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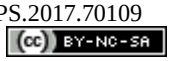
ISSN 2231-3354 

Fast disintegrating tablets of amiodarone for intra-oral administration

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ABSTRACT

Amiodarone is antihypertensive drug with variable bioavailability following oral administration due to poor solubility and pre-systemic metabolism. Accordingly, the study strategy was to enhance the dissolution rate of the drug by solid dispersion (SD) and surface solid dispersion (SSD) techniques, with optimum formulations being developed as fast disintegrating tablets with rapid release. Binary and ternary SD were prepared using Pluronic F68, Pluronic F127 and PVP k30 as the hydrophilic polymers. SSD were prepared employing Pluronics and Aerosil as polymer and carrier, respectively. Both SDs and SSDs increased the dissolution rate compared to pure drug and physical mixtures. Thermal analysis revealed reduced drug crystalinity Ternary SD and SSD were selected to prepare a series of fast disintegrating tablets. Unprocessed drug in the fast disintegrating matrix was used as control. Tablets were prepared by direct compression technique using croscarmelose as superdisintegrant. Effect of using Avicel PH102 or mannitol as filler was also investigated. All tablets showed better dissolution parameters compared to control. Tablets prepared using SSD and employed mannitol showed the highest drug release after 5-min. The study thus developed fast disintegrating tablets with rapid drug dissolution with the potential of increased oral bioavailability by reducing pre-systemic metabolism due to Pluronic polymers.

INTRODUCTION

The oral route of drug administration is more convenient for patients, with tablet considered as the most popular solid oral dosage form used today (Helliwell and Taylor, 1993). However oral administration of drugs has disadvantages such as first pass metabolism and enzymatic degradation within the GI tract (Shojaei, 1998). A major challenging problem facing pharmaceutical scientists is the formulation of poorly water-soluble drugs and it is expected to increase because approximately 40% or more of the new chemical entities evolved through drug discovery suffer from poor water solubility (Lipinski, 2002). Many techniques were used to enhance the solubility to face the formulation challenge but with limited use such as micronization, solubilization using cosolvents and permeation enhancers (Aungst, 1993 ; Aungst, 2000), solid dispersion (El Maghraby and Alomrani, 2009) and surface solid dispersion (Lawrence and Rees, 2000). However, more successful strategies were used such as microemulsions (Lawrence and Rees, 2000), inclusion complexes employing cyclodextrins (Essa and Balata, 2012), solid lipid nanoparticles and lipid formulations (Pouton, 2000). A new intra-oral formulation has gained interest recently called rapidly disintegrating and dissolving oral tablets. It is claimed to allow fast disintegration and rapid local drug dissolution with subsequent absorption from oral mucosa reaching the systemic circulation (Bhowmik *et al.,* 2009). An additional advantage of this dosage form is the convenience for children and elderly patients, stroke victims and patients with swallowing difficulties. This type of tablets improves safety due to reduced risk of chocking or suffocation during oral administration of conventional type (Parkash *et al.,* 2011). The main problem of such dosage form is the need for fast disintegration and rapid drug dissolution in small volume of saliva. Optimizing drug dissolution rate is thus the main limiting factor in formulation of these systems (El Maghraby and El Sergany, 2014). Amiodarone, antiarrhythmic drug, is a class II drug according to biopharmaceutical classification system (Emami, 2010; Elgart *et al.,* 2013). It is highly lipophilic with a log P of 7.57 (Avdeef *et al.*, 1997).

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This means that the dissolution rate of the drug is the rate limiting step in its absorption after oral administration (Yasir *et al.,* 2010). For this type of drugs, poor solubility and slow dissolution rate will result in slow absorption which is the primary reason for inadequate and variable bioavailability of the drug (Pillay *et al.,* 2011). In addition, amiodarone suffers from presystemic metabolism which provides an additional reason for reduced oral bioavailability of the drug (Gavhane and Yadav, 2012). It has low and variable bioavailability averaged to about 22 ± 65% (Pourbaixs *et al.,* 1985). Rapid disintegration with subsequent fast dissolution is thus expected to increase the bioavailability of this drug by exposing large amount of the drug to the metabolizing enzyme. This can provide greater chance for the drug to escape from the metabolism due to enzyme saturation (El Maghraby and El Sergany, 2014).

Up to date, few studies have been made to improve amiodarone bioavailability via oral route such as, complexation with ß-cyclodextrin (Riekes *et al.,* 2010), self –nano-emulsifying drug delivery system (Patel *et al.,* 2015; Elgart *et al.,* 2013) and amiodarone Hcl in binary solid dispersion (Zhao, 2008).

Accordingly the aim of this work is to enhance the dissolution rate of Amiodarone Hcl with the goal of formulating rapidly disintegrating oral tablets with subsequent fast dissolution. Solid dispersion and surface solid dispersion techniques were adopted for this purpose with different hydrophilic polymers being included as dissolution enhancers. Pluronics, tri-block copolymers, were used due to their known inhibiting effect on CYP3A4, an enzyme that contribute to hepatic metabolism of many drugs, including Amiodarone.

MATERIALS AND METHODS

Materials

Amiodarone Hcl, Polyvinyl pyrrolidone (P.V.PK30), and Pluronic F68 were supplied as a gift sample from Pharco pharmaceutical industries, Egypt. Croscarmellose sodium, Crosspovidone, magnesium stearate, PluronicF127, Avicel PH 102 FMC, Aerosil and mannitol were supplied as a gift samples from Sigma pharmaceutical industries, Egypt. Sodium lauryl sulfate, methanol, ethanol and dichloromethane were of high purity purchased from El-Nasr Co. for intermediate chemicals.

Method

Preparation of solid dispersions

Binary and ternary solid dispersions (SD), using different polymers, were prepared using solvent evaporation technique (Essa and Dwaikat, 2015). Table 1 represents the composition of the prepared solid dispersion formulations. The drug was dissolved in the least amount of a solvent composed of dichloromethane: ethanol 3:1, respectively. The required amount of polymer was added under stirring until complete solubility. Mixing was continued in a fume hood under ambient pressure and temperature until complete evaporation of the solvent. The residue was stored in a desiccator over silica gel at room temperature for 1-2 days until complete drying. The dry product was grinded and sieved through a 500µm sieve and stored in a tightly closed amber container.

Preparation of surface solid dispersion

Surface solid deposition (SSD) was prepared according to the compositions shown in Table 1. The aim was to increase the exposed surface area so as to improve drug dissolution. Additionally, improved powder flowability is expected which is an important criteria for good tablet manufacturing. Both drug and polymer were dissolved in the least amount of the solvent till a viscous phase was obtained.

Aerosil was then added with continuous stirring using magnetic stirrer at ambient temperature till complete solvent evaporation. The dry product was grinded and passed through a 500µm sieve and kept in a tightly closed amber container until use.

Preparation of physical mixtures

Physical mixtures (PM) were prepared for all SD and SSD formulations shown in Table1. This was achieved by geometric dry blending of the drug and polymer with the aid of a mortar and a pestle. The physical mixtures were passed through a 500µm sieve and packed in a tightly closed amber container.

Table: 1: Composition of the prepared solid dispersion(SD) and surface solid dispersion systems (SSD).

	formulation	Amiodarone	Pluronic F127	Pluronic F68	P.V.P K30	Aerosil	Q5	%DE
	control	1	0	0	0	0	25.2± 0.9	34±1.7
Binary Solid	**SD1**	1	0.5	0	0	0	85.2±0.95	87±2,5
Dispersion (SD)	**SD2**	1	1	0	0	0	91.8± 4.03	95±0.7
	SD3	1	2	0	0	0	72.0±2.7	87±0.28
	SD4	1	0	0.5	0	0	88.6±3.58	94±1.45
	SD5	1	0	1	0	0	85.8±5.1	95±0.77
	SD6	1	0	2	0	0	82.6±4.2	86±1.02
	SD7	1	0	0	0.5	0	46.3±0.94	70±2.46
	SD8	1	0	0	1	0	88.9±0.35	91±0.32
	SD9	1	0	0	2	0	57.9±3.3	72±1.12
Ternary SD	**SD10**	1	0.5	0	0.5	0	85.9±5.3	92±0.79
	SD11	1	0	0.5	0.5	0	70.3±2.95	91±2.27
Surface solid	**SSD1**	1	0.5	0	0	0.25	76.4±4.22	89±1.6
deposition SSD	**SSD2**	1	0	0.5	0	0.25	46.1±0.88	75±0.313

Drug content

The drug content was measured for all formulations by dissolving an amount equivalent to 25 mg of the drug in a 50 ml volumetric flask using methanol: dichloromethane (1:1). Then 1ml of the stock was diluted to in 50 ml flask using methanol as a solvent. The drug content was measured using the UV spectrophotometer (Thermo, EVO 300PC, USA) at wavelength of 242 nm.

Physical characterization of the prepared formulations:

Differential thermal analysis

Thermograms of the samples (amiodarone, polymers, SDs, SSDs and sample physical mixtures) were recorded using differential thermal analysis (DTA). Samples equivalent to 3 mg of the drug were loaded into aluminum pans and the lids were crimped using a shimadzu crimper. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 ^{o}C/min, covering a temperature range of 25-250 ˚C. The instrument was calibrated with an indium standard. Data analysis was conducted using TA-60 WS thermal analysis software.

Fourier-transform infrared spectroscopy

FTIR spectra of amiodarone, polymers and their binary SDs were recorded using BRUKER FT-IR spectrometer, Jermany. Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 5000 to 400 cm-^{1}.

Flow characteristics of tablet powder blend:

Flowability studies were conducted for each tablet mixture presented in table 2. The bulk density (ρb) was determined by pouring fixed weight of powder blend into a graduated cylinder and the bulk volume (Vb) was determined. The bulk density was calculated by dividing mass over volume. The tapped density was determined through tapping the measuring cylinder containing a known weight (M) of the powder for 15 minutes or until fixed volume.

The minimum volume occupied (V_t) in the cylinder was measured and the tapped density (ρ_t) was calculated using the equation ($\rho_t = M/V_t$). For each sample, Carr's compressibility index (CI) was calculated according to the following equation: CI =100 (ρt-ρb/ρt). Additionally, Hausner ratio (HR) was also calculated using the following equation: HR== ρt/ ρb

Preparation of fast disintegrating tablets

Fast disintegrating tablets were prepared using direct compression technique according to the compositions shown in Table2. Crosscarmelose sodium and sucralose were used as superdisintegrant and sweetening agent, respectively.

Unprocessed drug (control tablet) or its equivalent of SD or SSD was mixed with the excipients using the bottle method, before compression into tablets, weighing 580mg each. This process employed single punch tablet machine (Royal Artist, Mumbai, India) using 8mm punch. The compression force was adjusted to produce tablets having a hardness of about 4-5 Kp (El Maghraby and El Sergany, 2014).

Evaluation of fast disintegrating tablets:

Uniformity of weight:

The USP weight variation test was conducted by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The allowed percentage deviation is 7.5%. The tablets meet the USP test if no more than two tablets are outside the limit and no tablet differs by more than twice the limit (USP, 2000).

Tablet friability

The friability of the tablets was measured in friabilator (Varian, USA). A pre-weighed tablet sample (20 tablets) was placed in the friabilator and subjected to 100 revolutions. The tablets were carefully deducted and weighed again. The friability was calculated as the percentage loss which should not exceed 1%.(USP, 2000).

Drug content

To ensure uniform potency, a content uniformity test was applied by random selection of 30 tablets. At least 10 tablets of them were individually subjected to drug content determination. The tablets were considered acceptable if the content of each of at least 9 tablets was in the range of 85-115% of the labeled amount of Amiodarone.

The tenth tablet should not contain [<75% or ≥125%] of the labeled content. If these conditions were not met, the remaining 20 tablets must be analyzed individually and all of them should be within the limit (USP, 2000).

Table: 2: Master formula for Amiodarone fast disintegrating tablets.

ingredients	F1 of (SSD1) (mg/tablet)	F 2 of (SSD2) (mg/tablet)	F3 (SD10) (mg/tablet)	F4 (SD11) (mg/tablet)	F 5 Control tablet(mg/tablet)
Amiodarone or an equivalent formulation	350	350	400	400	200
Mannitol	0	157.5	0	0	0
Avicel PH 102	150	0	100	100	300
Croscarmellose sodium	25	25	25	25	25
Crospovidone	37.5	37.5	37.5	37.5	37.5
Magnesium stearate	10	10	10	10	10
sucrolose	7.5	0	7.5	7.5	7.5
Total tablet weight (mg)	580	580	580	580	580

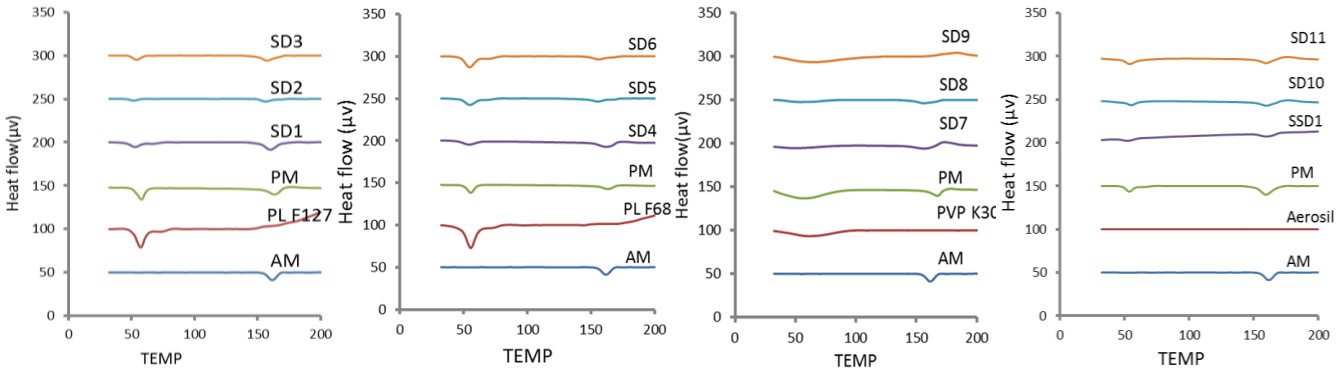

Fig. 1: Differential thermal analysis (DTA) of Amiodarone, polymers, solid dispersions (SD), surface solid dispersions (SSD) and corresponding physical mixtures (PM).

Disintegration test

The test was carried out on six tablets using tablet disintegration tester (Copley Scientific NE4-cop Nottingham, UK). Distilled water maintained at 37°C±2 was used as the disintegration media. The time required for complete disintegration of the tablets with no remaining palpable mass was recorded (Parmar *et al.*, 2009).

Wetting time

The wetting time of the tablets was monitored by placing a filter paper in a Petri dish containing 6ml of distilled water. A small amount of Allura red powder was placed on the surface of tablet before placing the tablet on the wet filter paper. The time required for developing a red color on the surface of tablet was recorded and taken as the wetting time (Jain and Naruka, 2009).

Dissolution studies

The dissolution rate of Amiodarone from different formulations were determined using the USP apparatus type II (Copley , Nottingham, UK), rotating at 100 rpm and maintained at 37°C C ± 0.5. The dissolution medium (1000ml) comprised of 1% sodium lauryl sulfate in distilled water. Samples were withdrawn at predetermined time interval for 90 min, filtered through a 0.45 µm membrane filter and the dissolution medium was suitably replenished after each sample. The samples were suitably diluted with the dissolution media before UV-analysis. The cumulative amount of Amiodarone dissolved (expressed as % of the labeled amount) was plotted as a function of time to produce the dissolution profile. The dissolution efficiency was obtained from the area under the curve of the dissolution profile using the non-linear trapezoidal rule and demonstrated as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).

RESULTS AND DISCUSSION

Content uniformity

The drug contents of the prepared SDs and SSDs were in the acceptable range. The drug content values were in the range of 96.5-105.5% w/w, excluding any segregation of the drug or polymer during formation.

Solid state characterization of SDs

Differential thermal analysis

Differential thermal analysis (DTA) of pure amiodarone, pure polymers, SDs and SSDs are shown in Figure 1. Pure drug produced a characteristic endothermic peak with a T_m being recorded at 161.4 ˚C, indicating a crystalline nature of unprocessed drug. This thermogram is in good agreement with published data for the same drug (Riekes *et al.*, 2010). For polymers, thermograms showed a characteristic broad peak for PVP at $T_m$of around 90 ˚C corresponding to the release of the adsorbed moisture. For Pluronic F127 and F68, there was a sharp endothermic peak with T_m of about 58.3˚C, corresponding to melting of the polymer, in agreement with the previously reported values (El Maghraby and Alomrani, 2009; Essa and Dwaikat, 2015). DTA traces for binary physical mixtures prepared using Pluronic F127 and F68 (at 1:1 drug:polymer concentration) showed reduction in the T_m and enthalpy of the endothermic peak of the drug. This could be due to the gradual interaction of the drug with the melted polymer that melts at much lower temperature, during the heating process. Similar explanation was suggested for recorded thermal pattern of the same material with other drugs in a physical mixture (Essa and Balata, 2012). Those prepared using PVP did not show a significant change in T_m. For SD and SSD formulations it is clear that increasing concentration of the polymer resulted in initial decrease in the$T_m$with peak broadening. The enthalpy was reduced gradually with increasing polymer concentration. This would indicate the possible transformation of the drug from the crystalline state to amorphous form.

Fourier-transform infrared spectroscopy

Figures 2-4 show the IR spectra of amiodarone, PLf127, PLf68, PVPK30 in pure state or as binary SDs with the drug. The spectrum of the pure drug shows absorption bands between 2800 and 3250 cm-¹, due to the stretching of aromatic and aliphatic C-H bond. The N-H+ stretching produced a band at 2476 cm-¹.

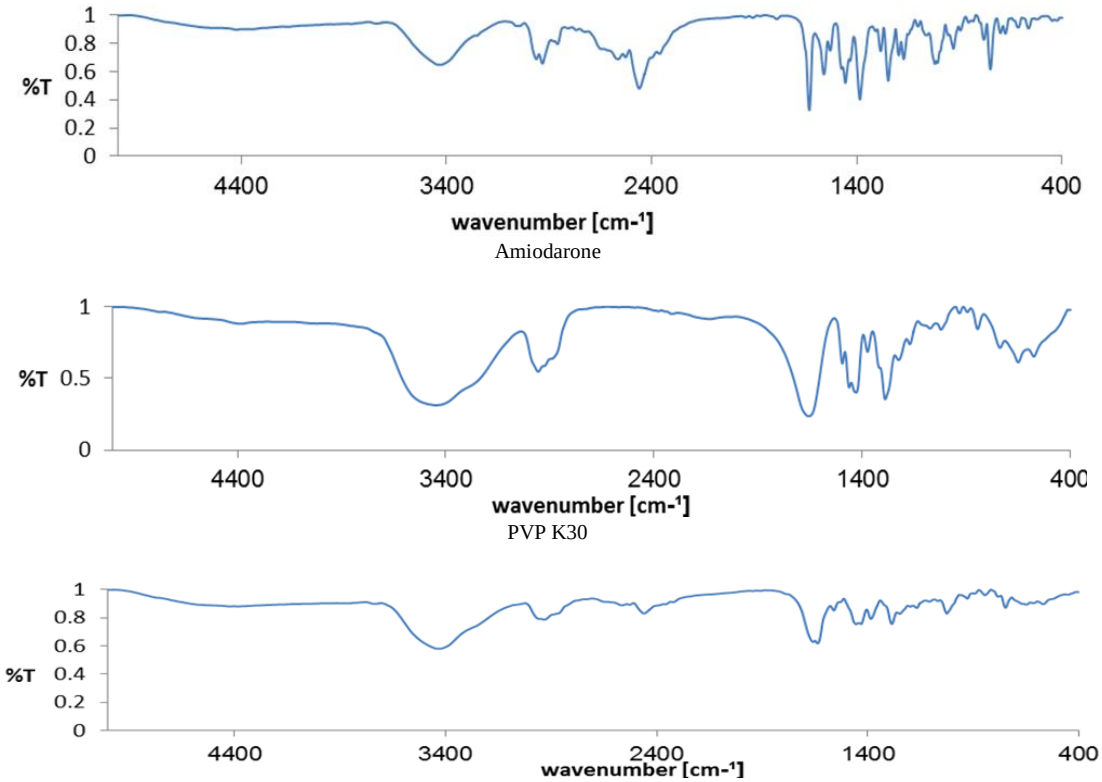

Fig. 2: FTIR spectra of Amiodarone, PVP K30 and their solid dispersion formulations.

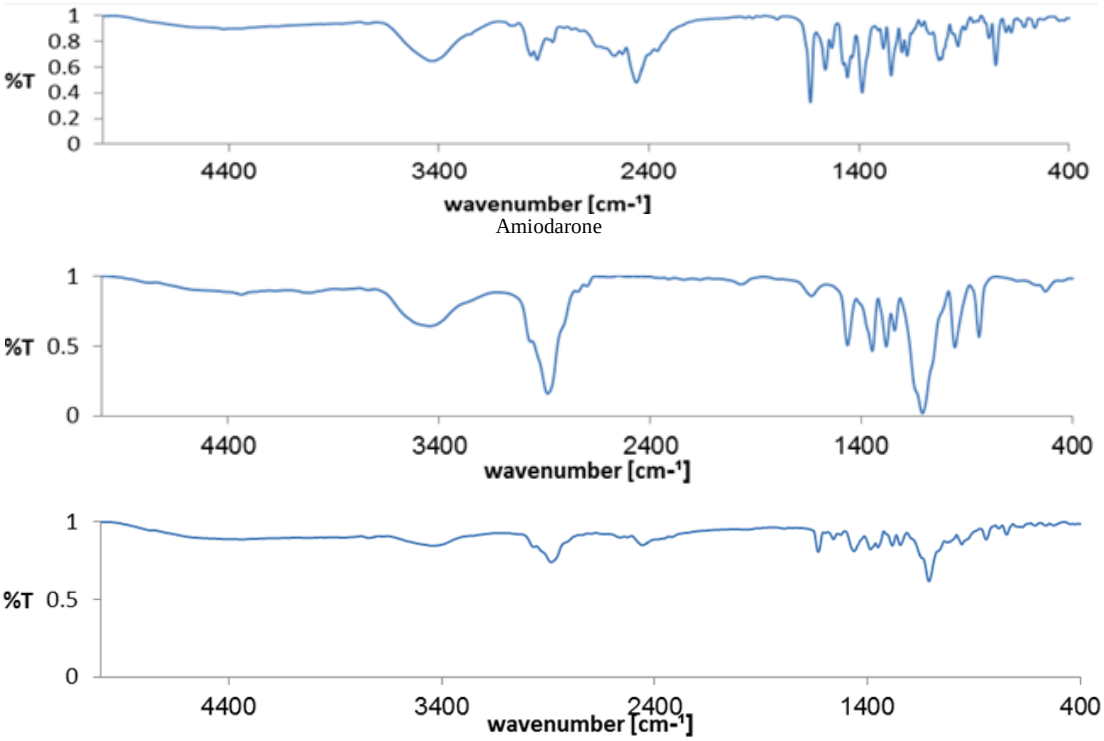

Fig. 3: FTIR spectra of Amiodarone, Pluronic F127 and their solid dispersion formulations

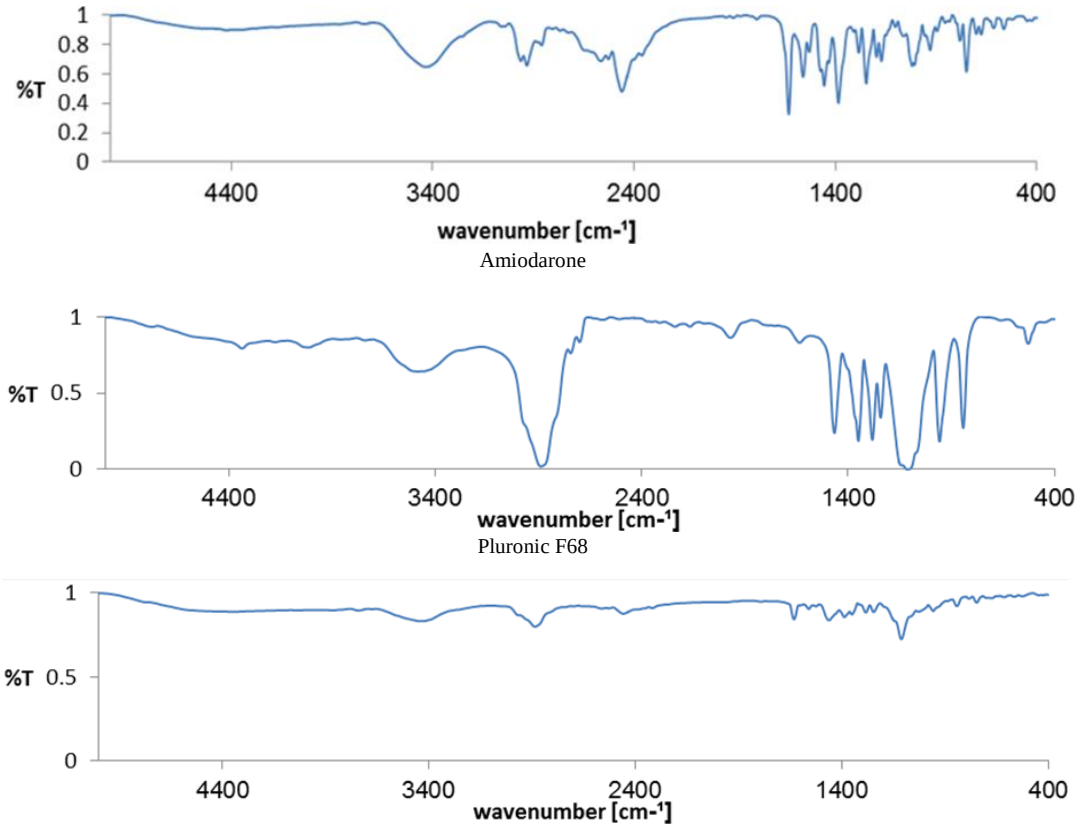

Fig. 4: FTIR spectra of Amiodarone, Pluronic F68 and their solid dispersion formulations.

Strong absorption band at 1635 cm^{-1} is attributed to carbonyl group of diiodophenylketone moiety of the compound. Stretching of C-N group produced a strong band at 1375 cm^{-1}. A band at 1249 cm^{-1} can be attributed to the ether group C-O-C stretching. The band at 1026 cm^{-1} is indication of furan ring breathing (Plomp *et al.*, 1992). The FTIR spectrum of pure PVP K30 (Figure 2) produced a characteristic absorption band at 1658 cm^{-1}. This can be attributed to the carbonyl group (Goddeeris and Vanden Mooter, 2008). The very broad band at 3440 cm^{-1} indicates the presence of moisture, revealing the hygroscopic nature of PVP K30. The FTIR spectrum of Pluronic F127 (Figure 3) showed characteristic peaks at 2971 and 2887 cm^{-1} due to C-H stretching vibration. The absorption band at 1469 cm^{-1} is attributed to C-H group bending vibration. The characteristic peaks at 1345, 1242, 1281, 1148, 1113 and 1061 cm^{-1} indicates C-O stretching vibration. This correlates well with the published spectrum for the surfactant (Parmar *et al.*, 2009). The FTIR spectrum of pure Pluronic F68 (Figure 4) showed a broad band at 3460 cm^{-1} which is due to the O-H group with a strong band at 2880 cm^{-1} due to aliphatic C-H bond. The C-O bond stretching appeared at 1112 cm^{-1}. This correlates well with the published spectrum for the surfactant (El Maghraby and Alomrani, 2009). The FTIR spectrum of the solid dispersion of the drug with PVP K30 (Figure 2) revealed the main absorption bands of the drug but the band corresponding to the C-H stretching overlapped with that of the C-H stretching vibration of PVP K30. Overall, the recorded spectrum indicated no interaction between the drug and PVP K30. For the binary solid dispersion with Pluronic F127 the spectrum (figure 3) is the sum of the spectra of the drug and polymer with the main bands being clear except for the overlapping of the band between 2880 – 2980 cm^{-1} indicating the stretching vibration of C-H bond for both the drug and polymer. This suggests that there is no interaction between the drug and Pluronic F127. Similarly, the solid dispersion of the drug with Pluronic F68 (Figure 4) did not result in significant interaction between the drug and the polymer Pluronic F68.

In vitro drug release from SD and SDD formulations

Dissolution profiles of all formulations and their physical mixtures are presented in Figure 5 as cumulative drug released versus time plots. Dissolution parameters represented as the percentage drug released after 5 min (Q_5), and the percentage dissolution efficiency (%DE) after 90 minutes were calculated and are presented in Table 1. Unprocessed drug showed slow drug dissolution with Q5 and %DE about25% and 35%, respectively. This is due to the poor drug solubility. For physical mixtures, blending the drug with the polymers significantly ($P<0.05$) improved dissolution parameters compared to pure drug with Q5 ranged from 42% (PM 9) to a maximum of 59% (PM 8) giving average of 2-fold enhancement in Q5. This could be attributed to the improved wettability of the hydrophobic drug particles due to the hydrophilic polymers (Ahuja *et al.*, 2007).

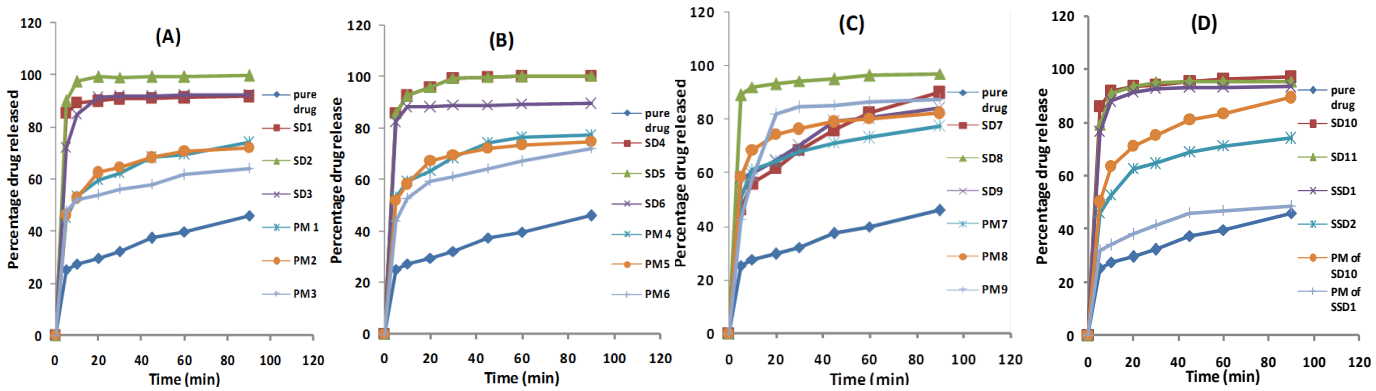

Fig. 5. Dissolution profiles of solid dispersion (SD) prepared using Pluronic F127 (A), Pluronic F68 (B), and PVP K30 (C), ternary SD and surface solid dispersion (SSD) formulations (D) together with their physical mixtures.

Preparation of the drug as binary SD with different polymers resulted in significant ($P<0.05$) increase in drug dissolution over that of physical mixtures and pure drug (Figure 5A-C). There was a prompt drug release with Q5 of a minimum value of 57% in SD7 to a maximum of 94% in SD4. The enhanced dissolution rates of SDs could be due to decreased drug crystalline structure as evidenced by DTA data. Another contributing factor could be increased drug wettability due to the hydrophilic carrier as both drug and carriers are in close proximity to each other (Tantishaiyakul *et al.*, 1999). In dissolution media, aggregation and agglomeration of the drug particles are barely present in SD, as dispersed drug particles are surrounded by and enclosed within the polymeric carrier particles (Chiou, 1971). It worth noting that there was a trend of reduced dissolution parameters at the higher polymer ratio of 1:2 (drug: polymer).This was more noted in SDs prepared using PVP (Figure 5C), most probably due to the increased viscosity as a result of the high molecular weight of the polymer and possible increased polymer chain entanglement leading to slow drug movement through the diffusion layer.For SDs prepared using Pluronics, this could be accredited to the thermoreversible gelation phenomenon of the polymer (El Kordy *et al.*, 2012). Being at saturation solubility in the diffusion layer, Pluronics may be able to form gel at the temperature of the dissolution media that would otherwise slow down drug movement through diffusion layer (El Kordy *et al.*, 2012).

Addition of PVP as a ternary component to binary SD with Pluronics to obtain ternary SDs (SD10 and SD11) improved drug dissolution parameters over that of pure drug and physical mixtures (Figure 5D). However, they did not add any significant advantages over that of binary systems.

SSD technique is reported to improve dissolution of poorly water soluble drugs (Essa and Dwaikat, 2015; Abd Elbary *et al.*, 2011). Based on the dissolution parameters, SD1 and SD4 were selected as best binary SD formulations and were used to prepare SSD1 and SSD2, respectively. Both drug and polymer were deposited over Aerosil particle using solvent evaporation method. Figure 5D shows the dissolution profiles of SSDs and their physical mixtures compared to pure drug. There was a significantly higher dissolution parameters compared to their physical mixtures and unprocessed drug. SSD1 showed significant ($P<0.05$) improve in dissolution parameters with Q5 of 76% and dissolution efficiency of about 90% (Table 1). The enhancement may be due to the drug particles adsorbed over the carrier surface in an extremely fine state of subdivision or molecular form. The resulting decrease in particle size and the concomitant increase in the surface area increased greatly the dissolution of the drug compared to the drug alone. Therefore, SSD1 was used as drug matrix in preparing fast disintegrating tablets.

Characterization of fast disintegrating tablets

Fast disintegrating tablets were prepared by direct compression method, after using suitable formulation aids, according to compositions shown in Table 2. Direct compression was used due to its simplicity and cost-effectiveness, as it can be produced using conventional tablet manufacturing. In addition to the availability of various tableting excipients that can improve flow, compressibility and disintegration properties. Based on the obtained dissolution results of different solid dispersion formulations, ternary solid dispersions (SD10 and SD11) and surface solid dispersion SSD1 were used to prepare fast disintegrating tablets. The former were used to utilize the benefit of PVP K30 in producing tablets with good physical properties, while the later was used as it could offer powder with good flow properties due to the presence of Aerosil.

The manufacture of tablets on high speed machinery necessitates the attainment of powder blend with optimal flow in order to produce a product with uniform dosing. Therefore, it was necessary to study the flow properties of each powder mixture prior to compaction. The results of powder flowability are shown in Table 3.The smaller the Carr's Index the better the flow properties, powders with values between 5 and 18 are suitable for producing tablets. For Hausner ratio, values of <1.25 indicate free flowing powders, while values >1.25 reflects poor flow ability (Sinko *et al.*, 2006). All formulations showed a good powder flow properties and were suitable for manufacture of tablets. Powder mix for formula F1and F2 prepared using SSD of the drug showed better flow properties compared to other formulations due to the presence of Aerosil.

Table: 3: Results of powder flowability, quality control tests of tablets, percentage drug released after 5 minutes (Q5) and dissolution efficiency (DE) of Amiodarone from fast disintegrating tablets.

	Flowability of powder		Content uniformity (%)	Disintegration time (min:sec)	Friability (%)	Wetting time (min:sec)	Q5 (%)	DE (%)
	Carr's Index (%)	Hausner ratio						
F1	8.56±0.38	1.09±0.0	100.8±5.7	00:53±16	0.059±0.0	00:33±4	74± 0.5	93.5±0.7
F2	9.2±2.2	1.099±0.02	97.76±4.55	00:47±7.3	0.556±0.38	00:22±7.6	85± 3.8	93.1±1.2
F3	15.2±3.25	1.178±0.05	98.6±7.39	0:53±13.6	0.119±0.1	00:50±5	76 ±1.0	94.7±1.1
F4	15.4±0.88	1.176±0.01	97.5±6.68	0:58±9.3	0.25±0.1	1:15±15.5	76± 0.2	92.7±0.3
F5	16.2±1.95	1.19±0.03	98.33±3.238	1:18±14.8	0.327±0.03	1:29±16.5	43 ±2.9	53.6±1.2

Regarding the quality control studies, all tablets complied with the US pharmacopeal requirements for the weight variation test as a reflection of good powder flowability. The recorded deviation from the mean tablet weight was <1%.Results of content uniformity, friability, disintegration and wetting time are represented in Table 3.

The recorded content uniformity values were in the range of 97 to 100%,. The friability values were in the range of 0.23% to 0.98%, indicating acceptable resistance of tablets to withstand handling. Formulations F3 and F4 showed the least % friability, may be due to the presence of PVPK30 with its known binding effect. Regarding Disintegration test, the recorded time ranged from 33 sec for F2 up to 1.2 min for the control tablet.

Tablets F3 and F4 showed a longer disintegration time, may be due to the presence of PVP in the ternary SD with its strong binding effect. The results of wetting time correlate well with the disintegration time, where tablets F1 and F2 showed the least wetting time.

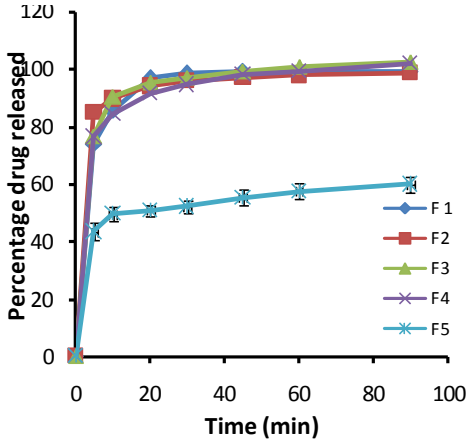

Fig. 6. The dissolution profiles of fast disintegrating tablet formulations. Detailed formulations are presented in Table 2.

The dissolution profiles of the prepared tablets are shown in Figure6, and dissolution parameters are presented in Table (3).The control tablets F5 showed a slow drug release with a dissolution efficiency of 55%. All fast disintegrating tablets revealed a better dissolution pattern compared to control tablets, where there was a prompt release of the drug.

Table F2 showed the highest initial drug release with Q5 of about 85% that was significantly higher than other formulations (P <0.05). This may be due to the use of mannitol with its high water solubility compared to Avicel PH 102 used in other formulations. All fast dissolving tablets showed a similar dissolution efficiency that was about 2-fold higher than control tablets.

CONCLUSION

Solid dispersion (SD) and surface solid dispersion (SSD) techniques were useful tools to improve the dissolution rate of Amoidarone. The enhanced dissolutions were mostly due to reduced crystalline nature of the drug. Binary SD using Pluronic F68 and F127 deposited over Aerosil producing SSD as well as ternary solid dispersion using Pluronic and PVP were selected to produce fast disintegrating tablets with subsequent fast dissolution rate. Tablets prepared with unprocessed drug was used as control. All fast disintegrating formulations were superior to control tablets with respect to dissolution parameters. Fast disintegrating tablets prepared using SSD and Mannitol, as filler, showed better initial drug release and was selected as optimum formulation. The study thus provide a fast disintegrating tablets of Amoidaraone with a potential for increased oral bioavailability by inhibiting its pre-systemic metabolism due to presence of Pluronic polymer.

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