Acyclovir Antiviral Drug Cocrystal with Theophylline: Screening Experimental and Physical Characteristic

MONTHA Meepripruk[1,a], NUSARA Wanachalermkit[1,b], AUNGKANA Chatkon[2,c], WEENAWAN Somphon[3,d] PEK Lan Toh[4,e],

[1]Kamphaeng Phet Rajabhat University, Kamphaeng Phet, Thailand
[2]Nakhon Ratchasima Rajabhat University, Nakhon Ratchasima, Thailand
[3]Kasetsart University Kamphaeng Saen Campus, Nakhon Pathom, Thailand
[4]UniversitiTunkuAbdulRahman, Perak, Malaysia

[a]<montha_mee@hotmail.com>, [b]<wanachalermkit@gmail.com>, [c]<tuy448@yahoo.com >, [d]<weenawan.s@ku.ac.th>, [e]<peklan_toh@yahoo.com.my>

Keywords: Screening experimental**,** physical characteristic, acyclovir, theophylline

Abstract. Acyclovir is the most common in antiviral drug used to treat herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). Acyclovir is low cytotoxicity and low HSV resistance as well as the availability of low cost generic forms. Advantage, acyclovir was low bioavailability, perhaps partially due to low solubility. The screening experimental of 1:1 acyclovir-theophylline (ACV-TP) by slow evaporation *via* solution base methods under 8 solvents. The cocrystal form was obtained in the solvent ethanol: water (1:2). The physical properties were characterized by FTIR and TGA/DSC techniques.

1. Introduction

Acyclovir is the most common in antiviral drug used to treat herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) that cause human herpesvirus including chickenpox. Acyclovir is low cytotoxicity and low HSV resistance as well as the availability of low cost generic forms [1]. Advantage, acyclovir was low bioavailability, perhaps partially due to low solubility. It was freely soluble in dimethyl sulfoxide (DMSO), good solubility in dilute aqueous alkali hydroxide and mineral acid solutions, very slight solubility in ethanol and maximum solubility in water of 2.5 mg/mL at 37 °C. Acyclovir contains alcohol and amine functional groups with pKa of the monocation at 2.27 and of the alcohol at 9.25 [2]. The combinations of acyclovir with other compounds, some of these demonstrated antiviral activity and have been demonstrated to possess synergistic effects against HSV.

The complexation between acyclovir (ACV) with β-cyclodextrin (β-CD) (1:1) used for the treatment of herpes simplex virus infection was found much more soluble than the uncomplexed drug [3]. To improve acyclovir solubility and/or its dissolution properties, two cocrystals of this drug were successfully produced with glutaric acid (AGA1:1) and fumaric acid (AFA1:1) as conformers, using a cogrinding method. The effective formation was investigated by thermal analysis, Fourier transform infrared spectroscopy, X-ray powder diffraction, solid state nuclear magnetic resonance, and scanning electron microscopy coupled with energy dispersive X-ray spectrometry [4]. The cocrystallization of acyclovir with ascorbic acid and zinc chloride forming a new complex of 1:1:1 acyclovir-ascorbic acid-$ZnCl_2$, ACV-ASc-Zn) with slow evaporation via solution-based methods under 10 solvents. The cocrystal forms in the solvent isopropanol-water (1:2) and physical properties were characterized by SEM/EDX, FT-IR and TGA. [5]. The Co-crystals of theophylline with oxalic acid, glutaric acid and maleic acid have been investigated with DSC, TGA and FTIR [6]. The cocrystallization of theophylline (TP) with salicylic acid (SA) and picolinic acid (PI). The TP-SA

and TP-PI products were characterized by XRD, FT-IR/FT-Raman, and DSC/TG. Crystals [7]. Theophylline, db3',5'-cAMP, decreased significantly the yield of HSV-1, whereas the addition of insulin or db3',5'-cGMP (cGMP-enhancing compounds) increased the viral yields [8]. This study was focused on screening experimental and physical characteristic acyclovir antiviral drug cocrystal with theophylline potentially improved solubility of acyclovir drug, or a possibly synergistic material useful for HSV/VZV treatment and may reduce the frequency and severity of herpes outbreaks.

2. Research Methodology

All chemicals and solvents were purchase in reagent grade and were used without purification. Acyclovir was separated from acyclovir drugs.

2.1 Separation of acyclovir

Acyclovir material was separated from an acyclovir drugs, (Vilerm, Siam Pharmaceutical Co.,) with 320 mL of deionized H_2O (2.5 mg/mL at 37°C), stirred at 250 rpm and heated at 70–80°C for 30 mins and filtered. The filtrate was heated at 70–80°C to reduce the volume until one third remained, cooled to room temperature, and left overnight to precipitate. The precipitate was filtered, washed with distilled H_2O, and dried in air at room temperature [5,9].

2.2 Cocrystal Screening by solution-base methods

The 1:1 molar ratio of acyclovir and theophylline were prepared into 8 solvents as follows: H_2O, 0.1 M HCl, 0.1 M NaOH, CH_3OH: H_2O (1:2), C_2H_5OH: H_2O (1:2), C_3H_7OH: H_2O (1:2), 0.1 M CH_3COOH and CH_3COCH_3: H_2O (1:2). The mixture was heated 70-80 ^oC and stirred 300 rpm for 30 minutes to obtain a clear solution, and filtered. The filtrate was cool at room temperature for several days until crystals formed.

2.3 Characterization

FT-infrared spectra were measured on a Perkin-Elmer model Spectrum GX, over the range 4000-400 cm^{-1} with KBr pellets. DSC was performed on an NETZSCH DSC 204 F1 Phoenix using sample placed in aluminum pans under nitrogen (flow rate 30 mL/min) at a heating rate 10 ^oC/min in the range of 25-450 ^oC.

3. Results and Discussion

Table 1 shows the screening experiment of the 1:1 acyclovir and theophylline into 8 solvents as H_2O, 0.1 M HCl, 0.1 M NaOH, CH_3OH: H_2O (1:2), C_2H_5OH: H_2O (1:2), C_3H_7OH: H_2O (1:2), 0.1 M CH_3COOH and CH_3COCH_3: H_2O (1:2). The acyclovir-theophylline (ACV-TP) cocrystal was obtained from the mixed solvent (CH_3OH: H_2O, 1:2) as white rectangular rod crystals, for about 70% of yields (Fig. 1).

Table 1. The screening experiment of 1:1 ACV- TP under 8 solvents.

Samples	Solvents	Crystals
1	Water (H_2O)	-
2	0.1 M CH_3COOH	-
3	0.1 M HCl	-
4	0.1 M NaOH	-
5	Methanol: water (CH_3OH: H_2O, 1:2)	-
6	Ethanol: water (C_2H_5OH: H_2O, 1:2)	White rectangular rod
7	Isopropanol: water (C_3H_7OH: H_2O, (1:2)	-
8	Acetone: water (CH_3COCH_3: H_2O, 1:2)	-

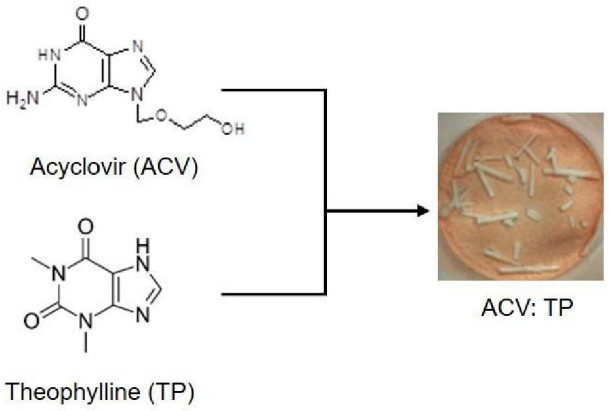

Fig. 1 Schematic of the preparation route of ACV-TP (6)

FTIR spectra of ACV:TP (6) crystals under ethanol: water (1:2) solvent compare to the starting materials, acyclovir and theophylline is shown in Fig.2. The product, ACV-TP (6) shows the shifted in the lower wavenumbers from ACV and TP starting: ν(N–H) 1º amine at 3386, 3326 to 3368 cm^{-1}, ν(N–H) 2º amine at 3135 to 3000 cm^{-1} (ACV) and ν(N–H) at 3123 to 3110 cm^{-1} (TP); ν(C=O) at 1699 (ACV) and 1666 (TP) to 1652 cm^{-1}. The ν(O–H) and δ(O–H) of ACV at 3757 and 1485 are disappeared. A new band for ν(O–H) of H-bond at 3500 cm^{-1} is present, and ν(C–H) at 3326, 3135 cm^{-1} (ACV) and at 3064, 2983, 2829 cm^{-1} (TP) are replaced by new bands at 3000 and 2916 cm^{-1}. These results indicate the possible hydrogen bonding interaction between ACV and TP.

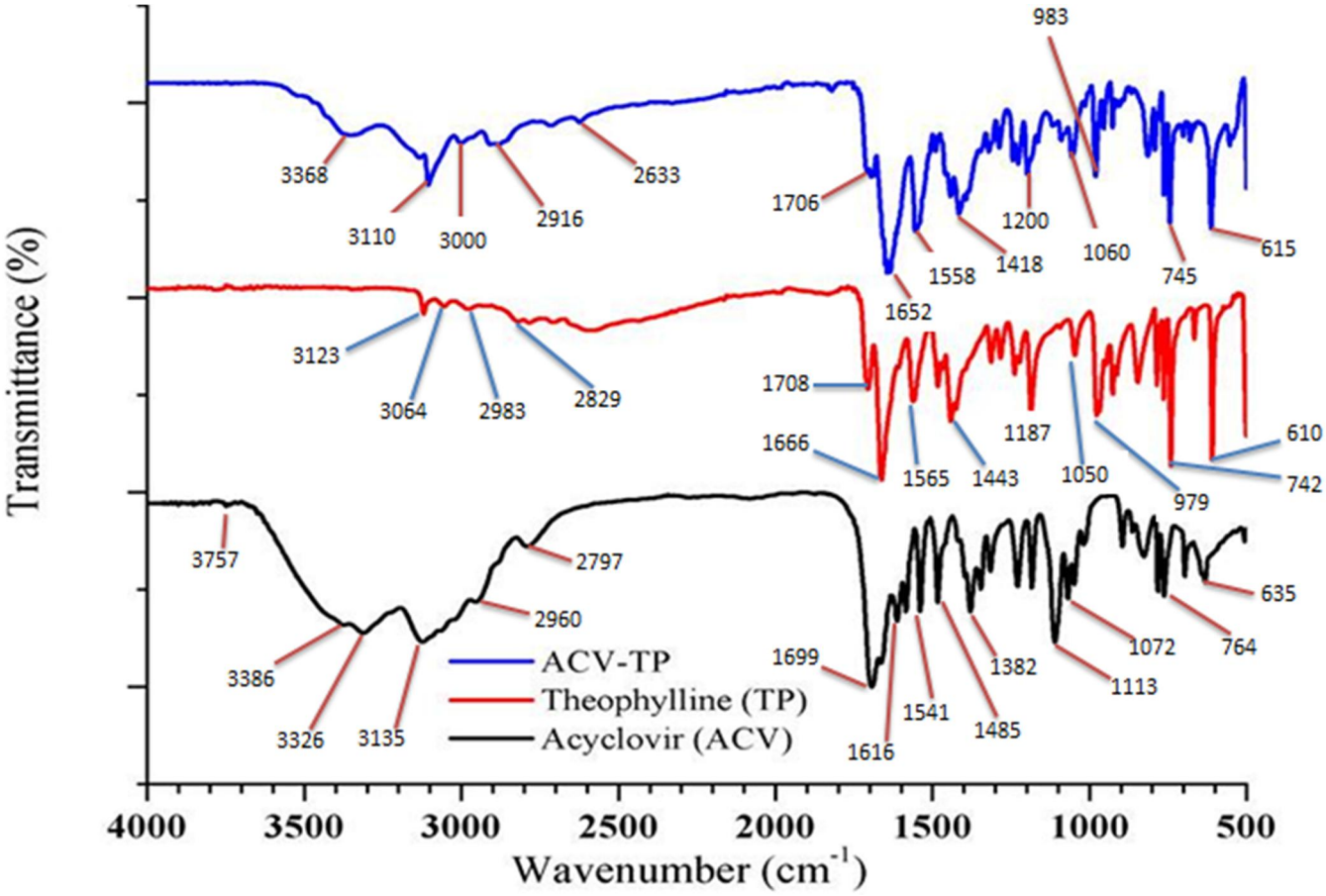

Fig. 2 FT-IR spectra of ACV-TP (6) compound.

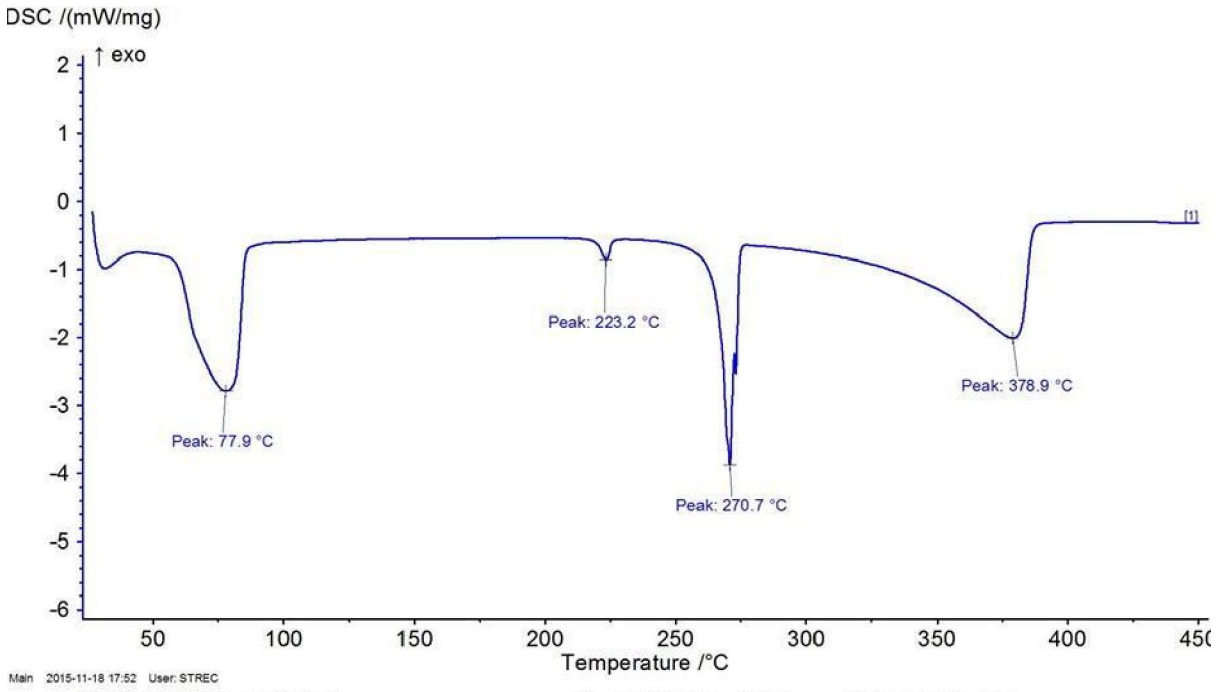

Fig. 3 Differential scanning calorimetry thermograms (DSC) of ACV-TP (6) compound.

The DSC thermogram of ACV-TP (6) in CH_3OH: H_2O (1:2) shows four endothermic peaks, at around 77.9, 223.2, 270.7 ºC and at around 378.9 °C. The first peak at 77.9 ºC is the loss of water molecules from acyclovir, and at 223.2 and 270 ºC are corresponding to the melting points of ACV and TP. The melt/decomposition of temperature of acyclovir is around 253.5 ºC [9, 10]. The theophylline melts at about 279 °C [6]. In this work, the melting temperature of ACV-TP (6) compound is around 270 °C, which is higher than the known melting temperature of acyclovir and lower than melting point of theophylline, suggesting a structure difference, a new compound may have been formed.

4. Conclusion

The screening experimental of 1:1 acyclovir: theophylline under ethanol: water (1:2) solvents by slow evaporation *via* solution base methods was conducted. Physical properties were characterized by FT-IR and DSC. The results confirm the formation of the new crystal formed with acyclovir and other component in the compounds. Which possible hydrogen bond interaction between two components. were generated by FTIR. A new compound may have been formed by DSC analysis.

Acknowledgements

Grateful Acknowledgements to Faculty of Science and Technology for equipment support and Research and Development Institute, Kamphaeng Phet Rajabhat University, Thailand for grant.

References

[1] J.-J, Greco,. D., Diaz, Thouvenot, and F. Morfin, “Novel targets for the development of anti-herpes compounds,” ***Infectious Disorders-Drug Targets***, Vol. 7, No. 1, pp. 11-18, 2007

[2] G., McEvoy, K., Miller, J., and Litvak, K. “AHFS Drug Information”. United States of American Society of Health-System Pharmacists, USA, pp. 765–775, (2004).

[3] C. von P. Rossel, J. S. Carreño, M. Rodríguez-Baeza, and J. B. Alderete, “Inclusion complex of

the antiviral drug acyclovir with cyclodextrin in aqueous solution and in solid phase", ***QUÍMICANOVA***, Vol. 23, No. 6, pp. 749-752, 2000.

[4] B. Giovanna, M. Mariarosa, M. Lauretta, M. Piercarlo, F. Chiara, B. Vittorio, M. Chiara, G. Alessandro, M. Amedeo, "Preparation and Physicochemical Characterization of Acyclovir Cocrystals with Improved Dissolution Properties", ***J. of Pharmaceutical Science***, pp. 1-8, 2013.

[5] M. Montha, B. Ratri, S. Weenawan, and T. Pek-Lan, "Crystal Growth and Physical Characterization of Acyclovir Crystallized with Ascorbic Acid and Zinc Chloride". ***J. Life Sciences and Technologies***, Vol. 4, No. 2, pp. 55-59, 2016.

[6] Shuo Zhang "Physical Properties and crystallization of Theophylline cocrystal", School of Chemical Science and Engineering Department of Chemical Engineering and Technology Division of Transport Phenomena, Stockholm, Sweden , 2010.

[7] S. Weenawan, K. Sopita, and J. H. Kenneth, "Theophylline Cocrystallized with Salicylic Acid and Picolinic Acid: Preparation and Physical Properties", ***Advanced Materials Research***, Vol.. 699, pp 682-688, 2013.

[8] Trevor L. Stanwick, Ronald W. Anderson and Andre J. Nahmias, (1977). "Infection and immunity", Vol.18, No. 2, pp. 342-347.

[9] M. Meepripruk, "Supramolecular structure of the herpes antiviral agent acyclovir and related compounds"," Dept. Chem., Suranaree Univ., Nakornratchasoma, Thailand, 2012.

[10] Lutker, Quinones, Xu J., Ramamoorthy and Matzger, "Polymorphs and Hydrates of Acyclovir", ***J Pharm Sci,*** Vol.100, No. 3, pp. 949–963, 2011.