FEL 472/2
Glass Forming Ability of Active Pharmaceutical Drugs

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Problem Statement

- Amorphous APIs has been reported to have better solubility as compared to their crystalline form (Kanaujia et al., 2015).
- However, the high energy of amorphous can contribute to the amorphous instability and tendency to crystallization (Laitinen et al., 2013).
- Recent reports by(Chan et al., 2015, Chan et al., 2016) shows that there is possibility of dissolution compromising effect upon amorphous solid dispersion production. With that, not every drug can be converted into its corresponding amorphous form for bioavailability performances enhancement.

Objectives

1. To produce amorphous by using quench-cooled method.
2. To identify key property of a drug that makes it a suitable candidate for amorphous form.
3. To investigate the ability of amorphous in maintaining its glassy.

Introduction

Amorphous form of APIs

- Solid APIs that do not posses three dimensional long range of molecular order is said to be in amorphous form which is also referred as glassy state (Kanaujia et al., 2015).
- Amorphous form of pharmaceuticals may enhance their solubility and thus improve their bioavailability.

Introduction

Glass forming ability

- Glass forming ability (GFA) is defined as the ease of a material to undergo amorphization(Blaabjerg et al., 2017).
- Reduced glass transition temperature (Trg) is the ratio of Tg/Tm which can be used as the indicator in predicting the GFA of the APIs (Blaabjerg et al., 2016).

$$Trg = Tg/Tm$$

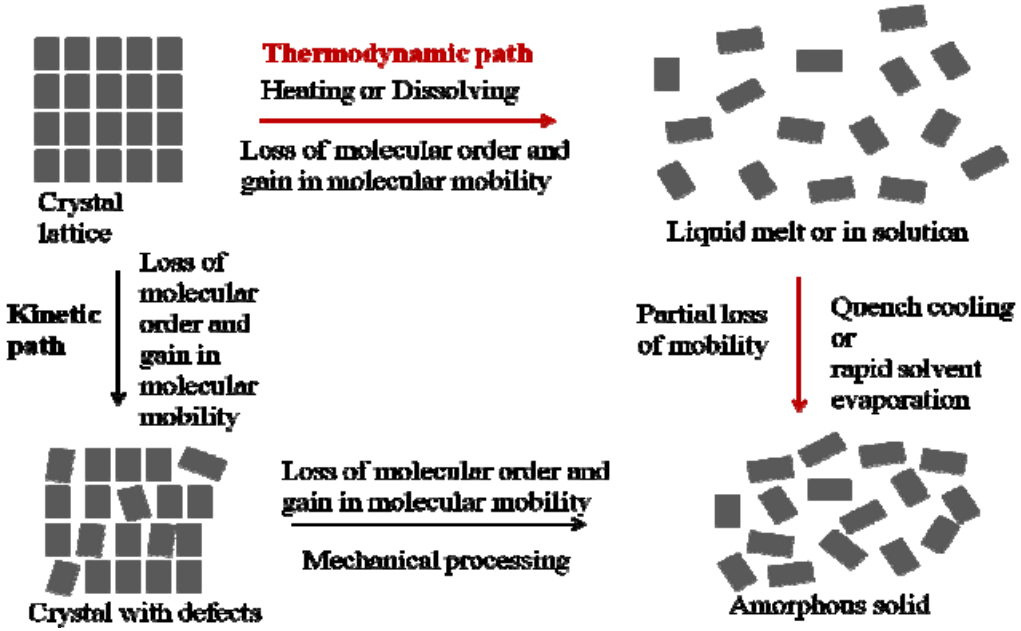
Stability of amorphous

- Amorphous form of API is thermodynamically unstable and thus it tends to convert into more stable crystalline form.

Introduction

Preparation of Amorphous

- Amorphous can be obtained through thermodynamic pathway and kinetic pathway.



- Generally, a material needs to bypass the thermodynamic tendency to nucleate and crystallize for it to become amorphous (Weber et al., 2017).

Introduction

Quench cooled

- Melt quenching method is suitable to be used for API that is thermally stable when exposed to a temperature slightly above its melting temperature (Weber et al., 2017).
- In this method, the solid material is melted using heat (above melting temperature) and rapidly cooled to obtain the amorphous form.

Materials and Methods

- Materials
  - 10 APIs : Caffeine, Clotrimazole, Etoricoxib, Flurbiprofen, Gliclazide, Ibuprofen, Ketoconazole, Ketoprofen, Paracetamol, Piroxicam
- Methods
  - TGA
  - Preparation of quench cooled APIs
  - DSC
  - FTIR
  - Calibration Curve and solubility
  - Amoprhous Advantage solubility ratio
  - Optical microscope
- Ten APIs models were selected in this study based on their solubility and different thermal properties. Amorphous forms of the selected drugs were prepared and analyzed together with the crystalline form of the APIs (raw materials). The samples were analyzed under thermal condition including Differential Calorimetric Scanning (DSC) and Thermogravimetric Analysis (TGA), FTIR and optical microscope.

Result and Discussion

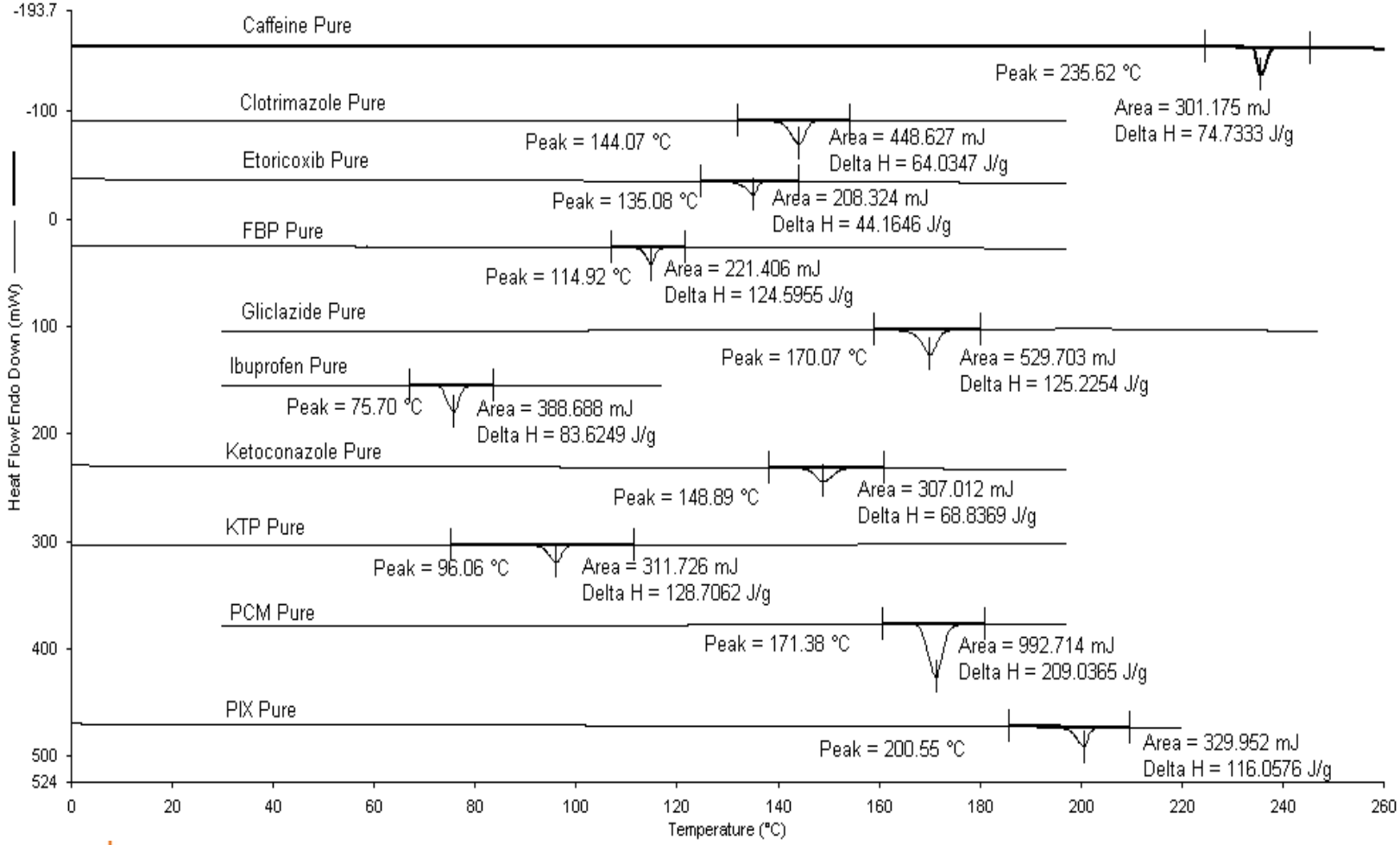


Figure 2: DSC Thermograms of first heating cycle of raw caffeine, clotrimazole, etoricoxib, flurbiprofen, gliclazide, ibuprofen, ketoconazole, ketoprofen, paracetamol and piroxicam

Result and Discussion

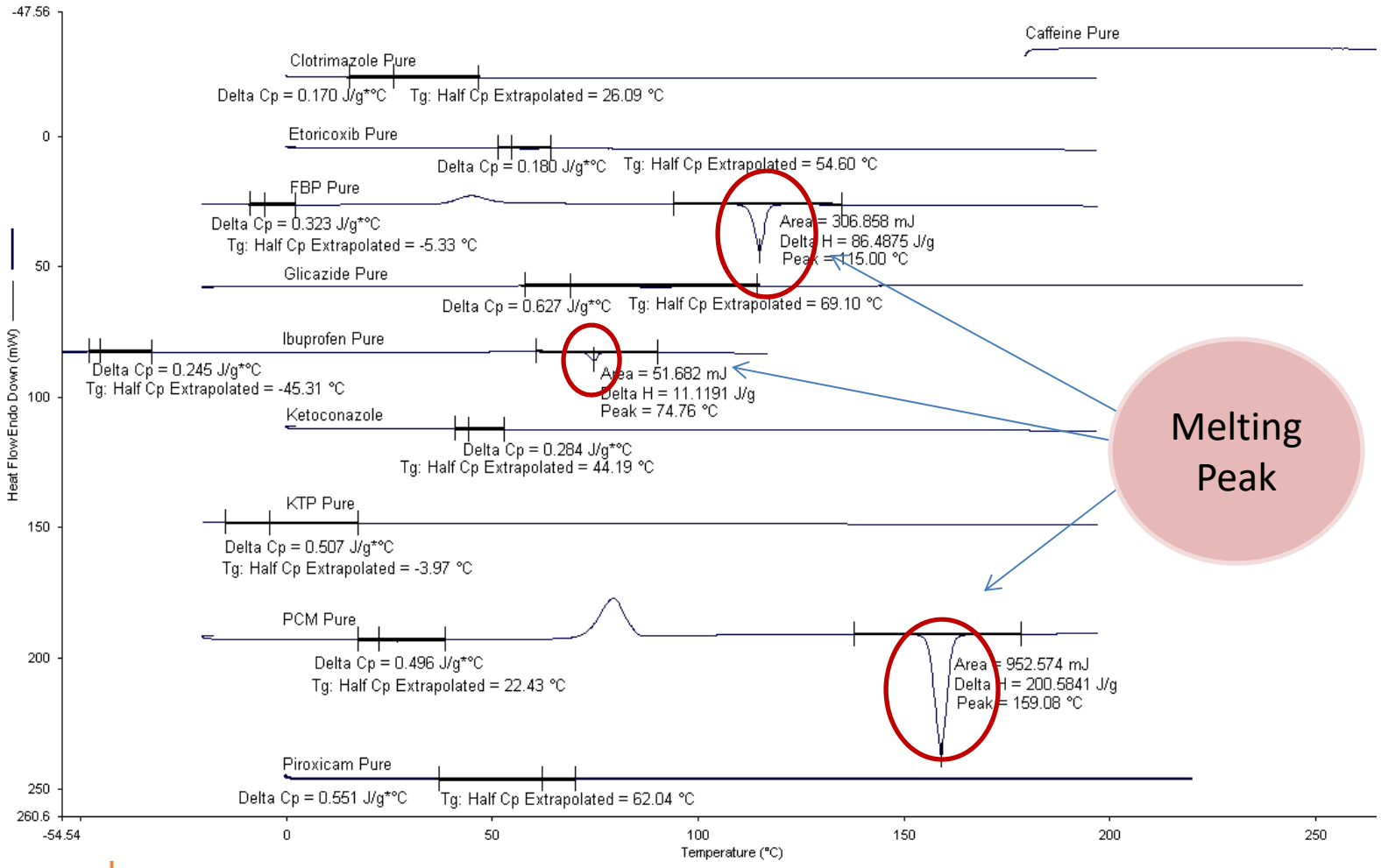


Figure 3: DSC Thermograms of third heating cycle of raw caffeine, clotrimazole, etoricoxib, flurbiprofen, gliclazide, ibuprofen, ketoconazole, ketoprofen, paracetamol and piroxicam

Result and Discussion

Table 1: Thermal Properties of Raw Materials

Drugs	Tg(˚C)	Tg(K)	Tm(˚C)	Tm(K)	Trg(K)
Caffeine	-13	**256.15**	235.62	**508.77**	**0.5034**
Clotrimazole	26.09	**299.24**	144.07	**417.22**	**0.7172**
Etoricoxib	54.6	**327.75**	135.08	**408.23**	**0.8029**
Flurbiprofen	-5.33	**267.82**	114.92	**388.07**	**0.6901**
Gliclazide	69.1	**342.25**	170.07	**443.22**	**0.7722**
Ibuprofen	-45.31	**227.84**	75.7	**348.85**	**0.6531**
Ketoconazole	44.19	**317.34**	148.89	**422.04**	**0.7519**
Ketoprofen	-3.97	**269.18**	96.06	**369.21**	**0.7291**
Paracetamol	22.43	**295.58**	171.38	**444.53**	**0.6649**
Piroxicam	62.04	**335.19**	200.55	**473.70**	**0.7076**

Pseudo Tg

- **Trg in decreasing sequence:-**

  Etoricoxib > Gliclazide > Ketoconazole > Ketoprofen > Clotrimazole > Piroxicam > Flurbiprofen > Paracetamol > Ibuprofen> caffeine

Result and Discussion

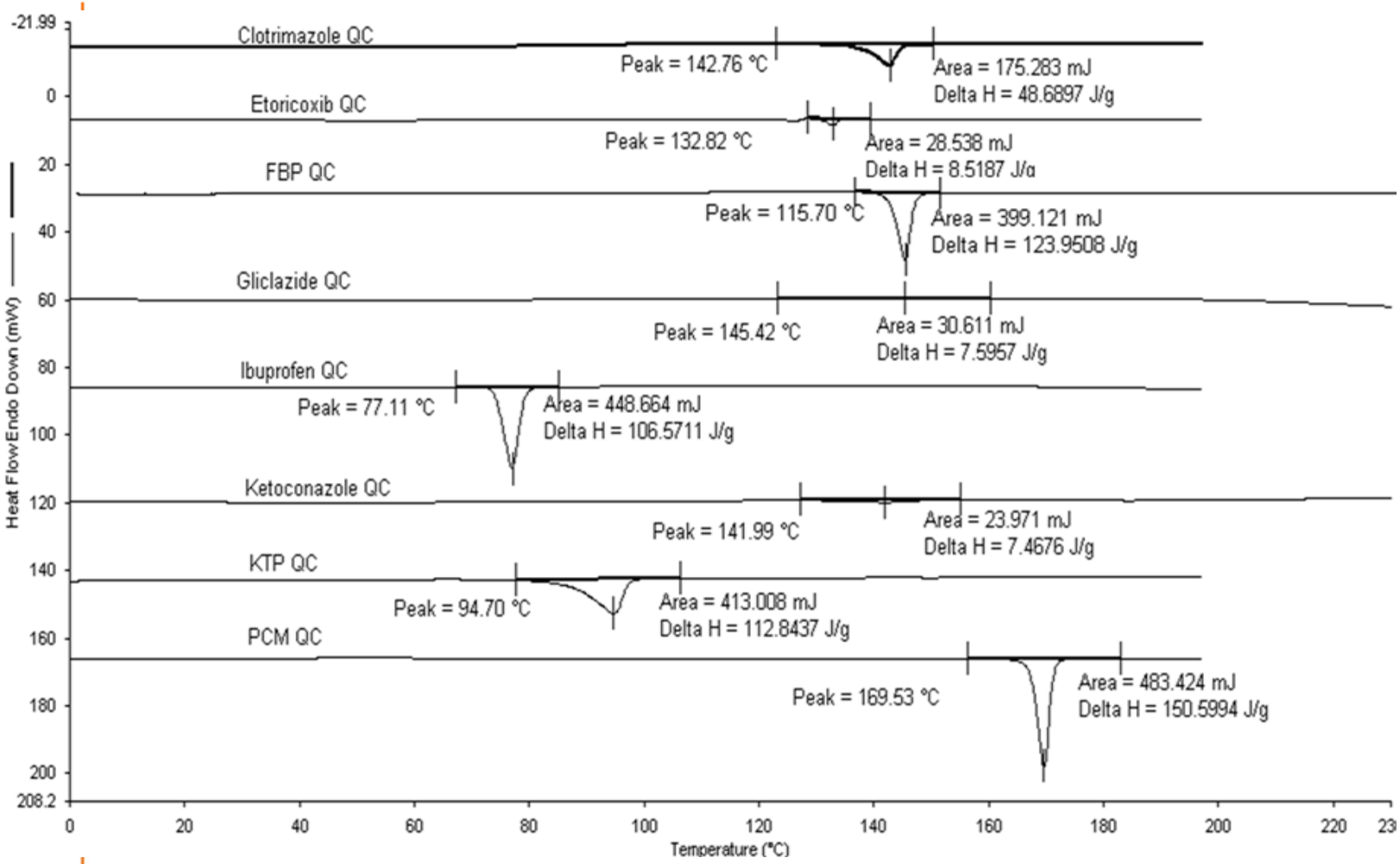


Figure 4 : DSC Thermograms of of quench-cooled clotrimazole, etoricoxib, flurbiprofen, gliclazide, ibuprofen, ketoconazole, ketoprofen and paracetamol

Result and Discussion

Table 2: Percentage of Amorphous after 24 hours storage			
Drugs	Melting enthalpy ΔH(J/g)		**Amorphous Percentage(%)**
	Raw APIs	Quench-cooled APIs	
Clotrimazole	64.0347	48.6897	**23.96357**
Etoricoxib	44.1646	8.5187	**80.71147**
Flurbiprofen	124.5955	123.9508	**0.517434**
Gliclazide	125.2254	7.5967	**93.93358**
Ibuprofen	83.6249	106.5711	**-27.4394**
Ketoconazole	68.8369	7.4676	**89.15175**
Ketoprofen	128.7062	112.8437	**12.32458**
Paracetamol	209.0365	150.5994	**27.95545**
Piroxicam	116.0576	*	**-**

Result and Discussion

Table 3: Amorphous Solubility Advantages Ratio :-						
APIs	**Tm (K)**	**ΔH (KJ/mol)**	**ΔG (KJ/mol)**	**Solubility (mg/ml)**	**σamorph/ σcrystal**	**Amorphous solubility (mg/ml)**
Caffeine	508.77	14.51	3.52	0.0617	**4.1381**	0.2553
Clotrimazole	417.22	22.08	4.50	0.00049	**6.1512**	0.0030
Etoricoxib	408.23	15.85	3.12	0.1327	**3.5220**	0.4674
Flurbiprofen	388.07	30.43	5.42	0.0270	**8.8954**	0.2402
Gliclazide	443.22	40.50	8.92	0.1081	**36.4917**	3.9435
Ibuprofen	348.85	17.25	2.14	0.3225	**2.3735**	0.7654
Ketoconazole	422.04	36.58	7.59	0.0889	**21.3337**	1.8965
Ketoprofen	369.21	32.73	5.09	0.1480	**7.7827**	1.1518
Paracetamol	444.53	31.60	6.98	14.00	**16.6960**	233.7441
Piroxicam	473.70	38.46	8.97	0.0400	**37.2791**	1.4912

Result and Discussion

Table 4 : Summary of QC APIs FTIR Spectra	
APIs	Remarks on FTIR Quenched Cooled APIs
Clotrimazole	Peaks become **broaden and less intense** might indicates amorphous form.
Etoricoxib	Peak at frequency 1431 cm^{-1} **broaden and less intense**. A broad peak at frequency of 1311 cm^{-1}. QC Etoricoxib possibly has turned into amorphous.
Flurbiprofen	Peak at 1217 cm^{-1} **disappears and become a merging of few peaks** within 1200 cm^{-1} to 1300 cm^{-1}. This can be possibly indicator of amorphicity.
Gliclazide	Charecteristic peaks of pure Gliclazide become **broaden and less intense** in QC sample might indicate amorphicity of the sample
Ibuprofen	Possible formation of amorphous may be seen as **shifting of peaks** in QC sample
Ketoconazole	**Merging of peaks** within 800 cm^{-1} to 1500 into few sharp peaks which possibly because of amorphous form present.
Ketoprofen	One **new peak** on the left side (beside peak 1705 cm^{-1}) of ketoprofen might be indicator of the amorphous formation.
Paracetamol	**Limited change occurred** because PCM is a well-known drug that not easily forms amorphous.
Piroxicam	**Peak** at 3338 cm^{-1}**disappear** in QC spectra which possibly due to amorphous formation occurred in the sample.

Result and Discussion

Birefringence:
i)Intense :- PCM,FBP,KTP, PIX
ii)Intermediate : ETO, GLI, KTC,IBU
iii)Minimal:- CLO, CAFF

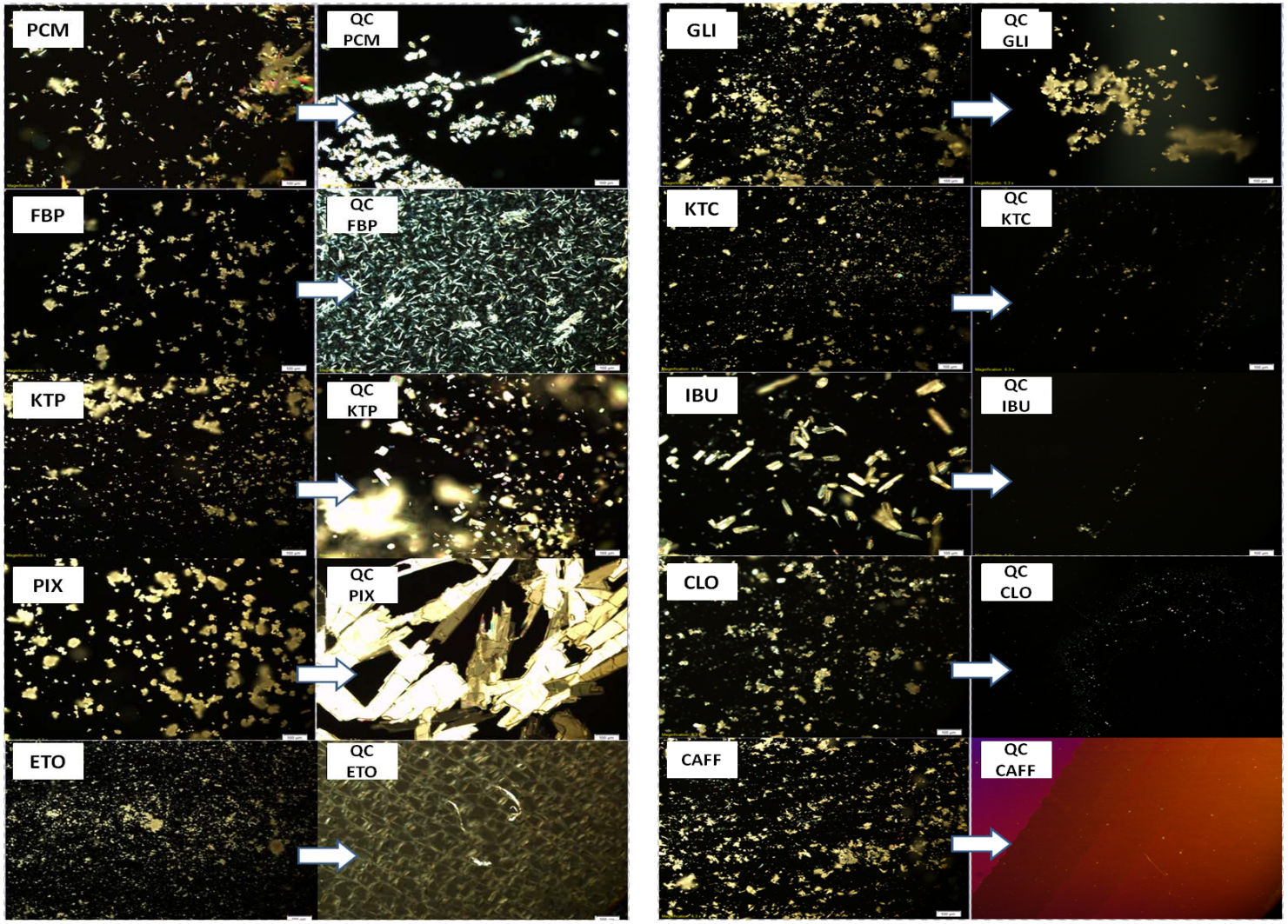


Figure 5 :Morphology of APIs under microscope. all are observed at 10x magnification except QC PPIX at 20x magnification.

Result and Discussion

Table 5 : Summary of the APIs performances under the study		
Properties	**Ranking**	**Remark**
Tg	GLI > PIX > ETO > KTC > CLO > PCM > KTP > FBP > IBU	Low Tg APIs will have higher mobility in room temperature and hence chance of crystallization is higher.
Trg	ETO > GLI > KTC > KTP > CLO > PIX > FBP > PCM > IBU	Higher Trg higher ability to form amorphous or glass state.
Amorphous solubility advantage ratio	PIX > GLI > KTC > PCM > > FBP > KTP > CLO > CAFF > ETO > IBU	Higher ratio, higher solubility of amorphous form compared to the crystal solid of APIs.
Crystallinity	PCM > FBP > KTP > PIX > ETO > GLI > KTC > CLO > IBU > CAFF	Presence of birefringence indicates crystallinity.
% amorphous	GLI > KTC > ETO > PCM > CLO > KTP > FBP > IBU	Gliclazide has the highest amorphous percentage after 24 hours storage.

- 9 drugs transform into glass state at certain temperature (presence of Tg)
- Ibuprofen, Paracetamol and Flurbiprofen are the three drugs with lower reduced glass transition temperature. This may explains the presence of melting peaks in third cycle DSC thermograms
- Etoricoxib has highest Trg but DSC scan involving QC APIs showed Etoricoxib has lower amorphous percentage than Gliclazide and Ketoconazole.
- The glass form of APIs showed improvement in the aqueous solubility compared to their crystal form.
- Presence of birefringence in the morphology indicates crystal form while absence of it may indicate the complete formation of amorphous.
- QC PCM shows the highest intensity of birefringence but based on percentage calculated Ibuprofen has the lowest amorphous content

Result and Discussion

Table 6 :Pearson Correlation of the factor affecting glass forming ability based on the percentage of amorphous after 24 hours storage in room condition, n=10					
Pearson Correlation Sig. (2-tailed)	**Solubility ratio**	**Trg**	**Tg**	**Tm**	**Degree of birefringence**
Amorphocity R^2	0.680*	0.693*	0.262	0.262	0.357
P value	0.044	0.038	0.496	0.496	0.346
*Correlation is significant at the 0.05 level (2-tailed).					

- Trg and ratio of amorphous to crystalline solubility are correlating to the glass forming ability of the tested APIs.
- The correlation was found intermediate with R^2 of 0.680 and 0.693 respectively for factors of solubility and Trg.
- This finding contributing new insight to the field of amorphous formation as ratio of solubility does affect the glass forming ability of API though with intermediate correlation.

Conclusion

- Generally, all drugs tested have the ability to form amorphous except caffeine. Caffeine is easily undergone sublimation in high temperature thus the determination of amorphous formation become difficult.
- Among all of the drugs evaluated under this study, Etoricoxib has shown the highest ability in forming a glass state based on the reduced glass temperature (Trg) calculated.
- However, Gliclazide has the highest amorphous percentage followed by Ketoconazole and Etoricoxib.
- Hence, Trg alone is not sufficient to determine the ability and stability of the glass state.
- Overall, ibuprofen consistently showed the lowest performances in all the properties investigated (Tg, Trg, solubility advantage ratio, %amorphous)

Future Studies

- **Stability of Amorphous Formulations**
  - challenges in the development of the amorphous formulation as there is no protocols in predicting the formulation stability.
  - Thus, crystallization tendency of APIs should be further evaluated so that amorphous formulations with long shelf-life can be successfully developed.
  - Crystallization or nucleation inhibitor can be utilized .The potential inhibitor that could be used to retard the crystallization of amorphous upon contact with water includes polyvinyl pyrrolidone(PVP), polyvinyl alcohol, polyethylene glycols, hydroxypropyl methycellulose(HPMC) and hydroxypropyl methylcellulose(HPMC) (Murdande et al., 2011).
- **Increase Solubility Performances of Amorphous Drugs**
  - The solubility may be improved further by incorporation of other materials that have better solubility performances.
  - Solid dispersion has been proved to be the most promising method in developing formulations with enhanced dissolution and bioavailability(Akter et al., 2015).

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