ORIGINAL ARTICLE

STUDIES ON THE INFLUENCE OF AMIODARONE COMPLEXATION WITH CYCLODEXTRIN DERIVATIVES ON THE *IN VITRO* RELEASE FROM MATRIX TABLETS

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Abstract

The release of the active substance from the matrix modified-release tablets based on Kollidon® SR and chitosan is dependent on its degree of solubility in the dissolution medium as well as on the matrix forming polymers. Through the complexation of amiodarone hydrochloride with hydroxypropyl-β-cyclodextrin, an inclusion complex was obtained that showed an increase in solubility by more than 200%. Matrix tablets were obtained through the direct compression method for both free and complexed amiodarone. The two formulations were comparatively studied in terms of the release kinetics of the active substance using *in vitro* release testing and the results were analysed by fitting into four representative mathematical models for the modified release oral formulations. The release tests were conducted using a paddle apparatus 2 for a 12 hours total in simulated gastrointestinal fluids: 2 hours at pH 1.2 and then 10 hours at pH 6.8. The released amiodarone from the studied formulations was quantified using a validated HPLC method. Two factors have been calculated to assess the release profile of amiodarone: f2 - the similarity factor and f1 - the difference factor. Akaike index and the correlation coefficient were the criteria used for selecting the model that most faithfully depicted the release profile of each formulation studied.

Rezumat

Eliberarea substanței active din comprimatele matriceale cu cedare modificată pe bază de Kollidon® SR și chitosan este dependentă de gradul de solubilitate a acesteia în mediul de dizolvare, precum și de polimerii formatori de matrice. Prin complexarea clorhidratului de amiodaronă cu hidroxi-propil-β–ciclodextrină, s-a obținut un complex de incluziune ce prezintă o creștere a solubilității cu peste 200%. Prin metoda de comprimare directă au fost preparate comprimate matriceale cu amiodaronă în stare liberă (necomplexată) și complexată. Cele 2 formulări au fost studiate comparativ sub aspectul cineticii de eliberare a substanței active prin efectuarea testelor de cedare *in vitro*, iar rezultatele au fost supuse analizei prin fitare pe patru modele matematice reprezentative pentru formele farmaceutice orale cu cedare modificată. Testele de cedare au fost efectuate la aparatul 2 cu palete, pe un interval de 12 ore în mediu de simulare a fluidelor gastrointestinale: 2 ore la pH = 1,2 și 10 ore la pH = 6,8. Amiodarona eliberată din formulările studiate a fost determinată cantitativ printr-o metodă HPLC validată. S-au calculat cei doi factori de evaluare a profilului de cedare a amiodaronei, factorul de diferență f1 și de similaritate f2. Indicele Akaike și coeficientul de corelație au fost criteriile pentru selectarea modelului care descrie cu cea mai mare fidelitate profilul de cedare a fiecărei formule studiate.

Keywords: HP-β-CD/AMD inclusion complex, Kollidon® SR, chitosan, sustained release tablets

Introduction

Amiodarone hydrochloride (AMD) is a benzofuran derivative that is rich in iodine. It is a white to pale yellow crystalline powder, very soluble in chloroform and dichloromethane, soluble in methanol and ethanol, but sparingly soluble in propanol and water [3, 22].
The absorption of AMD in the gastro-intestinal tract is variable and hard to predict. Oral bio-availability varies between 22 and 86% [2], as large individual variations are attributed to the dealkylation of the molecule to active metabolite desethyl-amiodarone [19, 22]. That unpredictable absorption may be explained by the poor solubility of AMD in aqueous solutions (0.2 - 0.7 mg/mL) and by the hepatic first-pass effect, which has not been clearly defined [3, 14]. AMD belongs to the class II BCS (Biopharmaceutical Classification System) that includes drugs characterized by high membrane permeability and a low rate of dissolution, due to the low solubility in water [7, 9]. Currently, AMD is used in therapy as conventional release tablets (200 mg/tablet) recommended to be administered in 2 - 3 doses per day [5].
The studies had as main objective the increase of the AMD availability, by preparing two formulations of

modified-release matrix tablets based on Kollidon® SR (KOL) and chitosan (CHT).

One of the studied matrix tablet formulation, that has been designated F1, contained amiodarone hydrochloride and the second formulation, that has been designated F10, contained the HP-β-CD/AMD complex. The inclusion of AMD in water-soluble complexes by complexation with hydroxypropyl-β-cyclodextrin (HP-β-CD) has been characterized from physico-chemical and pharmacotechnical points of view, in a previously published paper [18]. Kollidon® SR is a modern excipient consisting of a mixture of polyvinyl acetate and polyvinyl pyrolidone in an 8:2 ratio. The flow and compressibility properties of Kollidon® SR recommend this excipient as a matrix tablet hydrophilic forming agent for the direct compression method [5, 12]. CHT is a natural poly-saccharide that promotes hydration and diffusion properties of the matrix. In addition, at the gastro-intestinal level, CHT could act as an absorption promoter [7, 13].

Both matrix tablet formulations (F1, F10) have been comparatively studied in terms of the release profile of AMD. In order to identify the physical processes governing the release of AMD from the matrix tablets, the results obtained through *in vitro* AMD dissolution test were analysed by fitting into four representative mathematical models for the modified release formulations.

Materials and Methods

Materials: amiodarone hydrochloride 100.2% purity (Zhejlang Sanmen Hengkang Pharmaceutical Co. Ltd., China), Kollidon® SR, (BASF, Germany), chitosan practical grade (BASF, Germany), Aerosil® 200 (Degussa, Germany), magnesium stearate (Union Derivan S.A., Spain) and HP-β-CD/AMD ("P. Poni" Institute of Macromolecular Chemistry, Iaşi, România).

Methods

Preparation of matrix tablets was based on a previous study that established the optimum concentration of each polymer which leads to matrix tablets with optimum pharmaco-technical proprieties [15, 19]. Thus two AMD modified release matrix tablets (F1 and F10) have been formulated. Both formulations described in Table I were obtained by direct compression using a Korsch EK0 tablet press equipped with a 9 mm diameter punch and at an 8 - 10 kN compression pressure.

Table I

Matrix tablet formulations

Matrix components (% w/w)	Formulation	
	1	**10**
AMD·HCl	33.33	-
HP-β-CD/AMD	-	33.33
KOL	40	40
CHT	3	3
Aerosil	1	1
Magnesium stearate	0.5	0.5
Avicel	up to 100%	

In vitro release studies were performed according to the specifications of "Dissolution test for solid pharmaceutical forms" monograph from the European Pharmacopoeia 8th Ed. [10], following the experimental protocol: the dissolution medium was a pH 1.2 solution (0.1 N HCl as simulated gastric fluid) for the first 2 hours and then a pH 6.8 solution (phosphate buffer as simulated intestinal fluid) for the next 10 hours. A SR 8 Plus Series paddle apparatus 2 (ABL&E-JASCO) was used at 37 ± 0.5°C bath temperature and 50 rpm rotation speed. Sampling interval was set to every hour during the 12 hours of tests and 7 mL of sample were replaced at each harvest with the same volume of medium.

The chromatographic method applied for the quantitative assessment of AMD has been developed and validated in-house. The method development and validation were carried out on a Thermo Fisher Surveyor HPLC System with a Diode Array Detector [4].

The working conditions optimized for the chromatographic system involved the use of the mobile phase consisting of a 25:75 (v/v) mixture of 0.5% formic acid and methanol, 45 ± 0.2°C working temperature, on a Thermo Fisher Betasil C18 chromatographic column (4.6 x 150 mm, 5 µm), 20 µL injection sample and 254 nm detection wavelength. The method was validated by determining the following parameters: the method repeatability and intermediate precision for a concentration of 0.05 mg/mL, when RSD had values ≤ 2.5 for the peak area, the retention time and concentration; the method linearity was evaluated in the concentration range of 0.5 - 5 mg/mL; the detection limit was established to be 0.002185 mg/mL and the quantification limit was 0.00662 mg/mL [4]. The tests were carried out on three tablets and the results were the averages of the determinations.

Analysis of difference and similarity factors - f1 and f2.

According to pharmaco-technical specifications for the preparation of modified release tablets, the release profile of the active substance from that type of tablet must be analysed by determining the difference factor f1 and the similarity factor f2 between two or more formulations [1, 11].

Those two factors that assess the release profile of AMD from the studied formulations were calculated according to the equations:

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100,$$

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

where: n = the number of points for specimen collection, R_t = the amount of dissolved active substance from the reference formulation at the t moment, T_t = the amount of dissolved active substance of the studied formulation at the t moment and $\log_{10}X$ = 10 base logarithm of X.

The evaluation of the release profile kinetics of AMD from the matrix tablets based on KOL and CHT (F1, F10) with either AMD·HCl or its HP-β-CD inclusion complex was done using analysis by fitting into four representative mathematical models which are basic elements for understanding the mechanisms underlying the release of the active substance from the studied formulations.

To establish a correlation between the data obtained from the *in vitro* dissolution test and the characteristics of the formulated matrix tablet, the data were analysed by fitting into four representative mathematical models for modified release formulations [8, 16, 20].

The equations corresponding to the four models used in the study were:

Zero-order release model: $M_t = K_0 * t$,

First-order release model: $M_t = 100 * (1 - e^{-k*t})$,

Higuchi release model: $M_t = K_H * t^{0.5}$,

Korsmeyer-Peppas release model: $M_t = K_P * t^n$,

$(n = 0.45)$,

where: M_t = the amount of active substance released at t moment, K_0 = the constant of zero order release rate, K = the constant of first order release rate, K_H = the constant of Higuchi model release rate, K_P = the constant of Korsmeyer-Peppas model release rate, n = the exponential coefficient, an indicator of release mechanism of active substance and t = time.

The data fitting was carried out by linear or non-linear regression using Matlab 7.1. Akaike information criterion (AIC) and the correlation coefficient R^2 were the criteria for selecting the model that most faithfully depicted the release profile of each studied formulation. A prediction as good as possible of the model requires for R^2 to be as close to 1 as possible and the AIC to have minimum values.

The two prediction parameters of the model were calculated according to the following equations:

$$AIC = n * \ln(RSS/n) + 2*p,$$

where: n = the number of data points; RSS = the residual sum of squares and p = the number of estimated parameters.

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (yi - y\hat{}i)^2}{\sum_{i=1}^{n} (yi - \bar{y})^2}$$

where: y_i = the experimental data, y^i = the values approximated by model, and $\bar{y}$ = the average of experimental data.

Results and Discussion

The results showed that the two formulations of the tablets achieved the sustained release of AMD. It is worth noting that F10 formulation containing HP-β-CD/AMD inclusion complex generated a faster release of AMD compared to F1, but the kinetic release profile was unaltered. That observation was consistent with the results of the previous studies which showed that by complexing AMD with HP-β-CD its solubility increased significantly. Both formulations achieved a prolonged release of AMD for 6 - 8 hours (Figure 1). After six hours of study, F1 formulation released 80.95% of AMD, while F10 formulation released 86.59% of the active substance.

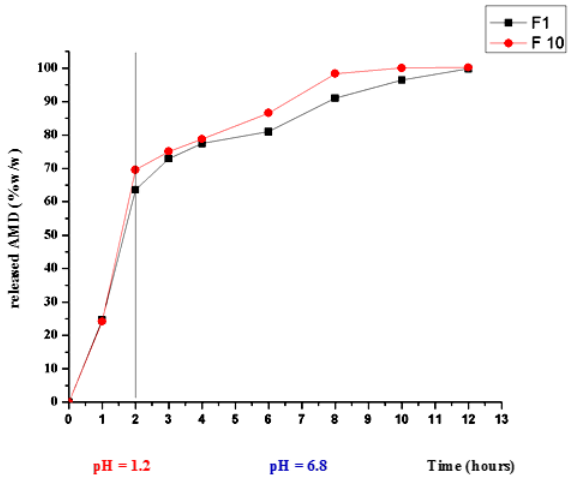

Figure 1.
The *in vitro* dissolution profile of AMD·HCl from F1 and F10

The influence of matrix forming agents on the release of AMD from the inclusion complex formulated into modified-release tablets was confirmed by the values of f1 and f2 factors shown in Table II.

Table II
Values of difference and similarity factors between formulations F1 and F10

Reference	Calculated factor	F10
F1	f1	43.697
	f2	68.263

The results obtained during that phase 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 by inclusion into HP-β-CD/AMD complex was reflected in a lesser extent in the release process of AMD. Thus we considered that the release of AMD from modified release tablets based on KOL and CHT was controlled only by those two matrix forming agents and the low solubility of the active substance had a low impact and it was overcome through the formulation of the prolonged release tablets. Although, the similarities between the two release profiles of AMD was confirmed by the value of the similarity factor (f2 = 68.263), the difference factor had a value greater than 15 (f1 = 43.697), which corresponded to a difference of more than 10% between the two analysed profiles. The results obtained after fitting the data into the four mathematical models are presented in Table III.

Table III

Parameters of mathematical equations corresponding to the release kinetics evaluation models and their predictability indicators

Kinetic model	Model parameters	Formulation	
		F1	F10
Zero order	K_0	10.8442	11.2567
	R^2	0.3371	0.2940
	AIC	76.7144	78.4984
First order	K_1	0.3951	0.9679
	R^2	0.9692	0.7389
	AIC	39.8839	66.5615
Higuchi	K_H	32.6511	33.9795
	R^2	0.8896	0.8675
	AIC	55.1982	58.4190
Korsmeyer-Peppas	n	0.35	0.42
	K_P	43.6926	46.3498
	R^2	0.9378	0.9226
	AIC	49.3169	52.9738

The results obtained through fitting into the selected mathematical models pointed out that the release of AMD occurred by diffusion from F1 and F10 matrix tablets that formulated AMD on its own and combined into HP-β-CD/AMD inclusion complex. However, a particular feature could be observed as F1 formulation showed a better fitting into the first order model. That model defined the release of the active substance through diffusion, but it was also an expression of the remnant substance. Diffusional characteristics were evident in the case of F10 formulation containing complexed AMD. Analysis of the release kinetics revealed the fitting of the release profile of AMD from F10 into Korsmeyer-Peppas model. The n exponent value (n = 0.42) showed that the tablet matrix behaved like a sphere from which the release of AMD occurred through diffusion because of hydratation, at a rate proportional to the square root of time. These results confirmed the optimization of AMD solubility by complexation, and the compatibility with the selected polymers in order to obtain prolonged release matrix tablets.

Conclusions

The conducted research assessed the *in vitro* release profile of AMD from matrix tablets that formulated AMD on its own and combined into HP-β-CD/ AMD inclusion complex. The results showed that the release processes of AMD from the studied formulas were different, although in a first phase the f2 factor value (f2 = 68.263) indicated the similarity of the two profiles. The analysis of the release kinetics of F10 formulation confirmed that AMD complexing had greatly enhanced its solubility. Thus the dissolution and diffusion processes of AMD through the polymer matrix based on KOL and CHT was confirmed by fitting into the Korsmeyer-Peppas mathematical model. All these results were consistent with the physical and chemical properties of the active substance and they confirmed the defining influence of both the active substance and the matrix forming agents on the release of AMD.

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