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PREPARATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF AMIODARONE HYDROCHLORIDE

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ABSTRACT
Amiodarone is one of the most common antiarrhythmic medicines used for the treatment of both supraventricular and ventricular arrhythmias. However, the bioavailability of Amiodarone is low due to its poor water solubility that results in poor bioavailability. This work aimed to improve amiodarone dissolution through co-processing with inert excipients with the aim of formulating fast disintegrating tablets. Mechanochemical method was adopted by dry co-grinding of amiodarone with increasing proportions of xylitol, mannitol or benzoic acid. The prepared binary mixtures were investigated using differential scanning calorimetry, Fourier Transform Infrared spectroscopy, powder X-ray diffraction and *in vitro* drug dissolution rate. Optimum co-processed mixtures were formulated into fast disintegrating tablets after addition of suitable additives. Dry co-grinding improved drug dissolution parameters compared to unprocessed (negative control) and processed (positive control) drug, with xylitol was superior to other excipients. Physical characterizations reflected possible salt formation between the drug and benzoic acid and suggested amorphousization of the drug in case of mannitol and xylitol. The selected co-processed mixtures were successively formulated into tablets with optimum drug release. The study introduced simple co-processing as a tool to enhance dissolution rate of amiodarone with subsequent formulation of fast disintegrating tablets.

KEY WARDS: Amiodarone, mannitol, xylitol, benzoic acid, salt form, co-grinding.

INTRODUCTION
Solubility is an essential parameter to obtain the desired amount of medication in systemic circulation to achieve the proposed pharmacological effect. Among all newly discovered chemicals a large percentage of medications are hydrophobic, confronting issues achieving market pipe line because of their poor water solubility. Enhancing drug solubility stays a standout amongst the most difficult perspectives in formational improvement. In this context, discovering ways to improve the dissolvability of medications is significant in the pharmaceutical business today. The dissolution of medications can be improved by numerous ways, for example, complexation with ß-cyclodextrin[1] solid dispersion [2] and surface solid dispersion.[3]

Recently, pharmaceutical co-crystals have gained attraction for their potential role in enhancing the physicochemical properties of many therapeutic agents. Co-crystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with characterized stoichiometry and are held together by weak interactions, basically hydrogen bonding.[4] In addition to offering potential enhancements in solubility, pharmaceutical co-crystals were reported to improve other fundamental properties of the active ingredients such as flowability, chemical stability, compressibility and hygroscopicity.[5]

The choice of appropriate and compatible co-formers which are consistent with the active ingredients could be a major challenge.[6] In case one of the inactive excipients regularly utilized in solid dosage form formation may act as a co-crystal co-former, the use of this technique will be more noteworthy.[7]

Several co-crystal manufacturing techniques have been revealed, including solution crystallization[8], reaction crystallization [9] and mechanochemical methods.[10] Changes in certain variables of formulation such as optimizing the chosen co-former concentration(s) can significantly affect the solubility and the dissolution rate.
Amiodarone hydrochloride is one of the world's most common antiarrhythmic medicines. It is a derivative of benzofuran, used for the treatment of both supraventricular and ventricular arrhythmias. The

bioavailability of Amiodarone is low due to its poor water solubility because it is classified as a compound of class II drugs, which are low water soluble and highly permeable by biopharmaceutical classification system.[11]

The objective of this work was to prepare and assess oral dispersible (also called rapidly disintegrating) tablets of amiodarone hydrochloride, after improving its dissolution rate. For this purpose, mechanochemical technique was applied by dry co-grinding the drug with sugar excipients (mannitol and xylitol) that impart good taste to the tablets in addition to its potential for forming co-crystal with the drug with the aim to improve its dissolution. Possible co-crystal formation will be evaluated by solid state characterization. Additionally, benzoic acid was also investigated as potential co-former for amoidarone. The selection of these excipients based on the reported ability to modify the crystalline structure of many drugs after co-processing. The work was extended to prepare and evaluate fast disintegrating tablets of amiodarone.

MATERIALS AND METHODS

Materials

Amiodarone hydrochloride was supplied as a gift sample from Pharco, Egypt. Mannitol was obtained as gift samples from Eva Pharma, Cairo, Egypt. Xylitol was obtained as a gift from Amriya, Alexandria, Egypt. Avicel, crospovidone, croscarmellose sodium and magnesium stearate were obtained as gift samples from Sigma Co, Qwesna, Egypt. Benzoic acid and Ethanol was of high purity purchased from El-Nasr Co. for intermediate chemicals.

Methods

Spectroscopic analysis of amiodarone

A precisely weighed amount of amiodarone was dissolved in ethanol to set up a stock solution of amiodarone at concentration of 1mg/ml. The standard concentrations were to contain 6, 8, 10, 12 and 14 µg/ml in 1% sodium lauryl sulfate in water (dissolution medium). The absorbance of the prepared solutions was recorded at 241 nm against blank. This utilized T80+ UV/Vis double beam spectrophotometer, PG instruments, Ltd (Leicestershire, United Kingdom). The calibration curve was developed by plotting the recorded absorbance versus corresponding concentration.

Preparation of amiodarone co-processed formulations

Table 1 shows the compositions of the prepared formulations. Solid state grinding, or also called dry co-grinding, was used for the preparation of amiodarone formulations. Amiodarone and the selected excipient, at Different molar ratios were dry grinded for 30 minutes using mortar and pestle[12]. The obtained powder samples were stored in air-tight containers till use. To evaluate the effect of grinding technique, Pure Amiodarone and excipients were similarly treated, with the former taken as positive control.

Table 1. Compositions of the tested formulations expressed as molar and weight ratios, together with dissolution parameters represented as percentage amount released after 5 minutes (Q5) and dissolution efficiency (DE).

Formulation	Amiodarone	Xylitol	Mannitol	Benzoic Acid	Q5	DE (%)
Pure drug	1	0	0	0	26.6(±7.5)	49.6(±1.15)
Positive control	1	0			34(±7)	64.7(±1.7)
Fx1	1(1)	3(0.708)	0	0	36(±4.4)	77.9(±1.09)
Fx2	1(1)	5(1.79)	0	0	51.3(±3.8)	79(±4.2)
Fx3	1(1)	7(1.65)	0	0	88(±2.64)	88.5(±0.45)
Fm1	1(1)	0	3(0.85)	0	49(±3.6)	75(±1.075)
Fm2	1(1)	0	5(1.41)	0	77.3(±2.3)	77.5(±0.92)
Fm3	1(1)	0	7(1.98)	0	79(±9.5)	80.4(±0.79)
Fb1	1(1)	0	0	3(0.57)	47(±7.1)	75.0(±7.1)
Fb2	1(1)	0	0	5(0.95)	72(±6.6)	77.5(±2.5)
Fb3	1(1)	0	0	7(1.32)	62(±8.7)	68.5(±3.0)

- Positive control is the dry ground drug.
- Values between brackets represent the weight ratios.

Physical characterization of the prepared formulations

Fourier Transform Infra-red (FTIR) spectroscopy

FTIR spectroscopy was conducted to amiodarone, pure excipients and selected formulations. This employed equipment supplied by Bruker Tensor 27 (Ettlingen, Germany). The dry sample was blended with potassium bromide and the blend was compressed into discs. The compressed sample was scaled with FTIR scanning from 4000 to 400cm^{-1}. A DLaTGS detector which was adjusted to potassium bromide diffuse reflectance mode was used to Data collection. The position of each absorption band was determined using Opus IR, FTIR spectroscopy Software.

Differential Scanning Calorimetry (DSC)

The thermal behavior of Amiodarone, pure excipients and their co-grinded formulations were monitored. Sample (about 5 mg each) was packed into aluminum pan which was tightly closed using Shimadzu crimper. The samples were heated up at a rate of 10 °C / min starting from 30°C through 400 °C under constant

nitrogen gas flow employing Perkin Elmer DSC 6 equivalent (Waltham, 94 MA, US). The entire process was controlled by computer with TA-60WS thermal analysis workstation and data collection and analyzing software.

Powder X-ray diffraction (PXRD)

The crystalline nature of unprocessed amiodarone, pure excipients and different formulations were investigated using PXRD. The study used GNR APD 2000 pro-X-ray diffractometer with Cu Ka radiation (Agrate, Conturbia, Italy). This system is supported by a primary Gobel mirror. Diffraction pattern were detected using and a position sensitive detector (VÅNTEC-1). Data collection was performed in the range of 3° through 65° with a scanning step size of 0.03°, using continuous scan mode with 2 theta (2θ) scan axis.

Dissolution studies

According to the FDA recommendations for amiodarone dissolution, the dissolution studies were conducted using USP apparatus type II manufactured by Copley Scientific Dis 6000(Nottingham, United Kingdom) with the paddle speed being adjusted to 100 rpm. The dissolution medium comprised of 1000 ml of 1% sodium lauryl sulphate in water and was equilibrated to 37 ± 0.5°C. An amount of 100mg of unprocessed amiodarone or its equivalent weight from each formulation was placed in each dissolution vessel. Samples (5 ml each) were withdrawn at predetermined time intervals for 60 minutes, filtered immediately and drug concentration in each sample was determined spectrophotometrically at 241 nm. To keep constant volume, the dissolution medium was replenished with an equal volume of fresh medium after each sample. The dissolution profiles were compiled by plotting the cumulative amount dissolved versus time. The amount of drug dissolved in the first 5 minutes (Q5) and the dissolution efficiency (DE) were calculated. The similarity factor test using the following equation was used to compare dissolution profiles of various formulations[13]

$$F2=50\times\log\left\{\left[1+\frac{1}{n}\sum_{t-1}^{n}(Rt-Tt)^2\right]^{-5}\right\}\times 100$$

Where:

- F2 is the similarity factor (that should be less than 50 for the data to be considered as similar),
- Rt is amount dissolved of the reference (%) at time t and
- Tt is amount of the test dissolved (%) at the same time, and n is the number of data points.

Preparation of oral dispersible tablets

Formulations Fx3 (1:7 drug:xylitol), Fm3 (1:7 drug:mannitol) and Fb2 (1:5 drug:benzoic acid) were selected to prepare Xyl-Tab, Man-Tab and Benz-Tab, respectively. These formulations were selected based on their highest dissolution parameters. For comparative purposes, control tablets (Cont-Tab) were prepared containing unprocessed amiodarone. Each tablet was prepared to contain 100mg of amiodarone or its equivalent weight from all co-processed formulations. Master formulas for different tablet patches are shown in Table 2. The selected microparticle formulations, or unprocessed drug, were geometrically mixed with other additives using bottle method[3]. Tablet blends were then directly compressed using single punch tablet machine (Royal Artist, Kapadia industry estate, BLDG, Mumbai, India) employing 12 mm rounded, flat surface punch.

Table 2: The master formula for the preparation of amiodarone tablets, together with dissolution parameters represented as percentage amount released after 5 minutes (Q5) and dissolution efficiency (DE).

Ingredients	X3 Tablet (mg/tablet)	M3 Tablet (mg/tablet)	B2 Tablet (mg/tablet)	Control tablet (mg/tablet)
Unprocessed Amiodarone	–	–	–	100
Co-processed formulations	165.12 (FX3)	197.5 (Fm3)	94.6 (Fb2)	–
Croscarmellose sodium	20	20	20	20
Crospovidone	20	20	20	20
Magnesium stearate	5	5	5	5
Avicel	100	60	160	255
Tablet weight	410	400	400	400
Hardness (Kp)	5.38(±0.18)	5.5(±0.23)	4.8(±0.29)	5.1(±0.33)
%friability	0.76	0.6	0.924	0.68
Wetting time (sec)	28.3(±2.06)	17.1(±1.0)	19.08(±1.3)	17(±1.1)
Disintegration time (sec)	32.6(±5.2)	30.5(±3.16)	16.3(±4.4)	9.76(±0.7)
Q5	74.8(±1.89)	77(±4.6)	84.46(±1.92)	54.5(±1.43)
Dissolution efficiency (%)	83.4(±0.2)	88.4(±1.24)	85.95(±0.27)	65.0284(±1.14)

-The amount of co-crystal is equivalent to 100 mg amiodarone based on the recorded drug content.

Evaluation of oral dispersible tablets

The prepared tablets were characterized with respect to the uniformity of weight, hardness, drug content uniformity, wetting time, disintegration time and drug release in reference to USP specifications.[14]

Weight uniformity

Based on USP weight uniformity standardization, the test performed using randomly selected 20 tablets where individual weights were compared to the average weight of the 20 tablets. The tablet batch meets the USP requirements when not more than 2 tablets deviate by more than 5%, but none is out the double limit.[14]

Tablet hardness: This test was carried out using six tablets with the Erweka hardness tester (Heusenstamm, Hesse, Germany). The time required to break each tablet was recorded.

Drug content uniformity: To ensure uniform potential, sample of 10 tablets have been individually examined for amiodarone content. The tablet was ground into powder then dispersed in 50ml ethanol. Complete dissolution of drug was hastened by bath sonicating for 15 minutes. The dispersion was filtered and the filtrate was examined for the drug concentration spectrophotometrically at 241 nm after being suitably diluted with ethanol. Tablets are deemed acceptable if the content of a minimum of nine tablets was in the range of 85-115% of the labeled amount of amiodarone.[14]

Wetting time: This was conducted by placing the tablet onto a Petri dish containing filter paper wetted with 6 ml distilled water. A small amount of Allura red powder was sprinkled on the tablet surface and the wetting time was calculated as the time required for the red colour to develop on the tablet surface. This was accomplished using 3 tablets and the results were expressed as the average wetting time.[15]

Disintegration time: Six tablets were loaded into the six tubes of the basket assembly immersed in 1 liter of distilled water, maintained at 37 ± 0.5°C, of the disintegration equipment (Copley Scientific, Model: NE4-COP, UK). Time needed for complete breakdown of tablets and passage through the mesh screen of the disintegration unit was taken as a measure for disintegration time.

In vitro drug dissolution: Amiodarone dissolution from tablets was determined using the same conditions described for the co-ground mixtures with the tablet being loaded in the dissolution vessel (see above).

RESULTS AND DISCUSSION

Physical characterization of the prepared formulations

Fourier-transform infrared spectroscopy

Figures (1) shows the FTIR spectra of amiodarone, xylitol, mannitol, benzoic acid in pure state or as co-processed mixture with the drug. The spectrum of the unprocessed amiodarone showed absorption bands between 2800 and 3100 cm^{-1}, due to the stretching of the aromatic and aliphatic C-H bond. Strong absorption bands appear at 1388, 1635 and 2468 cm^{-1} that are attributed to the C-N group, carbonyl group and NH groups, respectively. The absorption band at 1250 cm^{-1} can be attributed to the ether group C-O-C stretching. The recorded spectrum simulates the published spectrum for the same drug[3]. Grinding the drug alone did not change in the spectral pattern of the drug negating any modulation in the structure of the drug.

The FTIR spectrum of xylitol (Figure 1A) revealed the characteristic absorption bands of the stretching vibrations of the hydroxyl groups of the sugar and the adsorbed water in the region of 3200 to 3400 cm^{-1}. The OH out of plane bending appeared as a strong peak at 747 cm^{-1} and that for in-plane OH bending appeared as a broad peak at 1435 cm^{-1}. The absorption bands recorded at 1312, 1125, 1065, 1011 cm^{-1} were attributed to C–O stretching vibrations. This spectrum is in good agreement with the previously published data for the same material.[16] Figure 1B shows the FTIR spectrum of mannitol that revealed the characteristic absorption band of the stretching vibrations of OH groups of the sugar and the adsorbed water at 3200-3400cm^{-1}. Peaks at 2800 to about 3000 cm^{-1} attributed to the C-H stretching bands of the mannitol backbone. The C–O stretching vibrations appeared in the region of 1050 to 1085 cm^{-1}.[17] Treating xylitol alone produced IR spectrum with no modification in the main absorption bands of the sugars indicating no change in its structure (Figure 1A). Regarding the co-processed mixtures of the drug with either xylitol or mannitol, the main characteristic peaks of both materials and the drug can be detected. This would suggest no interaction between the drug and the used sugar excipients.

For benzoic acid (Figure 1C), The FTIR spectrum revealed the characteristic absorption band of the stretching vibrations of aromatic ring at 1427 and 1606 cm^{-1}. The C=O stretching vibrations appeared at 1712 cm^{-1} and that for OH of carboxylic group appeared as a very broad strong peak at 2500-3400 cm^{-1}[18]. Co-processed mixture of benzoic acid and amiodarone showed a compromised spectrum. The peak for carbonyl group of the drug was reduced in intensity and slightly shifted to 1669cm^{-1}. Meantime, the broad peak for the carboxylic OH group was reduced and became more broader. This might suggest interaction between the basic amiodarone and the acidic excipient.

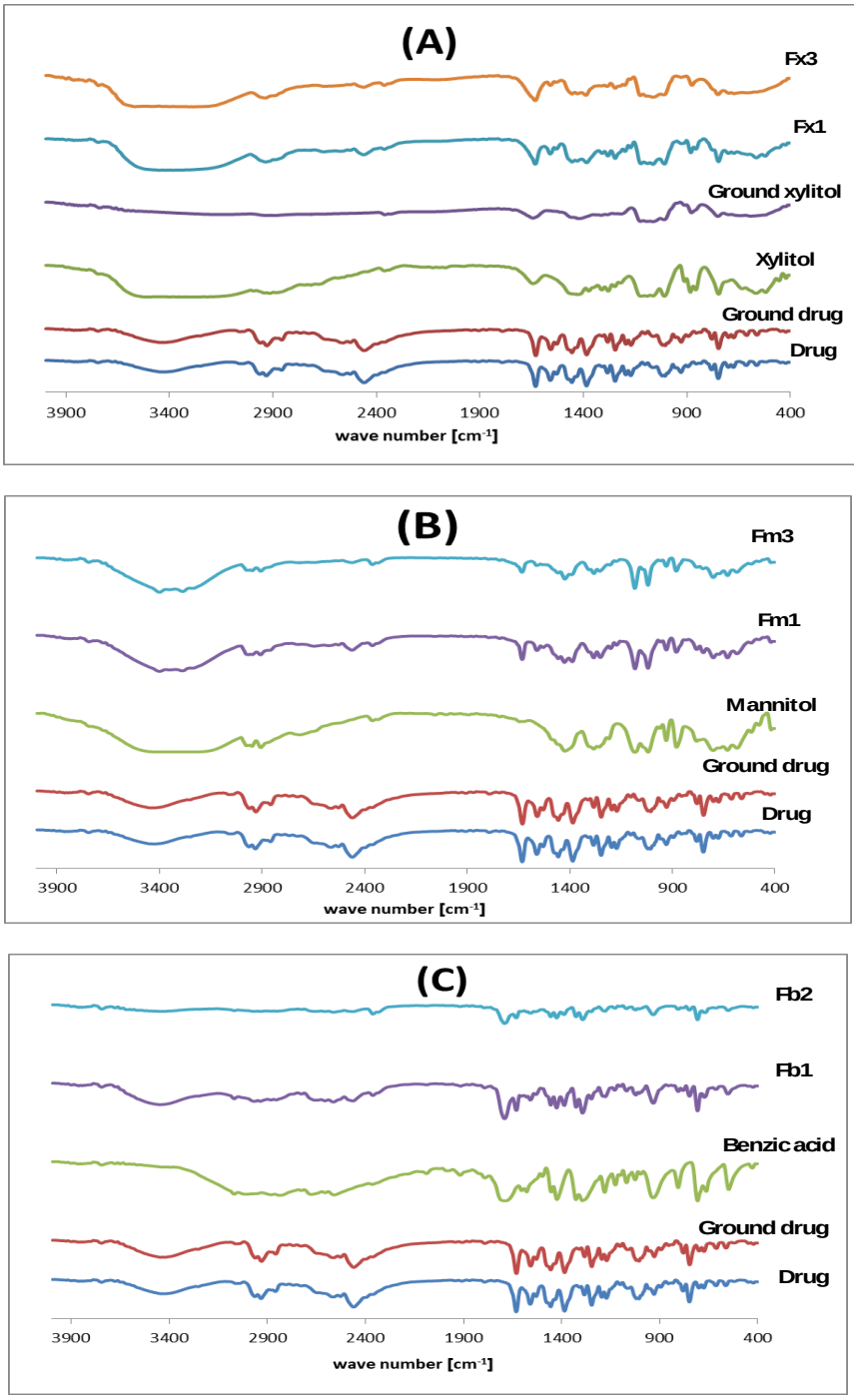

Figure 1: FTIR spectra of amiodarone from different co-ground formulations prepared using, xylitol (A), mannitol (B) and benzoic acid (C). Detailed formulations are shown in Table 1.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) of pure amiodarone, pure excipients and co-processed formulations are shown in Figure 2. Amiodarone thermogram showed the characteristic endothermic peak with onset of 141ºC, endset of 162ºC and Tm at 159.4ºC, indicating a crystalline nature of the drug. Immediately after the fusion event an exothermic shoulder was observed and can be taken as drug degradation. This thermogram is in good agreement with published data for the same drug.[3,19]

For xylitol (Figure 1A), the thermal event showed sharp endothermic peak at Tm of around 95.1ºC corresponding to the release of the adsorbed moisture [16]. A broad endothermic peak at about 313ºC can be taken as decomposition of the sugar. The thermogram of co-processed drug and xylitol revealed peak broadening and shifting to lower temperature. The main peak of amiodarone in the binary mixtures FX1 and FX3 reduced to 114 and 109ºC, respectively. This indicates partial amorphousization of the drug. This was accompanied by broadening of the decomposition peak of the sugar and shifting to lower Tm of about 203ºC.

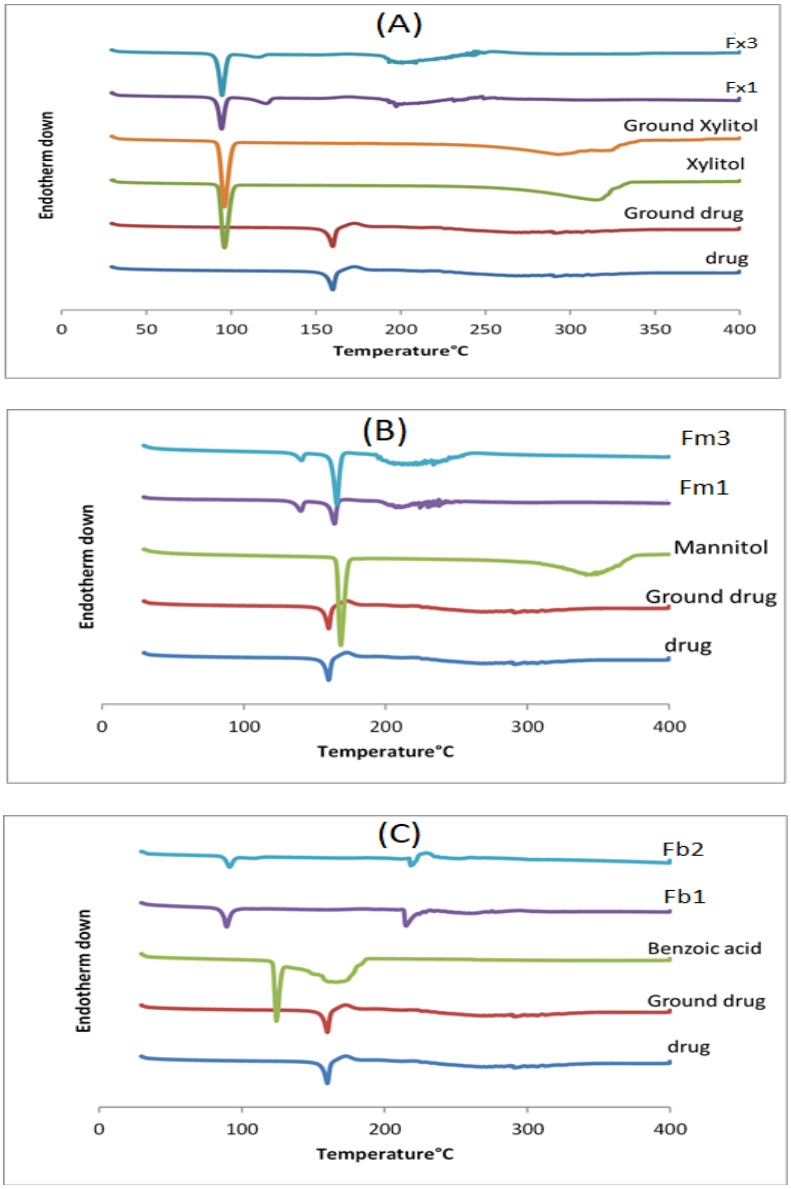

Figure 2: DSC thermograms of amiodarone from different co-ground formulations prepared using, xylitol (A), mannitol (B) and benzoic acid (C). Detailed formulations are shown in Table 1.

The thermogram of pure mannitol (Figure 2B) showed a sharp endothermic peak with Tm of about 167.6ºC, corresponding to melting of the sugar. In addition, a broad peak was recorded at 349.35ºc reflecting its decomposition at such high temperature. Similar thermogram was report for the same excipient [17]. The thermogram for the binary co-processed mixtures FM1 and FM3 showed three thermal events with broadening and shifting of drug characteristic peak. The first event was recorded at about 133ºC and can be attributed to the partial transformation of the drug to amorphous form. The second (at 167ºC) and third (at 204ºC) events are for the fusion and degradation of the sugar, respectively.

Regarding benzoic acid (Figure 2C), there was a sharp endothermic peak with Tm of about 123.8˚C.[18] For benzoic acid co-processed mixtures both the endothermic peaks of amiodarone and the co-former disappeared and new peaks at 88.1 ˚C and 213.2 ˚C were detected. This may suggest formation of new species, most probably salt form.

Powder X-ray Diffraction (PXRD)

Figure (3) shows the recorded X-ray difractograms of the unprocessed and processed amiodarone, excipients and their co-processed products. The characteristic diffraction peaks of unprocessed amiodarone were noticed at 10.1, 16.1, 18.76, 19.42, 20.71, 21.4, 23.26, 28.09, 28.24, 32, 34.9 and 37.93º. This diffractogram is in good agreement with the reported data for the same drug[19]. Dry grinding of amiodarone for 30 minutes produced diffractogram with the main diffraction peaks but of lower intensity and slight broadening. Such changes were previously taken as a result of size reduction[20].

The characteristic diffraction peaks of Xylitol shown in Figure 3A were recorded at two theta of 14.2, 14.8, 17.9,

19.9, 22.5, 22.8, 23.8, 24.9, 25.4, 28.4, 29.6, 30.5, 31.8, 33.6, 35.9, 36.4, 38, 38.5, 39.8, 41.9, 44.4 and 49º. This is similar to published values for xylitol and reflects the crystalline nature of the sugar[16] The diffractogram of the grinded xylitol showed a similar pattern of unprocessed form with less sharpness most probably due to reduced particle size.

For mannitol (Figure 3B), the diffractogram showed a typical crystalline form with the main diffraction peaks appears at 10.45, 11.47, 14.5, 18.58, 20.39, 21.25, 23.23, 24.4, 25.85, 28.24, 29.38, 31.63, 32.62, 33.43, 35.74, 38.65, 42.73 and 44º (Figure 3B). This diffractogram is in agreement with the previously reported data[17]. The X-ray spectra of co-grinded drug with either xylitol or mannitol showed the sum of the diffraction peaks for sugars as well as the drug. This indicates no interaction between the drug and the excipients and confirms the results of the DSC. This support the results of FTIR and DSC (see above).

Regarding benzoic acid (Figure 3C), the diffractogram reflects its crystalline property with multiple diffraction peaks at two theta values of 7.87, 16.39, 16.78, 18.88, 20.68, 23.44, 23.86, 25.62, 27.46, 29.53, 34.45, 36.7 and 38.44º. This diffrcatogram is similar to the published data for the same material. [18] For co-processed drug with benzoic acid produced crystalline materials having slight compromised X-ray diffraction pattern compared with that of the individual components of the co-ground mixture. The appearance of new diffraction peaks at 11.6 and 13.8º would indicate formation of new species. This result coincides with the DSC data that suggested salt formation between the drug and the additive.

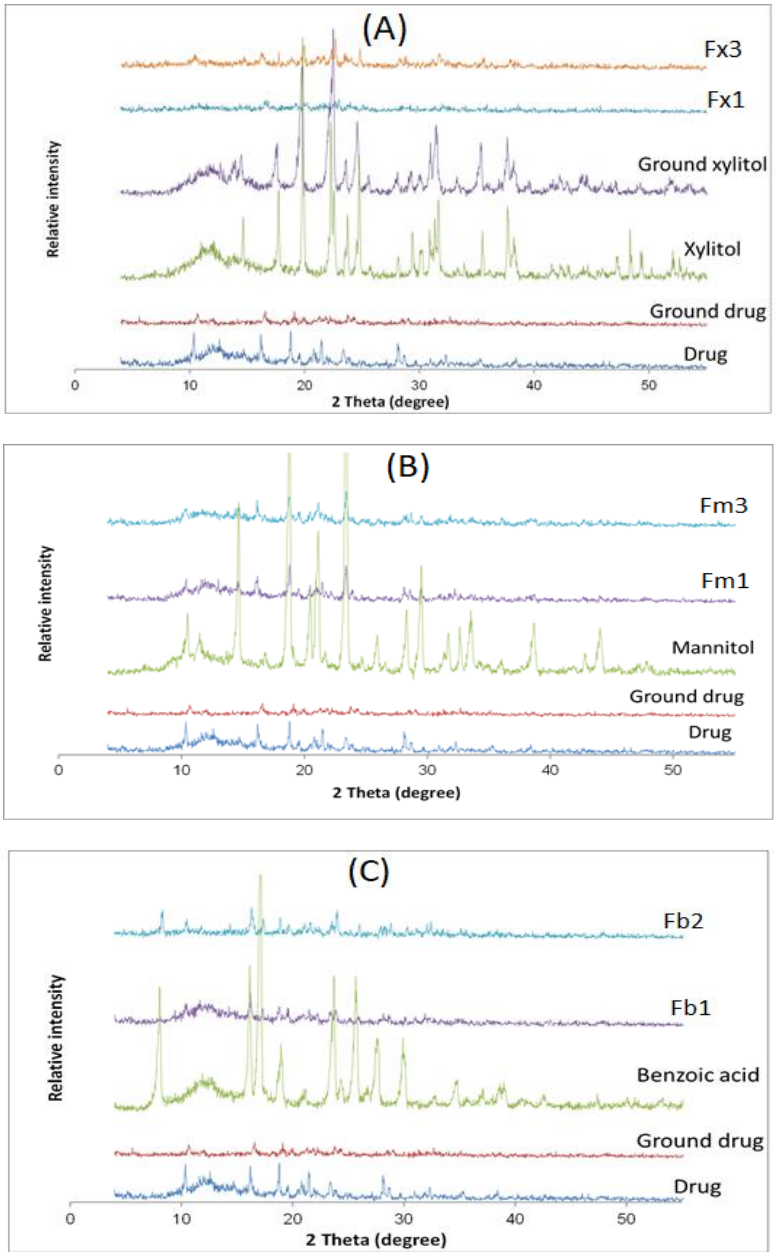

Figure 3: Powder X-ray diffractograms of amiodarone from different co-ground formulations prepared using, xylitol (A), mannitol (B) and benzoic acid (C). Detailed formulations are shown in Table 1.

***In vitro* drug dissolution studies**

The cumulative amount of drug released were plotted against time to obtain the dissolution profiles (Figure 4). The dissolution parameters are presented as the amount released after 5 minutes of the dissolution time (Q5) and the dissolution efficiency in Table1. The latter was calculated using the area under the dissolution profile at time t in relation to the area of the rectangle described by 100% dissolution in the same time [21].

Unprocessed amiodarone, negative control, showed slow dissolution indicating its poor solubility with Q5 of 25%. The calculated dissolution efficiency was 49%. This performance could be due to its hydrophobic nature in addition to its crystalline structure as shown by DSC and X-ray diffraction data. Similar dissolution pattern for the same drug was previously reported[3]. For positive control, ground drug, there was a slight improvement in dissolution, most probably due to particle size reduction as reflected from the X-ray diffractogram. Reducing particle size is expected to hasten dissolution as a result of increased surface area in contact with the dissolution media, in accordance to Noyes-Whitny equation [22,23].Though the increase in Q5 was insignificant ($P > 0.05$), the overall dissolution efficiency was significantly higher than that for the negative control ($P < 0.05$). As our aim was to formulate rapidly dissolving tablets of amiodarone, a prompt initial release was important. Therefore, amiodarone was co-ground with inert materials expected to produce co-crystal with the drug while maintaining their function as excipients used in formulating fast disintegrating tablets (i.e. sweetening agents).

Xylitol was successively used as co-crystal conformer to felodipine[16]. Therefore, xylitol was tested as a potential co-crystal co-former to amiodarone. Amiodarone:xylitol co-grinded mixtures were prepared at different molar ratios of 1:3, 1:5 and 1:7 (Fx1, Fx2 and Fx3, respectively). The dissolution profiles are shown in Figure 4A. Though solid state characterization didn't confirm co-crystal formation, drug dissolution was significantly improved compared to control. The enhancement in dissolution parameters increased by increasing xylitol content in the formula. The initial amount of amiodarone liberated from formula Fx2 (1:5 drug:xylitol) was higher than that for Fx1 (1:3), though similar dissolution efficiency was obtained ($P < 0.05$). Formula Fx3 (1:7 molar) was superior compared to other two mixtures with prompt release of 88±2.6% of loaded dose after 5 minutes. Dissolution efficiency was similarly improved reaching about 80%. The improved dissolution of drug after neat grinding with xylitol could be due to the reduced particle size, as shown by X-ray data. Partial amorphousization, as reflected by DSC results, and possible adsorption of drug over the excipient surface should be taken into account.

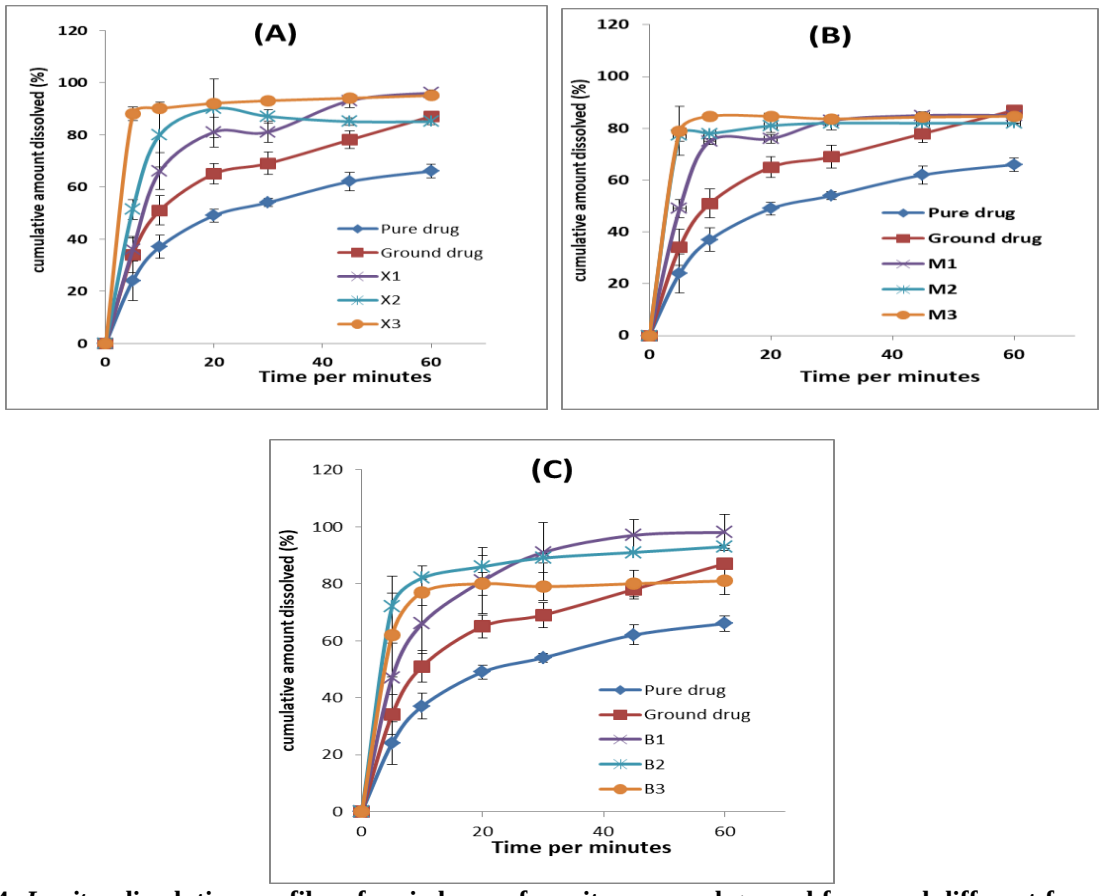

Figure 4: *In vitro* dissolution profiles of amiodarone from its pure and ground form and different formulations prepared using xylitol (A), mannitol (B) and benzoic acid (C).

Mannitol was previously used as co-crystal conformer for hydrochlorothiazide with reported marked improvement in drug dissolution [24]. Therefore, it was selected as potential co-crystal conformer for amiodarone. In addition to its sweet taste and cooling effect, mannitol has good compactibility [25]. The dissolution profiles for co-grinded mixtures using mannitol are shown in Figure 4B and dissolution parameters are listed in Table 1. As for xylitol, mechanochemical treatment of the drug with mannitol markedly increased drug dissolution compared to either negative and positive control. Both Fm2 and Fm3 showed similar dissolution parameters ($P>0.05$) indicating that 1:5 molar ratio is the optimum ratio. The reason for the obtained results can be explained as for xylitol.

For Benzoic acid-amiodarone co-grinded mixtures, the dissolution profiles indicated improved dissolution of amiodarone relative to unprocessed drug, as well as positive control (Figure 4C). In addition to the above mentioned reasons for the enhancement of drug dissolution after neat co-grinding with xylitol and mannitol, such improvement could be due to salt formation. This salt was a result of possible interaction between the amine group of amiodarone and the carboxylic group of benzoic acid. The assumption of salt formation was proved by the instrumental analysis of the prepared mixtures. It worth noting that benzoic acid was successively used as co-crystal co-former with theophylline, where co-crystallization was induced in solution via slurry and cooling crystallization [26]. It seems that mechanochemical technique adopted in our work was not enough to initiate the interaction between amiodarone and benzoic acid.

Evaluation of oral dispersible tablets

According to the *in vitro* release studies, optimum co-processed binary systems were selected for each excipient and used to prepare ODT. Therefore, co-processed mixture FX3, FM3 and FB2 were selected from co-processed amiodarone with xylitol, mannitol and benzoic acid, respectively. For comparison, control tablets were prepared containing unprocessed drug. Tablets were prepared using direct compression technique and prepared to contain an amount equivalent to 100mg of drug after adding suitable excipients, importantly the superdisintegrants croscarmellose and crospovidone (Table 2).

All tablet batches were subjected to quality evaluation and the results were judged according to the acceptance criteria for USP 2000. All batches were of acceptable weight ranging from 397 to 407mg with a percent deviation of less the ±2% indicating good flowability of the powder blend and suitability for tableting. The uniformity of drug in tablets ranged from 97 to 103% of the stated potency reflecting efficient mixing. Tablet hardness was found to be in the range of 5.2 and to 5.8 Kp with a good friability values ranging from 0.6 to 0.9% indicating that the tablets will withstands handling and transportation. Though tablets showed good hardness and friability values that coincide with the USP specifications, nevertheless all batches showed rapid disintegration within short time ranged from 10 seconds for control tablets up to 33 seconds for xylitol tablets. Wetting time was very short and coincide with the disintegration time values (Table 2). This indicates that the used superdisintegrant was at its optimized concentration.

Regarding *in vitro* dissolution studies, the results are presented as cumulative amount released versus time plots in Figure 5. Control tablets, (containing unprocessed drug) showed Q5 of 54.5%. This is significantly higher than that obtained from pure drug powder. This could be due to adsorption of drug particles over the tablet additives leading to increased surface area. The total dissolution efficiency was similarly increased to 65%. Fast disintegrating tablets prepared using different co-ground mixture of the drug with each one of the used excipients showed prompt release of drug with benzoic acid tablets being superior to other excipient with the release of 85% of the loaded dose within 5 minutes (Table 2).

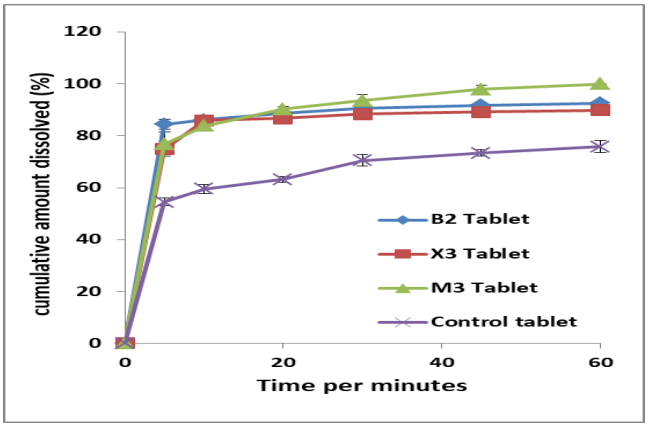

Figure 5: In vitro drug released from different fast disintegrating tablets prepared using unprocessed drug (control tablet), or co-processed drug with either mannitol (M3 tablet, xylitol (X3 tablet) or Benzoic acid (B2 tablet). For detailed formulations refer to Table 2.

CONCLUSION

The results of this study negate the suitability of mannitol, xylitol and benzoic acid as potential co-crystals conformer. However, the study introduced these additives as promising excipients for enhanced dissolution rate of amiodarone after dry co-grinding. Solid state characterization suggested reduced crystallinity and particle size of the drug as the main reason for such enhancement, in addition to adsorption over the used excipient. For benzoic acid, salt formation was added factor, as evidenced by physical characterization. Salt formation in absence of water is considered advantageous to eliminate concerns about residual solvent. The co-ground mixtures were successfully formulated into oral dispersible tablets that will liberate most of the labeled drug immediately after administration.

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