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Original Article

# SOLID DISPERSION OF CANDESARTAN CILEXETIL WITH HPMC: A COMPARATIVE STUDY OF FREEZE-DRYING AND SPRAY-DRYING TECHNIQUES

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**ABSTRACT**

**Objective:** The angiotensin II receptor antagonist candesartan cilexetil (CC) exhibits low bioavailability in humans, principally as a result of its limited aqueous solubility at low pH and the presence of a carboxyl moiety. To enhance the solubility of CC, this study aimed to develop solid dispersion (SD) systems incorporating hydroxypropyl methylcellulose (HPMC) as the polymer.

**Methods:** SD was fabricated through freeze-drying and spray-drying methods. utilizing HPMC as a hydrophilic polymer, eschewing the use of any organic solvents. Intact material and physical mixture were prepared as a comparison. Physicochemical properties of the intact material, physical mixture and SD were characterized employing the differential scanning calorimetry (DSC), x-ray diffractometry (XRD), fourier transform infrared (FT-IR) spectroscopy, and scanning electron microscopy (SEM). Solubility test was performed using shake flask method.

**Results:** The XRD analysis revealed a reduction in peak intensity for the SD. Additionally, thermal analysis indicated that the SD exhibited lower melting points than both the intact CC and the physical mixture. Moreover, the morphology of the SD displayed distinct shapes compared to the intact materials and the physical mixture. Additionally, Fourier-transform infrared (FT-IR) spectroscopy analysis revealed no shifts in the characteristic wavenumbers of the functional groups, indicating the absence of new functional group formation. Significantly, the solubility of the SD was markedly improved, as evidenced by the solubility test results: 3.37±1.12 µg/ml for intact CC, 31.39±1.45 µg/ml for the physical mixture, 35.43±1.87 µg/ml for the spray-dried SD, and 53.40±1.05 µg/ml for the freeze-dried SD.

**Conclusion:** The SD of candesartan cilexetil and hydroxypropyl methylcellulose successfully altered the physicochemical properties of the drug, resulting in a significant enhancement of its solubility.

**Keywords:** Candesartan cilexetil, Solid dispersion, Freeze drying, Spray-drying, Solubility


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## INTRODUCTION

The therapeutic efficacy of poorly water-soluble drugs can be compromised by their low solubility and dissolution rate [1]. Solid dispersions (SD) offer a promising strategy to enhance the solubility and dissolution rate of these drugs. SD are molecular dispersions of poorly water-soluble drugs in hydrophilic polymers [2, 3]. The improved wettability, reduced particle size, and altered crystallinity of the drug within the SD matrix contribute to enhanced drug dissolution both *in vitro* and *in vivo* [4].

Candesartan cilexetil (CC) is an orally active angiotensin II receptor antagonist characterized by low bioavailability in humans, approximately 23-39% [5]. This limited bioavailability is primarily attributed to its poor aqueous solubility at low pH [6]. The dissolution rate of CC is constrained by its low solubility under non-buffered or acidic conditions, whereas it exhibits rapid and complete dissolution at pH 5.0 and higher [7]. Moreover, the chemical structure of CC (fig. 1) reveals the presence of a carboxyl group and is a major contributor to its poor absorption in the gastrointestinal tract [7].

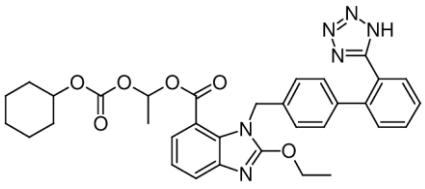

**Fig. 1: Chemical structure of candesartan cilexetil**

Previous studies have been reported to enhance the solubility of CC, such as nanosuspension [8], complex with cyclodextrin [9], mesoporous silica [10], self-emulsifying drug delivery system (SNEDDS) [11], and liquid compact [12]. Meanwhile, CC have been developed into SD with various polymer's PVP [6,7], natural p-glycoprotein [13], hydroxypropyl methylcellulose acetate succinate (HPMCAS) [14], and polyethylene glycol (PEG) 6000 [15].

Hydroxypropyl methylcellulose (HPMC) is a highly water-soluble polymer that significantly facilitates the absorption of water into the solid dispersion matrix [16]. HPMC has been widely employed as a carrier in the production of solid dispersions using both spray drying and freeze-drying methods. Previous studies have demonstrated that the use of HPMC as a carrier in solid dispersions can enhance the solubility and dissolution of various drug compounds, including usnic acid [17], curcumin [18], gefitinib [19], piperine [20], tenoxicam [21], dipyridamole, and cinnarizine [22].

To the best of our knowledge, previous studies have not reported the formation of SD of CC with hydrophilic polymers. This study investigates the preparation of SD of CC with the hydrophilic polymer HPMC to enhance CC solubility and compare different preparation methods. Characterization of the intact materials and SD was performed using powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier-transform infrared (FT-IR) spectroscopy, and scanning electron microscopy (SEM).

## MATERIALS AND METHODS

### Materials and reagents

Candesartan cilexetil (CC) was obtained from PT. Kimia (Jakarta, Indonesia), HPMC (Shin-Etsu Chemical, Japan), ethanol (Bratachem, Indonesia) and distilled water (Bratachem, Indonesia).

### Preparation of solid dispersion by spray drying

Solid dispersions (SDs) were fabricated using a 1:1 (w/w) ratio of CC to HPMC. CC was moistened with 2 ml of ethanol, while HPMC

was dispersed in 100 ml of distilled water. The mixture was homogenized using a magnetic stirrer at 100 rpm and room temperature. Subsequently, the SD was formed using a spray dryer with an inlet temperature of 120 °C, an outlet temperature of 60 °C, a flow rate of 35 $m^3$/h, and a nozzle diameter of 0.7 mm. The dried powder was stored in a desiccator [17]. The operational parameter was selected based on the preliminary research that considering the thermal stability of CC.

**Preparation of the solid dispersion by freeze-drying**

Freeze-dried powders were produced using the same ratio and process as the spray-dried powders up to the point of homogeneous CC dispersion within HPMC. The mixture was then frozen using liquid nitrogen. Primary drying was carried out at-20 °C and 0.056 atm for 12 h, followed by secondary drying at 20 °C for 12 h. The dried powder was stored in a desiccator. The dried powder was then removed from the freeze dryer flask and stored in a desiccator [23]. The operational parameter was selected based on the preliminary research that considering the thermal stability of CC.

**Preparation of physical mixture**

A physical mixture of CC and HPMC was prepared in a 1:1 (w/w) ratio by physically mixing the components in a sealed container for 5 min. The resulting physical mixture powder was subsequently stored in a desiccator [20].

**X-ray diffraction (XRD) analysis**

The crystallinity of the intact materials, physical mixture, and SD was assessed using an X-ray diffractometer (X'Pert XRD Powder type PW 30/40 PAN alytical, The Netherlands). Samples were analyzed over a 2θ range of 5° to 70°. The diffractometer was configured with a Cu target, Kα filter, and operated at 45 kV and 40 mA at room temperature [17].

**Differential scanning calorimetry (DSC) analysis**

The thermal properties of SD, HPMC, CC, and physical mixtures were evaluated using a differential scanning calorimeter (SETARAM Type EVO-131, France). Before the measurement, a small amount of the studied material was placed on a calibrated aluminium pan using indium. The temperature range of the DSC device was set to 30–250 °C, with a heating rate of 10 °C/minute [17].

**FT Infra-red spectroscopy analysis**

The infrared spectroscopy analysis was performed using a spectrophotometer (Perkin Elmer FT-IR, USA) over a wavenumber range of 4000-600 $cm^{-1}$. The absorbance spectra of the intact materials, physical mixtures, and SDs were measured [17].

**Scanning electron microscopy (SEM) analysis**

The surface morphology of CC, HPMC, physical mixtures, and SD was investigated using a scanning electron microscope (SEM, Hitachi S-3400N, Japan). Small samples were mounted on a sample holder, and the SEM was operated at a voltage 10 kV and a current of 12 mA [17].

**Solubility study**

The solubility of CC, physical mixtures, and SDs was determined by adding an excess amount of each sample to 100 ml of distilled water and shaking the mixture for 24 h in a water bath. The amount of dissolved CC in the filtered solution was measured using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan) at the maximum absorbance wavelength (λmax) of CC in aqueous solution (255 nm). All experiments were performed in triplicate. Data were analyzed using one-way ANOVA to compare the means of multiple groups.

**RESULTS AND DISCUSSION**

**X-ray diffraction (XRD) analysis**

Powder X-ray diffraction (XRD) is a fundamental technique employed to characterize the crystallinity of materials. This analysis utilizes high-energy X-ray radiation to probe the atomic structure [17]. Crystalline phases exhibit characteristic diffraction peaks on the diffractogram, resulting from the ordered arrangement of atoms within the crystal lattice. Conversely, amorphous phases, characterized by a disordered atomic arrangement, display broad, diffuse diffraction peaks with typically one or two maxima [24]**.** The broad diffraction pattern observed for HPMC suggests an amorphous phase [20]. In both the physical mixture and the SD, the 2θ peak characteristic of CC was observed. However, a decrease in peak intensity was noted for the solid dispersion, indicating a potential reduction in crystallinity. Furthermore, SD prepared by freeze-drying exhibited a more pronounced reduction in peak intensity at equivalent 2θ angles, further supporting a decrease in crystallinity (fig. 2, table 1). The substantial reduction in peak diffraction intensity of the SD confirms a significant decrease in the crystallinity of the solid-phase CC within these formulations [25].

**Table 1: The peak intensity of CC, HPMC, physical mixture of CC and HPMC, SD of CC and HPMC prepared by freeze-drying, and SD of CC and HPMC prepared by spray-drying**

| Position 2θ | Peak diffraction intensity | | | |
|---|---|---|---|---|
| | Candesartan cilexetil | Physical mixture | Freeze-dried powder | Spray dried powder |
| 9.79 | 3757.54 | 6448.39 | 1114.69 | 3836.37 |
| 17.12 | 4464.06 | 2222.67 | 554.50 | 3484.77 |
| 19.07 | 1961.23 | 2919.67 | 551.29 | 1729.47 |
| 20.11 | 2444.04 | 3081.01 | 356.19 | 1599.09 |
| 21.98 | 1511.09 | 2096.78 | 745.78 | 1172.85 |
| 23.07 | 3548.26 | 3432.19 | 297.79 | 2419.21 |
| 24.96 | 1400.53 | 1602.10 | 115.57 | 836.89 |

**Differential scanning calorimetry (DSC) analysis**

DSC is a versatile analytical technique employed to assess the thermodynamic behaviour of solid substances under controlled thermal conditions [26]. The DSC thermogram reveals characteristic endothermic and exothermic peaks indicative of melting, phase transformations, recrystallization, and dehydration processes [27]. As depicted in DSC thermogram fig. 3, CC, a crystalline compound, exhibits a hight intensity of endothermic peak at 173.3 °C, indicative of its melting point. The HPMC polymer displays a broad endothermic peak spanning 58.9-108.6 °C. While the endothermic peak of CC remains discernible in the physical mixture, the melting point and enthalpy are observed to be lower than those of pure CC. The endothermic peak of CC is slightly reduced in both SD compared to the physical mixture, suggesting that the spray-drying and freeze-drying techniques employed for SD preparation result in the dispersion of CC in an amorphous form within the hydrophilic HPMC polymer carrier**.**

**FT Infra-red Spectroscopy analysis**

Fig. 4 depicts the Fourier-transform infrared (FT-IR) spectra of CC, HPMC, physical mixtures, and SD. The FT-IR spectrum of CC reveals characteristic peaks associated with O-H bond stretching at 3448.33 $cm^{-1}$ and C-H bond stretching at 2940.87 $cm^{-1}$. The FT-IR spectrum of HPMC exhibits a C-H bond stretching peak at 2922.79 $cm^{-1}$, which falls within the typical range of 4000-3000 $cm^{-1}$ for C-H bonds. There were no shifts in the wavenumbers of the physical mixtures and SD were observed. The O-H bond stretching peak of physical mixture and SD were constantly at 3448.33 $cm^{-1}$. Furthermore, a slightly shift in the α-C-H stretching peak was observed, with

corresponding wavenumbers of 2939 $cm^{-1}$ for freeze-dried powder but for the physical mixture and spray-dried powder, the wavenumbers remine. The absence of new peaks in the FT-IR spectra of the SD confirms the lack of new functional group formation, suggesting that the SD are formed through physical interactions rather than chemical reactions [28].

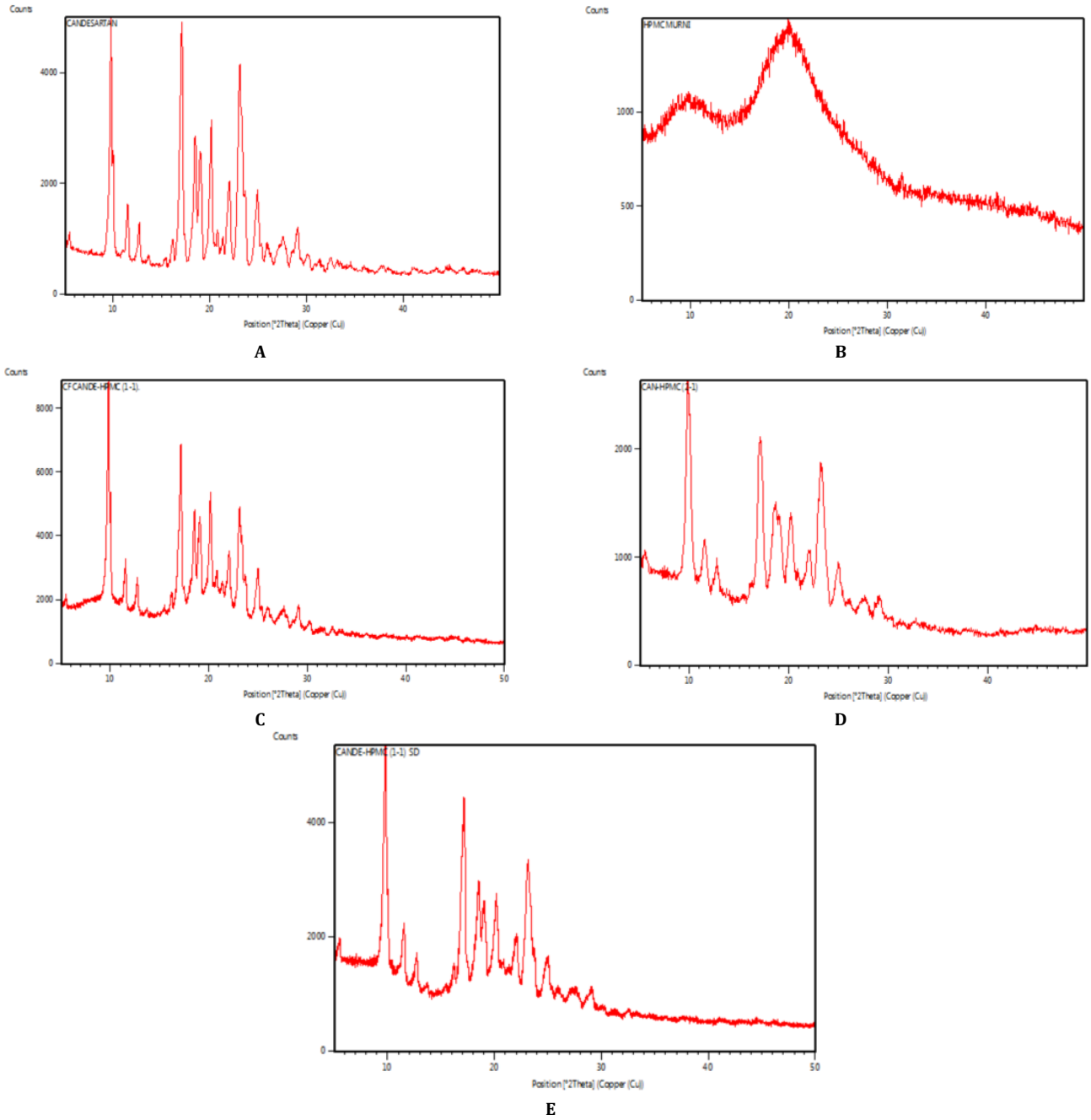


**Fig. 2: XRD diffractograms of (A) CC, (B) HPMC, (C) the physical mixture of CC and HPMC, (D) SD of CC and HPMC prepared by freeze-drying, and (E) SD of CC and HPMC prepared by spray-drying. XRD patterns showing reduced crystallinity in freeze-dried formulations compared to spray-dried samples**

**Scanning electron microscopy (SEM) analysis**

SEM is a widely utilized instrument for the characterization of material morphology, owing to its exceptional resolution. SEM analysis provides valuable insights into the influence of processing techniques on the morphology of materials [24]. Fig. 5 illustrates the morphology of CC, physical mixtures, and SD. As show in fig. 5A, CC exhibits a rod-like morphology, while HPMC (fig. 5B) appears as irregular particles. The physical mixture (fig. 5C) retains the morphologies of both intact materials, as the low-energy mixing process did not induce significant morphological changes. Conversely, the fabrication of SD through spray-drying as well as freeze-drying techniques resulted in altered particle morphologies. The spray-dried particles, generated using a nozzle-based spray dryer, exhibit a spherical morphology (fig. 5E). Furthermore, the freeze-drying process, which involves sublimation, resulted in the formation of pores within the particles and an irregular particle shape (fig. 5D).

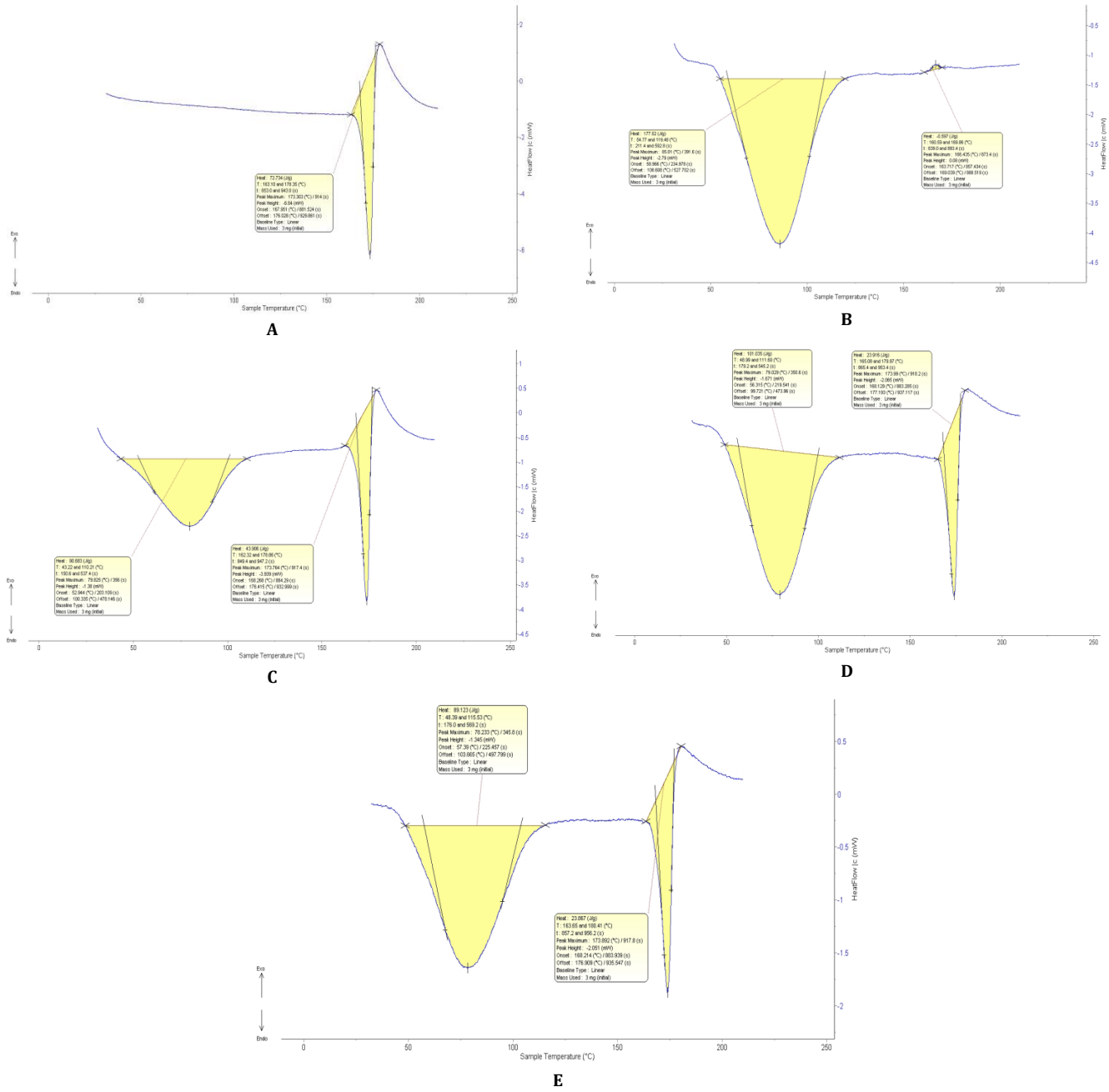


**Fig. 3: DSC thermogram of (A) CC, (B) HPMC, (C) the physical mixture of CC and HPMC, (D) SD of CC and HPMC prepared by freeze-drying, and (E) SD of CC and HPMC prepared by spray-drying**

### Solubility study

The solubility of intact compound, physical mixture and SD of CC was presented in table 2. A significant ($p<0,05$) enhancement in the solubility of CC was observed in the SD, which aligns with the findings from XRD and DSC analysis. Several factors likely contribute to the observed enhancement in solubility. The hydrophilic polymer HPMC, incorporated into both the physical mixture and SD, possesses excellent water solubility, which is a probable contributor to the increased solubility [21]. Furthermore, the incorporation of HPMC is associated with a decrease in the crystallinity of the SD, particularly without the formation or modification of new functional groups, as confirmed by infrared spectroscopy. Another contributing factor to the enhanced solubility is the specific preparation methods employed for the SD. The spray-drying method is well-known to produce micro spherical particles, as illustrated in the microphotograph (fig. 5), which leads to an increase in the total surface area and consequently enhances solubility. Conversely, the freeze-drying method results in the formation of porous particles, which can also influence the interaction with water. This result was anticipated, given that the SD were prepared by combining crystalline CC with an amorphous polymer. The solubility of SD of CC prepared using freeze drying was higher compared to those prepared using spray drying. This finding is consistent with previous studies comparing these two methods [17]. Solubility is a critical factor influencing the absorption of active pharmaceutical ingredients from the gastrointestinal tract following oral administration. Poorly soluble drugs frequently exhibit limited bioavailability in the systemic circulation. Consequently, modifying the solubility characteristic of drug compounds can substantially enhance their bioavailability and pharmacological efficacy. The solid-state and crystallinity significantly influence the solubility of hydrophobic drugs. In general, amorphous phase perform higher solubility than crystalline phases [17].

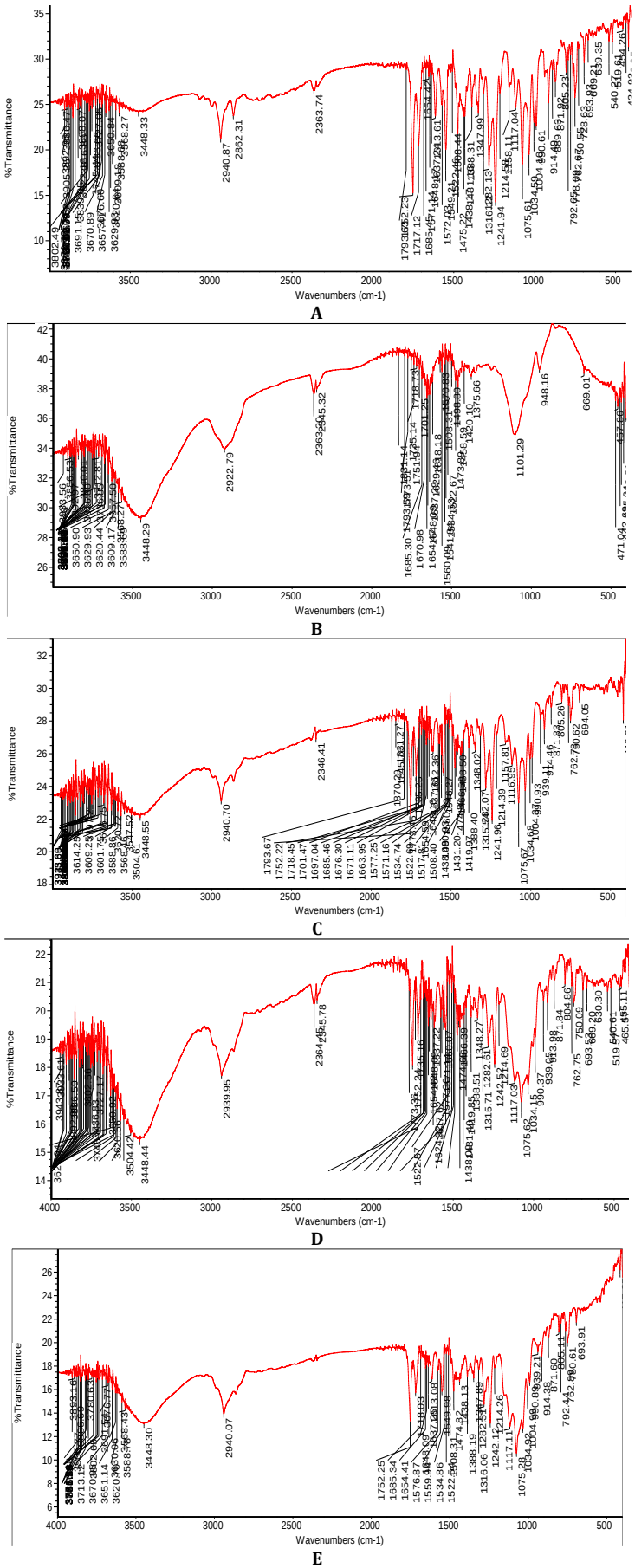


**Fig. 4: FTIR Spectrum of (A) CC, (B) HPMC, (C) the physical mixture of CC and HPMC, (D) SD of CC and HPMC prepared by freeze-drying, and (E) SD of CC and HPMC prepared by spray-drying**

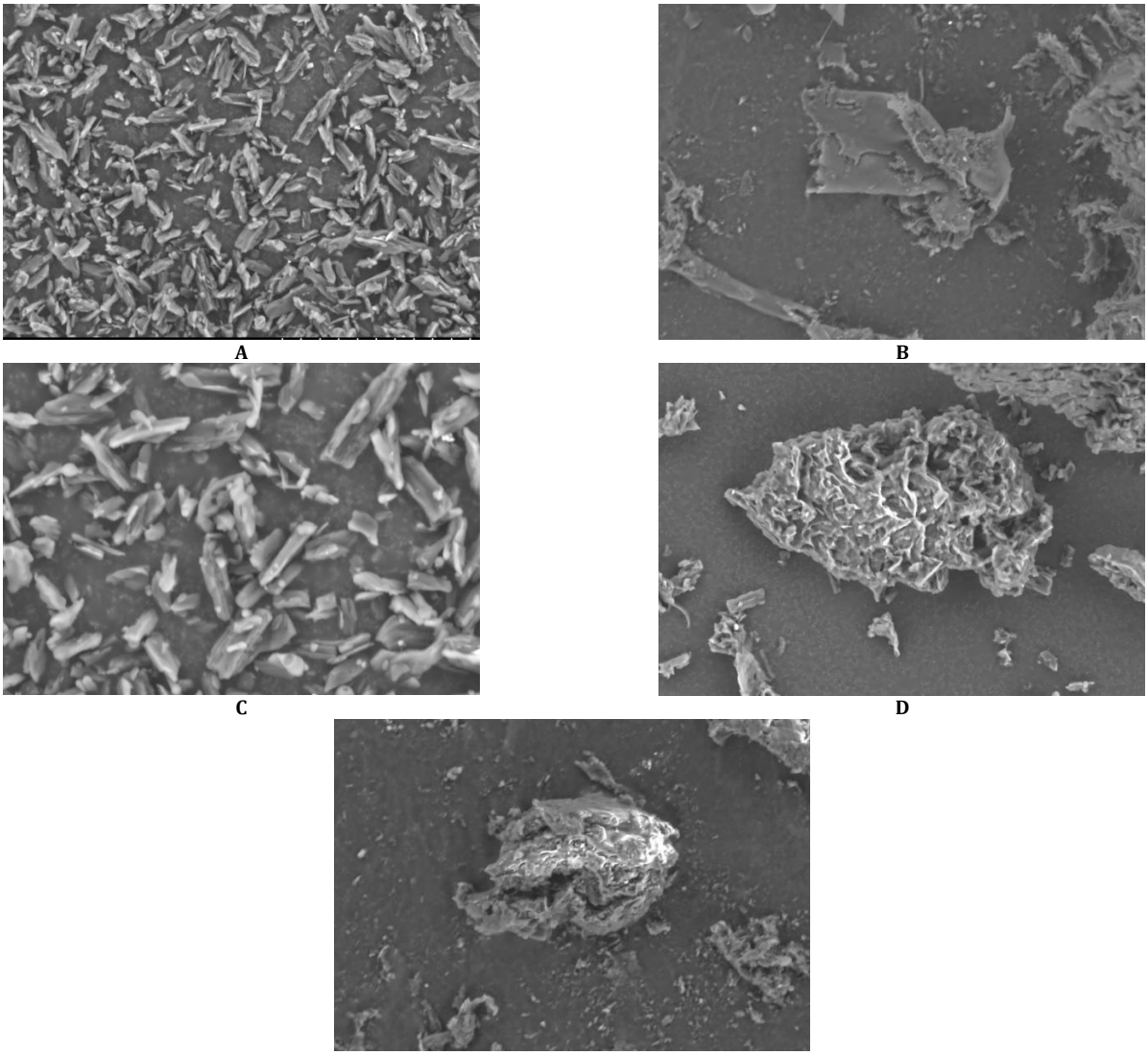


**Fig. 5: SEM microphotograph (1000x magnification) of (A) CC, (B) HPMC, (C) the physical mixture of CC and HPMC, (D) SD of CC and HPMC prepared by freeze-drying, and (E) SD of CC and HPMC prepared by spray-drying. SEM photo showed that the processing procedure affects the surface morphology of CC**

**Table 2: Solubility studies**

| Materials | Solubility (µg/ml) |
|---|---|
| Candesartan cilexetil | 3.37±1.12 |
| Physical mixture | 31.39±1.45 |
| Spray Dried SD | 35.43±1.87 |
| Freeze Dried SD | 53.40±1.05 |

Data are expressed as mean±SD (n=3)

## CONCLUSION

SD of CC and HPMC prepared using both spray-drying and freeze-drying techniques significantly enhance the water solubility of CC. The freeze-dried powder exhibits lower crystallinity, as evidenced by reduced diffraction peak intensities and lower endothermic properties compared to the spray-dried powder, which likely contribute to its superior solubility.

## ABBREVIATIONS

CC-Candesartan Cilexetil, HPMC-Hydroxy Propyl Methyl Cellulose, SD-Solid Dispersion DSC-Differential Scanning Calorimetry, XRD-X-ray diffractometry, FTIR-Fourier Transform Infra-Red, SEM-Scanning Electron Microscopy.

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Nil

## AUTHORS CONTRIBUTIONS

Deni Noviza: Project planning and management, securing funding, supervision, resource allocation, conceptualization, and manuscript preparation; Azwita: Research investigation.

## CONFLICT OF INTERESTS

Declared none

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