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EFFECT OF ACIDIFIERS ON THE DISSOLUTION RATE OF DRONEDARONE: DEVELOPMENT OF ORO-DISPERSIBLE TABLETS

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ABSTRACT
Dronedarone Hydrochloride is an antiarrhythmic agent that is commonly prescribed to treat atrial fibrillation. Unfortunately, it shows poor and erratic bioavailability owing to its limited aqueous solubility. The aim of this work was to improve Dronedarone Hydrochloride dissolution employing pH modulation approach. Being a weak basic compounnd, Dronedarone Hydrochloride was mixed with acidifiers to elucidate their effect on its dissolution behaviour. The work was extended to develop Oro-dispersible tablets to facilitate adminstration by geriateric patients. Dronedarone Hydochloride was physically mixed with different weak acids namely citric acid, succnic acid, tartaric acid and fumaric acid at 1:1 and 1:2 molar ratio (drug to acid, respectively). All acidifiers, apart from fumaric acid, markedly improved Dronedarone Hydochloride dissolution. The propmt release of about 72 %,58.9%, 72. 88% of the loaded dose after 5 minutes was obtained from equimolar blends of citric, succinic and tartaric acid, respectively, compared to only 13.7% from pure drug. The drug/acid physical mixtures were used to prepare tablets. The prepared Oro-dispersible tablets perserved the prompt drug release. This work provides simple stratigy for overcoming the dissolution problems of Dronedarone Hydochloride with a convenient means for drug adminstration.

KEYWORDS: Fumaric acid, Tartaric acid, Succnic acid, Citric acid, Dronedarone Hydochloride, Fast disintegrating tablets.

INTRODUCTION
Atrial fibrillation is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity and/or mortality. Accordingly, many bodies like the American College of Cardiology, the American Heart Association, and the European Society of Cardiology created a committee to establish guidelines for optimum management of this frequent and complex arrhythmia.[1]

The administration of oral dosage forms is increasingly in demand amongst patients because their convenience. However, considerable percentage of the newly approved drugs suffer from poor aqueous solubility. Therefore, it is important to take into consideration the drug solubility at different physiological media to ensure considerable bioavailability.

Dronedarone hydrochloride (Fig. 1) is such an example of molecules that show poor aqueous solubility. Dronedarone Hydrochloride is an antiarrhythmic agent usually prescribed to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter. It is a multichannel blocker that have been used to control rhythm and atrial fibrillation.[2] By the year 2009, the Food and Drug Administration (FDA) approved the clinical application of Dronedarone Hydrochloride and is commercially known as Multaq®. The maintenance dose is one 400 mg tablets taken twice daily preferably during meals.[3] Dronedarone Hydrochloride effectively reduced hospitalization due to cardiovascular events or death due to any cause by 24.2% when compared to the placebo group.[4] The drug is usually indicated in patients with atrial flutter or partial atrial fibrillation associated with recent episodes, exhibiting cardiovascular risk factors. Dronedarone Hydrochloride is a BCS class II drug (meaning it is low soluble but high permeable moiety). The bioavailability of DRN is about 4% and increased up to 15% when administered with a high fat meal.[5] Such low bioavailability is reported to be due to its poor water solubility (8.0 µg/mL) and extensive first-pass metabolism (more than 84%) by CYP3A4 enzyme.[6] Dronedarone Hydrochloride was reported to show a pH

dependent solubility. It is more soluble in the pH values ranging from 3.0 to 5.0.[7] To improve Dronedarone Hydrochloride aqueous solubility, several approaches have been reported using many approaches as the preparation of solid dispersion[8] and complexation with β-Cyclodextrin and HP β-CD,[9] proliposomal formulation[10] and solid lipid nanoparticles[11] However, the presence of various limitations of these technologies reflected the need for newer strategies.

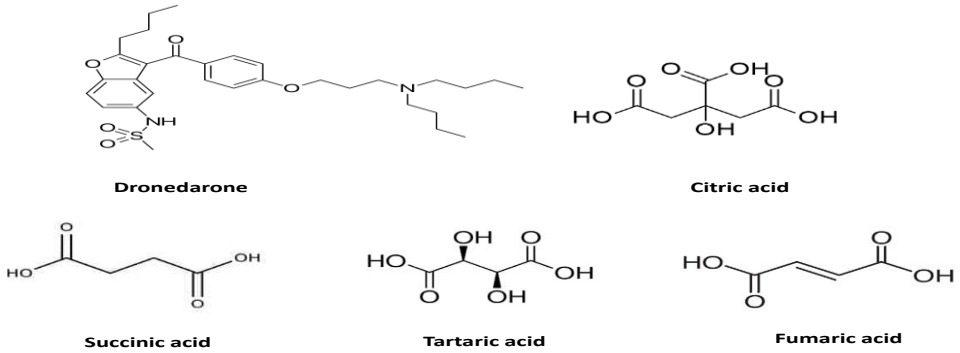

Figure 1: Structure of the drug and the used weak organic acids.

The strategy of using weak acid or basis as an approach to improve the aqueous solubility of drugs showing pH-dependent solubility have been reported. Dissolution of telmisartan (weak acid) was improved using meglumine as alkalinizer.[12] Increasing the pH value in the micro-environment of telmisartan crystals was taken as the reason for such enhancement. On the other hand, the solubility of haloperidol was improved by increasing the concentration of weak organic acids.[13]

The objective of this study was to improve the dissolution of DRN via mixing with weak organic acid with the aim of improving its in vitro dissolution and consequently its oral bioavailability. The effect of different organic acids was evaluated. The optimum formulation were developed into fast disintegrating tablets with rapid Dronedarone Hydrochloride release. prepare oral disintegration tablets of Dronedarone Hydrochloride for intra-oral administration. To achieve this goal, drug dissolution was improved by physical mixing of the drug with different weak acid acids. Comparisons were made to obtain the best combination that produced optimum drug dissolution parameters. The optimized mixtures were used to prepare fast disintegrating tablets with optimum Dronedarone release.

MATERIALS AND METHODS

Materials

Dronedarone Hydrochloride was a generous gift sample from Al Andalous Pharmaceutical company (Cairo, Egypt**).** Citric acid Monohydrate, Tartaric acid, Succinic acid, Fumaric acid, Croscarmellose Sodium, Crospovidone, Microcrystalline Cellulose (Avicel PH 102), Aeroprel®300, Allura red and magnesium stearate were kindly supplied by Sigma Pharmaceutical Company (Cairo, Egypt). All other chemicals were of analytical grade.

Methods

Construction of the calibration curve

Calibration curve of Dronedarone Hydrochloride was constructed by preparing serial dilutions of methanolic stock solution of the drug (1mg/ml) to obtain serial concentrations in the range of 10-40 µg/ml. The prepared samples were analyzed spectrophotometrically at λ max of 288nm using UV-spectrophotometer (Copley Scientific, Dis 6000, Nottingham, UK), and the absorbencies obtained were recorded. The standard curve was linear (R^2=0.997) over the range of concentrations determined.

Preparation of physical mixtures

Physical mixtures (PM) were prepared according to the compositions presented in Table 1. Each acidifier was mixed with Dronedarone at two different molar ratios of 1:1 and 1:2 drug: acidifier, respectively. Mixtures were prepared by geometric dry blending of Dronedarone and different acidifiers for 10 min with the help of a mortar and a pestle. All mixtures were kept in a closed container till used.

Table 1: Composition of different Dronedarone hydrochloride physical mixtures (PM) with different acids expressed as molar ratios, together with dissolution parameters expressed as amount released after 5 minutes (Q5) and percentage dissolution efficiency (DE%).

Code	Dronedarone hydrochloride	Citric acid	Succinic acid	Tartaric acid	Fumaric acid	Q5%	%DE
Pure drug		--	--	--	--	13.7±6.9	35.1
PM 1	1	1	--	--	--	72.3±0.2	84.2
PM 2	1	2	--	--	--	74.5±6.2	86.6
PM 3	1	--	1	--	--	58.9±0.8	82.1

PM 4	1	--	2	--	--	60.7±0.9	84.2
PM 5	1	--	--	1	--	72.8±5.9	84.5
PM 6	1	--	--	2	--	78.6±6.3	86.1
PM7	1	--	--	--	1	30.0±4.7	56.6
PM 8	1	--	--	--	2	23.4±6.5	57.2

Dissolution studies

The dissolution rate of unprocessed Dronedarone Hydrochloride (control) and the prepared physical mixture was determined using the USP II dissolution apparatus (Copley Scientific Dis 6000, Nottingham, UK). The paddle rotation was adjusted to 75 rpm and the dissolution medium (1000 ml phosphate buffer pH 4.5±0.5) was maintained at 37 ºC ±0.5 ºC. An amount of 400 mg of Dronedarone Hydrochloride (as control) or its equivalent weight of different formulations was placed in the dissolution medium. Aliquots of 5 ml each were taken at predetermined time intervals for 60 minutes and replaced with fresh dissolution medium. The samples were filtered using 0.45 mm Whatman membrane filter. The filtrate was suitably diluted, if required, with the fresh medium before spectrophotometric analysis for drug content at 288 nm. Dissolution profiles were obtained by plotting cumulative amount of Dronedarone hydrochloride dissolved (expressed as % of the loaded amount) versus time. These profiles were used to extract the dissolution parameters to compare between different formulations.

Preparation of oral dispersible tablets (ODTS)

Oro-dispersible tablets (ODTs) were prepared using different drug/acid mix. Mixtures MC1, MS1, MT1 and MF1, containing citric acid, succinic acid, tartaric acid and fumaric acid in the same orders, were used to prepare Tcit, Tsuc, Ttar and Tfum tablets, respectively. All tablets were prepared to contain an amount equivalent to 400 mg of Dronedarone. For comparison, control tablets (Tcont) were prepared containing 400mg of unprocessed drug. The composition of the prepared tablets is presented in Table 2. Crospovidon in combination with croscarmellose are used as super-disintegrants to fasten tablets breakdown and rapid drug release. Avicel PH 102 as filler, magnesium stearate as lubricant and Aeroprel®300 as glidant.

Table 2: Composition of the prepared Oro-dispersible tablets together with the quality control tests.

Ingredients (mg/tablet)	Tabcont	Tabcit	Tabsuc	Tabtar
Pure drug	400	400	400	400
Acidifier	--	141.7	79.6	101.15
Croscarmellose sodium	35	35	35	35
Crospovidone	35	35	35	35
Avicel PH 102	213	71.3	133.4	111.85
Aeroprel®300	10	10	10	10
Magnesium Stearate	7.0	7.0	7.0	7.0
Total tablet weight	700	700	700	700
Q5	19.3 ±3.0	59.9±1.6	58.8±1.7	58.7±0.9
%DE	47.5	88.5	88.40	91.27
Hardness (Kp)	5.0 ±0.5%	5.0 ±0.5%	5.0 ±0.5%	5.0 ±0.5%
Disintegration time (sec)	38.0 ±1.41	35.0 ±0.7	35.0±0.7	35.0±0.8
Wetting time (sec)	35 ±1.53	33 ±0.8	30 ±1.14	25 ±1.7
Friability	0.24 %	0.23 %	0.2 %	0.19 %

Each physical mix was blended with the excipients for 10 min employing the bottle mixing technique.[14] The blends were then directly compressed into compacts employing 14mm punch using single punch tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India). The compression force was adjusted to produce tablets having a hardness ranging between 4 and 5 kp.

Quality attributes of ODTS

The prepared tablets were evaluated regarding their quality in reference to US Pharmacopeial specifications (2000).[15] The tablets were characterized with respect to weight uniformity, crushing strength, friability, disintegration time and drug dissolution. Additionally, the wetting time test was also conducted.[16]

The uniformity of weight was performed by noting the average weight of 20 tablets. Each tablet was then weighed and the deviation of each tablet from average weight was calculated and expressed as percentage. The crushing strength of tablets was conducted, to ensure that tablets will withstand handling, employing Copley scientific hardness tester (TBF 1000, Nottingham, UK). Tablet friability was performed by pre-weighed 20 tablets before placing in the Friabilator (Erweka, Heusenstamm, Germany). The chamber was rotated 100 revolutions at the end of which the weight of the remaining intact tablets was determined after cautious de-dusting. The friability was calculated as the percentage weight loss in relation to the initial weight. Tablets accepted if the %loss in weight is below 1% (USP, 2000).

The disintegration time was determined using 6 tablets employing disintegration equipment (Copley Scientific NE4-cop, Nottingham, UK). Each tablet was placed into one of the 6-unit basket which was immersed in 1 liter of distilled water kept at 37± 0.5°C. The time necessary for complete breakdown of tablets with no pieces remained on the screen of the disintegration unit was taken as the measure of disintegration time.

Tablet porosity was assessed using wetting time test, employing Allura red (dark brown) as an indicator. Allura red powder was sprinkled on the top surface of each tablet prior to placing over a filter paper (previously wetted with about 6ml water) placed in a Petri dish. The wetting time was calculated as the time taken for the color to convert from the dark brown color to red color on the tablet top surface. The test was conducted in triplicate and the results were expressed as the average wetting time.[16]

The dissolution rate of the drug from the prepared tablets was performed using USP II dissolution apparatus (Copley Scientific Dis 6000, Nottingham, UK). The dissolution media and experimental conditions was similar to those used for testing the prepared mixtures (see above). For each tablet batch, one tablet was place in each dissolution vessel and sampling was continued for 30 min. Dissolution profiles were obtained by plotting cumulative amount of Dronedarone hydrochloride dissolved (expressed as % of the loaded amount) versus time.

Statistical analysis

All experiments were conducted in triplicates and Statistical analysis employed Student *t*-test. Results were taken as significant when *P* value less than 0.05. Additionally, similarity factor (f_2) test was employed to compare between the dissolution profiles. This employed the following equation:

$$F_2=50\times\log\left\{\left[1+\frac{1}{n}\sum_{t-1}^{n}(Rt-Tt)^2\right]^{-5}\right\}\times 100$$

Where "n" is the number of the used data points, "Rt" is the amount released from the control (%) at time t, and "Tt" is the amount released of the test formula (expressed as percentage) at the same time [17] .Value of f2 >50 indicates similarity of the compared profiles, while value <50 indicate dissimilarity.

RESULTS AND DISCUSSION

***In vitro* drug release from the prepared formulations**

The aim of this study was to enhance Dronedarone hydrochloride dissolution by pH modifying approach. Physical mixing the drug with weak acids was taken as a strategy to achieve this goal. The dissolution profiles of Dronedarone hydrochloride and its physical mixtures are shown in Figure 2A. The dissolution parameters were expressed as the percentage amount of drug released after 5 min (Q5) and the dissolution efficiency expressed as percentage (Table 1). The dissolution efficiency was computed from the area under the dissolution profiles at time (t) expressed as the percentage relative to the area of the rectangle presuming complete (i.e.100%) dissolution at the same time interval.[18] These parameters are shown in Table 1 and graphically presented as histogram in Figure 2B.

Unprocessed drug showed slow and incomplete dissolution with only 13.7% of the loaded dose dissolved after 5 minutes with overall release of 47% at the end of the experiment. The calculated dissolution efficiency was 35.05%. Such inadequate dissolution could be due to the hydrophobic nature of Dronedarone that resisted wettability and, therefore, slowed the dissolution. The obtained data is in close agreement with the reported the Dronedarone under similar conditions.[4]

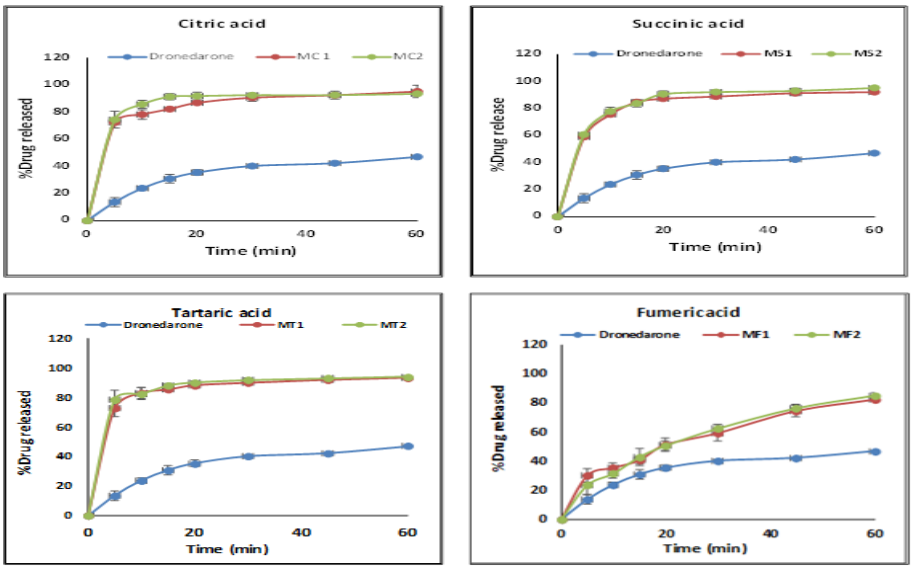

Figure 2: Dissolution profiles of Dronedarone Hydrochloride from blends with different organic acids. For detailed formulations refer to Table 1.

All combined Dronedarone/weak acid (1:1, 1:2 molar ratios) blends showed significant enhancement in drug release compared to pure drug (P<0.05). The dissolution parameters of Dronedarone from mixtures prepared using citric acid was similar to those prepared using tartaric acid (P>0.05). Dronedarone being a weak base, decreasing the pH value in the microenvironment around the drug particles had a great impact on drug dissociation. This modulation was an effective tool in maximizing the drug dissolution rate. The effect of increasing the molar ratio of the acid to the drug was insignificant (P>0.05), meaning that drug to acid ratio of 1:1 is the optimal ratio to give the best dissolution rate. This was further confirmed by similarity factor (f2) of more than 50 between the two ratios for each acid. At 1:1molar ratio, the percentage amount released after 5 min (Q5) were 72.3, 59.0 and 73.0% for mixtures containing citric acid, succinic acid and tartaric acid, respectively. The dissolution efficiency for blends in same rank order was 84, 82 and 84%, respectively. Meantime, though Fumaric acid significantly improved drug dissolution compared to control (P <0.05), it showed the least improvement in drug dissolution with Q5 and DE of only 30% and 56%, respectively, at the same ratio. Other investigators reported that the extent of increase in solubility of weak basic compound in presence of weak acids is related to be the aqueous solubility of acids themselves. It was also reported that the aqueous solubility of citric acid and tartaric acid is about 1.5, and 1.6 g/ml of water, while that for fumaric acid is only 0.05g/ml under the same conditions.[13] This would explain the marginal effect of fumaric acid in enhancing Dronedarone dissolution when compared to other acids.

Characterization of the prepared ODTs

Based on the *in vitro* dissolution studies, only physical mixtures of Dronedarone with Citric acid (Tcit), Succinic acid (Tsuc) and Tartaric acid (Ttar) at 1;1 molar ratios were used to prepare Oro-dispersible tablets. Control tablets (Tcont)containing unprocessed Dronedarone was also prepared for comparison purpose. The results of quality attributes are shown in Table 2.

Tablet friability values were between 0.19 –0.24%. This is acceptable according to the criteria set the US Pharmacopeia.[15] The recorded wetting time was 35, 33 and 30 and 25 seconds for Tcont, Tcit, Tsuc and Ttar, respectively, reflecting good porosity. Tablet hardness ranged from 4. Kp to 5.1Kp which is acceptable for oral dispersible tablets. Regarding tablet disintegration, values ranged from 35 to 38 seconds were recorded. These values are slightly high considering the FDA specification of Oro-dispersible tablets suggesting a disintegration time of equal to or less than30 seconds when determined employing USP method.[19],[15] This could be explained by the fact that the drug constituted most of the tablet weight due to its high dose strength.

The dissolution profiles of the prepared tablets are presented as cumulative percentage drug released versus time plots in Figure 3, and dissolution parameters are listed in Table 2. Tcont showed slow dissolution with Q5 and DE of 19% and 47%, respectively. These values are slightly higher than those obtained from Dronedarone powder. This could be due to the adsorption of the drug over the surface of the added tablet excipients.[20] For Oro-dispersible tablets prepared to contain different acidifiers all tablets showed improved dissolution profiles with subsequent fast dissolution.

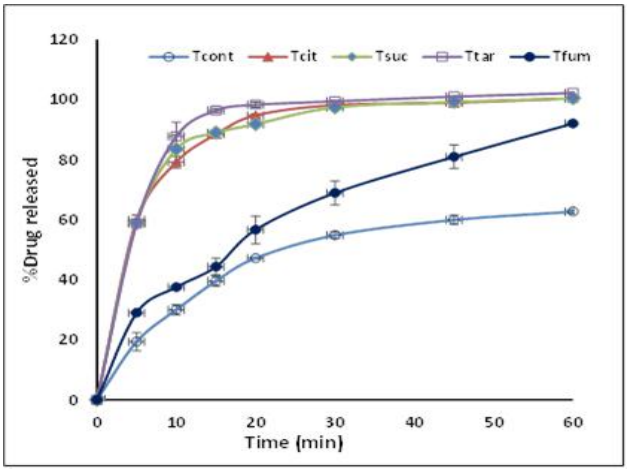

Figure 3: Dissolution profiles of Dronedarone Hydrochloride from Oro-dispersible tablets. Detailed tablet compositions are shown in Table 2.

CONCLUSION

Mixing of Dronedrone hydrochloride with weak organic acids (namely citric, succinic, tartaric and fumaric acids) resulted in marked improvement in the dissolution rate. The proposed mechanism behind such enhancement was due to the reduction in the pH value in the microstructural environment around the drug particles. The prompt release of Dronedarone hydrochloride was utilized in fabrication of fast disintegrating Oro-dispersible tablets with rapid release of the drug. This dosage form has a dual benefits of bypassing the hepatic first pass metabolism by a considerable amount of the

drug, with expected increase in its bioavailability. The other benefit is to improve patient, especially elderly, compliance to the medication due to ease of administration.

Disclosure statement

The authors report no conflicts of interest in this work.

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