RECRYSTALLIZATION OF HOT MELT EXTRUDED PARACETAMOL IN PVP POLYMERS

Chan Siok Yee

OUTLINE

1. Introduction
2. Objective and Aims
3. Material and Methods
4. Result & Discussion
    1. Interaction energy density, B estimation
    2. Fresh sample
    3. Age sample
5. Conclusion

INTRODUCTION

- Hot melt extrusion is a cost-effective manufacturing method. This technique was of interest due to its ability in producing solid dispersion
- However, daunting issue related to this system is the stability due to the fact of thermodynamically unstable.
- On the other hand, PVP and its derivative which is found to have great stabilizing effect was less focused in term of Hot melt processing. This is ascribed to the concerns of degradation
- Thus, knowledge gaps in term of glorifying HME coupling with PVP need to be explored

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OBJECTIVES AND AIMS

- To couple the use of PVP polymer and hot melt extrusion in stability enhancement of solid dispersion
- To understand the recrystallization behavior of Hot melt extruded of a model drug with PVP and its derivatives.
- To understand the factors governing stability of drug-PVP systems solid dispersion prepared by HME.

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MATERIAL AND METHODS: Binary systems

API	Polymer system	Tg
Paracetamol (Highly unstable as amorphous)	**Polyvinylpyrrolidone K29/32 (PVPK29/32)**	**164.91°C**
	Polyvinylpyrrolidone K12 (PVPK12)	**124.02°C**
	Polyvinylpyrrolidone K17 (PVPK17)	**117.24°C**
	Polyvinylpyrrolidone vinyl acetate 6:4 (PVPVA 6:4)	**106.61°C**

HME PARAMETERS

Processing Parameter	conditions
Extrusion temperature	160^{o}C
Screw rotation	100rpm
Total weight	5 gram
Residence time	5 minutes

METHODS

Methods	purpose
1) Thermogravimetric Analysis **(TGA)**	**•Degradation** **•Water content**
2) Modulated Differential Scannig Calorimetry **(mDSC)**	**•To estimate interaction energy density,B in physical mixture (paudel et al 2010)** **•To identify the thermal properties of HME and age samples.**
3) Fourier transform Infrared Spectroscopy-Attenuated Total Reflectance **(FTIR-ATR)**	**•Chemical bond changes** **•To detect recrystallization**
4) Powder X-ray Diffraction **(XRPD)**	**Solid state characterisation**
5) Microscope	**SEM or optical microscope were used to investigate surface morphology**

STABILITY STUDIES

- Samples were subjected to different humidity conditions
  - 75%RH
  - 53%RH

- Crystal contents were recorded daily with ATR-FTIR in the **first 14 days** and subsequently in **weekly** basis.

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RESULT & DISCUSSION:

- Interaction energy density, B , was estimated by melting point depression approach (Paudel et al 2010).
- It represents the intensity of molecular interaction during mixing

Carrier systems	Interaction energy density (B)
PVP K12	-30.51
PVP K17	-20.25
PVP K29-32	-33.81
PVPVA 6:4	-9.588

- PVP K29-32>PVP K12 > PVP K17 > PVPVA 6:4

Paudel, A., J. Van Humbeeck, and G. Van den Mooter, *Theoretical and Experimental Investigation on the Solid Solubility and Miscibility of Naproxen in Poly(vinylpyrrolidone). Molecular Pharmaceutics, 2010. 7(4): p. 1133-1148.*

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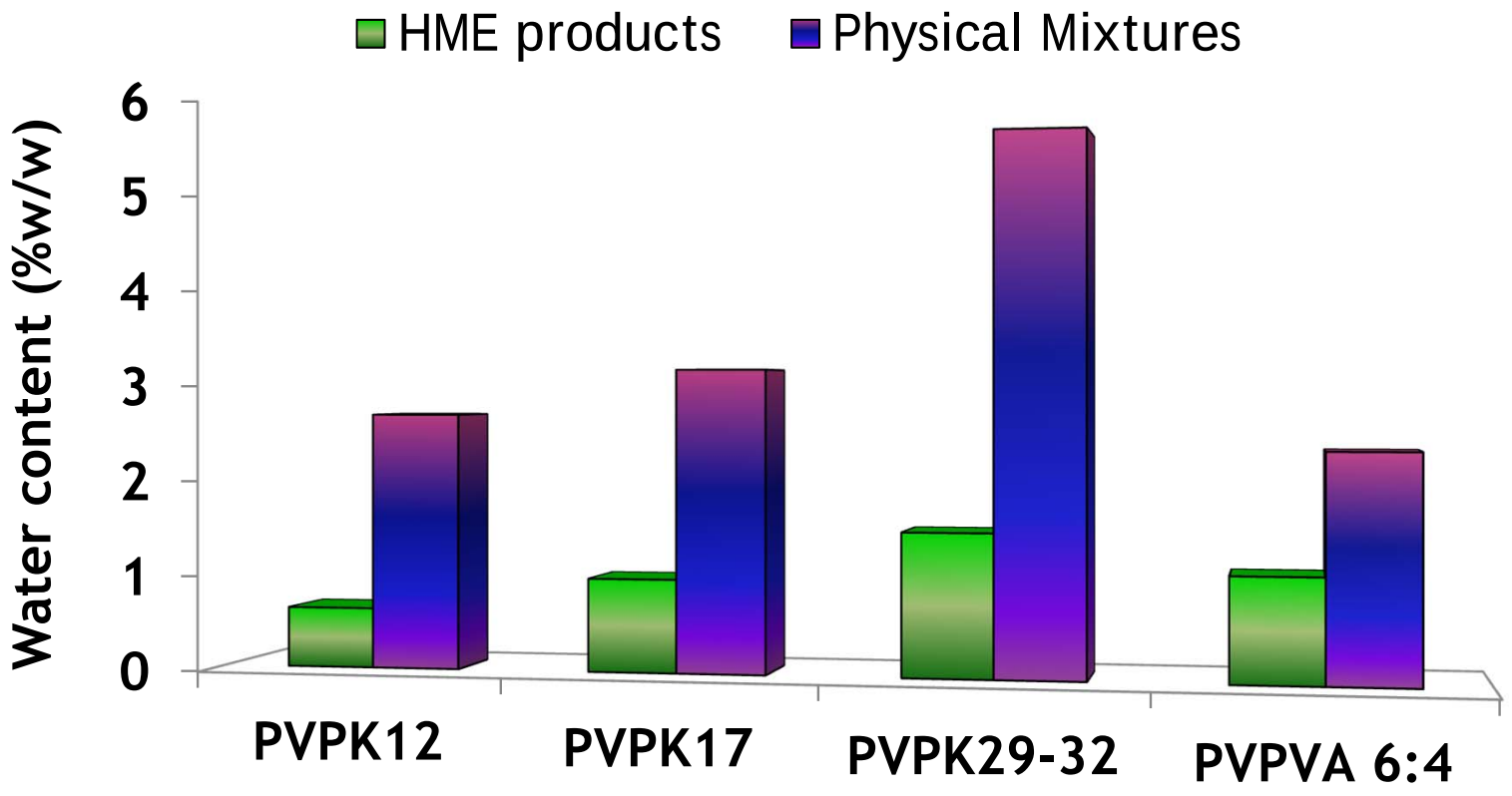
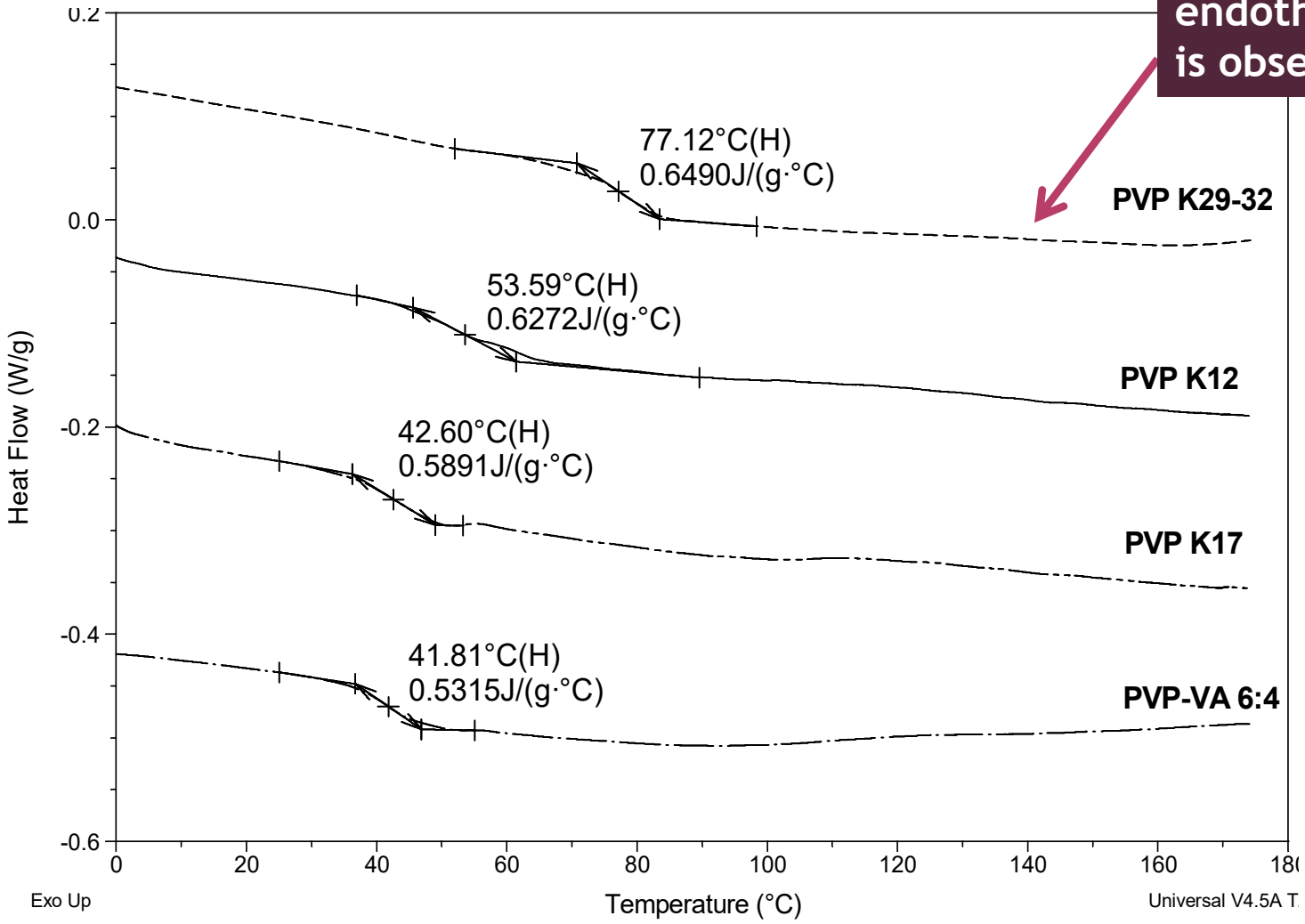
CHARACTERISATION: water content HME<PM

- TGA

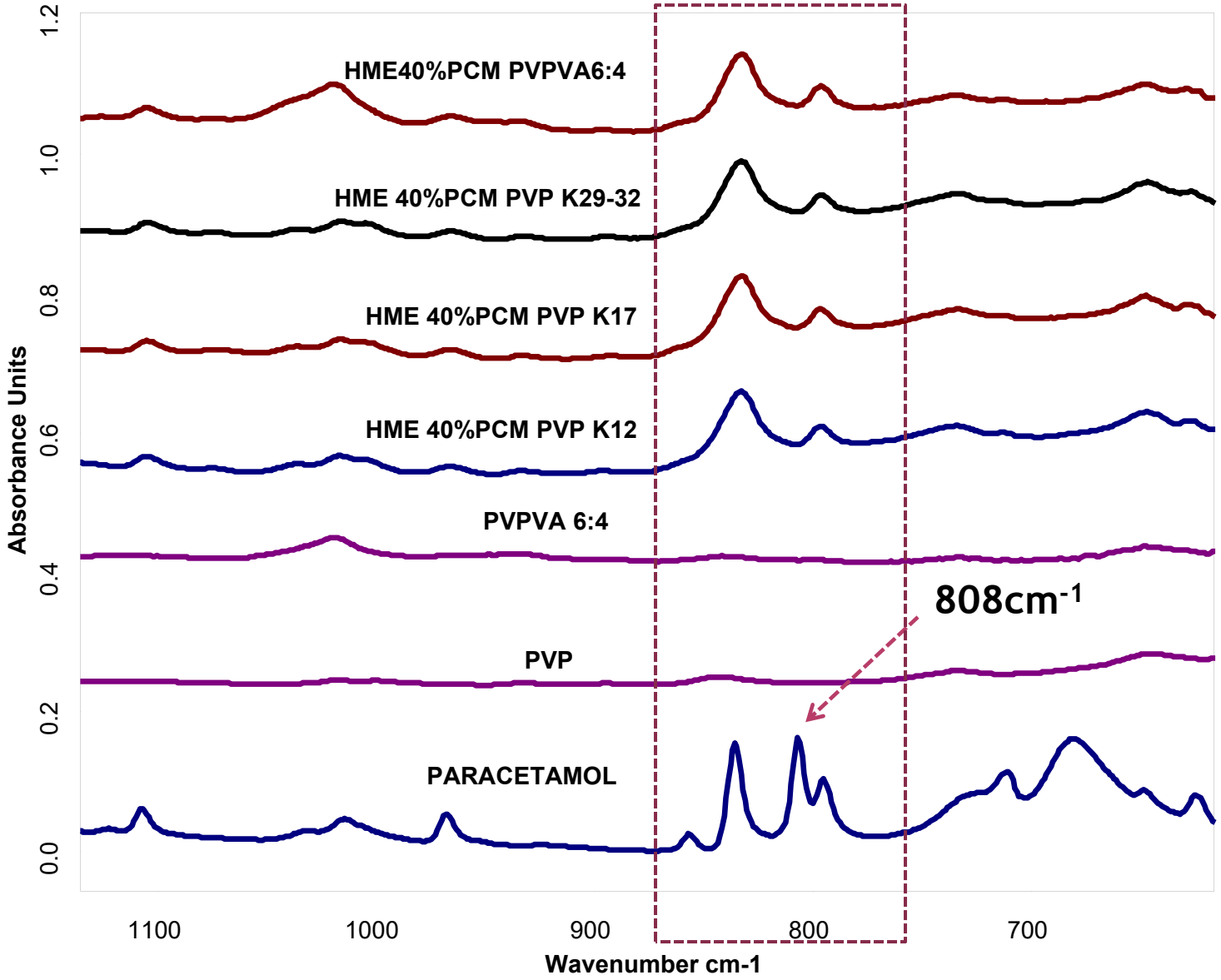
Hygroscopicity: PVP K29-32> PVP K17 > PVP K12 > PVPVA 6:4



MODULATED DSC (±0.212°C 40sec 2°C/MIN): amorphous

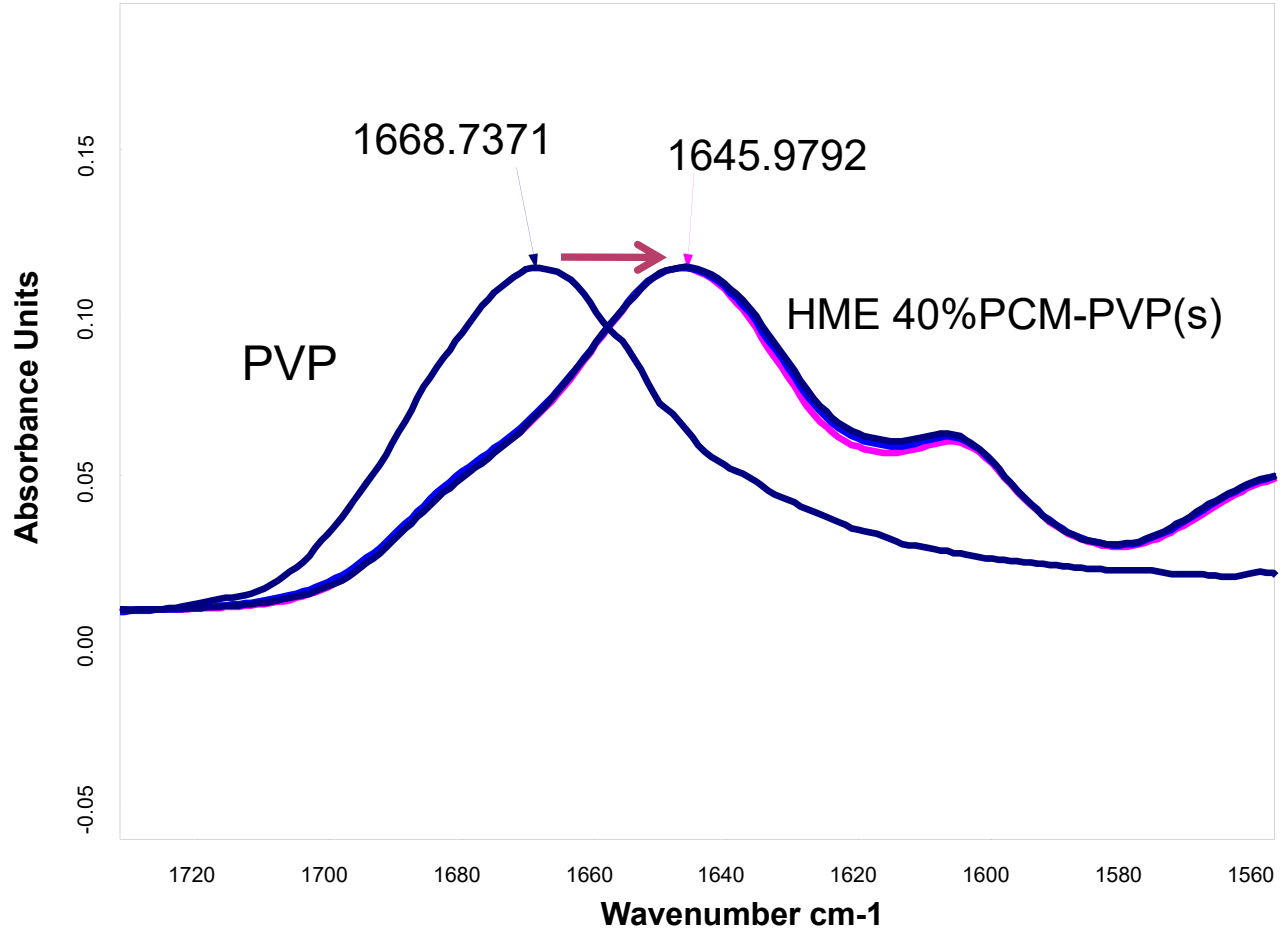


ATR-FTIR: absence of crystal



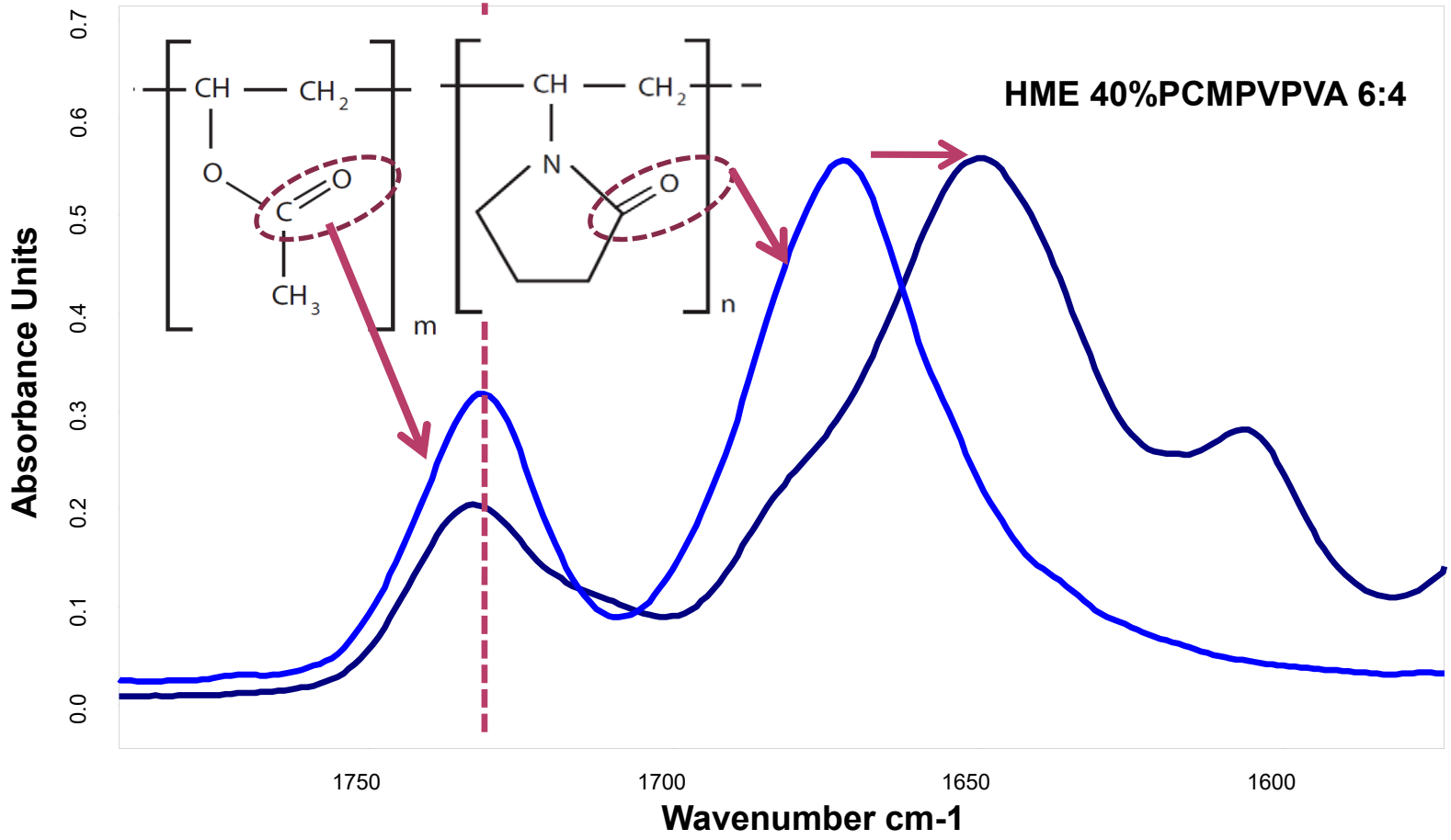
FTIR: indicate interaction

- Besides theoretical estimation, the extent of interaction can also be confirmed from FTIR with the extent of down shift in the carbonyl stretching region



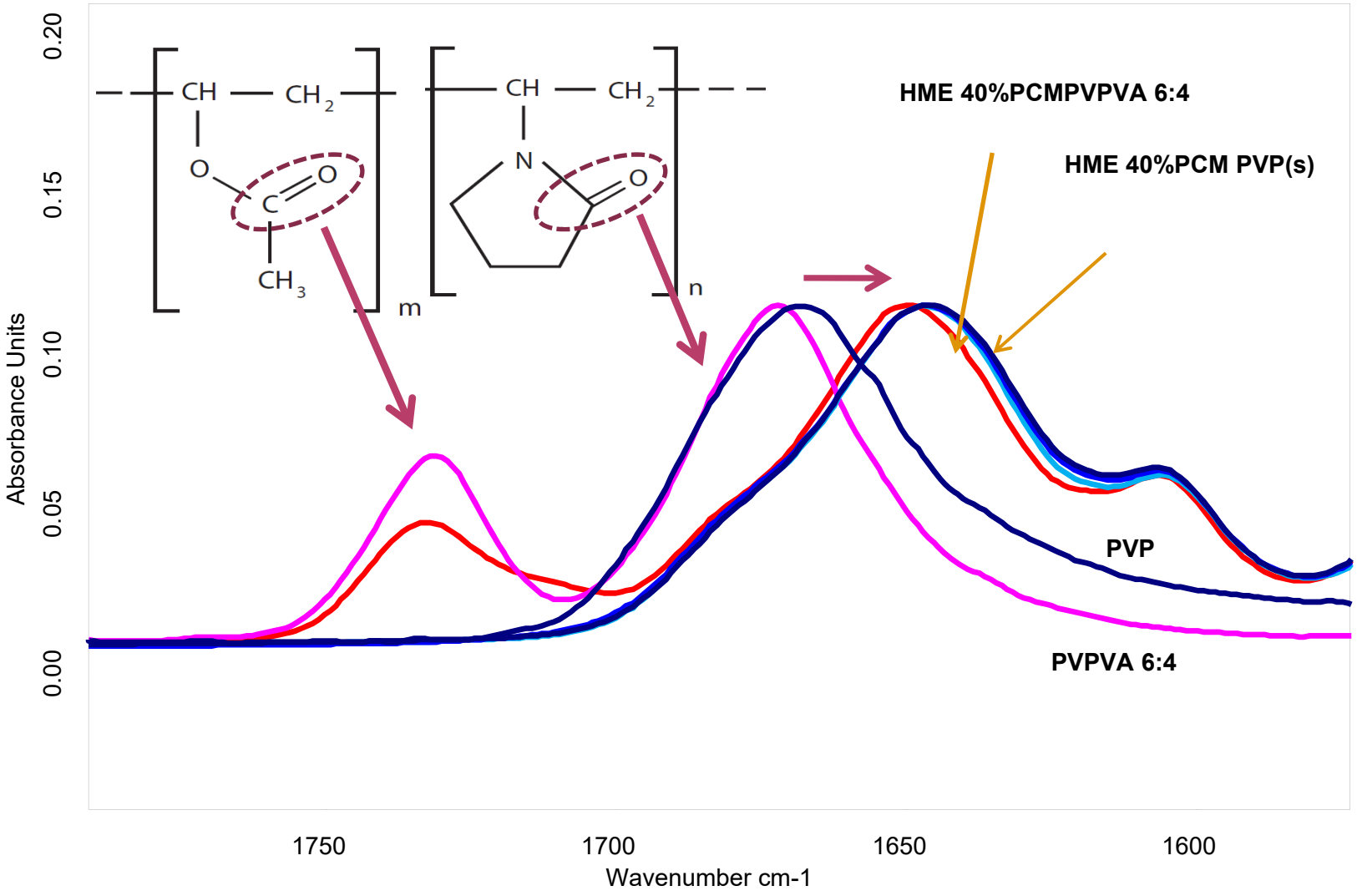
FTIR: indicate interaction

- Carbonyl stretching from pyrrolidone was shifted but in carbonyl stretching from vinyl-acetate did not showed down-shift.



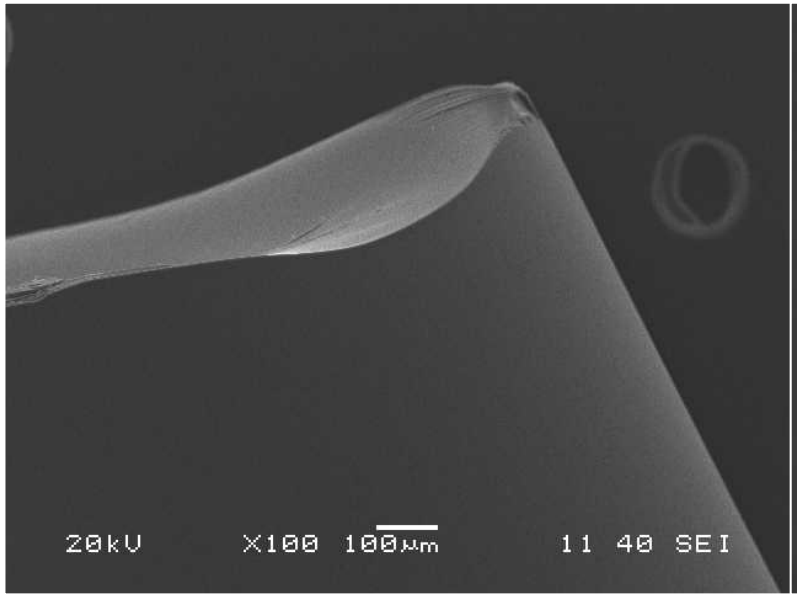
FTIR: indicate interaction

- Thus it is assumed that vinyl-acetate play a minimum role in hydrogen bonding which leads to less extent of interaction as predicted from theoretical value, B

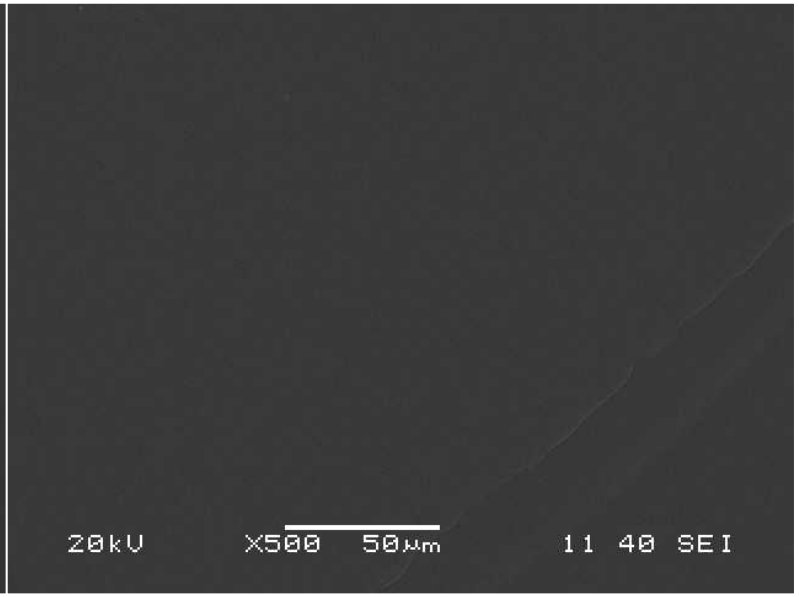


XRD & SEM : Amorphous nature

- XRPD showed halo pattern for all the tested drug-polymer systems
- SEM showed smooth surface



Surface of Fresh HME 40%PCMPVPVA 6:4



Cross section of Fresh HME 40%PCMPVP K29-32

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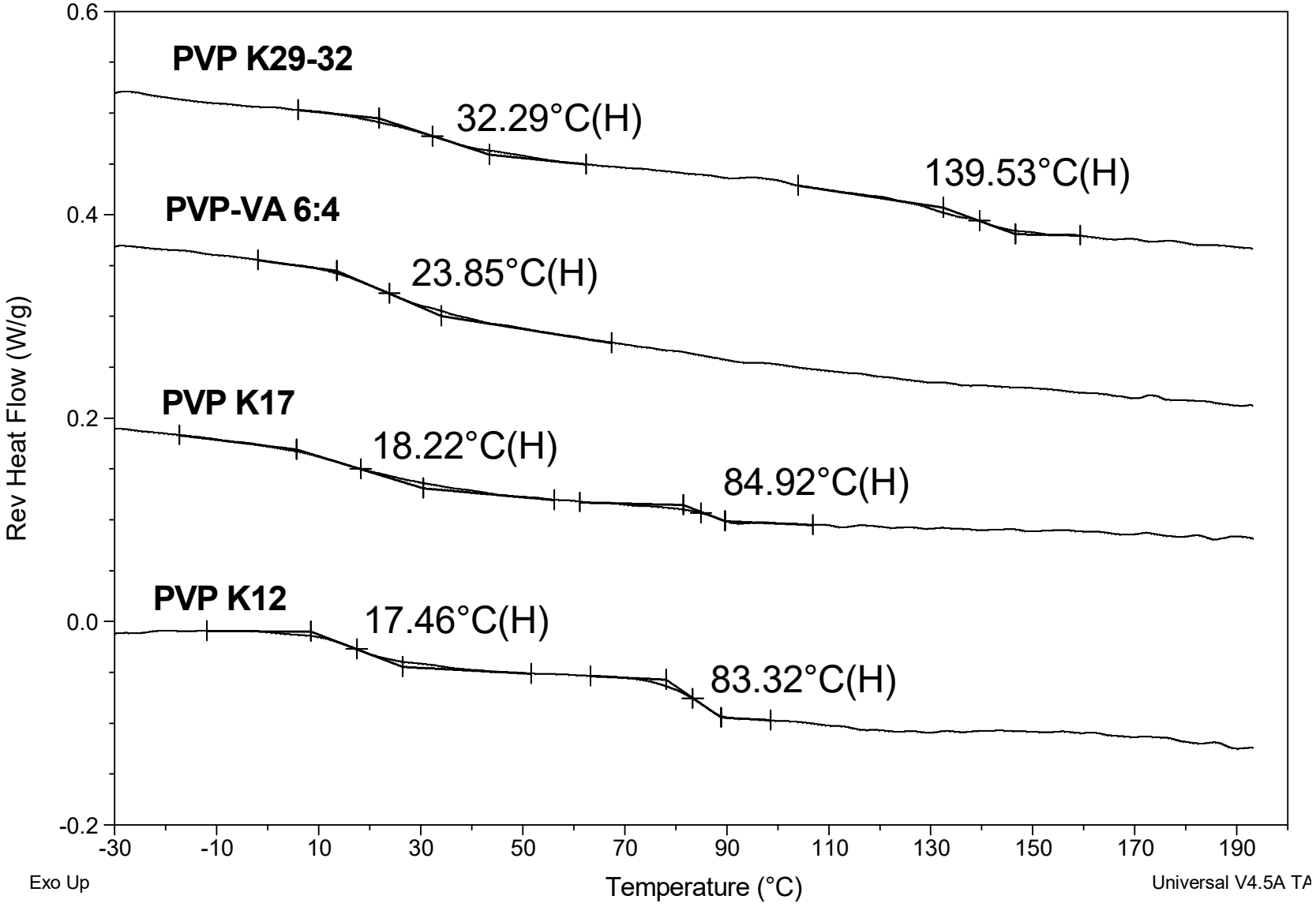
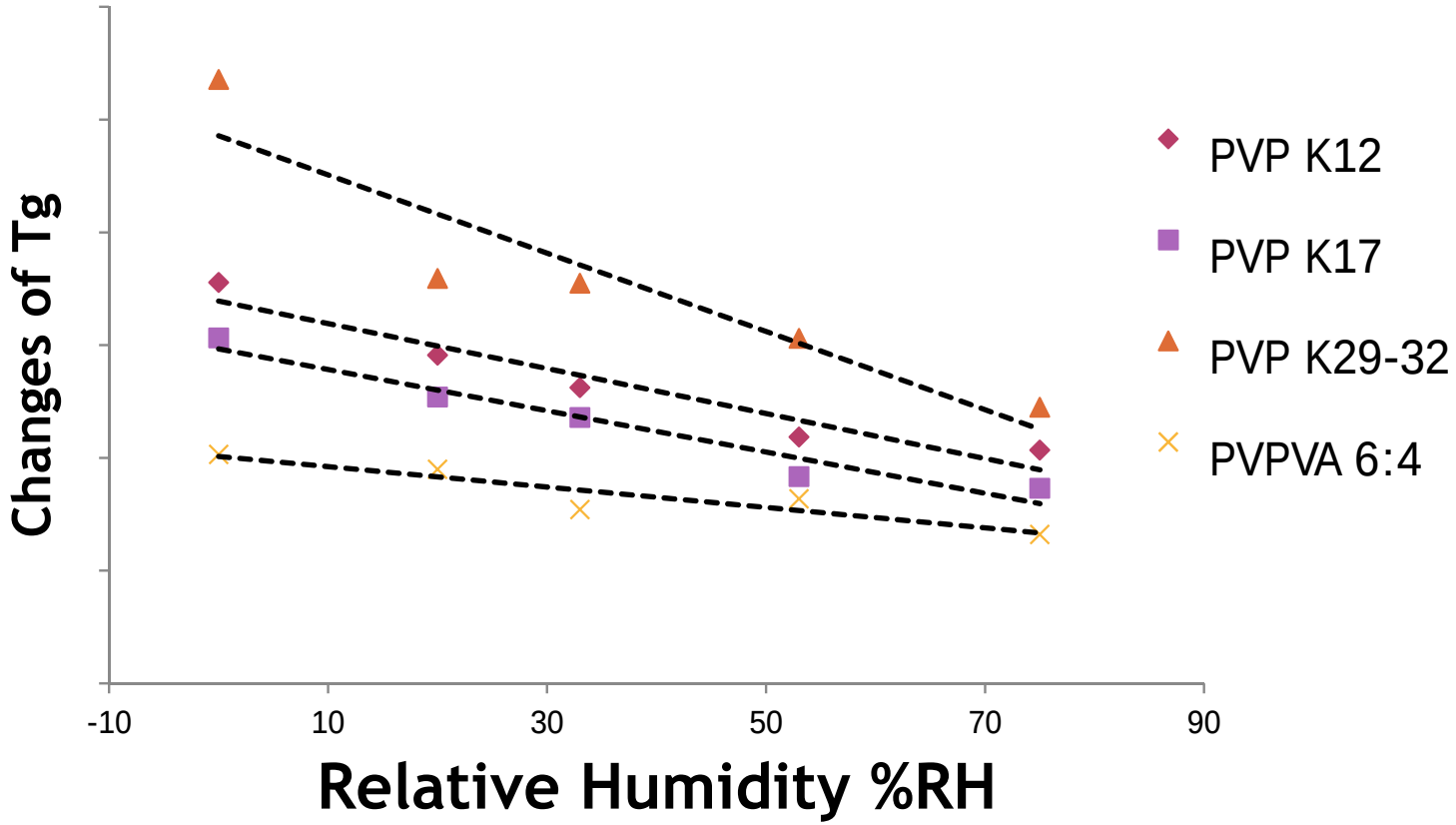
TG CHANGES : after storage in 53%RH

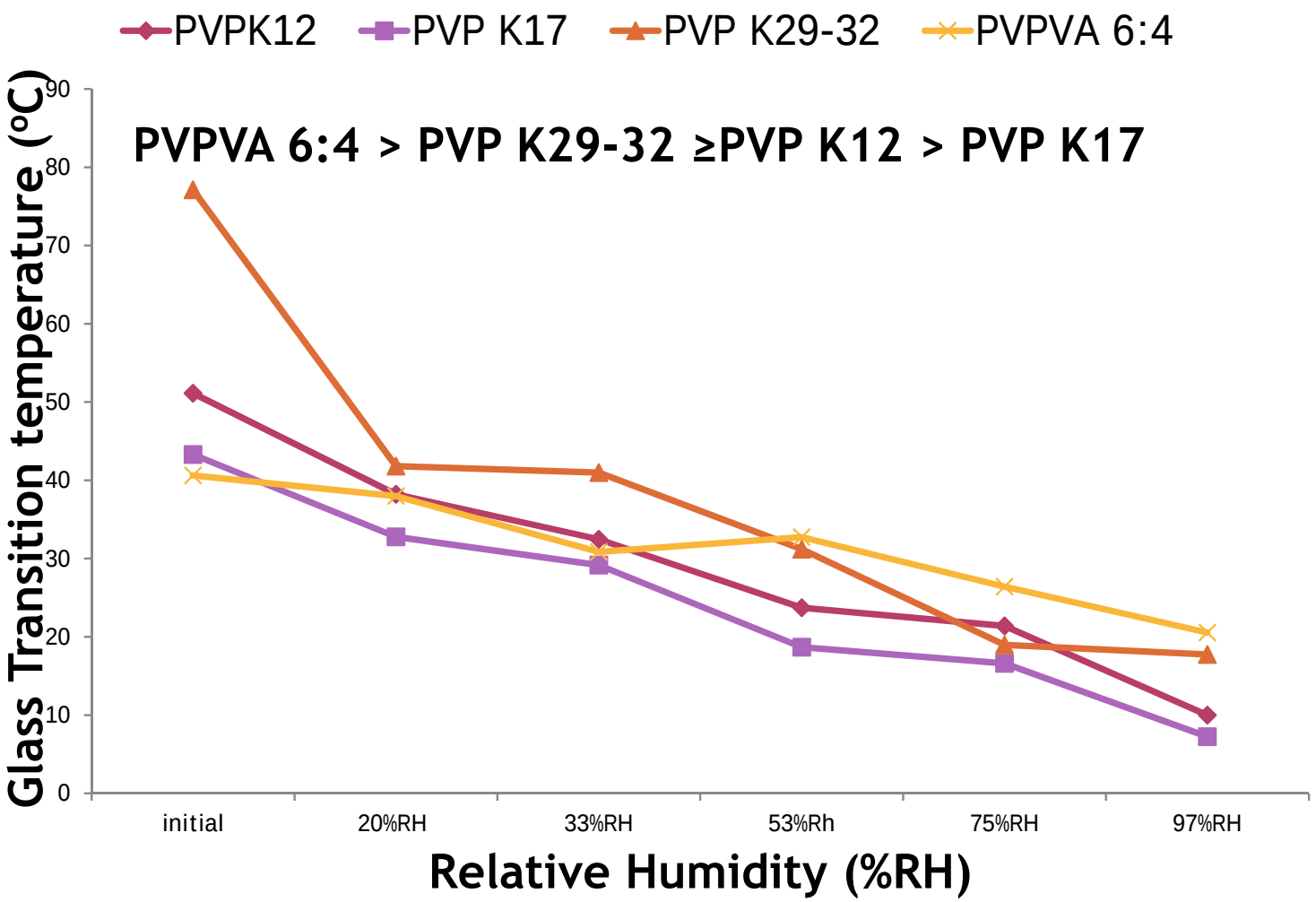


TG CHANGES: at different humidity

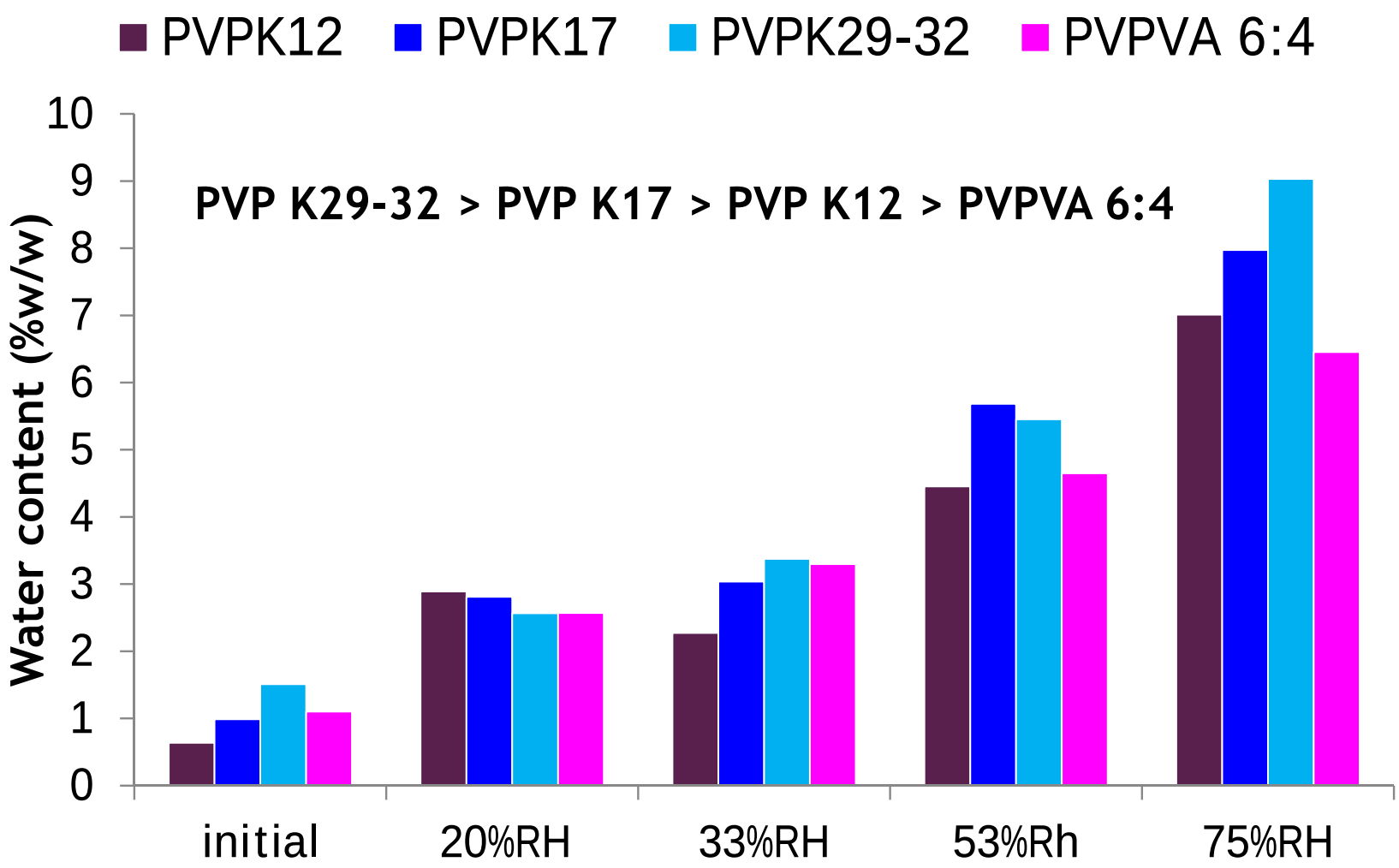
Hygroscopicity: PVP K29-32> PVP K17 > PVP K12 > PVPVA 6:4



TG CHANGES: at different humidity



WATER CONTENT: at different humidity



RECRYSTALLIZATION

- Up to 3weeks stability study…

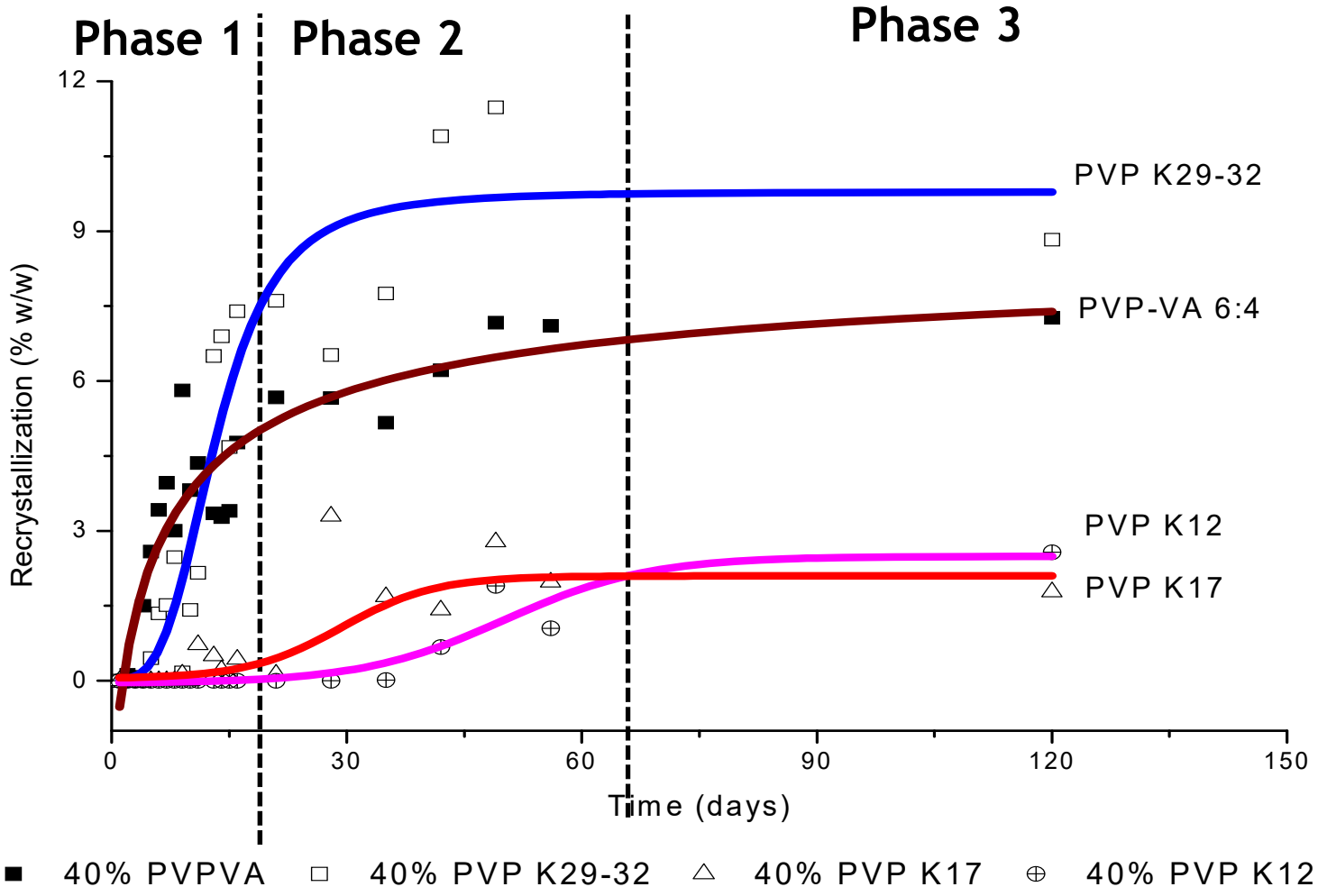
Carrier	75%RH	53%RH	33%RH	21%RH	0%RH
PVPVA 6:4	√	√	√	X	X
PVP K29-32	√	X	X	X	X
PVP K17	√	X	X	X	X
PVP K12	√	X	X	x	X

- However PVP K29-32,PVP K12 and K17 carrier systems start to show crystal at the end of 4 weeks at 53%RH

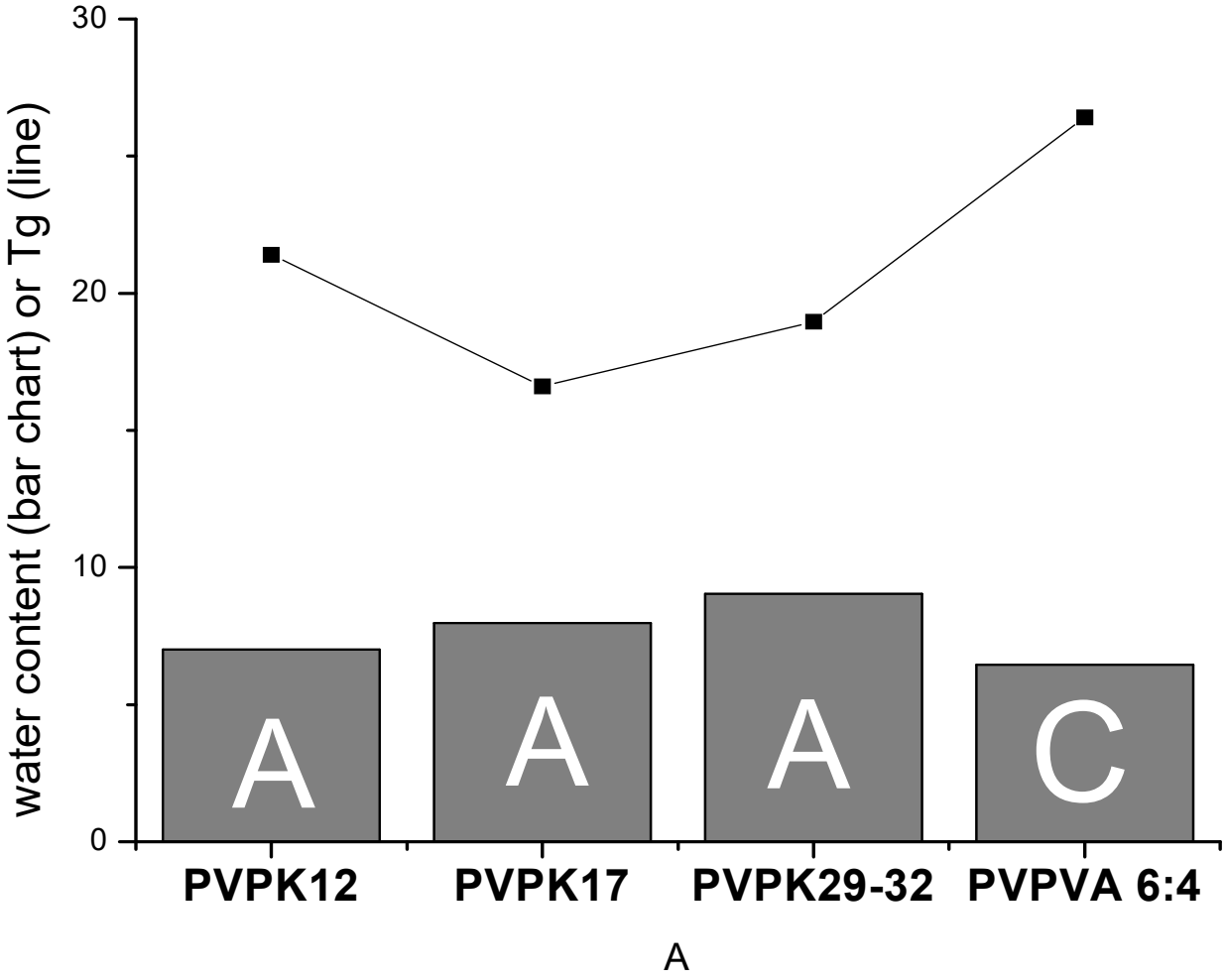
OPTICAL MICROSCOPE

OPTICAL MICROSCOPE

RECRYSTALLIZATION: at 75%RH



Water-Tg-Recrystallization?



THEREFORE…

- Therefore, it is suggested that interaction (specifically hydrogen bond) between drug-polymer superseded the effect of Tg and water content in maintaining the stability of HME 40%PCM-carriers.

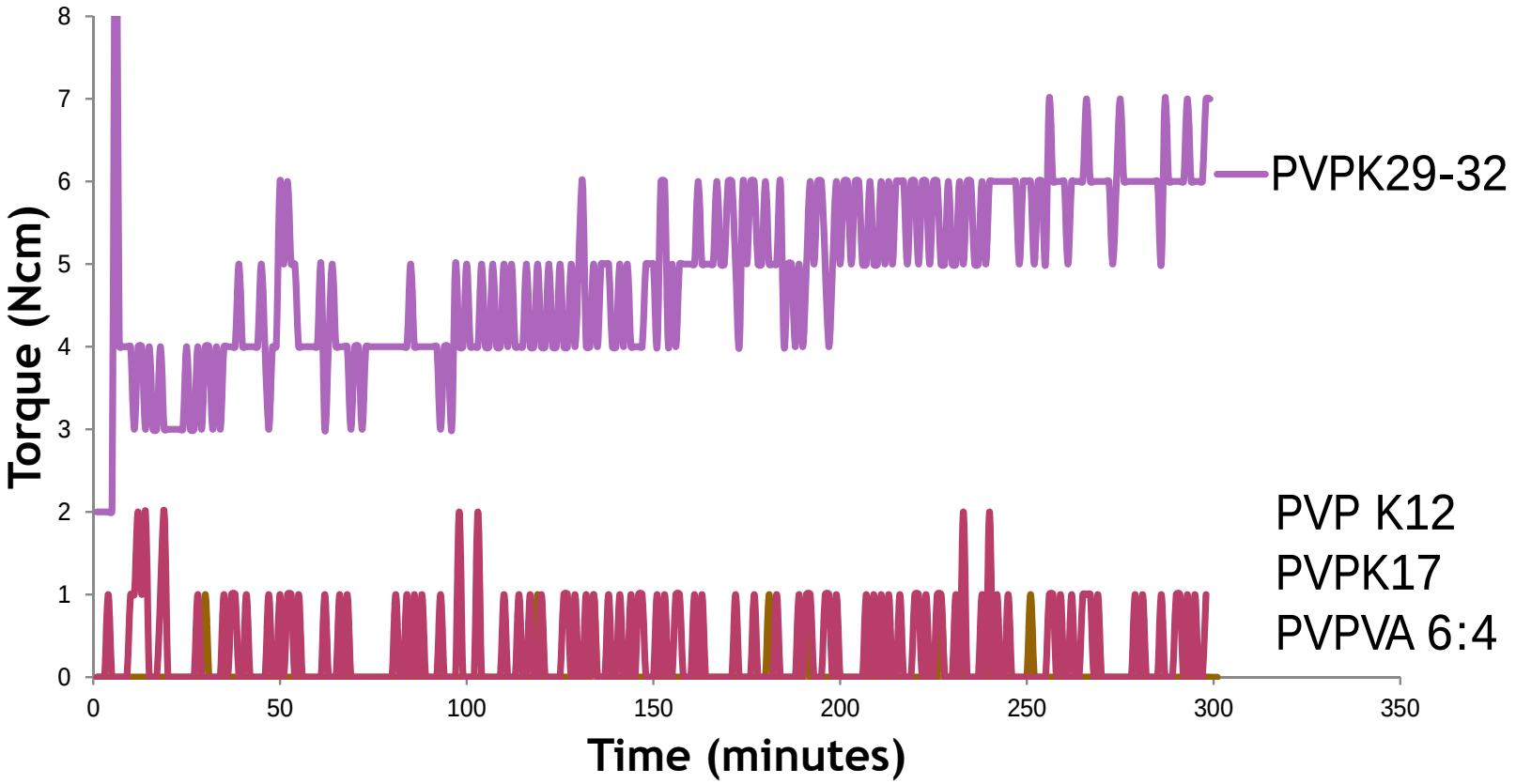
PVP(s) Polymer

- Within different grade of PVP(s) polymer, PVP K12 exhibited greatest stabilizing effect which is not directly correlated to the theoretical interaction energy density, B
- interaction energy density, B:
  - PVPK 29-32>PVP K12> PVP K17 >PVPVA 6:4
- Experimental stability:
  - PVP K12> PVP K17 > PVP K29-32>PVPVA 6:4
- This might be ascride to
  - Polymer chain conformation or intensity interaction of drug–terminal group of polymer chain (Sekizaki et al 1995)
  - Processing condition, i.e. Extrusion temperature

Haruo Sekizaki, Kazumi Danjo and Hiroshi Eguchi, *Solid-State Interaction of Ibuprofen with Polyvinylpyrrolidone* .Chemical & pharmaceutical bulletin 43(6), 988-993, 1995-06-15

TORQUE DURING HME PROCESS

1. At 160°C which is below Tg of PVP K29-32, 40% of drug loading did not achieve an optimum plasticizing effect and thus lead to lesser extent of interaction between drug-polymer



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CONCLUSION

- Recrystallization of HME 40%PCM-PVP and PVPVA6:4 system are humidity dependent.
- Interaction showed to be a critical factor for recrystallization of HME 40% Paracetamol-PVP/VA (s) systems.
- This interaction superseded the effect of water content and lowered Tg
- Optimum processing parameters are needed in maximizing the stabilizing potential of PVP.
- Lower grade (lower molecular weight) of PVP are deemed to be a better choice for HME process due to the wider “processing window”, i.e. lower Tg

Suggestion?

ACKNOWLEDGEMENT

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Thanks for your Attention!!