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RESEARCH ARTICLE

Synthesis of cocrystals of sulfonyl urea class drug using suitable coformers for enhancement of aqueous solubility

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Abstract: The pharmaceutical cocrystals and its engineering is widely accepted phenomenon regarding to the enhancement of aqueous solubility of poorly soluble drugs. The pharmaceutical cocrystals have the great ability to improve the physicochemical properties of drug substance. Cocrystals are formed by the stoichiometric combination of drug substance and the coformer. The drug glimepiride is a third generation oral hypoglycemic sulfonylurea class. Glimepiride is a drug which is get classified as biopharmaceutical classification system (BCS) class II which indicates the glimepiride having low aqueous solubility and high permeability. Cocrystal engineering is a perfect way to increases glimepiride solubility without changing its therapeutic property. The cocrystals were synthesized by the solvent drop grinding as a green chemistry approach. The coformers used to form the cocrystals are succinic acid (SA), Theobromine (TB), caffeine (CF). The synthesized cocrystals are get characterized by vibrational spectroscopy, thermal analysis, molecular crystallography, and optical microscopy. The obtained results shows the formation of cocrystal phase between the drug glimepiride and its coformers.

Keywords: cocrystals, cocrystal engineering, biopharmaceutical classification system, green chemistry

1 Introduction

The development in cocrystal by the pharmaceutical industries has having great importance in las several years[1] . The synthesis of cocrystals is very much promising strategy for increasing the aqueous solubility of drug along with the stability and bioavailability, study also proven that the formation of cocrystals increases the dissolution rate also[2]. Cocrystal is defined as crystalline form of a mixture of different molecules. Researchers have developed various approaches for enhancement of solubility. Amongst all other techniques cocrystals approach is unique technique because this techniques does not affects the pharmacological properties of drug, but may improves the drug's bioavailability, solubility, tablet ability, stability, and permeability[3]. About 40% of compounds available in market and drugs under development phase, and 80% of the drug substances that are in the production stages, appear to have problems in solubility[1].(Figure 1)

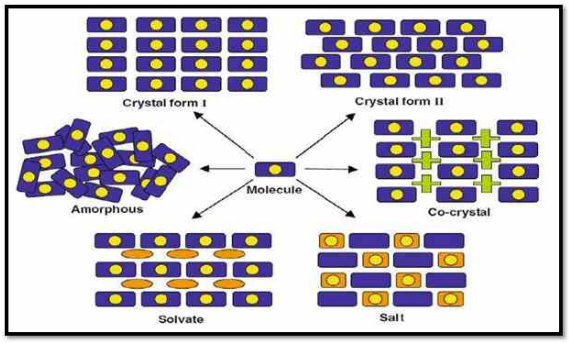

Figure 1. Modified forms of solids and its arrangements

As per the International Diabetic federation 415 million adults are estimated to have diabetes and about 318 million adults with impaired glucose tolerance. India stands at the second position after China, with 69 million persons diagnosed with diabetes[4].

Type 2 diabetes mellitus (T2DM), the most common form of diabetes that is accounting for around 90-95% diabetics. Erroneous action of insulin cause the blood sugar level to rise more than 100 mg/dl in fasting condi-

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tion and more than 140 mg/dl postprandial. It is a morbid and progressive condition initially marked by insensitivity of adipose and muscle tissues to the insulin, followed by decrease in beta cell activity and high level of blood glucose[4].

1.1 Management of type 2 diabetes mellitus

The glimepiride also acts as an insulin secretogogue like other sulphonylureas. It belongs to BCS class II, having poor water solubility (practically insoluble in water), this poor aqueous solubility and slow dissolution may lead to irreproducible clinical response. To overcome this coocrystalization approach is used[5].(Figure 2)

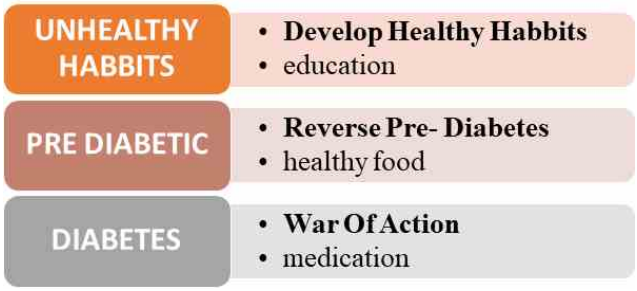


Figure 2. Pictorial representation for management of type 2 diabetes mellitus

1.2 Crystal engineering

Crystal engineering, a branch of crystallography, originated way back in 1930's, when chemical bond was defined with respect to both covalent as well as noncovalent[6]. This field gained fame when the focus shifted to the engineering of properties rather than engineering the structures. crystal engineering may define as *"the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties"*[7].

The heart of crystal engineering is intermolecular interactions and among them the non-covalent interactions are of utmost importance that includes hydrogen bonding, halogen bonds, electrostatic interactions, metal coordination bonds and π-π stacking, Van der Waals interactions[8].(Figure 3)

Intermolecular interactions playing the integral role in crystal engineering are non-covalent in nature. The packing of molecule in the crystal lattice is dependent on these interactions.[9] To large extent, the crystal packing is subjective to the nature, direction, strength and distance properties of intermolecular in.teractions.[10] The crystal engineering exploits the predictability, directionality, and specificity of these non-covalent intermolecular interactions, to form supramolecular synthons between crystalline materials.[11] The most prominent non covalent interactions among these are halogen bonds and hydrogen bond. Halogen bond is formed when a halogen atom interacts with atoms having lone pair. Only recently, halogen bonds came into limelight as they provide considerably fair direction and strength, making them better intermediates between strong and weak hydrogen bonds[2].

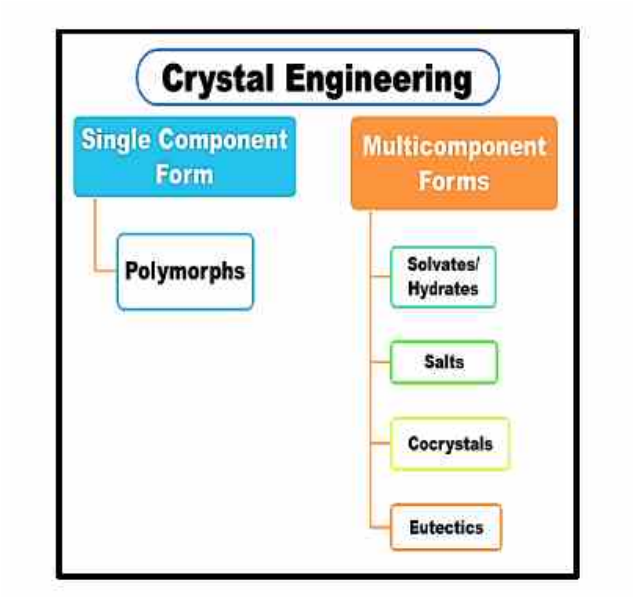


Figure 3. Diverse Forms obtained via crystal engineering

2 Materials and methods

2.1 Hydrogen bonding

An attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation[2].

Hydrogen bonds are the basic bonding between the molecules. The hydrogen bond between the drug substance and the coformer have impact on the formation of cocrystals. Hydrogen bond gives information about the interactions between the donor of hydrogen atom and the acceptor[12].(Figure 4)

The bonding of hydrogens within the structure is get systematically arrange by the following rules:

(1) Mostly all good proton donors (such as –COOH, –NH4 +) and acceptors (such as –OH, –NH3) are utilized in hydrogen bonding.

(2) Six-membered ring intramolecular hydrogen

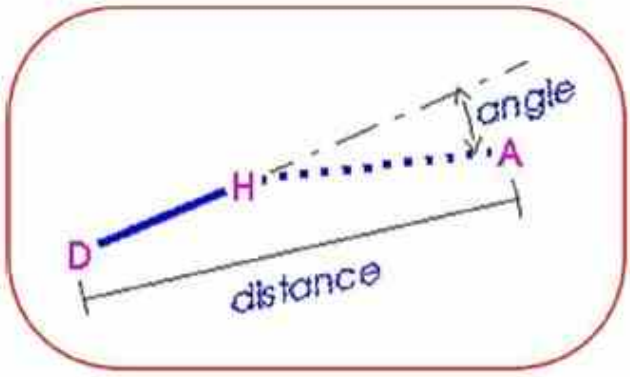


Figure 4. Angle of hydrogen bond

bonds (such as C-H. . . O) are formed first in Preference to intermolecular hydrogen bonds (such as N-H. . .O and O-H. . . O)

(3) The best acceptors and donors of proton available after intramolecular hydrogen bond formation then participate in intermolecular hydrogen bonds.

(4) All acidic hydrogen atoms are included in hydrogen bonding in the structure of crystal[13].

2.2 Supramolecular synthons

(1) Supramolecular homosynthon: composed of identical self-complementary functionalities.

(2) Supramolecular heterosynthons: composed of different but complementary functionalities[2]. a) The term synthon can be define as "structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions"; b) Single-component or compounds containing the functional groups can be sustained by supramolecular homosynthons whereas; supramolecular heterosynthons can dominate in the presence of other competing functional groups[14].Figure 5, 6.

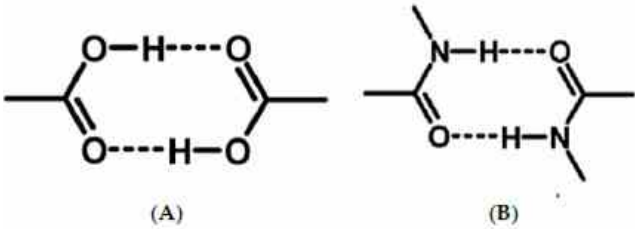


Figure 5. Structural representation of supramolecular homosynthone. (A) acid- acid dimer; (B) acid- pyridine dimer

2.3 Hansen solubility parameter

It's a parameter which indicates the formation of cocrystals by the miscibility of drug with the coformers. The solubility parameter can be used to predict the

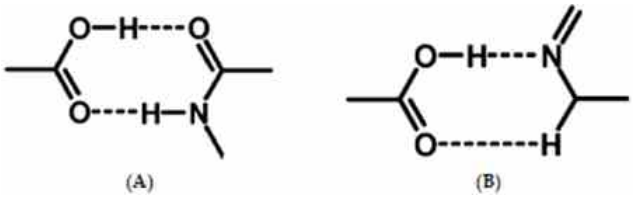


Figure 6. Structural representation of supramolecular hetrosynthone. (A) acid- acid dimer; (B) acid- pyridine dimer

physicochemical properties[2]. The Hansen solubility parameter is a tool used in the stage of preformulation and formulation study. Prediction of melting points is done by this solubility parameter, solubility and other physicochemical properties.[15]

2.4 Synthesis of cocrystals

For the preparation of cocrystals glimepiride (GLM), various GRAS coformers containing complementary functional groups were tried. Solvent drop grinding method was used for preparation of all the cocrystals, which is a green and viable approach. The experiments for the re-crystallization of the prepared cocrystals from the various solvents were also done but the suitable crystals for single crystal X-ray diffraction analysis were not isolated[16].(Figure 7)

Three coformers are used to synthesized the glimepiride cocrytstals which was succinic acid (SA), theobromine (TB), and caffeine (CF).

The drug glimepiride and the coformers are taken in stoichiometric ratio and by using neat grinding the cocrystals were synthesized.

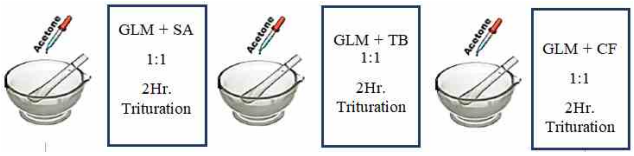


Figure 7. Synthesis of cocrystals by solvent drop grinding

3 Results

3.1 Differential Scanning Calorimetry (DSC)

This method used to record the events of change in the solids on heating and helps in identification of new crystalline solid forms (single as well as multiple component).[17] Along with the melting point; desolation, solid-solid transitions and crystallization are also observed[16].

DSC thermogram of GLM showed melting endotherm at (212.39°C) while the thermograms of respective coformers showed melting endotherm for CF at 236.08°C;

SA 192.29°C and TB at 335.42°C. The DSC thermograms of the new isolated solid forms namely GLM-CF, GLM-SA and GLM-TB showed a single melting endotherm at 192.80°C, 169.85°C and 173.83°C, respectively. These melting peaks are sharp and different from parent components (Figure 5). This indicates the emergence of novel and pure crystalline solid phases. The melting endotherm of all the new crystalline phases is positioned before the melting endotherms of GL Iand their respective coformers. This suggests the synthesis of either cocrystal or eutectics. However, the DSC of the physical mixtures (Figure 5) of all the crystalline phases in stoichiometric ratio 1:1 showed the presence of two broad peaks, representing individual components. This confirmsthe formation of cocrystals and at the same time negates the possibility of eutectics.(Figure 8)

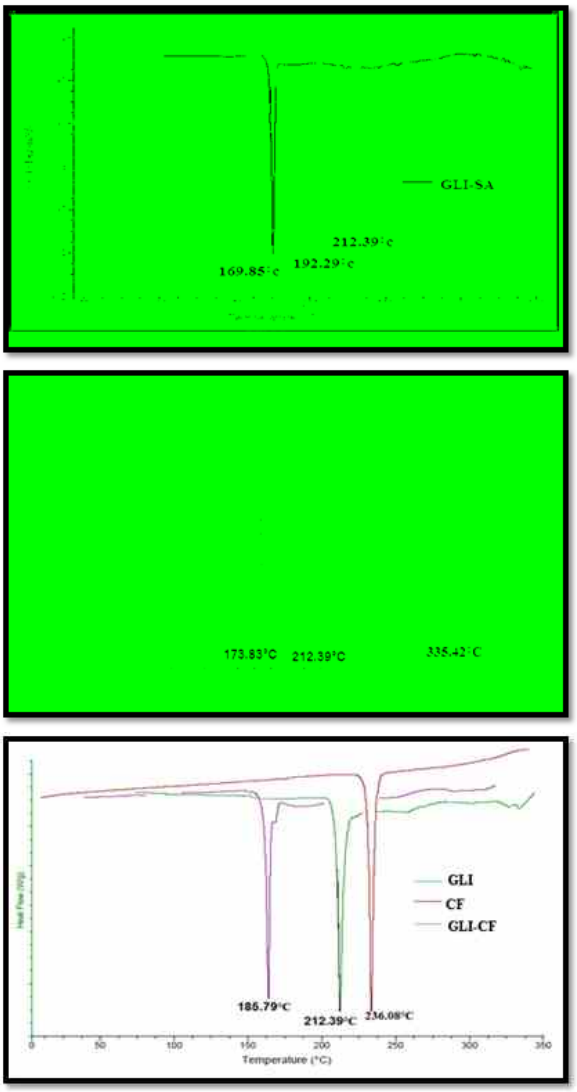


Figure 8. DSC Thermogram A. GLM + SA, B. GLM + TB, C. GLM + CF

3.2 Vibrational spectroscopy

FT-IR, is a broadly used analytical technique for studying the changes in vibrational bands during cocrystallization. This technique aids in identifying functional groups which are interacting together to form hydrogen bonds. In the recent years, Fourier Transform Infra-Red (FT-IR) spectroscopy has been established an excellent technique for studying the pharmaceutical solids[11]. The FT-IR instrument is economical, gives results with high resolution and equipped advance software. The adoption of reflectance technique for the sample analysis has allowed obtaining IR of solids in their innate state. In the cocrystals, for the determination of the vibrational changes which are the consequence of supramolecular interactions, FT-IR is used[18].

3.3 GLM-SA

Shifts in the hydroxyl region of SA from 3209 cm-1 to 3200 cm-1 as well as in the –NH stretch of GLM shifted from 3369 cm-1 and 3289 cm-1 to 3350 cm-1and 3281 cm-1 , respectively implied the interaction between these regions.(Figure 9)

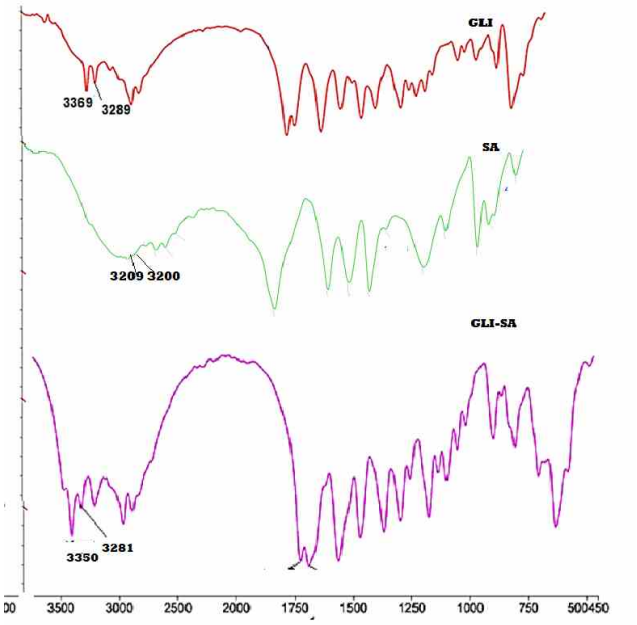


Figure 9. FT-IR spectrum A. GLM- SA

3.4 GLM-CF

The of –NH stretch of GLM shifted from 3369 cm-1and 3289 cm-1 to 3374 cm-1 and 3290 cm-1 , respectively. The -C=N stretch in caffeine at 1547 cm-1 have shifted to 1553 cm-1, showing involvement of N-aromatic of imidazole ring.(Figure 10)

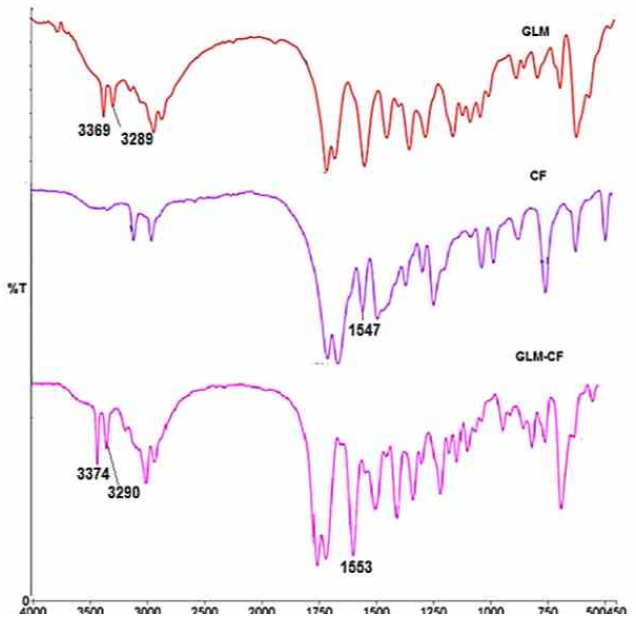


Figure 10. FT-IR spectrum B. GLM- CF

3.5 Powder X-ray Diffraction (PXRD)

It helps in distinguishing the different crystalline phases. It is based on the concept that the electrons in the atoms diffract X-rays as explained by the Bragg equation. The diffraction of X-rays provides a pattern in which intensity of diffraction is plotted against the 2θ values[9]. The units for expressing intensity are counts or counts per second whereas 2θ or d-spacing are expressed in A° or nm. PXRD pattern represents the fingerprint of the crystal structure and is helpful in estimating the position of atoms in the crystal structure[8].

The advancement in this technique has assisted in rapid data analysis and time resolved study. Controlled environmental changes helped to study the polymorphic transitions at specific temperature or humidity level[14].

In the diffraction pattern of GLI-SA, new peaks appeared at 14.75°, 16.20°, 20.69°, 21.87°, 24.56° and 26.09°, while peak of GCM at 23.50° have disappeared. Some peaks of GCM at 11.25°, 12.06°, 12.62°, 18.36°, 19.26°, 19.79°, 21.07°, 21.53° and 22.18° has significantly shifted to 10.83°, 11.70°, 12.21°, 18.54°, 18.91°, 19.41°, 20.94°, 21.37° and 22.83° (Figure 11).

In case of GLM- TB, new peaks appeared at 16.28°, 24.16° and 29.02°. Few significant peaks of GLM at 11.25°, 12.06°, 16.5°, 19.26°, 19.79°, 21.53°, 23.19°, 23.49°, 24.93° and 27.99° have shifted to 10.94°, 11.80°, 16.74°, 23.22°, 24.66° and 27.76°, respectively, while one of the peak of TB has shifted from 14.60° to 14.46°. Peaks of TB at 12.62° and 25.86° has merged with peaks of GLM at 12.62° and 25.47° resulting in a single peak at 12.74° and 25.76°, correspondingly in GLM-TB (Figure 12).

In case of GLM-CF, some new peaks have appeared at 15.77°, 36.67°, 37.61° and 38.46°. Some peaks of GLM at 15.55°, 15.93°, 20.85°, 23.35°, 26.01°, 26.57°, 28.11° and 32.09° have disappeared while some peaks have shifted from 6.63°, 13.63°, 16.91°, 25.46° and 30.46° has been shifted to 6.79°, 13.77°, 17.02°, 25.58° and 30.58°, respectively. Some of the peaks of caffeine (CF) at 14.7°, 16.05°, 20.03°, 20.86° and 26.27° have disappeared and peak at 24.36° has shifted to 24.31°. Few peaks of GLM and CF like 23.89° and 23.93°, 24.88° and 24.36°, 26.88° and 26.72°, 27.81° and 27.39°, 29.61° and 29.94° merged to give single peak at 23.95°, 24.32°, 26.71°, 27.31° and 29.71°(Figure 13).

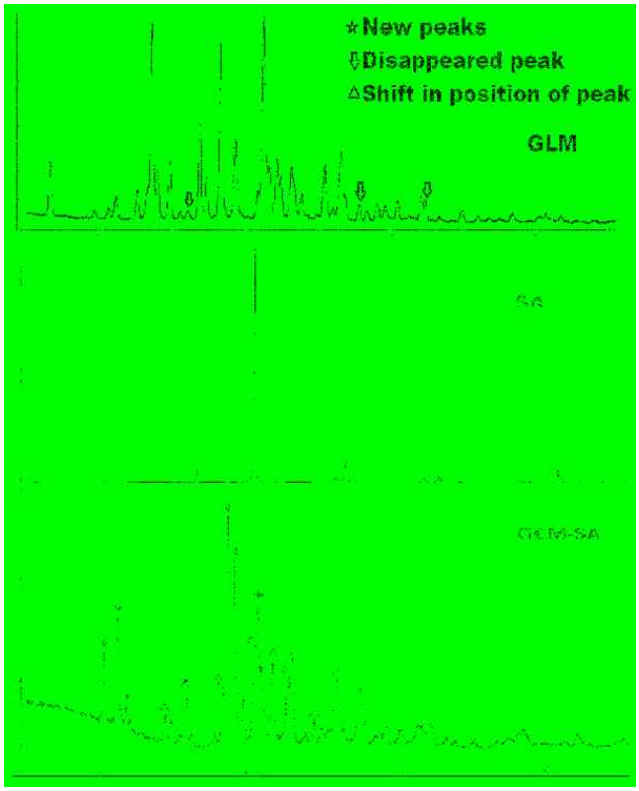


Figure 11. PXRD Pttern A. GLM- SA

3.6 Equilibrium solubility and intrinsic dissolution study

Crystal engineering of GLM by preparing its cocrystal will only be successful when there is significant enhancement in physicochemical properties like solubility and dissolution as in comparison to pure drug. The equilibrium solubility and dissolution studies of cocrystals of GLM were performed at 37°C as per procedure. The results are graphically represented in tabulated in Fig-

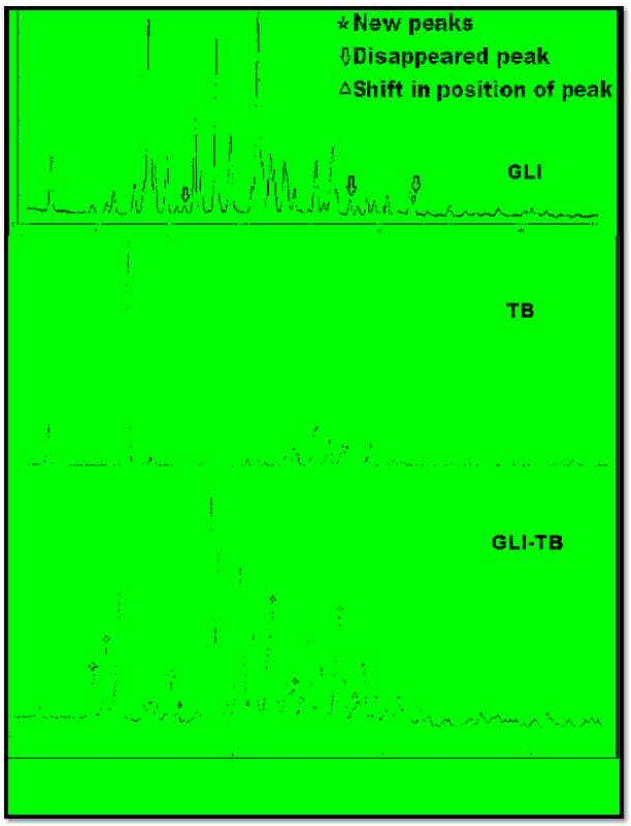


Figure 12. PXRD Pttern B. GLM- TB

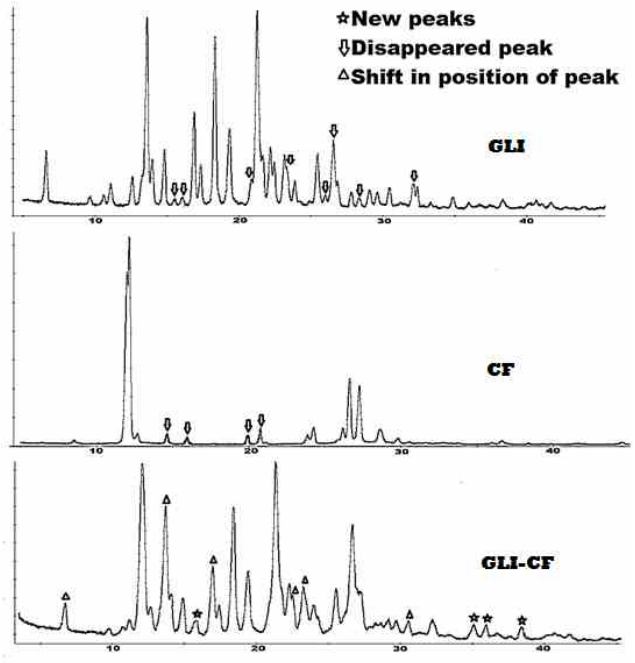


Figure 13. PXRD Pttern C. GLM- CF

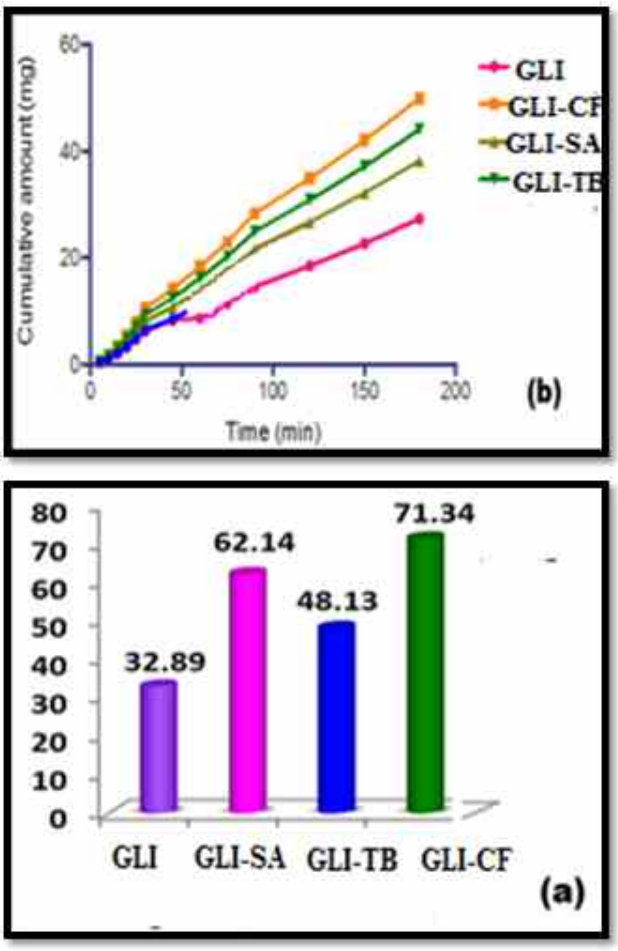


Figure 14. Equilibrium Solubility after 6 hours and (b.) Intrinsic dissolution profile of GLM, GLM-CF and GLM-TP

ure 14(a) and Figure 14(b). The solubility of cocrystals after 6 hours follows the order: GLI-CF > GLI-SA > GLI-TB. The residual material after 6 and 24 hours of the solubility study were analyzed by FT-IR to study for any change in composition of the cocrystals. The FT-IR analysis revealed that all the cocrystals were intact and in equilibrium up to 6 hours. However, after 24 hours, the FT-IR spectra of residual material matched the FT-IR spectra of drug. This indicates the conversion of cocrystals to drug after 24 hours.(Figure 14)

3.7 Scanning electron microscopy (SEM)

Morphological evaluation of glimepiride, succinic acid, and glimepiride – succinic acid cocrystals was performed by scanning electron microscopy (JEOL JSM-7600F Field Emission Scanning Electron Microscopy)[12]. A small piece of carbon double-sided adhesive tape was fixed onto an aluminum stubs. The powders were sprinkled and dispersed onto the stubs surface. Prior to examination, the samples were sputter

coated with iridium under argon atmosphere to render them electrically conductive[19].

3.8 SEM analysis

The particle morphology of Glimepiride (Figure 15(a)) was stone like, and Succinic acid (Figure 15(b)) displayed a needle -like shape with a strict and glossy surface. Obviously, the particle size of succinic acid (approximately 400 μm) was much bigger than that of glimepiride (approximately 10 μm). However, the glimepiride – succinic acid cocrystal (Figure 15(c)) was composed of stone shape particles with rough surfaces, and the particle size (approximately 1μm) was smaller than that of glimepiride, which was indicative of the presence of a new phase. In brief, by inspecting the IR and DSC, it can be concluded that a new crystalline phase was formed, which was different from that of two free molecules. This result is possibly due to the formation of the intermolecular hydrogen bonding between Glimepiride and succinic acid.

3.9 Pharmacokinetic study

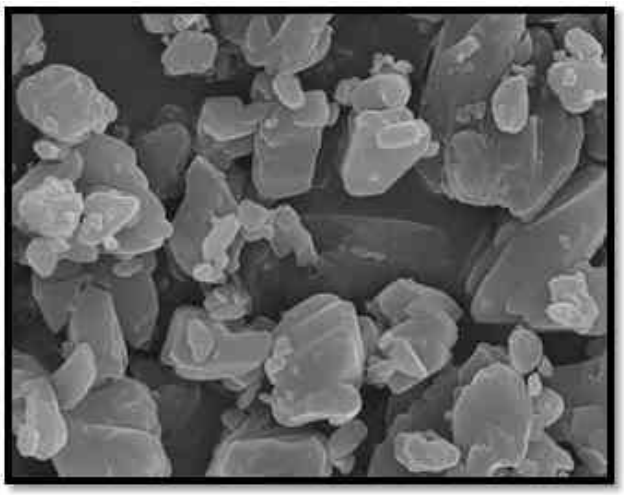
The pharmacokinetic activity of GCM and GLM was performed on normal rats. The sampling of the blood was done at specified intervals of time and the processed plasma was analyzes by HPLC.

3.10 *In vivo* study of synthesized form

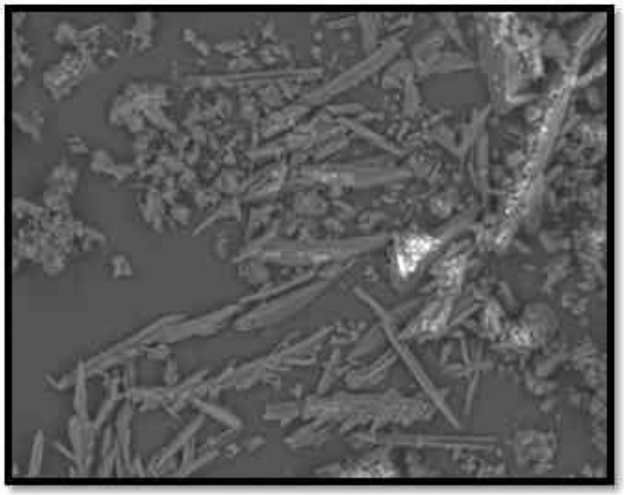
The rats will housed three per cage. The rats will be fasten about 4-6 hr. before drug administration. Ten rats divided into two groups. *Group **1:*** Drug API and *Group **2*:** Modified dosage form. Both groups will be administrated 6 mg/ kg Glimepiride Per oral using animal feeding needle. Following pre-determine points (1, 2, 4, 8, 12 and 24 hr.) after drug administration, approximately 0.7ml blood will be withdrawn from the retro-orbital plexus of the rats, collected in heparinized tubes, and centrifuged at 3000 rpm for 10 min at 4°C to obtained the plasma. Concentration of drug and modified form will be measure by using RP-HPLC method of analysis.(Table 1)

Table 1. *In vivo* study protocol

Sr. No.	Groups	Dose (mg/kg)	No. of animals
1	Drug API	6.0	6
2	Modified form	6.0	6
Total			12



(a)



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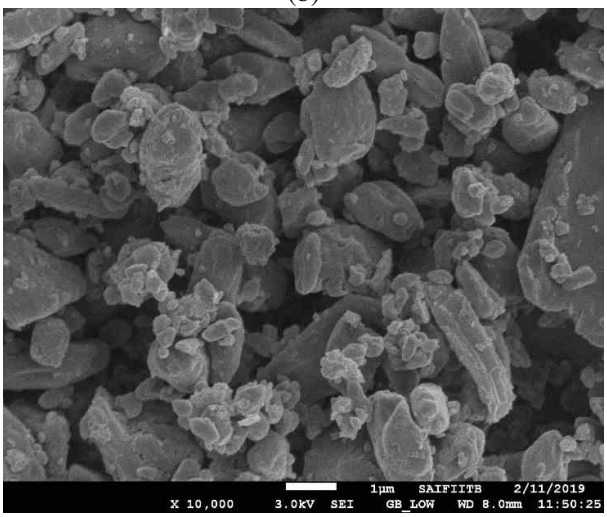

(c)

Figure 15. SEM of A. Glimepiride, B. succinic acid, C. glimepiride + succinic acid

3.11 Pharmacodynamics studies

The antidiabetic activity was done in the diabetic wistar rats as per the protocol. Firstly the glimepiride HPLC analysis has been done. Then the quantitative bioavailability of glimepiride and its cocrystals get analyzed.(Table 2, Figure 16, 17)

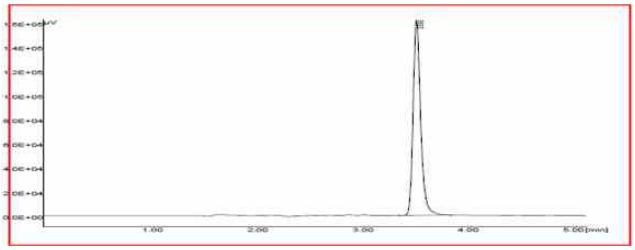

Figure 16. RP-HPLC analysis of GLM

Table 2. *In vivo* study

TIME (Hr.)	GLM	GLM+SA	GLM+CF	GLM+TB
1	1378.56	1423.36	1430.25	1421.45
2	1420.36	1542.34	1560.23	1556.72
4	1498.36	1669.99	1688.23	1694.01
8	1449.26	1556.21	1565.23	1560.85
12	1409.36	1452.18	1468.56	1454.00
24	1374.23	1423.98	1420.15	1414.37

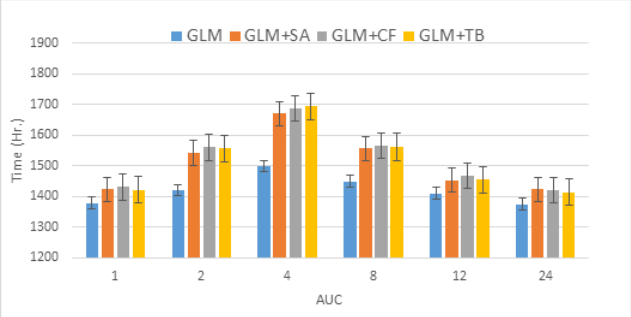

Figure 17. Graphical representation of bioavailability

The comparative in vivo study of glimepiride and its cocrystals are as follows: GLM+CF > GLM+TB > GLM+SA > GLM.

4 Conclusion

Using the solvent drop grinding method for cocrystal synthesis we were able to obtain Glimepiride – Succinic Acid 1:1; Glimepiride – Theobromine 1:1; Glimepiride – caffeine 1:1 cocrystal. The DSC, PXRD results show that a new pure and crystalline phase was obtained. The vibrational spectroscopic techniques also show that the hydrogen bounds between the API and coformer. The Equilibrium Solubility and Intrinsic Dissolution Study shows that the synthesized cocrystals enhances the aqueous solubility of glimepiride.

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