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# Structure Study of Metformin Drug an AFM-Investigations

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**A B S T R A C T**
**Objective:** Studying the impact of three different types of organic solvent namely toluene, methanol and acetone on the main crystallographic phase of metformin drug.
**Methods:** Calculations of solubilities rates accompanied with XRD analyses, plus accurate monitoring of metformin microstructural features as function of applied solvent of crystallization process.
**Results:** XRD analyses indicated that applied solvent has no impact on the crystal structure of metformin. The roughness of metformin surface's were monitored by using high resolution SEM and AFM-microscope.
**Conclusion:** Surface roughness plays an important role on dissolution rates process and consequently solvation rates. Enhancing or decreasing dissolution rates could be benefit in metformin drug industries.
**Keywords**: Introduction, Experimental, Results and discussion, Benefits, Conclusion, Reference.

## I. INTRODUCTION:

Metformin has applied mainstay of therapy for diabetes mellitus for many years; however, the mechanistic action of metformin still ill-defined. It is well known that 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 anti-hyperglycemic agent that is not associated with weight gain. Lower doses should be used in the elderly and those with decreased renal function. Metformin decreases fasting plasma glucose, postprandial blood glucose and glycosylated hemoglobin (HbA1c) levels, which are reflective of the last 8-10 weeks of glucose control. Metformin may also have a positive effect on lipid levels6-8.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.

## II. EXPERIMENTAL:

### 2.1.Crystallization of metformin:

Three equivalent weights of highly pure metformin powders (each of 0.3 gm) were dissolved in 30 ml of tolune, 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.

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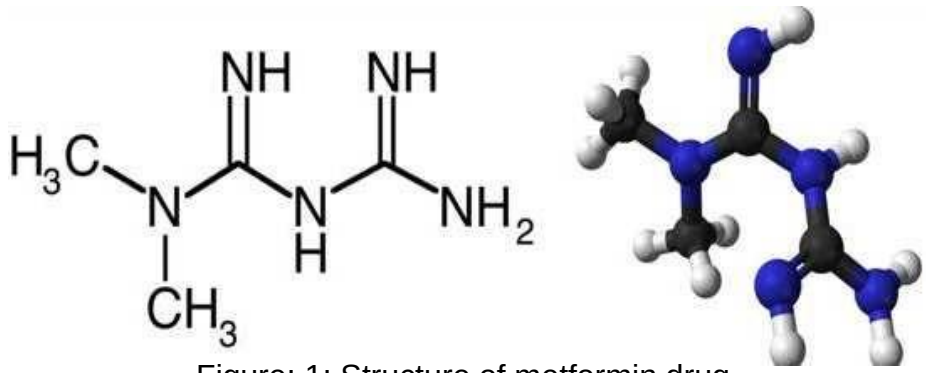


Figure: 1: Structure of metformin drug.

**2.2.Structural measurements:**

Metformin, a widely prescribed oral medication for the management of type 2 diabetes, belongs to the biguanide class of drugs. Its molecular formula is C4H11N5, and its systematic name is 1,1-dimethylbiguanide. Understanding the structure of metformin is crucial for comprehending its pharmacological actions and therapeutic effects.[14]

- ***Chemical Structure:***

Metformin's chemical structure consists of a biguanide moiety, which is characterized by two guanidine groups (-C(NH2)2) connected by a central carbon atom. The two methyl groups (-CH3) attached to this central carbon contribute to the molecule's overall structure. This structural arrangement imparts specific properties to metformin, allowing it to interact with various biological targets within the body.

- ***Functional Groups:***

The functional groups present in metformin play a key role in its mode of action. The guanidine groups are essential for its antihyperglycemic effects. These groups interact with cellular membranes, influencing several cellular processes. The molecule's amphiphilic nature enables it to traverse biological membranes efficiently.

- ***Pharmacophore:***

The pharmacophore of metformin refers to the specific arrangement of its atoms that is responsible for its pharmacological activity. In metformin, the guanidine groups are critical components of the pharmacophore. These groups facilitate interactions with proteins involved in glucose metabolism and insulin sensitivity, contributing to the drug's therapeutic effects.

- ***Mechanism of Action:***

Metformin primarily acts on the liver, reducing gluconeogenesis and inhibiting the release of glucose into the bloodstream. It also improves insulin sensitivity in peripheral tissues, such as muscle and adipose tissue. The molecular structure of metformin allows it to activate AMP-activated protein kinase (AMPK), a key cellular energy sensor. AMPK activation leads to various downstream effects, including the inhibition of gluconeogenesis and increased glucose uptake in tissues, ultimately lowering blood glucose levels.

- ***Bioavailability and Formulations:***

The structural features of metformin influence its pharmacokinetics, including absorption, distribution, metabolism, and excretion. Metformin is well-absorbed in the gastrointestinal tract, and its hydrophilic nature contributes to its low binding to plasma proteins. The kidneys primarily excrete unchanged metformin, and its elimination half-life is relatively short.[1]

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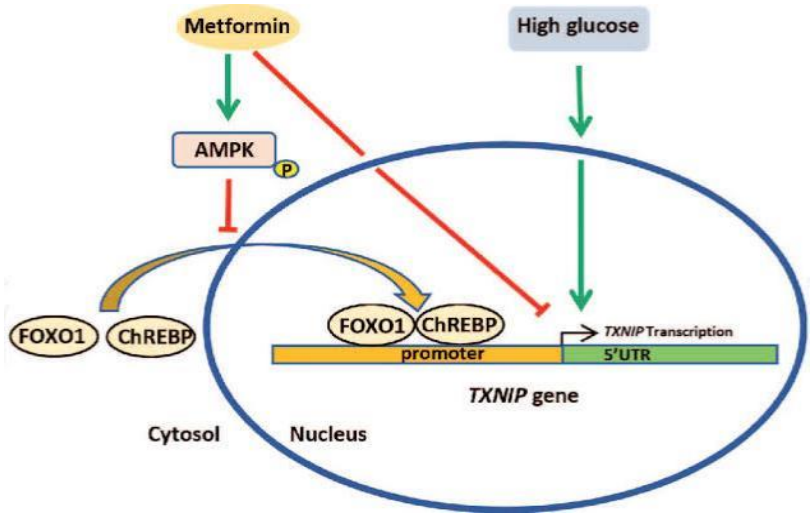


Structure: Flow Chart of mechanism of action [Metformin]

- ***Structural Modifications and Analogues:***

Researchers have explored structural modifications of metformin to enhance its pharmacological properties or reduce side effects. Structural analogues and derivatives have been synthesized to improve bioavailability, increase specificity for certain targets, or mitigate adverse effects.

**2.2.1.The 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.

**2.2.2.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 new trend to get high resolution 3D-mapped surface for very small area.[9]

**2.2.3.FT-Infrared spectroscopy:**

The infrared spectra of the solid products obtained were recorded from KBr discs using a Shimadzu FT-IR Spectro- photometer in the range from 400 to 4000 cm-1.[1]

## III. RESULTS AND DISCUSSION:

**3.1.Phase identification:**

Fig. (2) shows the X-ray diffraction patterns of pure metformin extracted from methnol as model of applied solvent which was identical to those measured for metformin extracted form acetone and tolune respectively. These facts and 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 (A˚) proved that, the compound mainly belongs to monoclinic crystal structure a ≠ b ≠ c with P21/a space group. The calculated lattice parameters were found a= 7.9721, b= 13.8765 and c =8.0032Å respectively. These results are fully consistent with those reported by Rodbard et al.9.

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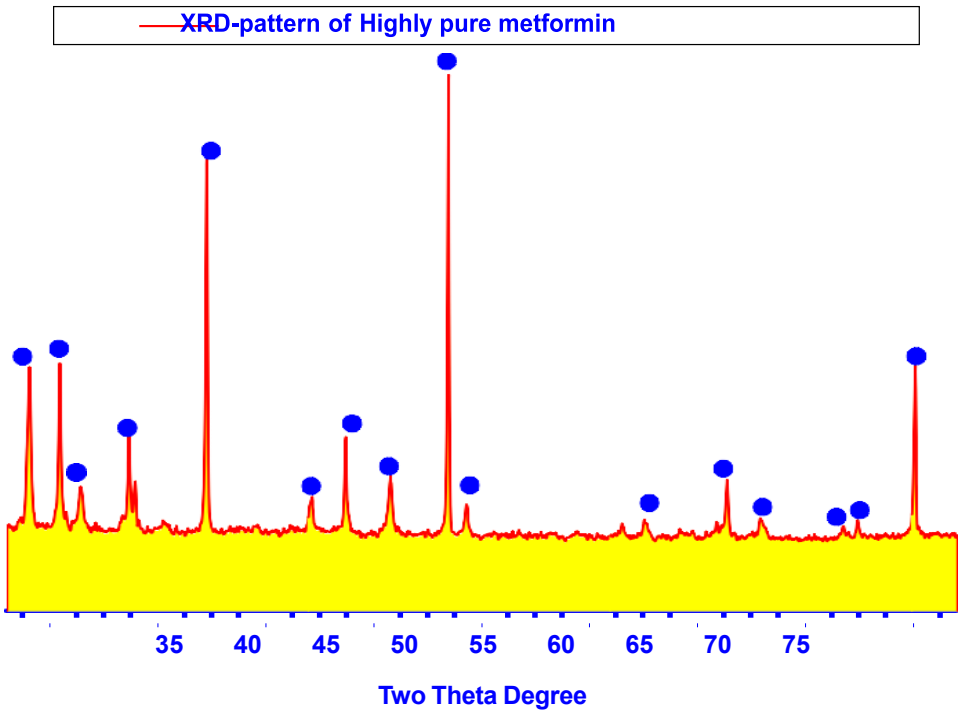


**Figure 2.** XRD pattern recorded for highly pure metformin extracted from methanol

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.

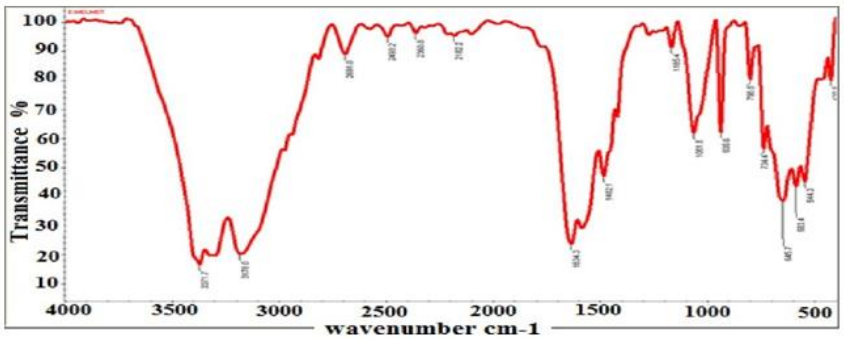


**Figure 3.** FT-IR spectra recorded for pure metformin

**3.2.AFM-Surface investigations:**

Fig. 4a shows 3D-AFM-mapping surface of highly pure metformin crystallized from methanol as it clear 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.[12]

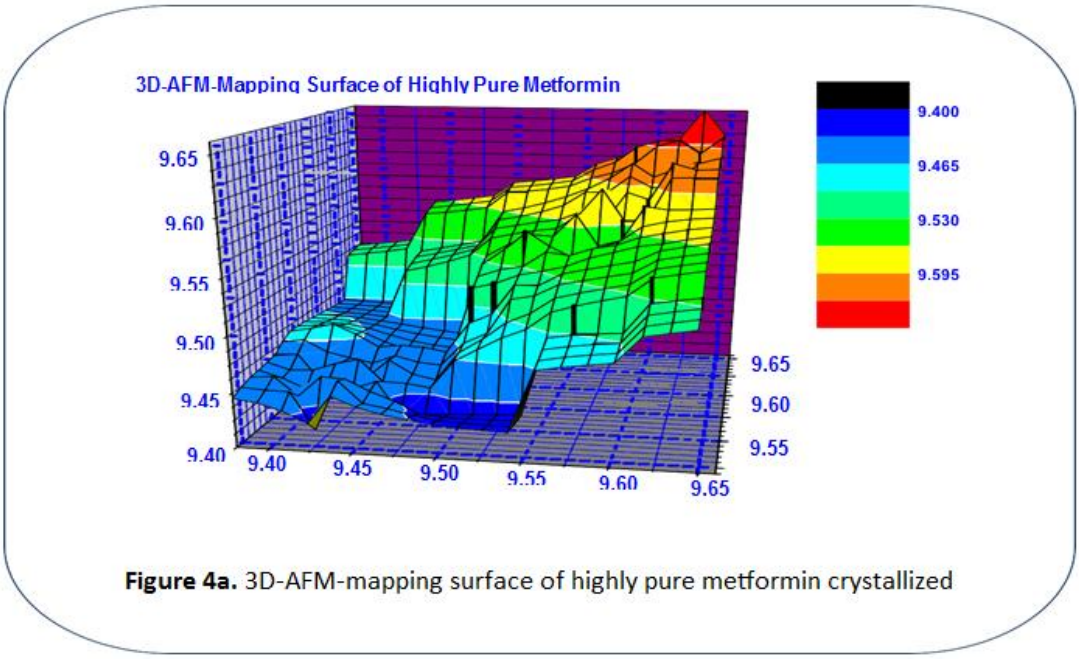


**Figure 4a.** 3D-AFM-mapping surface of highly pure metformin crystallized

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. 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.[5]

Fig. 5 shows 3D-AFM-micrographs recorded for metformin extracted from (a) tolune 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 tolune and acetone. The calculated AFM-average roughness of metformin was 77 in case of methanol while it is ~ 56 and 39 for acetone and tolune 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 in which the ratio of heights in case of methanol is higher than those estimated in tolune and acetone.[2]

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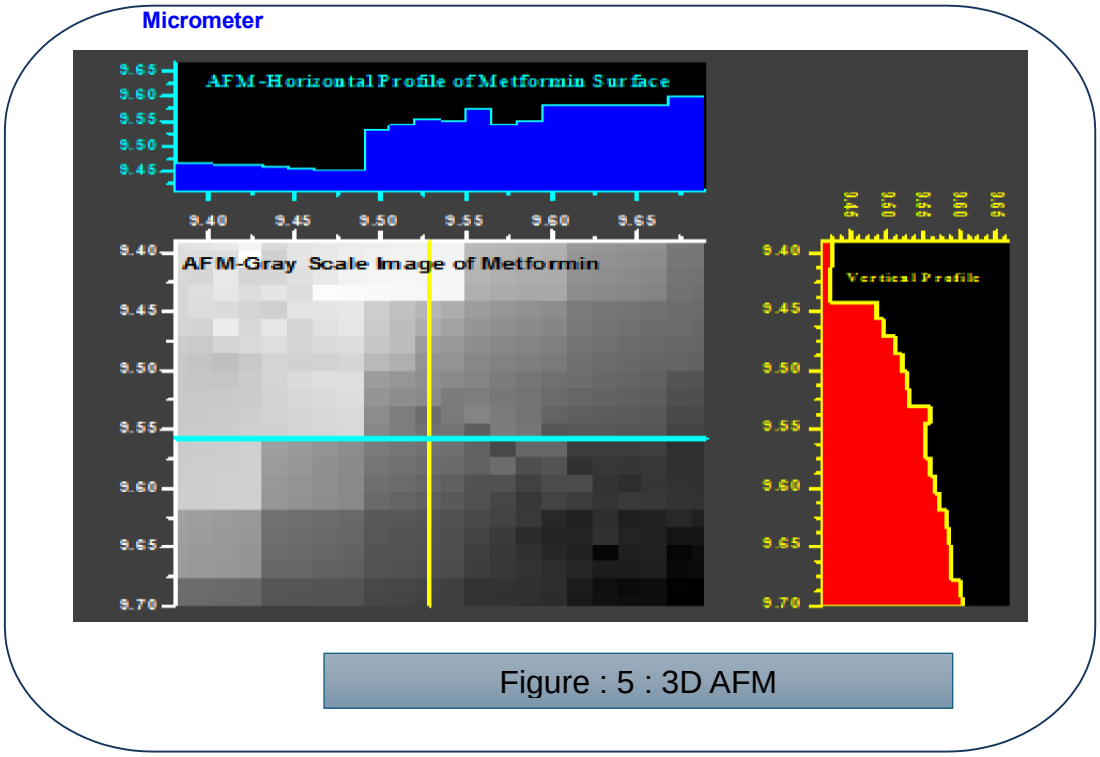


Figure : 5 : 3D AFM

These results are in partial agreement with those reported10-14 specially at the point of view effect of solvent type on the crystallization process and consequently impacts on micro-structural features.[1]

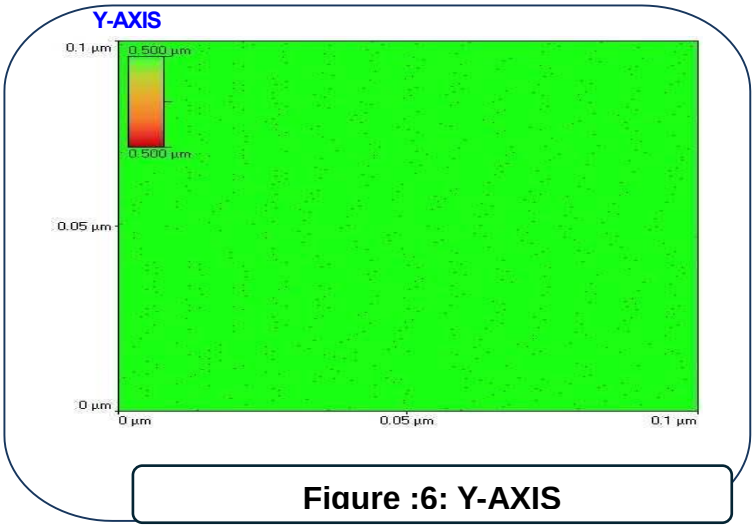


**Figure :6: Y-AXIS**

Fig. 6 displays 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 ~ 77 while acetone and tolune recorded 56, 39 respectively.[14]

The solubility of the obtained highly pure metformin was tested applying 0.1 gm metformin/10ml solvent, it was observed that metformin crystallized from methanol achieved

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highest dissolution rate followed by acetone then finally non-polar tolune .These results confirmed that as surface area axposed 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 at the point of view controlled released drug as it discussed before15-21.Fig. 7 shows SE-micrograph of pure metformin captured with magnification factor 5 µm for metformin extracted from tolune and acetone respectively. The grain sizes were estimated and found to be in between 0.44 m and 0.88 m respectively which confirm that applied solvent in crystallization process is correlated with grain size (i.e. grain size of metformin is applied solvent dependent)16,17.[15]

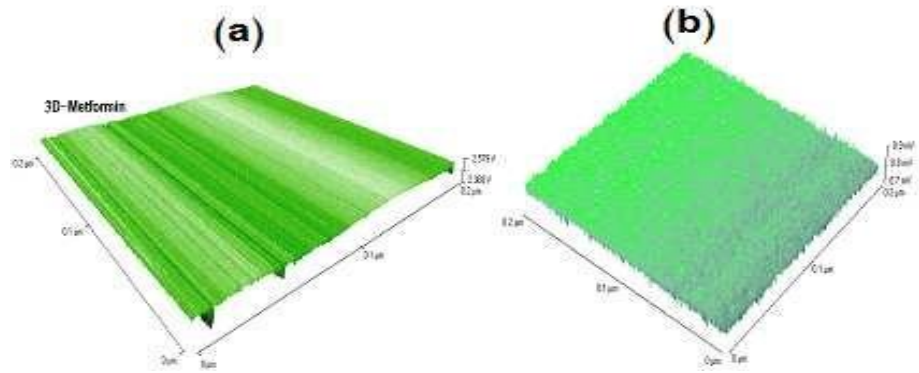


**Figure: 7 :Surface structure**

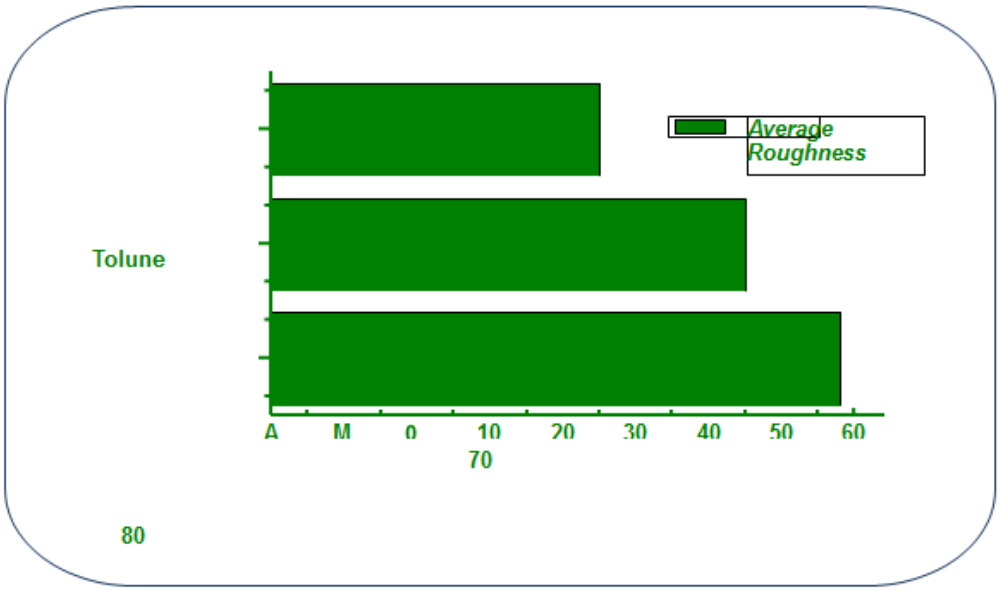


Figure :8:Solvent investigation

## IV. BENEFITS :

Metformin is a widely used medication that belongs to the class of drugs known as biguanides. It is primarily prescribed for the management of type 2 diabetes mellitus. Metformin helps control blood sugar levels by reducing the amount of

glucose produced by the liver and improving the body's response to insulin. However, metformin is also being investigated and used in various other fields for its potential benefits. Here are some areas where metformin has shown promise or is being explored:[21]

**4.1.Type 2 Diabetes Management:** Metformin is a first-line treatment for type 2 diabetes. It is often prescribed in conjunction with lifestyle modifications, such as diet and exercise, to help control blood sugar levels.

**4.2.Polycystic Ovary Syndrome (PCOS):** Metformin is sometimes prescribed to women with PCOS to improve insulin sensitivity and regulate menstrual cycles. It may also assist in managing other symptoms associated with PCOS, such as infertility.

**4.3.Weight Management:** Metformin has been studied for its potential to help with weight loss, particularly in people with obesity and insulin resistance. However, it is not typically prescribed as a primary weight-loss medication.

**4.4.Gestational Diabetes:** In some cases, metformin may be used to manage gestational diabetes, a type of diabetes that occurs during pregnancy.

**4.5.Anti-Aging and Longevity Research:** Some research suggests that metformin may have potential anti-aging effects and could extend lifespan. This area of study is still in its early stages, and more research is needed to fully understand the implications.

**4.6.Cancer Prevention and Treatment:** There is ongoing research exploring the potential anti-cancer properties of metformin. Some studies suggest it may have a role in cancer prevention and as an adjuvant therapy for certain types of cancer.

**4.7.Cardiovascular Health:** Metformin has been associated with cardiovascular benefits, including improvements in lipid profiles and a potential reduction in the risk of cardiovascular events in people with diabetes.

**4.8.Neurological Disorders:** Some studies have investigated the use of metformin in neurological disorders, including neurodegenerative diseases like Alzheimer's and Parkinson's. The potential neuroprotective effects of metformin are an area of active research.

## V. CONCLUSIONS:

The conclusive remarks can be summarized in the following points.The crystallographic phase of metformin (monoclinic) is not impacted by solvent applied in crystallization process only surface roughness and topological features are changed and affected remarkably.

- Solubility or dissolution rates are solvent dependent specially in case of polar solvent.
- There are strong correlation between metformin grain size formed and applied solvent of salvation process (i.e. grain size is applied solvent dependent).
- Enhancing or decreasing dissolution rates could be benefit in metformin drug industries.

In summary, metformin's structure is characterized by a central carbon atom linking two guanidine groups and two methyl groups. This chemical arrangement, along with its functional groups, is crucial for its pharmacological activity. Metformin's mechanism of action involves interactions with key cellular pathways, primarily through AMPK activation. Understanding the structure of metformin is essential for optimizing its therapeutic use and developing new compounds to address the challenges associated with diabetes management. Ongoing research in structural modifications and analogues continues to contribute to the evolution of diabetes pharmacotherapy.

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