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Original Article

Impact of Particles Size on Solubility Limits and 3D-AFM-Nano-Structural Features of Cefixime Drug

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ABSTRACT

Objective: The present investigations are focusing to give informative data on the effect of particles size on the solubility limits of cefixime antibiotic.
Methods: 3D-AFM, SEM and XRD will be applied to monitoring the effect of grain size on solubility limits and to introduce complete image with analysis for micro-structural features of cefixime drug.
Results: Solubility of cefixime drug was grain size dependent and 3D-AFM features of cefixime play important role in solubility limits besides solvent type .Obtained results confirmed that, there are strong correlation between surface area and solubility limits of cefixime.
Conclusion: Hyperfine nano-structural features for cefixime have vital role in its solubility limits and answer the question why this hetero-molecule is suitable structurally to their function as antibacterial drug.

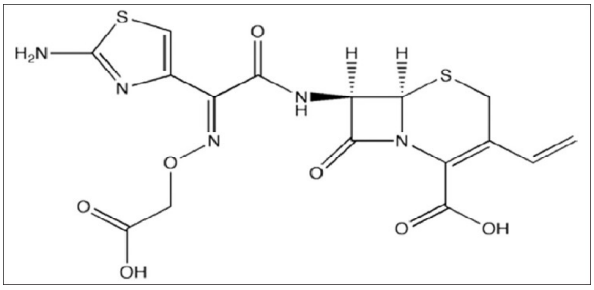
Keywords: 3D-AFM; XRD; Cefixime; Microstructure; Particle Size; Antibacterial; Solubility Limits.

INTRODUCTION

Cefixime is one of most common applicable drug as antibiotic due to its strong efficiency towards most of viruses specially those of gram negative[1]. The present investigations are handled the point of view why this hetero-molecule is structurally suitable to their functions as antibiotic and discuss deeply role of microstructure features in salvation and solubility limits. It is well known that cefixime is a synthetic

fluoroquinolone antibiotic. It is prescribed for kinds of infections of reproductive organs.[2]

Determination of cefixime was reported in literature survey by many of different analytical techniques not only by UV,HPLC[3-9], but also flow injection analysis[10] and HPTLC[11].



Cefixime is (6*R*,7*R*)-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(carbomethoxyimino) acetyl]amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Cefixime is a β-lactam third-generation antibiotic applied in treatment of various infections caused by gram negative bacteria like Haemophilius influenzae, Moraxella catarrhalis, Escherichia coli, Klebsiella spp. Literature survey revealed HPTLC determination of Cefixime, Reversed phase HPLC determination of Cefixime are the few methods available for it's estimation[13-15]. It is well known that cefixime is poorly soluble in water. Special techniques are required to solubilize poorly water-soluble drugs[16,17]. Several methods have been reported in the literature to enhance the aqueous solubilites of poorly water-soluble drugs[18].

Hydrotropic solubilization is the technique applicable to promote the solubility limits of poorly water-soluble drug as cefixime. The general idea of this technique is addition of large amount of second solute results in an increase in aqueous solubility of another solute.

Concentrated aqueous hydrotropic solutions such as sodium benzoate, niacinamide, sodium citrate, sodium glycinate and urea were reported to enhance aqueous solubility of insoluble and slightly soluble drugs. Hydrotropic solutions can be employed to replace organic solvents employed in analysis of poorly water-soluble drugs.

The primary objective of many investigations[19-23] were to employ the solubilising agent in the tablet formulation and in analytical stock solutions to a poorly water-soluble drug, Cefixime, from its dosage form, is well dissolved precluding the use of costlier organic solvent.

EXPERIMENTAL

Sample Source

A commercial structurally well confirmed sample of highly pure solid-phase Cefixime which is a β-lactam third-generation antibiotic used in treatment of various infections was supplied from EDWIC company of pharmaceutics (EGYPT) and applied as model for testing micro-structural features and surface topology of Cefixime which is a β-lactam third-generation antibiotic.

Particle Size Fractionation and Solubility Tests

A commercial solid sample of cefixime drug which structurally and spectrophotometrically well confirmed was ground for two hrs in a gate mortar then sieved by molecular sieving into three types of particle size fraction 1st one $\leq$ 100µm ,2nd $\leq$ 50 µm and 3rd fraction $\leq$ 25 µm. The solubility tests were performed applying 10 mg for each fraction type and 10 ml ether as organic solvent turbidity method was applied to reach to solubility limits.

Nano-/Micro-Structural Investigations

Scanning electron microscopy (SEM): measurements were carried out along ab-plane using a small amount of sample powder by using a computerized SEM camera with elemental analyzer unit Shimadzu (Japan).Atomic force microscopy (AFM): High-resolution Atomic Force microscopy (AFM) is used for testing morphological features and topological map (Veeco-di Innova Model-2009-AFM-USA).The applied mode was tapping non-contacting mode. For accurate mapping of the surface topology AFM-raw data were forwarded to the Origin-Lab version 6-USA program to visualize more accurate three dimension surface of the sample under investigation Cefixime which is a β-lactam third-generation antibiotic .

This process is new trend to get high resolution 3D-mapped surface for very small area ~ 0.1x0.1 μm^2.

FT-Infrared Spectroscopy

The infrared spectra of the solid products obtained were recorded from KBr discs using a Shimadzu FT-IR Spectrophotometer in the range from 400 to 4000 cm^{-1}.

RESULTS & DISCUSSIONS

Structure Identification

Cefixime which is a β-lactam third-generation antibiotic was examined and detected well structurally and spectrophotometrically by both of X-ray diffractionFig.1a and measuring infrared absorption spectrum in the whole range as shown in Fig.1b .The marked red cycles refer to different kind of functional group that present in the structure moiety of cefixime namely –COOH ,NH2- ,-OH ,-NH and C=O respectively as it clear in Fig.1b [3,4,5 and 6] .

Fig. 1a display x-ray diffraction pattern of poly crystalline cefixime phase and red circles refer to pure tri-clinic crystal phase of cefixime drug.

As it clear in Fig.1b the broad band ~ lies in the region 3600-3750 cm-1 may be attributable to the overlapping and intercoupling of groups such as N=C and S=C with surrounding function groups (interference coupling groups effects).

Nano- and Micro-structural features of cefixime were investigated carefully via two different technique 1st scanning electron microscopy (SEM) Fig.2a,b and atomic force microscope (AFM) Fig.3A,B .

As antibacterial drug cefixime interfacial properties is important to evaluate its strength as reactive surface sensitive to bacteria. Fig. 2a,b shows SE-micrograph captured for cefixime with 2 and 5 μm magnification factors with grain size averaged in between 0.25-2.5μm which confirm that the cefixime drug has wide range fractionation of particle and grains which are experimental condition dependent[12,13]. Black and white arrows in Fig. 2a,b refer to variation of estimated grain size that confirm the experimental conditions play an important role and control in the synthesized grain size.

Fig. 3A: describes 3D-image of cefixime drug surface topology with 0.2x0.2μm scanned area applying non-contact tapping mode for sensitive samples .One can notify that the arrays are repeated regularly without violation on the whole scanned area 0.2x0.2μm only depth pattern which appeared at ~ 0.035 μm does not repeated in regular manner on the scanned area.

Fig. 3B show TM-deflection centers which can be benefit to understand conductivity behavior of cefixime drug or mapping charts of the surface topology . It is clear that back dots could be represent pinning centers of the material bulk and consequently reactivity of the surface is function and dependent on theses pinning centers numbers.

For accurate mapping of the surface topology AFM-raw data were forwarded to the Origin-Lab version 6-USA program to visualize more accurate three dimension surface of the sample under investigation Cefixime which is a β-lactam third-generation antibiotic see Fig. 4.

As it clear in Fig.4 which represent very narrow 3D-scanned area with dimensional 0.2x0.2x0.2 µm. The accurate analysis of this figure one can conclude the following facts; 1st the maximum heights gradient ranged in between (1.065 – 1.10 µm) orange-red zones, 2nd the minimum depth gradient is ranged in between (0.96-0.995 µm) pale –dark blue zones .3rd higher than 50 % of the scanned area moderate in heights and ranged in between 0.99-1.048 µm.

Those represented by blue-green colors .These accurate investigations interpret why cefixime drug has huge unique surface area with different gradients on the surface topology in contrast with others drugs.

Solubility Limits and Particle Size Effect

The solubility tests were performed applying 10 mg highly pure solute cefixime per 10 ml ether as organic solvent turbidity method was applied to reach to solubility limits. It was found that the less particle size the better solubility limits as shown in Fig. 5.

One can conclude that the solubility limits increase due to two effective factors 1st one is exposure surface area and 2nd factor is interaction between solid solute surface and solvent molecule (interaction during salvation process to produce solubility) and of course strength of interaction is surface area (particle size) dependent .

CONCLUSION

In conclusion The smallest particle size the higher surface area and consequently maximum solubility limits and generally cefixine antibiotic drug has specific nano-structured features with unique huge reactive surface topology qualify it to be one of the most strongest antibiotic families .

Conflict Interest

Author declares that there is no any kind of conflict of interest, and this article is funded by author himself.

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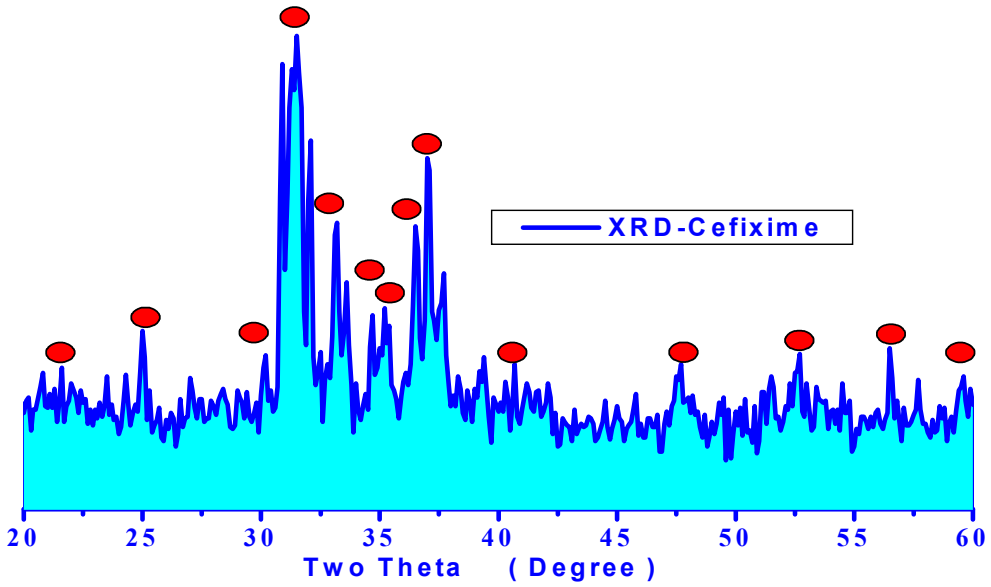

Figure No. 1a: XRD-profile for poly-crystalline Cefixime.

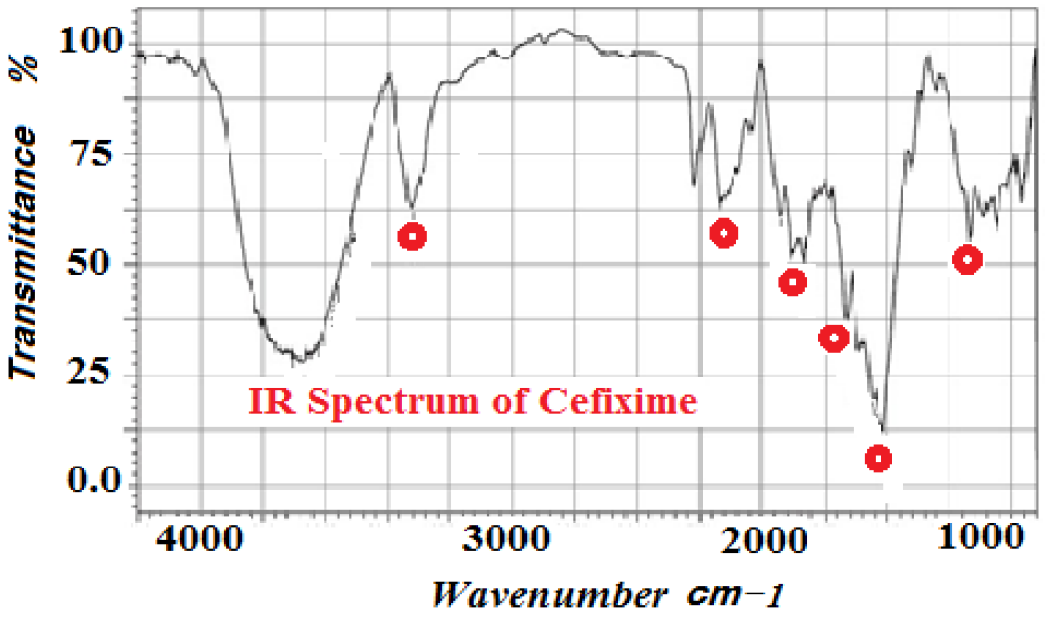

Figure No. 1b: FT-IR spectrum of Cefixime antibiotic drug powder.

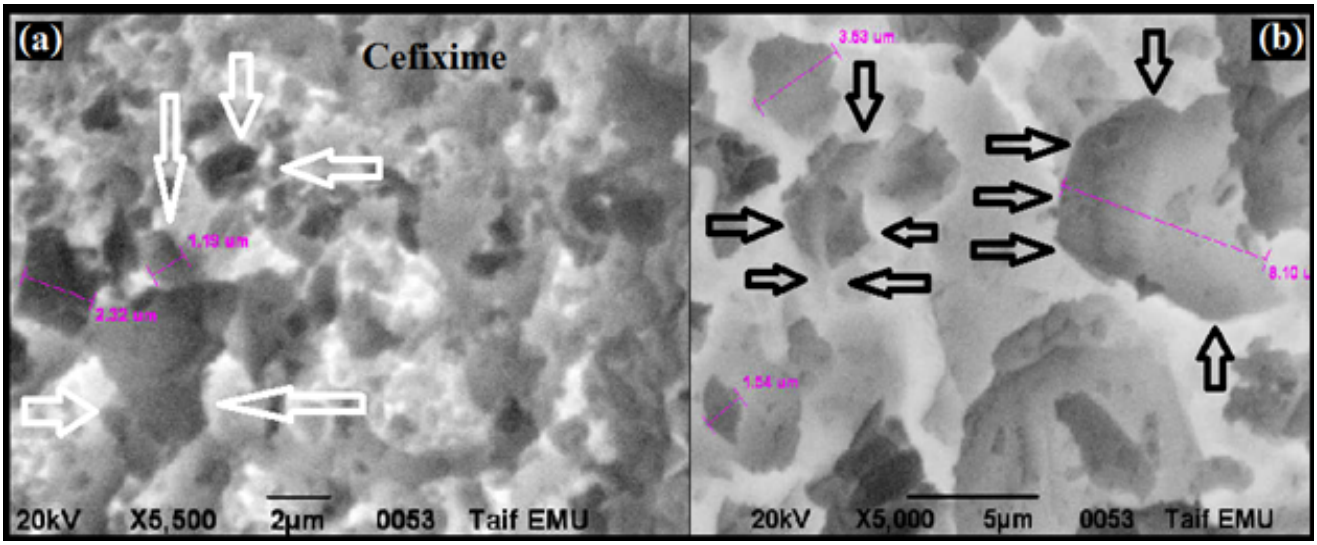

Figure No. 2a,b: SE-micrograph captured for cefixime with 2 and 5 µm magnification factors.

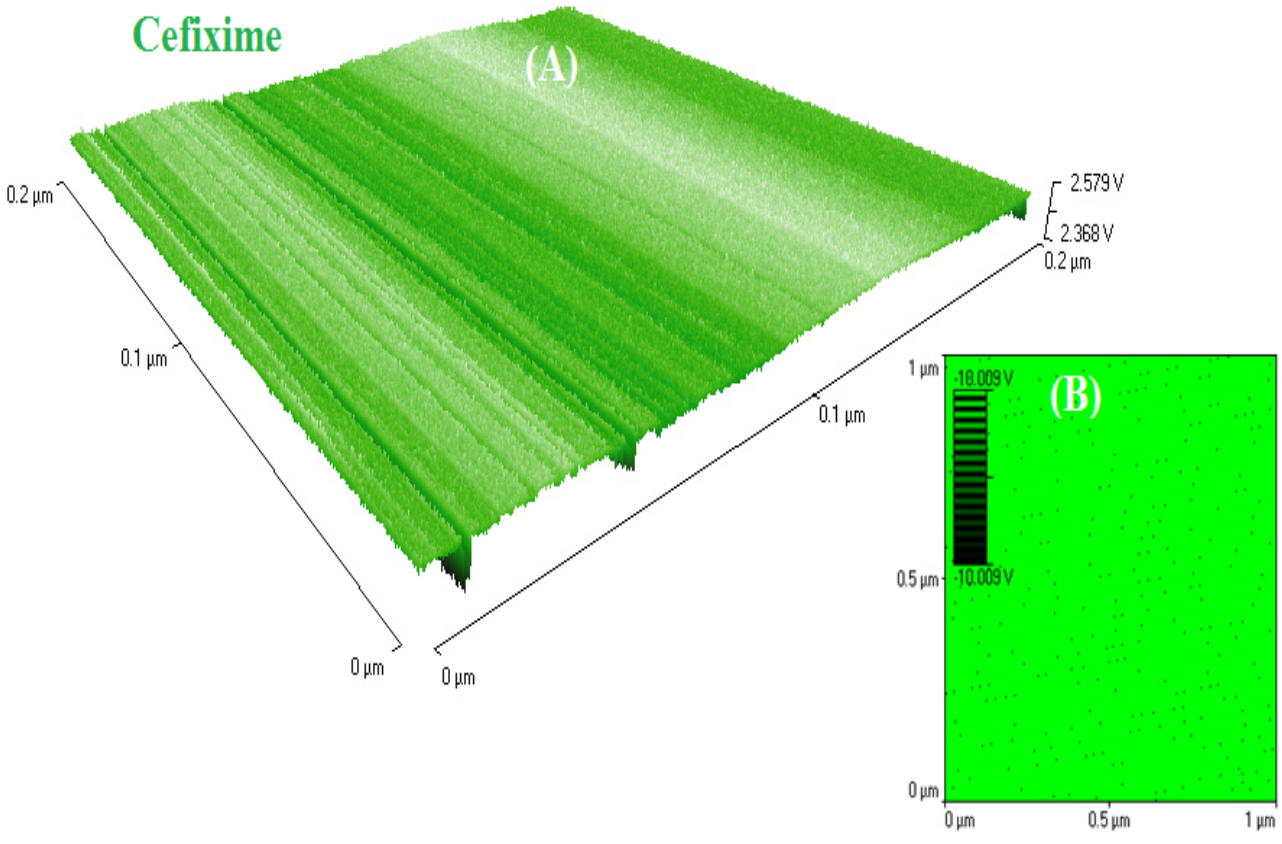

Figure No. 3a,b: 3D-AFM nano-graph and TM-deflection centers of Cefixime drug.

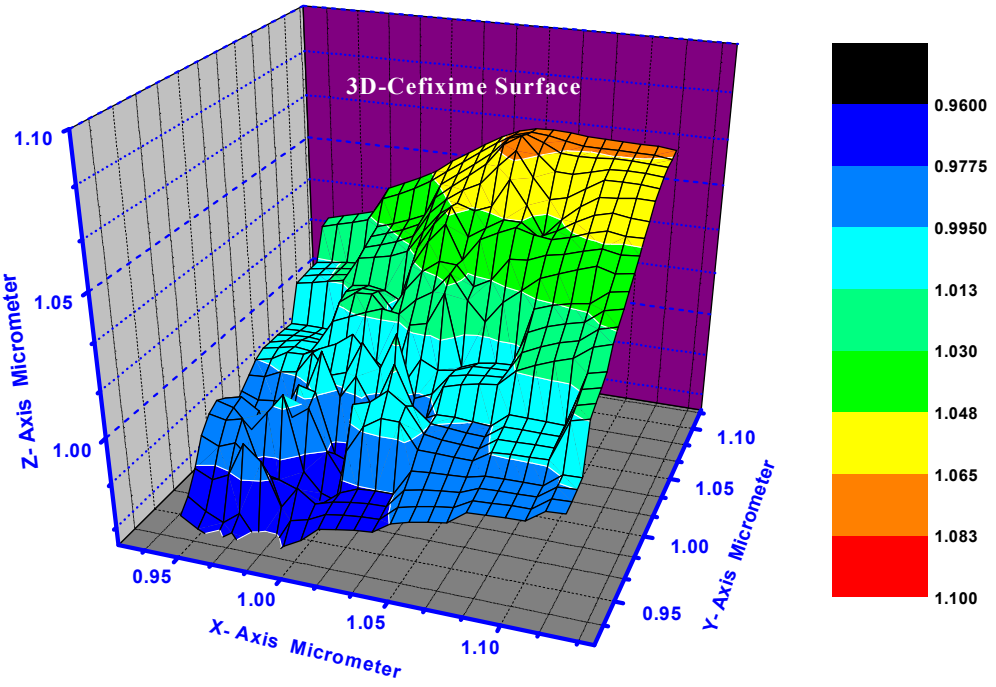

Figure No. 4: 3D-visuallized AFM-image for Cefixime Drug.

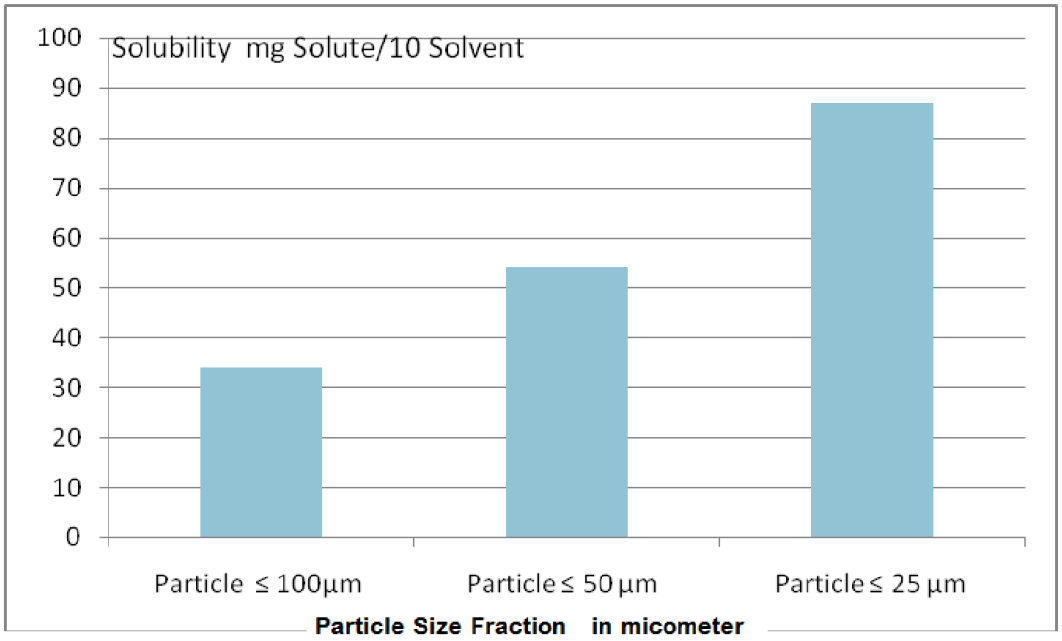

Figure No. 5: Interaction during salvation process to produce solubility.