IN VITRO DISSOLUTION STUDIES OF AMIODARONE HYDROCHLORIDE FROM HYDROXY-PROPYL-β-CYCLODEXTRIN/AMIODARONE INCLUSION COMPLEX FORMULATED INTO MODIFIED-RELEASE TABLETS

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IN VITRO DISSOLUTION STUDIES OF AMIODARONE HYDROCHLORIDE FROM HYDROXY-PROPYL-β-CYCLODEXTRIN/AMIODARONE INCLUSION COMPLEX FORMULATED INTO MODIFIED-RELEASE TABLETS (Abstract) Aim: Drug release from modified-release matrix tablets made of Kollidon® SR and Chitosan is dependent on its degree of solubility in the dissolution medium as well as on the matrix forming polymer. By complexing hydrochloride amiodarone with hydroxypropyl-β-cyclodextrin, an inclusion complex was obtained, which showed an increase in solubility by more than 200%. The complex was used to obtain modified-release matrix tablets based on Kollidon® SR and Chitosan. Materials and Methods: Matrix tablets were obtained through direct compression method of non-complexed amiodarone and inclusion complex, and they were marked F1 and F10, respectively. The two formulations were studied comparatively in terms of release kinetics of the active substance through in vitro drug release tests. Those tests were conducted using a paddle apparatus II for 12 hours and two gastrointestinal simulation liquids with different pH values relevant for oral administration - 2 hours at pH 1.2 and 10 hours at pH 6.8. The release of hydrochloride amiodarone was quantified using a validated HPLC method. Two factors were calculated to assess the release profile of amiodarone: the similarity factor f1 and difference factor f2. Results: The increase in Kollidon® SR concentration resulted in a slower release of amiodarone at both pH values. The use of Chitosan resulted in a decrease of AMD release only at pH 6.8. Conclusions: The similarities between the two release profiles of AMD were confirmed by the values of the similarity factor (f1 = 43.697) and difference factor f2 (f2 = 68.263). Keywords: AMIODARONE, INCLUSION COMPLEXE, MATRIX TABLETS, SUSTAINED RELEASE, KOLLIDON® SR, CHITOSAN.

Amiodarone [2-butyl-3-(3,5-diido-4-β-dihyethylaminoetoxybenzoyl)benzofuran] (AMD) originally used as an antianginal, is currently administered as cardiovascular medication in the treatment of severe supraventricular and ventricular arrhythmias (1). AMD is a Class III antiarrhythmic substance which prolongs the duration of action potential and effective refractory period in both the atria and ventricles. The absorption of
amiodarone in the gastro-intestinal tract is variable and hard to predict. The oral bioavailability ranges from 22% to 86%. Large individual variations were attributed to the dealkylation of the molecule to its primary metabolite desethylamiodarone (2,3). This unpredictable absorption may be explained by the low solubility of amiodarone in aqueous solutions and by the hepatic first-pass effect, which has been not clearly defined (4).

In terms of pharmacokinetics, amiodarone is included in the II BCS class (bio-pharmaceutical classification system), as it is characterized by increased membrane permeability and a low rate of dissolution, due to the low solubility in water (5). The formulation of AMD-based polymer matrix tablets can alter the dissolution rate and oral bioavailability of this active substance.

Currently, AMD is used in therapy as conventional release pharmaceutical products - 200 mg AMD oral tablets, under the trade name Cordarone®.

The aim of this study was to improve the biopharmaceutical properties of AMD by various pharmacotechnical methods. In the first stage AMD was included in hydroxypropyl-β-cyclodextrin (HP-β-CD) which resulted in the HP-β-CD/AMD inclusion complex that has been physicochemical and pharmacokinetic characterized (6-9).

In the second phase modified release matrix tablets were formulated based on Kollidon® SR (KOL) and Chitosan (CHT) in which AMD was used as non-complexed active substance and as HP-β-CD/AMD inclusion complex. Two matrix tablet formulations were comparatively studied in terms of AMD release profile.

MATERIAL AND METHODS

The raw materials used were 100.2% pure Amiodarone hydrochloride (Zhejiang Sanmen Hengkang Pharmaceutical Co. Ltd., China.), Kollidon® SR and practical grade Chitosan (BASF, Germania), Aerosil 200 (Degussa, Germania) and Magnesium stearate (Union Derivan S.A., Spain) and HP-β-CD/AMD inclusion complex (“Petru Poni” Institute of Macromolecular Chemistry Iași, România).

The preparation of matrix tablets: In a previous study we analyzed the concentration of polymer matrix for tablets with optimal technical and pharmacokinetic properties. Based on the results of that study two formulations of AMD modified-release matrix tablets were formulated and their pharmaceutical formulation is presented in Table I. AMD matrix tablets were obtained by direct compression method using a Korsh EK0 machine with 9 mm ponson diameter and 8-10kN compression force.

<table>
<thead>
<tr>
<th>Material components (%) w/w</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMD-HCl</td>
<td>33.33</td>
</tr>
<tr>
<td>HP-β-CD/AMD</td>
<td>-</td>
</tr>
<tr>
<td>KOL</td>
<td>40</td>
</tr>
<tr>
<td>CHT</td>
<td>3</td>
</tr>
<tr>
<td>Aerosil 1</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
</tr>
<tr>
<td>Avicel</td>
<td>up to 100%</td>
</tr>
</tbody>
</table>

In vitro dissolution studies were performed according to the specifications of "Dissolution test for solid pharmaceutical forms" monograph of the European Pharmacopoeia 8th Ed. (10) according to the following experimental protocol: pH 1.2 dissolution medium (0.1N HCl solution) for the first 2 hours (simulation medium for gastric fluids) and pH 6.8 dissolution medium (phosphate buffer) for the next 10 hours (simulation medium for intestinal fluids); SR 8 Plus Series II Apparatus with
In vitro dissolution studies of amiodarone hydrochloride from hydroxy-propyl-β-cyclodextrin/amiodarone inclusion complex formulated into modified-release tablets

paddle (ABL&E-JASCO); 37±0.5°C bath temperature; 50 rpm rotation speed. Sampling interval was set to every hour during the 12 hours of the test (7 mL of sample were replaced at each harvest with the same volume of medium).

AMD quantitative determination was performed by high performance liquid chromatography (HPLC), using an octyldodecysilyl solid phase and a 0.5% formic acid and methanol mixture as mobile phase in a 25:75 ratio. The temperature of the column was 45±0.2°C. The HPLC method has been validated (11).

The tests were carried out on three tablets, and the results are the mean of determinations.

Analysis of difference factor $f_1$ and similarity factor $f_2$: According to pharmacotechnical specifications for the preparation of modified release tablets, the release profile of the active substance in that type of tablet was analyzed by determining the difference factor $f_1$ and similarity factor $f_2$ between two or more formulations.

These two factors for assessing the AMD release profile from the studied formulations were calculated according to the following equations:

$$f_i = \left[\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right] \times 100$$

$$f_2 = 50 \log_{10} \left\{1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2\right\}^{0.5} \times 100$$

where: $n$ = the number of samplings, $R_t$ = the amount of dissolved drug substance of reference formula at $t$ moment, $T_t$ = the amount of dissolved drug substance of tested formula at $t$ moment.

RESULTS AND DISCUSSION

The results showed that the two tablet formulations achieved a sustained AMD release. It was noted that F10 formula containing HP-β-CD/AMD inclusion complex generated a faster release of AMD compared to F1, but the release kinetic profile did not change. This finding was consistent with the results of previous studies which had shown that the solubility of AMD had increased considerably by complexation with HP-β-CD (7,12).

The studied formulations achieved a prolonged release of AMD for 6 to 8 hours. Within six hours F1 formula has released 80.95% of AMD while F10 formula 86.59% of the active substance (fig. 1).

![Fig. 1. The in vitro dissolution profile of AMD-HCl from F1 and F10](image-url)
The influence of matrix forming agents on the release of AMD from the inclusion complex formulated as modified-release tablets was confirmed by the values of f1 and f2 factors shown in tab. II.

### TABLE II

<table>
<thead>
<tr>
<th>Reference formulation</th>
<th>Determined factor</th>
<th>F1</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>f1</td>
<td>43.697</td>
<td>68.263</td>
</tr>
<tr>
<td></td>
<td>f2</td>
<td></td>
<td></td>
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</table>

The results obtained in that step revealed that the two formulations were the same in terms of the release profile of the active substance. It appeared that improving the solubility of AMD in the HP-β-CD/AMD inclusion complex was reflected to a lesser extent in AMD release. Thus, we believe that AMD release from modified-release tablets based on KOL and CHT is controlled only by those two matrix formers and that the low solubility of the substance had a low impact and it can be overcome by extended release formulation. Similarities between the two release profiles of AMD were confirmed by the values of difference factor (f1 = 43.697) and of similarity factor (f2 = 68.263).

### CONCLUSIONS

During our conducted research, we assessed the *in vitro* release profile of AMD when formulated in a tablet matrix in two different states: as hydrochloride, and as HP-β-CD/AMD inclusion complex. Our results showed that AMD release in both studied formulas was similar and it was controlled only by the two matrix formers. The values of difference factor and similarity factor led us to confirm the similarities between the two release profiles of AMD. The studied tablets were obtained through direct compression and they contain low cost excipients, which will facilitate the transfer of optimal formulation to industrial production.

### REFERENCES

In vitro dissolution studies of amiodarone hydrochloride from hydroxy-propyl-β-cyclodextrin/amiodarone inclusion complex formulated into modified-release tablets


NEWS

GENETIC SUSCEPTIBILITY TO INSULIN RESISTANCE ASSOCIATED WITH LOWER ADIPOSY

The researchers tried to demonstrate the relationship between adiposity, genetic susceptibility to insulin resistance or insulin secretion and the response to GH treatment in short children born small for gestational age( SGA). The study was realised on 89 short prepubertal SGA children treated with GH for one year in a multicentre study. Combined multiallele gene scores based on single nucleotide polymorphisms with known associations with lower insulin sensitivity and insulin secretion were analysed. The results showed that during GH treatment, GS-In Res was related to a lesser decline in trunk fat and a higher trunk- limb fat ratio at 1 –year. GS-In Sec was positively associated with truncal fat. (Thankamony A1,2, Jensen RB1, O’Connell SM3 et al. Adiposity in children born small for gestational age is associated with β-cell function, genetic variants for insulin resistance and response to growth hormone treatment. J Clin Endocrinol Metab. 2015 Nov 20;jc20153019).

Diana Tatarciuc

AGGRESSIVE PERIODONTITIS: THE SUBGINGIVAL MICROBIAL PROFILE OF AN AFRICAN POPULATION

The aim of this study was to determine the subgingival microbial profile of African individuals from Sudan. The study was conducted on 34 patients from Kartoum, 19 of which presented a form of aggressive periodontitis (AgP). The other 15 patients were periodontally healthy and considered as controls. For the determination of the subgingival microbial profile the following tests were used: real time PCR and DNA-DNA hybridization checkerboard. Porphyromonas gingivalis was absent from the samples in the AgP group, but present in two control patients. On the other hand, Aggregatibacter actinomycetemcomitans was present in 6 of the 19 patients from the AgP group. The two periodontal „classic” pathogens were not significantly present in the AgP group, compared with the control group. More studies are needed in order to fully understand the subgingival microbial profile of aggressive periodontitis (Elabdeen HRZ, Mustafa M, Hasturk H et al. Subgingival microbial profiles of Sudanese patients with aggressive periodontitis. J Periodont Res 2016; 50: 674–682).

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