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PREPARATION AND EVALUATION OF RAPIDLY DISSOLVING TABLETS OF CARVEDILOL

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ABSTRACT
The aim of this work was to fasten the rate of dissolution of carvedilol via controlled precipitation, in presence or absence of hydrophilic polymers. The goal was to develop rapidly disintegrating tablets with fast dissolution of carvedilol. Aerosil was dispersed in methanolic solution of carvedilol in the presence or absence of hydrophilic polymers. Distilled water was added as antisolvent to produce controlled precipitation. The precipitate was centrifuged and dried at ambient conditions before monitoring the dissolution pattern. The properties of solid products were investigated using FTIR spectroscopy, thermal analysis and X-ray diffraction. FTIR studies revealed significant alteration in spectrum of carvedilol after controlled precipitation. These changes can be taken as possible indicators for hydrogen bonding. The thermal analysis reflected possible co-crystallization between carvedilol and aerosil and in presence of hydrophilic polymers. This was further confirmed by X-ray diffraction. Changes recorded in crystalline nature of carvedilol were associated with enhancement in dissolution rate of carvedilol. Optimum formulations were formulated as rapidly disintegrating tablets with subsequent fast dissolution. In conclusion, optimized sedimentation of carvedilol via controlled precipitation technique in presence of aerosil and different hydrophilic polymers resulted in development in co-crystal development which enhance dissolution rate of carvedilol.

KEYWORDS: Carvedilol, controlled precipitation, enhance dissolution, fast disintegrating tablets.

INTRODUCTION
Carvedilol is used in the treatment of hypertension and mild to moderate heart failure. The drug performs its function via blocking of □1 and □ adrenergic receptors.[1] Carvedilol is a poorly soluble drug with good membrane permeability. Accordingly, it was classified as class II based of the Biopharmaceutical Classification System (BCS).[2] The drug has poor oral bioavailability with the recorded values ranging from 25 to 35%.[3] This poor bioavailability is attributed to slow dissolution in addition to pre-systemic metabolism.[4] Accordingly, enhancing the dissolution rate of this drug can improve its oral bioavailability. The benefit can be maximized if the drug is formulated as oral rapidly disintegrating tablet which liberates significant amount of the drug in the oral cavity. Several strategies have been employed to enhance the dissolution rate of poorly water soluble drugs. These techniques include solid dispersion of the drug[5], inclusion complexation with cyclodextrins[6], microsphere[7] and addition of surfactant as solubilizing agent.[8] Modification of crystalline structure of the active pharmaceutical ingredient (API) is another effective strategy which has been shown to enhance drug dissolution. This modification can be achieved by formation of co-crystalline product with inert co-crystal co-former such as aerosil 200 and sucralose.[9,10] The crystalline structure can be modified in situ during solid dispersion formation.[11] Extensive grinding of the API can also modify the crystalline structure of materials forming weaker crystals which liberate drug molecules in short time.[12] Controlled precipitation has been recently employed to enhance the dissolution rate of hydrophobic drugs. In this technique the given drug is precipitated on the large surface area of solid particles. The specification of the deposited drug may depend on the solvent and anti-solvent used in the precipitation process. Further modification is expected by addition of hydrophilic excipient.[13] Development of the rapidly soluble drug as rapidly disintegrating tablets can further improve the performance of the solid dosage form. It can liberate significant quantity of the drug in the buccal cavity for transmucosal absorption avoiding the problems associated with gastrointestinal absorption of drugs.[11,14]

The objective of the current study was to enhance the dissolution rate of carvedilol using controlled precipitation. This was extended to develop rapidly disintegrating tablets for intra-oral administration

MATERIALS AND METHODS

Materials

Carvedilol, Avicel PH102, cross carmelose, cross povidone, magnesium stearate, Aerosil 200 , polyvinylpyrillidone (PVPk30), polyethylene glycol 4000 (PEG4000) and hydroxypropyl methyl cellulose (HPMCE5) were obtained as gift samples from Sigma for Pharmaceutical Industries, Egypt. Gelucire 50/13 was obtained from Cattefosseé, Saint Priest, Cedex, France. Methanol was purchased from El Nasr Pharmaceutical Chemicals Company, Cairo, Egypt.

METHODS

Preparation of drug crystals by controlled precipitation technique

The drug was subjected to controlled precipitation in presence of hydrophilic excipients. This process was conducted in presence of solid surface with high surface area. The composition of the tested formulations is presented in Table (1). Aerosil 200 was selected as the insoluble solid material with the hydrophilic polymers including PVPK30, HPMCE5, Gelucire and PEG4000. Carvedilol was dissolved in the least amount of methanol and the polymer was added to produce clear solution. Aerosil 200 was added with continuous mixing using magnetic stirrer till complete mixing. Controlled precipitation on the surface of Aerosil was achieved by addition of distilled water (three times the volume of methanol) as antisolvent. The precipitate was separated by centrifugation and was dried at ambient conditions. The product was stored in a tightly closed amber container.

Table 1: The composition of the formulations used in controlled precipitation.

Formula	Drug (g)	Aerosil (g)	PVP (g)	HPMCE5 (g)	Gelucire (g)	PEG (g)	Q_5 (%)	DE_{45} (%)
Control	0.5	-	-	-	-	-	11.6 ±1.3	14.9±1.1
F1	0.5	0.25	-	-	-	-	52.1±1	62.3±1.5
F2	0.5	0.25	0.2	-	-	-	90.7±1.1	90.2±0.2
F3	0.5	0.25	-	0.2	-	-	81.9±0.8	80.5±0.3
F4	0.5	0.25	-	-	0.2	-	85.1±0.7	86.2±1.3
F5	0.5	0.25	-	-	-	0.2	80.3±0.8	79.2±0.2

Drug content

The drug content in each formulation was determined by dissolving 50mg of the formula 50ml of methanol. To ensure complete solubility of the deposited drug the suspension was subjected to magnetic stirring for 15 minutes at the end of which the liquid was filtered. The filtrate was suitably diluted in methanol and the concentration of the drug was determined spectrophotometrically at 242nm. The drug content was calculated according to the following equation:

Drug content (%) = (amount of drug recovered in each sample/50) x 100

Fourier- transform infrared spectroscopy (FTIR)

The FTIR spectra of carvedilol, Aerosil 200, polymers and the products of controlled precipitation were recorded using FTIR spectrophotometer (Bruker Tensor 27, Ettlingen, Germany). Powdered sample was mixed with spectroscopic grade potassium bromide. The mixture was compressed into disks using hydraulic press. The prepared disk was loaded into the sample holder before scanning from 4000 to 400 cm^{-1}.

Differential Thermal Analysis (DTA)

Thermal analysis of the samples was performed on differential thermal analyzer (DTA) (TGA/DTA, Shimadzu, Kyoto, Japan). Dry samples (2-4 mg) were loaded into aluminum pans which were crimped using Shimadzu crimper. The thermal behavior of each sample was monitored using an empty pan as reference. This was achieved under continuous flow of nitrogen gas (40ml/minutes) with the samples being heated from 20 to 400°C at a rate of 10°C/minute. The instrument was equipped with a refrigerated cooling system.

Powder X-ray Diffraction (PXRD)

The X-ray diffraction pattern was recorded for carvedilol, Aerosil 200, polymers and the products of controlled precipitation prepared formulations. This employed GNR APD 2000 pro-X-Ray diffractometer with Cu Ka radiation (1.54056A) (Italy). The equipment is supported with a primary a position sensitive detector. The diffraction pattern was monitored at ambient temperature, using 2Theta scan axis with continuous scan mode at scanning step size of 0.03° and scan range of 3 to 65°.

Evaluation of the flow properties of the prepared powdered formulations

Angle of Repose

A funnel was mounted of the stand at predetermined height (h). The powdered formulation is allowed to pass through the funnel to form a pile covering the height of the funnel outlet. The radius (r) of the pile was measured and the angle of repose was calculated[15] according to the following equation:

$$\tan \theta = h/r$$

Apparent Bulk Density (□b)

The apparent bulk density was determined by transferring an accurately weighed amount of the powdered formula to a graduated measuring cylinder. The measuring cylinder was subjected to three taps before measuring the volume of the powder. The bulk

density was calculated as the ratio between the powder mass and the recorded volume. This was repeated three times and the average apparent bulk density was calculated.[16]

Tapped Density (□t)

The tapped bulk density was calculating by introducing an accurately weighed quantity of the powder into a graduated measuring cylinder. The measuring cylinder was subjected to successive tapping until constant volume. The volume of powder was recorded and the tapped density was calculated from the ratio between the powder mass and the tapped volume.[16]

Carr's Index (CI)

The percent compressibility of the powder can be taken as a measure for the flow properties. The index can be calculated from the data recorded for the apparent bulk density and the tapped density. This can be achieved using the following equation[17]:

$$CI = [(\square t - \square b)/\square t] \times 100$$

Hausner's Ratio

Hausner's ratio is another measure for the flow properties of the powder. It was determined by the ratio of tapped density / bulk density. The test was done in triplicate.[17]

Preparation of fast disintegrating tablets

The formulations showing fast drug release were employed in preparation of fast disintegrating tablets. The tablets were prepared according to the composition presented in Table (2). Each tablet contained 25 mg of carvedilol or an equivalent weight of the formulation. Tablet preparation involved geometric mixing of carvedilol or its equivalent formulation with excipients. The mixtures were compressed into tablets, weighing 200 mg using 10 mm punch. This process employed a single punch tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India) with the compression force being adjusted to give tablet hardness in the range of 4 to 5 KP.

Table 2: The composition of the prepared rapidly disintegrating tablets, tablet quality control tests, and in vitro dissolution parameters of different tablets represented as percentage drug released after 5 min (Q_5) and dissolution efficiency after 45 min (DE_{45}).

Ingredients(mg/tablet)	Control tablet	PVPK30 Tablet	HPMCE5 tablet	Gelucire Tablet	PEG4000 tablet
Carvedilol or an equivalent formula	25	39.4	40.7	42.8	38.5
Avicel PH 102	152	137.6	136.3	134.2	138.5
Crosscarmellose	10	10	10	10	10
Crosspovidone	10	10	10	10	10
Magnesium stearate	3	3	3	3	3
Q5 (%)	10.6±0.4	64.0±0.9	61.3±1.6	68.7±2.1	69.3±1.6
DE (%)	13.1%±0.7	69.2%±1.6	67.1±1.3	70.4±0.9	72.1±2.1
Weight uniformity (%)	198.9±0.6	199.8 ± 0.4	197.9 ± 0.8	199.8± 0.4	199.6 ± 0.5
Friability (%)	0.7	0.5	0.1	0.2	0.6
Drug content (%)	99.0 ±1	98.4±0.925	97.24±2	97.22±2	98.2±1
Disintegration time(s)	70±1	50±1	30±3	58±1	28±2
Wetting time(s)	65±0.6	48± 0.6	28± 0.6	53 ± 1.5	25 ± 1.00

Evaluation Tests of fast disintegrating tablets

Uniformity of weight

The uniformity of weight was monitored using randomly selected 20 tablets. The weight of each tablet was recorded and the average weight and the deviation from the average were calculated. The tablets pass the test if no more than two tablets were outside the acceptance limit (7.5%) with no tablet differing by more than twice the limit.[18]

Tablet friability

The friability of the prepared tablets was recorded using Erweka friability tester (Erweka, Heusenstamm, Germany). A pre-weighed tablet sample (15 tablets) was loaded in the friability tester which was allowed to revolve for 100 revolutions at the end of which the intact tablets were dedusted and weighed again. The friability was calculated as the percentage loss which should not exceed 1%.[18]

Drug content

The content uniformity was assessed by random selection of 30 tablets. The content of each of 10 tablets was determined by powdering and dissolving the drug in methanol. The resultant mixture was filtered before dilution with methanol and measuring the drug concentration spectrophotometrically. The tablets pass the test if not more than one was outside the acceptance limits (85-115% of the labeled content). If two tablets were outside this limit the test is repeated using 20 tablets all of which must be with the limit. The tablets are rejected if any tablet was outside the limits of 75-125% of the labeled content.[18]

Disintegration test

This test employed Copley disintegration tester (Copley scientific NE4-cop, Nottingham, UK). This utilized 6 tablets with the disintegration medium being distilled

water maintained at 37°C. The time taken for complete disintegration of the 6 tablets was recorded.

Wetting time

The wetting time was determined according to the method reported by Jain and coworkers.[19] A filter paper was mounted in a Petri dish containing 6ml of distilled water. Allura red was sprinkled on the surface of the tablets before being placed on the wet filter paper. The wetting time was calculated as the time needed for the liquid to diffuse through the tablet reaching the tablet surface. This was indicated by the development of a red color on the surface of tablet.

In vitro Dissolution Studies

The dissolution rate of carvedilol was determined using the USP II dissolution apparatus (Copley, NG 42 JY, Nottingham, UK) which was adjusted to 50 rpm. The dissolution medium was 0.1 N HCL and was maintained at 37°C. The powdered formulation or the prepared tablets were loaded in the dissolution vessels. Samples (5ml) of the dissolution medium were collected at a predetermined time intervals (5, 10, 20, 30 and 45). The samples were filtered immediately using a 0.45 mm membrane filter. The dissolution medium was replenished with equal volume of fresh medium to maintain constant volume throughout the experiment. The drug content in each sample was assayed using UV spectrophotometer at 242nm. The dissolution pattern was constructed by plotting the cumulative amounts of carvedilol dissolved as a function of time. The dissolution pattern was employed to calculate the dissolution efficiency (DE) and the amount of drug dissolved in the first 5 minutes (Q5). DE was calculated from the area under the dissolution pattern curve relative to the area recorded assuming 100% dissolution in the same time.[20]

RESULTS AND DISCUSSION

Solid state characterization of prepared formulations

The drug content of the prepared formulations was calculated to determine the actual amount of the drug precipitated by the controlled precipitation. This was used to calculate the weight equivalent to the dose of the drug in dissolution studies and in preparation of tablets. The carvedilol content in the tested formulations was 63.49 $\pm$ 0.97, 61.40 $\pm$ 1.23, 58.4 $\pm$ 1.89, 65 $\pm$ 1.67 for formulations precipitated on the surface of aerosil in presence of PVP, HPMC, gelucire and PEG, respectively.

Fourier-transform infrared spectroscopy

FTIR spectroscopy was conducted to monitor possible interaction of carvedilol with aerosil and/or the polymers used during the controlled precipitation process. The infrared spectra of carvedilol, aerosil, polymers and the products of controlled precipitation are shown in "Fig.1". The FTIR spectrum of the unprocessed carvedilol revealed the principle peaks which correspond to its structure. These absorption bands appeared at 3346 cm^{-1} for the NH stretching vibrations associated with broad peak for the hydroxyl group. The CH stretching vibration was recorded at 2993cm^{-1} and the NH bending was seen at 1599cm^{-1}. The peak of C-O stretching was noticed at 1256 cm^{-1} "Fig. 1". This spectrum correlates with the chemical structure of carvedilol and is similar to that published by other investigators.[21]

For Aerosil, the FTIR spectrum showed an intense broad peak at 3449 cm^{-1} due to hydroxyl group originating from the intermolecular hydrogen bonding of the adsorbed water and silica oxygen. The H-O-H bending vibration was revealed as sharp peak at 1636 cm^{-1}. This is attributed to the water of crystallization. The SiO was characterized by symmetric and asymmetric stretching vibrations which were noticed at 1109 cm^{-1} and 803 cm^{-1}, respectively. The SiO bending mode was shown at 473cm^{-1}.

This spectrum correlates with the chemical structure of silica and is similar to the published spectrum for aerosol.[9] The FTIR spectrum of pure PVP K30 showed strong sharp absorption band at 1658 cm^{-1}, for the carbonyl group. The hygroscopic nature of the polymer was indicated from the presence of moisture which was highlighted by the existence of very broad absorption band at 3438 cm^{-1}. This spectrum is similar to that recorded by other researchers.[22]

The FTIR spectral pattern of PEG 4000 showed broad absorption band at 3432cm^{-1} reflecting the OH group. The C-O stretching was evident at 1113cm^{-1} with the C-H stretching being seen at 2887cm^{-1}. This is similar to that published for the polymer.[23] The spectral pattern of HPMCE5 reflected the existence of hydroxyl group which was manifested as broad band at 3454 cm^{-1}. The peaks at 1063cm^{-1} and 1121cm^{-1} are due to C-O-C stretching vibrations. The CH stretching appeared at 2934 cm^{-1}. This pattern is similar to that recorded by other investigators.[24] The FTIR spectrum of Gelucire showed a broad absorption band at 3442 cm^{-1} corresponding to the OH stretching. The bands at 2920 and 2857cm^{-1} are due to the CH stretching. The characteristic ether C-O stretching was noticed at 1111cm^{-1} "Fig.1". This agrees with the published spectrum for the same compound.[22]

Controlled precipitation of carvedilol on the surface of aerosil in absence and presence of hydrophilic polymers produced dry powder with compromised FTIR spectral pattern. The principle peaks of carvedilol underwent shifting and broadening after controlled precipitation in absence of polymers. The peaks corresponding to NH stretching and bending vibrations were broadened after controlled precipitation. This was associated with shifting of the peak corresponding to the symmetric SiO stretching. The band of SiO bending was broadened "Fig 1". Similar changes have been noticed in presence of hydrophilic polymers. These changes can be taken as possible indicators for hydrogen bonding. Changes like

these have been similarly explained by other investigators.[9]

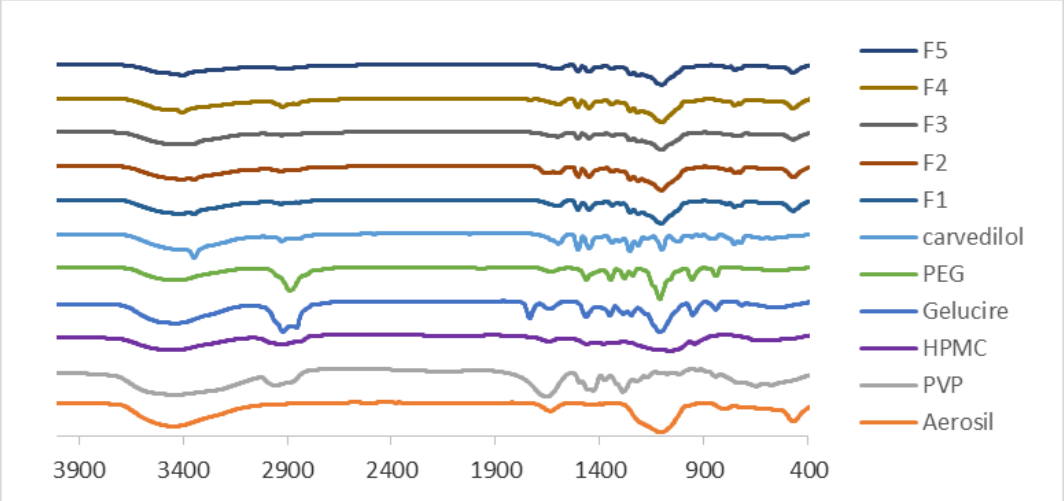

Figure1: FTIR spectra of carvedilol, excipients and different formulations.

Differential Thermal Analysis (DTA)

DTA was conducted to monitor the effect of controlled precipitation on the surface of aerosil in presence and absence of hydrophilic excipients. "Fig. 2" shows representative thermograms of pure carvedilol and the developed products. The thermogram of pure unprocessed carvedilol produced an endothermic peak with a Tm at 118.59 ºC. This endotherm can be attributed to the melting transition of carvedilol reflecting its crystalline nature. Another endothermic peak was noticed at 345 ºC reflecting the decomposition of carvedilol "Fig. 2". This thermogram is similar to that published by other investigators.[25] The thermal behavior of unprocessed HPMC revealed the characteristic broad endotherm below 100ºC which originates from the evaporation of bound moisture. The degradation of the polymer was shown by very broad endotherm at about 293.3 ºC "Fig. 2". This endotherm is similar to that recorded in other investigations.[24] The thermal behavior of aerosil 200 was characteristic for the amorphous material with the thermogram being baseline like which simulate the published data on the same material.[9] The thermogram of pure PVP K30 reflected the hygroscopic nature of the polymer as indicated form the evaporation of moisture which was shown as a broad endothermic peak at 63.13 ºC "Fig. 2". This is similar to the previously reported in literature.[26] Pure PEG 4000 underwent melting at 63.17 ºC producing thermal behavior similar to that documented by other researchers.[27] The unprocessed Gelucire 50/13 showed a melting transition at 50.19 ºC corresponding to the characteristics of the material and agreeing with the available literature reports.[28]

Precipitation of carvedilol on the surface of aerosil produced solid product with compromised thermal behavior. The change was manifested as a reduction in the Tm of the melting transition of the drug to be detected at 116.9ºC. This was associated with appearance of new exothermic peak at 323ºC. This behavior suggests the development of new crystalline species or presence of interaction which can be at least hydrogen bonding as revealed from the FTIR data (see above).

Controlled precipitation of carvedilol on the surface of silica in presence of PVP produced solid material which underwent melting at 114.48 ºC with the development of broad exothermic peak at 331.3ºC "Fig 2". This again reflects a change in the thermal behavior after addition of PVP. The same behavior was recorded after controlled precipitation in presence of HPMC where the melting Tm was recorded at 115.3ºC with weak broad exotherm being seen at 332.16ºC. Controlled precipitation of carvedilol on the surface of silica in presence of gelucire produced solid material with thermal pattern showing significant reduction in the main endothermic which was recorded at 96.25ºC. This change was associated with strong exothermic peak at 302.3ºC. Replacing gelucire with PEG 4000 produced similar pattern with the Tm of the main endotherm being seen 98.1ºC but the exothermic peak was noticed at 321.7ºC as strong broader peak. These changes indicate that the nature of developed solid product is changing depending on the nature of the hydrophilic excipient. The thermal behavior of the developed solid products after controlled precipitations suggests possible co-crystallization between carvedilol and silica with the nature of resulting crystals changing in presence of hydrophilic polymers. The change depended on the polymer. The overall process requires confirmation with X-ray diffraction studies (see below).

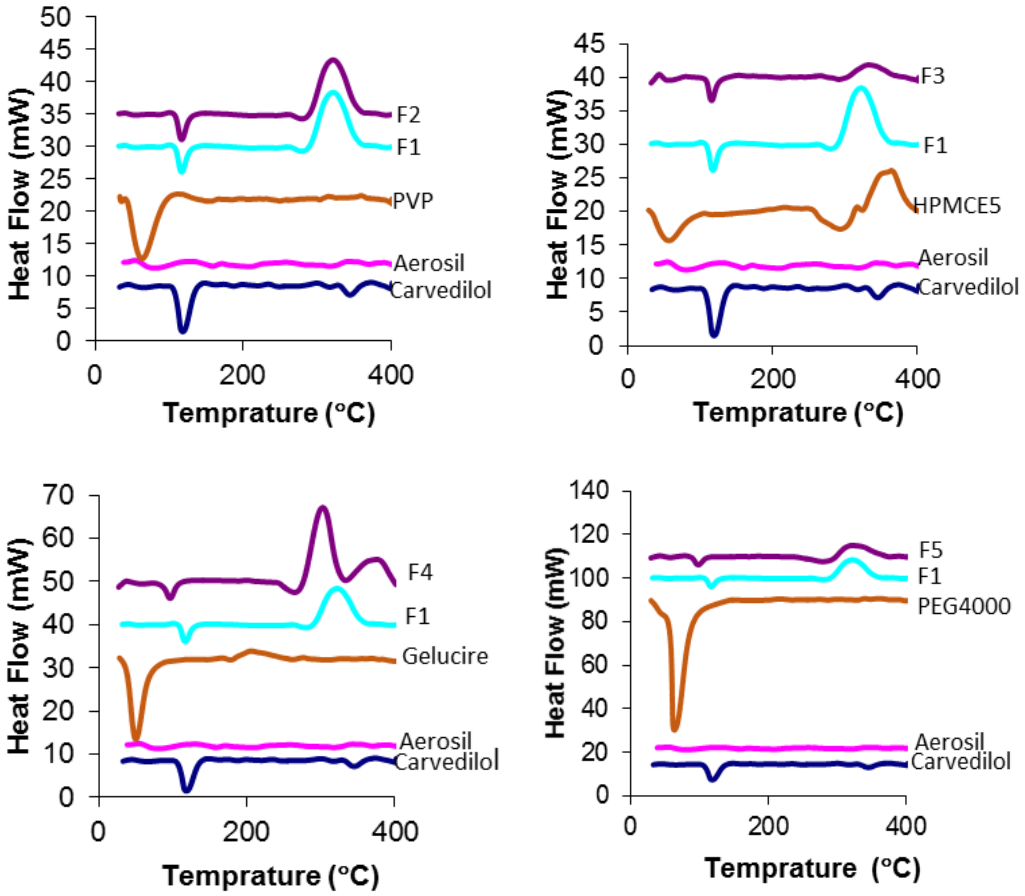

Figure 2: DTA thermograms of carvedilol in pure state or after controlled precipitation on solid surface.

X-ray powder diffraction

X-ray diffractometry was used to monitor the change in the crystalline structure of carvedilol after controlled precipitation on the surface of silica in absence and presence of various hydrophilic polymers.

"Fig. 3" shows representative diffractograms of carvedilol and excipients before and after processing. Table (3) presents the 2 values of the recorded diffraction peaks. The diffraction pattern of pure carvedilol reflected the crystalline nature of carvedilol as indicated from the strong diffraction peaks which were seen at diffraction angles of 5.99°, 11.55°, 11.86°, 13.17°, 13.81°, 15°, 15.36°, 16.65°, 17.15°, 17.71°, 18.61°, 19.42°, 20.5°, 21.25°, 21.87°, 23.02°, 23.76°, 24.49°, 26.39°, 27.67°, 28.26°, 29.62°and 31.6° "Fig.3" and Table (3). This diffractogram is similar to that published for carvedilol.[29] For aerosil, PVP and HPMC E5, the diffractograms did not show any diffraction peaks confirming the amorphous nature of these materials. These findings are similar to that published for these excipients and correlate with their specifications.[9,30,31] The diffraction pattern of pure PEG showed characteristic peaks at 19.05° and 23.37°. This pattern complies with the specification of PEG 4000 and correlates with the published data on the same polymer.[32] For gelucire 50/13, the diffraction pattern showed two weak peaks at 19.14° and 23.55°. This correlates with the waxy nature of the surfactant and is similar to the published data.[33]

Controlled precipitation of carvedilol on the surface of aerosil (F1) produced solid material having different diffraction pattern compared to that of the unprocessed drug. The difference was manifested in the appearance of new diffraction peaks which were detected at 6.45°, 13.5°, 15.4°, 15.81°, 18.09°, 18.99°, 19.77°, 20.88°, 24.84°, 25.89°, 26.88°, 28.71°. Repeating the controlled precipitation process in presence of PVP (F2) produced new diffraction pattern which is different from that recorded in case of unprocessed drug or in case of F1. The new diffraction peaks were seen at 6.10°, 16.77°, 17.28°, 17.76°, 18.66°, 20.55°, 23.07°. Replacing PVP with HPMC (F3) resulted in further change in the crystalline structure of carvedilol with new peaks being noticed at 6.35°, 11.46°, 13°, 14.85°, 15.27°,16.6°, 17.85°, 19.26°, 20.4°, 24.33°. Using gelucire as the hydrophilic component in controlled precipitation changed the crystalline structure with new diffraction peaks being evident at 8.67°, 17.49°, 20.82°, 21.54°, 22.17°. The use of PEG 4000 during the controlled precipitation process (F5) developed crystalline product with new peaks being

seen at 8.56°, 9.51°, 11.79°, 13.74°, 14.37°, 15.96°, 17.49°, 18.57°, 20.79°, 21.54°, 22.14°. In all cases the product of controlled precipitation showed diffraction peaks of reduced intensity "Fig.3" and Table (3). Development of new diffraction peaks after controlled precipitation on the surface of aerosil indicated the development of new crystalline species which can be of co-crystalline type. The application of aerosil as co-crystal co-former has been reported for hydrochlorothiazide but the co-crystallization process was conducted by wet co-grinding after liberation from organic solution.[9] Reduction in the intensity of the peaks after controlled precipitation reflects development of smaller particles. This expected taking into consideration the small particle size of colloidal silicon dioxide (aerosil). It is important to emphasize that the crystalline structure of the developed co-crystals depended on the existence of hydrophilic polymer and its type.

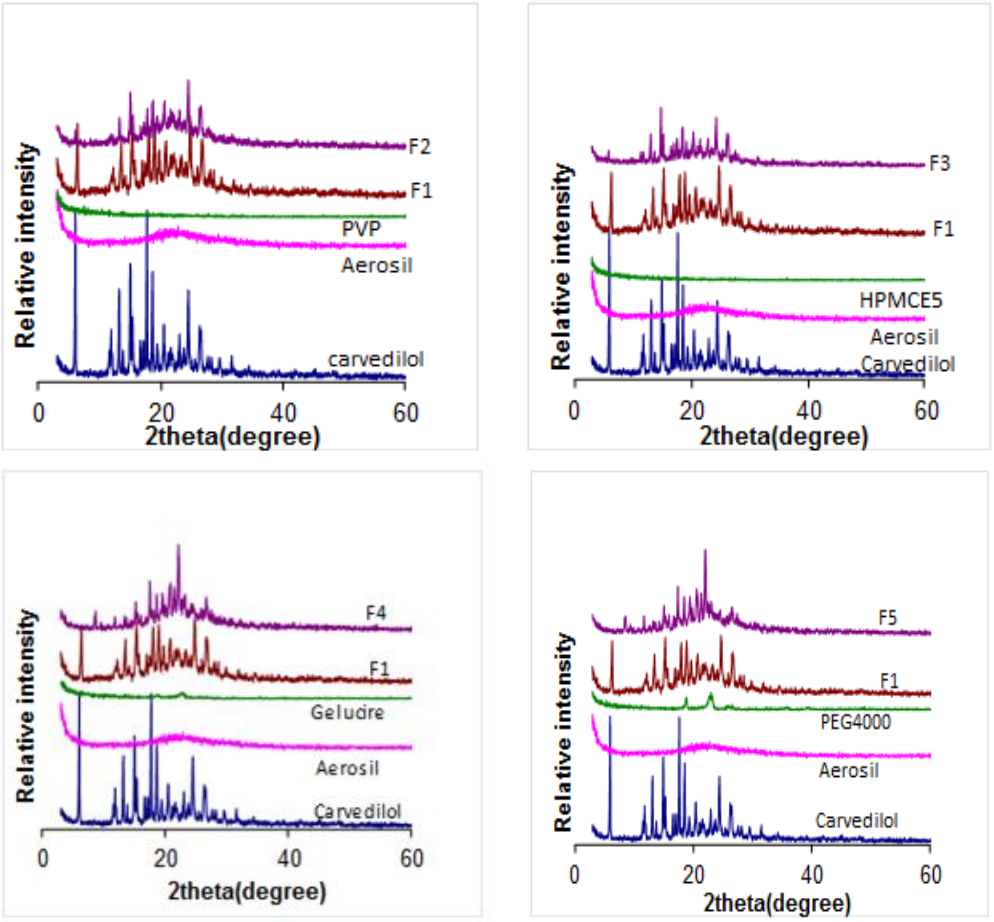

Figure 3: X-ray diffractograms of carvedilol in pure state or after controlled precipitation on solid surface.

Table 3: presents the 2□□□□values of the recorded diffraction peaks.

Formula	Peaks 2□□
Pure carvedilol	5.99, 11.55, 11.86, 13.17, 13.81, 15.00, 15.36, 16.65, 17.15, 17.71, 18.61, 19.42, 20.5, 21.25, 21.87, 23.03, 23.76, 24.49, 26.39, 27.67, 28.26, 29.26, 31.6
Pure Aerosil200	NO diffraction peaks
Pure PVP	No diffraction peaks
Pure HPMCE5	No diffraction peaks
Pure Gelucire	19.17, 23.97 (broad)
Pure PEG4000	19.05, 23.37
F1	6.27, 12.58, 13.45, 15.26, 17.43, 18.37, 19.68, 20.75, 22.27, 23.46, 24.75, 26.72, 28.57, 29.88, 31.86
F2	6.10, 11.99, 13.30, 15.09, 17.83, 18.73, 19.48, 20.63, 23.12, 24.56, 26.56
F3	6.35, 11.72, 13.63, 14.76, 15.15, 16.48, 18.44, 19.15, 21.15, 21.6, 22.79, 24.24, 26.71
F4	8.53, 11.73, 13.71, 15.18, 16.08, 17.49, 18.63, 19.78, 20.71, 21.41, 21.15, 22.10
F5	8.56, 11.79, 14.33, 15.95, 17.49, 18.57, 19.91, 20.68, 21.43, 22.13, 23.22, 26.64, 27.45

Dissolution studies

"Fig. 4" shows the dissolution profiles of carvedilol from the unprocessed powder and from the products of controlled precipitation. The amounts of drug dissolved in the first 5 minutes (Q5) and the overall dissolution efficiency values are presented in Table (1). The dissolution profile of the unprocessed carvedilol reflected its poor and erratic dissolution with only small fraction of the drug dissolving in the first 5 minutes. Poor dissolution was also evident from the calculated dissolution efficiency which was less than 15% "Fig 4". This poor dissolution pattern correlates with the published data and was attributed to hydrophobic nature of carvedilol.[34] Preparation of carvedilol by controlled precipitation on the surface of aerosil 200 (F1) resulted in a significant increase in the rate of drug release as indicated from the recorded Q5 and dissolution efficiency values which were significantly higher ($P< 0.05$) than the control. This was reflected further from the similarity factor test which reflected the dissimilarity between F1 and the unprocessed carvedilol "Fig.4" and Table (1). The increase in the dissolution parameters after controlled precipitation was attributed to possible precipitation of the drug in the form of ultrafine crystals on the large surface area of aerosil.[13] This explanation is a possibility but the combined instrumental analysis of the product of controlled precipitation revealed co-crystallization between carvedilol and the silica. This can provide another possible reason for enhanced dissolution rate of carvedilol. Enhanced dissolution rate has been shown after co-crystallization of hydrochlorothiazide with aerosil.[9] Repeating the controlled precipitation process in presence of PVP (F2) produced new co-crystalline product which liberated carvedilol at a faster rate compared to both the unprocessed drug and F1. This was evident from the values of the Q5 and dissolution efficiency ($p < 0.05$) and was reflected from the results of the similarity factor test "Fig. 4" and Table (1). The recorded dissolution enhancement in presence of PVP can be attributed to the possibility increased hydrophilicity of the developed co-crystals. The same trend was recorded after replacing PVP with HPMC, gelucire or PEG 4000. The developed co-crystals in presence of hydrophilic polymers liberated the drug at comparable dissolution rate irrespective to the type of polymer with all of them enhancing the dissolution of carvedilol compared to the developed co-crystals in absence of those polymers. Overall, controlled precipitation on the surface of silica was able to impart co-crystallization which hastened the dissolution rate of carvedilol with the magnitude of dissolution enhancement being augmented further in presence of hydrophilic polymers. Co-crystal formation was considered as a promising technique for dissolution enhancement with developed co-crystals liberating the drug faster if the co-crystal co-former was of hydrophilic nature.[35] This can explain the contribution of hydrophilic polymer to dissolution enhancement after co-crystallization.

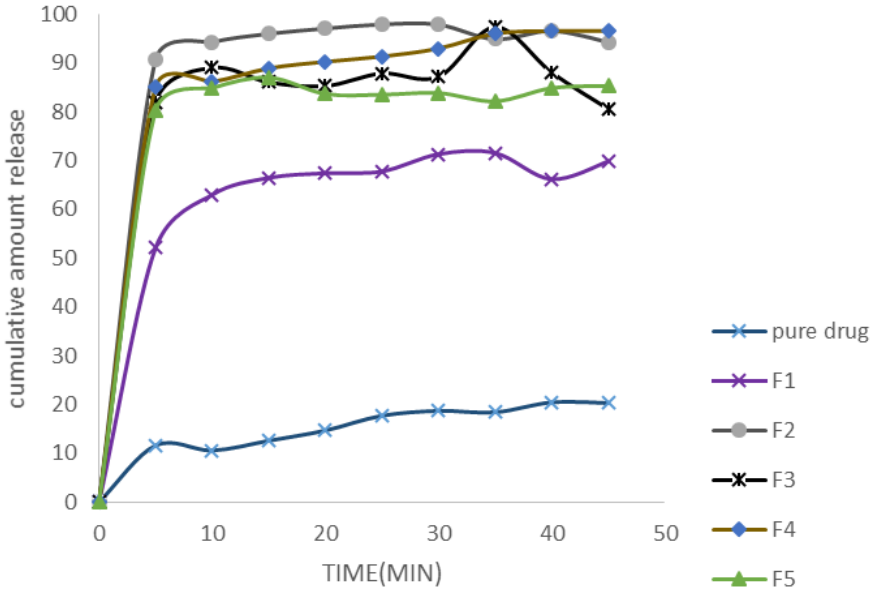

Figure 4: In-vitro drug dissolution of carvedilol from different crystal formulations.

Evaluation of the flow properties of the powdered tablet formulation

Table (4) presents the flow parameters of the powdered formulations. The calculated values of Hausner`s ratio, Carr`s index and angle of repose reflect the acceptable flow characteristics of the powdered formulation. This is expected taking into consideration the composition of the formulation which utilized avicel PH 102 as the main component of the tablet in addition to the presence of aerosil 200 in the processed formulation. These materials are known to have good flow properties.[36]

Table 4: Flow parameters of the tested powder formulations.

Formula	Hausner`s ratio	Carr's index (%)	Angle of repose (ø)
Control tablet	1.52±0.9	33.13±1.8	44.5±1.3
PVP tablet	1.26±0.1	20.8±1	30.9±1.00
HPMCE5 tablet	1.25±0.2	20.31±2	27.8±0.8
Gelucire tablet	1.28±0.1	22.45±1	35.2±2.1
PEG tablet	1.30±0.2	23.53±2	36.2±1.2

Characterization of fast disintegrating tablets

The formulations exhibited fast dissolution rate of carvedilol were utilized in the preparation of fast disintegrating tablets. The characteristics of the prepared tablets are shown in Table (2). With respect to tablet weight all the prepared tablets were uniform with a deviation from average weight of less than 1% indicating good powder flowability. The friability test results revealed that the % loss for all tablets was in the range of 0.1–0.7% demonstrating good mechanical strength of the tablets. The recorded drug content was in the acceptable range (96.3–103.3%). The measured wetting time values were 48, 28, 53 and 25 seconds for the PVP tablets, HPMCE5 tablets, Gelucire tablets and PEG4000 tablets, respectively. These tiny wetting time values proved the ability of the prepared tablet to swell in presence of little amount of water. And this was reflected on the disintegration time values which were recorded to be 50, 30, 58, 28 second for PVPK30 tablets, HPMCE5 tablets, Gelucire tablets and PEG4000 tablets respectively. This rapid disintegration can be attributed to the presence of high amount of superdisintegrants.[10]

The dissolution rate of carvedilol from the prepared tablets was monitored. This aimed to investigate if the applied compression force during tablet preparation will have a negative effect on the rate of drug dissolution from the formulations produced using controlled precipitation technique or not. Tablets containing unprocessed carvedilol (control tablets) were prepared and used for comparison. The dissolution profiles of carvedilol from the prepared tablets are shown in Figure (5) with the calculated dissolution parameters being presented in Table (2). These dissolution profiles revealed the superiority of tablets containing processed drug using controlled precipitation technique compared with control tablet. The recorded Q5 values were 64, 61.3, 68.7, 69.3% for PVPK30 tablet, HPMCE5 tablet, Gelucire tablet and PEG4000 tablet respectively compared to a value of 10.6% for control tablet. The calculated dissolution efficiency values were significantly higher for the tablets containing processed drug compared to control tablet Table (2). It was noticed that, there was a reduction in the rate of carvedilol dissolution from the prepared formulations after tableting process as revealed from the recorded Q5 and DE values. This reduction in dissolution rate can be attributed to good compression property of the carvedilol itself or increase in the binding property of the powder formulations after compaction. However this reduction in the dissolution rate of carvedilol is not problematic as the dissolution rate is still significantly higher than that recorded for control tablet containing unprocessed drug.

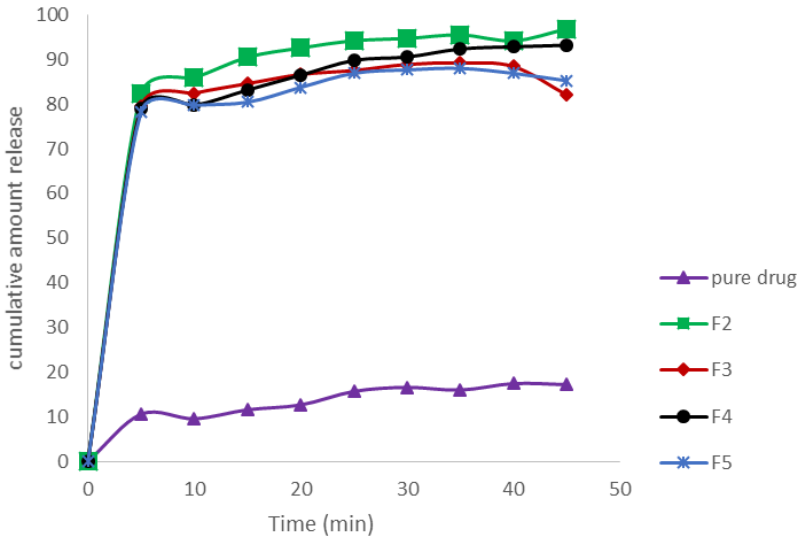

Figure 5: Dissolution profiles of carvedilol from fasting dissolving tablets and control tablet.

CONCLUSION

Controlled precipitation of carvedilol on the surface of aerosil in absence or presence of hydrophilic excipients produced solid materials which showed significant alteration in the physical properties compared with the parent drug, carvedilol.

Recorded thermal and spectral changes confirmed the development of new crystalline product of co-crystal type. The physical and crystalline changes were associated with significant increase in the dissolution rate compared with the unprocessed carvedilol. The developed co-crystals were successfully formulated as rapidly disintegrating tablets with subsequent fast dissolution of carvedilol.

The study introduced controlled anti-solvent recrystallization as a new strategy for formulation of co-crystals for fast liberation of carvedilol.

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