THE COMPARISON BETWEEN CO-MELTED AND SPRAY DRIED CLOTRIMAZOLE-PVP/VA SOLID DISPERSIONS SYSTEMS

Introduction

- Clotrimazole is a broad spectrum of anti-fungal drug but it is classified in Class II in the BSC.
- Poorly soluble characteristic of clotrimazole can pose a hurdle in the flux across the skin.
- By forming amorphous state of solid dispersion, supersaturated state generated by the amorphous counterpart can help to increase the drug absorption through topical route with the high concentration gradient between the membranes of the skin.

Objective of Study

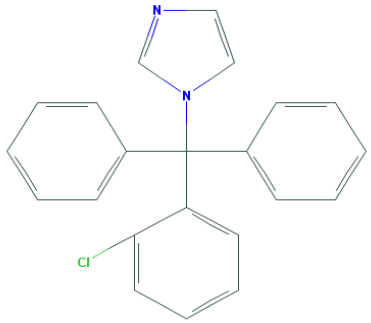
- To produce amorphous solid dispersion of Clotrimazole-PVPVA system
- To investigate the physicochemical properties of clotrimazole-PVPVA solid dispersion system.
- To compare the dissolution performances of clotrimazole-PVPVA systems prepared by two different methods, i.e. co-melting method and spray drying method.

Materials and Methods

Materials

Clotrimazole

- Clotrimazole is an imidazole derivative with a broad spectrum of antimycotic activity
- It is used for the treatment for disease like vaginal yeast infection, pityriasis versicolour and jock itch.
- It is the active ingredient for this paper.



Carrier: PVP/VA : SCSY1 SCSY3

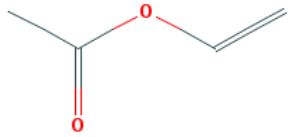
- PVP/VA is used as the carrier for clotrimazole for this study. PVP/VA SCSY2 is a type of polymer which is white, odourless, water soluble polymers.
- It also being use as binder for tablets and granules, Dry binder for direct compression, during wet granulation, film-coating, sub coating, for controlled-released preparation and

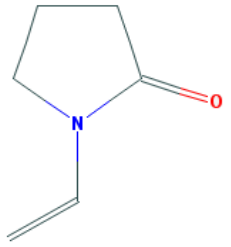
  hot melt extrusion process to

  increase the solubility and bioavability

  of poor soluble active pharmaceutical

  ingredient





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SCSY1 Sam Chan Siok Yee, 5/24/2017

SCSY3 What is the title of this slide?
Sam Chan Siok Yee, 5/24/2017

SCSY2 why use PVPVA?
Sam Chan Siok Yee, 5/24/2017

Preparation Physical Mixture (PM) SCSY4

- 30mg of Clotrimazole is mix with 70mg of PVP/VA homogenously using a mortar and pestle for approximately 2 minutes
- Hence, the physical mixtures of Clotrimazole in PVP/VA (100mg) is 30%,

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SCSY4 it should be under method right??
Sam Chan Siok Yee, 5/24/2017

Preparation Co-melting Method

- Co-melt of Clotrimazole with with PVP/VA (1000mg) was SCSY5 prepared by dissolving 700mg of PVP/VA in distilled water.
- Then it is being slowly poured into a petri dish containing melted 300mg Clotrimazole heating on the hot plate at temperature of 200°C while being stirred continuously with a spatula until all water evaporated to obtain a homogeneous mixture of Clotrimazole and PVP/VA.
- Then the products were collected with spatula and cooled over at room temperature to solidify and then being pulverized using a mortar and pestle.
- The powders product contained 70.0/30.0 %w/w of PVP/VA/Clotrimazole.

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SCSY5 1000mg is total?

Sam Chan Siok Yee, 5/24/2017

Preparation Spray Dried (SD)

- To prepare the spray dried 30% Clotrimazole PVP/VA
- 30 mg of clotrimazole is transferred into 200ml of 50% ethanol in a beaker and stir it for 5 minute using a magnetic stirrer.
- Then PVP/VA with the weight of 70mg is added and stirred until dissolve.
- Then the solution is being transferred to the spray-dry machine to be dried.
- Clotrimazole/ PVP/VA was collected from collecting chamber.

Method

1. Determination of λmax.

2. Characteristic of solid state of the prepared solid dispersion and physical mixture of 30% Clotrimazole and PVP/VA was done by using :

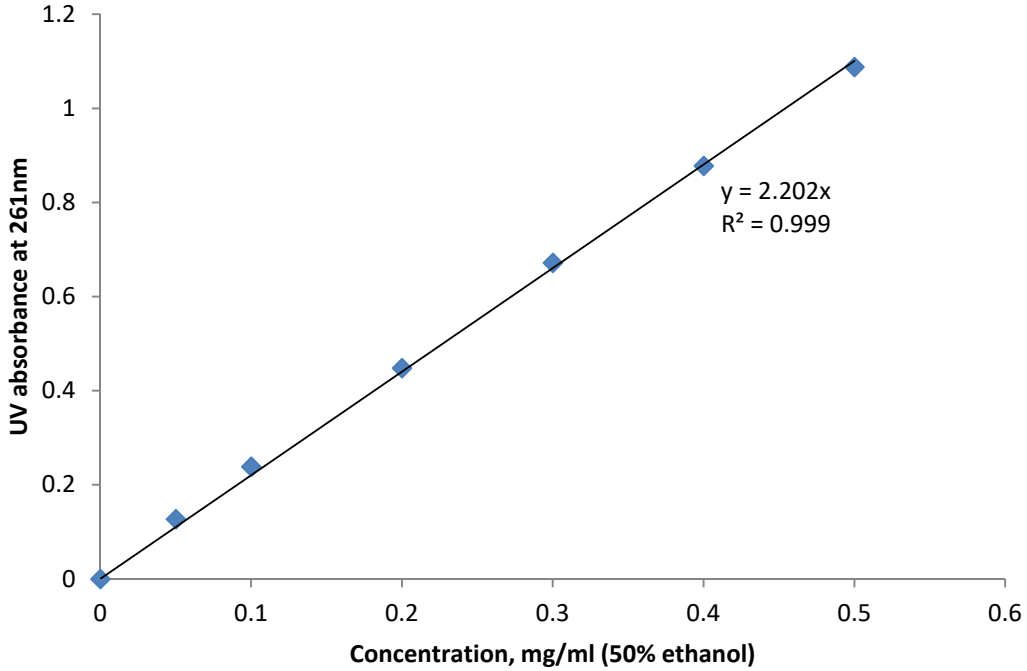
- Differential Scanning Calorimetry (DSC),
- Microscopy
- and Fourier transform infrared (ATR-FTIR).

3. Dissolution Studies

Result and Discussion

UV-Visible Spectrophotometer

- **Calibration curve of Clotrimazole:**
- Figure 3.1 shows the calibration curve graph that being use for this paper at 261nm for the analysis of clotrimazole with linearity of R^2=0.999.
- **Figure 3.1: Standard curve of Clotrimazole in 50% ethanol**



Thermal properties of raw material and binary system

- Differential Scanning Calorimetry (DSC) is used to analyse the thermal properties of samples of pure clotrimazole and the solid dispersion samples. Figure 3.1, shows one of the three DSC thermograms for pure clotrimazole. SCSY6

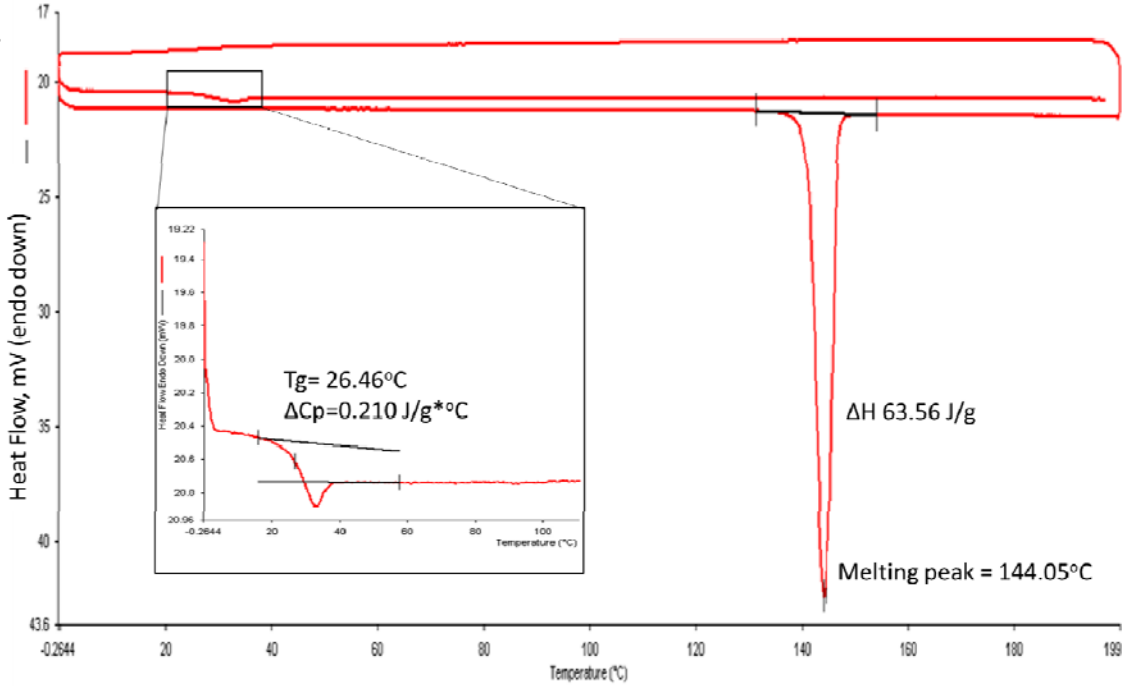


Figure 3.2: DSC thermogram of pure Clotrimazole which showed a melting peak at 144.05˚C and Tg at 26.46˚C

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SCSY6 try to explain that it is with heat-cool heat cycle.....and mention why you do heat cool heat?
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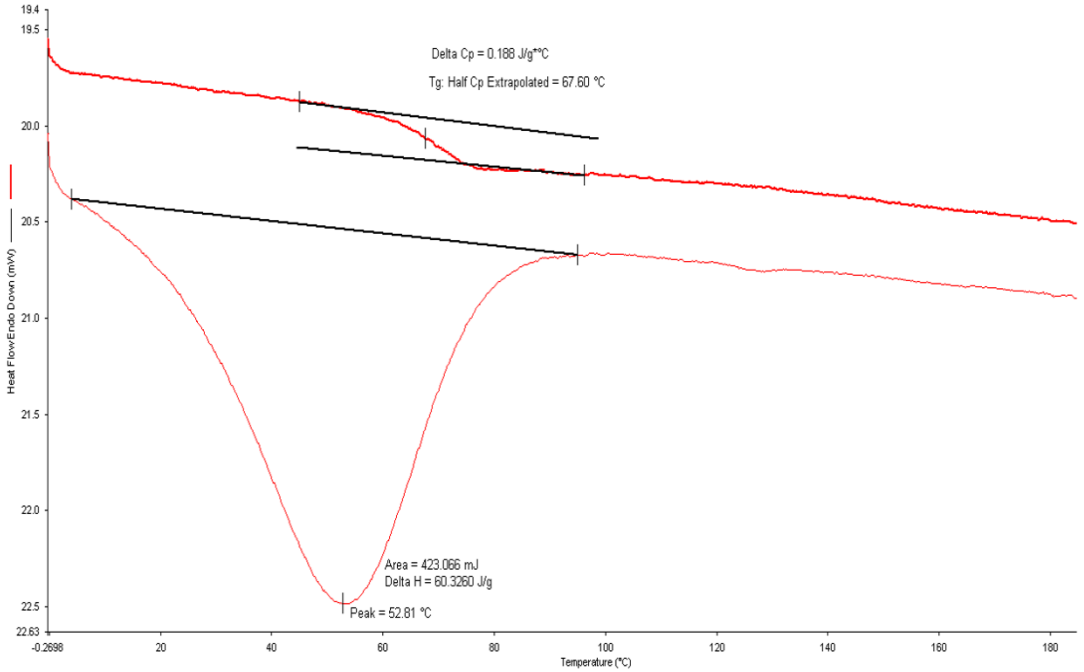
DSC thermogram of Co-melt sample

- *Clotrimazole-PVP/VA (70.0/30.0%) co-melting*



- **Figure 3.3: DSC thermogram of Solid Dispersion using co-melting method (Sample 3) which showed a water loss peak at 52.81˚C and Tg at 67.60˚C**

DSC thermogram of spray dried sample

- *Spray-dried 30% Clotrimazole-PVP/VA system*

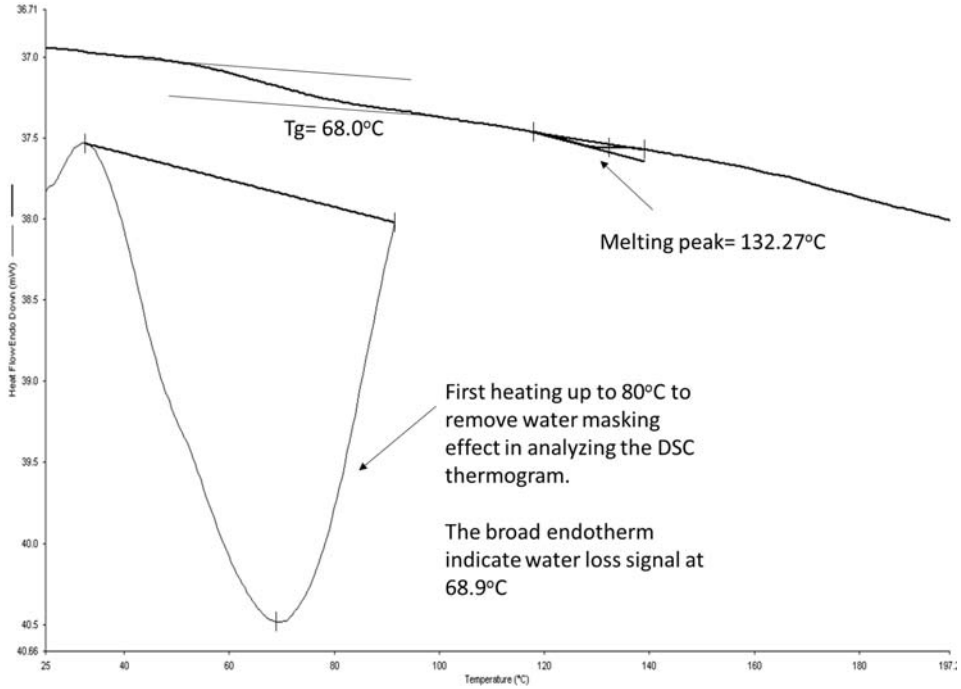


Figure 3.4: DSC thermogram of Solid Dispersion using spray-dried method which showed a water loss peak at 68.92˚C and Tg at 68.0˚C

Theoretical Estimation on the Tg of binary system.

- The theoretical Tg is estimated using the Gordon-Taylor equation shown in equation 3.1

$$Tg = \frac{W_1 Tg_1 + KW_2 Tg_2}{W_1 + KW_2}$$

Table 3. 1: Numeric values used to calculate the theoretical Tg and the estimated theoretical

Component	Numeric values
ΔCp1 (drug)	0.2427
ΔCp2 (polymer)	0.6320
K(ΔCp2/ ΔCp1)	2.6040
Tg1 (drug)	26.36
Tg2 (polymer)	106.4
Calculated Theoretical Tg of Clotrimazole-PVPVA	95.0885

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SCSY7 explain that GT euqation assumption...why you compare???
Sam Chan Siok Yee, 5/24/2017

Microscopy

Clotrimazole pure

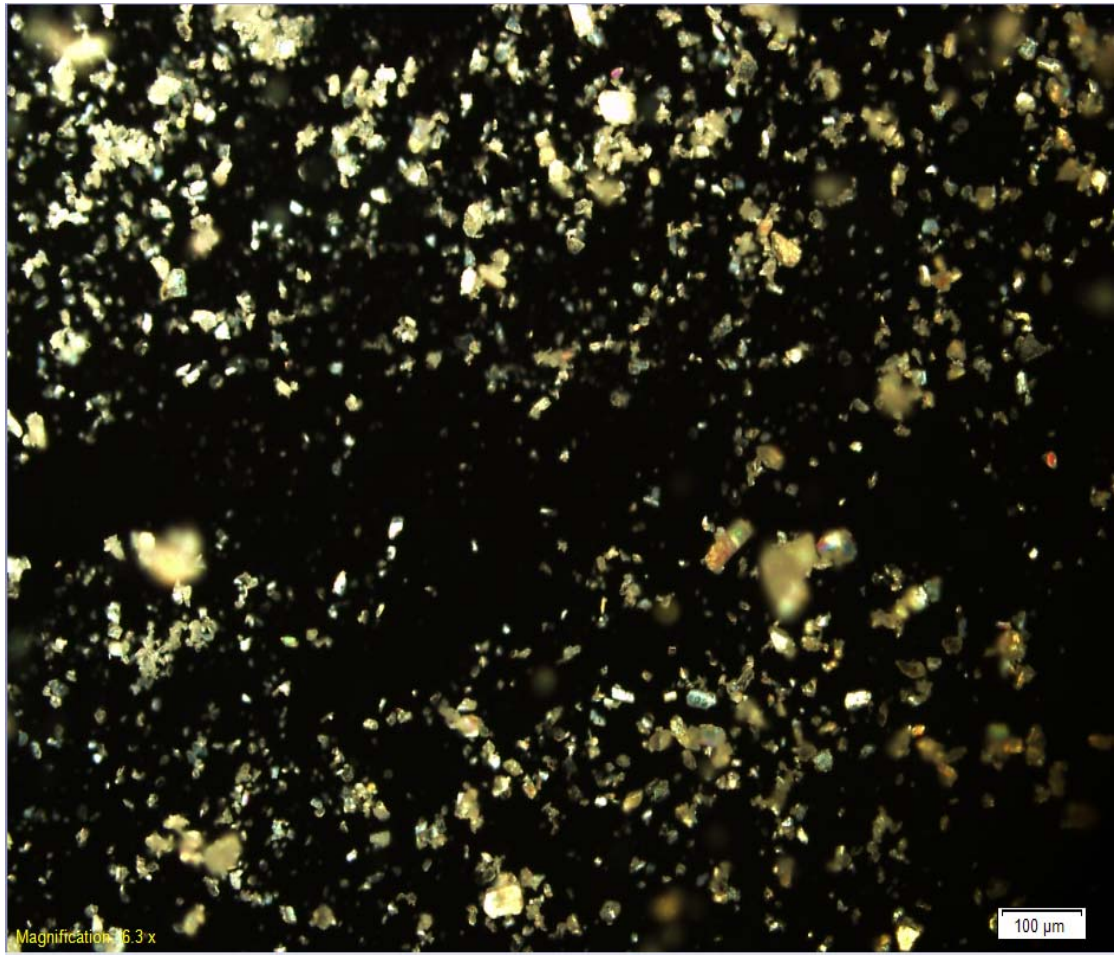


Figure 3.5: Microscope image of particle from pure Clotrimazole at 6.3x magnification

Microscopy

Co-melt 30% Clotrimazole-PVPVA

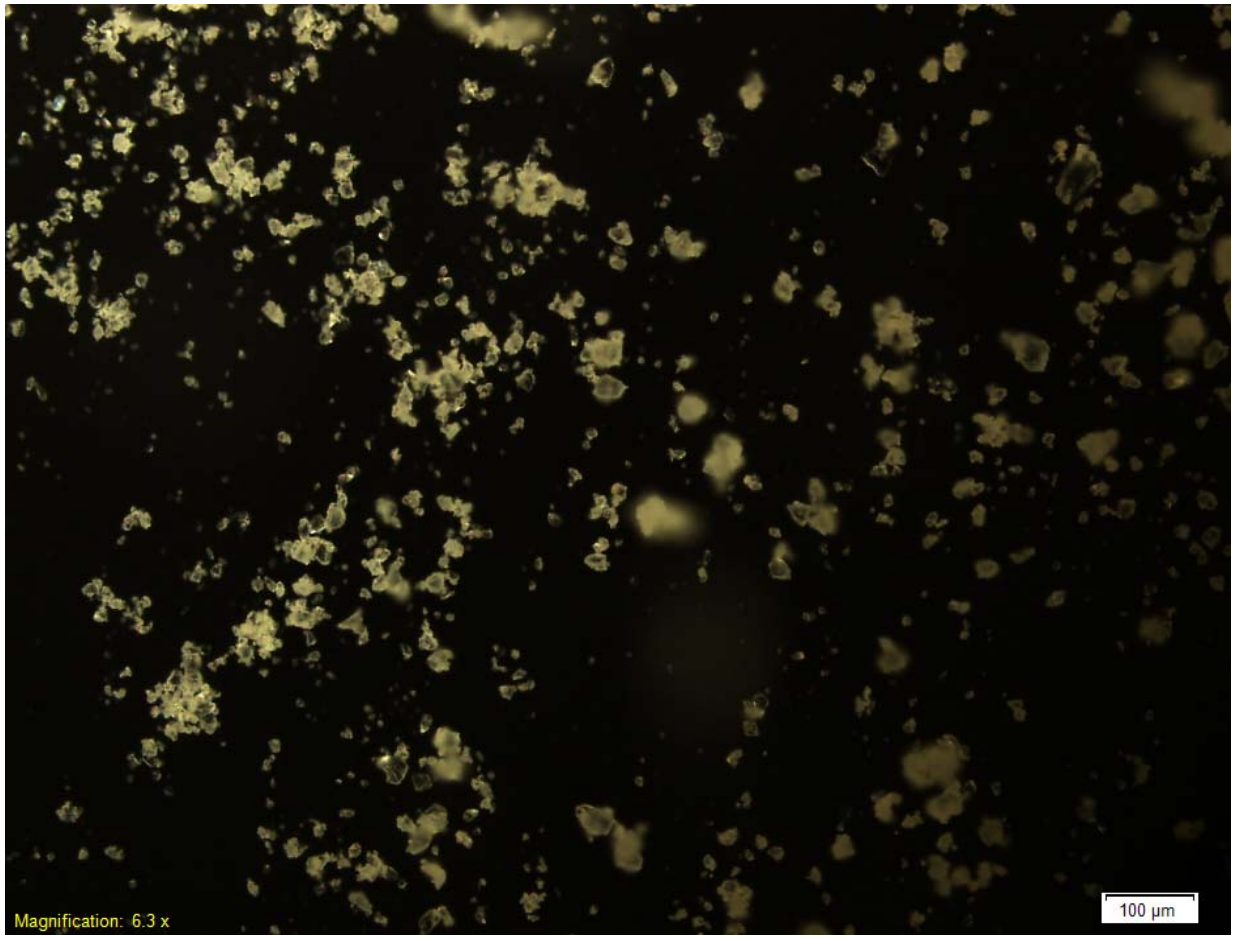
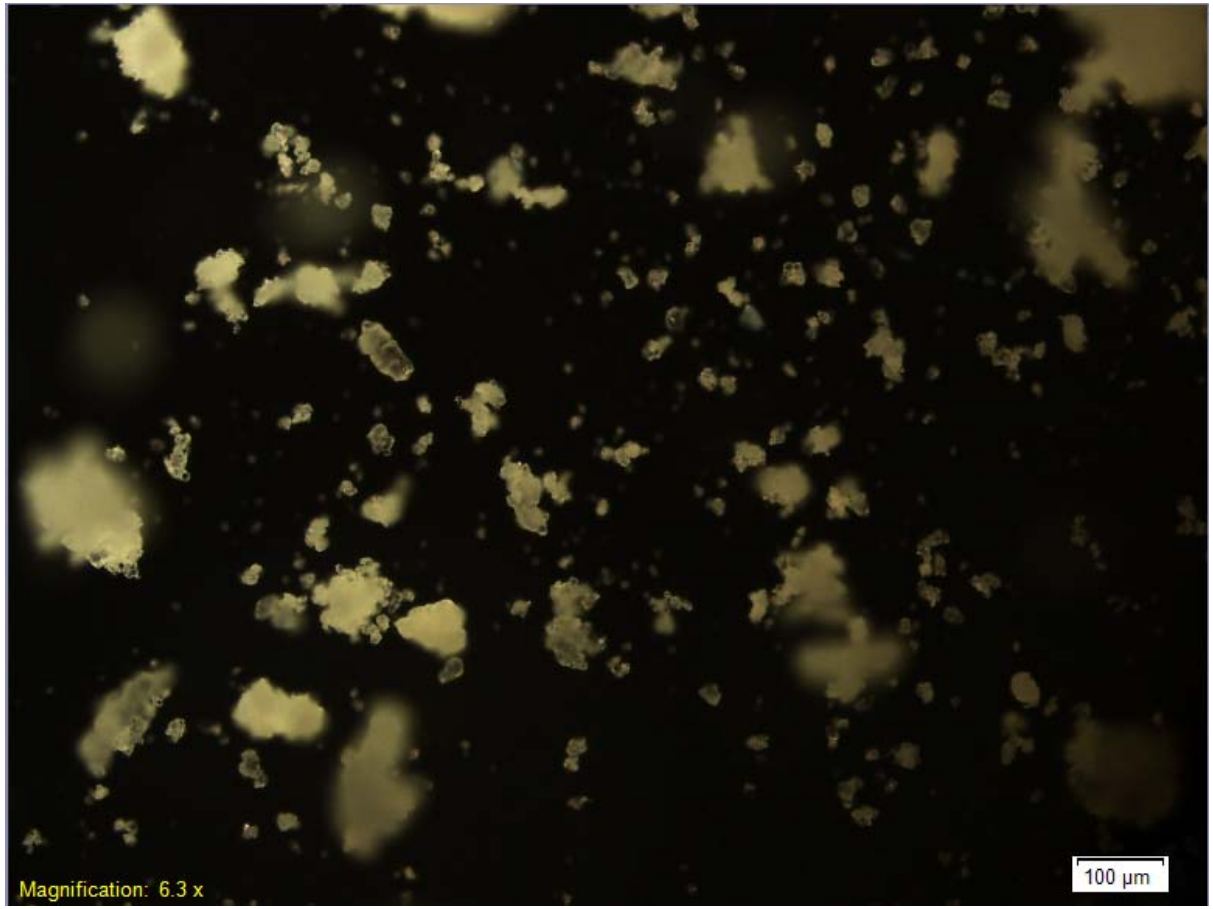


Figure 3.6: Shows the image of particle from co-melt sample of Clotrimazole-PVP/VA (70.0/30.0% w/w) at 6.3x magnification under a microscope.

Microscopy

Spray-dried 30% Clotrimazole-PVPVA



- **Figure 3.7: Shows the image of particle from spray-dried sample of Clotrimazole-PVP/VA (70.0/30.0% w/w) at 6.3x magnification under a microscope.**

Fourier Transform Infrared (FTIR) Spectroscopy

- ATR-FTIR is used to investigate the possible interactions between Clotrimazole and PVP/VA solid dispersion of co-melt method and spray-dried method.
- characteristic of pure clotrimazole can be seen at bands at 3166 cm^{-1}, 1584 cm^{-1}, 1487 cm^{-1} and 741 cm^{-1}.

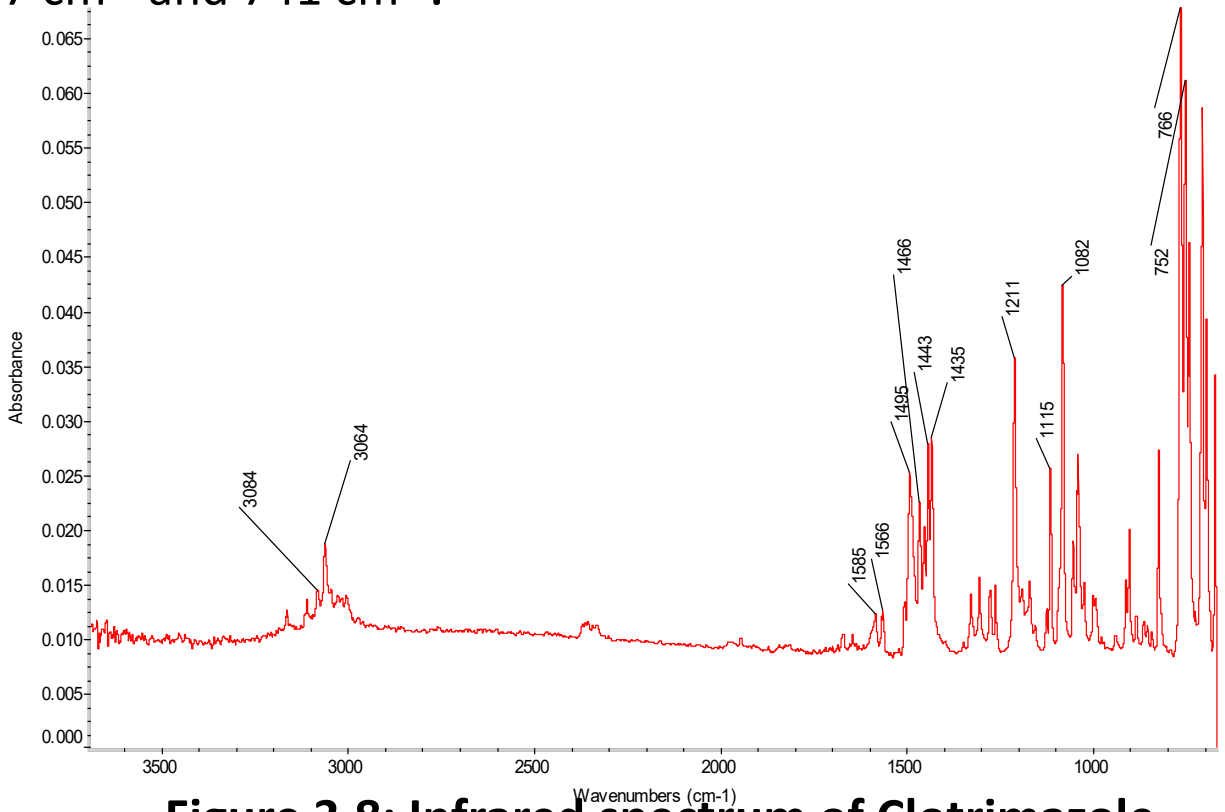


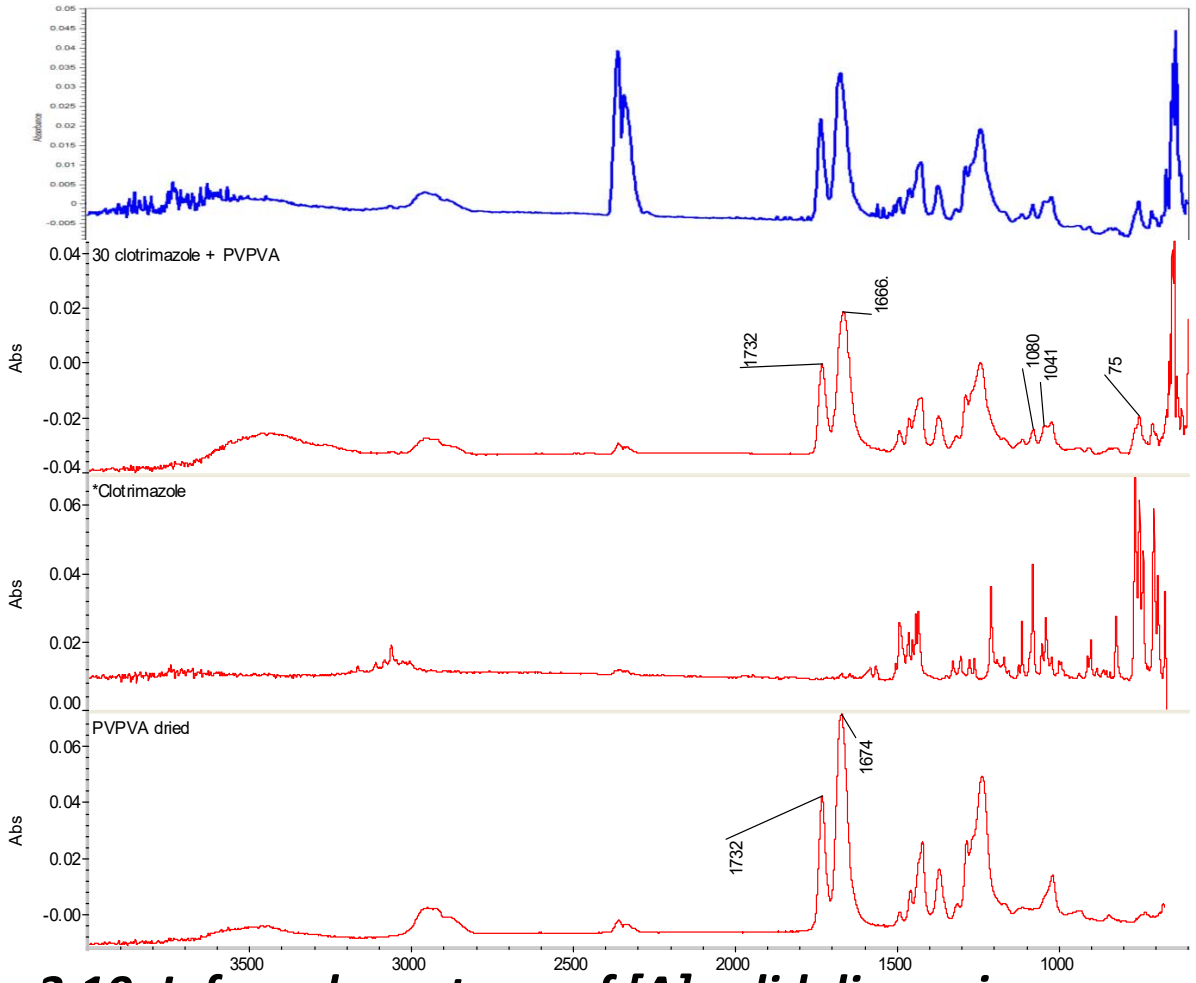
Figure 3.8: Infrared spectrum of Clotrimazole

Table 3.2: Peak observed in infrared spectrum of Clotrimazole

Origin	Group frequency, Wavenumber (cm^{-1})	Assignment
C-H	3084-3064	C-H stretching vibration of aromatic compounds
N-H	3700-3500	Amide N-H Stretch
C-Cl	766-752	Aliphatic chloro compounds, C-Cl Stretching
C=C	1585-1435	C=C stretching
C-H	1211-1082	In-plane C–H bending
C-H	970–960	Out-of-plane C-H bending
C-N	1360-1250	Aromatic C-N stretching
N–H	1615	Secondary amide N–H bending band
C=N	2330	C=N Stretch of imidazole ring

SCSY8

FTIR spectra for solid dispersion of Clotrimazole with PVP/VA.



A

B

C

D

Figure 3.10: Infrared spectrum of [A] solid dispersion prepared by spray-dried method [B] solid dispersion prepared by co-melting method (30%clotrimazole + PVP/VA), [C] Clotrimazole, [D] PVP/VA from 600-4000 cm^{-}

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SCSY8 are you sure you can explain this slide???please add the explanation
Sam Chan Siok Yee, 5/24/2017

- At band 1041 and 1080 (C-O bonding of alchoholes & phenols) had been supress for Clotrimazole-PVP/VA of comelt and spray-dried sample that the pure clotrimazole.
- The 1732 (C=O saturated aldehyde) shows the (The difference between co-melt and spray-dried is lower than present in PVPVA.
- The band at 1674 shows the α, β-unsaturation of aldehydes and ketones present at both comelt and spray dried. This band has been down shifting in both the spray dried and co-melting sample which indicate the possible interaction occurred at C=O of PVPVA

SCSY9

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SCSY9 the α, β-unsaturation , you need to be able to show where is the location in the structure

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FTIR spectra for solid dispersion of Clotrimazole with PVP/VA.

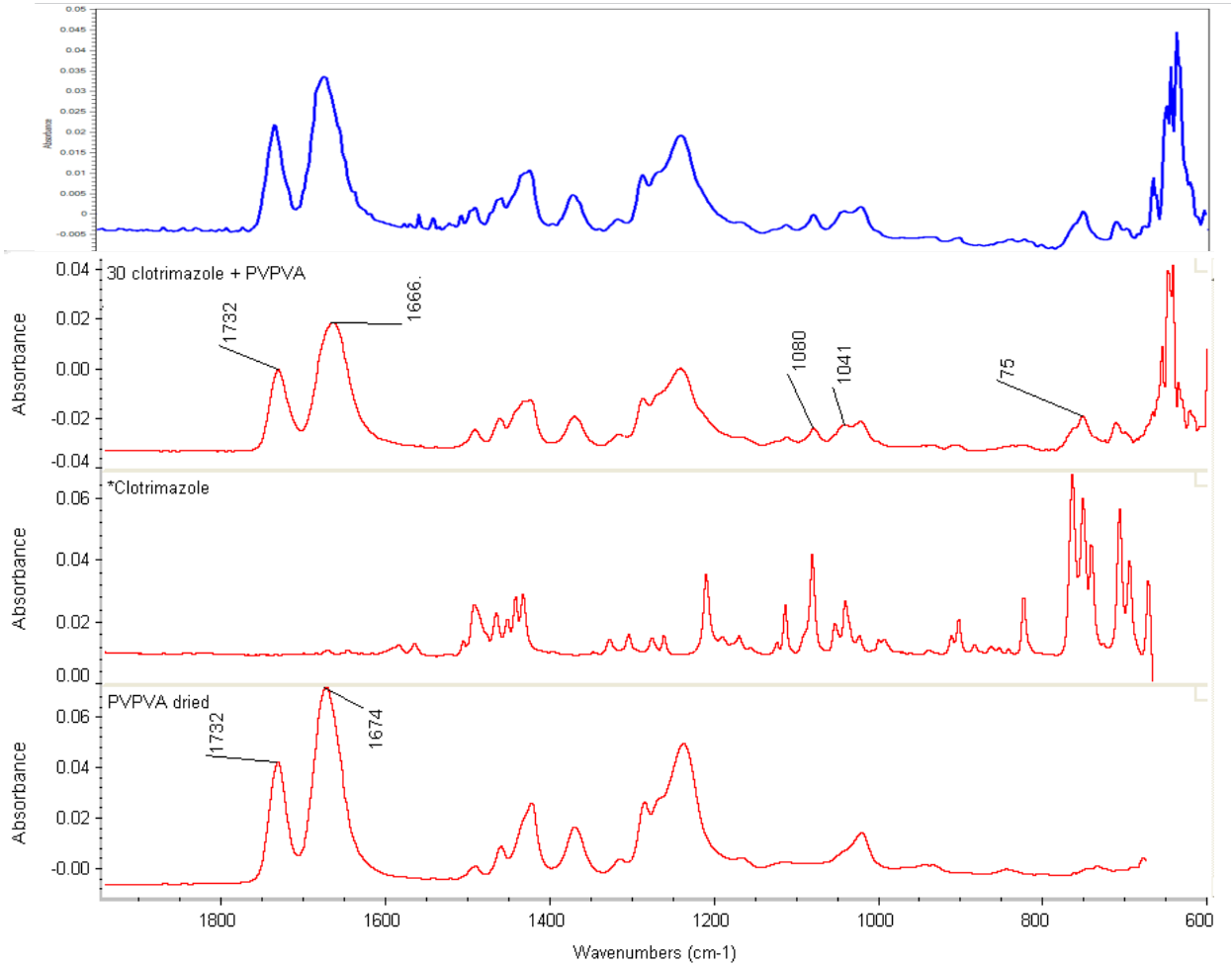

Figure 3.11: Infrared spectrum within range 600-1800cm^{-1} of [A] solid dispersion prepared by spray-dried method (30%clotrimazole + PVP/VA), [B] solid dispersion prepared by co-melting method (30%clotrimazole + PVP/VA), [C] Clotrimazole, [D] PVP/VA

- That the finger print of the solid dispersion of co-melt and spray-dried sample of Clotrimazole-PVP/VA (70.0/30.0% w/w) from 600 cm^{-1} to 1900 cm^{-1} is really similar.

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SCSY10 this slide is not neccesary
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FTIR spectra for solid dispersion of Clotrimazole with PVP/VA.

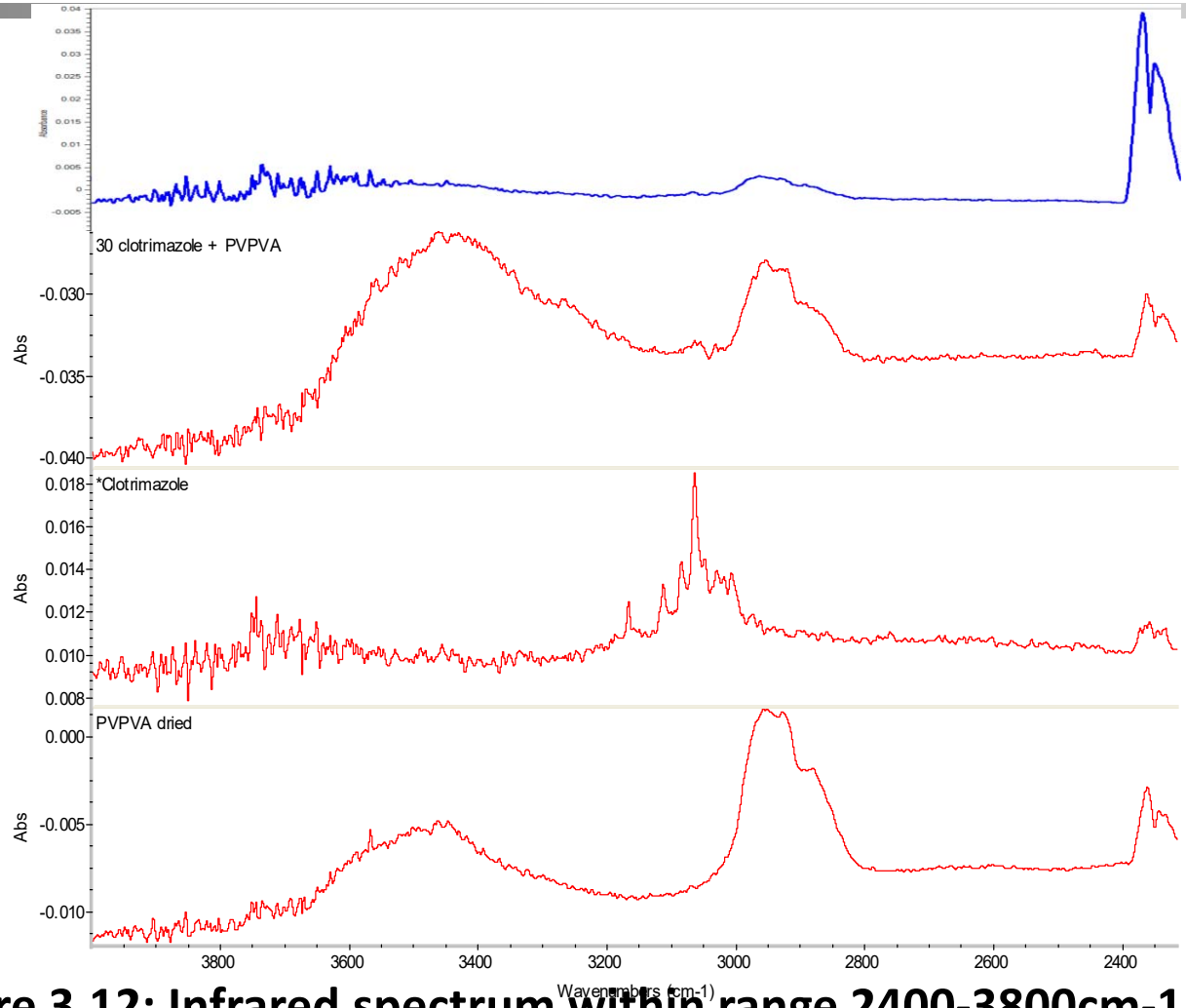

Figure 3.12: Infrared spectrum within range 2400-3800cm-1 of [A] solid dispersion prepared by spray-dried method (30%clotrimazole + PVP/VA), [B] solid dispersion prepared by co-melting method (30%clotrimazole + PVP/VA), [C] Clotrimazole, [D] PVP/VA

- The studies showed that there was no chemical interaction between clotrimazole with PVA/VA. Hence there are no changes of the Clotrimazole drug activity.

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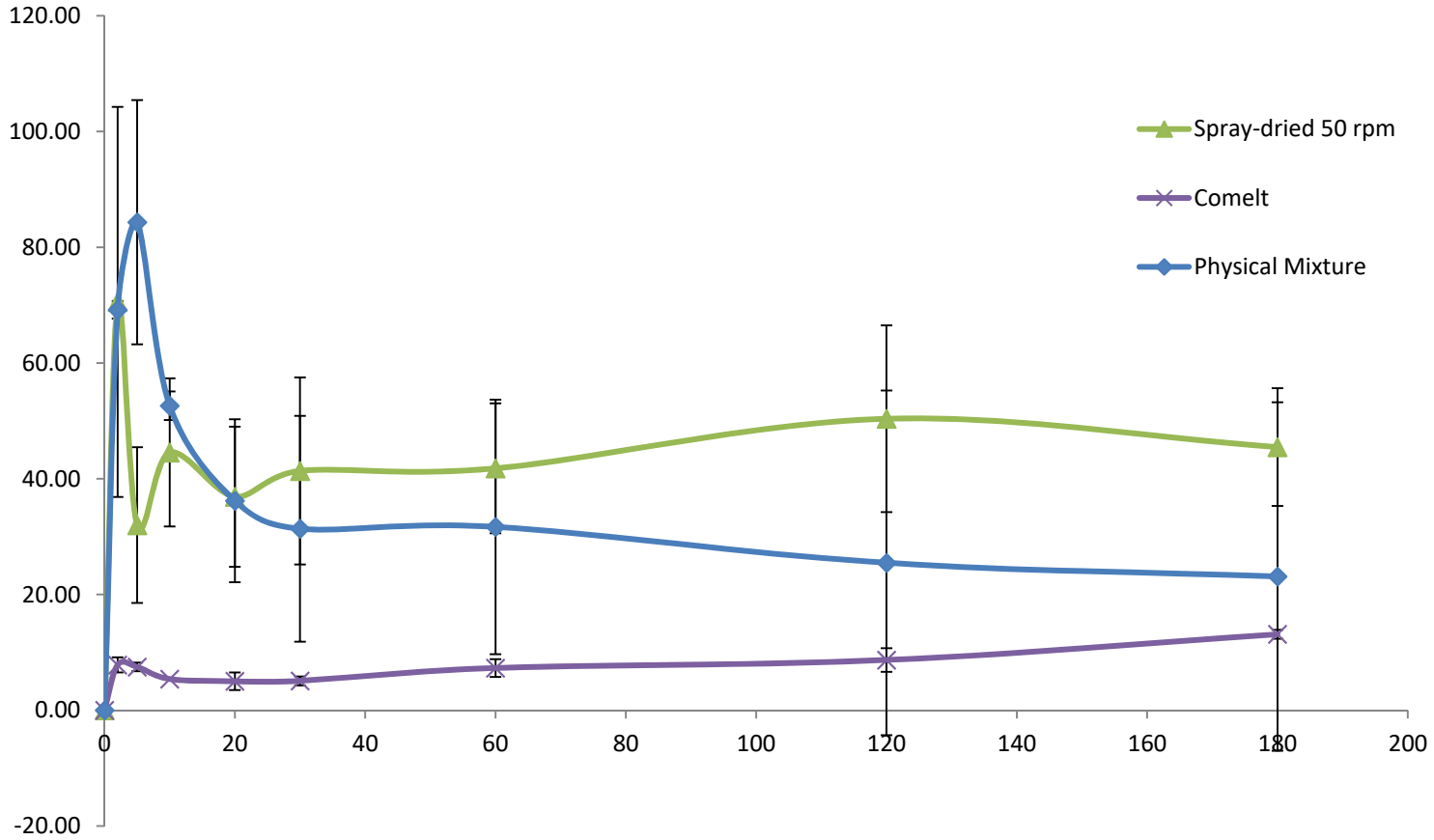
SCSY11 just now you were saying there is possible interaction? why suddenly no interraction??
Sam Chan Siok Yee, 5/24/2017

Dissolution



- ***Figure 3.13: Comparison of drug release profiles of physical mixture and solid dispersion systems***

Dissolution

- minute 0-19 minutes, dissolution rate of physical mixture is the highest, followed by spray dry at and co-melt sample which reveal a very slow release of clotrimazole.
- At minute 20, spray-dried sample and physical mixture have the same rate SCSY12 of drug dissolution which was 36% while the dissolution rate of co-melt sample was the lowest with release percentage of 5%.
- At later release stages, i.e. from minute 21 to 180 shows the spray dry sample have the highest drug release followed by the physical mixture and finally co-melt sample.

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SCSY12 for the result observed you need to say why they behave like this?
Sam Chan Siok Yee, 5/24/2017

Dissolution

Table 3.3: The dissolution efficiency of the samples

SYSTEM	DISSOLUTION EFFICIENCY
Spray-dried (50 rpm)	4.50
co-melting	0.82
physical mixture	3.08

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SCSY13 this slide no need
Sam Chan Siok Yee, 5/24/2017

Conclusion

- This study has successfully produced amorphous solid dispersion of clotrimazole in PVPVA system using both the melting and spray drying method.
- In contrast to usual expectation, the fully amorphous characteristic of clotrimazole-PVPVA solid dispersion systems did not reveal a better dissolution performance in comparison to its physical mixture.
- It was also disappointed to realize that there is no dissolution performance enhancement of spray dried clotrimazole-PVPVA as compared physical mixture.
- Melting method may produce dispersion system that is dense and non-porous for hot-melt.

SCSY14

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SCSY14 so what cause the unexpectation....need explain
Sam Chan Siok Yee, 5/24/2017

SCSY15

UNIVERSITI SAINS MALAYSIA

Thank you

Presented by
Name | Centre/Schools/Units etc

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SCSY15 where is reference slide?

Sam Chan Siok Yee, 5/24/2017