4, allowing greater penetration of water, but apparently this has not resulted in enhanced erosion, which would result in a greater release. Possibly, the amount of Kollidon SR in formulation 2 was enough to form a tough matrix, with erosion similar to that of the formulation 4, leading to the dissolution profiles registered.

Among the proposed formulations, formulation 1 showed

table

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Korsmeyer-Peppas</th>
<th>Diffusion exponent ($n$)</th>
<th>Type of release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8733</td>
<td>0.0354</td>
<td>0.9817</td>
<td>0.3470</td>
<td>0.9964</td>
<td>0.9605</td>
<td>Super case II</td>
</tr>
<tr>
<td>2</td>
<td>0.8991</td>
<td>0.0382</td>
<td>0.6981</td>
<td>0.3940</td>
<td>0.9980</td>
<td>0.9393</td>
<td>Super case II</td>
</tr>
<tr>
<td>3</td>
<td>0.8974</td>
<td>0.0386</td>
<td>0.7176</td>
<td>0.4026</td>
<td>0.9980</td>
<td>0.9480</td>
<td>Super case II</td>
</tr>
<tr>
<td>4</td>
<td>0.9147</td>
<td>0.0413</td>
<td>0.5961</td>
<td>0.4349</td>
<td>0.9988</td>
<td>0.9349</td>
<td>Super case II</td>
</tr>
</tbody>
</table>

Table 4. In vitro release kinetics of formulations 1 to 4 of sustained release matrix tablets of atenolol (100 mg).
Figure 1. DSC curves of (A) atenolol and excipients alone, (B) binary mixtures (1:1) of the drug with excipients and formulation 3 of sustained release matrix tablets.
faster drug release than desired, with Q%_{2h} = 48%.
Formulation 3 presented an intermediate dissolution profile, with Q%_{2h} = 33%, Q%_{6h} = 64% and Q%_{8h} = 72%, and could be improved for sustained release over 12 h, whereas formulations 2 and 4 had a slower drug release profiles, with Q%_{2h} = 26/23%, Q%_{6h} = 49/46% and Q%_{8h} = 56/53%, respectively, and could be improved for sustained release over 24 h.

**Conclusion**

The compatibility between atenolol and excipients used was demonstrated, allowing their use in formulations. In general, mechanical strength of tablets was satisfactory, indicating that the direct compression method is suitable for obtaining the developed matrix systems (except for one formulation that had a high friability).

The formulations proposed in this study were able to sustain the release of atenolol, through a mechanism modulated by matrix erosion, and the use of higher concentrations of Kollidon SR and carnauba wax reduced the dissolution profile of the drug. Thus, it was proved that matrices of Kollidon SR and carnauba obtained by direct compression are promising systems for the sustained release of atenolol.

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**Conflict of interest**

The author(s) have not declared any conflict of interests.

**REFERENCES**


