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SOLVENT IMPACT ON AVERAGE ROUGHNESS AND MICROSTRUCTURAL FEATURES OF METFORMIN DRUG AN AFM INVESTIGATIONS

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ABSTRACT

These investigations were performed on three different sources of highly pure metformin crystallized and extracted from three different types of solvent namely toluene, methanol and acetone. The roughness of metformin surface's were monitored by using high resolution AFM-microscope. Results indicated that as roughness of surface increases, dissolution rates increase due to surface area exposure to the solvated molecules are increased; moreover, the estimated grain sizes decreased as detected by AFM-investigations specially in case of methanol solvent.

Key words: Metformin, Microstructure, AFM, Roughness, Dissolution rate.

INTRODUCTION

Metformin is a biguanide antihyperglycemic agent having chemical formula as shown in Fig. 1, used for treating non-insulin-dependent diabetes mellitus (NIDDM)[1-5]. It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin is the only oral antihyperglycemic agent that is not associated with weight gain. Metformin may induce weight loss and is the drug of choice for obese NIDDM patients. When used alone, metformin does not cause hypoglycemia; however, it may potentiate the hypoglycemic effects of sulfonylureas and insulin. Its main side effects are dyspepsia, nausea and diarrhea. Dose titration and/or use of smaller divided doses may decrease side effects. Metformin should be avoided in those with severely compromised renal function (creatinine clearance < 30 mL/min), acute/decompensated heart failure, severe liver disease and for 48 hours after

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the use of iodinated contrast dyes due to the risk of lactic acidosis. Lower doses should be used in the elderly and those with decreased renal function. Metformin decreases fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels, which are reflective of the last 8-10 weeks of glucose control. Metformin may also have a positive effect on lipid levels[6-8].

The major goal of these investigations is understanding the relationship between roughness of metformin drug as a function of applied solvent used in crystallization process.

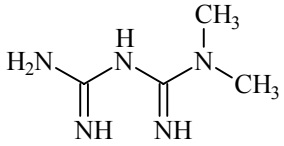

Fig. 1: Metformin (1-Carbamimidamido-N,N-dimethylmethanimidamide)

EXPERIMENTAL

Crystallization of metformin

Three equivalent weights of highly pure metformin powders (each of 0.6 g) were dissolved in 50 mL of toluene, methanol and acetone, respectively with supporting ultrasonic instrument. The crystallization process was performed using gently microwave assist to avoid any traces from applied solvent. The highly pure crystals were dried in oven the forwarded for structural investigations.

Structural measurements

X-ray diffraction (XRD): Measurements were carried out at room temperature on the fine ground samples using Cu-Kα radiation source, Ni-filter and a computerized STOE diffractometer/ Germany with two theta step scan technique. Rietveld and indexing of structure were made via Fullprof package and Gesas program.

Scannig electron microscopy (SEM): Measurements were carried out along ab-plane using a small pieces of the prepared samples 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. This process is a new trend to get high resolution 3D-mapped surface for very small area.

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 AND DISCUSSION

Phase identification

Fig. 2 displays the X-ray diffraction patterns of pure metformin extracted from methnol, which was indentical to those measured for metformin extracted form acetone and toluene, respectively. These observations confirm that applied solvent applied in extraction process of crystallization has no impact on the internal crystal lattice structure. Analysis of the corresponding 2θ values and the inter-planar spacing d(Å) proved that, the compound mainly belongs to monoclinic crystal structure $a \neq b \neq c$ *with* $P2_1/a$ space group. The calculated lattice parameters were found a = 7.9721, b = 13.8765 and c = 8.0032 Å, respectively. These results are fully consistent with those reported by Meena et al.[9] Furthermore FT-IR spectra recorded for pure metformin extracted from methanol (Fig. 3) confirmed existence of metformin in highly pure state. All characteristics peaks of metformin were observed specially –C=N- and –N-H function groups .

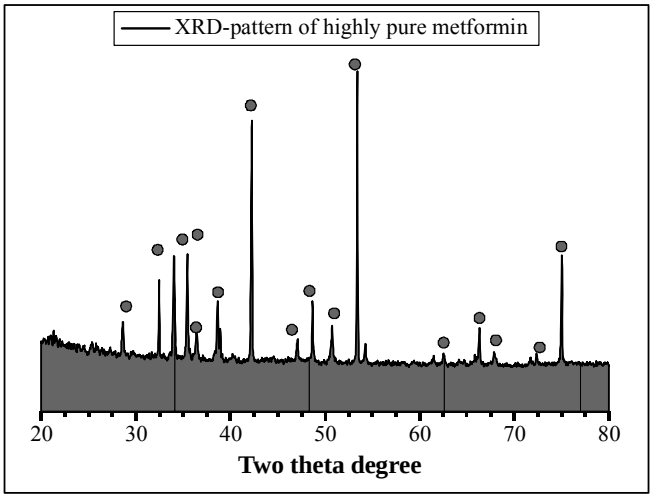

Fig. 2: XRD pattern recorded for highly pure metformin extracted from methanol

Fig. 4a shows 3D-AFM-mapping surface of highly pure metformin crystallized from methanol as it is clear that the topological features of the surface can be divided into five

principle zones with different heights namely 1st zone is red zone color, which represents ~7% with heights ranged in between 9.64-9.68 μm, 2nd zone with orange color occupies ~13% and its heights ranged in between 9.57-9.61 μm, 3rd zone represents 15% of the whole scanned area with yellow color, 4th zone is green color zones (pale and dark color each occypies ~12.5 %) with heights ranged in between 9.5-9.57 μm and finally 5th zone (blue zones cyan and dark blue) cyan color represents 10% and dark blue color occupies 30% of the whole scanned area with heights ranged in between 9.4-9.43 μm. These heights details are for metformin crystallized in methanol.

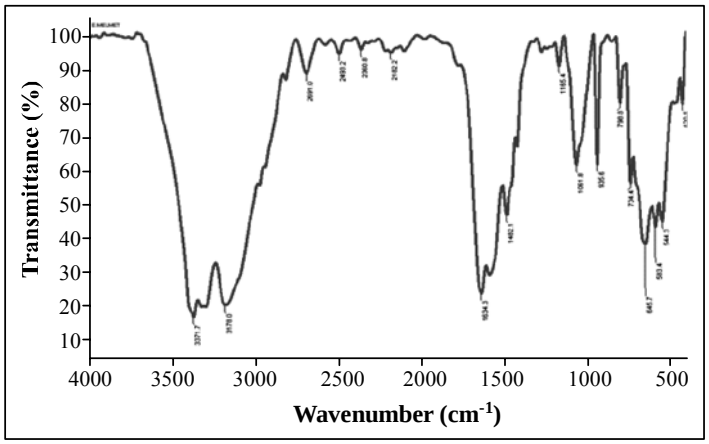

Fig. 3: FT-IR spectra recorded for pure metformin

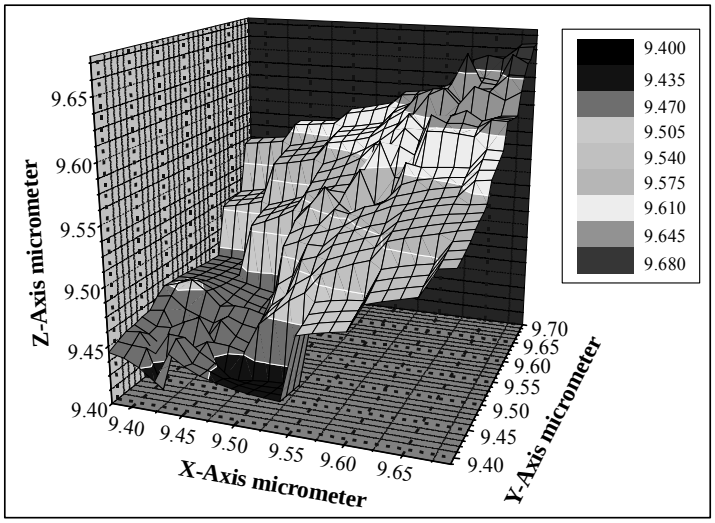

Fig. 4a: 3D-AFM-mapping surface of highly pure metformin crystallized from methanol

Fig.4b displays AFM-horizontal and vertical profiles of metformin surface extracted from methanol. As it clear in Fig. 4b, the minimum depth in horizontal sector is 9.46 µm and maximum heights is ~9.6 µm while minimum depth in the vertical profile is 9.43 µm and maximum height is 9.6 µm, respectively.

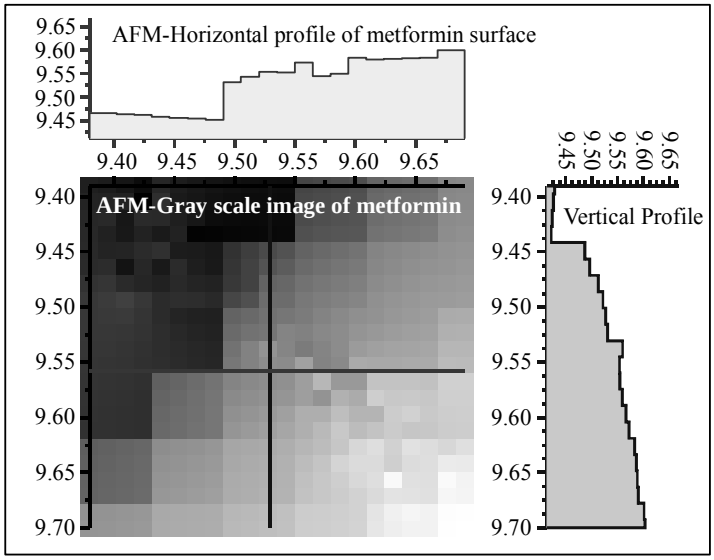

Fig. 4b: AFM-Horizontal/Vertical profiles of metformin surface extracted from methanol

Fig. 4c shows AFM-deflection points profile of metformin surface extracted from methanol. The points of deflection distribution levels are important to understand how the grains aggregates and how large could be reached.

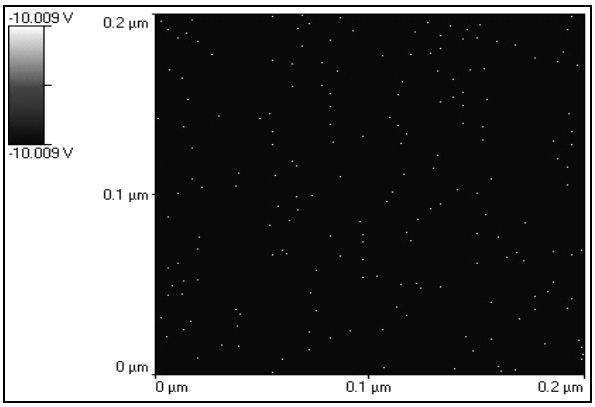

Fig. 4c: AFM-Deflection points profile of metformin surface extracted from methanol

Fig. 5 shows AFM-micrographs recorded for metformin extracted from (a) toluene and (b) acetone, respectively. The analysis of the two micrographs indicated that the ratio of heights in case of methanol crystallization is higher than those of toluene and acetone. The calculated AFM- average roughness of metformin was 75 in case of methanol while it is ~65 and 45 for acetone and toluene, respectively. These results confirmed that methanol as solvent of crystallization enhance the grain size formation to higher size as confirmed in the analysis of surface topology (Fig. 4a) where the ratio of heights in case of methanol is higher than those estimated in toluene and acetone. These results are in patial agreement with those repoted[10-14] specially with the point of view of effect of solvent type on the crystallization process and consequently impacts on microstructural features.

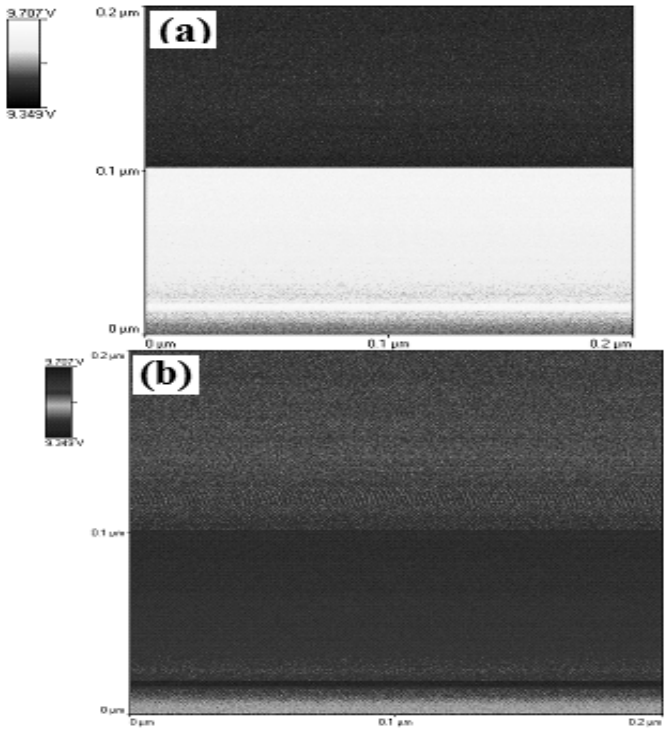

Fig. 5: AFM-micrographs recorded for metformin extracted from (a) toluene and (b) acetone, respectively

Fig. 6 shows the calculated AFM-roughness as a function of applied solvent. As clear in Fig. 6, the average roughness of metformin extracted from methanol is the maximum one with average roughness ~ 75 while acetone and toluene recorded 65, 45, respectively. The solubility of the obtained highly pure metformine was tested applying 0.1 g metformin/10 mL solvent. It was observed that metformin crystallized from methanol

achieved highest dissolution rate followed by acetone then finally non-polar toluene. These results confirmed that as surface area exposed to solvated molecules increases dissolution or solubility rate will be increased as occurred in our investigations. These results can be used to develop technology of metformin drug industry specially from the point of view controlled released drug as discussed before[15-21].

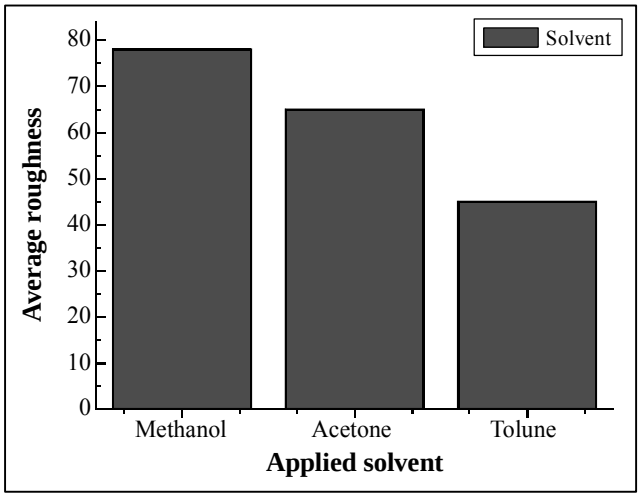

Fig. 6: The calculated AFM-roughness as a function of applied solvent

CONCLUSIONS

The conclusive remarks can be summarized in the following points

(i) Average roughness impact by solvent applied in crystallization process.

(ii) Increasing surface roughness lead to corresponding increase in solubility or dissolution rates specially for polar solvents.

(iii) Solvent type impact on the grain size of metformin formed.

(iv) Controlling dissolution rates could be of benefit in metformin drug industries.

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