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Thermoanalytical and Microscopic Investigation of Interaction between Paracetamol and Fatty Acid Crystals

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The objective of this study was to investigate the possibility of interaction between paracetamol and saturated fatty acids. Although literature is replete with the interaction study of fatty acids with different drugs, few have examined the interaction with NSAIDs. Keeping in view the crystalline nature of paracetamol and fatty acids and to provide the intimate contact between the interacting molecules, crystals of binary mixture of drug with fatty acids were prepared by the solvent evaporation method. These crystals were subjected to FT-IR, DSC, XRD, optical microscopy, SEM and AFM. DSC and XRD studies were unable to detect any interaction. Some changes were observed in FT-IR spectrum of a binary mixture of drug with fatty acid. A better probe into interaction was obtained by microscopic techniques, especially atomic force microscopy.

Keywords: AFM; DSC; FTIR; SEM; XRD; interaction; paracetamol; saturated fatty acid

1 Introduction

Paracetamol, (PCM, N-(4-hydroxyphenyl) acetamide), also known as acetaminophen, was first launched as a drug in 1956. It is a popular and the most widely accepted over-the-counter antipyretic and analgesic in the world (1).

Two crystalline polymorphs of paracetamol have been reported, although evidence has been published which suggests that a third polymorph could exist. The crystal structures of the two known forms of paracetamol are monoclinic and orthorhombic. The monoclinic form is thermodynamically stable and commercially available as PCM (2).

A primary feature of the paracetamol crystal structure is hydrogen bonding. This bonding leads to the formation of hydrogen bonded chains of molecules, packed in a herringbone conformation within the crystal structure. The degree of hydrogen bonding, which occurs within the paracetamol crystal has been quantified as 8.31 kcal mol^{-1}, which corresponds to approximately 30% of the total lattice energy. Thus, any additive, which disrupts the hydrogen-bonding network within the crystal, has the potential to significantly alter its growth rate and ultimately its morphology (3). Hydrogen bonding interactions and their effect, along with other adsorption forces play important roles for the adsorption of macromolecules onto various solid surfaces. Many methods have been reported to study excipient adsorption on a solid surface, such as solid state NMR, FTIR, UV, Raman, electron spin resonance (ESR), microcalorimetry and surface plasmon resonance (SPR). However, all these methods can only detect the change in the adsorbed excipient molecules themselves, no direct information could be obtained on how the solid surface is involved during adsorption on a molecular level (4). At present, the most efficient technique available for probing the interactions in systems is the atomic force microscopy, which was originally developed as an imaging tool (5). The atomic force microscopy first emerged as a useful tool for the study of surface interactions (6). Since then, it has been applied to a number of pharmaceutical related problems. This is mainly due to its ability in characterizing the surface morphology of materials at very high resolution. It can provide insight into the interaction between the polymer and crystal surface on a molecular level (1).

Fats and lipids of a natural and synthetic origin have been extensively explored in the pharmaceutical research to achieve the desired therapeutic goal by controlling the drug release, especially of poorly water-soluble drugs. Saturated fatty acids such as lauric acid, myristic acid, palmitic acid and stearic acid are crystalline in nature (7).

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There are many reports on the use of fatty acids in formulation of different dosage forms (8–11). In a few, interaction between drug and fatty acids have been studied (12, 13) but reports on the study of interaction between the drug and fatty acid keeping in mind their crystalline nature, are rare. Additionally, interaction from the solid-solid surface contacts, especially with paracetamol and fatty acid, which is an important consideration in pharmaceutical processing and formulation development, is absent.

The aim of the present work was to examine the possibility of interaction and its nature, between crystals of paracetamol and saturated fatty acids namely; lauric acid, myristic acid, palmitic acid and stearic acid using FTIR, DSC, XRD, optical microscopy, scanning electron microscopy and atomic force microscopy.

2 Experimental

2.1 Materials and Methods

Paracetamol was obtained from Aristo Pharmaceuticals Ltd., Raisen, India. Lauric acid, myristic acid, stearic acid and palmitic acid were purchased from Merck, Schuchardt, Germany. All other materials used were of A.R. Grade.

2.2 Preparation of Crystals

Paracetamol and each fatty acid (1 g) were dissolved separately in 10 ml of methanol. A Paracetamol solution was mixed with individual fatty acid to prepare a 1:1 binary mixture and the solvent was allowed to evaporate at room temperature. The 1:1 ratio was selected to maximize the likelihood of observing any interaction (14).

2.3 Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectra were obtained using an IR Prestige-21 (Shimadzu, Japan) equipped with an IR solution version 1.21 (Shimadzu, Japan) in the 400–4000 cm^{-1} range with a resolution of 4 cm^{-1} (20 scans). Dry potassium bromide (50 mg) was gently ground in an agate mortar, followed by the addition and mixing of (1–2 mg) crystals of paracetamol, fatty acids and their binary mixture.

2.4 Differential Scanning Calorimetry (DSC)

All measurements were carried out on an Indium calibrated DSC Q 10 V9.4 Build 287 (TA Instruments, USA) equipped with a refrigerated cooling system (RCS). Data acquisition and analysis was carried out using the Universal Analysis 2000 program (TA Instruments, USA). 2–4 mg of crystal of paracetamol, fatty acid and their binary mixture was weighed into pin-holed aluminum pans (TA Instruments, USA) and heated under dry nitrogen (50 ml/min) in the scanning range between 0 and 200°C at a rate of 10°C/min. An empty pan was used as reference. Experiments were carried out in duplicate.

2.5 X-Ray Diffraction Study (XRD)

X-ray diffraction of crystal of paracetamol, fatty acid and their binary mixture was carried out on a Rigaku rotating anode diffractometer RUH3R (Tokyo, Japan). Measurements were performed at 40 kV voltage, 15 mA current, at a scanning speed of 2°/min, step size 0.02 and scanning range from 5–60° 2θ.

2.6 Microscopy

Optical microscopy was performed using Leica microscope FW4000 attached with digital camera. Samples were mounted on a glass slide before they were seen under the microscope.

For scanning electron microscopy crystals of paracetamol, fatty acid and their binary mixture were mounted on scanning electron microscope stubs with double-sided carbon tape and observed under a Jeol JSM 5600 Scanning Electron Microscope (Jeol, Japan).

Atomic force microscopy was done for crystal of paracetamol, fatty acid and their binary mixture on a Scanning Probe Microscope (Digital Instruments: Nanoscope IV, USA) in contact mode using a triangular cantilever made up of silicon nitride, having force constants of 0.38 N/m. Scan sizes were taken from 50 to 1 μm.

3 Results and Discussion

3.1 Fourier Transform Infrared Spectroscopy

In paracetamol, the bands in the region 800–860 cm^{-1} are attributed to C-H out-of-plane bending of p-substituted benzene ring. The bands of aromatic vibrations are present at 1440, 1505 and 1560 cm^{-1}. The bands at 1651, 3160 and 3324 cm^{-1} represent C═O stretching, O-H stretching and N-H stretching, respectively (15).

In fatty acids, the presence of bands at 3300–2500 cm^{-1} and at 1708 cm^{-1} and a few additional bands at 1431, 1300, and 938 cm^{-1} may be attributed to a carboxylic acid dimer (16).

The FT-IR spectrum of crystals of binary mixture of paracetamol with fatty acids (Figure 1) did not record any significant change in terms of absence or presence and shifting of characteristic bands of either drug or fatty acid however, changes in the shape and decrease in intensity of carboxylic acid bands of fatty acid and -NH stretching band of paracetamol were observed. The broad bands of $\nu_{as}CH_2$ of fatty acid at 2920 and 2850 cm^{-1} were converted into sharp bands with the increase in intensity.

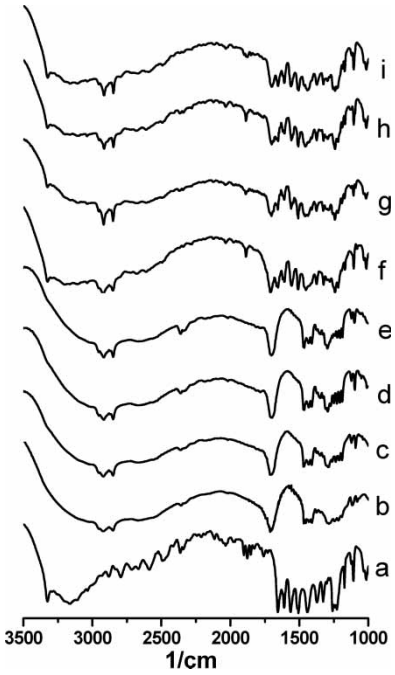

Fig. 1. (a) FT-IR patterns of crystal of paracetamol, (b) lauric acid, (c) myristic acid, (d) palmitic acid, (e) stearic acid, (f) binary mixture of paracetamol with lauric acid, (g) with myristic acid, (h) with palmitic acid, (i) with stearic acid in 1:1 ratio.

3.2 Differential Scanning Calorimetry

Tables 1 and 2 record the thermal parameters of crystal of paracetamol, fatty acid and their binary mixtures. The DSC thermogram of paracetamol crystal showed an endotherm with an onset at 168°C and enthalpy value 192.5 j/g, in the scanning region from 0°C to 200°C (Figure 2). The endotherm at 168°C showed that the crystals of paracetamol are monoclinic in nature (2). In the thermogram of myristic acid crystal, a fusion endotherm was observed at 50.38°C. The thermogram of the crystals of binary mixture of myristic acid with paracetamol records two sharp endothermic peaks corresponding to their melting point with the onset at 50°C and 163.38°C, respectively, along with approximately 5% gain in enthalpy values. A slight shift in the melting peak of drug was observed, which might be attributed to the lowering in purity of paracetamol on the addition of myristic acid. The lauric acid crystal showed an endotherm at 46°C with an enthalpy value of 79.50 j/g. The thermal profile of crystals of lauric acid with paracetamol records two endothermic peaks at 46°C and 162°C, with a loss of 4.28% in enthalpy. The probability of interaction was ruled out since it was not as significant to predict any interaction between the two substances. A DSC thermogram of crystals of palmitic acid with paracetamol retained the characteristic thermal feature of drug, as well as palmitic acid with a enthalpy loss of 7.15%, ruling out any possibility of interaction.

Table 1. Thermal parameters of paracetamol and fatty acids

Drug/fatty acid	T_{onset} (°C)	T_{peak} (°C)	ΔH (J/g)
Paracetamol	168.81°C	169.97°C	192.50
Lauric acid	43.33	44.67	173.2
Myristic acid	50.38	53.41	175.70
Palmitic acid	61.37	63.33	183.30
Stearic acid	55.26	59.24	177.60

In the DSC scan of stearic acid crystal, a sharp melting endotherm was observed at 55°C with the enthalpy value of 177.6 j/g. In the thermogram of crystals of binary mixtures of stearic acid with paracetamol, individual fusion peaks of both the drug as well as stearic acid was retained. The thermogram represented the mere addition of the features of individual components. An estimation of enthalpy of the system ($\Delta H_{observed}$) revealed no significant change in comparison to $\Delta H_{calculated.}$ El-Shattawy has proposed that the enthalpy of a system remains unchanged if no interaction occurs (17). Thus, there was no interaction between paracetamol and stearic acid. Out of the four binary mixtures, the DSC curve of binary mixture of paracetamol with lauric acid showed the lowest melting point of paracetamol. Paracetamol exists in two polymorphic forms. The melting points of monoclinic and orthorhombic form of paracetamol are in the range of 168–172°C and 157–159°C, respectively (2). In the binary mixture of paracetamol with lauric acid, the melting point of paracetamol is closer to the melting range of orthorhombic form, suggesting the possibility of polymorphic changes in the paracetamol, especially in this mixture. Overall, all the fatty acids displayed no interaction with paracetamol on the basis of enthalpy values and retention of melting endotherm.

3.3 X-Ray Diffraction

The X-ray diffraction patterns showed the crystalline nature of the drug as well as fatty acids (Figure 3). In the diffraction pattern of the crystals of binary mixture, drug and fatty acids retained their respective peaks at their positions. Almost no change was detected in their diffraction pattern.

3.4 Microscopic Studies

The microscopic picture in Figure 4 illustrates the habit of the pure monoclinic paracetamol crystals. In the admixture of paracetamol with fatty acids, paracetamol crystals were entrapped in the fatty acids matrix, which can be seen as dark black aggregates. Some of the crystals of drug lost their crystal habit while the habit of remaining was modified in the presence of fatty acid.

Scanning electron micrographs of binary mixture of paracetamol with fatty acid (Figure 5) showed that crystals of fatty acids not only entrap drug crystals, but in some cases (Figure 5 b,d), crystals of fatty acid were seen adhering on the surface of drug crystal, while in others (Figure 5 c,e) the crystal memory of paracetamol and fatty acid was changed or lost in such a manner that it was not possible to identify the individual crystal of the drug as well as fatty

Table 2. Thermal parameters of crystal of binary mixtures of paracetamol with fatty acid

	1st Transition			2nd Transition					
Binary mixture	T_{onset} (°C)	T_{peak} (°C)	ΔH (J/g)	T_{onset} (°C)	T_{peak} (°C)	ΔH (J/g)	ΔH_{cal} (J/g)	ΔH_{obs} (J/g)	% Change in ΔH
Lauric acid	43.0	46.0	79.5	159.0	162.0	93.65	180.57	173.15	−4.28
Myristic acid	49.90	53.16	92.96	163.38	165.36	97.34	181.82	190.93	+4.77
Palmitic acid	60.0	65.0	103.0	165.0	168.0	96.92	185.62	199.92	+7.15
Stearic acid	55.0	58.0	97.29	166.0	169.0	89.86	182.77	187.15	+2.34

acid. For a crystalline material, changes in the surface chemistry can occur as a result of shifts in polymorphic form and crystal habit. The resultant changes in the spatial arrangement of molecules and dominance of faces can lead to different moieties being presented at the surface, which will in turn influence the polar and apolar components of surface energy. As a consequence, polymorphism and crystal habit is a subject of great interest to many different areas (18, 19).

Figure 6 shows AFM images of the surface of a paracetamol crystal. The large, multi molecular steps were found to have straight edges. This feature of paracetamol crystal was lost in the crystals prepared from binary mixture of drug with fatty acid. Atomic force microscopic pictures showed that the crystal of paracetamol might be docked onto the surface of fatty acid crystal and become incorporated into the crystal lattice. These types of interactions depends upon the molecular similarity of the additives, in this case fatty acids, to paracetamol (1). AFM study suggests that the fatty acid molecules significantly disrupted the crystal lattice of paracetamol during growth. The crystal of paracetamol with lauric acid (Figure 6b) showed the self-assembly of the crystal in a triad fashion, may be due to of some sort of

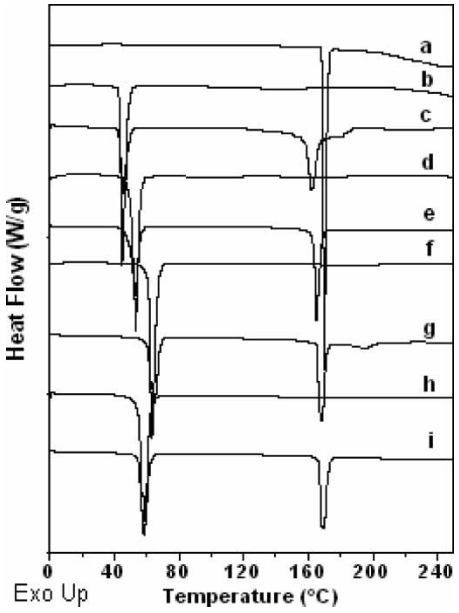

Fig. 2. (a) Thermal profile of crystal of paracetamol, (b) lauric acid, (c) binary mixture of paracetamol with lauric acid, (d) myristic acid, (e) binary mixture of paracetamol with myristic acid, (f) palmitic acid, (g) binary mixture of paracetamol with palmitic acid, (h) stearic acid, (i) binary mixture of paracetamol with stearic acid in 1:1 ratio.

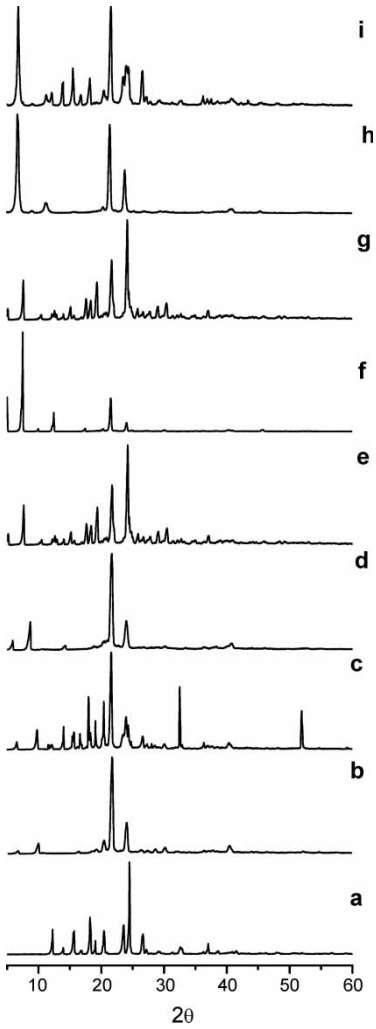

Fig. 3. (a) XRD pattern of crystal of paracetamol, (b) lauric acid, (c) binary mixture of paracetamol with lauric acid, (d) myristic acid, (e) binary mixture of paracetamol with myristic acid, (f) palmitic acid, (g) binary mixture of paracetamol with palmitic acid, (h) stearic acid, (i) binary mixture of paracetamol with stearic acid in 1:1 ratio.

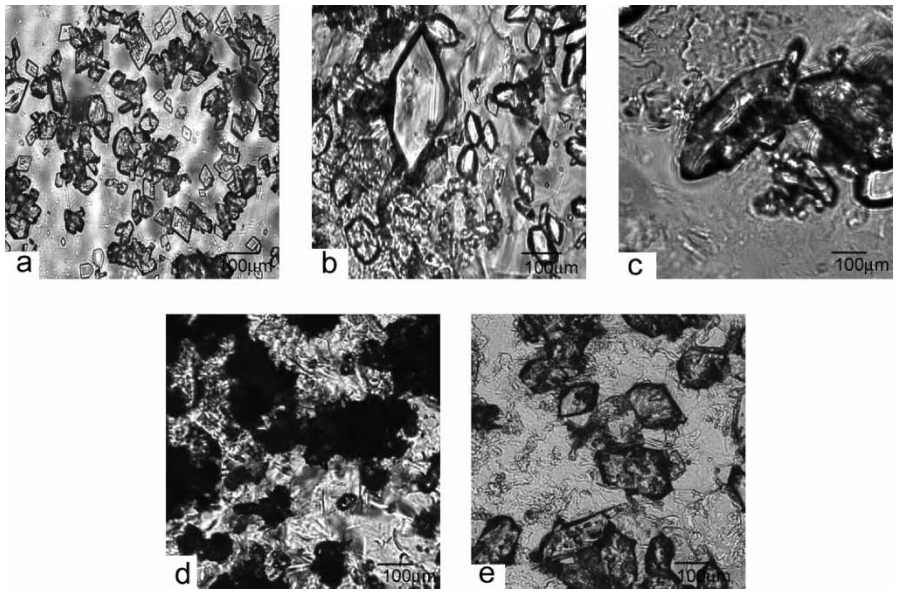

Fig. 4. (a) Microscopic pictures of crystals of paracetamol, (b) binary mixture of paracetamol with lauric acid, (c) with myristic acid, (d) with palmitic acid and, (e) paracetamol with stearic acid.

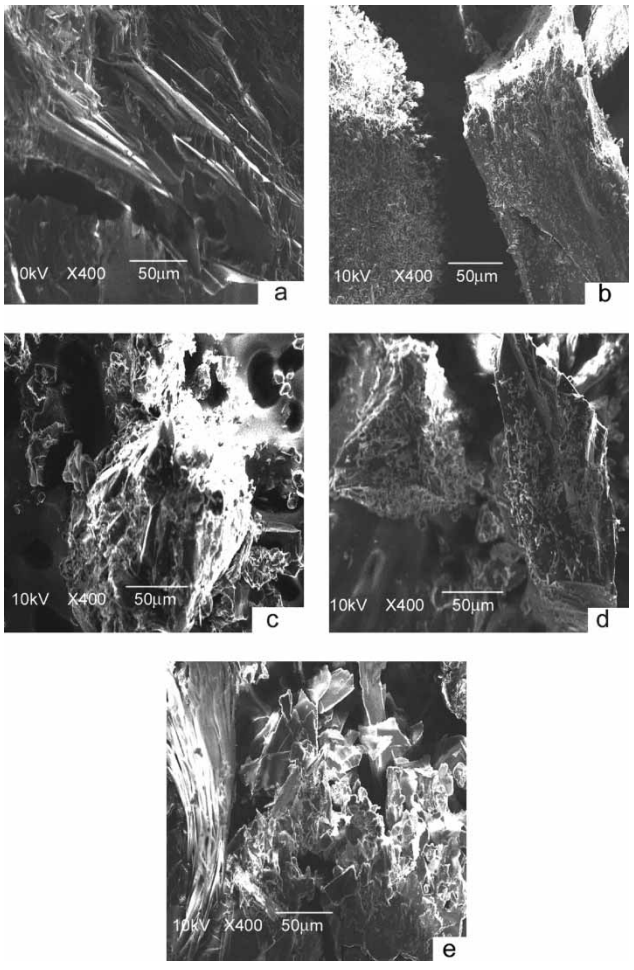

Fig. 5. (a) SEM of crystal of paracetamol, (b) binary mixture of paracetamol with lauric acid, (c) with myristic acid, (d) with palmitic acid and, (e) paracetamol with stearic acid.

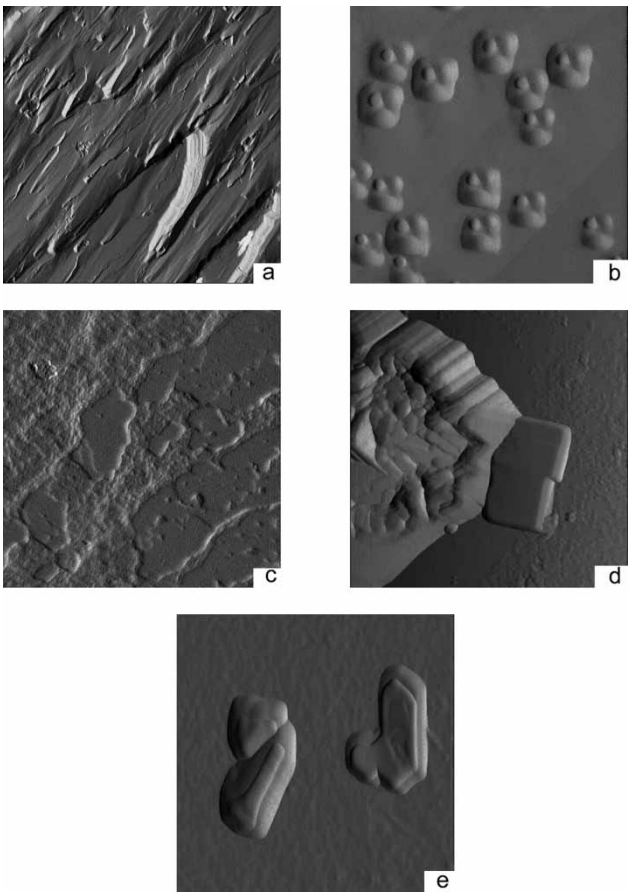

Fig. 6. (a) AFM image of paracetamol 50 µm × 50 µm, (b) binary mixture of paracetamol with lauric acid 1 µm × 1 µm, (c) with myristic acid 2 µm × 2 µm, (d) with palmitic acid 3 µm × 3 µm, and (e) paracetamol with stearic acid 2 µm × 2 µm.

blocking. Blocking is the ability of an adsorbed additive molecule to hinder the subsequent adsorption of further layers of host molecules. As the additive, molecules block different faces of the crystal to varying degrees, the growth rates of some faces will be dramatically altered, while others will remain unchanged (1). Consequently, the morphology of the resulting paracetamol crystal may be altered. The crystals of binary mixture of paracetamol with myristic acid (Figure 6c) showed some clefts and holes on the surface, which might have originated from defects in the crystal surface. A better picture of surface adhesion was observed in the crystal of binary mixture of paracetamol with palmitic acid or stearic acid (Figure 6d,e) in which the surface of crystal of paracetamol was joined with the surface of the fatty acid crystal. The degree of attachment between the two surfaces may be the determining factor in the diffusion or dissolution of paracetamol in the presence of fatty acid or other release modifying substance.

4 Conclusions

In general, DSC studies are considered sufficient enough to detect the interaction between two substances but in this case DSC and XRD both were unable to find out any interaction between the paracetamol and fatty acid because the interaction involving the surface phenomenon between the two substances was more physical and less chemical in nature. The FT-IR study detected some significant changes in the form of change in shape and intensity of carboxylic acid band of fatty acid and amino group of paracetamol. Both substances are known to form hydrogen bonds (1, 20). Therefore, the possibility of hydrogen bonding between the carboxylic acid group and amino group exists, as suggested by FT-IR data. Optical microscopy showed the entrapment of drug crystals in the fatty acid matrix, which was substantiated by SEM pictures. SEM further elucidated the adherence of fatty acid molecules on crystal of paracetamol. The significant role of surface in binding the crystal of paracetamol with the fatty acid was evident by AFM. The self- arrangement of crystals in a particular fashion as in paracetamol with lauric acid as a triad is interesting. The DSC profile of this mixture indicated the occurrence of some polymorphic transition of paracetamol, however, this requires further investigation, especially in terms of polarity of drug and fatty acids.

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