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Original Article

ENHANCEMENT OF DISSOLUTION RATE OF HYDROCHLOROTHIAZIDE

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ABSTRACT

Objective: The aim of this study was to enhance the dissolution rate of hydrochlorothiazide (HCTZ).

Methods: Binary solid dispersions (SDs) of HCTZ with increasing weight ratios of poloxamer 407, polyethylene glycol 6000 (PEG 6000) or gelucire 50/13 were prepared by solvent evaporation technique. The solid dispersions were deposited on the surface of aerosil 200 to produce a dry product with large surface area. The SDs were characterized with respect to drug dissolution. The mechanism of dissolution enhancement was researched using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

Results: The unprocessed drug showed erratic, slow dissolution which can be explained on the basis of its hydrophobic nature. Preparation of SDs with hydrophilic carriers resulted in a significant increase in the dissolution rate with most of the drug being liberated in the first 5 min. The dissolution pattern of the drug from the prepared SDs depends mainly on the type of polymer used, and the best dissolution pattern was observed in the SD prepared using 1:1 ratio of the drug to gelucire 50/13 in the presence of aerosil 200 as a carrier. FTIR studies revealed no interaction between the drug and polymers. DSC showed a change in the crystalline structure of the drug after SDs formation. This change can explain the recorded dissolution enhancement.

Conclusion: The study presented a system capable of increasing the dissolution rate of HCTZ using polymers which can increase the intestinal permeability as well.

Keywords: Hydrochlorothiazide, Poloxamer 407, PEG 6000, Gelucire 50/13, Solid dispersion, Dissolution

INTRODUCTION

Hydrochlorothiazide (HCTZ) belongs to an important group of drugs benzothiadiazine thiazide diuretics [1]. It is used alone or in combination with other therapeutic agents in the treatment of hypertension [2]. It is also indicated in the management of edema resulting from mild-to-moderate congestive heart failure or from chronic hepatic or renal disease [3-4]. The drug is categorized in class IV according to the Biopharmaceutical Classification System (BCS). This classification is based on the poor solubility of HCTZ which is associated with poor membrane permeability. It is thus characterized by poor and variable bioavailability which is believed to be due to poor solubility and slow dissolution with a contribution from the poor membrane permeability [5-6]. Its peak plasma concentration (t_{max}) was recorded within 1 to 5 h of dosing, and ranged from 70 to 490 ng/ml, depending on the dose. The variability in the t_{max} can be attributed to the same factors contributing to poor bioavailability.

Alternative techniques have been adopted to enhance the dissolution rate of HCTZ. These included preparation of spheres based on starch, microcrystalline cellulose or crospovidone [7-9]. Other techniques included micellar solubilization, inclusion complexation, and development of liquisolid systems [10-12]. Other investigators utilized the solid dispersion (SD) technique which was prepared by fusion, solvent evaporation or spray drying [13-14]. The benefits of the dissolution enhancement can be even greater if the selected excipient was able to enhance the membrane permeability of drugs. Such excipient will be efficient with class IV drugs as it will serve a dual function by improving the dissolution rate and membrane permeability. Accordingly the objective of this work was to enhance the dissolution rate of HCTZ by the formulation of SDs with polymers having the potential to enhance the membrane permeability.

MATERIALS AND METHODS

Materials

Hydrochlorothiazide, poloxamer 407 and aerosil 200 were obtained as gift samples from Sigma Pharmaceutical Company, Quwessna, Egypt. Gelucire 50/13 was kindly provided by Gattefosseé, France. Polyethylene glycol 6000 (PEG 6000) was purchased from El Nasr Pharmaceutical Chemicals Co, Egypt. All other chemicals and reagents were of analytical grade.

Assay of hydrochlorothiazide

The *in vitro* dissolution studies employed spectroscopic determination of the drug which was measured at 272 nm using a spectrophotometer (Thermo, Evo300pc, USA) [15].

Table 1: Composition of the tested formulations

Formulation code	Drug	Poloxamer 407	PEG 6000	Gelucire 50/13	Aerosil 200
X111	1	1	-	-	1
X122	1	2	-	-	2
X134	1	4	-	-	3
E111	1	-	1	-	1
E122	1	-	2	-	2
E134	1	-	4	-	3
G111	1	-	-	1	1
G122	1	-	-	2	2
G134	1	-	-	4	3

Preparation of solid dispersions

Binary and ternary SDs of the drug with various polymers were prepared by solvent evaporation according to the composition presented in table 1[16]. The drug and the polymer(s) were dissolved in a mixture of methylene chloride with ethanol and acetone (1:1:1). The organic solvent was removed by evaporation over a water bath at 50 °C with continuous stirring until complete evaporation. Solid dispersions of the drug with poloxamer 407, PEG 6000 and gelucire 50/13 were of low melting points. Accordingly, aerosil 200 was added to these systems to produce a dry powder with large surface area. The resulting SDs were passed through 0.8 mm Sieve.

Fourier transforms infrared spectroscopy

The Fourier transform infrared (FTIR) was used to investigate any interaction between the drug and polymers. FTIR spectra of HCTZ, Poloxamer 407, PEG 6000, gelucire 50/13 and their SDs were recorded using FTIR spectrophotometer (Bruker Tensor 27, Germany) which was used in potassium bromide diffuse reflectance mode for collecting the IR spectra of the samples. The system is equipped with a DLaTGS detector. Samples were mixed with potassium bromide (spectroscopic grade) and were compressed into disks using hydraulic press before scanning from 4000 to 400 cm^{-1}. Data analysis was performed using Opus IR, FTIR spectroscopy Software.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to characterize the SDs. This employed differential scanning calorimeter equipment (Differential scanning calorimeter DSC6, Perkin Elmer, USA). Samples of the drug, the polymers and their SDs were loaded into aluminum pans and the lids were crimped using Perkin Elmer crimper. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 °C/min, covering temperature ranges of 30–300 °C. The instrument was calibrated with an indium standard. Data analysis was conducted using Pyris thermal analysis software.

Determination of the drug dissolution

The dissolution pattern of the drug was monitored for the drug from its unprocessed powder and from the binary and ternary SDs with various hydrophilic polymers. This employed USP type II dissolution apparatus (Copley, NG 42JY, Nottingham, UK). The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2) which was maintained at a temperature of 37°C with a paddle speed being adjusted to 100 rpm. Powdered samples equivalent to 50 mg HCTZ were added to the dissolution vessels while stirring. Samples (5 ml) were taken at 0, 5, 10, 15, 30, 45 and 60 min. These samples were immediately filtered through 0.45 µm filters, discarding the first 2 ml of the filtrate before determination of the drug concentration by spectrophotometry at 272 nm. The withdrawn volume was replaced with dissolution medium at each time interval to maintain a constant volume of dissolution medium. The dissolution profile of the dissolved HCTZ was constructed by plotting the cumulative amount of drug dissolved (expressed as % of the total amount of HCTZ added) as a function of time. The amount of drug dissolved in the first 5 and 10 min (Q5 and Q10) was calculated. The dissolution efficiency (DE) was obtained from the area under the curve of the dissolution profile using the nonlinear trapezoidal rule and demonstrated as a percentage of the area of the rectangle described by 100 % dissolution in the same time [17].

RESULTS AND DISCUSSION

Solid state characterization of the binary and ternary systems

Solid state characterization of binary and ternary SDs employed FTIR and DSC. This was conducted in an attempt to explain the mechanism of enhanced dissolution (if any) after SDs formation.

FTIR dispersions studies

Fig. 1 shows the FTIR spectra of HCTZ and its SDs with various polymers. The FTIR spectrum of pure HCTZ reveals the characteristic peaks which included those corresponding to NH-stretching, which was recorded at 3362, 3267 and 3169 cm^{-1}. The spectrum also revealed the characteristic peaks for the SO_2. The characteristic peaks for the SO_2 group were detected at 1319 cm^{-1} for SO_2 asymmetric stretching vibrations and at 1166 and 1059 cm^{-1} for the SO_2 symmetric stretching vibrations. The CH-stretching was recorded as a band at 3098 cm^{-1}, CH_2 stretching was noticed at 2947 and 2836 cm^{-1} with the C=C stretching vibrations being recorded at 1605 and 1521 cm^{-1}. This spectrum is in good agreement with the published data on the same drug [6].

The FTIR spectrum of poloxamer 407 (fig. 1a) showed characteristic peaks at 2972, 2887 cm^{-1} for C–H stretch, at 1469 cm^{-1} for C–H bending vibrations, and at 1345, 1242, 1282, 1148, 1112, and 1061 cm^{-1} for the C-O stretching vibration. This correlates well with the published spectrum of the surfactant [18].

In the case of PEG 6000, the spectrum (fig. 1b) was characterized by the appearance of a broadband at 3421 cm^{-1} which corresponds to the OH group. The band at 1114 cm^{-1} is for C–O stretching and that at 2882 cm^{-1} for the CH stretching vibrations. The recorded spectrum is in good agreement with the published work on the same polymer [19].

The FTIR spectrum of gelucire 50/13 (fig. 1c) reveals the characteristic absorption band of the OH stretching at 3444 cm^{-1}, that for C–H stretching at 2920 cm^{-1}, that C=O stretching at 1737 cm^{-1}, and the C–O stretching at 1110 cm^{-1} [20].

The FTIR spectrum of aerosil 200 (fig. 1) revealed an absorption band at 3448 cm^{-1} which can be attributed to hydroxyl group which results from intermolecular hydrogen bonding between the water of crystallization and silica oxygen or formation of chelate compounds. The peak of H–O–H bending of water of crystallization was recorded at 1632 cm^{-1}. The Si–O symmetric stretching vibration of silica was observed at 1110 cm^{-1} with the bands corresponding to the asymmetric Si–O stretching and Si–O bending modes of silica being recorded at around 808 cm^{-1} and 475 cm^{-1}. This spectrum is similar to that previously reported for aerosil 200 [6, 21].

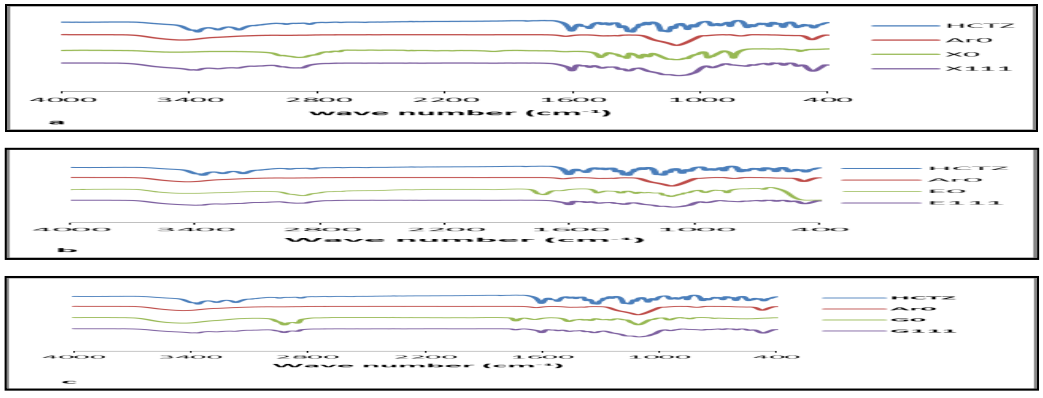

Fig. 1: FTIR of binary SDs of HCTZ using (a) poloxamer 407, (b) PEG 6000 or (c) gelucire 50/13 in the presence of aerosil 200 (formulation details are presented in table: 1)

The FTIR spectrum of the SD of the drug with poloxamer 407 revealed the characteristic peaks of the drug which were recorded in positions similar to those of pure drug (fig. 1a). This indicates the absence of interaction between the drug and the polymer. With respect to the FTIR spectrum of the drug in the SD with either PEG 6000 or gelucire 50/13 in the presence of aerosil 200, there were some changes in the spectrum relative to that of pure drug (fig. 1b, fig. 1c). These changes were in the form broadening of the peaks corresponding to the NH group. This can be taken as a sign of hydrogen bonding between the drug and the polymer. A Similar conclusion was previously reported based on similar changes in the FTIR spectra of other drugs after incorporation in the SD with the same polymer [22, 23].

Differential scanning calorimetry

Fig. (2-4) show examples of the DSC traces of HCTZ and its SDs with poloxamer 407, PEG 6000 or gelucire 50/13 in the presence of aerosil 200 as a carrier. The calculated thermodynamic parameters are presented in table 2.

The pure drug produced a characteristic sharp endothermic peak with a Tm of 269 ^{o}C (fig. 2). This reflects the crystalline nature of the unprocessed drug. A similar thermogram was recorded for the same drug by other investigators [6]. With respect to aerosil 200, the DSC pattern was free from any endothermic or exothermic peak (fig. 2). This thermal behavior can be taken as a reflection of the amorphous nature of this material. A Similar finding was recorded in literature and was explained similarly. This explanation is supported by the published X-ray diffraction pattern for the same material [6]. The thermogram of pure poloxamer 407 showed a very sharp endothermic peak at 57.5 ^{o}C (fig. 2). This peak corresponds to the melting transition of the polymer. The melting transition of poloxamer is in good agreement with the published work on the polymer [18]. Pure PEG 6000, the thermogram revealed a sharp endothermic peak at 63.4 ^{o}C (fig. 3). This endotherm corresponds to the melting point of PEG 6000 and agrees with the published data [24]. The thermogram of pure gelucire 50/13 showed a very sharp endothermic peak at 45.2 ^{o}C corresponding to the melting point of the polymer (fig. 4). The melting transition of gelucire 50/13 is in good agreement with the recorded data for the polymer [23].

Formulation of HCTZ as a binary SD with poloxamer 407 in the presence of aerosil 200 as a carrier resulted in the broadness of the endothermic peak of the drug with a significant reduction in the Tm of the transition. This reduction depended on the proportion of poloxamer, increasing poloxamer concentration in the SD, reducing the Tm of the drug. The reduction in the Tm was associated with the reduction in the enthalpy of the transition (fig. 2, table: 2). This pattern can be explained on the basis of the possible partial transformation of the drug to an amorphous structure. Another possible explanation can depend on possible eutectic mixture formation. A Similar effect was reported for poloxamer 407 when formulated with glibenclamide and was similarly explained [18].

Formulation of HCTZ as an SD with PEG 6000 in the presence of aerosil 200 resulted in the broadness of the endothermic peak of the drug with the Tm being shifted to the lower value in case of 1:1 weight ratio (drug to polymer). This was associated with a reduction in the enthalpy for the transition. Increasing the proportion of PEG 6000 resulted in a thermogram with the Tm of the drug nearly disappeared (fig. 3, table: 2). This effect can be due to the transformation of the drug to the amorphous structure or eutectic mixture formation. The same trend was reported for the same polymer with other drugs [25].

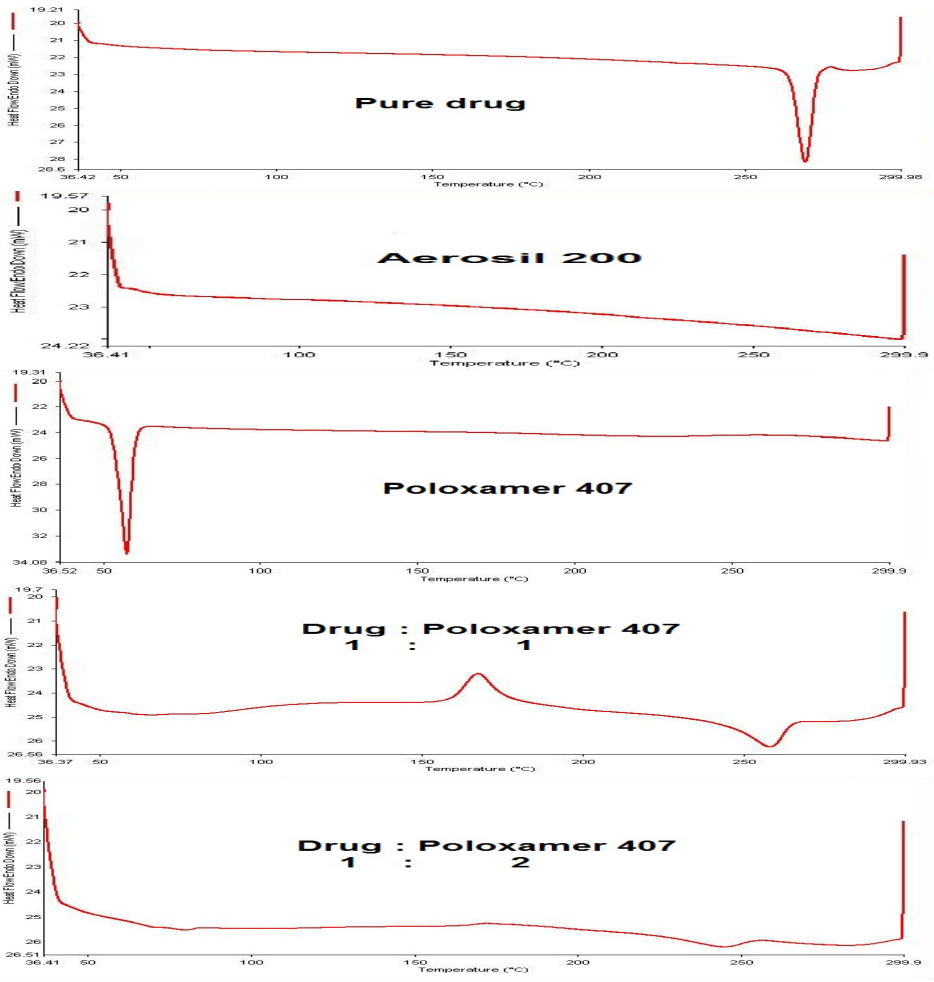

Fig. 2: DSC traces of HCTZ and its SDs with poloxamer 407 in the presence of aerosil 200

Preparation of SD of the drug with gelucire 50/13 in the presence of aerosil 200 resulted in a reduction in the Tm and intensity of the endothermic peak of the drug compared with the unprocessed drug. The reduction in the peak intensity was manifested as a decrease in the enthalpy of the transition with the effect increasing as the proportions of the surfactant increased (fig. 4, table: 2). This suggests the partial transformation of drug crystals into an amorphous structure or possible solubility in the carrier. The possibility of mixture eutectic formation was suggested for similar effects with other drugs [20, 23].

It is important to emphasize that SD formation of HCTZ affected the melting transition of the polymers as well. This was manifested as the broadening of the melting transition of poloxamer 407, PEG 6000 and gelucire 50/13 (fig. 2, 3 and 4). Broadening of the transition endotherm is due to the reduction in the cooperativity of the transition. This highlights the physical interaction between the drug and the polymer and confirms the recorded changes in the melting transition of the drug. A similar finding has been recorded by other investigators for SDs of other drugs and was similarly explained [20].

Dissolution studies

The dissolution profiles of pure HCTZ and the prepared SD formulations are shown in fig. 5. The calculated dissolution parameters are presented in table 2. The dissolution profiles of HCTZ in a pure state revealed poor and slow dissolution with only 29.74 and 37.06 % of the drug being liberated in the first 5 and 10 min respectively. The dissolution efficiency (DE) was calculated to be 55.9 %. This poor and slow dissolution rate of the drug can be attributed to its hydrophobic nature. Similar dissolution pattern was recorded by other investigators [6].

Preparation of binary SDs of the drug with poloxamer 407 resulted in an increase in the dissolution rate of the drug. For 1:1 drug to polymer ratio the Q5, Q10, and DE were significantly increased to be 73.96, 80.62 and 77.4 % respectively. Further increase in the polymer ratio to 2 and 4 resulted in an additional increase in the dissolution rate of the drug (fig. 5a, table: 2). Different possible explanations for enhancing the dissolution rate of the drug after SD formation with poloxamer 407 were previously reported. The first possible one is the wetting effect of the polymer which resulted in an improvement in the wetting characteristics of the drug. This was revealed from the rapid dispersion of the dry SD formulation in the dissolution medium compared to the pure, unprocessed drug which tends to float [26]. The second possible explanation for the dissolution rate enhancement after the formation of SD with poloxamer 407 is the alteration in the crystalline structure of the drug which was clear from the results of thermal analysis. Micellar solubilization is another possible mechanism for enhancing the dissolution rate [27, 28]. Solid dispersions formation for poorly water soluble drugs with poloxamer 407 was successfully reported for enhancing their dissolution rate [17, 25, 26].

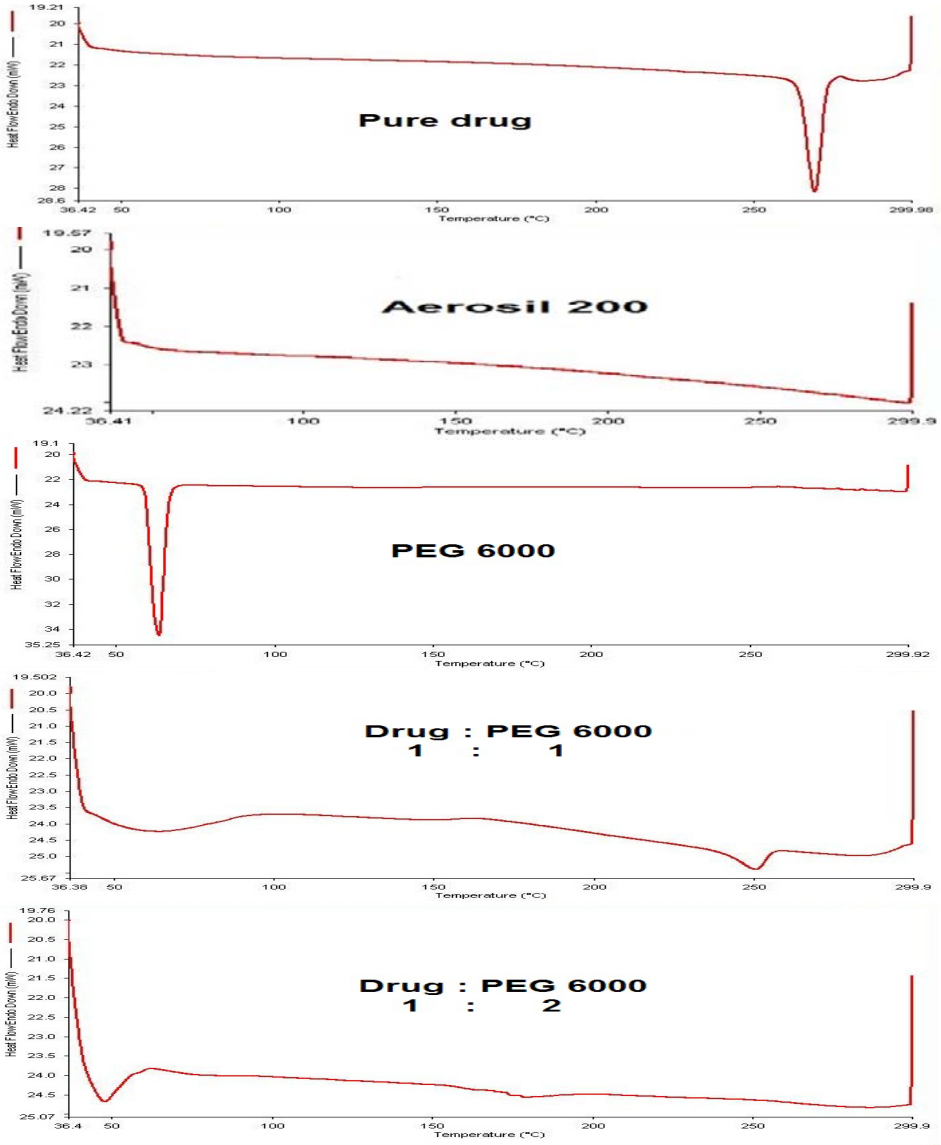

Fig. 3: DSC Profiles of HCTZ and its SDs using PEG 6000 in the presence of aerosil 200

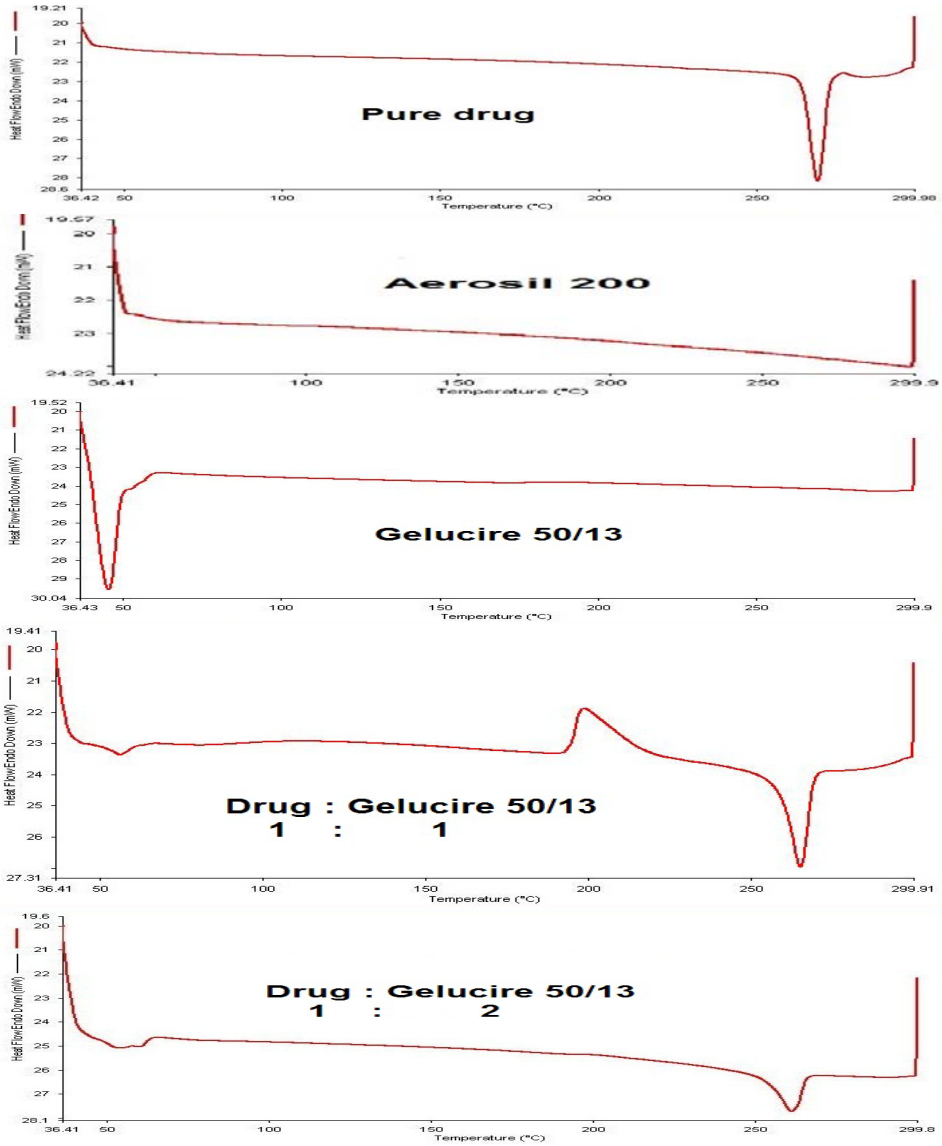

Fig. 4: DSC Profiles of HCTZ and its SDs using gelucire 50/13 in the presence of aerosil 200Table 2: The melting transition parameters and the dissolution efficiency of HCTZ and its binary SDs

Formulationcode	Tm (°C)	Enthalpy(ΔH) J/g	DE %*	Q5 %*	Q10 %*
Pure drug(HCTZ)	269.3	86.740	55.9 (0.53)	29.74 (0.58)	37.06 (0.92)
X111	258.14	11.09	77.4 (0.73)	73.96 (0.40)	80.62 (0.46)
X122	244.7	2.8	82.73 (0.87)	82.18 (1.3)	84.07(0.57)
E111	250.4	4.19	74.90 (0.57)	57.93 (1.25)	72.79 (1.68)
E122	No	No	81.33 (0.33)	79.64 (1.14)	81.14 (1.55)
G111	265.2	20.2	87.99 (0.24)	83.56 (0.63)	86.38 (1.10)
G122	261.08	9.9	84.66 (0.83)	74.38 (0.98)	86.29 (1.71)

*n = 3, data represent mean of three observations, Values between brackets are SD (n = 3), DE= dissolution efficiency, Q5= amount of the drug dissolved at first 5 min, Q10= amount of the drug dissolved at first 10 min, Formulation details are presented in table: 1

Fig. (5b) shows the dissolution profiles for SDs prepared using PEG 6000 with HCTZ in the presence of aerosil 200. These dissolution profiles revealed the enhanced dissolution rate of the prepared formulations compared to the unprocessed drug. This enhancement was also reflected in the calculated dissolution parameters which were significantly increased in the case of SDs containing the drug with PEG 6000 at weight ratios of 1:1, 1:2 (table: 2). Further increase in the polymer ratio to 4 did not result in significant change in the drug release pattern (fig. 5b). The amount of the drug dissolved from SD formulation that was prepared at 1:4 drug to polymer weight ratio in the first 5 and 10 min (Q5 and Q10) was 75.66 % and 82.00 %. The calculated dissolution efficiency was 79.82 %.

The dissolution enhancement after SDs formation with PEG 6000 can be attributed mainly to the possible formation of the amorphous structure of the drug or eutectic mixture formation. This finding is in a good agreement with the results of thermal analysis. A similar explanation was reported for PEG 6000 induced dissolution enhancement of other poorly water soluble drugs [22, 29].

An improvement of wettability of the powder due to the formation of a film of polyethylene glycol around the drug particles which modifies the hydrophobicity of the surfaces is another suggested mechanism for enhancing the dissolution rate of the SD [22, 30].

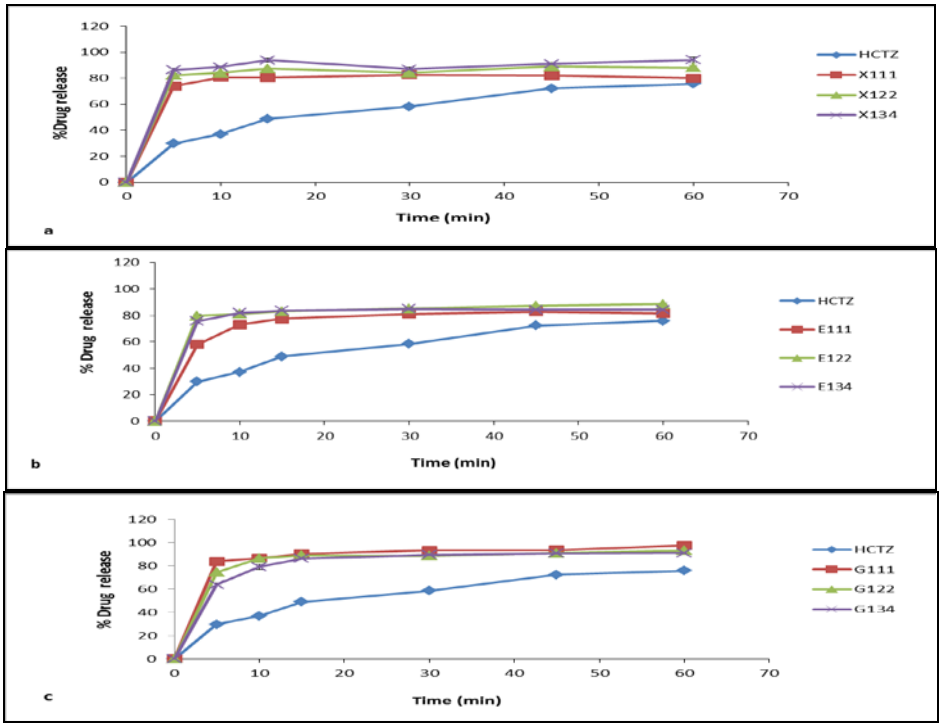

Fig. 5: Dissolution profiles of HCTZ as a pure drug and its binary SDs using (a) poloxamer 407, (b) PEG 6000 or (c) gelucire 50/13 in the presence of aerosil 200 (Error bars were omitted for clarity, formulation details are presented in table: 1) *n=3

The dissolution profiles of the SDs prepared using gelucire 50/13 in the presence of aerosil 200 are presented in fig. 5c. With the calculated dissolution parameters presented in table 2, the dissolution profiles showed enhanced dissolution rate of the drug from the binary SD formulations compared to the unprocessed drug with the enhancement being slightly decreased upon increasing the concentration of gelucire 50/13. This decrease in the dissolution rate was reflected in the calculated dissolution efficiency which was decreased from 87.99 % to 84.66 % and 82.63 % in the case of SDs containing the drug with gelucire 50/13 at weight ratios of 1:1, 1:2 and 1:4, respectively (table: 2).

The rapid dissolution obtained in the case of the dispersion prepared using gelucire 50/13 can be attributed to micellar solubilization and the self-emulsifying property of gelucire 50/13 [23, 31, 32]. The slight decrease in the drug release at higher polymer ratios may be due leaching out of the carrier during dissolution forming a concentrated layer of the solution around the drug particles slowing down the migration of the released drug particles to the bulk of the dissolution [31].

CONCLUSION

Formation of a binary SD of HCTZ with different polymers in the presence of aerosil 200 resulted in significant enhancement in the dissolution rate of the drug. This enhancement may be attributed to change in the crystalline structure of the drug after SD formation and the wetting effect or the micellar solubilization and the self-emulsifying property of the polymer.

CONFLICT OF INTERESTS

Declared none

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