CHAPTER 1

1.0 INTRODUCTION

Drug formulation development takes more than a great idea, it takes technology, experience, expertise, and commitment from a team to find the best route for the product. The successful formulation of good tablet or solid dosage form depends on careful selection of the excipients. Therefore, in the design of dosage forms it will be very useful to have an information of potential physical and chemical interactions between drugs and excipient. With such information it give an ideas in a choosing of correct excipients that might affect the chemical nature, stability, solubility and in vivo absorption of drugs.

In this respect, thermal analytical technique by using Differential Scanning Calorimetry has been used as a tool for drug and excipient interaction for assessing the compatibility study. In recent years, applications ofthermal analytical techniques at the preformulationstage of development of solid dosage formshave increased immensely (Ford and Timmins, 1989; Giron, 1986; Ford, 1993). The robustness and sensitivity of instrumentation, the introduction of automation and of reliable software according to the needs widened considerably the areas of applications. It involve a technique in which a property of the sample is measured against time or temperature while the temperature of the sample in a specified atmosphere is heated or cooled at a fixed rate of temperature change or hold at constant temperature.

Nowadays, with sophisticated drug delivery technology have been developed an extremely wide variety of functionalities in solid dosage form can be achieved. One of the technology is spray granulator or also known as fludized bed. It is a very efficient

way to apply uniform layer of materials onto solid particles.A fascinating advancement in fluid bed coating is reported by Matsuda, Hatano, Kuramoto, and Tsutsumi (2001) for the fluidization and coating of very fine particles by fluidized beds. There are many types offluidized beds technology. Ranging from top-spray to Wurster or rotational type, the basic concept of fluidization relies on the compensation of the gravity force experienced by the particles by an upward moving air flow, which ensures complete fluidization of the particles.

Due to the advances of technology in drug delivery, excipients are currently included in novel dosage forms to fullfil specific functions. The excipients were included in drug formulations as an inert vehicles for the correct administration of active ingredient. Today, people has made effective use of materials of natural origin in the pharmaceutical field as natural drugs and excipients due to the advantages of the materials which are non toxic, less expensive and freely available.

Carrageenans are natural origin material obtained from species of red seaweed that has potential in pharmaceutical applications as controlled release excipients (Gupta et al., 2001; Tapia et al., 2005). Today, the developement of carrageenan as a polymer or binder in pharmaceutical industry increasingly becomes a demands.

Taking the obove factor into consideration, the objectives for the experiment were as follows;

- Compatibility of kappa-carrageenan with paracetamol.

- Feasibility of kappa-carrageenan as binder.

- Thermal characteristics of the paracetamol granules from kappa-carrageenan as a binder.

CHAPTER 2

2.0   LITERATURE REVIEW

2.1   Paracetamol Drug

Paracetamol was first discovered to have both analgesic and antipyretic properties in the late nineteenth century. Prior to this, cinchona bark, which was also used to make the anti-malaria drug quinine, had been used to treat fevers. As cinchona became scarcer, people began to look for cheaper synthetic alternatives. Two of these alternative compounds were acetanilide and phenacetin, developed in 1886 and 1887 respectively. By this time, Harmon Northrop Morse had already synthesized acetaminophen in 1878 through the reduction of p-nitrophenol with tin in glacial acetic acid. In 1893, the white, odourless crystalline compound with a bitter taste that became known as paracetamol was discovered.

Paracetamol, also known as acetominophen is a major ingredient in numerous cold and flu remedies and commonly used for the relief of headaches and other minor aches and pains. It is soluble in organic solvents such as methanol and ethanol but slightly soluble in water and ether. It's pH range from 5.5 to 6.5 based on saturated aqueous solution.
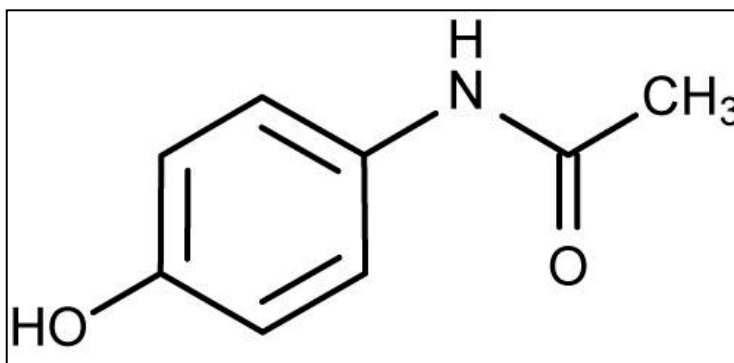

Figure 2.1:   Chemical structure of Paracetamol

Paracetamol or Acetaminophen is an antipyretic commonly used to children and a large amount of it is required in one dose (generally 500 mg). Due to its bitter taste, it can be a model drug to evaluate taste-masking efficiency for several kinds of oral formulations.

The most effective method to achieve maximum taste-masking effectiveness is to coat the drug particles, thereby creating a physical barrier around the drug, using microencapsulation techniques such as spray-drying (Wilson et al., 1994 and Yajima et al., 1996), spray-congealing (Shimano et al., 1995 and Robson et al., 1999), coacervation (Chukwu et al., 1991 and Al-Omranm et al., 2002) and solvent evaporation method (Hashimoto et al., 2002).

2.2   Spray Granulation: The Fluid Bed Technology

Fluid bed technology is one of the innovative techniques that provided an edge to the advencement in pharmaceutical research and industry. With the capabilities of the technology,it produces a superior tool in the development of new trends of drug formulation. It is known to be as wet granulation method and as one step ,enclosed operation due to several ingredients able to be mixed, granulated, and dried in the same vessel. The advantageous of the technique reduces material handling and shortens process times compared with other wet granulation processes (Saurabh & Garima, 2010).

There are three patterns of fluid bed processes that characterised by the position of spray nozzle; top spray, bottom spray or tangential spray. The fluid-bed top-spray method produces highly dispersible granules with a characteristic of porous structure that enhances wettability to granulation for tabletting. For bottom spray fluid bed method

often used for coating and powdered layering or pelletizing applications for modify or control drug release. While, the tangential spray method has been used for granulating and pelletizing with subsequent coating (Ylirussi, J., Rasanen, E., Rantanen, J., & Mannermaa, J.P., 2004). Top spraying typically the method chosen for granulation. As mention by Saurabh and Garima, (2010), granulated particles are more desirable than fine powders for reasons; improve of flowability, improve compressibility for tabletting, reduce dust for operator and environmental safety, improve dispersibility and improve uniformity by combining all ingredients together or by distributing low dose actives uniformly by dissolving and spraying a solution of actives.
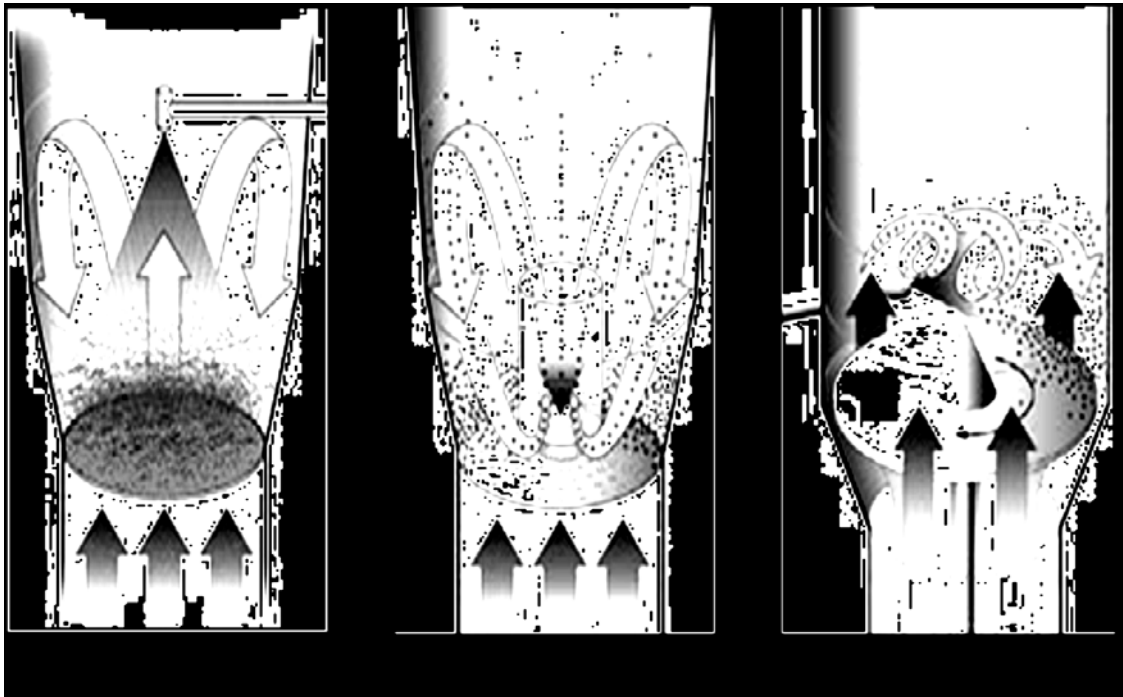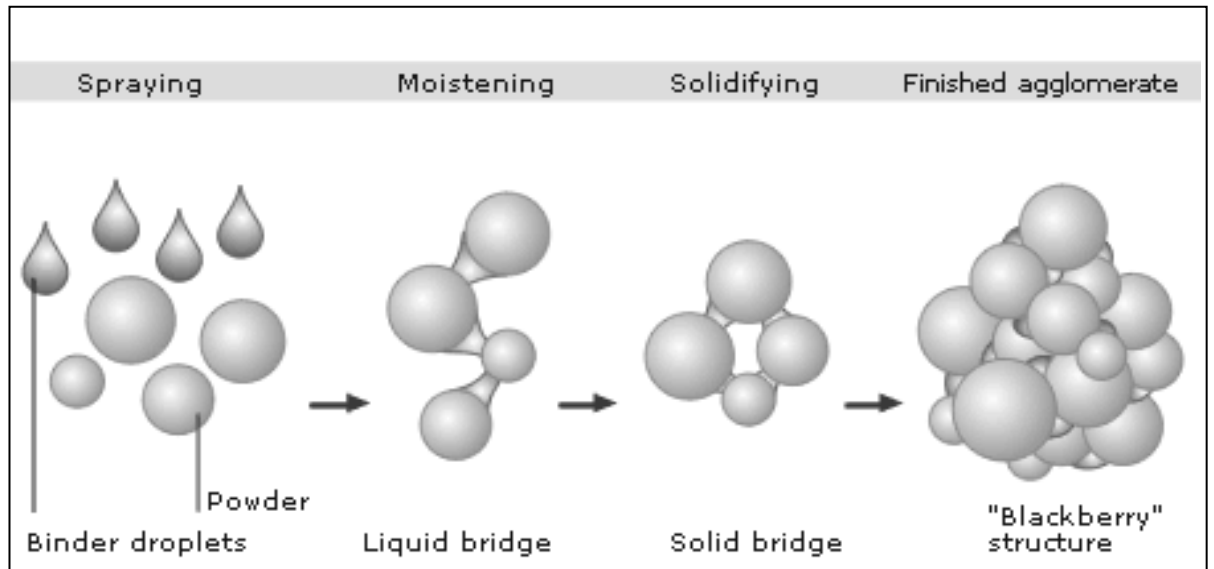

Source : Saurabh and Garima (2010)

Figure 2.2:   Different Patterns of Fluid Bed Processing

Previous studies (e.g Vuppala et al., 1997) stated that fluid bed spray agglomeration is also often in colloquial terms referred to as fluid bed granulation. Powders are fluidized and a binder solution or suspension is sprayed onto the fluidized particles, creating

liquid bridges which form agglomerates from the powder. As soon as the desired size of the agglomerates is achieved, spraying is stopped and the liquid evaporated. The structures created by the liquid bridges are then maintained by solid binder bonds.

Source: Saurabh and Garima, 2010

Figure 2.3   Process Principle of Spray Agglomeration

For top spraying method, it is typically used in three applications: granulation with binder, granulating with water and fluid bed spray drying. The process variables involve the liquid addition rate, inlet air temperature, fluidization air volume, process air humidity, and the atomization air pressure (Gu et al., 2004). Researchers (Leuenberger et al., 1990; Vuppala et al., 1997; Ylirussi et al., 2004) have conducted studies on the effects of process parameters for top-spraying on the physical properties of the granules. Studies discovered that faster rate of liquid binder addition resulted in a larger average granule size and less-friable granules. With an increasing of the inlet air temperature will cause to a decrease in average granule size. In both cases, the effects resulted from an increased ability of the solution to wet and penetrate the solids when the spray rate was increased or when inlet air temperature was decreased. Atomization air pressure

also had a significant effect on average granule size. An increase in atomization air pressure resulted in a decrease in average granule size because of smaller liquid droplet sizes.

Therefore, Saurabh and Garima (2010) has summarized that the two most critical process parameters in top spray fluid-bed granulation are atomization air pressure and the liquid addition rate. While, inlet air temperature, inlet air humidity, and inlet air volume have lesser effects on granule formation. Also mentioned good control of all these parameters is important to minimize batch-to-batch variation in production. In addition, the effect of these less-critical parameters may increase as binder strength decreases. Binder type and concentration also play important roles in granule formation.

2.3   Kappa-Carrageenan as pharmaceutical excipient

Drug and excipient is a must combination in pharmaceutical drug formulation. Traditionally, excipients funtion as an inert vehicles that provided to consistency to weight and volume for the correct administration of drugs. But todays in modern pharmaceutical dosage forms excipients play more than one roles such as improvement of stability, release and bioavaibility of the drug, enhancement of patient acceptability and performance of technological functions that ensure ease of manufacture. Excipients may come from synthetic or natural sources. However, natural sources of excipient are more attractive due to its renewability, if it cultivated or harvested in a sustainable manner, the sources can still provide a constant supply of raw material. Nowadays the most famous natural sources of excipient in pharmaceutical research area are carrageenans (Picker, et al., 1999; Katharina 1999; Gupta, et al., 2001; Mohamadnia, et al., 2008; Sorenti, et al., 2010).

Carrageenan known to be one of the natural polysaccharides that can be obtained from the extraction of plant. These natural polysaccharides do hold many advantageous with varying physicochemical properties as it can be extracted from plants at relatively low cost, can be chemically modified to suit specific needs, non toxic and freely available. Since most of the properties comply with requirement expected for pharmaceutical excipients, carrageenan has extensively investigated for use in the developement of drug dosage forms.

Rhodophyceae is a class of group for carrageenan. The carrageenans are marine hydrocolloids that can be obtained from the extraction process with water or alkaline water of seaweed. The most important members of this class are Chondrus crispus, Euchema spp, Gigartina stellata and Iridaea spp (Nerurkar et al., 2005; Coviello et al.,2007). Carrageenan extracted from seaweed is not assimilated by the human body and provides only bulk but no nutrition. There are three basic types of carrageenan; kappa (κ), iota (ι) andlambda (λ).Sudhakar et al., (2006) and Nerurkar et al., (2005) stated that the λ-type carrageenan results in viscous solutions but is non-gelling, while the κ-type carrageenan forms a brittle gel. The ι-type carrageenan produces elastic gels.
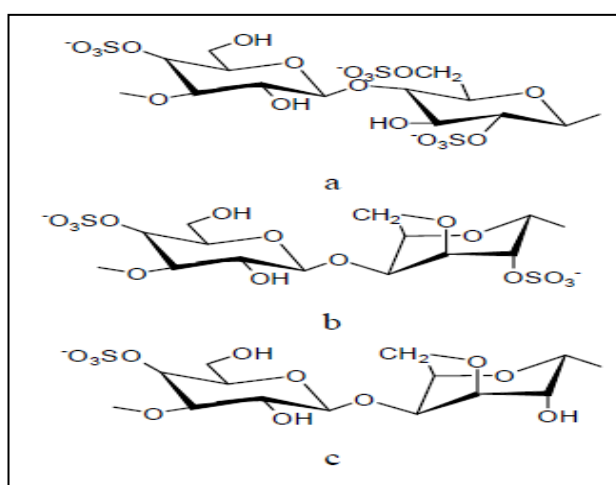
Source: Carien et al., 2009

Figure 2.4   Chemical structure of a) λ-carrageenan b) ι-carrageenan and c) κ-carrageenan

Picker (1999) discovered that the compaction ability of two κ-carrageenans (Gelcarin® GP-812 NF and GP-911NF) and one ι-carrageenan (Gelcarin® GP-379 NF) showed that these carrageenans are able to form strong compacts with a high elastic recovery. The results indicate that the carrageenans were suitable tableting excipients for the manufacturing of controlled-release tablets.

In another study, a mixture of cross-linked κ-carrageenan with potassium and cross-linked alginate with calcium was prepared for hydrogel beads. They exhibited smoother surface morphology than one-polysaccharide network beads. The carrageenan parts of the hydrogel pronouncedly enhanced the thermostability of the polymeric network. These beads were introduced as novel carriers for controlled drug delivery systems (Mohamadnia et al., 2008).

According to Bhardwaj et al., (2000) in recent studies, the compaction and consolidation behaviour of carrageenan were determined to prove their usefulness in tabletting excipients for controlled release tablets. The results indicated that carrageenans were suitable tabletting excipients due to easily formed compaction process, and the material behaved viscoelastically during compression. The resulting compacts were of high robustness, good compactibility, indicated by a high tensile strength. Therefore, in this study κ-carrageenan has been chosen as an area of interest for excipient with binding properties and presumably as non-trivial.

2.4 Differential Scanning Calorimetry (DSC): Understanding the Response of Drug Formulation.

Precise and accurate techniques with low sample requirements, able to provide detailed information about new chemical entities at the very earliest stages of drug discovery and development are the advantageous of Differential Scanning Calorimetry. The information or result provided from this technique can be obtained as accurately, easily and quickly as compared to other instrumental technique. Thus, DSC becomes an important tool for thermal analysis in the development of modern medicine with the ability to analyse both physical and energetic properties of a substances (Clas, Dalton & Hancock, 1999).

Clas, et al., (1999) stated that there are two main types of differential thermal instruments commercially available, differential thermal analysers (DTA) and differential scanning calorimeters (DSC). These instruments provide quantitative information about exothermic, endothermic and heat capacity changes as a function of temperature and time (such as melting, purity and glass transition temperature). Both techniques consist of a two-pan configuration (sample and reference). The basic difference between DTA and DSC is that the former measures temperature differences between the sample and reference pan whereas DSC measures energy differences.

Class et al., (1999) in the reviews stated that single components can exhibit the following thermal behaviour: melting, crystallization, boiling, sublimation, dehydration, desolvation, solid–solid transitions, glass transitions and polymorphic transitions. These transitions may be endothermic or exothermic. A standard DSC scan for an amorphous

compound undergoing a glass transition, crystallization, melting and degradation is shown in Figure 2.5. For all DSC experiments it is important to clearly define the transition in terms of the onset, extrapolated onset, and offset temperature and to indicate the scanning rate used.
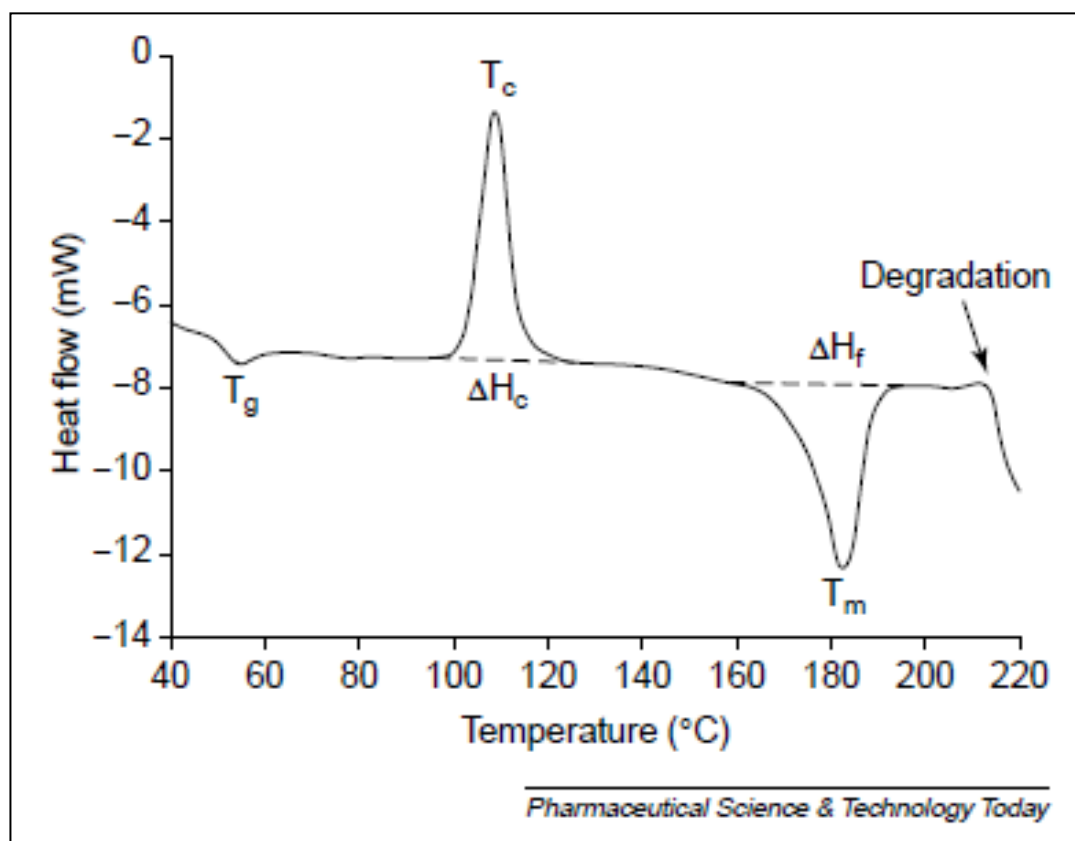

Figure 2.5:   Differential scanning calorimetry scan of sucrose (undried), showing the glass transition temperature, (Tg), recrystallization exotherm temperature (Tc) and enthalpy (ΔHc), melting endotherm temperature (Tm) and enthalpy (ΔHf) and onset of degradation 10K min^{-1}. Endothermic transitions are down.

Crystalline materials undergo a first-order melting transition from the ordered solid state to the disordered liquid or molten state. A melting endotherm can be described by the onset temperature, the temperature where the transition starts to deviate from the baseline. The extrapolated onset melting temperature, is reported as the temperature at the intersection of the extrapolated baseline prior to the transition with the extrapolated leading edge of the transition. Tm is defined as the peak temperature. In general, the

melting point is defined as the extrapolated onset temperature, though some authors report the peak temperature. The extrapolated end of the transition defines the melting of the most perfect crystals.

The enthalpy of fusion, or area of the endothermic transition, is frequently affected by the selection of the baseline. In general, the baseline of the endotherm is obtained by connecting the point at which the curve departs from the baseline of the scan to where it rejoins the baseline. However, for some samples there is a significant heat capacity change on melting. For such materials other baseline approximations should be used. These include using a sigmoidal baseline or extrapolation of the high or low temperature baseline.

2.4.1   Compatibilty study using Differential scanning calorimetry

The application of Differential Scanning Calorimetry (DSC) in the compatibility study of solid dosage forms have increased immensely. It provides fast and reliable information about chemical incompatibilities between the components used in the formulation. Any physicochemical interactions between components can be identified through the appearance, shift, or disappearance of endotherms or exotherms and variations in the relevant enthalpy values (Botha and Lotter, 1990; Lin and Han, 1992; Mura et al., 1994). Therefore, it is a very useful analytical method in selecting suitable compatible excipients.

There are several advantages in using DSC to evaluate drug–excipient compatibility such as no long-term storage is required, only small quantities of

drug are needed, which is important early on in the development programmed and studies can be performed early in the development programmed before a stability-indicating chromatographic assay is available.

2.5   Scanning Electron Microscopy (SEM)

The development of nanomaterials requires advanced tools and skills to survey in high magnifications, understand nanostructures, and improve fabrication strategies. Light cannot be used to see the nanoworld, as its resolution is limited by its own wavelength, so optical microscopes are useless for nanotechnology. Electron microscopes use electrons instead of photons, because electrons have a much shorter wavelength than photons and so allow observing matter with atomic resolution.

SEM images the sample surface by scanning it with electron beams in a raster scan pattern. The electrons interact with the sample atoms producing signals that contain information about the sample's surface topography, composition and other properties. Materials made with unique sizes and structures are expected to find various novel applications. The discovery of novel materials, processes, and phenomena at the micro- and nanoscale, as well as the development of new experimental and theoretical techniques for research provide fresh opportunities for the development of innovative nanosystems and nanostructured materials, which is likely to have a profound impact in areas such as electronics, medicine, energy, and biotechnology.

SEM has been used as a complimentary technique to assist in the interpretation of DSC results (Mura et al., 1997).

CHAPTER 3

3.0   METHODOLOGY

3.1   Materials

The kappa-carrageenan (Batch no. 405301, Marine Science Co. Ltd. Tokyo, Japan) were used as tableting excipients. Paracetamol (Batch No. 096k0072, Sigma Life Sciences) was used as the model drug. All the materials were sieved accordingly and only particles, were used for tabletting. Carmosine powder (Colour Index: 14720 & 16255, Batch No. 986630, Zulat Pharmacy Sdn. Bhd.) were used as colourant reagent for binding solution as to observed the spray granulation process.

3.2   Methods
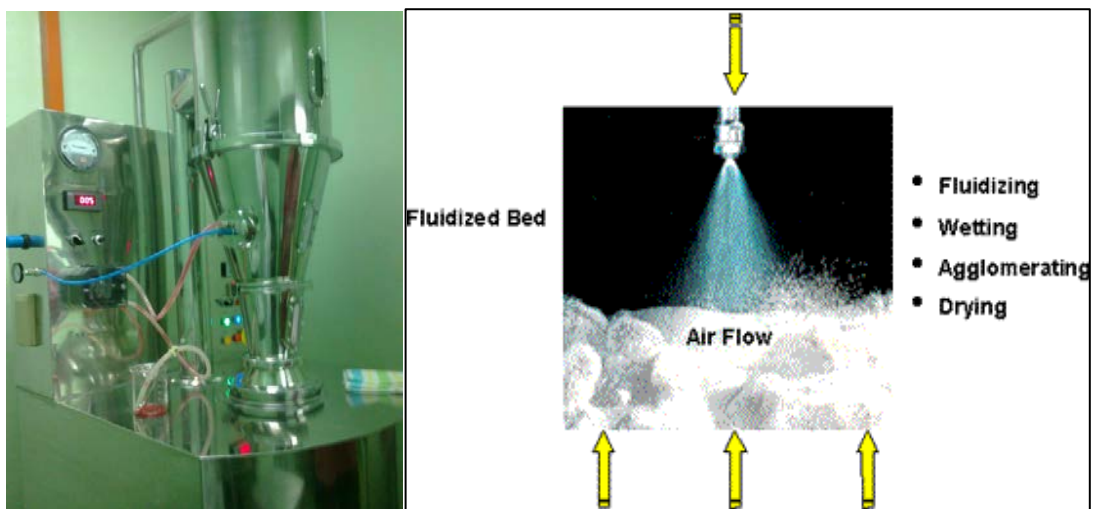
3.2.1   Spray granulation process

Figure 3.1:   Fluid Bed Dryer Spray Granulator, FBS-1 (left) and Granulation Liquid Top Spray Fluid Bed Granulation Process (right).

The granules were prepared in a laboratory scale Fluid Bed Dryer Spray Granulator (FBS-1, NR. Industries Co., Ltd. Samutprakarn, Thailand) equipped with an electrical heater. The batch size was 200g of paracetamol powder and kappa-carrageenan as binding solution with 2g in 250ml of deionized water.

In order to avoid moisture on the wall of the granulator, the bowl was preheated to $50^{o}C$ before the experiment begin. The parameters used for the granulation process are as listed below.

Table 3.1:   Parameters for granulation process

List of parameters	Setting
Blower speed	120 rpm
Inlet Temperature	$60^{o}C$
Pressure regulator	4 bar
Pump flow rate	5 rpm

3.2.1.1 Preparation of binding solution

The kappa-carrageenan binding solution were prepared by dissolving 2g of kappa-carrageenan in 250ml of deionized water. The process of dissolving the kappa-carrageenan was done by adding hot water to the amount and stirred using the magnetic stirrer. Less than 1mg of carmosine powder added to the solution as colouring agent.

3.2.2   Tabletting and the pysical characteristic analysis

Tablets were produced on an instrumented single punch machine (GlobePharma, USA) 12 mm diameter concave with faced punches.The granules manually filled into the die and compressed at 2500 psi. Weight for each of the tablets were estimated at 500mg ± 5%.

There are many tests are frequently applied to tablets for which there are non-pharmacopoeial requirements but will form a part of manufacture's owner product specifications. While for the compendial tests are by refering to standard procedure obtained from British Pharmacopeia (B.P).

The tablet physical characteristics was analyzed with a reference to British Pharmacopeia Quality Control Tests for uncoated tablet. Test involved for tablets are 1) Uniformity of weight; 2) Hardness test 3) Friability test and 4) Disintegration test.

For uniformity of weight, twenty units of tablets were weighed individually at random and average weight mass were determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation for uncoated tablets with weight from 250mg or more is 5 percentage deviation.

Hardness test; Dr Schleuniger Pharmatron tablet tester was used for the analysis. In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet sof tenough to disintegrate properly

after swallowing. Hardness of the tablet is controlled by or is affected by the degree of the pressure applied during the compression stage.

The other compendial test for tablet is friability test. The istrument used were ERWEKA TAR-10 friability tester. According to British Pharmacopeia 2000, tablet weighing up to 0.65 g each, a sample of twenty tablets were used; for tablets weighing more than 0.65 g each, only ten tablet s used. The tablets were weighed accurately and place in the drum. Drum rotated at 100 times. Any loose dust were removed from the tablets and weighed. A maximum loss of 1% of the mass of the tablets tested is considered to be acceptable for most products.

The Disintegration test run as for determines whether tablet disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is considered to be achieved when no residue, except fragments of undissolved tablet coating or of capsule shell, remains on the screen of the apparatus or adheres to the lower surface of the disc if a disc has been used; if any other residue remains, it consists of a soft mass having no palpably firm, unmoistened core.

3.2.3 Thermal Analysis by using Differential Scanning Calorimetry (DSC)

DSC were used to analyzed thermal characteristics of the samples. The instrument was calibrated using indium standard (Perkin Elmer, Norwalk, USA) and a 20µl hermetically sealed aluminium pan (Perkin Elmer, Inc., USA) were used to performed the experiments.

About 2 - 3 mg samples were measured (Mettler Toledo UMT 2) and hermetically sealed in flat bottomed aluminum pans. These samples were heated in an atmosphere of nitrogen (Purified nitrogen, Malaysian Oxygen MOX Sdn. Bhd.) and thermograms were obtained with DSC 6 system equipped with Perkin Elmer Pyris software. The thermograms were obtained by heating from $50^{o}C$ to $250^{o}C$ at a heating rate of $10.0^{o}C/min$.

The individual substances, as well as physical mixtures of paracetamol and kappa-carrageenan was prepared by mortar and pestle, and heated over the set temperature range. The various sample scanned using DSC were shown in Table 3.1.

Table 3.2   List of samples scanned using the DSC

No.	Name of Material	Information of material
1	Paracetamol	Pure Paracetamol (100%)
2	Kappa-Carrageenan	Pure Kappa-Carrageenan (100%)
3	Sample A	Mixture of Paracetamol and Kappa-Carrageenan with 1: 1 ratio (Direct powder mixture)
4	Sample B	Mixture of Paracetamol and Kappa-Carrageenan with 1: 2 ratio (Direct powder mixture)
5	Sample C	Mixture of Paracetamol and Kappa-Carrageenan with 4: 1 ratio (Direct powder mixture)
6	Sample D	Paracetamol powder coated with Kappa-Carrageenan (Granules form)

The blends were considered homogeneous when the DSC traces of two samples from the same preparation. Each of the samples runs for three times to get the sample mean.

3.2.4   Scanning Electron Microscopy

The morphology of the samples was examined using a scanning electron microscope (Leica S440 SE Microscope, Software: LEO) and viewed at different magnification. The samples were previously sputter-coated with gold.

3.2.5   Statistical analysis

Returns the probability associated with a Student's t-Test. A t-test was used as to determine whether two samples are likely to have come from the same two underlying populations that have the same mean.

CHAPTER 4

4.0   RESULTS

4.1   Granulation of Paracetamol powder with Kappa-Carrageenan as binder

The process of spray granulation has tranformed the paracetamol powders to granules form. After granulation process, the granules was compressed to tablet form using single punch tabletting machine. The appearance for both of the product can be seen in Figure 4.1.

Figure 4.1:   Granules of paracetamol produced by spray granulation method (left), and tablets produced from single punch tabletting machine (right).

4.2   Physical characteristic and tablet test

Round concave of shape, with 12mm of diameter, and pink in colour due to colouring agent used in order to ease the observation of the granulation process.

4.2.1 Uniformity of weight

Table 4.1:   Result for uniformity of weight

No. of tablet	Weight (mg)	No. of tablet	Weight (mg)
1	501.0	11	500.1
2	495.6	12	503.4
3	499.0	13	490.8
4	508.0	14	505.3
5	511.0	15	498.0
6	500.2	16	502.0
7	491.7	17	501.7
8	501.2	18	499.8
9	500.3	19	503.4
10	496.4	20	500.1

Limit : Not more than 2 tablets can be more or less than 475mg to 525mg (500mg ± 5%)

4.2.2 Tablet Hardness

Table 4.2:   Results for tablet hardness

No. of tablet	Hardness (N)	No. of tablet	Hardness (N)
1	50	11	55
2	52	12	60
3	47	13	45
4	48	14	48
5	43	15	50
6	50	16	51
7	57	17	60
8	58	18	61
9	55	19	60
10	60	20	51

Limit : No Limit due to non compandial test.

4.2.3 Tablet Friability

Percentage of
weight loss (%) = Weight before friability – Weight after friability x 100%
                                Weight before friability

$$= \frac{105g - 104.8g}{105g} \times 100\%$$

= 0.19%

Limit : Not more than 1%

4.2.3 Disintegration Test

Disintegration Time = 5 minutes

Limit : Not more than 15minutes

4.3 Differential Scanning Calorimeter Analysis

Samples were scanned using Differential Scanning Calorimeter, Perkin Elmer DSC 6. Data are treated mathematically using the Pyris Software Version 7.0 (Perkin Elmer, Norwalk, CT, USA). The raw data obtained from thermograms were entered and calculated of mean and standard deviation value by using Microsoft Excel software. The thermograms obtained from this study shows a thermal transition of melting profile and degradation only.

4.3.1 Analysis of data from DSC thermogram

Thermal parameters calculated from DSC curves of individual components and drug-excipient combinations are presented in Tables 4.1 to 4.6, respectively. The values shown are on the sample weight, onset temperature, end temperature, melting temperature and enthalpy of fusion.

Table 4.3   The results for DSC scanning on melting profile of pure paracetamol

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
PCM 100%	1	2.400	169.150	174.910	172.510	207.265
	2	2.695	168.890	175.020	171.820	210.598
	3	2.293	169.150	174.910	172.510	208.005
	MEAN	**2.463**	**169.063**	**174.947**	**172.280**	**208.623**
	STDEV	**±0.208**	**±0.150**	**±0.064**	**±0.398**	**±1.750**

Table 4.4   The results for DSC scanning on melting profile of pure kappa-carrageenan

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
Kappa-carrageenan 100%	1	2.525	104.750	156.540	126.640	112.412
	2	2.508	101.060	152.130	124.660	104.223
	3	2.565	100.980	156.870	124.300	108.328
	MEAN	**2.533**	**102.263**	**155.180**	**125.200**	**108.321**
	STDEV	**±0.029**	**±2.154**	**±2.647**	**±1.260**	**±4.094**

Table 4.5   The results for DSC scanning on melting profile of Sample A

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
Sample A	1	2.347	168.220	175.300	171.610	102.950
	2	2.658	168.310	174.330	171.600	102.404
Mixture of	3	2.707	167.450	173.570	170.590	103.106
Paracetamol	**MEAN**	**2.571**	**167.993**	**174.400**	**171.267**	**102.820**
and Kappa-	**STDEV**	**±0.195**	**±0.473**	**±0.867**	**±0.586**	**±0.368**
Carrageenan			76.170	145.690	109.670	104.075
with 1: 1			74.470	146.160	107.000	115.873
ratio			81.610	146.830	114.660	106.465
(Direct			**77.417**	**146.227**	**110.443**	**108.804**
powder mixture)			**±3.730**	**±0.573**	**±3.888**	**±6.237**

Table 4.6   The results for DSC scanning on melting profile of Sample B

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
Sample B	1	2.700	167.690	170.820	169.620	62.920
	2	2.570	168.160	171.610	169.960	57.084
Mixture of	3	2.954	168.260	172.590	170.630	65.260
Paracetamol	**MEAN**	**2.741**	**168.037**	**171.673**	**170.070**	**61.755**
and Kappa-	**STDEV**	**±0.195**	**±0.304**	**±0.887**	**±0.514**	**±4.210**
Carrageenan			79.970	121.280	109.500	131.906
with 1: 2			80.850	139.480	108.160	116.155
ratio			84.300	137.910	103.490	139.680
(Direct			**81.707**	**132.890**	**107.050**	**129.247**
powder mixture)			**±2.289**	**±10.085**	**±3.155**	**±11.985**

Table 4.7   The results for DSC scanning on melting profile of Sample C

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
Sample C	1	2.721	168.980	174.520	172.480	190.396
	2	2.895	169.030	174.800	172.490	184.495
Mixture of	3	2.515	168.910	174.540	172.160	197.007
Paracetamol	MEAN	2.710	168.973	174.620	172.377	190.633
and Kappa-	STDEV	±0.190	±0.060	±0.156	±0.188	±6.259
Carrageenan			70.010	105.980	85.330	4.521
with 4: 1			78.000	117.720	94.010	6.075
ratio (Direct			71.010	118.870	92.010	9.398
powder			73.007	114.190	90.450	6.665
mixture)			±4.353	±7.133	±3.711	±2.034

Table 4.8   The results for DSC scanning on melting profile of Sample D

Sample	No. of sample	Sample Weight (mg)	Onset (^{o}C)	End (^{o}C)	Melting Temperature (^{o}C)	Enthalpy of Fusion ΔH (J/g)
Sample D	1	2.452	168.990	178.560	171.900	199.291
	2	2.541	169.020	175.510	172.520	207.048
Paracetamol	3	2.373	168.970	176.540	171.540	224.014
powder	**MEAN**	**2.455**	**168.993**	**176.870**	**171.987**	**210.118**
coated with	**STDEV**	**±0.084**	**±0.025**	**±1.552**	**±0.496**	**±12.644**
Kappa-Carrageenan (Granules form)						

4.3.2 Review of DSC Thermogram

Figures 4.2 to 4.7 illustrate selected thermograms of the various systems investigated.
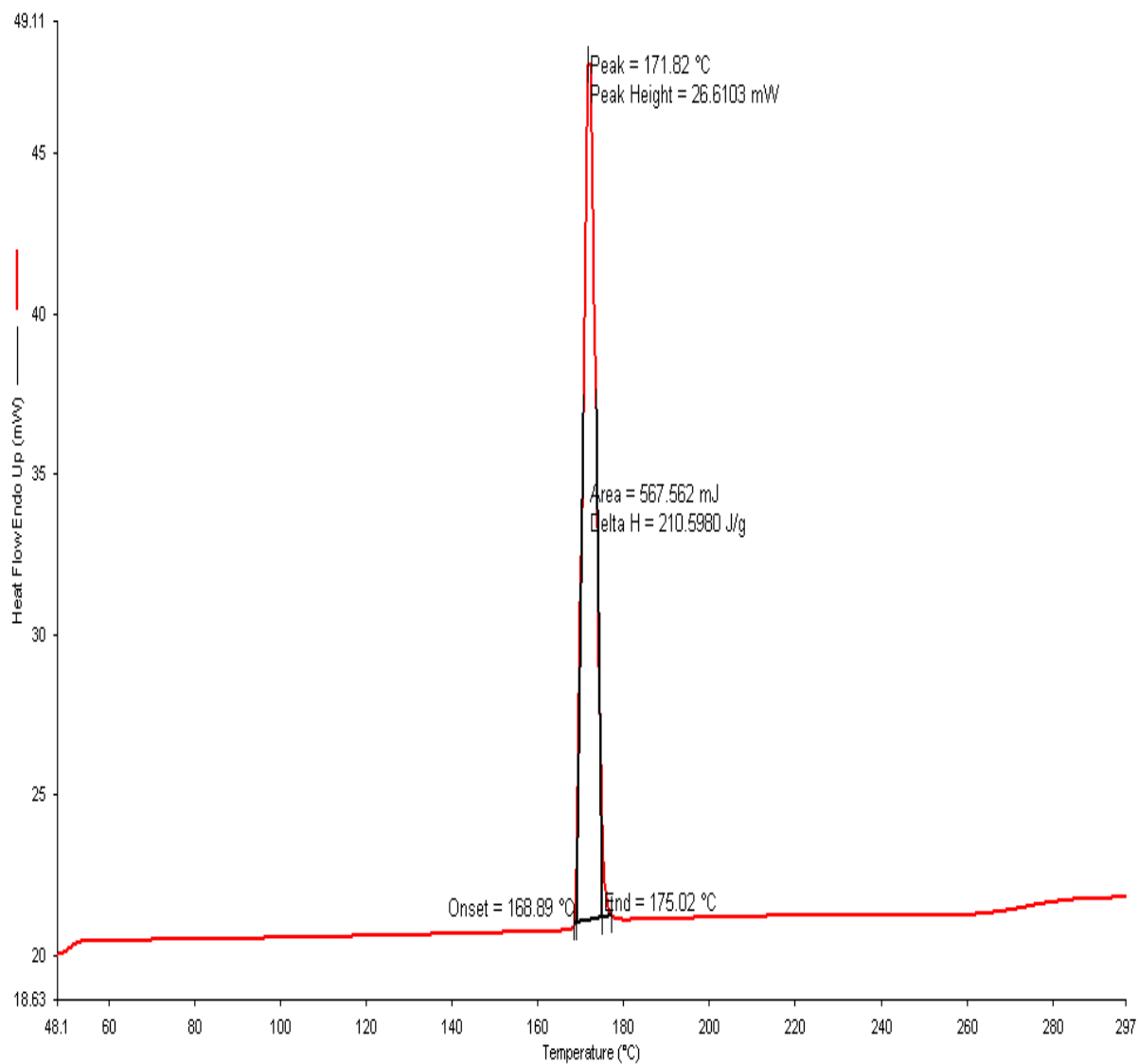

Figure 4.2   Representative one of DSC thermogram for pure Paracetamol

The above thermogram, shown the thermal transition profile appear at $172.28 \pm 0.40^{o}C$. This can be identifying as melting event (melting temperature, T*m*) and the enthalphy of fusion ΔH is 208.62 ± 1.75 J/g.
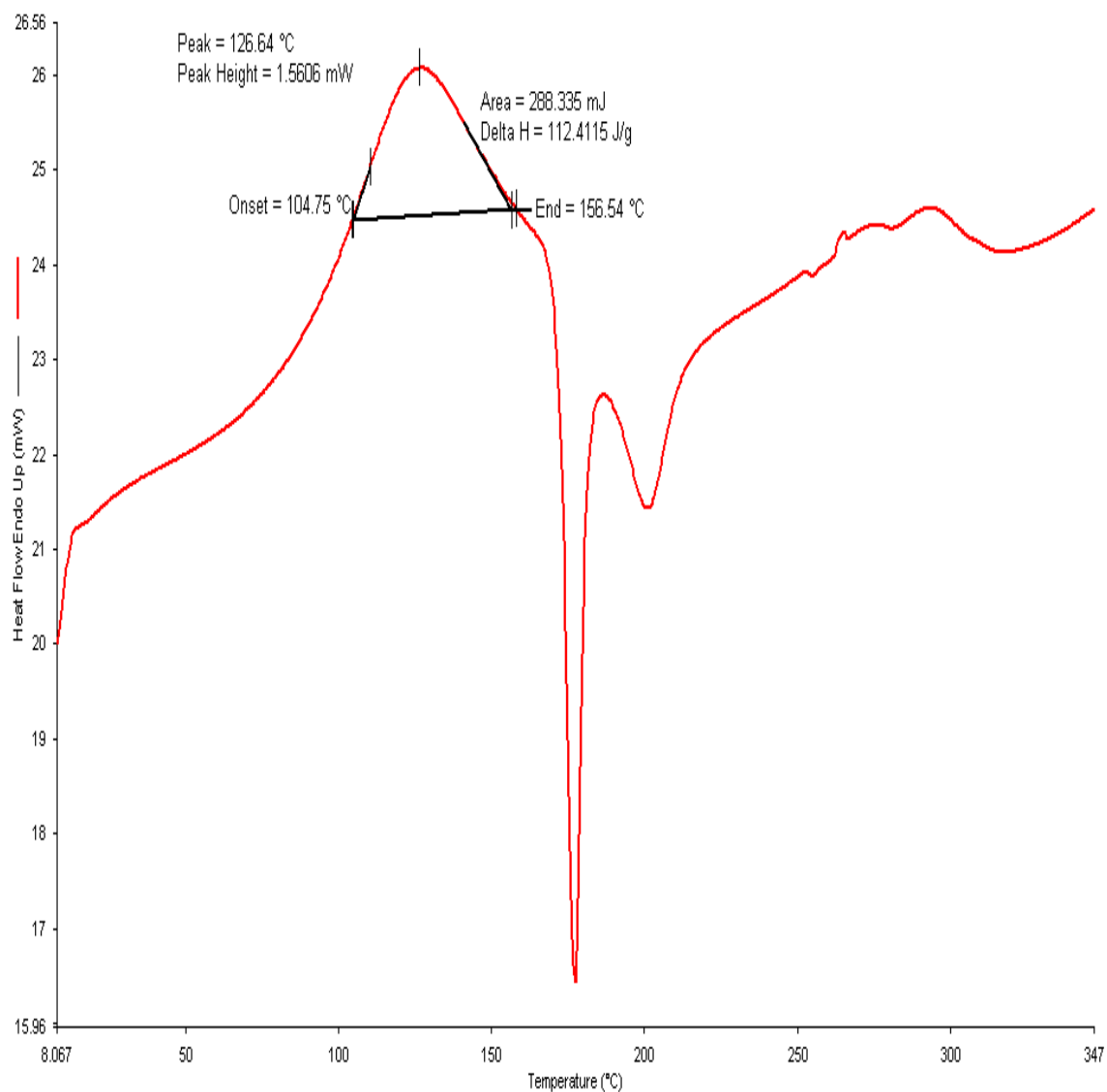
Figure 4.3 Representative one of DSC thermogram for pure Kappa-Carrageenan

In pure kappa-carrageenan, the thermal transition profile which is melting, T*m* occurred at 125.20±1.26 ^{o}C and with enthalpy of fusion, ΔH is 108.32±4.09 J/g. As the temperature increased to 160°C few peak started to develope indicates that kappa-carrageenan had started to decompose.
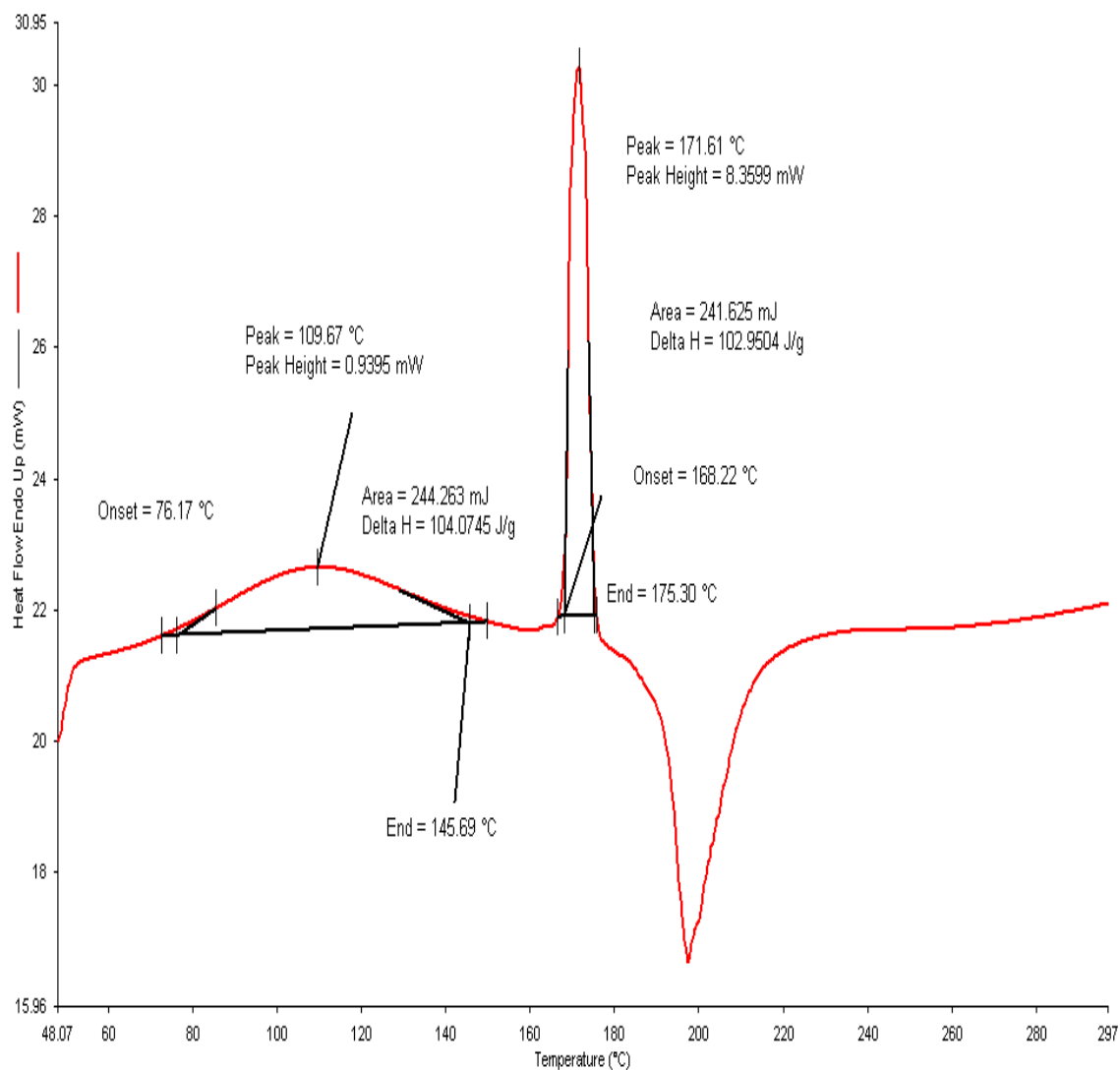
Figure 4.4   Representative one of DSC thermogram for Sample A

In Sample A with a physical mixture of 1:1 ratio, DSC thermogram shows both of the thermal transition profile for the two materials. The first broad melting peak at Tm, 171.27±0.59^{o}C indicate the present of kappa-carrageenan and second endothermic peak at Tm, 110.44±3.90 J/g belongs to Paracetamol follows with decomposition peak of kappa-carrageenan when temperature reaches 200°C.
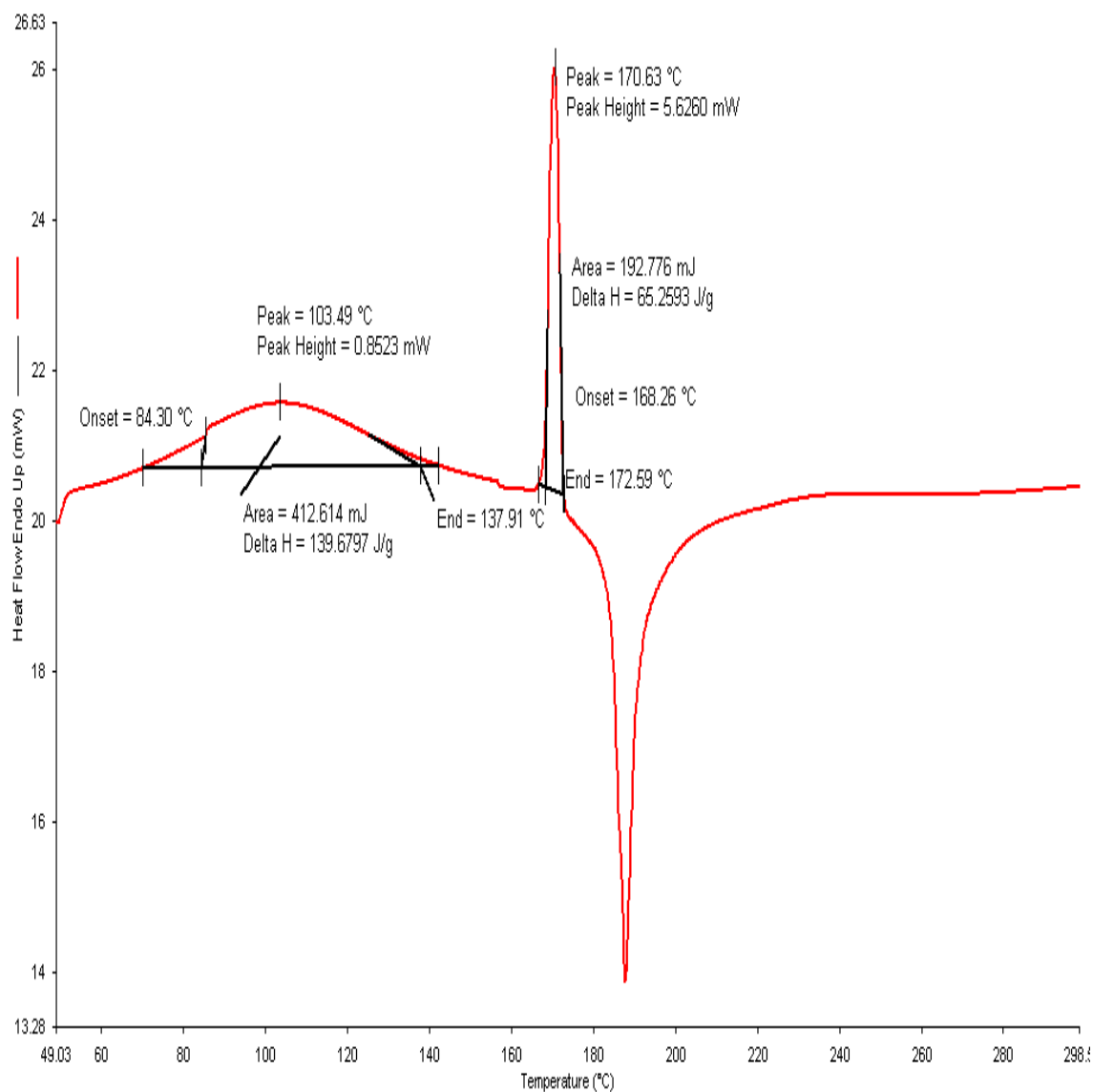
Figure 4.5 Representative one of DSC thermogram for Sample B

Sample B are combination of higher kappa-carrageenan as compared to paracetamol with ratio of 2:1. It is proven by higher ΔH of kappa-carrageenan which is 129.25±11.99 J/g while Paracetamol with ΔH 61.76 ±4.21 J/g. The melting temperature for kappa-carrageenan appeared at 107.05±3.16^{o}C and Paracetamol at 170.07±0.51^{o}C.
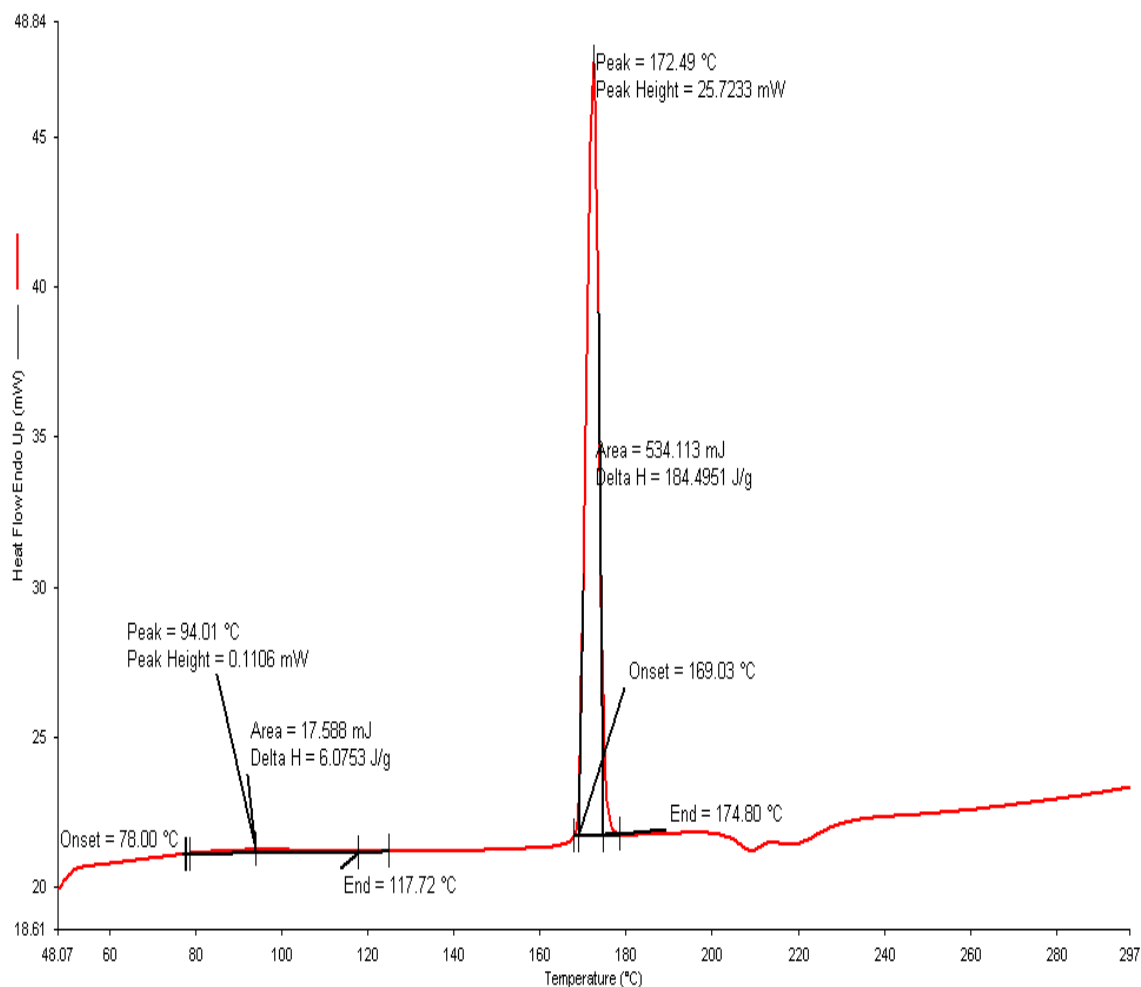
Figure 4.6   Representative one of DSC thermogram for Sample C

For Sample C, the thermogram obtained with an obvious endothermic peak of paracetamol and almost hidden peak of kappa-carrageenan. This happens due to combination of higher paracetamol, four times as compared to kappa-carrageenan with ratio of 4:1. It is obviously represented by higher enthalpy of fusion, ΔH of paracetamol which is 190.63 $\pm$6.26 J/g while kappa-carrageenan with enthalpy of fusion, ΔH 6.67 $\pm$2.03 J/g. The melting temperature for paracetamol appeared at 172.38$\pm$0.19^{o}C and kappa-carrageenan at 90.45$\pm$3.71^{o}C.
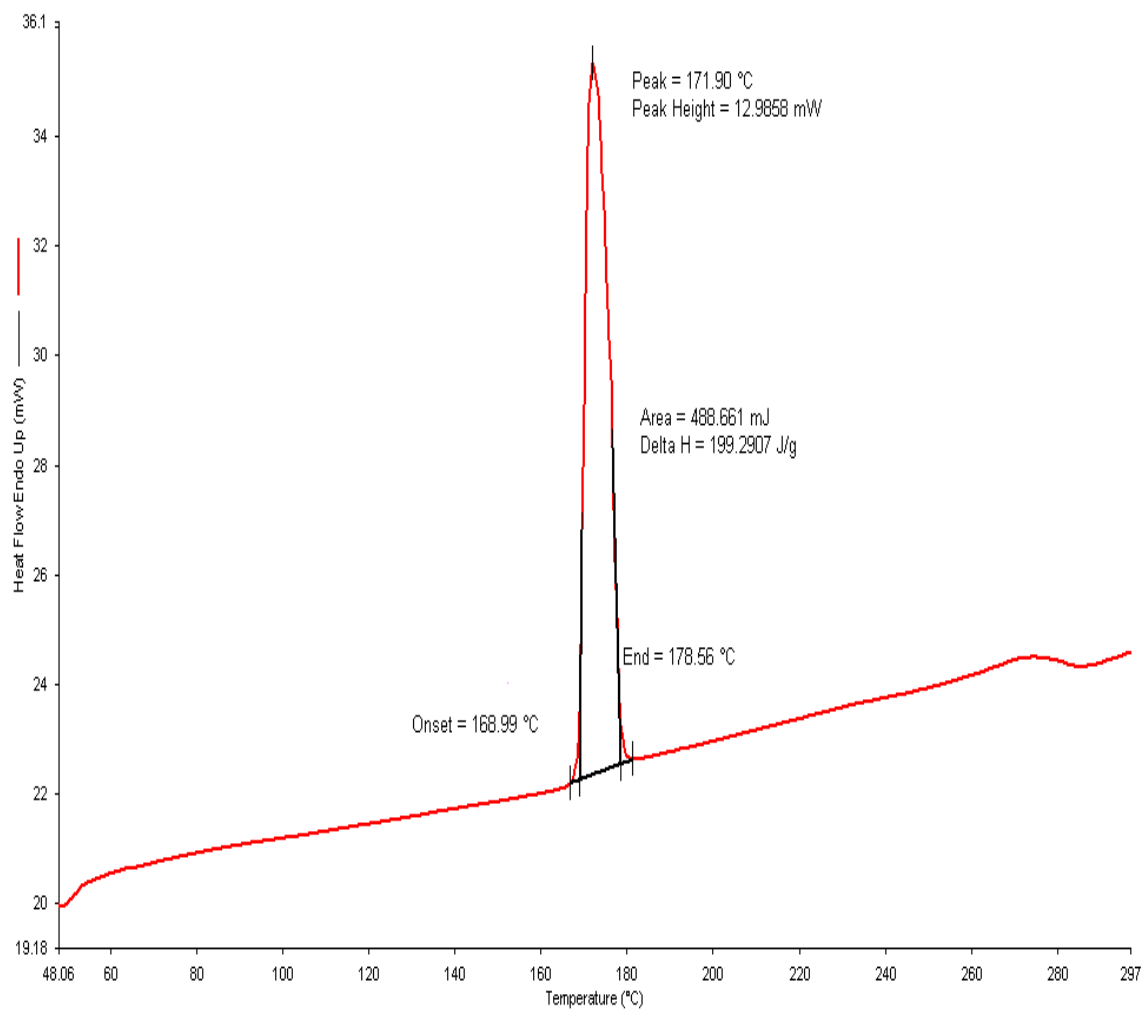
Figure 4.7   Representative one of DSC thermogram for Sample D

The above thermogram is for paracetamol granule sprayed with kappa-carrageenan as binder. Only paracetamol peak that can be clearly observed while peak for kappa-carrageenan is totally hidden or undetectable. The melting temperature for paracetamol granules are 171.99±0.50^{o}C with enthalpy of fusion, ΔH at 210.12 ±12.64 J/g.
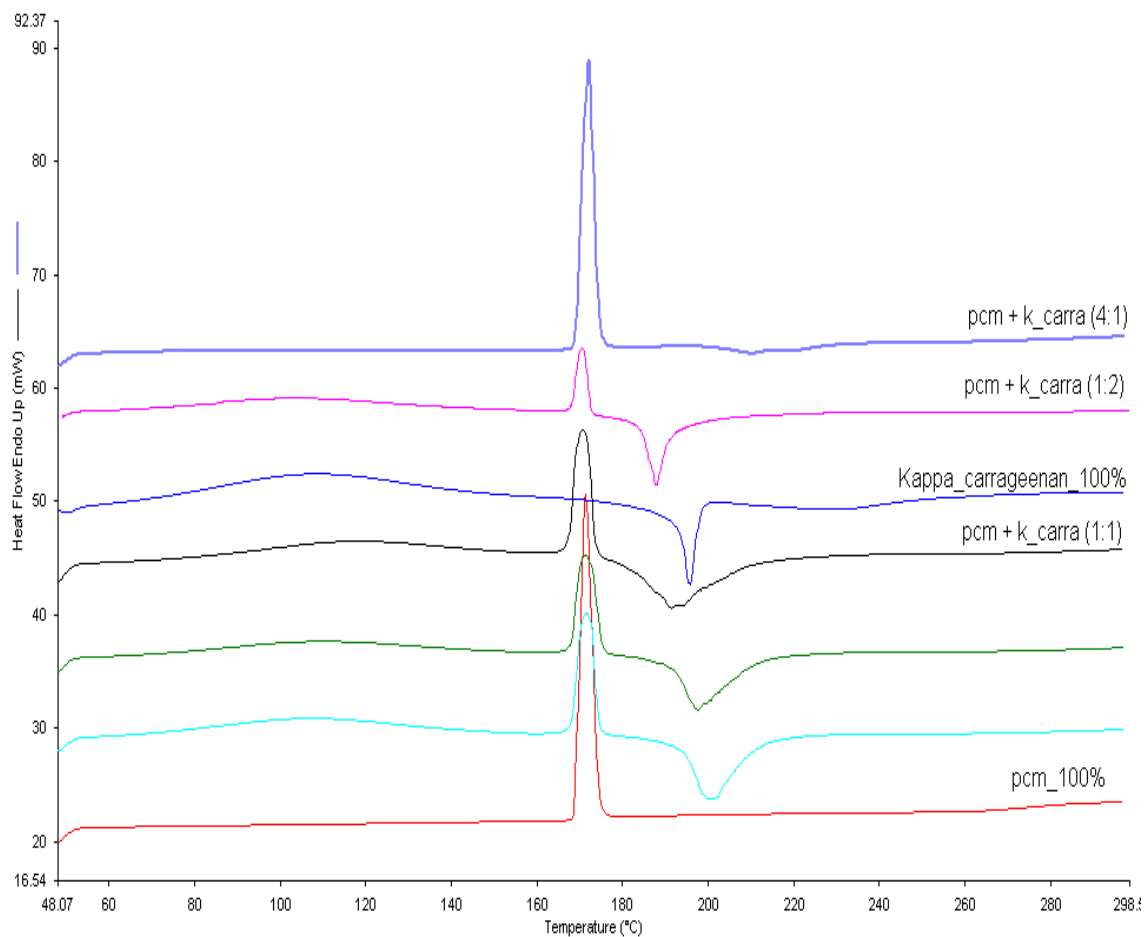
Figure 4.8   DSC thermograms of the various systems investigated.

The above figure shows an overlapping of DSC thermograms of various systems investigated (as per label). Overall, the melting peak for paracetamol occurs at 169°C to 170°C. While kappa-carrageenan peak appeared to be inconsisted at varios system due to broad melting peak ranging from 50°C to 120°C.

4.4 Scanning electron micrographs

(a)
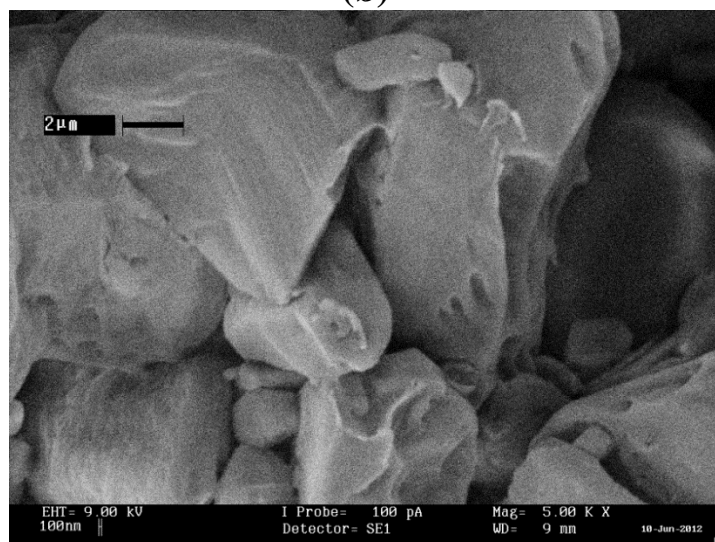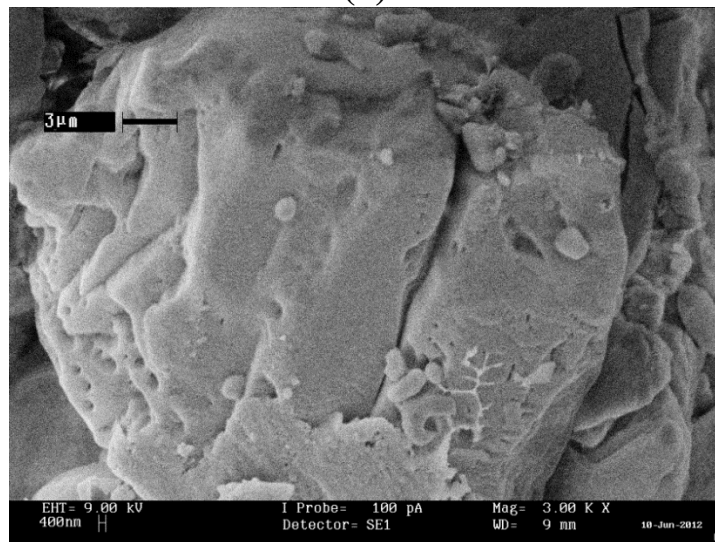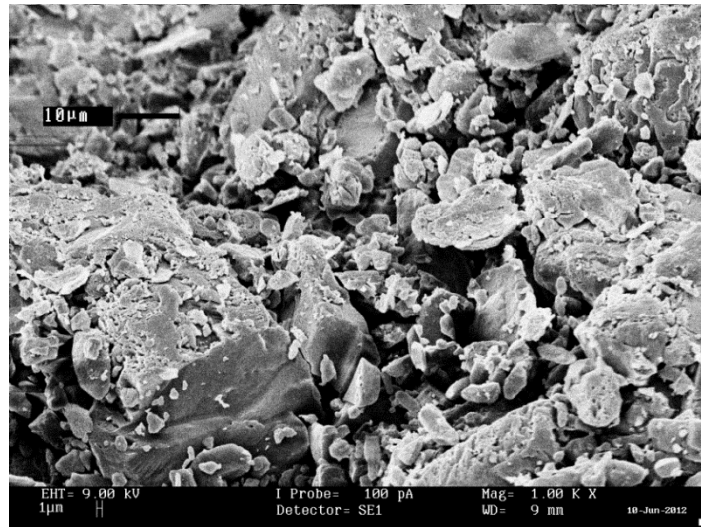

(b)

(c)

Figure 4.9   Scanning electron micrographs of (a)1000X; paracetamol, (b)3000X; kappa-carrageenan powder and (c) 5000X; binding solution granule.

CHAPTER 5

5.0   DISCUSSION

5.1   The Paracetamol granules

Nowadays granules are used as an intermediates for compression of tablets, the most often dosage form and it is widely used in different industries. Granules can also be found in pharmaceutical used, that are produces by using many method. Wet granulation is one of the methods used, where solvents or binder solutions are used to agglomerate powders. Wet granulation methodologies are the fluid bed granulation, high shear granulation or the spray drying processes. As in dry granulation methods, the mechanical pressure for agglomeration were used, such as roller compaction and slugging. In all these processes powder particles are enlarged up to granules with a particle size range from 0.1 to 2.0mm (Kristensen and Schaefer 1987).

By definition granules are agglomerates made of primary particles. With several advantages offered, granules has become an interest in comparison to pharmaceutical powders. Good flowing properties which are improved with larger particle size (Rumpf 1958, Guerin et al. 1999) is a necessarry for the production of solid dosage form. Thus free-flowing granules assure a good dosing accuracy during a tablet compression or capsule filling process (Gabaude et al. 2001). According to Faure et al. (2001) the increase in bulk density after an agglomeration step which enables a better control of drug content uniformity at low drug concentrations and avoids demixing or segregation processes. Augsburger and Vuppala (1997) also mentioned that granulation leads to a reduction in dusting, an especially important fact for the production of high potent drugs.

Therefore, it is clearly showed in this study that the making of paracetamol powder to granule form by using spray granulation method were relevant due to the advantages of granules properties.

5.1.1   The spray granulation method

The FBS-1 is a fluid bed spray granulator designed for lab scale. The product container is an inverted truncated cone, which has reinforced screen in its bottom. The purpose of the screen is to allow sufficient air flow through the product bed without passing down through into the inlet plenum or air handling section. Directly above the product container is an elongated expansion chamber. As air pass through the product bed particles are carried upward into the expansion chamber where the air velocity quickly diminished to the point where it can no longer entrain particles. The materials, Paracetamol travel toward the wall of expansion chamber, drop back into the product container and continues it's cycling. In the expansion chamber a noozle is placed for the application of the binder solution which is Kappa-carrageenan. The liquid is sprayed at a controlled rate into the randomly fluidized powder. The filter function as to seperates the product from the fluidizing air. The permeability and porosity of the filter are chosen to accomodate the physical characteristics of the raw material componets.

The paracetamol granules was successfully produce using parameters in Table 3.1 with spray granulation method.

5.2   The feasibility of kappa-carrageenan as binder

In this study, the used of kappa-carrageenan as tablet binder is fisible. It is shown in the results obtained from the tablet testing (Table 4.2.1 - 4.2.3). The uniformity of weight, tablet hardness, friability test and disintegration time for tablet produced from kappa-carrageenan as binder complies with B.P requirements.

5.3   DSC Analysis : The compatibility of paracetamol and kappa-carrageenan

The used of DSC in drug-excipient compatibility study has been widely used as a screening technique in pharmaceutical research area. Previous research that has been published are using other drugs such as ketoprofen, nanproxen and ibuprofen (Mura et al. 1997).

5.3.1   Sample preparations and operating conditions

In this study, a heat flux DSC was used as technique for thermal characteristic screening. It consists of sample and reference disk that positioned symmetrically in a furnace. The sample and reference pans are heated from the same source and the differential temperature is measured. The resultant voltage signal is converted to heat flow rate usually in unit J/s (Coleman et al. , 1996).

Coleman et al., (1996) also coded that the nature of sample and instrumental condition such as scan rate, atmosphere, pan configuration and reference system are the main factors that should be taking into consideration in order to generate good results from a DSC scanned. By using small amount of sample the heat flow can accurately measured due to the minimised of thermal gradients within the samples. With small amount of sample used can contributed to better

resolution and better heat transfer within sample, but it also have the drawback when involve a mixture of two different items, component with lowest amount will have low detection limit which produce small peak. Whereas, larger sample size can give better detection limit which is represented by larger peak, but poor in resolution and reduce heat transfer wihin sample. Taking all this into consideration, in this study the sample size used were ranging from 2 to 3 mg only. Samples were carefully weighted and loaded into sample pan to ensure each sample placed into the pan. The pan was than sealed properly together with pan cover by using crimper and transfered to the heating chamber by using tweezer. Transferring sample pan by hand is not alloud as it can leads to contaminaion of sample pan with fats/oils.

The reference pan used in this study were the same material as for sample pan. A hermetically sealed aluminium pan were used due to the ability of the pan to cope with high temperature up to $600^{\circ}C$ and not react with the sample used. The heating rate used in this study was $10^{\circ}C/min$. Normally for DSC the heating rate used are in between $10^{\circ}C$ to $20^{\circ}C$. Heating rate can highly influence the temperature distribution inside the sample. The phase transition of polymers can be speed up by increasing the heating rate especially for higher temperature region.

Nitrogen gas was choosen as the atmosphere in this study as to minimize the oxidation process or burning of the samples tested. With the used of nitrogen, will keep the furnace dry and prevent from any moisture.

5.3.2 DSC thermograms analysis

Thermal parameters calculated from DSC curves of individual components and drug-excipient combinations are presented in Tables 4.3 to 4.8, respectively. Figures 4.2 to 4.7 illustrate selected thermograms of the various systems investigated. The DSC thermal curve of pure paracetamol (figure 4.2) showed a sharp endothermic peak at its melting point. At a scan rate of 10^oC/min, the observed melting peak temperature was 172.28 ± 0.40^oC (Tonset $169.0 \pm0.15°$C) with an apparent enthalpy of fusion of 208.63 ± 1.75 J/ g. In general, the process of thermal transition start when the samples are heated. The molecules started to moved and after certain period of time they gain a lot of mobility which causes them to wiggle and squirm. With that conditions make them not able to stay for longer time as they cant make anymore move. Therefore, the molecules started to arrange themselves into a better order when reaches at the correct temperature and at the same time gain a lot of energy. This phenomenon called as crystallization stage. When more heat supplied the molecules started to create more vibrations and will cause the crystals order fall apart and at this point the molecules are in the melting stage. The molecules now able to move freely from the previous arrangement.

The excipient or binder, kappa-carrageenan exhibited a broad endothermic effect in the 50^oC to $160°$C range due to the polymer characteristics, followed by an intense exothermal effect attributable to the drug decomposition process. The endothermic effect for pure kappa-carrageenan (figure 4.3) was peaked at $125.20\pm1.26°$C with a relevant enthalpy value of 108.32 ± 4.09 J/g. The broad melting peak of kappa-carrageenan indicates to large molecule structure, with

highly flexible molecules that curl to form helical structures. Due to the large, curl and helical structure of kappa-carrageenan contributed to broad melting peak as more energy needed for process of phase transition. Normally in DSC the peak shape for decomposition stage appeared to be in many small sharp peak, but for kappa-carrageenan its appeared by an intense exothermal effect due to its polysaccharide group. A self checked has been done for the conformation of decomposition stage by heating the sample until $180^{o}C$. Obviously the burning kappa-carrageenan was observed by breaking the sample pan.

Figure 4.4 to 4.7 indicates the DSC thermograms of different ratio (1:1, 1:2 and 4:1) on physical combination of drug-excipients and the granulation method. Mixed systems of paracetamol with Kappa-carrageenan, regardless of the method of sample preparation, exhibited the characteristic thermal profile of the drug, suggesting that no problems of compatibility should occur. Some changes in peak shape and height-to-width ratio or slight reduction of temperature of drug melting were sometimes observed but they can be ascribed to the mixing of the components. Curves of their 1:1, 1:2, and 4:1 w:w combinations of paracetamol and kappa-carrageenan showed a solid–solid interaction. This is due to paracetamol drug melting temperatures as evident, which are not significant for every combination ($P>0.05$). While kappa-carrageenan for the combination shows significantly decrease or a noticeable downward shift of melting peak temperature of about $41^{o}C$ was observed ($P <0.05$). On the other hand, no particular effects due to the sample manipulation were observed.

In figure 4.7 shows a thermogram of paracetamol granules layerred with kappa carrageenan solution. Only one endothermic peak observed which belong to

paracetamol with Tm, $171.99\pm0.50^{o}C$ and enthalphy of fusion at 210.12 ± 12.64 J/g . The peak for kappa-carrageenan is undetectable due to very small amount were used in preparing the binding solution, less than 1%. This can be proven from figure 4.6 , with the combination of 4 PCM: 1 kappa-carrageenan w:w. In addition to this, the results had proved of the successfulness of paracetamol granules prepared by using spray granulation method with kappa-carrageenan as binder.

5.4   The morphology of materials

The morphology of the samples is shown in Figure 4.9. The Paracetamol (Figure 4.9 a) have different shape and size; the smaller ones are quite spherical, while the larger ones are elongated. The kappa-carrageenan powders (figure 4.9 b) are view at different magnification (3000X). Figure 4.9(c) report the SEM photographs of binding solution granules at the 5000x magnification. The surface of both samples (b and c) are similar, with a smooth pattern which seem to be the polymer characteristic and film layer that binding to the drug. Moreover Figure 4.9(c) shows the surface clearly becomes homogeneous due to disappearence of surface cavities and the drug. In term of the porosity image of the samples, higher magnification need to be used. Thus compatibility of paracetamol with kappa-carrageenan can be reasonably expected, considering the binding solution present in this study at concentration of only less than 1%.

CHAPTER 6
6.0   CONCLUSION

Thermal analysis of pharmaceutical substances are suitable methods for screening drug–excipient interactions. As it is only requires a few milligrams of sample per experiment and is not so time-consuming and expensive. The differential scanning calorimetry (DSC) were an analytical instrumental that used extensively to evaluate the physical properties of drugs, including melting and vaporization temperatures and with the corresponding enthalpies, glass transitions, vapor pressures, as well as to study the compatibility and stability of the components of pharmaceutical preparations.

DSC in particular, allows a rapid evaluation of possible incompatibilities by revealing changes in the appearance, shift or disappearance of melting or other exothermic processes, and variations in the corresponding enthalpies of reaction. The differences in DSC curves of mixtures as compared to the individual components may arise for reasons other than chemical incompatibility and the interaction may be advantageous, as in the case of a more desirable form of drug delivery.

Therefore, a complementary analytical techniques should be used as to validate or as confirmation to the interpretation of results due to DSC profiles changes of mixture from the pure component. As in this study the used of Scanning Electron Microscopy used as a complimentary techniques to assist in the interpretation of DSC results.

As a conclusion, the present studied had successfully carried out an experimental exploring the possibilities of producing paracetamol granules by using spray granulation method with kappa-carrageenan as binder. Based on the findings, the used of paracetamol with kappa-carrageenan are compatible.