สมบัติด้านความร้อนและพฤติกรรมการเป็นผลึกของยาไฮโดรคลอโรไทอะไซด์และยาโพรพราโนลอลไฮโดรคลอไรด์ในยาพื้นเมทริกซ์ไขเชลแล็กและโพลอกซาเมอร์

Thermal Properties and Crystallinity Behavior of Hydrochlorothiazide and Propranolol HCl Incorporated in Shellac Wax-Poloxamer Matrix Bases

นิพนธ์ต้นฉบับ **Original Article**

พรศิษย์ ไชยะ[1], ใจเอก ชลชีวะ[2], วรากร ธรรมสุทธิ์[2] และ ธวัชชัย แพชมัด[2,3,4]*

[1] สำนักวิชาเภสัชศาสตร์ มหาวิทยาลัยวลัยลักษณ์ อ.ท่าศาลา จ.นครศรีธรรมราช 80000
[2] ภาควิชาเทคโนโลยีเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร จ.นครปฐม 73000
[3] สาขาวิชาวิศวเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร จ.นครปฐม 73000
[4] กลุ่มวิจัยสารออกฤทธิ์ทางชีวภาพและวัสดุจากธรรมชาติสำหรับการส่งเสริมสุขภาพและระบบนำส่งยา คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร จ.นครปฐม 73000

*** Corresponding author:** phaechamud_t@su.ac.th

วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ2564;16(3):239-254.

Pornsit Chaiya[1], Chai-ek Choncheewab[2], Warakon Thammasut[2] and Thawatchai Phaechamud[2,3,4]*

[1] Shool of Pharmacy, Walailak University, Thasala, Nakhonsrithammarat, 80000, Thailand
[2] Department of Pharmaceutical Technology, Faculty of Pharmacy, Sipakorn University, Nakhon Pathom 73000 Thailand
[3] Department of Pharmaceutical Engineering, Faculty of Pharmacy, Sipakorn University, Nakhon Pathom 73000 Thailand
[4] Natural Bioactive and Material for Health Promotion and Drug Delivery System Group (NBM), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000 Thailand

*** Corresponding author:** phaechamud_t@su.ac.th

Thai Pharmaceutical and Health Science Journal 2021;16(3):239-254.

บทคัดย่อ

วัตถุประสงค์: ระบบเมทริกซ์ชนิดไม่ชอบน้ำเป็นรูปแบบสำหรับควบคุมการปลดปล่อยยา ระบบนี้สามารถดัดแปลงอัตราการปลดปล่อยยาได้โดยการปรับปริมาณไขหรือพอลิเมอร์ชนิดชอบน้ำ งานวิจัยนี้ศึกษาสมบัติด้านความร้อนและพฤติกรรมสภาพเป็นผลึกของยาต้นแบบ (โพรพราโนลอล ไฮโดรคลอไรด์ และไฮโดรคลอโรไทอะไซด์) ในอัตราส่วนต่าง ๆ ของเมทริกซ์ที่มีส่วนประกอบไขเชลแล็กและโพลอกซาเมอร์ซึ่งมีวิธีการเตรียมที่แตกต่างกัน ได้แก่ การผสมร่วมทางกายภาพ และการหลอมรวม **วิธีการศึกษา:** ทำการเตรียมตัวอย่างด้วย 1. การผสมร่วมทางกายภาพ โดยยาต้นแบบและยาพื้นทั้ง 3 ชนิดถูกผสมเข้าด้วยกันด้วยโกร่งและลูกโกร่ง 2. การเตรียมตัวอย่างด้วยการหลอม ยาพื้นแต่ละชนิดถูกหลอมก่อนผสมยาต้นแบบลงไปและปล่อยให้เย็นตัวลงที่อุณหภูมิห้อง ตัวอย่างจากการเตรียมทั้งสองวิธีได้ถูกประเมินสมบัติด้านความร้อนด้วยวิธี thermogravimetric (TGA), differential scanning calorimetry (DSC) hot stage microscope (HSM) และพฤติกรรมสภาพเป็นผลึกด้วย powder X-ray diffractometry (PXRD) นอกจากนี้ ยังใช้เทคนิค FT-IR ตรวจสอบอันตรกิริยาระหว่างยาต้นแบบและยาพื้นด้วย **ผลการศึกษา:** ลักษณะภาพจาก TGA แสดงให้เห็นว่ายาต้นแบบและสารชนิดอื่นไม่สลายตัวที่อุณหภูมิเตรียมตัวอย่าง การทดสอบคุณสมบัติด้านความร้อนและพฤติกรรมสภาพเป็นผลึกบ่งชี้ว่าไม่เกิดอันตรกิริยาระหว่างยาโพรพราโนลอลและยาพื้น ส่วนยาไฮโดรคลอโรไทอะไซด์ที่ความเข้มข้นต่ำ (10 เปอร์เซ็นต์โดยน้ำหนัก) กับโพลอกซาเมอร์อาจเกิดโซลิดดิสเพอร์ชัน (solid dispersion) ซึ่งมักเกิดเมื่อยาที่ไม่ชอบน้ำผสมกับพอลิเมอร์ชนิดชอบน้ำ นอกจากนี้ยังพบว่าไม่เกิดอันตรกิริยาระหว่างยาไฮโดรคลอโรไทอะไซด์กับยาพื้นซึ่งยืนยันได้ด้วยเทคนิค FT-IR **สรุป:** ยาโพรพราโนลอล ไฮโดรคลอไรด์และไฮโดรคลอโรไทอะไซด์ไม่เกิดอันตรกิริยากับเมทริกซ์ไขเชลแล็กและโพลอกซาเมอร์ การเข้าใจคุณสมบัติด้านความร้อนและพฤติกรรมสภาพเป็นผลึกของยาต้นแบบทั้งสองในตัวอย่างที่เตรียมด้วยวิธีต่างกันเป็นประโยชน์ในการพัฒนายาเม็ดชนิดเมทริกซ์ด้วยการใช้ยาพื้นชนิดนี้เป็นสารก่อเมทริกซ์

คำสำคัญ: เมทริกซ์, โพรพราโนลอล ไฮโดรคลอไรด์, ไฮโดรคลอโรไทอะไซด์, ไขเชลแล็ก, โพลอกซาเมอร์

Editorial note
Manuscript received in original form: August 14, 2020;
Revised: October 1, 2020;
Accepted in final form: June 29, 2021;
Published online: September 26, 2021.

Abstract

Objective: Hydrophobic matrix system is a controlled-release dosage form that could affect the drug release. It can modify drug release rates by adjusting the amount of wax or incorporating hydrophilic polymers. This research investigated thermal properties and crystallinity behavior of model drugs (propranolol hydrochloride (PRN) and hydrochlorothiazide (HCTZ)) in various ratios of shellac wax (SHW) and poloxamer matrices from different preparation methods (physical mixture (PM) and molten sample (MS)). **Method:** The model drugs and three base types (SHW, poloxamer and mixed base (SHW:Poloxamer)) were mixed together by mortar and pestle for PM preparation. In addition, each base was melted following the incorporation of the model drug and then solidified at room temperature for MS preparation. Both PM and MS were evaluated for their thermal properties with the thermogravimetric method (TGA), differential scanning calorimetry (DSC), hot stage microscope (HSM) and crystallinity properties with powder X-ray diffractometry (PXRD). In addition, FT-IR techniques was used to investigate the interaction between model drugs and bases. **Results:** TGA results indicated that the model drugs and another compounds did not degrade at the preparation temperature. The characterization of thermal properties and behavior of crystallinity did not show any interactions between PRN and other bases, but both PM and MS of HCTZ at a low content (10% w/w) incorporated in poloxamer may be described by the solid dispersion which usually occurred when a hydrophobic drug was mixed with a hydrophilic polymer. In addition, there was no interaction between HCTZ and all bases which confirmed with FT-IR. **Conclusion:** There is no interaction between PRN and HCTZ with matrix comprising shellac wax and poloxamer. Understanding thermal properties and crystallinity behavior of these two drug compounds in physical mixture and molten mixtures of shellac wax-poloxamer is useful for developing the matrix tablet using these bases as the matrix formers.

Keywords: matrix, propranolol hydrochloride, hydrochlorothiazide, shellac wax, poloxamer

Journal website: http://ejournals.swu.ac.th/index.php/pharm/index

Introduction

A controlled release dosage form delivers drugs locally or systemically at a predefined rate for a specified period of time. The purpose of controlled release dosage form is to provide desirable drug release profiles that can achieve therapeutic plasma levels.[1] The matrix system is one type of controlled release dosage form. It is designed to solve many drawbacks

of the conventional dosage form[2] such as reducing the frequency of dosing[3] and reducing or avoiding side effects due to high plasma drug concentrations[4]. The different types of matrix systems can be classified with different drug release mechanisms including reservoir matrix systems, monolithic matrix systems and osmotic pump systems. In this study, the authors focused on the monolithic matrix system which involves drugs to be encapsulated or dispersed in a matrix.[5] These systems can be employed by forming hydrophobic matrices which release drugs after being dissolved by a solvent and/or hydrophilic matrices which swell on hydration and dissolve to release drugs.[6,7] Hydrophobic matrix systems are mainly formulated by waxes and can be suitable for drugs which have high solubility.[8] Wax-based matrices have been investigated to ascertain factors that would affect the release of drugs. They can modify release rates by increasing the amount of drugs or wax concentration, as well as incorporating hydrophilic polymers which would enhance drug release.[9] A wax-based matrix tablet could be prepared by sintering method based on heating the waxy material and blending other excipients into the molten wax.[2] Some methods could be used to prepare the wax matrix including hot melt extrusion[10] or injection molding.[11] On the other hand, hydrophilic matrix systems tend to be more popular in tablet manufacture for controlled release systems.[8] On contact with water, the hydrophilic matrix systems can expand due to the entry of the water molecules. This then allows the polymer to swell up forming a gel layer which is a barrier to drug release. The drug's particles would then move through the gel layer via diffusion or erosion eventually allowing the drug to be released.[4]

Shellac wax (SHW) is a natural by-product obtained from *Laccifer lacca* which is a class of insect. Shellac is secreted to prevent blockage of cell pores and acts as an anti-constipate to alleviate discomfort of the natural secretive activity of the insect.[12] This wax has been found in India, Thailand and other Southeast Asian countries. The SHW is obtained from about 5% of a by-product of shellac. The appearance of SHW is brownish or yellow, shiny, translucent, hard or brittle, and thinly flaked.[13] SHW is composed of four fatty materials including fatty acid esters (70 - 82%), free fatty alcohols (8 - 14%), free fatty acids (1 - 4%) and hydrocarbons (1 - 6%).[14] The three main fatty acid monomers in SHW are aleuritic acid, shellolic acid and jalaric acid. These monomers can interact together to form fatty acid ester and fatty alcohol products.[13] The chemical structure of these fatty acids are shown in Figure 1. Normally, SHW is used as a coating material to protect agriculture products from moisture and air.[15] In pharmaceuticals, SHW is used as a sustained release material in pellet dosage form which can slow down water penetration into pellets[16] (Lantz et al., 1964) and is used as a powder coating material in tablets which can provide a homogeneous and stable film.[17]

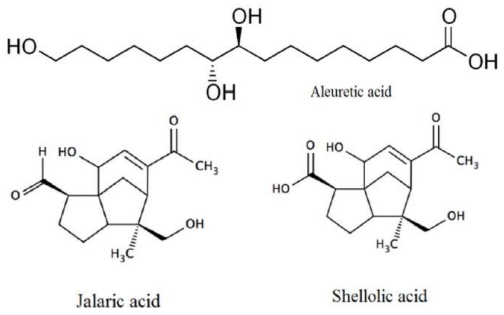


Figure 1 Chemical structure of fatty acid monomer in shellac wax (SHW).[13]

Poloxamer is a synthesized tri-block copolymer which consists of ethylene oxide (EO) and propylene oxide (PO) blocks arranged in a tri-block structure. Registered trademarks of these copolymers (e.g., Pluronic, Synperonic or Tetronic) cover a large range of liquids, pastes and solids. These copolymers have amphiphilic properties.[18] The hydrophilic polymer can modify the drug release profile for a wax-based matrix due to the hydrophilic property of poloxamer; hence, it could create the pores and channels on the wax matrix which allow a higher content of dissolution medium penetration.[19] The incorporation of this polymer might enhance the drug release of shellac wax matrix; therefore, this poloxamer is used to tune up the drug release from shellac wax matrix in this experiment. The chemical structure of poloxamer is shown in Figure 2.

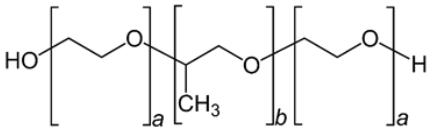
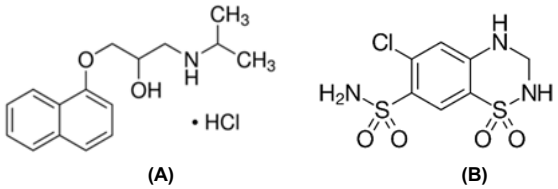


Figure 2 Chemical structure of poloxamer.

Propranolol hydrochloride (PRN) is classified as nonselective beta-adrenergic blocking agent which is widely used in the treatment of hypertension and many other

cardiovascular disorders.[20] The oral bioavailability of PRN is low at about 15-23%. It is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular formula is $C_{16}H_{22}ClNO_2$ and has a molecular weight of 295.8 g/mol. The chemical structure of PRN is shown in Fig.3. It is a highly water-soluble drug with a relatively short biological half-life of 3 - 5 hours with the usual dose being 40 mg thrice daily.[21] The high frequency of administration affects the fluctuation of the plasma drug concentration. Therefore, it would be convenient for patients if it is prepared in controlled drug release dosage forms which are administered once daily.

Hydrochlorothiazide (HCTZ) is an antihypertensive drug acting as a diuretic. It belongs to the thiazide class that acts by inhibiting the kidneys' ability to retain water. It is a white crystalline powder which is slightly soluble in water. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and has a molecular weight of 297.7 g/mol. The chemical structure of HCTZ is shown in Fig.3. The plasma half-life and oral bioavailability vary between 5.6 – 14.8 hours and between 60 - 80%, respectively, depending on the subject. The main side effects of HCTZ are an increase in serum urate concentration, weakness and confusion due to low blood levels of potassium, sodium, and magnesium, and a high dose-dependent level of calcium.[22] To avoid excessive fluctuation in the plasma level that can induce side effects, HCTZ should be developed as the controlled release dosage form. Therefore, PRN and HCTZ were used as hydrophilic and hydrophobic model drugs in this experiment, respectively. In this study, thermal properties and crystal behavior of model drugs in various ratios of SHW and poloxamer matrices were studied and different preparation methods (physical mixture (PM) and molten sample (MS)) were also investigated.



(A) (B)

Figure 3 Chemical structures of PRN (A) and HCTZ (B).

Methods

Materials

Hydrochlorothiazide (HCTZ) (Batch No.: I1413891, supplied by Government of Pharmaceutical Organization, Thailand) and propranolol hydrochloride (PRN) (Lot. No.: M080311, procured from PC Drug Co., Ltd., Bangkok, Thailand) were used as hydrophobic and hydrophilic model drugs, respectively. Poloxamer 407 or Lutrol® F127 (Lot. No.: WPDF563B, purchased from BASF, Ludwigshafen, Germany) and shellac wax (SHW) (purchased from Ake shellac Co., Ltd., Lumpang, Thailand) were used as the matrix formers for the controlled release system.

Methods

Preparation of physical mixture (PM) and molten sample (MS)

The physical mixture (PM) of the drug loaded matrix was prepared by mixing the model drug (HCTZ or PRN) into three bases which were SHW, poloxamer and mixed base. A model drug and base were mixed together by mortar and pestle for 10 min. In the case of the mixed base, SHW and poloxamer were firstly mixed and then the model drug was mixed by mortar and pestle. For the molten sample (MS), each base was melted followed by incorporating the model drug. In the case of the mixed base, SHW was firstly melted and then the same weight ratio of poloxamer was melted afterward. Finally, the model drug was added into the molten base. The MS was mixed using a stirrer at 100 rpm at 80ºC and then solidified at room temperature. Both PM and MS were kept in the desiccator.

Evaluations

1. Thermal degradation study of each compound in matrix using TGA

Thermogravimetric analysis (TGA) was used to investigate the thermal degradation property of each compound in formulation, including HCTZ, PRN, SHW and Poloxamer. The 5 mg of each compound was weighed and placed in the standard aluminum sample pans. The pan was then sealed and placed in a thermogravimetric analyzer (TG/DTA 6200, Chiba, Japan) with a heating rate of 10 ºC/min. The heating range was 30-550 ºC in an atmosphere of nitrogen of 200 mL/min.

2. Thermal behavior study of each compound in matrix

2.1 Differential scanning calorimetry (DSC) method

Each pure compound of both model drugs (HCTZ and PRN), SHW, poloxamer, mixed base and drug loaded matrices, which included PM and MS, were used as samples

for this thermal analysis. The drug loaded matrix was prepared by mixing 10-50% w/w of the model drug into SHW, poloxamer and mixed bases. All samples weighed about 5 mg and were placed in the standard aluminium pan. The pan was then sealed and heated in the DSC chamber (DSC 6200, Chiba, Japan) with a heating rate of 10 ºC/min. The heating range was 30-350 ºC in an atmosphere of nitrogen at 40 mL/min. The components of sample for DSC analysis including pure compound, PM and MS in various ratios of model drug and bases are shown in Table 1.

Table 1 Samples for DSC analysis.

Pure compound	Physical mixture (Poloxamer:SHW)	Molten mixture (Poloxamer:SHW)
HCTZ	10% w/w model drug* in 10:0, 5:5, 0:10	10% w/w model drug in 10:0, 5:5, 0:10
PRN	20% w/w model drug in 10:0, 5:5, 0:10	20% w/w model drug in 10:0, 5:5, 0:10
Poloxamer	30% w/w model drug in 10:0, 5:5, 0:10	30% w/w model drug in 10:0, 5:5, 0:10
SHW	40% w/w model drug in 10:0, 5:5, 0:10	40% w/w model drug in 10:0, 5:5, 0:10
Mixed base (Poloxamer:SHW = 5:5)	50% w/w model drug in 10:0, 5:5, 0:10	50% w/w model drug in 10:0, 5:5, 0:10

* **Remark:** the model drugs including HCTZ and PRN were separately mixed into the bases.

2.2 Hot stage microscopic (HSM) method

A hot stage microscope (stage from Mettler Toledo, Bangkok, Thailand and microscope from Olympus, Bangkok, Thailand) was used to observe the melting behavior of each compound under heating conditions. In addition, the change of each compound's morphology and crystallinity was also observed. PMs of the model drugs with poloxamer, SHW and mixed base were also investigated with this technique. The 10% w/w of model drugs were mixed with poloxamer, SHW or mixed base by mortar and pestle. Both PM and MS were heated at 10 ºC/min from 30-180 ºC. A picture of each sample was photographed from room temperature to 180 ºC and when it was cooled down to 30 ºC. The components of PM and MS are shown in Table 2.

Table 2 Samples for HSM analysis.

Physical mixture (PM)	Molten mixture (MS)
10% w/w model drug* in SHW	10% w/w model drug in SHW
10% w/w model drug in poloxamer	10% w/w model drug in poloxamer
10% w/w model drug in mixed base	10% w/w model drug in mixed base

* **Remark:** the model drugs including HCTZ and PRN were separately mixed into the bases.

3. Crystallinity determination of each compound in matrix using powder X-ray diffractometry (PXRD)

PXRD of PRN, HCTZ, SHW, poloxamer and mixed base were carried out. In addition, PM or MS that exhibited significant alterations in DSC thermogram was also analyzed with PXRD. The samples were grinded into fine particles by mortar and pestle and then placed into the PXRD disc. All samples were evaluated using a powder X-ray diffractometer (MiniFlex II, Tokyo, Japan) by scanning through the range of 0-30 º2θ.

4. The intermolecular interaction study of each compound in matrix using Fourier transform-infrared spectroscopy (FT-IR)

The spectra of PRN, HCTZ, SHW, poloxamer and mixed based were carried out. In addition, PM or MS that exhibited significant alterations in DSC thermogram and PXRD diffractogram was also analyzed with FT-IR (Nicolet 4700, Madison, USA). The small amount of sample was blended with potassium bromide and compressed with plunger and die to make a pellet using hydraulic press at compression force of 4 tons. The sample pellet was mounted in IR chamber. The %transmittance of sample was recorded. The spectra were acquired at a resolution of 2 cm^{-1}, in the range of 400 - 4000 cm^{-1}.

Results and Discussions

1. Thermal degradation study of each compound in matrix using TGA

The TGA thermograms are shown in Figure 4. From the TGA thermograms, HCTZ began degradation at 295 ºC and degraded rapidly approximately at 336 ºC, which corresponded the previous study by Menon et al. (2002)[23]. The degradation was due to thermal oxidation between HCTZ and oxygen or air in the system.[23] PRN exhibited degradation at 215 ºC and rapid degradation was observed at 300 ºC, which was different from the report of Macêdo et al. (2000).[24] They reported 4-step of degradation for PRN at 285.6, 324.1, 667.2 and 898.1 ºC, respectively.[24] The different result might have been due to the difference in the study's condition. The thermal degradation temperature of poloxamer was found only one step at 401.5 ºC which was close to the result of previous research work of Hritcu et al (2009).[25] Therefore, multistep degradation was observed in natural waxes which are composed of numerous natural fat compounds.[26] In this study, the TGA curve of SHW also exhibited in multistep degradation at temperatures ranging from 240 to 500 ºC. Thus, the results

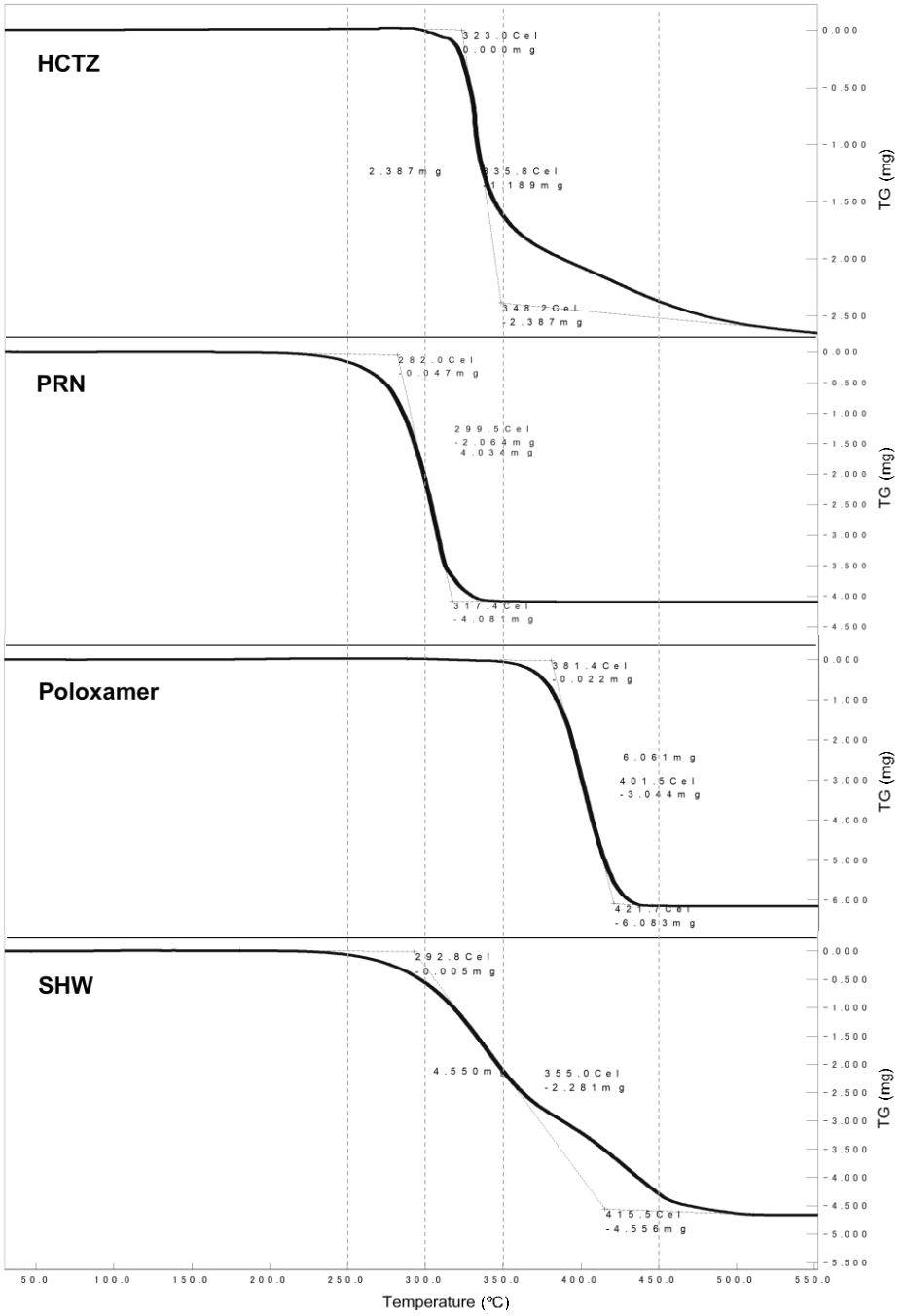


Figure 4 TGA Thermograms of HCTZ, PRN, Poloxamer and SHW.

signified that the model drugs and other compounds would not degrade at the preparation temperature of 80 ºC.

2. Thermal behavior study of each compound in matrix tablets

2.1 Differential scanning calorimetry (DSC)

The thermal parameters from DSC analysis, including endothermic peak and enthalpy of pure compounds which consist of model drugs (HCTZ and PRN) and bases (poloxamer and SHW), are shown in Fig 5. The sharp endothermic melting peak was found at 272.2 ºC and 166.7 ºC for HCTZ and PRN, respectively. As for the bases, poloxamer showed a sharp endothermic melting peak at 56.2 ºC. There were two sharp endothermic peaks at 64.8 ºC and 79.5 ºC and a slight endothermic peak at about 50 ºC for SHW. The mixed base of poloxamer:SHW in ratio 5:5 still unchanged endothermic melting peak of both poloxamer and SHW, which indicated that there is no interaction between poloxamer and SHW.

The endothermic melting peak of HCTZ disappeared in PM and MS at 10, 20 and 30% HCTZ in poloxamer (Figures 6A and 6D) and also at 10 and 20% HCTZ in mixed base (Fig.

6C), respectively as marked with red square. It may be concluded that HCTZ could disperse as a particulate form in the poloxamer. On the other hand, the endothermic melting peak of HCTZ and SHW were clearly observed for both PM and MS (Fig.6B and 6E). It may be that the chemical interaction or solid dispersion of HCTZ could not occur in SHW. In the cases of PM and MS of PRN, there was not any change in the melting peak of their individual matrix bases (Fig. 7). Thus, PRN did not interact or disperse as a solid in the matrix bases. Additionally, the one new endothermic peak of SHW appeared at about 84.0 ºC in the MS of mixed base (red arrow marker in Fig. 6F and 7F), containing PRN or HCTZ with the decrement of the 79.5 ºC endothermic peak of SHW, signifying the interaction between poloxamer and SHW in preparation by the heating method.

Results indicated that there was no any interaction between PRN and other bases (poloxamer and SHW). However, at a low content (10% w/w) of HCTZ in poloxamer there could be a solid dispersion that usually occurred when the hydrophobic drug was mixed with the hydrophilic polymer.[27] This phenomenon was observed from the absence of HCTZ peak when mixed together with poloxamer for both PM and MS. For example, the HCTZ solid dispersion was found when it was incorporated with PEG 6000.[28] The active surface property of poloxamer could promote the solubility of the hydrophobic drug in the molten poloxamer resulting in the absence of a drug melting peak.[29]

The multicomponent endothermic peaks of the DSC thermogram were found in SHW, indicating the multi-compositions of the natural waxes. SHW composes four components including fatty acid esters (70-82%), free fatty alcohols (8-14%), free fatty acids (1-4%) and hydrocarbons (1-6%).[30] The two sharp endothermic peaks of SHW were the melting peak of the fatty acid esters and the fatty alcohols because their highest amounts were in SHW. The peak of free fatty acids and hydrocarbons were crowded by those two peaks.[14] When SHW was incorporated into poloxamer, it was possible that some components of SHW, especially for fatty ester and fatty alcohol, were easily dissolved in the medium because their functional groups were rather hydrophilic. Moreover, poloxamer could promote more wettability and spreadability of the dissolution medium on those components from its surface-active property.

2.2 Hot stage microscopy (HSM)

The melting behaviors and crystal morphologies of HCTZ and PRN in PM are presented in Fig. 8 and Fig. 9, respectively. These melting behaviors were similar to that in MS as presented in Fig. 10 and Fig. 11 for HCTZ and PRN, respectively. It started with melting the bases followed by melting PRN at about 160 ºC. After the system was cooled, PRN started to recrystallize at a temperature below 160 ºC. The needle-like crystal of PRN was obtained especially in both PM and MS of PRN in poloxamer (white circle marker in Fig. 9 and Fig. 11). This result indicated a lack of interaction between PRN and all the bases since the crystal presented and melted and recrystallized near its melting point. In the case of HCTZ, this phenomenon did not occur because the melting temperature of HCTZ was higher than 180 ºC at which the temperature of this HSM study could not be reached. Therefore, the HCTZ crystal did not exhibit any change through the experiment although some seemed to disperse into the poloxamer liquid phase (white circle marker in Fig. 8 and Fig.10). This result was similar to the thermal behavior of each compound as observed by DSC.

Although the HCTZ crystal remained in all bases, the amount was quite different. The crystals in poloxamer were rarely found when compared with those in SHW (white circle marker in Fig. 8 and Fig.10). Moreover, the needle-like crystal of PRN was only found in poloxamer while there were many crystal nuclei in SHW. In the previous study, Savolainen et al. reported the HSM characterization of poloxamer and other wax-based systems described the drug solubility in the molten bases and also the drug's crystal structure in each base.[31] The recrystallization of the drug in the molten base was also reported by Bruce et al. (2007).[32] They reported the characterization of guaifenesin recrystallization in the hot-melted extrudates. Surprisingly, the report stated that poloxamer and other hydrophilic polymers exhibited as crystal growth inhibitors due to their active surface property.[32] However, this experiment found the recrystallization of PRN in poloxamer because PRN could not dissolve into poloxamer. Hence, their crystal habit could still be observed unlike those of HCTZ of which most of them were dispersed in the poloxamer and, thus, only a small amount of the HCTZ crystal remained to be observed.

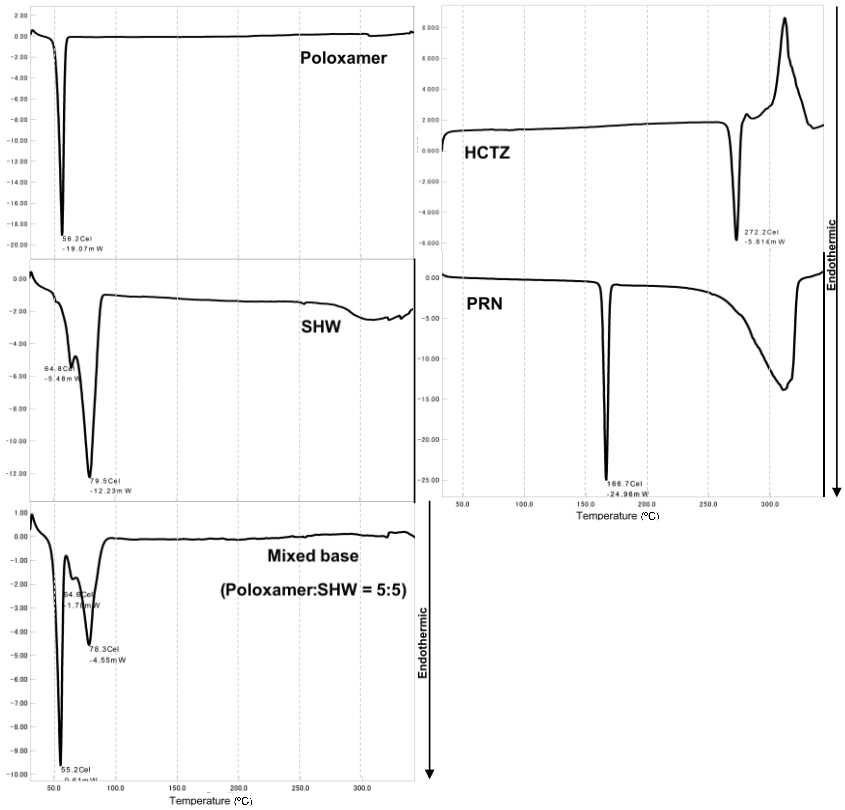


Figure 5 DSC Thermograms of pure compounds (HCTZ, PRN, poloxamer, SHW) and mixed base of poloxamer:SHW at ratio 5:5.

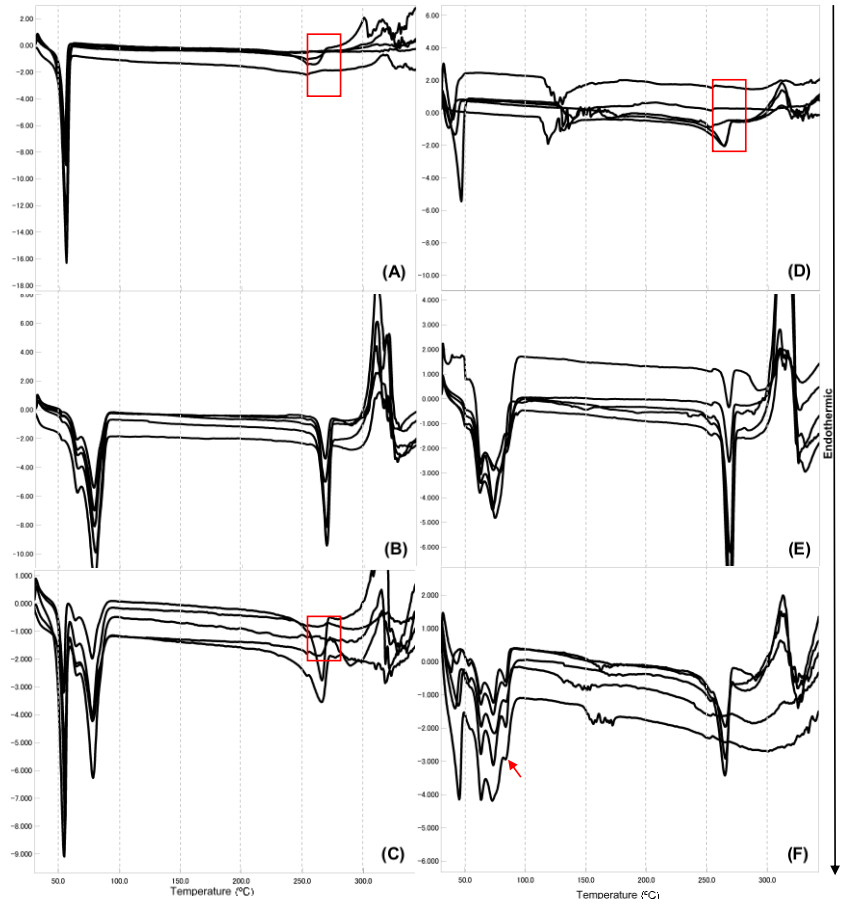


Figure 6 DSC thermograms for PM of 10 - 50% of HCTZ in poloxamer (A), SHW (B), mixed base (C) and MS of 10-50% HCTZ in poloxamer (D), SHW (E) and mixed base (F).

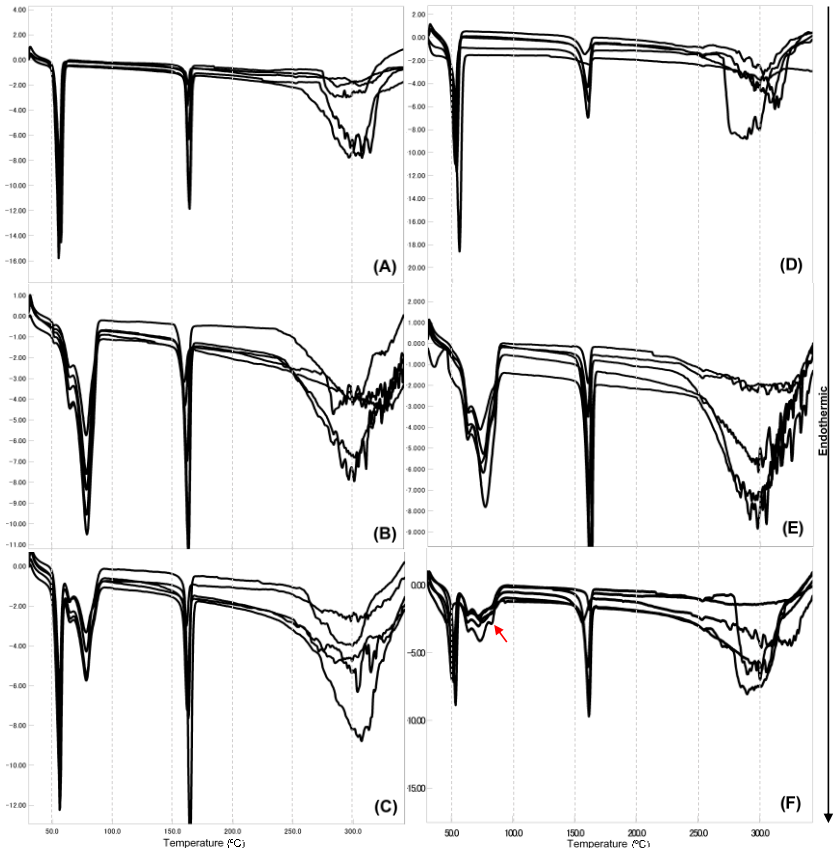


Figure 7 DSC thermograms for PM of 10 – 50% of PRN in poloxamer (A), SHW (B), mixed base (C) and MS of 10 – 50% PRN in poloxamer (D), SHW (E) and mixed base (F)

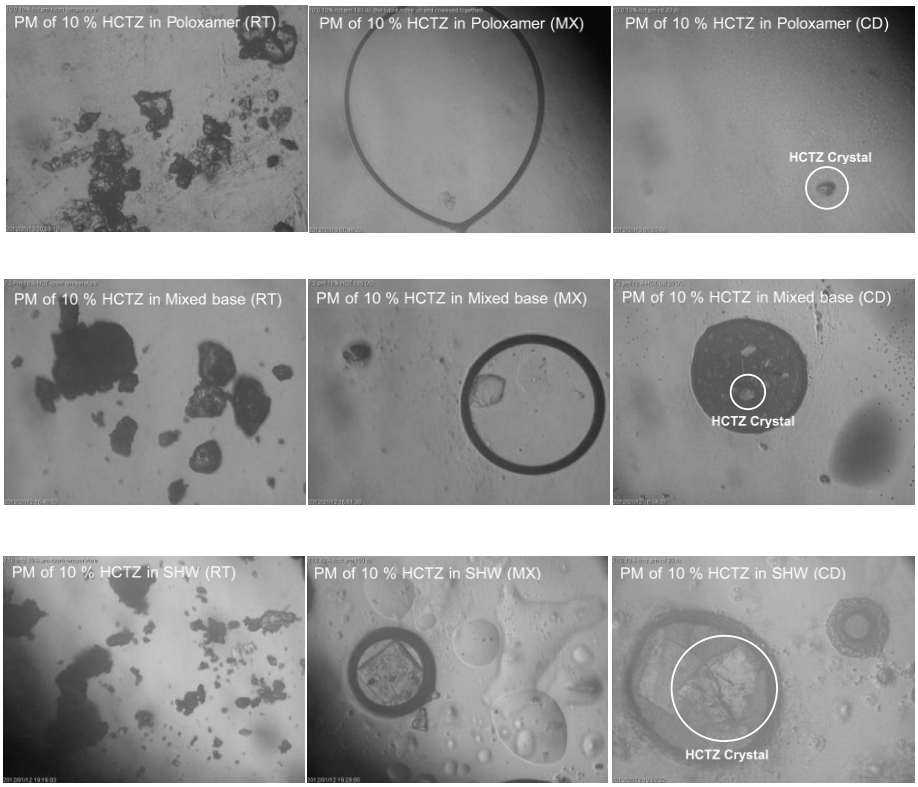


Figure 8 HSM micrographs of 10% HCTZ in PM containing poloxamer, SHW and mixed base at room temperature (RT), maximum temperature at 180 ºC (MX) and after cooling to room temperature (CD).

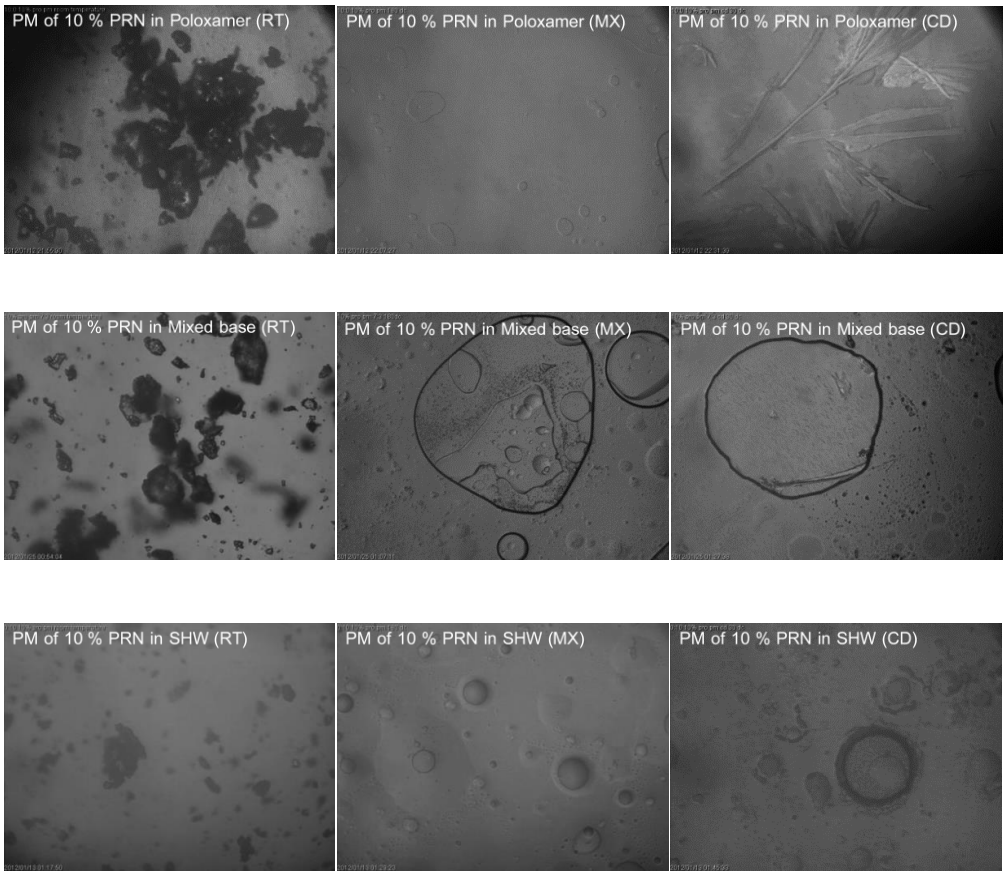


Figure 9 HSM micrographs of 10% PRN in PM containing poloxamer, SHW and mixed base at room temperature (RT), maximum temperature at 180 ºC (MX) and after cooling to room temperature (CD).

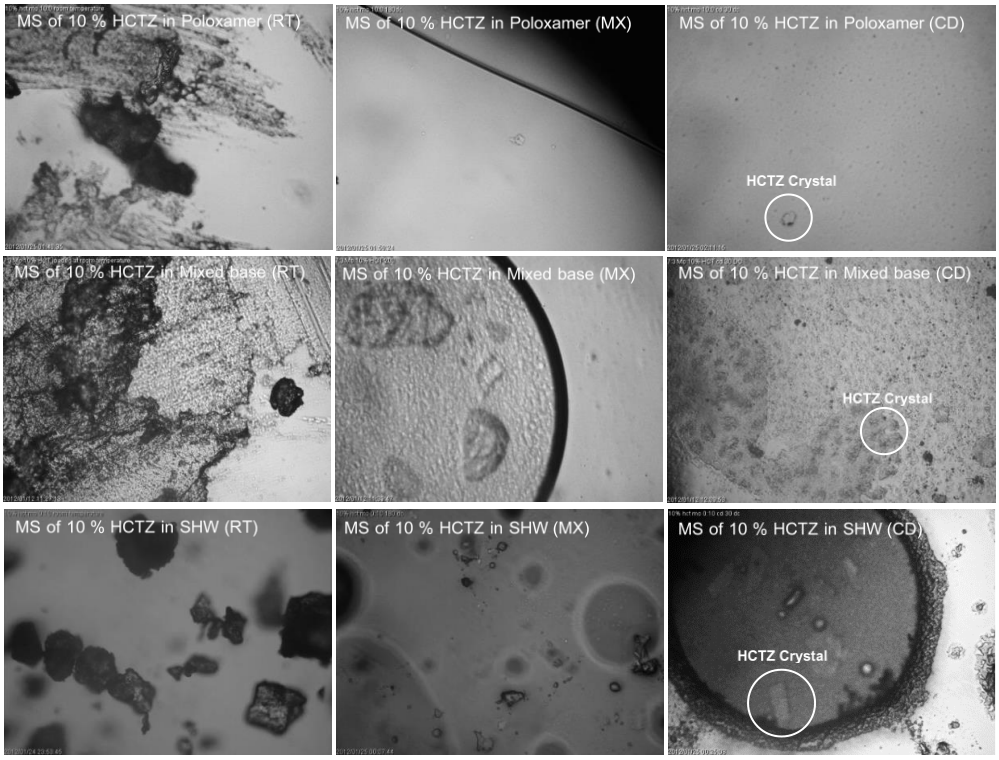


Figure 10 HSM micrographs of 10% HCTZ in MS containing poloxamer, SHW and mixed base at room temperature (RT), maximum temperature at 180 ºC (MX) and after cooling to room temperature (CD).

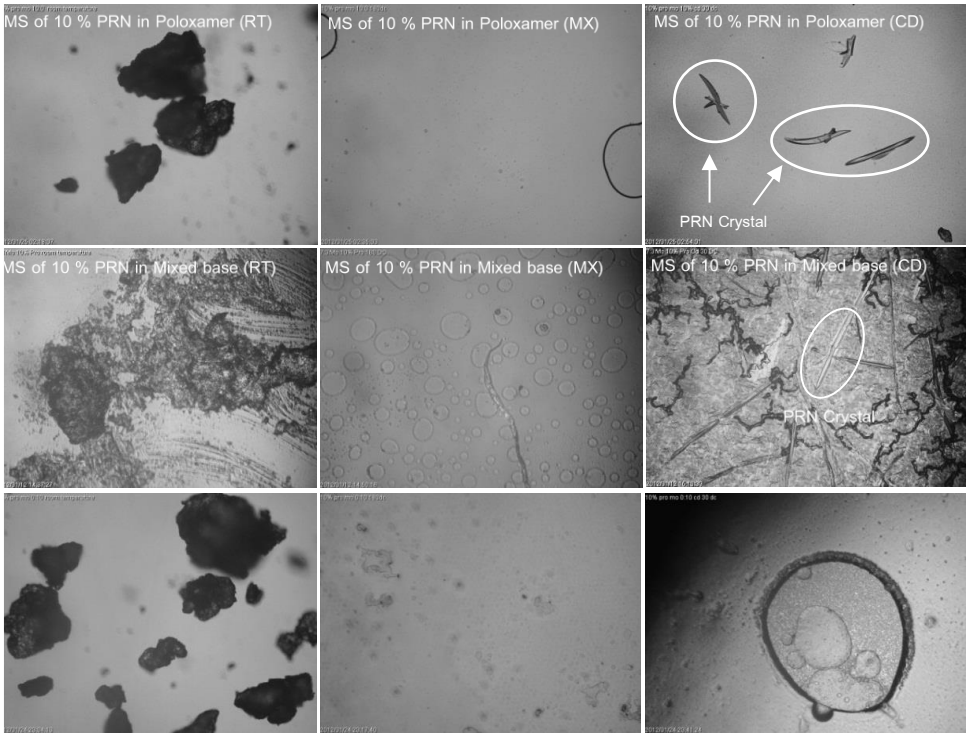


Figure 11 HSM micrographs of 10% PRN in MS containing poloxamer, SHW and mixed base at room temperature (RT), maximum temperature at 180 ºC (MX) and after cooling to room temperature (CD).

3. Crystallinity determination of each compound in matrix using powder X-ray diffractometry (PXRD)

The diffractograms of each pure compound are shown in Figure 12. HCTZ showed three characteristic diffractogram peaks, including two small peaks at about 17 and 28.5 º2θ and a sharp diffractogram peak at about 19 º2θ, which were the same as previously reported by Johnson et al. (2007)[33]. It was reported that there were two existing HCTZ polymorphs but only form I was in the commercial.[33] PRN displayed many diffractogram peaks from 8 to 30 º2θ of which most indicated crystalline form II of PRN.[34] Poloxamer displayed two characteristic peaks at 19 and 23 º2θ that exhibited the same diffractogram with the previously reported result.[35] There was no report of SHW's PXRD characterization yet. It showed two dominant characteristic peaks at 21 and 23 º2θ. In the case of the mixed base, it still showed characteristic peaks of poloxamer and SHW at 19, 21 and 23 º2θ. The DSC thermograms showed a significant change in both the PM and MS of HCTZ in poloxamer and mixed based. Therefore, PXRD analysis was used to confirm the interaction between HCTZ and bases and identify the crystalline behavior of the system. The PM of 10% HCTZ in poloxamer and mixed base revealed a different characteristic of HCTZ peak. Only the drug characteristic peak at 17 º2θ was found when 10% HCTZ was mixed in poloxamer (Figure 13A), unlike the systems in which this drug was mixed with mixed base, the drug's peaks at 17 and 28.5 º2θ could be observed (Figure 14A). However, the increasing content of HCTZ showed a greater characteristic drug peak. Therefore, both peaks at 17 and 28.5 º2θ were clearly observed when the content of HCTZ in PM formulation was more than 20% in all formulas. Moreover, the peak at 19 º2θ also increased as the content of HCTZ increased. For MS of HCTZ in poloxamer and mixed base, a halo pattern was observed when 10% HCT was incorporated in poloxamer (Figure 14F). In the case of mixed base, the small drug peak at 17 º2θ disappeared in the 10% HCTZ incorporated system, but the peak at 28.5 º2θ was still evident (Figure 14F). The diffractograms of mixed base PM and MS showed a different pattern. The heating method may be able to promote the interaction between poloxamer and some components of SHW resulting in a little decrement of poloxamer content and a change of broad peak of SHW (Figure 14). The PXRD results confirmed the DSC and HSM results that HCTZ could disperse as a particulate form in the poloxamer. The halo pattern and the absence of a drug peak obtained from a low amount (10%) of HCTZ in poloxamer for both PM and MS

indicated the solid dispersion as previously discussed in DSC results. The halo pattern indicated the amorphous form of the drug compound dispersed in the bases. The halo pattern of the meloxicam PXRD diffractogram of this drug dispersed in poloxamer 188 has been reported.[36]

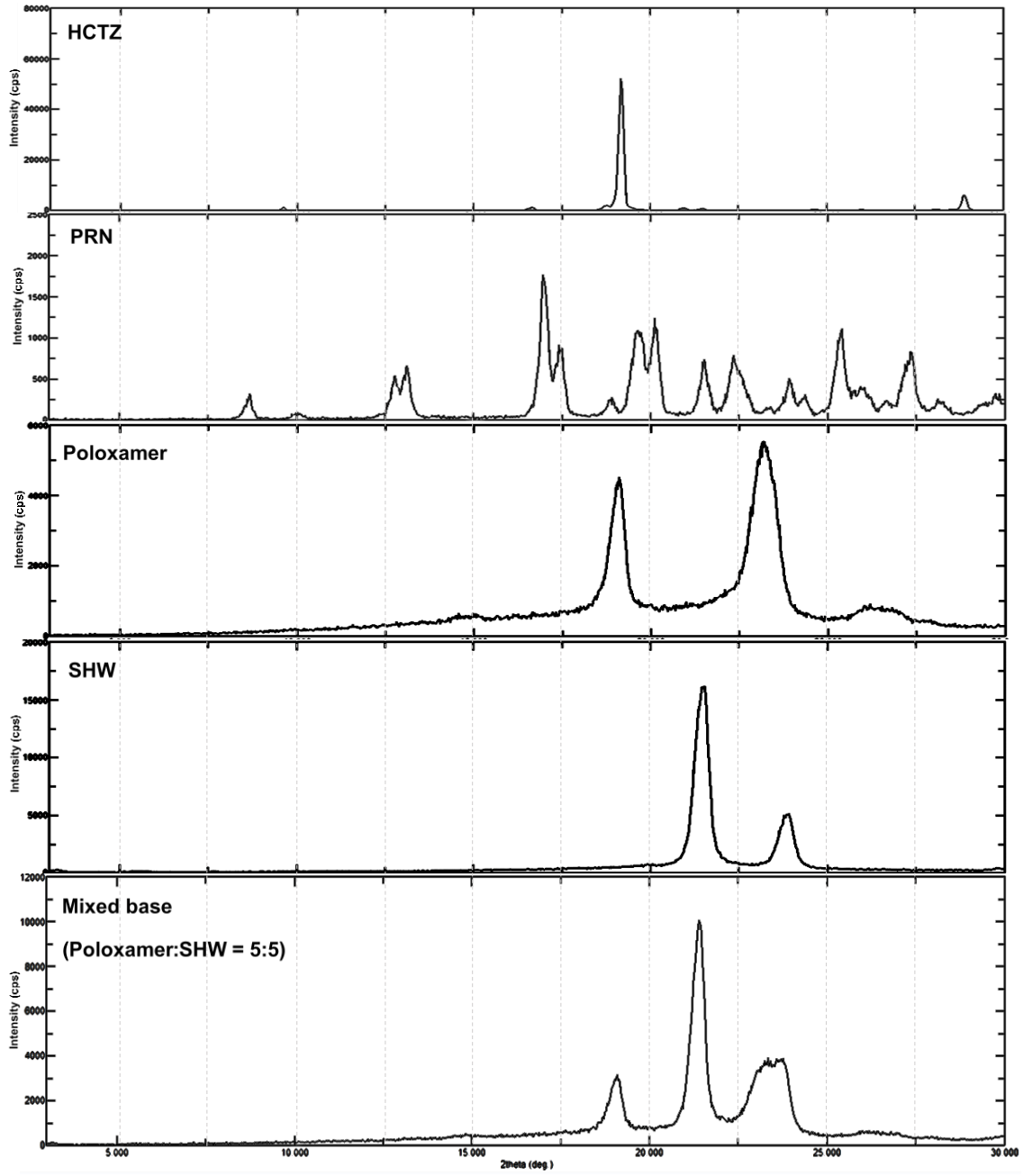


Figure 12 PXRD diffractograms of HCTZ, PRN, Poloxamer, SHW and mixed base.

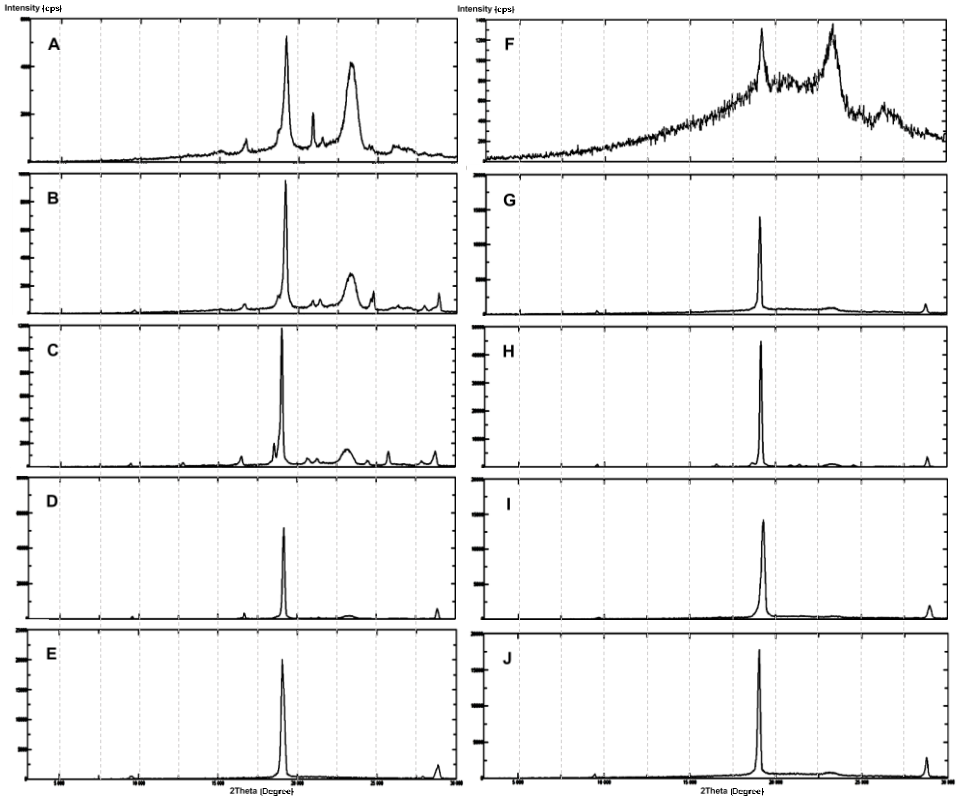


Figure 13 PXRD diffractograms for PM of 10% (A), 20% (B), 30% (C), 40% (D) and 50% (E) HCTZ in poloxamer and MS of 10% (F), 20% (G), 30% (H), 40% (I) and 50% (J) HCTZ in poloxamer.

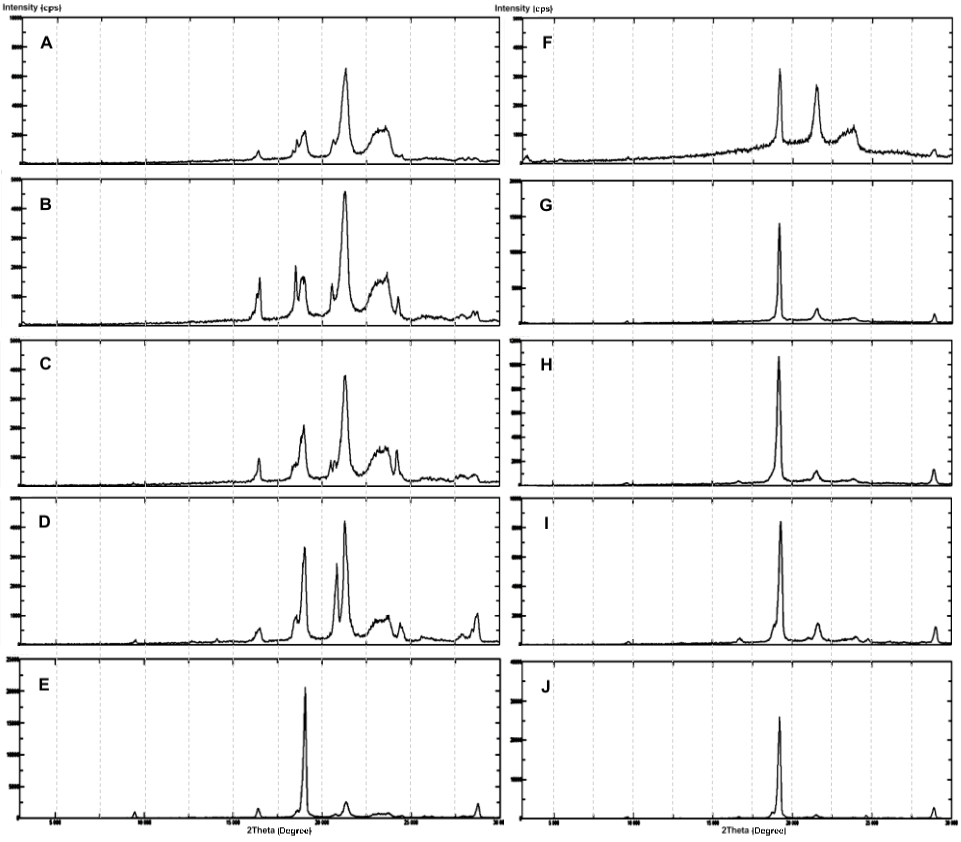


Figure 14 PXRD diffractograms of PM of 10% (A), 20% (B), 30% (C), 40% (D) and 50% (E) HCTZ in mixed base and MS of 10% (F), 20% (G), 30% (H), 40% (I) and 50% (J) HCTZ in mixed base.

4. The intermolecular interaction study of each compound in matrix using Fourier transform-infrared spectroscopy (FT-IR)

The FT-IR spectra of each pure compound are shown in Fig. 15. The HCTZ spectra showed N-H stretching of amine group at about 3362.7 cm^{-1}. The characteristic peaks of HCTZ were at 1604 cm^{-1} referring to the C-C stretching of aromatic ring and the 742 cm^{-1} which was the bending mode vibration of NH and NH_2 group, respectively. Spectra of poloxamer showed the C-H stretching of aliphatic chain at 2887.0 cm^{-1} and there were the characteristic peaks at 1353.3 and 1111.3 cm^{-1} which were O-H bending in plane and C-O stretching, respectively. FT-IR spectrum of SHW revealed the stretching vibration of CH_3 and CH_2 at 2920.0 and 2848.0 cm^{-1}, respectively. The peaks found at 1467.5, 1173.0 and 1244.2 cm^{-1} referred to stretching vibration of C=O, C=C and twisting vibration of CH_2, respectively. The DSC thermograms and PXRD diffractograms exhibited a significant change in both the PM and MS of 10% HCTZ in poloxamer and mixed based. Therefore, FT-IR technique was used to confirm the interaction between HCTZ and bases in matrix. To observe the interaction between HCTZ and bases, the spectra of HCTZ at wavenumber 1604 cm^{-1} was selected as the characteristic drug peak. This peak is presented in the square marker of HCTZ's spectra in Fig. 15 and 16. The other peaks of HCTZ's spectra were disturbed with the base peaks. Although the peak at wavenumber higher than 2000 cm^{-1} seemed to be more appropriate as characteristic drug peak they were overlaid by poloxamer or SHW broad peak at wave number range of 3400-3500 cm^{-1}. Moreover, the loaded drug sample exhibited the lower %Transmittance of drug peak hence it could not observe the peak clearly at these ranges. The PM and MS of 10 % HCTZ in poloxamer, SHW and mixed base are shown in Fig. 16. Both PM and MS samples of HCTZ in poloxamer, SHW or mixed base could be observed a small characteristic drug peak therefore it might state that there was no chemical interaction between HCTZ and all bases.

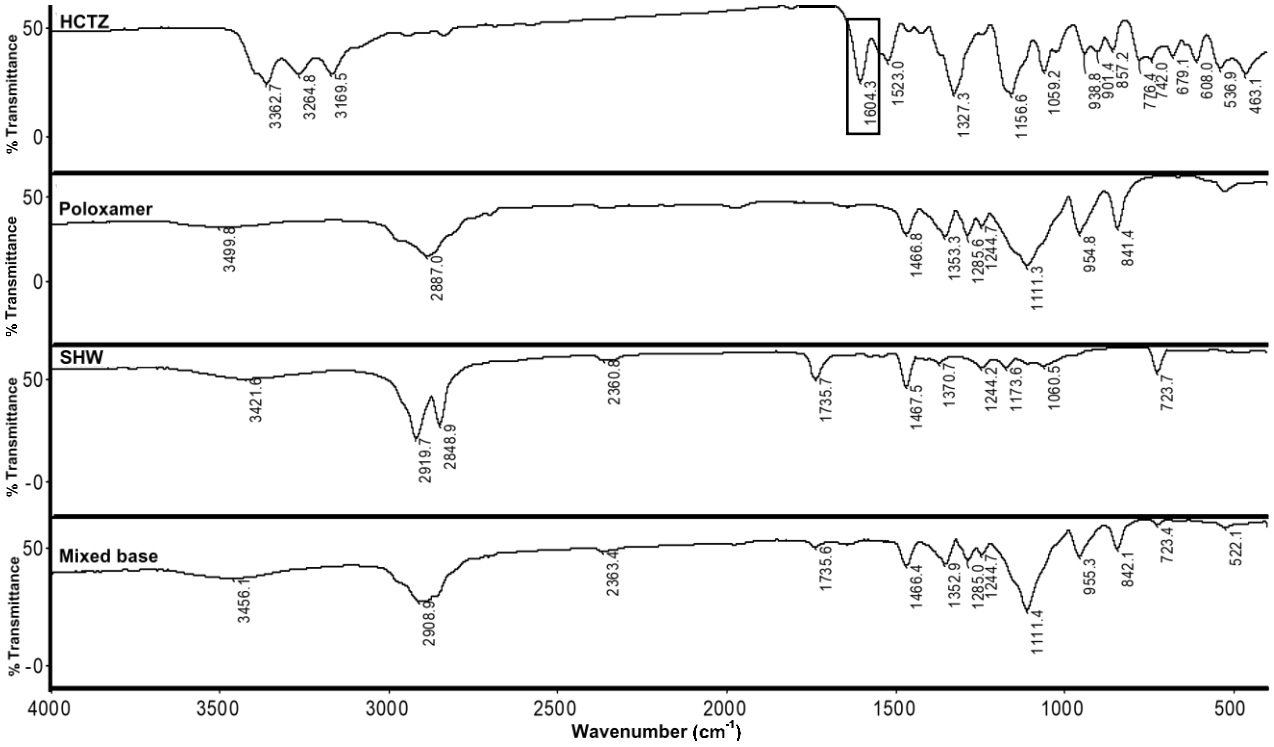


Figure 15 The FT-IR spectra of HCTZ, poloxamer, SHW and mixed base.

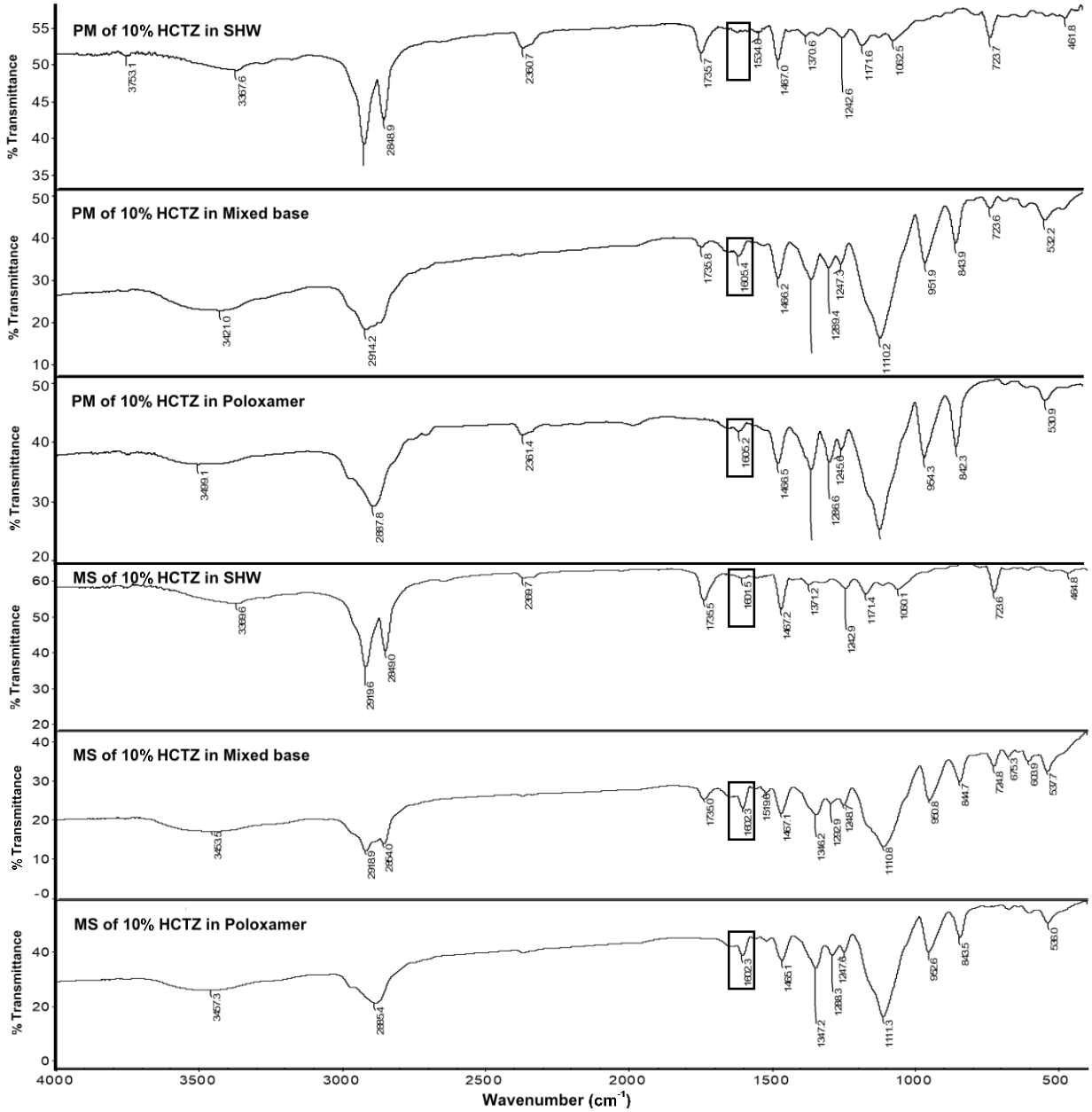


Figure 16 The FT-IR spectra of PM and MS of 10% HCTZ in poloxamer, SHW and mixed base.

Conclusion

The thermal properties of PRN and HCTZ, which are model drugs incorporated in SHW, poloxamer and mixed base, were investigated with TGA, DSC and HSM. The thermogram from TGA clearly exhibited that model drug and the other compound did not degrade at the preparation temperature which was 80 ºC. For thermal analysis with DSC, the results did not indicate any interaction between PRN and the other bases (poloxamer and SHW), but the absence of HCTZ peak was observed in DSC thermogram of a low content (10% w/w) HCTZ when mixed together with poloxamer for both PM and MS. This phenomenon might be described by the solid dispersion which usually occurred when the hydrophobic drug was mixed with the hydrophilic polymer. This result was similar with the thermal behavior of each compound as observed by HSM. In addition, mixed base fabricated with a heating method showed one new endothermic peak which indicated an interaction between poloxamer and SHW. The crystallinity behavior of these matrix systems confirmed the results of DSC and HSM to signify that HCTZ dispersed as crystalline particulate in the poloxamer. In addition, FT- IR technique was used to confirm the intermolecular interaction between model drugs and bases especially 10% w/w of HCTZ incorporated in poloxamer and mixed base which exhibited significant alterations in DSC thermogram and PXRD diffractogram. The FT- IR spectra showed no chemical interaction between HCTZ and all bases.

Understanding the thermal and crystallinity behaviors of these two drug compounds in physical mixtures and molten samples of shellac wax-poloxamer is useful for developing the matrix tablet using these bases as the matrix formers.

Disclosure

The authors report no conflicts of interest in this work.

Declaration of interest:

The authors declare that they have no conflict of interest with this investigation.

Statement of human and animal rights

The authors of this article did not conduct any studies on human or animal subjects.

Acknowledgements

The researchers are grateful to School of Pharmacy, Walailak University and the Research and Creative Fund, Faculty of Pharmacy, Silpakorn University for their kind support, assistance and facilities. We thank Laboratory of Pharmaceutical Technology at Graduate School of Pharmaceutical Sciences, Chiba University for supporting research facility and investigation. We also thank John Tique for his nice contribution of language check.

References

1. Chen X, Wen H, Park K. Challenges and new technologies of oral controlled release. In: Wen H, Park K (eds.). Oral controlled release formulation design and drug delivery: Theory to Practice. John Wiley & Sons, Inc; 2010: pp.257-277.
2. Tiwari BM, Khare S, Mishra V, Bhargava S. Matrix tablet: a potential drug carrier for oral drug delivery. *J Pharm Res* 2012;5(5):2448-2456.
3. Kojima H, Yoshihara K, Sawada T, Kondo H, Sako K. Extended release of a large amount of highly water soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets. *Eur J Pharm Biopharm* 2008;70:556-562.
4. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. *J Control Release* 2011;154:2-19.
5. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems. *BioImpacts* 2012;2(4):175-187.
6. Nerurkar J, Jun HW, Price JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rates. *Eur J Pharm Biopharm* 2005;61:56-68.
7. Thawatchai P. Variables Influencing Drug Release from Layered Matrix System Comprising Hydroxypropyl Methylcellulose. *AAPS Pharm Sci Tech* 2008;9(2):668-674.
8. Tiwari SB, Murthy K, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS Pharm Sci Tech* 2003;4:1-6.
9. Sudha BS, Sridhar BK, Srinatha A. Modulation of Tramadol Release from a Hydrophobic Matrix: Implications of Formulations and Processing Variables. *AAPS Pharm Sci Tech* 2010;11:433-440.
10. Chokshi R, Hossein Z. Hot-melt extrusion technique: a review. *Iran J Pharm Res* 2004;3(1):3-16.
11. Quinten T, Beer DT, Vervaet C, Remon JP. Evaluation of injection moulding as a pharmaceutical technology to produce matrix tablets. *Eur J Pharm Biopharm* 2009;71:145-154.
12. Edwards HGM, Falk MJP. Fourier-transform raman spectroscopic study of unsaturated and saturated waxes. *Spectrochim Acta A* 1997;53(14):2685-2694.
13. Buch K, Penning M, Wächtersbach E, Maskos M, Langguth P. Investigation of various shellac grades: additional analysis for identity. *Drug Dev Ind Pharm* 2009;35(6):694–703.
14. Ruguo Z, Hua Z, Hong Z, Ying F, Kun Li, Wenwen Z. Thermal analysis of four insect waxes based on differential scanning calorimetry (DSC). *Procedia Engineering* 2011;18:101-106.
15. Dou H, Ismail MA. Reduction of post-harvest pitting of citrus by changing wax by changing wax component and their concentration. *Proceed Florida State Horticult Soc* 1999;112:159-163.
16. Lantz RJ, Pa N, Robinson MJ. Method of preparing sustained release pellets and products thereof. US Patent No. 3,146,167. Aug 25, 1964.
17. Mollohan K, Makhlouf JM. Wax-containing powder coatings. US Patent No. 3,872,040. Mar 18, 1975.
18. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006;23(12):2709-728.
19. Jannin V, Pochard E, Chambin O, Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing precirol® ATO 5. *Int J Pharm* 2006;309:6-15.
20. Derle D, Joshi O, Pawar A, Patel J, Jagadale A. Formulation and evaluation of buccoadhesive bi-layer tablet of Propranolol hydrochloride. *Int J Pharm Pharm Sci* 2009;1(1):206-212.
21. Cid E, Mella F, Lucchini L, Carcamo M, Monasterio J. Plasma concentrations and bioavailability of Propranolol by oral, rectal and intravenous administration in man. *Biopharm Drug Dispos* 1986;7:559-566.
22. Chemsa SI, Maiza A, Arnaud P. Sustained-Release Tablets of Hydrochlorothiazide, A Slightly Water-Soluble Molecule Using Glyceryl Behenate. *Pharm Chem J* 2018;52(1);15-18.
23. Menon D, El-Ries M, Alexer KS, Riga A, Dollimore D. A thermal analysis study of the decomposition of hydrochlorothiazide. *Instrum Sci Technol* 2002;30(3):329-340.
24. Macêdo RO, Gomes do Nascimento T, Soares Aragao CF, Barreto Gomes AP. Application of thermal analysis in the characterization of anti-hypertensive drugs. *J Therm Anal Calorim* 2000;59(3):657-661.
25. Hritcu D, Popa MI, Popa N, Badescu V, Balan V. Preparation and characterization of magnetic chitosan nanospheres. *Turk J Chem* 2009;33:785-796.
26. Craig RG, Powers JM, Peyton FA. Thermogravimetric analysis of waxes. *J Dent Res* 1971;50(2):450-454.

27. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. *Pak J Pharm Sci* 2009;22(2):234-246.
28. Panneerselvam M, Natrajan R, Selvaraj S, Rajendran NN. A novel drug-drug solid dispersion of hydrochlorothiazide losartan potassium. *Int J Pharm Biol Sci* 2010;1(4):68-80.
29. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur J Pharm Biopharm* 2007;65(1):26-38.
30. Craig DQM. Pharmaceutical application of DSC. In: Craig DQM, Reading M (eds.). Thermal analysis of pharmaceuticals. Florida: CRC Press, 2007: pp.53-68.
31. Savolainena M, Herder J, Khoo C, et al. Evaluation of polar lipid–hydrophilic polymer microparticles. *Int J Pharm* 2003;262:47–62.
32. Bruce C, Fegely KA, Rajabi-Siahboomi AR, McGinity JW. Crystal growth formation in melt extrudates. *Int J Pharm* 2007;341(1-2):162-172.
33. Johnston A, Florence AJ, Shankland N, Kennedy AR, Shankland K, Price SL. Crystallization and crystal energy landscape of hydrochlorothiazide. *Cryst Growth Des* 2007;7(4):705-712.
34. Bartolomei M, Bertocchi P, Ramusino MC, Santucci N, Valvo L. Physico-chemical characterisation of the modifications I and II of (R,S) propranolol hydrochloride: solubility and dissolution studies. *J Pharm Biomed* 1999;21(2):299-309.
35. Hemelrijck CV, Müller- Goymann CC. Characterization of a pseudo ternary phase diagram of poloxamer 407 systems for potential application of 5-aminolevulinic acid in photodynamic therapy. *Int J Pharm* 2011;420(2):297-303.
36. Ambrus R, Kocbek P, Kristl J, Sibanc R, Rajko R, Szabo- Revesz P. Investigation of preparation parameters to improve the dissolution of poorly water-soluble meloxicam. *Int J Pharm* 2009;381:153-159.