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Nanocrystal Formation of Hydrochlorothiazide: Effect of a Surfactant on the Solid-State Properties

[*1]Emmanuel O. Olorunsola, [1]Sifon O. Edet, [1]Stephen O. Majekodunmi and [2]Emmanuel E. Attih

[1]Department of Pharmaceutics and Pharmaceutical Technology, University of Uyo, Uyo, Nigeria
[2]Department of Pharmaceutical and Medicinal Chemistry, University of Uyo, Uyo, Nigeria

ABSTRACT

Background: Modification of solid-state properties is associated with nanocrystallization of drug substances, and crucial to processability of materials during formulation. This work was aimed at assessing the effect of a surfactant on the solid-state properties in nanocrystal formation of hydrochlorothiazide.

Methods: The drug powder was subjected to two forms of nanocrystallization: with and without the inclusion of Tween 80, a surfactant. The two generated nanocrystal forms, in comparison with the unprocessed drug, were subjected to Fourier transform infrared spectroscopy, differential scanning calorimetry and particle size analysis.

Results: All the major peaks in the FTIR spectrum of hydrochlorothiazide powder (HCTZ1) were retained in the spectrum of crystals generated without the addition of Tween 80 (HCTZ2) and in that of the crystals generated with the addition of Tween 80 (HCTZ3). The thermogram of HCTZ1 showed a sharp endothermic transition with a peak at 77 ^{0}C followed by a diffuse endotherm with a peak at 235 ^{0}C; that of HCTZ2 was characterized by a diffuse endotherm with a peak at 110 ^{0}C and a diffuse exotherm with a peak at 250 ^{0}C while that of HCTZ3 was characterized by a single endotherm with a peak at 133 ^{0}C. The average size of the particles was in the order HCTZ3 < HCTZ2 < HCTZ1.

Conclusion: Simple nanocrystallization causes a decrease in the particle size of hydrochlorothiazide but with a disruption in the thermal properties while the inclusion of a surfactant in the nanocrystallization process causes a further decrease in the size and an improvement in the thermal behaviour of the drug.

Keywords: Surfactant, hydrochlorothiazide, nanocrystals, solid-state properties.

1. INTRODUCTION

Hydrochlorothiazide with the chemical name 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide belongs to the thiazides class of diuretics (Figure 1). It is insoluble in ether, chloroform and dilute mineral acids, very slightly soluble in water, sparingly soluble in alcohol but soluble in acetone, dimethylformamide and dilute alkalis [1, 2]. It is a BCS (Biopharmaceutics Classification System) Class IV drug having low solubility and low permeability [3, 4]. Various physicochemical properties are responsible for low solubility of drugs. Such properties include large particle size, complex structure, high molecular weight, high lipophilicity, intramolecular H-bonding, intermolecular H-bonding (crystal packing), compound H-bonding to solvent, crystallinity, pH, ionic charge status, polymorphic forms, as well as salt form [5]. On the other hand, properties such as high molecular weight and low partition coefficient are responsible for low permeability of drugs [6]. Generally, up to 50% of orally administered drugs present formulation problems related to poor hydrophilicity [7]. Poor aqueous solubility creates major problems during drug formulation; and also results in low dissolution rate of the compact solid dosage forms [8, 9]. The consequences become worse if the drug's permeability is low since solubility and permeability of drugs are important determinants of bioavailability of pharmaceutical formulations. The problem of low solubility and low permeability can be addressed during formulation development [10]. One of the most direct approaches for enhancing the solubility of substances is to generate a salt. However, if the substance is non-ionizable, solubility concern is

[*] Corresponding author: Email: emmanuelolorunsola@uniuyo.edu.ng; Phone: +2348035067306

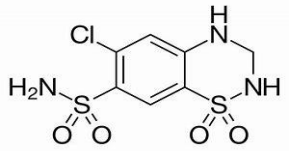

Figure 1: Chemical structure of hydrochlorothiazide

more easily addressed by particle size reduction, use of co-solvents, addition of surfactants or incorporation of complexing agents [11]. Particle size reduction has been a successful strategy used in enhancing the delivery of poorly water-soluble drugs [12, 13]. Formulation of nano-sized particles can be implemented to all drug compounds belonging to the biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and/or permeability [14]. Formulation scientists have developed and have been employing the concept of nanotechnology to overcome the problem of low bioavailability of drugs [15, 16]. Nanotechnology focuses on reducing the size of the drug substance to nano dimension so as to increase the surface area [17] and the process of size reduction usually affects the solid-state properties of the drug. This work was designed to investigate the effect of a surfactant on the solid-state properties in the course of nanocrystal formation of hydrochlorothiazide.

2. MATERIALS AND METHODS

2.1. Materials

The materials used were: hydrochlorothiazide powder (Hopkins & Williams, England), acetone (Fisher Scientific International Company, United Kingdom) and Tween 80 (BDH Chemicals Ltd., England).

2.2 Methods

2.2.1. Preparation of Nanocrystals Without the Use of a Surfactant

Antisolvent precipitation technique as described by Mokale *et al*. [18] was used for the preparation of nanocrystals. A 5 g quantity of hydrochlorothiazide powder was weighed into a 250 mL capacity beaker, and 100 mL acetone was added for dissolution. The beaker was placed on a magnetic stirrer for homogenization at 500 rpm for 45 min. The homogenized system was quickly added to 500 mL of water for precipitation. The whole content was transferred into a separating flask and allowed to stand for 1 h for proper separation. The precipitate was gently separated, air-dried for 3 h and then dried in an oven at 60 ^{0}C for 8 h to form HCTZ2.

2.2.2 Preparation of Nanocrystals with the Use of a Surfactant

A 5 g quantity of hydrochlorothiazide powder was weighed into a 250 mL capacity beaker; 2.5 g Tween 80 (surfactant) and 100 mL acetone (solvent) were added. The beaker was placed on a magnetic stirrer for homogenization of the content at 500 rpm for 45 min and the homogenized system was quickly added to 500 mL of water for precipitation. The precipitate (HCTZ3) was separated and dried using the same method described in Section 2.2.1.

2.2.3 Characterization of the Drug Powder and the Nanocrystals

2.2.3.1 Fourier transform infrared spectroscopy

The drug powder and the two batches of prepared nanocrystals were subjected to Fourier transform infrared spectroscopy. Adequate quantity of the sample was placed in a potassium bromide disk and the spectrum recorded over a scanning range of 500 to 4,000/cm using a spectrophotometer (model 8400S, Shimadzu Corporation, Kyoto-Japan) [19].

2.2.3.2. Differential scanning calorimetry

Differential scanning thermogram of each sample was obtained using a DSC-204F1 machine (NETZSCH Co., Germany). The analysis was carried out in an A1 40 uL crucible and the scanning was done at 20 ^{0}C per minute heating rate over a temperature range of 40-300 ^{0}C [16].

2.2.3.3 Particle size analysis and polydispersity index (PDI) determination

Determination of the particle size and polydispersity index (PDI) of each sample was carried out by means of dynamic light scattering. The sample was diluted, and a suitable quantity of the diluted sample was transferred into the appropriate cell/cuvette in the cell area. Determination of the particle size and polydispersity index was done using Nano-ZS Zetasizer (Malvern Instruments, UK) [16].

2.3 Statistical Analysis
Statistical analysis of the particle sizes was done automatically by the Nano-ZS Zetasizer (Malvern Instruments, UK).

3. RESULTS AND DISCUSSION

3.1. Yields of the Nanocrystals
The nanocrystallization process without the use of a surfactant gave a yield of 21.8% while the same process but involving the use of a surfactant gave a yield of 40% nanocrystals. The result shows that the surfactant enhanced the production of the nanocrystals. This can be explained by the fact that the presence of the surfactant caused higher amount of the drug powder to be solubilized so that on precipitation by the antisolvent, a higher yield could be obtained [20]. The disparity in the yields of nanocrystals obtained from the nanocrystallization with and without surfactant is in agreement with the report of Muller *et al*. [21]. In their work, it was stated that inclusion of surfactant enhances the generation of nanocrystals and also modulates the particle size distribution.

3.2. Fourier Transform Infrared Spectra
The Fourier transform infrared spectra of the drug powder, nanocrystals generated without a surfactant and the nanocrystals generated with the inclusion of a surfactant are shown in Figure 2.

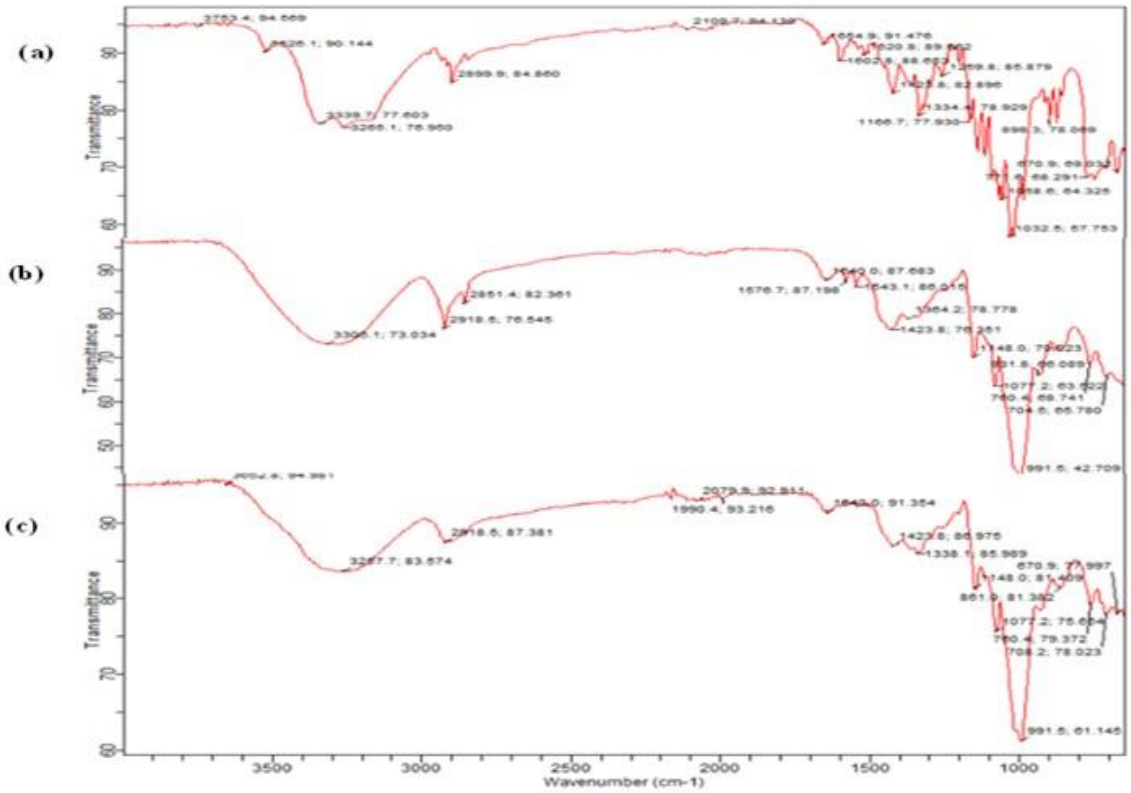

Figure 2: FTIR spectra of (a) Hydrochlorothiazide powder; (b) Hydrochlorothiazide nanocrystals prepared without a surfactant; (c) Hydrochlorothiazide nanocrystals prepared with a surfactant

The FTIR spectrum of hydrochlorothiazide powder (Figure 2a) showed many peaks from 670.9 to 3,753.4 cm^{-1}. The absorption peaks at 670.9 and 898.3 cm^{-1} are indicative of C-Cl stretching and C-H bending of aromatic ring respectively while those at the finger print region 900 – 1400 cm^{-1} reflect the presence of C-C and C-N bonds. The peak between 1140 and 1180 cm^{-1} also indicates the presence of S=O bond. Several peaks observed within the double bond region (1,500-2000 cm^{-1}) are indicative of carbon-carbon double bond of the aromatic ring. Many peaks were detected in the single bond area (2,500-4,000 cm^{-1}) especially from 3,000-3,800 cm^{-1} showing the presence of aromatic bonds (C-H stretching) and primary amine stretching. These observations are characteristic of hydrochlorothiazide as shown in the work of Olorunsola *et al*. [3]. The Absorption peaks in the FTIR spectra of nanocrystals generated without the use of a surfactant (Figure 2b) and nanocrystals

generated with the use of a surfactant (Figure 2c) are similar to that of the hydrochlorothiazide drug powder. The major differences are in the position of the peaks. For example, while the peak indicating C-Cl stretching was observed at 670.9 cm^{-1} in the spectrum of pure hydrochlorothiazide powder and nanocrystals generated using a surfactant, it was observed at 704.5 cm^{-1} in nanocrystals generated without a surfactant showing that non-inclusion of the surfactant in the nanocrystallization process caused a shift in the absorption peak of the C-Cl group. Also, while the peak indicating the presence of S=O bond was observed at 1166.7 cm^{-1} in the spectrum of the drug powder, it was observed at 1148.0 cm^{-1} for the two types of nanocrystals. This shows that nanocrystallization process with or without the inclusion of the surfactant results in same change in the absorption peak position of the S=O bond.

3.3. Differential Scanning Thermograms

The differential scanning thermograms of the drug powder, nanocrystals generated without a surfactant and the nanocrystals generated with inclusion of a surfactant are shown in Figure 3 with the exothermic direction being upward. The thermogram of the drug powder showed a sharp endothermic transition with a peak at 77 ºC followed by a diffuse endotherm with a peak at 235 ºC. The first endotherm can be ascribed to the enthalpic relaxation of the drug powder while the second endotherm can be ascribed to the melting [22]. Hence, the peak at 235 ºC represents the melting point of the drug. The diffuse nature of the melting endotherm is a reflection of the amorphous nature of the drug powder. The thermogram of the nanocrystals HCTZ 2 was characterized by a diffuse endotherm with a peak at 110 ºC and a diffuse exotherm with a peak at 250 ºC while the thermogram of nanocrystals HCTZ 3 was characterized by a single endotherm with a peak at 133 ºC. From the diffuse exotherm in the thermogram of HCTZ 2, it can be inferred that the drug particles crystallized before melting. The single endotherm in the thermogram of HCTZ 3 can be ascribed to enthalpic relaxation. Since no other transition was observed, it can be inferred that melting did not occur within the heating temperature limit. As such, nanocrystallization in the presence of the surfactant led to increase in the melting point of hydrochlorothiazide.

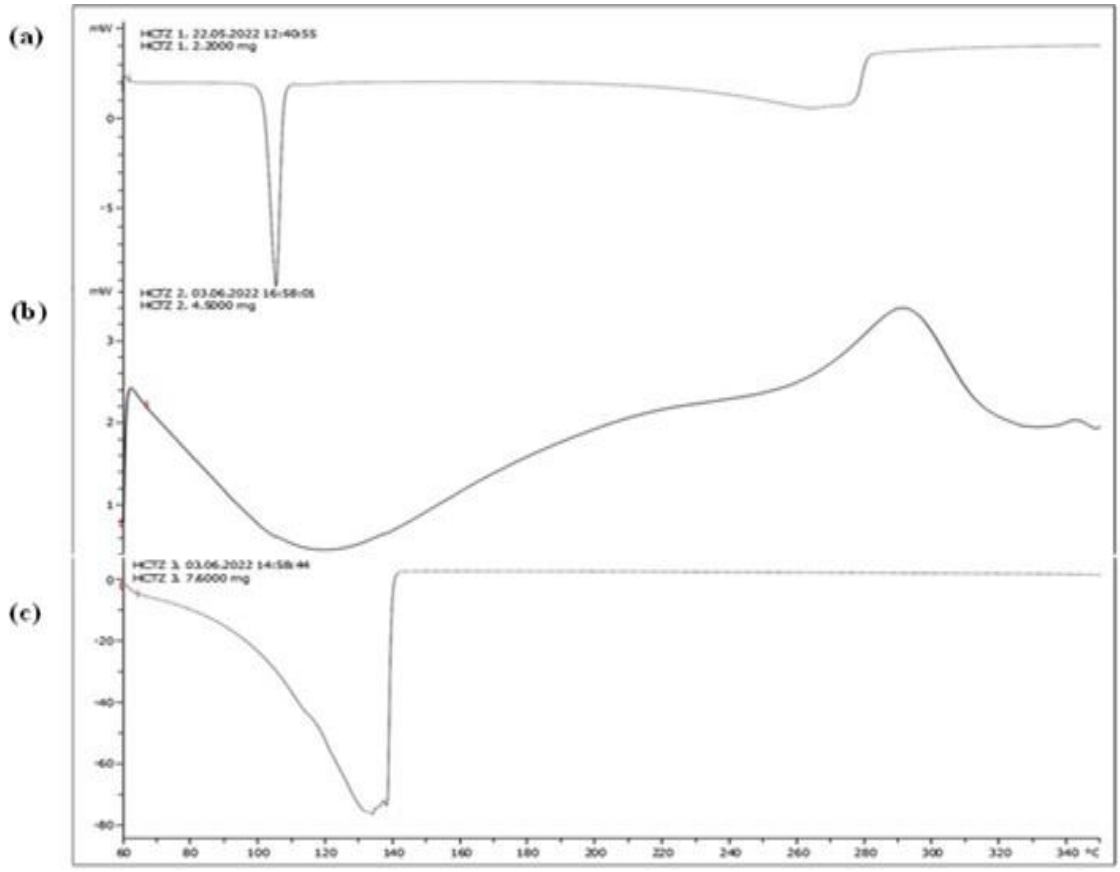

Figure 3: DSC thermograms of (a) Hydrochlorothiazide powder; (b) Hydrochlorothiazide nanocrystals prepared without a surfactant; (c) Hydrochlorothiazide nanocrystals prepared with a surfactant

3.4. Particle Size Distribution and Polydispersity Index

Particle size distribution and the polydispersity index of the pure powder and the two types of nanocrystals (HCTZ 2 and HCTZ 3) are shown in Table 1.

Table 1: Particle size distribution and polydispersity index of the various solid particles

S/N	Material	Z-Average (nm)	Polydispersity index	Peaks	Mean diameter (nm)	% Volume
1	HCTZ 1	45.20	0.554	Peak 1	0.88	46.8
				Peak 2	10.52	8.1
				Peak 3	60.03	44.9
2	HCTZ 2	36.70	0.699	Peak 1	0.88	66.5
				Peak 2	10.50	5.4
				Peak 3	63.61	28.0
3.	HCTZ 3	29.47	0.776	Peak 1	0.88	77.30
				Peak 2	10.56	4.0
				Peak 3	48.43	18.6

HCTZ 1 = hydrochlorothiazide powder; HCTZ 2 = hydrochlorothiazide nanocrystals generated without the use of a surfactant; HCTZ 3 = hydrochlorothiazide nanocrystals generated with the use of a surfactant

The order of Z-average is HCTZ 3 < HCTZ 2 < HCTZ 1 showing that the nanocrystals generated with the use of a surfactant has the smallest average particle size followed by the nanocrystals generated without a surfactant. Therefore, the nanocrystallization caused a reduction in the particle size of the drug, with the inclusion of the surfactant causing further reduction in the particle size. This is in agreement with the work of Zirak and Pezeshki [23]. The width of particle size distribution was not well modulated with nanocrystallization since the polydispersity index increased. However, there was skewing of the particle size distribution toward small size upon nanocrystallization; and the skewing became more when a surfactant was introduced during nanocrystallization. For instance, 46.8% of HCTZ 1 had mean particle diameter of 0.88 nm while 66.5% of HCTZ 2 and 77.3% of HCTZ3 had the same mean particle size.

4. CONCLUSION

Inclusion of a surfactant improves the yield of hydrochlorothiazide nanocrystals and the chemical composition of the crystal is not adversely affected whether the nanocrystallization is done with or without the inclusion of a surfactant. For nanocrystallization without the inclusion of Tween 80, hydrochlorothiazide crystallizes before melting while nanocrystallization in the presence of the surfactant leads to increase in the melting point of the drug. The process of nanocrystallization causes a reduction in the mean particle size of the drug, with the inclusion of the surfactant causing further reduction. This suggests that nanocrystallization could improve the biopharmaceutical properties of the drug especially if a surfactant is included in the process.

Conflict of Interest

There is no conflict of interest.

Funding Information

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Authors' Contributions

This study was conceived and designed by Emmanuel Olorunsola. Data collection was done by Sifon Edet. Data analysis was done by Sifon Edet and Stephen Majekodunmi while the interpretation was done by Emmanuel Olorunsola and Emmanuel Attih. The manuscript was written by Sifon Edet and Emmanuel Olorunsola while the critical revision was done by Stephen Majekodunmi and Emmanuel Attih.

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