Study on the Formulation and Pharmacotechnical Characterization of Hydrophilic Matrix Tables with Amiodarone Chlorhydrate

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The study is based on new oral matrix tablets based on Kollidon®SR and chitosan, formulated in order to optimize the low oral bioavailability of amiodarone, a class III antiarrhythmic drug. Pharmacotechnical characterization included the analysis of flowability and compressibility properties (flow time, friction coefficient, angle of repose, Hausner ratio, Carr Index), and of pharmaco-chemical characteristics (mass and dose uniformity, thickness, diameter, mechanical strength, friability, degree of softening, in vitro release profile) of the tablets obtained using direct compression method. The results obtained have shown that both Kollidon®SR and chitosan may be used as matrix forming agents when combined with amiodarone. In vitro dissolution tests revealed that the nine formulations studied provided a prolonged release of amiodarone when compared to an industrial pharmaceutical product formulated as conventional release tablets.

Keywords: amiodarone, Kollidon®SR, chitosan, oral matrix tablets.

Amiodarone hydrochloride (AMD) is a class III anti-arrhythmia drug prescribed as the first therapeutic option in the treatment of ventricular fibrillation or pulse ventricular tachycardia. AMD is also used for the treatment of ventricular arrhythmias and supraventricular arrhythmias, including atrial fibrillation and reintroduction tachyarrhythmia [1]. Currently, AMD is administered as an injectable solution for intravenous use for unstable arrhythmia, and as oral tablets used for chronic therapy once the patient has been stabilized.

From the pharmacokinetic point of view, it is well-known that after oral administration AMD is absorbed from the gastrointestinal tract slowly and with a very high variability (22-86%). The factors that determine the poor oral bioavailability of AMD are not fully known, but it is said that the phenomenon is mainly due to the metabolization of AMD into the active metabolite N-desethylamiodarone in the gut lumen, to the first-pass metabolism in the liver, and to the poor dissolution of the drug. However, if AMD is ingested with fatty foods, the rate and extent of absorption are increased [2]. Due to its reduced solubility (0.2-0.5 mg/mL) and high intestinal permeability, AMD belongs to category II of the biopharmaceutical classification system. Low aqueous solubility is one of the most important limiting factors of gastrointestinal absorption of any active substance. In our previous studies we have investigated both the influence of formulation factors on the stability of AMD and various techniques, in order to increase the solubility of the active substance [3-5].

Kollidon®SR (KOL) is a physical mixture of polymers, consisting of 80% polyvinyl acetate (M_r = 450000 Daltons) and 20% polyvinylpyrrolidone (povidone) (M_r = 40000 Daltons) [6, 7]. KOL is included in the category of hydrophilic excipients used in the formulation and preparation of modified release matrix tablets. Numerous studies demonstrating the efficacy and versatility of that matrix-forming agent are provided in the literature [8]. Similar studies were carried out in the literature [9-21].

In the studied KOL-based formulations, we have also associated chitosan (CHT), a biodegradable and biocompatible polymer that acts as an absorption promoter for hydrophobic active substances with high molecular weight, in the gastrointestinal tract [21, 22].

The objective of the study was to develop and pharmacologically characterize matrix tablets, formulated in order to optimize the oral availability of AMD, taking into account the above mentioned pharmacodynamic and biopharmaceutical properties of the antiarrhythmic drug substance.

Experimental part

Materials and Methods

The main substances used were amiodarone hydrochloride (100.2% purity, Zhejlang Sanmen Hengkang Pharmaceutical Co. Ltd., China), Kollidon®SR (BASF, Germany), Chitosan (practical grade, BASF, Germania), Avicel®PH Microcrystalline Cellulose (Chemtrec, U.S.A. & Canada), Aerosil®200 (Degussa, Germania), magnesium stearate (Union Derivan S.A., Spain).

Determination of flow and compressibility parameters of powder mixtures was done on mixtures of powder for the nine proposed formulations, using 40%-60% KOL and

Table 1
FORMULATION OF AMD MATRIX TABLETS

Substance (%)	Formulation								
	1	2	3	4	5	6	7	8	9
AMD	33.33	33.33	33.33	33.33	33.33	33.33	33.33	33.33	33.33
KOL	40	40	40	50	50	50	60	60	60
CHT	3	5	7	3	5	7	3	5	7
Aerosil	1	1	1	1	1	1	1	1	1
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Avicel	up to 100								

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3-7% CHT, while AMD and the auxiliary substances were formulated in constant concentrations according to table 1 [23-25].

The following indicators were determined for the evaluation of the flow and compressibility parameters of the powder mixtures:

- flow time (g/s) was determined by recording the time required for 50 g of powder to flow through a funnel with a 10 mm hole;

- coefficient of friction (tg α) was determined using the dynamic method, using the equation: $tg\,\alpha = h/r$, where: h = height and r = the radius of the powder cone;

- angle of repose (α) was determined using the dynamic method;

- Hausner ratio (R_H) was determined by measuring the density before (ρi) and after compaction (ρc), according to the equation: $R_H = \rho c/\rho i$;

- Carr index (Ic) was determined using the density measurements done for the Hausner ratio, according to the equation: $Ic = (\rho c - \rho i/\rho c).100$ [26, 27]

Preparation of matrix tablets was done using the mixtures of powder for the nine proposed formulations for the matrix tablets with AMD by direct compression with the Korsh EK0 compression machine (9 mm ponson diameter, 8-10 kN compression force) [28, 29].

The quality of the matrix tablets was assessed by d*etermining the pharmaco-chemical characteristics of hydrophilic matrix tablets with modified release* [25, 30]*:*

-mass uniformity was determine according to Romanian Pharmacopoeia, Xth Edition, by weighing 20 tablets on the Radwag WPE 60 electronic scale [31, 32];

-dose uniformity was evaluated through the quantitative determination of AMD in tablets using a previously validated HPLC method [33];

-thickness, diameter, and mechanical strength were evaluated on a 10-compressed Schleuninger tablet according to European Pharmacopoeia, 8th Edition [8];

-friability was determined on 20 tablets using the EFII friabilator (100 rotations in 4 min).

The degree of moisture/hydration of hydrophilic matrix tablets with modified release was determined using a Type 2 Dissolution Test Station SR 8 Plus Series (ABL&E-Jasco) by placing the tablets in 100 mL of distilled water at 37 ± 2°C while the rotation speed of the dissolution apparatus blades was set to 60 rpm. The matrix tablets were removed at various intervals (1h-12h) from the dissolution medium and weighed after the excess water was eliminated from their surface.

The degree of moisture, expressed as a percentage of the amount of water absorbed, was calculated according to the equation:

$$W_s = [(W_t - W_o / W_o] \,.\, 100$$

where: W_s = degree of moisture, W_t = mass of the matrix at t time and W_0 = initial mass of the matrix.

In vitro dissolution studies were performed in accordance with the specifications of the "Dissolution Test for Solid Pharmaceutical Forms" from the European Pharmacopoeia, 8th Edition [31]:

-dissolution medium was a *p*H 1.2 solution (0.1N HCl) for the first 2 hours (simulated gastric fluid), and then pH 6.8 solution (phosphate buffer) for the next 10 hours (simulated intestinal fluid);

-SR 8 Plus Series (ABL&E-Jasco) blades apparatus Type 2 set at 37 ± 0.5°C and 50 rpm; the sampling interval was set every hour during the 12 htest (7 mL of sample were replaced with the same volume of medium).

The quantitative determination of AMD was performed using a validated HPLC method. In parallel, the release of AMD from conventional release tablets was evaluated. The results were interpreted and statistically analyzed using Matlab7.9 [34].

The dissolution profile of AMD in the studied tablets was analyzed based on the difference factor f_1 and the similarity factor f_2, calculated according to the following equations:

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

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

Results and discussions

Table 2 presents the results obtained during the determination of flow and compressibility parameters of the studied formulations.

The results showed that the formulations containing KOL in 40-50% concentration presented a good flow, whereas the increase in KOL concentration above 50% influenced negatively the flow properties, and thus sorted the F7-F9 formulations, as powders with deficient flow.

The results obtained for both Hausner ratio and Carr index set the F1-F6 formulations into the group of powders with good and even very good flow. The values of those two parameters proved that formulations with high concentrations of KOL, F7-F9, had poor and very poor flow.

The results of all flow parameters determined showed a positive influence of CHT on the flowability and compressibility properties.

Table 2

FLOW PARAMETERS OF THE POWDER MIXTURES

Parameter \ Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flow time T (g/s)	0.1388 (0.103)	0.1176 (0.092)	0.1538 (0.111)	0.3333 (0.054)	0.6666 (0.065)	0.2173 (0.781)	0.1250 (0.047)	0.1470 (0.098)	0.1057 (0.873)
Friction coefficient tg α	0.4615	0.4375	0.4512	0.7142	0.6923	0.7253	0.8108	0.8857	0.8888
Angle of repose α (°)	25 (0.145)	23.7 (0.129)	24.5 (0.836)	35.5 (0.108)	34.8 (0.987)	36 (0.165)	39.2 (0.945)	41.5 (0.567)	41.7 (0.789)
Hausner ratio	1.1785 (0.056)	1.3 (0.149)	1.3461 (0.157)	1.3913 (0.199)	1.3333 (0.096)	1.3157 (0.047)	1.5740 (0.835)	1.596 (0.668)	1.6666 (0.098)
Carr index (%)	15.151 (0.049)	23.076 (0.151)	25.714 (0.154)	28.125 (0.092)	25 (0.099)	24 (0.045)	36.470 (0.832)	37.373 (0.645)	40 (0.095)

 # Standard deviation for n = 3 is mentioned in round brackets

Table 3

PHARMACOTECHNICAL PARAMETER VALUES OF MATRIX TABLET FORMULATIONS

Formulation / Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diameter (mm)	12.0766 (0.0103)	12.0916 (0.0040)	12.1066 (0.0051)	12.0766 (0.0175)	12.0750 (0.0151)	12.0850 (0.0137)	12.0616 (0.0075)	12.0650 (0.0054)	12.0600 (0.0141)
Thickness (mm)	4.6166 (0.0163)	4.8566 (0.02650)	4.865 (0.0251)	4.9866 (0.2516)	5.145 (0.1832)	4.6466 (0.0338)	4.5983 (0.0664)	4.5766 (0.1556)	4.5533 (0.0413)
Average mass (g)	0.576 (1.1260)	0.588 (0.8239)	0.566 (1.3454)	0.6 (1.1011)	0.596 (0.9560)	0.592 (0.7773)	0.566 (0.8152)	0.584 (0.8802)	0.558 (0.8469)
Mass uniformity (%)	-2.7777	-3.0612	-4.5936	-3.3333	-2.6845	-3.7162	-2.8268	-4.1095	-5.0179
	+2.4305	+2.0408	+4.2402	+3.3333	+2.3489	+3.0405	+6.0070	+4.4520	+5.734
Dose (mg) uniformity	198 (1.2899)	203 (0.9831)	200 (1.0168)	197 (0.9231)	199 (1.2632)	201 (0.8721)	205 (0.6999)	198 (1.3981)	202 (1.2666)
Mechanical strength (N)	100.1 (3.3340)	98.85 (2.6059)	98.55 (3.8614)	93.35 (3.2971)	92.38 (2.9376)	90.08 (2.4959)	83.93 (2.5625)	84.18 (2.7396)	82.70 (2.6321)
Friability (%)	1.0362 (0.019)	0.8561 (0.025)	0.7547 (0.034)	1.4754 (0.027)	1.2924 (0.028)	1.3937 (0.033)	2.2304 (0.029)	2.1868 (0.033)	1.9841 (0.029

 # Standard deviation for n = 3 is mentioned in round brackets

The results obtained for the pharmacotechnical parameters of matrix tablet formulations are shown in table 3.

The analysis of the values proved that formulations F7-F9 containing the highest percentage of KOL exhibited large variations in mass uniformity, even beyond the 5% limit set by Romanian Pharmacopoeia, Xth Edition. It could also be correlated to the data recorded for the flow and compressibility parameters that indicated a poor flow for those formulations. Formulations F1-F6 showed variations in tablet mass within the limits set by Romanian Pharmacopoeia, Xth Edition.

Mechanical strength varied between 82.7 and 100.1 N and it is noticed that the values decrease directly proportional to the increase in the concentration of KOL. Those results contradicted the technical specifications of KOL, which stated an increase in the mechanical strength of the tablets directly proportional to the increase in the concentration of polymer in the formulation as a result of its plastic behavior imprinted by the povidone-linked polyvinyl acetate [22]. That behavior to compression had been also observed in other studies when KOL was combined with other matrix formers hydrophilic polymers [30].

Friability, a pharmacotechnical parameter directly correlated with the mechanical strength of the tablets, showed increasing values directly proportional to the increase in the concentration of KOL in the formulation. As far as friability was concerned, it was notice that the decrease in mechanical strength had led to an increase in tablet friability. Furthermore, the F7-F9 formulations showed a stripping tendency both during compression and during the friability test.

The hydration characteristics and the evolution of the pharmaco-chemical characteristics of the hydrophilic matrix tablets with AMD are plotted in figures 1-3.

The hydration characteristics of hydrophobic matrix tablets with modified-release were directly influenced by the matrix-forming polymers. Thus, F1-F7 formulations with 40-50% KOL concentration exhibited absorbent properties in the first 5 h of the test, after that there was a slight decrease in mass in the following 2-3 h. From the 8th hour, the matrix tablets were almost unchanged in terms of size and mass.

It is worth mentioning that formulations F1-F3 with 40% KOL showed hydration properties superior to formulations with a higher content of KOL and CHT. Formulations F7-F9 were characterized by adsorbent properties inferior to the other formulations. All the formulations studied retained their integrity during the 12 h of the hydration study. Increasing the CHT concentration caused a slight erosion of the outer layers of the matrices, but we could not determine whether that phenomenon could influence the

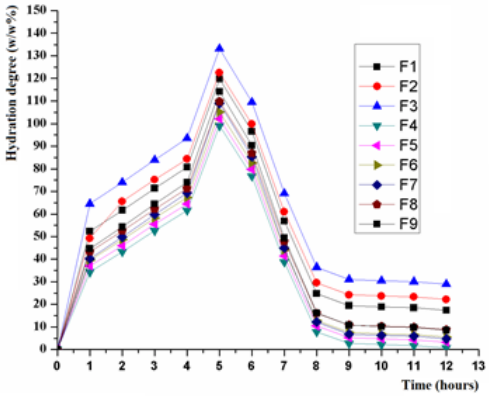

Fig. 1. Variation of hydration degree of the matrix tablets

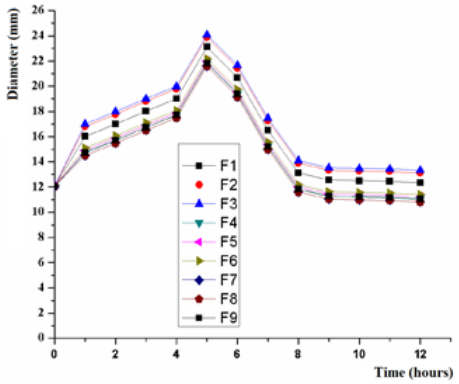

Fig. 2. Variation of diameter of the matrix tablets in hydrated state

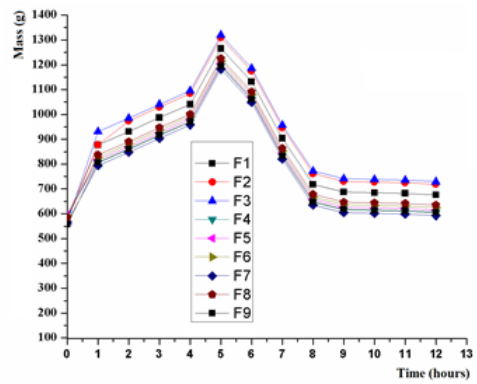

Fig. 3. Variation of mass of the matrix tablets in hydrated state

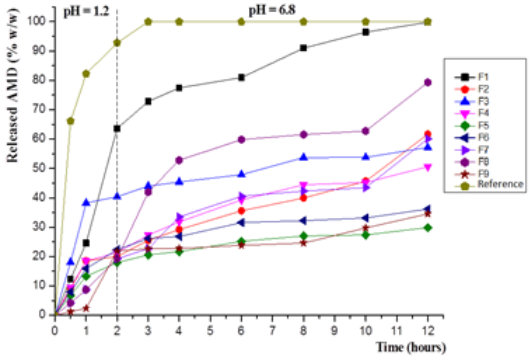

Fig. 4. In vitro dissolution profile of AMD in F1-F9 and reference industrial product

Table 4
VALUES OF f1 AND f2 FACTORS FOR THE MATRIX TABLET FORMULATIONS

Reference formulations	Test formulations	Difference factor f_1	Similarity factor f_2
F1	F4	54.0972	18.2164
	F7	55.4043	18.1286
F2	F5	33.8046	41.5353
	F8	47.5047	37.2517
F3	F6	41.0670	35.3246
	F9	52.0821	29.8467

release characteristics of the active substance in the studied matrix tablets.

The results obtained during the *in vitro* dissolution test reveal the prolonged release of AMD from the formulations, when compared to the release of AMD from an industrial product, formulated as conventional release tablets that was used as reference. On the other hand, the major role KOL exerted on matrix tablet release characteristics was also highlighted by those results. The released amount of AMD varied inversely to the percentage of KOL in the formulation for all formulations studied (fig. 4).

A particular behavior was observed for F1 that released 63.63% of AMD during the first 2 h of the dissolution test in simulated gastric fluid. Moreover, that formulation released AMD almost completely (99.77%) at the end of the 12 hours of testing.

We also found that increasing the CHT concentration in the formulation resulted in a decrease in the rate of AMD release from the matrix tablets. Thus, in the F1-F3 formulations containing 40% KOL, at the end of the dissolution test, F1containing 3% CHT released 99.77% of AMD, while F2 with 5% CHT released 61.68% AMD and F3 with 7% CHT generated a release of only 57.18%. That evolution of the dissolution profile was observed for all three series of formulations with a constant KOL concentration but variable CHT concentration.

Based on that observation, we compared the dissolution profile of AMD from the formulations studied by calculating the similarity factor f2 and the difference factor f1, considering formulations F1-F3 as reference formulations, and formulation F4-F9 as test formulations. The results obtained (table 4) confirmed that both CHT and KOL influenced the release characteristics of the matrix tablets and virtually each studied formulation had its own release kinetics.

Conclusions

In the present study, nine formulations of matrix tablets with AMD were obtained and characterized in order to develop AMD tablets with modified release. KOL and CHT were used as matrix forming agents, and their influence on the flow and the compressibility properties of the powders were analyzed as well as their effect on the pharmaco-chemical characteristics of the matrix tablets. The formulations of matrix tablets F1-F6, obtained through direct compression, containing 40-50% KOL, exhibited optimal flow properties and compressibility, while formulations with more than 50% KOL had a poor flow or even lacking.

The pharmaco-chemical characteristics of the tablets defined both by the working conditions and the flowing and compressibility characteristics of the powders were directly influenced by the matrix-forming polymers used to obtain hydrophilic matrix tablets with modified release. The mechanical strength of the tablets varied inversely to the KOL concentration in the formulation. Concentrations of KOL greater than 50% lead to improper matrices in terms of friability and mechanical strength. CHT did not have a significant influence on the pharmaco-chemical properties of the formulations studied (mechanical strength, friability, diameter, thickness, mass uniformity), but that polymer influenced the matrix matrix release characteristics, as increasing CHT concentration resulted in a decrease of AMD release rate. All formulations studied showed a prolonged release of AMD compared to the industrial pharmaceutical product. The values of the difference factor f1 and the similarity factor f2 showed that the nine formulations studied differed in terms of the release profile. In conclusion, the results obtained confirmed that AMD can be formulated as hydrophilic matrix tablets based on KOL and CHT, with up to 50% KOL and 3-7% CHT. Formulations F1-F6 will be studied *in vivo* to determine the oral bioavailability of AMD.

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