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STUDYING THE EFFECT OF DISPERSED DRUG CRYSTAL IN THE ORGANIC PHASE ON THE ENCAPSULATION BY SOLVENT EVAPORATION TECHNIQUE; (2) X-RAY DIFFRACTION AND DSC AS TOOLS TO STUDY THE MICROCAPSULE STRUCTURE IN RELATION TO THE SUGGESTED DIVISION MECHANISM

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ABSTRACT: The method of entrapment of the drug in the microcapsules structure prepared with different theoretical drug content (TDC) and having different particle size ranges were studied using x-ray diffraction and DSC analysis methods. Also, in the light of the analysis methods, a trial to correlate the actual microcapsule structure with the actual drug content (ADC) and the division mechanism suggested by the author was also studied. The results showed that the drug entrapped in more than one form in the microcapsule structure. At the first, the drug entrapped in the microcapsules structure as a solid solution form which is concluded as the result of disappearance of all characteristic peaks of the drug in both x-ray diffraction pattern and DSC. The amount of drug in solid solution form depends on the physico-chemical characters of the drug and the polymer. After that increasing TDC leads to increasing the amount of the drug crystal in the microcapsule structure. Between those two forms another minute form may be formed as a result of increasing TDC or /and certain kind of physic-chemical interaction between the drug and the polymer. The physical interaction between the drug and the polymer could be concluded from x-ray diffraction patterns and DSC but the chemical one needs further explanations using FTIR. The entrapment process of the drug was found to be reflected on the product sphericity. All analysis results supported what is suggested mechanism during microcapsules formation (Division Mechanism) as a result of appearances or disappearances of drug crystals in addition to its effect on actual drug content.

INTRODUCTION: Polymer microspheres are employed to deliver medication in a rate-controlled and sometimes targeted manner. Then the drug is generally released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix.

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The factors affecting the drug release rate revolve around the structure of the matrix where the drug is contained and the chemical properties associated with both the polymer and the drug [1]. Since the rate of drug release is controlled by these two factors, it is important to study the mechanism(s) of drug entrapment in relation to the physico-chemical structure of the microspheres. XRPD, DSC and FTIR scans were directed to inspection of crystallinity properties as well as scrutinizing any possible interaction between the drug and the polymer [2].

DSC can detect phase transitions including the melting of crystalline regions, whereas XRD directly detects the crystallinity properties of the materials. LeCorre *et al* [3] studied the crystallinity of a lipophilic drug in polymer microspheres by DSC and found that the drug is molecularly dispersed inside a polymer matrix and its crystallinity is not observed [3-6]. However, LeCorre *et al* [3] found that the relatively highly loaded drug existed in a particulate dispersion instead of a molecular dispersion and suggested that is due to its lack of solubility in the polymer matrix.

Yuksel *et al* [7] used XRD and DSC to investigate crystallinity and drug-polymer interactions. The physical mixture of drug and polymer exhibited crystallinity; the drug was amorphous after dispersion in the microspheres. Attempts to crystallize the drug inside the microspheres by annealing above the polymer's Tg and by heat–cool cycles were unsuccessful showing clear molecular dispersion of the drug.

The authors also reported that the drug was released more readily from molecular dispersions microsphere system than from a particulate form and concluded that the polymer matrix likely disturbs the drug crystallinety and initiates rate-controlled delivery with higher drug delivery efficiencies. Mura *et al* [8], using x-ray diffraction and DSC to study the drug state in the microspheres and stated that, a very strong reduction in intensity of the drug peak was observed in the case of the theophylline microspheres, suggesting of a marked loss of the crystallinety but not complete drug amorphization in microspheres structure.

Not only the effect of the drug on the polymer studied but also other additives. Yuksela *et al* [9] studied the effect of the plasticizer Triacetin on the DSC of PMMA in the physical mixture and reported that the flash point of triacetin was shifted to a higher temperature while the glass transition peak of PMMA disappeared due to the effect of the plasticizer. Increasing the flash point of triacetin might have resulted from the placement of the molecules of triacetin into the PMMA macromolecules.

At the same time the flash point of triacetin was depressed to a lower temperature due to the presence of indomethacin and sucrose stearate with disappearance of the crystalline melting peak of indomethacin. The same results are obtained from DSC of the microspheres. The Tg of PMMA was markedly lower due to the plasticizer, triacetin, and to some extent, indomethacin and sucrose stearate. These substances reduced the secondary intermolecular forces between the polymer chains by separating them, and hence, the mobility of the chains increased.

The drug molecules are uniformly dispersed between the macromolecular chains of the polymer within microspheres. Also as a general conclusion, Pegnatello *et al* [10] studied the dispersion of Diflunisal in Eudragit RS100 and RL100 using x-ray diffraction and DSC and stated that, drug signals are totally disappeared in the system with higher polymer ratio and appeared again when the drug concentration is over its solubility in the polymer.

The aim of this work is a trying to study the method of entrapment of the drug in the microcapsules structure prepared with different theoretical drug content and having different particle size range using x-ray diffraction and DSC analysis methods. Also, in the light of the analysis methods, a trial is conducted to correlate the actual microcapsule structure with the actual drug content (ADC) based on the division mechanism suggested by the author.

MATERIALS AND METHODS:

Materials: Acetylsalicylic acid crystals (ADWIC, Egypt), Eudragit RS100 (Rhom Pharma, Germany), Gelatin (Pharma Production, Austria). All other chemicals were of analytical grades.

Equipment: Differential scanning calorimeter (Perken-Elemer DSC4, USA), Mechanical stirrer (Heidolph,RZR-2000,Germany), powder x-ray diffractometer (Phillips PW 1840, Germany), Vibrating set of sieves (VEB / letalweberei Neustadt, Orla, Germany).

Methods:

1. **Preparation of microcapsules**: Microcapsules were prepared by solvent evaporation technique. The aqueous solution was 200 ml of 0.1N HC1 containing 0.5 gm of gelatin as an anti-aggregating agent. The organic phase was composed of a constant volume of dichloromethane (20 ml) containing the required weight of Eudragit RS100. The required weight of drug was dispersed with stirring in the organic phase until a homogeneous dispersion was obtained. Then, the prepared homogeneous organic phase was poured onto the stirred aqueous phase at 500 rpm. Stirring was continued until complete evaporation of the dichloromethane. The microcapsules were collected by filtration and air dried. In every case, the total amount of polymer and drug was 10 gm. Microcapsules containing 20%, 33.33%, 50%, 66.66% and 80% theoretical drug content (TDC) were prepared.

2. **Product size analysis**: The mean particle sizes of the microspheres were determined by sieving method. A definite weight of Eudragit RS100 microspheres containing drug was placed on a set of standard sieves and shaken for 10min using mechanical sieve shaker. The resulting fractions remaining on the sieves were weighed to determine the particle size distribution.

3. **Powder x-ray diffraction analysis:** X-ray diffraction profile of the different products was determined using powder x-ray diffractometer. The measurement conditions were CuKά; filter Ni; Voltage 40kV; current 20 mA; slit 0.1 mm; scanning speed 20 mm^{-1} counts per second were related to a step scan through the peak at this speed corrected for background.

4. **Differential Scanning Calorimetry:** Differential scanning analysis of Eudragit RS100, Aspirin crystal, and some Eudragit RS100 microcapsules containing aspirin prepared with different TDC and has different particle size ranges were carried out to evaluate the internal structure of microspheres. The heating cycle ranged from 20 to 240°C.

RESULTS AND DISCUSSION: XRPD, DSC and FTIR scans were directed to inspect of crystallinity properties as well as scrutinizing any possible interaction between the drug and the polymer [2]. X-ray diffraction pattern of a pure substance is like a fingerprint of the substance. It is the method that ideally suited for characterization and identification of polycrystalline phases [11] and also is a powerful tool to identify any changes in the crystallinity of drug [12].

Figure 1 showed the presence of numerous distinct peaks in the x-ray diffraction spectrum of Aspirin indicates the crystallinity of the drug [13]. Eudragit RS100 is amorphous in nature due to the absence of complete stereo regularity and presence of bulky side groups[13]. Comparing the x-ray diffraction pattern of Eudragit RS100 microcapsules prepared on using 20% TDC and has particle size range of 315-400µm with that of pure aspirin crystal, it can be noticed that, all characteristic peaks of the drug are completely disappeared [14-17] although the scan pattern is completely parallel to that of pure aspirin with some noise in the same places of pure drug peaks. Theses noises are completely disappeared in the x-ray pattern of microcapsules prepared on using 20% TDC with the larger particle size range of 400-500 µm which looks like a base line. It was reported that the x-ray diffraction studies revealed that the sorbed salicylic acid was in solution with the polymer (Eudragit RS100) rather than present as dispersed crystalline material [18].

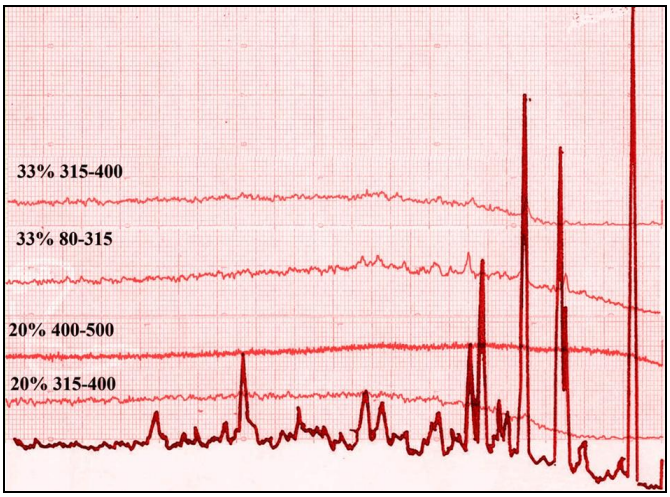

FIGURE 1: X-RAY DIFFRACTION OF EUDRAGIT RS100 MICROCAPSULES PREPARED ON USING 20% AND 33.33% TDC HAVING DIFFERENT PARTICLE SIZE RANGES

Also from figure (1), the shape and size of the noises increased in the x-ray pattern of microcapsules prepared on using 33.33% TDC with small particle size range 80-315µm in addition to its parallel form to the x-ray pattern of the pure drug.

Not only that but also it can be noticed the presences of some small intensity peaks in the same position of the characteristic peaks of the pure drug. Again, the size and shape of noises decreased in case of using larger particle size range (315-400µm) prepared with the same TDC (33.33%).

It was reported that Aspirin-fulvic complex prepared by solvent evaporation in molar ratio of 1:0.5 exhibited a partially crystalline nature as an evident by the lack of some characteristic peaks of Aspirin and the rest with reduced intensity. Complex of drug: polymer molar ratio 1:1 and 1:2 exhibited amorphous nature because it does not show any intense peak of the drug [19]. Also Semalty *et al* [20] found that the x-ray diffraction pattern of Aspirin complex revealed a broad peak similar to the PC indicating that Aspirin was in amorphous form in phospholipid which also confirmed the formation of a phospholipid complex.

Loveymi *et al* [21] stated that when the nanoparticles were prepared with different polymer/drug ratios it is clear that the nanoparticles with lower polymer concentration showed similar peaks as the blank nanoparticles. At higher concentration of the drug, some drug distinguish peaks of are detectable with very low intensity due to the presence of lower concentration of the drug in the sample in comparison with the pure drug sample.

Suryanrayanan *et al* [22] reported that, there are two physical possibilities of the drug in the ointment base which are (A) drug is dissolved in the base and (B) a fraction of the drug is dissolved and the rest is dispersed in the matrix, then x-ray diffraction is potentially useful to identify the drug in the formulation. The author also reported that identification of chlordiazepoxide in a mixture with microcrystalline cellulose was no problem so long as its weight fraction was > 0.1. When the drug weight fraction was decreased to 0.05, its presence was not readily discernible.

The pattern subtraction technique permitted ready identification of the drug. From above, it can be concluded that, the complete disappearance of the characteristic peaks of the drug indicates the change of the drug from the crystal form as a pure substance to amorphous one in the microcapsule structure [14-17]. The presence of noise in the x-ray pattern in case of the smaller particle size range, in addition to its parallel form to the scan pattern of the pure drug, may be suggesting the presence of another form of drug which may be a very minute crystal form beside the amorphous structure. This suggested form is supported with what stated before about the presence of small peaks in the x-ray pattern of microcapsules prepared on using 33%TDC.

Increase the noise shape and intensity in the x-ray diffraction of the microcapsules prepared on using 33.33% TDC than that on using 20% TDC indicates that after saturation of polymer with the drug molecules (solid solution form) a minute drug crystal started to appear. Pignatell *et al* [10] stated that the drug signals totally disappeared in the system with a higher polymer ratio and appeared again when the drug concentration over the drug solubility in the polymer.

The base line form of x-ray pattern of microcapsules prepared on using 20% TDC with larger particle size range 400-500µm indicates the presence of the drug mainly in a pure amorphous form. Since the intensity and shape of the noise of x-ray pattern of smaller particle size range is higher than that of the bigger particle size one, it can be concluded that, the smaller particle size range of the same product have higher drug content than that of the bigger particle size range. This theoretical explanation which based on the result of x-ray diffraction pattern of different particle size ranges of the product prepared on using 20% TDC was found practically on determination of the actual drug content [23].

The above findings and their explanations which based on the x-ray diffraction analysis and determination of drug content are again completely in agreement with what is suggested by the author which is (Division mechanism) [23]. Division mechanism depends on two forces.

The first one (which enhances the division process) is the solid dispersed drug particles in the emulsified droplet in addition to the effect of centrifugal force of stirring on the emulsified droplet. The second one (which is opposing the division force) is due to the viscosity of the emulsified droplet which depends on the concentration of the polymer.

Logically fact is the presence of solid particles in the emulsified droplet before the microcapsule structure formation and as a result of their weight and centrifugal force will enhance the division of the solid particles with a film of organic solvent containing dissolved polymer and also dissolved drug. This leads to formation of smaller particle size range microcapsules with higher drug content and also higher particle size range with lower drug content as a result of inability of the second divided bigger emulsified droplet to division due to the high viscosity of the organic phase (80% polymer). The amount of drug dissolved in the organic solvent after microcapsule formation will be (a part or all) the solid solution form of the drug in the microcapsule structure. The solid solution form will have no effect in the x ray diffraction pattern. The other forms of the drug could be expected to change in the x-ray pattern in direction to the pure drug pattern depending on its concentration as will see on studying the x-ray pattern of products prepared on using higher TDC.

Figure 2 shows the most peaks of x-ray diffraction pattern of pure aspirin in the x-ray diffraction pattern of the microcapsules prepared on using 50% TDC with lower intensity. As a result it could be concluded that the presence of drug crystal in the microcapsules structure. Also it could be noticed that, the intensity of the peaks of x-ray diffraction pattern of the microcapsules with larger particle size range 500-800µm is clearly higher than that of smaller particle size range (315-400 µm) of the same product prepared on using 50%TDC. Accordingly, it could be concluded that the amount of the crystal form of the drug in the larger particle size range is more than that in case of smaller one which is the opposite of that found in case of using 20% TDC. This is also in agreement with what is suggested division mechanism because increase TDC lead to enhance the division of the emulsified droplet as stated before with the higher concentration of crystalline drug which led to larger particle size range. Since both particle size ranges have the same actual drug content [23], it could be suppose that, that is due to the presence of more drug in the amorphous and minute forms in the smaller particle size range of the same product.

The same finding can be also noticed from the two size ranges of the product prepared on using 33.33%TDC.

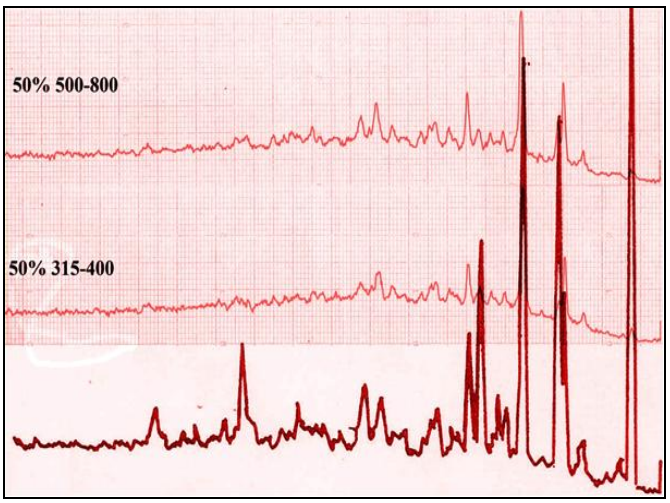

FIGURE 2: X-RAY DIFFRACTION OF EUDRAGIT RS100 MICROCAPSULES PREPARED ON USING 50% TDC WITH DIFFERENT PARTICLE SIZE RANGES.

Also from figure 2, it can be noticed that although all characteristic peaks of the drug can be clearly noticed, it can also notice the difference in the intensity of some peaks i.e. some peaks in drug pattern have higher intensity showed in that of microcapsules with lower intensity and vice versa. This indicated the presence of another form of drug crystal which similar to the pure drug with some physical difference as a result of certain interaction.

The x-ray diffraction pattern of the microcapsules prepared on using 66.66% TDC (**figure 3**) shows also all characteristic peaks of x-ray diffraction pattern of pure aspirin crystal. The intensity of the peaks of larger particle size in the x-ray diffraction pattern is clearly higher than that of smaller one. Since there is also a big difference in the actual drug content [23], it can be concluded that, this is due to the difference in the amount of drug crystal form in the microcapsule structure.

This finding could be also more clearly noticed from the x-ray diffraction pattern of microcapsules prepared on using 80% TDC (**figure 4**). Again the above result supported what is suggested before about the division mechanism and its role in the microcapsule formation. This is because increase TDC will enhance the division process with formation of large particle size containing high amount of drug crystal which reflected on the x-ray diffraction pattern.

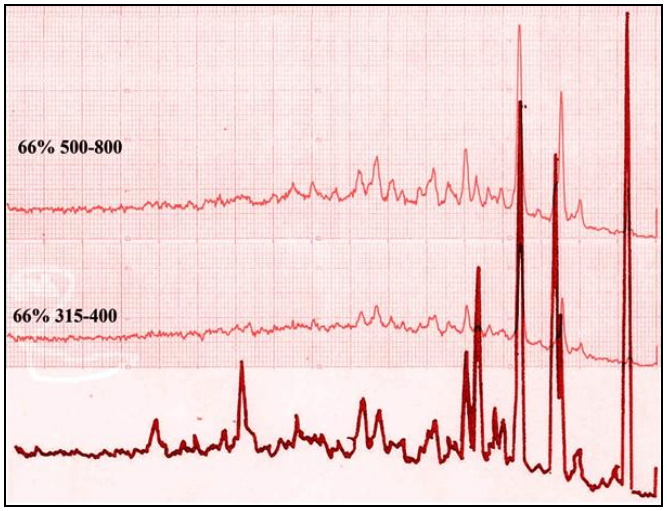

FIGURE 3: X-RAY DIFFRACTION OF EUDRAGIT RS100 MICROCAPSULES PREPARED ON USING 66.66% TDC WITH DIFFERENT PARTICLE SIZE RANGE.

Also it could be noticed the difference in the intensity of some peaks i.e. some peaks in drug pattern have higher intensity, showed in that of microcapsules with lower intensity and vice versa. This is again support the hypothesis of the presence of another form of drug crystal which similar to the pure drug with some physical difference as a result of certain interaction.

As a support for the above finding, explanation, comparison and studying the effect of increase the TDC on the encapsulation mechanism of the drug, the x-ray diffraction pattern of same particle size range of different microcapsules prepared by using different TDC was collected in **figure 5**. From the figure it can be noticed that the appearance or disappearance of the drug characteristic peaks depend on the using TDC. Also, increasing the appearance of the characteristic peaks of the drug and their intensities increased with increasing the TDC.

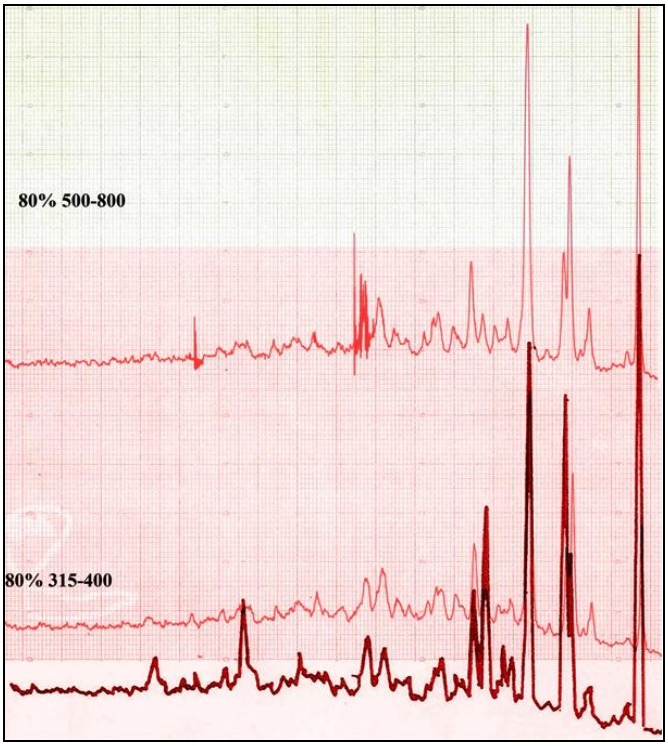

FIGURE 4: X-RAY DIFFRACTION OF EUDRAGIT RS100 MICROCAPSULES PREPARED ON USING 80% TDC WITH DIFFERENT PARTICLE SIZE RANGE

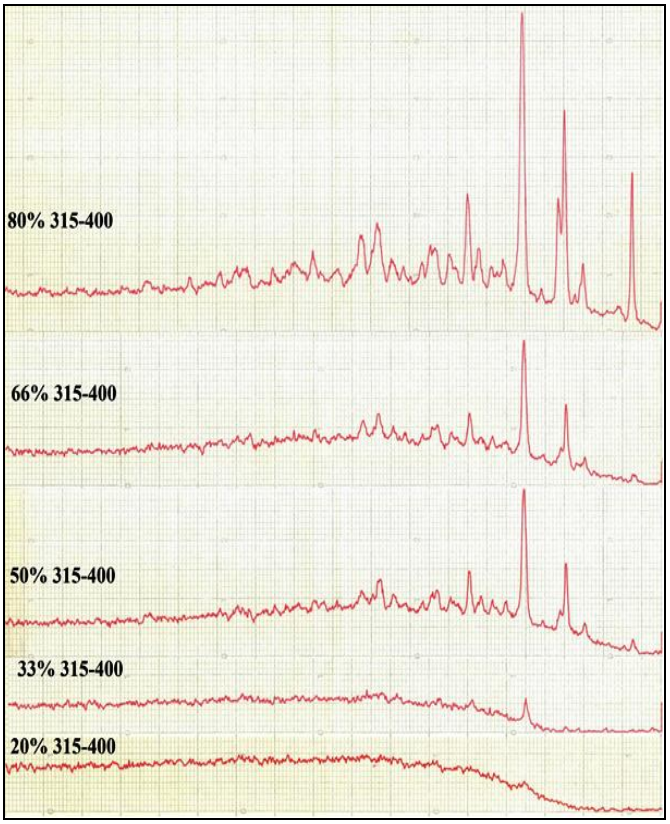

FIGURE 5: X-RAY DIFFRACTION OF EUDRAGIT RS100 MICROCAPSULES PREPARED ON USING DIFFERENT TDC WITH THE SAME PARTICLE SIZE RANGE

Accordingly it can be concluded that after the amount of drug entrapped in solid solution form, which depends on the physic-chemical characters of the drug and the polymer, increasing TDC led to increase the amount of the drug crystal in the microcapsule structure. The entrapment process started with solid solution form then minute structure and ended with solid dispersion crystal mechanism which will be reflected on the product spherecity morphology [23] and could be also expect its effect on drug release.

It was reported that x-ray diffractogram of the solid dispersion confirmed the existence of the drug probably in the microcrystalline form in the polymer matrix. Microcrystallization of NSAIDs from the Eudragit matrices when the drug concentration exceeded its solubility in the polymer matrix has been cited in literature [24, 25]. The DSC and PXRD studies collectively indicated that a portion of the drug incorporated as solid-solid solution in the polymer matrix whereas the excess drug crystallized in the microcrystalline form from the polymeric matrices [26].

Accordingly, the thermal behavior of the drug in the microcapsule structure was studied as a tool to elucidate the drug entrapment mechanism. The peak shape and size of DSC scan are useful in determining the crystallinity of the drug and the carrier. Any sudden or forceful change in the thermal behavior of the drug or polymer may indicate a possible drug-polymer interaction [27, 28]. DSC scan of Eudragirt RS100, Aspirin and selected microcapsule containing drug are represented in **figure 6**.

Figure 6 shows that Aspirin exhibits a sharp endotherm melting peak at an onset temperature 125°C, ended at 155°C and a peak temperature at 139°C. Another small broad peak was present with an onset temperature of 163°C and a peak temperature of 210°C which may represent salicylic acid as product from the decomposition of aspirin. DSC scan of Eudragit RS100 showed the Tg of the polymer at 59.9°C. Also there is another broad between 135°C and 160°C. The third one is another broad between 180°C and 230°C centered at 195°C [29].

The nature of the second and the third phase transition is not clear, but dissociation of intermolecular hydrogen bonds and anhydride formation has been suggested [30]. From above it is clear the crystallinety of the pure drug and the amorphous form of the pure polymer [31].

DSC scan of Aspirin-Eudragit RS100 microcapsules prepared by using 20%TDC with Particle size range 80-315 µm showed completely disappearance of the melting endothermic peak of the drug and disturbance in the characteristic peaks of the polymer.

The Tg of the polymer is represented with a wide broad event fall and the other broad between 180°C and 230°C is completely disappeared. Disappearance of the melting endothermic peak of the drug indicates the change of the drug from crystal form to amorphous one [13]. This result is in agreement with the result of x-ray diffraction. It was reported that, at the glass transition, the polymer undergoes changes in volume and expansion, heat flow and heat capacity [32]. This may be led to solubility of the drug molecules in the polymer matrix (solid solution form) which led to disappearance of the drug crystal and change in the Tg of the polymer [13, 33-35]. Also as a result, the dissociation of intermolecular hydrogen bonds and anhydride formation would be also stopped [7].

DSC of the microcapsules prepared on using 33.33% TDC and has the same size range showed the reappearance of a broad with small intensity in the same position of the endothermic melting peak of the drug. The onset, ended and intensity of the broad increased with increasing of TDC used till reached to the maximum on using 80% TDC which looks like a huge peak.

Also it can be notice decreasing the onset, ended and intensity of the broad event fall of the Tg of the polymer with increasing TDC till became minimum or disappeared on using 80%TDS. The effect is accompanied with disappearance of the other broad between 180°C and 230°C centered at 195°C of the polymer which reappeared again on using 80%TDCas a combination of the two broads of the drug and the polymer.

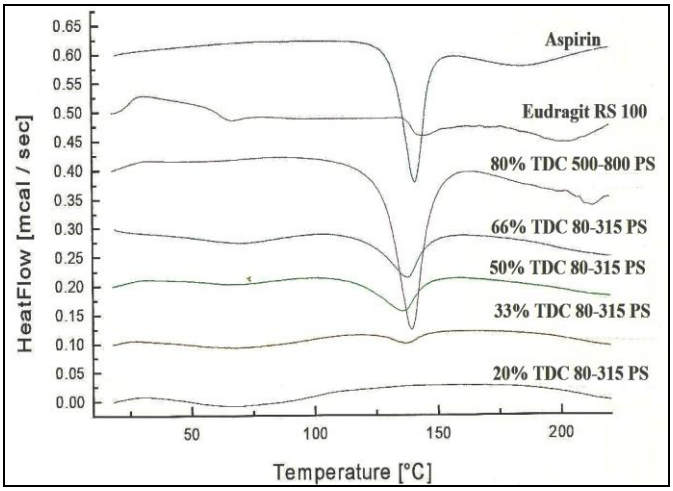

FIGURE 6: DSC SCANNING OF SOME EUDRAGIT RS100 MICROCAPSULES CONTAINING DIFFERENT CONCENTRATIONS OF ASPIRIN

Ranpise et al [36] , reported that, DSC scan showed that, there was no significant change in the position of peak of the drug in the spherical agglomerates of Aspirin but there is change in the relative intensities of the peak of the drug indicating decreased crystallinety. At the same time Shivakumar et al [26] , reported that the drug endothermic peak was suppressed in the thermogram of the solid dispersion suggesting that the drug was able to dissolve partially in the polymer to form a solid-solid solution. The appearance of low intensity endothermic peak also indicated some of the drug still managed to crystallize out from the saturated Eudragit matrices during evaporation. Also, it was reported that, the appearance of the endothermic peak of the drug at lowered position compared to the untreated drug and lost its distinct sharpness appearance suggested the presence of an interaction between the drug and the polymers used in cast film preparation [13] or microspheres [37].

Anwer *et al* [19] stated that the appearance or disappearance of the melting endothermic peak of the drug depend on the drug /polymer ratio. This is may be as a result of the insufficient quantity of fulvic acid used in ratio 1:1 and complete disappearance on using 1:2 drug/polymer ratios. Looking in earlier literature, it was reported that, the solubility of the salicylic acid and chlorpheniramine maleate in the polymeric films of Eudragit RS100 was determined to be greater than 10% w/w using DSC, SEM and powder x-ray diffraction.

At a 10% drug loading, the drug molecules were dissolved in the polymer and the matrix existed as a solid solution [18]. Also it was found that, the physical state of the Aspirin incorporated into the microspheres of Eudragit RS100, as confirmed by SEM and thermal analysis, was amorphous in nature until a drug loading of 24% was reached [38].

From above it can be concluded that, the presence of a broad in the same position of the endothermic melting peak of the drug indicates the presence of a drug in a crystal form in the microcapsule structure. Increasing the intensity of the peak with increasing TDC indicates the increasing of the amount of drug crystal in the microcapsule structure.

The shifting of the onset, ended and melting point with increasing TDC indicates some kind of interaction between the drug and the polymer. Also decreasing the Tg of the polymer with increasing TDC of the drug indicates increasing the amount of the drug in solid solution form with increasing TDC used. Since the same volume of the organic phase used it can be suggested that the concentration of the polymer is the main factor controlling the solid solution entrapment form of the drug in the polymer especially if we noticed the limit solubility of aspirin in the organic phase. That is may be due to the polymer solubility form in the organic phase or its lower concentration increase the amount of the drug dissolved in organic phase which will be encapsulated as a solid solution form.

All of the above results are completely in agreement with what stated before as a results of x-ray diffraction study. To explain the finding of there are some kind of interaction between the drug and the polymer in the microcapsule structure, FTIR analysis of the products was carried out which will be the subject of the next article.

CONCULSION: X-ray diffraction and DSC are good tools to study the role of drug dispersion in the organic phase on the microcapsule structure. At the first, the drug entrapped as a solid solution form which is concluded as the result of disappearance of all characteristic peaks of the drug in both x-ray diffraction pattern and DSC. The amount of drug in solid solution form depends on the physico-chemical characters of the drug and the polymer.

After that increasing TDC leads to increasing the amount of the drug crystal in the microcapsule structure. Between those two forms another minute form may be formed as a result of increasing TDC or /and certain kind of physic-chemical interaction between the drug and the polymer.

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