iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 11 **Issue:** II **Month of publication:** February 2023

DOI: https://doi.org/10.22214/ijraset.2023.49022

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue II Feb 2023- Available at www.ijraset.com

Enhancement of Glimepiride Bioavailability by Co-Crystallization Technique

Mohamed F. Zidan[1], Mohsen I. Afouna[2], Hatem R. Ismael[3], Mohamed F. Ibrahim[4]
Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar, University, Cairo, Egypt

Abstract: ***Drugs with low aqueous solubility show limited oral bioavaibility and dissolution enhancement is a promising strategy for improving drug bioavailability. Co-crystallization is a promising technique used to improve the oral solubility and dissolution rate of the drugs and hence their oral bioavailability. In general pharmaceutical co-crystals improve the physical properties such as crystallinity, solubility, wettability and dissolution behaviors of the drug without altering its pharmacological activity. The aim of this study was to enhance the solubility, dissolution rate and limited oral bioavailability of glimepiride (GLM) by co-crystallization with different carboxylic acid co-formers. Different co-crystal formulations were successfully prepared by ultrasound assisted suspension co-crystallization technique and then suspected to solubility study to choose the best formula to complete the study. Co-crystal of glimepiride -oxalic acid was characterized by X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), and then further evaluated for dissolution behavior. The result showed that co-crystal could increase solubility and dissolution rate of glimepiride. The results of XRPD, FTIR and DSC indicating the presence of a new crystalline phase and formation of co-crystal while the SEM micrograph revealed the definite shape with crystalline composition of co-crystal. In vivo bioavailability study in rats showed higher C_{max} , longer $t_{1/2\ el}$ and $MRT_{0-\infty}$ and increased $AUC_{0-\infty}$ of 2.66 fold compared to the plain GLM. Therefore, co-crystallization technique can be expected to represent a promising tool for enhanced delivery of glimepiride.***

I. INTRODUCTION

Diabetes mellitus (DM) is one of the major causes of death in the world especially in developing countries and about 422 million people worldwide have diabetes in 2014 and are expected to reach 700 million patients by 2045(Bahari et al., 2022). DM is a chronic metabolic disease characterized by high blood glucose level resulting from insulin deficiency, insulin resistance or both. Glimepiride (GLM) is a potent hypoglycemic drug used for treatment of non-insulin dependent diabetes mellitus (NIDDM) or type II diabetes (Reginald-Opara et al., 2015). According to the Biopharmaceutics Classification System (BCS), GLM can be assigned to class-II with high permeability and low aqueous solubility (log *P* = 4.7) (Taupitz et al., 2013). In addition, glimepiride shows a low pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37 ˚C (<0.004 mg/ml) while at pH > 7, the solubility of the drug is slightly increased to 0.02 mg/ml (Dixit et al., 2012; Reginald-Opara et al., 2015).The poor aqueous solubility and slow dissolution rate of glimepiride have some difficulties in its dosage design, leads to unpredictable bioavailability, irreproducible clinical response or therapeutic failure in some cases due to low therapeutic plasma drug levels (Li et al., 2015).

Recently, several formulation techniques have been designed to overcome these problems including micronization (Ning et al., 2011), nanosuspension (Rahim et al., 2019), solid dispersion (Chaudhari et al., 2012), self-emulsifying system (Ahmed et al., 2014) , complexation with cyclodextrins (Ammar et al., 2006) and formation of co-crystal which is considered as one of the most promising approaches used to enhance the dissolution rate and eventually oral bioavailability of the poorly water soluble drugs. Co-crystal is defined as a non-single component system formed of various components that are solid under ambient conditions and attached with non-covalent bonds such as hydrogen bonds and van der Waals bonds (Wicaksono et al., 2017). Pharmaceutical cocrystals improve the physical properties of drugs such as solubility, wettability and compaction behaviors of the drug without affecting pharmacological nature of the drug (Ganesh et al., 2015). Pharmaceutical co-crystal consists of an active pharmaceutical ingredient (API) and co-former which may not have pharmacological activity.

Co-former generally forms hydrogen bonding with the API. Both the API and Co-former should contain hydrogen donors or accepting group like carboxylic acids and amides **(Vinesh et al., 2013).** The main objective of the current study was to investigate the formation of GLM co-crystal in order to enhance the solubility, dissolution rate and hence oral bioavailability of GLM.

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue II Feb 2023- Available at www.ijraset.com

II. MATERIALS

Glimepiride (GLM) was kindly provided by South Egypt Drug Industries Company, (SEDICO), (6th of October City, Egypt). Metformin was supplied by Sigma for Pharmaceutical Industries, (Quesna, Egypt). Sodium Lauryl Sulfate (SLS), Ascorbic acid, Citric acid, Oxalic acid, Benzoic acid and Succinic acid were purchased from El Nasr Pharmaceutical Chemicals Company (ADWIC), (Cairo, Egypt). Alloxan monohydrate was purchased from Alpha Chemika (Mumbai, India). Distilled water was used throughout the studies. All the other chemicals and reagents used were of analytical reagent grade used without further purification.

III. METHODS

A. *Preparation of Cocrystals*

Cocrystals were prepared by ultrasound assisted suspension co-crystallization technique.

Several co-crystal formulations containing GLM and co-former in molar ratios 1:1 and 1: 2 as shown in table 1 were prepared by dissolving solids in 50 ml methanol and solutions were subjected to several ultrasound pulses in a cold water jacketed glass bakers for 5 min. using a high intensity ultrasound probe (an ultrasound pulse of 10 s with relaxation time of 2 s was employed to avoid excess heating). Solids were separated by filtration, rinsed with cold methanol and dried overnight at 30 ◦C**.**

Table 1:The weight ratio of GLM and different co- formers

Formulation	Co-former	Ratio	GLM conc. (mg)	Co-former conc. (mg)
F1	Ascorbic acid	1:1	490	176.4
F2	Ascorbic acid	1:2	490	352.8
F3	Citric acid	1:1	490	192
F4	Citric acid	1:2	490	384
F5	Oxalic acid	1:1	490	126
F6	Oxalic acid	1:2	490	252
F7	Benzoic acid	1:1	490	122.5
F8	Benzoic acid	1:2	490	245
F9	Succinic acid	1:1	490	117.6
F10	Succinic acid	1:2	490	235.2

B. *Solubility Studies*

The solubility of GLM co-crystals and pure GLM in distilled water were determined by shake-flask method. An excess amount of each sample was placed in stoppered conical flask and distilled water added. The flasks were stirred at 37 ±0.5 °C for 72 h in a shaking water bath to achieve equilibrium. The equilibrated samples were then filtered through a 0.45 μm millipore filter and the concentration of the dissolved drug was measured spectrophotometrically at 229 nm against blank. The experiment was repeated in triplicate. Physicochemical characterization of GLM-OA co-crystal

C. *Fourier Transform Infrared (FT-IR) Spectroscopy*

Fourier transform infrared (FT-IR) spectroscopic studies were carried out for plain GLM, OX, and F7 formula, co-crystal of Glimepiride and Oxalic acid 1:2 molar ratio, (GLM-OX) using potassium bromide (KBr) disc method. Approximately samples of 2-3 mg of each were carefully mixed with KBr, palletized under vacuum and then analyzed using FT-IR spectrophotometer at range of 400-4000 cm^{-1} to evaluate the functional groups of each prepared sample.

D. *Differential Scanning Calorimetry (DSC)*

Differential Scanning Calorimetry (DSC) studies were carried out for plain GLM, OX, and GLM-OX co-crystal. Samples of 5 mg were hated in a temperature range of 40-240 °C at rate of 10 ˚C/min in flat-bottom aluminum pans in presence of nitrogen at flow rate of 30 ml/min to obtain the endothermic peaks. An empty aluminum pans were used as a reference.

E. *X-ray Powder Diffraction*

The diffraction patterns for plain GLM, OX, and GLM-OX co-crystal were performed using Philips analytical X-ray diffractometer) based with Cu tube anode of wave length Kα1 =1.54A° and Kα2 = 1.54439A°. The generator tension was 40KV and the generator current was 30 mA. The start angle (2θ) was 10°, end angle was 70°, step size (2θ) was 0.02 and the step time was 1.0 sec.

F. Scanning Electron Microscopy (SEM)

Scanning electron micrograph of the surface morphology of the GLM-OX was taken using scanning electron microscope (SEM) (JSM 5500, JEOL, Tokyo, Japan) under high vacuum mode.

G. In Vitro Dissolution Study

Dissolution study was carried out for plain GLM, physical mixture (1:2) as control and GLM-OX using USP rotating dissolution apparatus type II. The study was carried out in 900 ml phosphate buffer solution (pH 6.8) containing 0.5% sodium lauryl sulfate (SLS) maintained at 37±0.5 ˚C and the stirring speed was 100 rpm. Samples of 10 mg of GLM and its equivalent of physical mixture and GLM-OX co-crystal were suspended in the dissolution medium. Samples of 5ml were withdrawn at predetermined time intervals and replaced with an equal volume of preheated dissolution media to maintain sink condition. The samples were analyzed by UV spectrophotometer at 229 nm against blank in triplicate.

IV. IN VIVO STUDIES

A. Animals

The bioavailability study was performed in a parallel experimental design using healthy male albino rats 3-4 months-old (250±25 g. average body weight). All animals were adapted for one week in the animal house (faculty of pharmacy, Alazhar University, Cairo) prior to the beginning of the experiment. Rats were fed standard rat diet with free access to tape water and kept under constant environmental conditions (22 ±3 °C; 50 ±5% relative humidity).

B. Chromatographic Conditions

The chromatographic separation was done by isocratic elution using mobile phase consisted of filtered and degassed mixture of 0.02 M phosphate buffer (pH=3.5): acetonitrile (38:62% v/v) and was pumped at a flow rate of 1 ml/min. The sample, 30 µl volume, was injected into the HPLC (Parkin Elmer, USA) employing C-18 column (Phonomenex, 250×4.60 mm, particles size 5 µm). The detection was carried out at a wavelength 230 nm.

C. Pharmacokinetic Studies

Animals were fasted overnight and they were divided arbitrarily into two groups with three rats for each group (n=3). **Group I** was administered a single orally dose of GLM suspension (GLM suspended in distilled water by vortex for 5 minutes). **Group II** was administered GLM-OX suspension (formula suspended in distilled water by vortex for 5 minutes). All animals under the study were administrated GLM at dose equivalent to 2.5 mg/kg body weight **(Yadav et al., 2012).**

Blood samples, 0.3ml were collected from orbital sinuses into heparinized Eppendorf tube at predetermined time interval (zero time, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h) in micro-centrifuge tubes each containing 10 µl Ethylene Diamine Tetra Acetic Acid (EDTA) Plasma was separated directly by centrifuge at 10,000 rpm for 5 minutes and preserved at −20 ^{o}C until analysis.

D. Quantitative Determination of GLM in Plasma

Plasma proteins were precipitated by adding 0.5 ml of mixture of acetonitrile-methanol (1:1) to the plasma samples, vortexed for 1 minute and then centrifuged at 5000 rpm for 10 min. Afterwards, the precipitates were removed by using a polytetrafluoroethylene (PTFE) syringe filter (pore size 0.22 µm) and supernatant was transferred to another Eppendorf tube. Thirty microliters of the supernatant were injected onto the column of the high performance liquid chromatography (HPLC).

E. Analysis of Pharmacokinetic (PK) parameters

Pharmacokinetic parameters (± SD) were calculated using the Kinetica 5.1 software. The pharmacokinetic parameters included the maximum plasma drug concentration after drug administration (C_{max}), the time required to reach the maximum plasma drug concentration (t_{max}), the area under the plasma concentration time curve ($AUC_{0-\infty}$), half-life of elimination phase ($t_{1/2\ el}$) and the mean residence time (MRT). Data were analyzed using student t test for comparisons. *P* values less than 0.05 were considered statistically significant.

V. RESULTS AND DISCUSSION

A. Preparation of cocrystals

Products observed after cessation of sonication were in the form of particles suspended in methanol. These particles formed a hard cake after subsequent drying and were easy to ground into powder using a mortar and pestle and were subjected to solubility studies.

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue II Feb 2023- Available at www.ijraset.com

B. Solubility Studies

The evaluation of GLM solubility in the synthesized co-crystals with different co-former and molar ratios is the primary step for selection of the appropriate co-former and molar ratio to complete the study. Figure 1 shows the equilibrium solubility data of various formulations of co-crystals compared to plain GLM. Formula F6 exhibit maximum solubility with significant difference ($P > 0.05$) out of all co-crystal formulation, whereas significant enhancement ($P < 0.05$) of solubility was observed in case of all formulations compared to plain GLM. The improvement in solubility of GLM in co-crystal formulation could be attributed to the hydrogen bond formation between carbonyl groups of GLM and hydroxyl groups of different carboxylic acids used as co-formers.so, F6 formula (GLM-OX) was selected to complete the study.

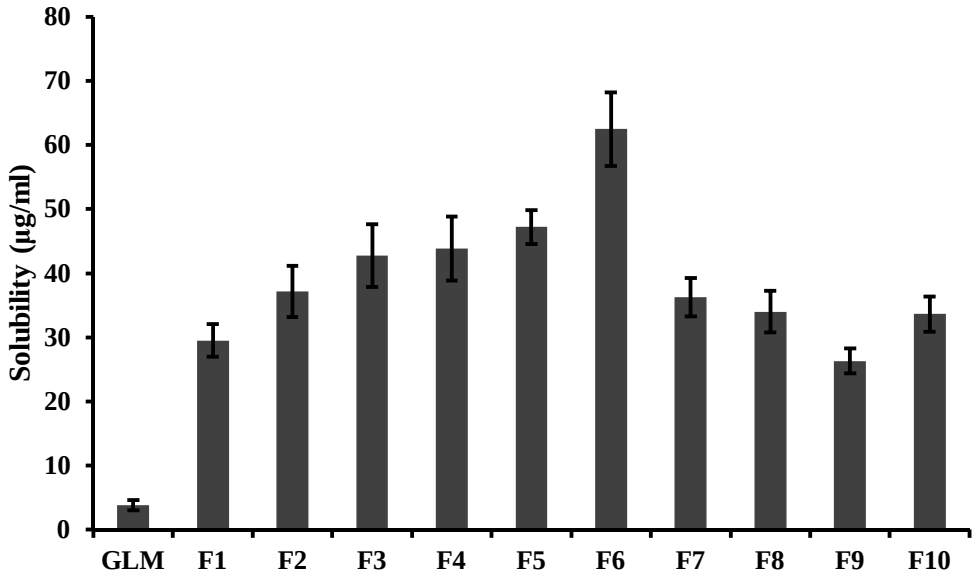


Figure 1: The solubility profile of GLM and its cocrystals

C. Fourier Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectra of GLM, OX and GLM-OX are illustrated in Figure Fig 2. The IR spectrum of GLM showed the presence of characteristic peaks at 3369 and 3288.4 cm^{-1} due to N-H stretch for urea, peaks at 1345 and 1153.7 cm^{-1} corresponding to the sulphonamide group and peaks at 1705 and 1676 cm^{-1} corresponding to the carbonyl group. The IR spectrum of oxalic acid showed characteristics peaks corresponding to carbonyl group and carboxylic acid group at 1690 cm^{-1} and 3481 cm^{-1} respectively. The spectrum of GLM-OX co-crystal showed changes in peaks corresponding to sulphonamide group of GLM as decrease in intensity and a little shift to lower wave number. Also the absorption band corresponding to the hydroxyl group of oxalic acid was disappeared suggesting hydrogen bond formation between the hydroxyl group of oxalic acid and sulphonamide group of GLM. There was no new peak appeared which confirmed that no chemical interaction occurred between drug and co-former.

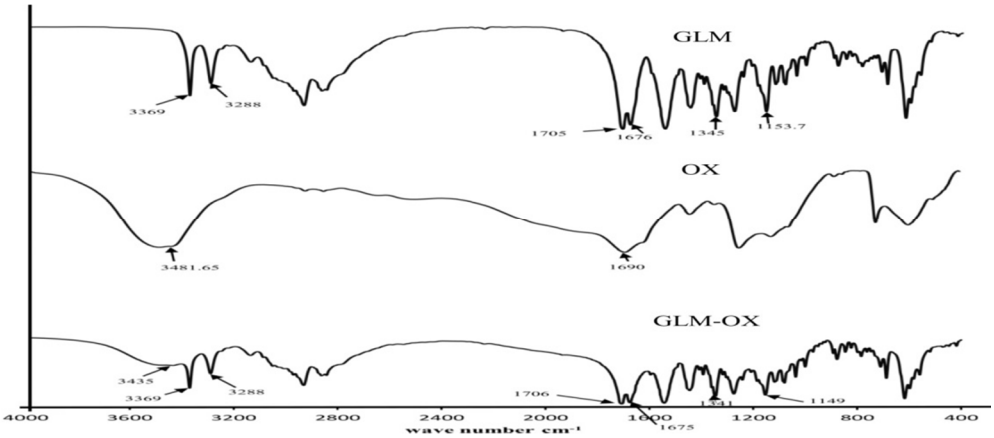


Figure 2: FTIR spectra of GLM, OX and GLM-OX co-crystal

D. Differential Scanning Calorimetry (DSC)

DSC analysis is performed to determine the thermal behavior of the pure drug, co-former and co-crystal formula. The DSC thermograms of GLM, OX and GLM-OX are shown in Fig3. The thermogram of plain GLM displayed a sharp endothermic peak at 217.3 ℃ representing the melting point of GLM. The thermogram of oxalic acid showed endothermic peak at 193.1 ℃ corresponding to the melting point of oxalic acid and another peak appeared at 101.4 °C corresponding to dihydrate characteristic of oxalic acid. This is due to an adsorption of water molecules on oxalic acid particles (Othman et al., 2018). The thermogram of GLM -OX co-crystal showed a single endothermic peak occurred between the melting points of GLM and Oxalic acid which is attributed to the melting of the co-crystal phase at 205.3 °C indicating hydrogen bond formation between GLM and oxalic acid.

A single endothermic transition for the GLM OX co-crystals indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point (Basavoju et al., 2008).

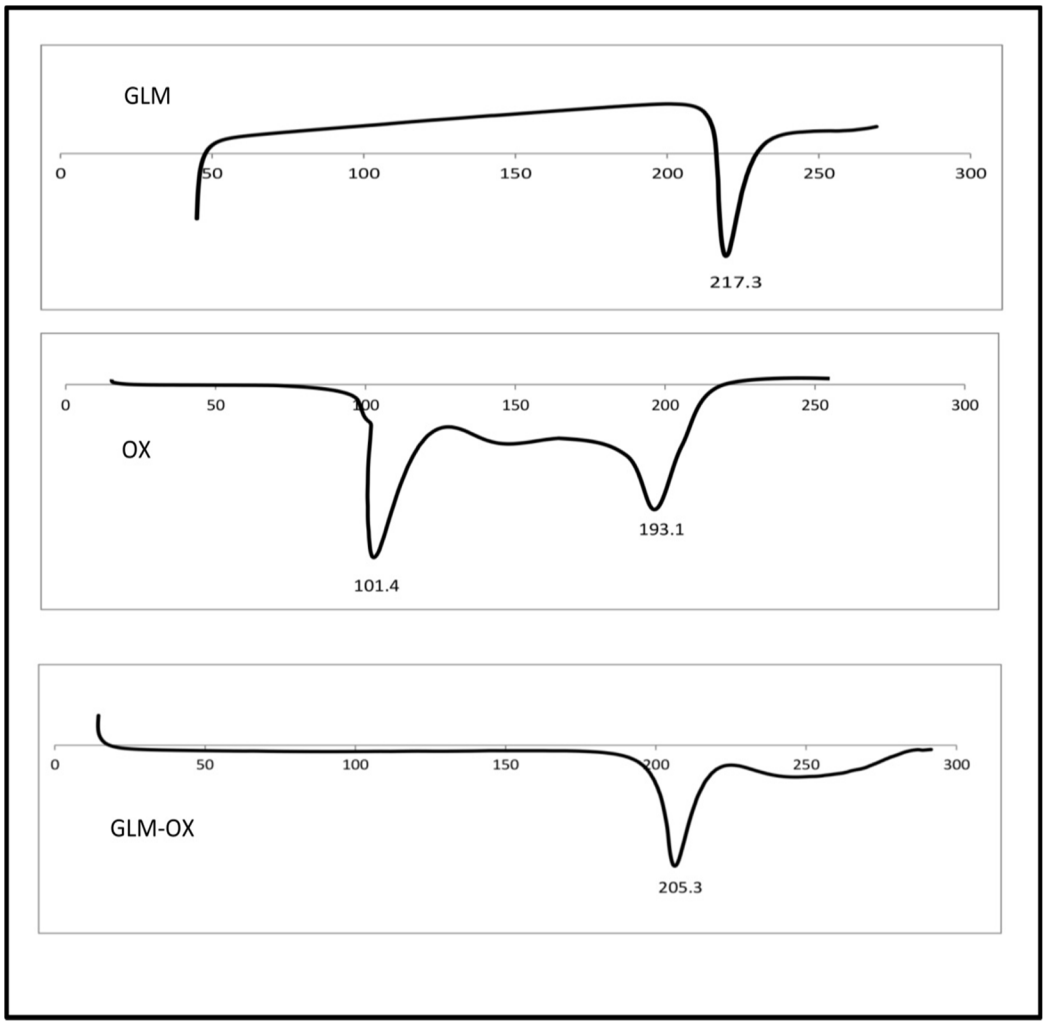


Figure 3: DSC thermogram of GLM, OX and GLM –OX co-crystal

E. X-ray Powder Diffraction

The diffraction patterns of GLM-OX compared to plain GLM and OX are shown in figure 4

The diffraction pattern of plain GLM powder showed characteristic high-energy diffraction peaks at 2θ values between 13° and 27°, indicating the crystalline structure of GLM (Du et al., 2013), while the diffraction pattern of OX showed characteristic crystalline peaks at 2θ values of 14.65, 18.84, 29.06 and 31.5°. A different powder X-ray pattern for the GLM – OX co-crystal from those of the GLM and OX confirms the formation of a new co-crystal phase , also formation of new peaks at 2θ = 30-50° with intensity peaks at 34.21° and 43.53° representing hydrogen bond formation which is Compatible with DSC study. This indicated that there has been an increase in size, change in crystal form or the addition of a crystal lattice (Budiman et al., 2016).

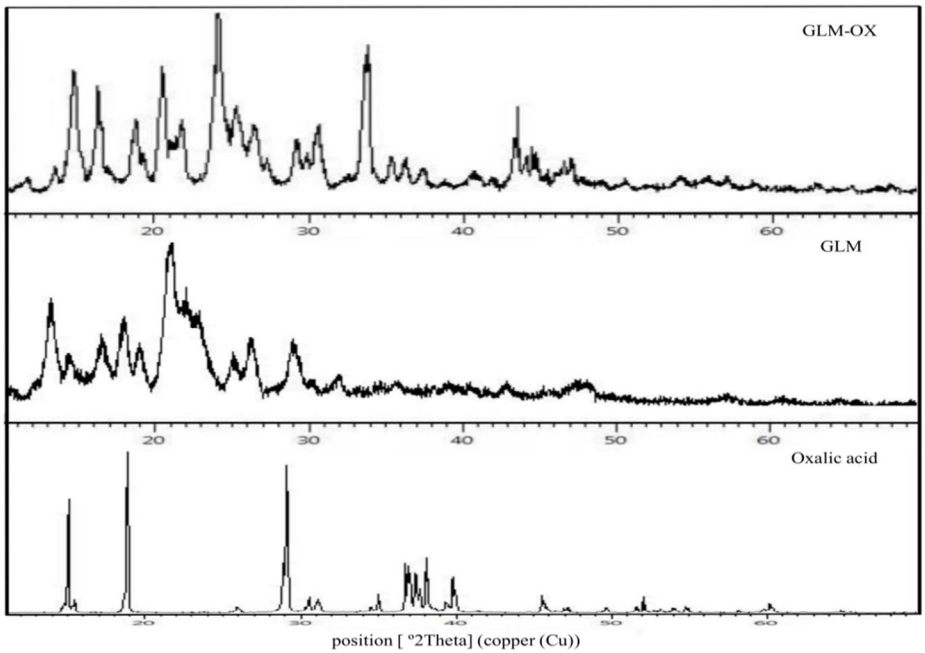


Figure 4: PXRD patterns for plain GLM, OX and GLM-OX co-crystal

F. Scanning Electron Microscopy (SEM)

SEM micrographs of GLM-OX co-crystal were illustrated in figure 5. The prepared co-crystals showed definite shape with crystalline composition.

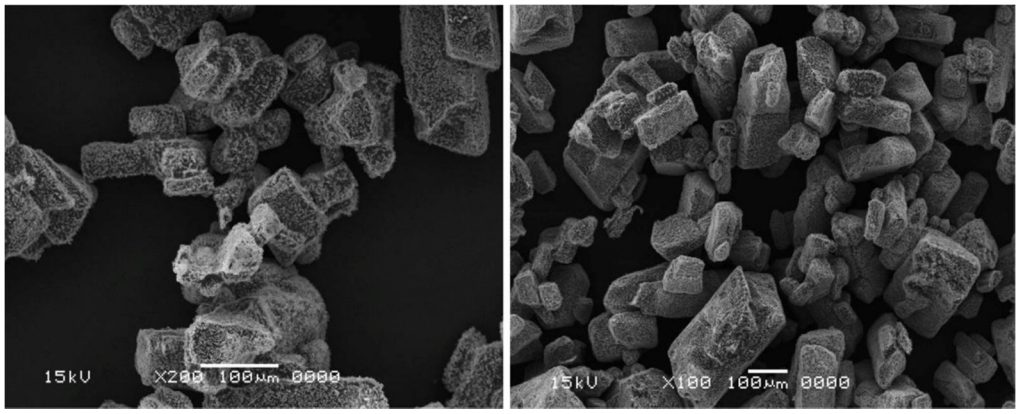


Figure 5: SEM image of GLM-OX co-crystal

G. In Vitro Dissolution Study

The dissolution profiles of plain GLM, PM and GLM-OX are presented in Figure 6. The dissolution of GLM in co-crystal formula reached 71.93 % within 5 min. However, only 7.83% of plain GLM was dissolved during the same period. After 120 min. about 97.3 % of GLM was dissolved from GLM-OX, while only 22.06 % of pure GLM was dissolved. The recorded dissolution data for physical mixture showed liberation of 18.65% of the dose in the first 5 min. and 36.82 % after 60 min., these findings reflect the importance of co-crystalline structure for enhanced dissolution rate of GLM in presence of oxalic acid. These results indicate that GLM-OX co-crystal dissolves faster than the pure GLM. The enhancement of dissolution rate of co-crystal can be explained by effects of changing crystal morphology of GLM into co-crystal formulation. The difference of GLM-OX co-crystal surface forms a new surface nature of the crystal. Thus, it changes the dissolution stage of the co-crystal. Overall, the increased dissolution rate of GLM-OX co-crystal appears as a combination of crystal packing and morphology changes in the co-crystal (Wicaksono et al., 2017).

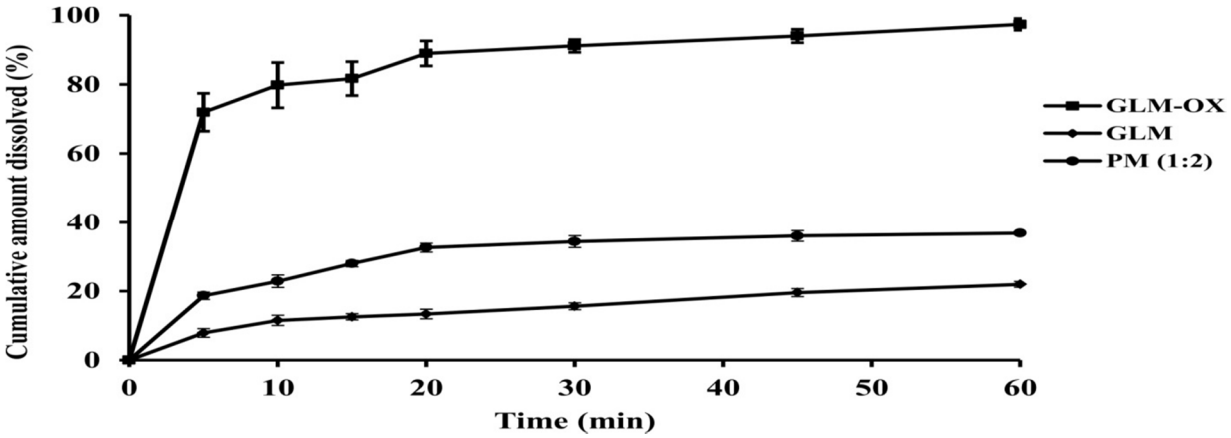


Figure 6: Dissolution profiles of the pure GLM, PM (1:2) and the GLM-OX co-crystals

H. In Vivo Pharmacokinetic Study

Poor aqueous solubility and slow dissolution rate of the GLM lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels. The present study was focused to investigate the feasibility of using co-crystal technique to improve dissolution rate and eventually oral bioavailability of GLM .Average GLM plasma concentration time profiles and pharmacokinetic parameters following administration of single oral dose of GLM-OX and plain GLM suspension to male albino rats are shown in figure 6 and table 2.

GLM-OX and GLM suspension differed markedly in their pharmacokinetic parameters ($P < 0.05$).The average peak plasma concentration (C_{max}) of GLM-OX was 2.62-folds higher than GLM suspension. The time to reach maximum concentration (T_{max}) for both GLM-OX and GLM suspension was 3 hr. The area under the curve ($AUC_{0-\infty}$) was 2.66-folds higher in the GLM-OX group as compared to group received GLM suspension. The mean residence time (MRT) was significantly differ (P=0.0115) and was about 1.17 folds higher in GLM-OX compared to GLM suspension. Finally, the elimination half-life ($t_{1/2}$) was significantly differ (P =0.0046) and was about 1.3 folds higher in GLM-OX compared to GLM suspension.

These results indicated that oral absorption of GLM was significantly improved by physical interaction with Oxalic acid via co-crystallization technique, which enhanced free GLM concentration and increased drug supersaturation levels in the GIT. This might be correlated with the improved solubility and dissolution rate of GLM-OX and thus making it available at the surface of the biological membrane, where it partitions into the membrane and hence improved GLM average plasma concentration.

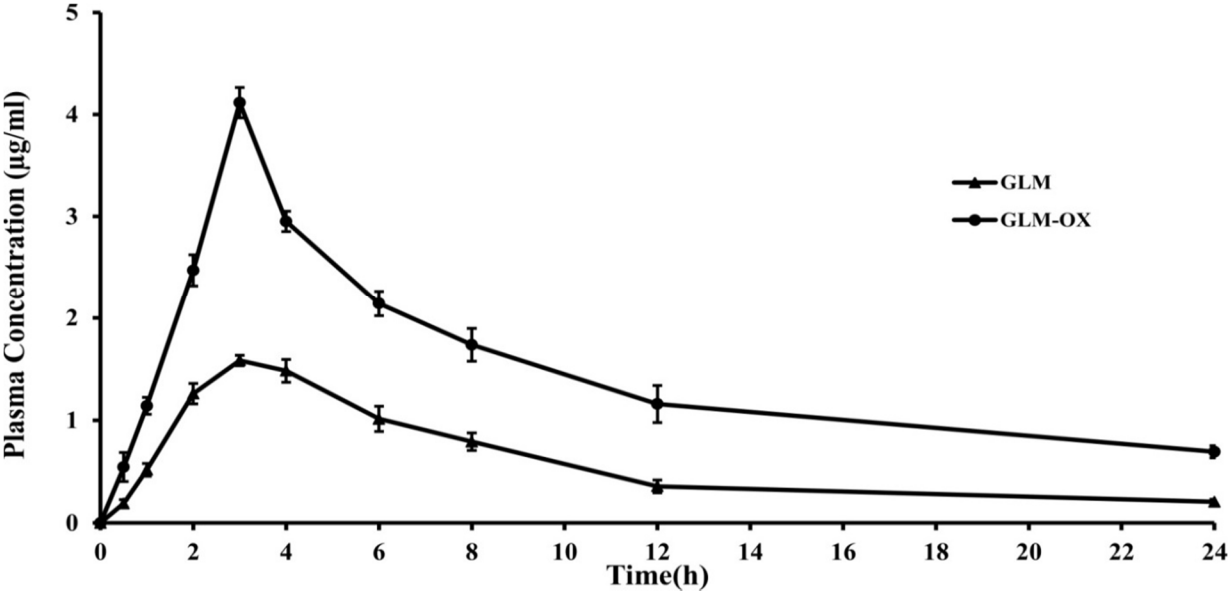


Figure 7: Plasma concentration vs. time profile after oral administration of GLM-OX and GLM suspension. Each value represents the mean ±SD (n=3).

Table 2: Pharmacokinetic parameters after oral administration of plain GLM and GLM-OX to rats (n = 3)

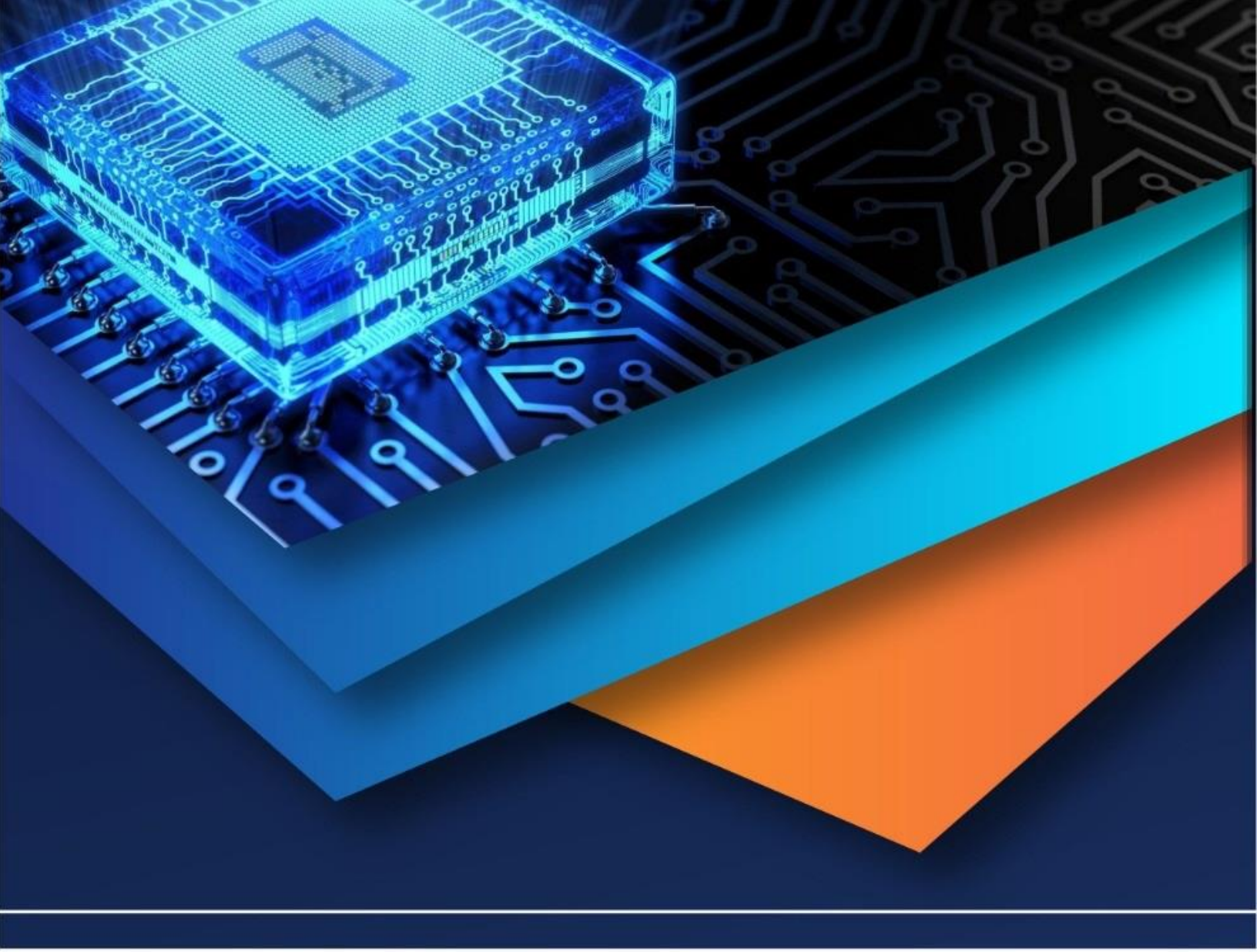
Formulation	C_{max} (µg/ml)	T_{max} (h)	$t_{(1/2)\ el}$ (h)	$MRT_{(0-\infty)}$ (h)	$AUC_{(0-\infty)}$ (µg*hr/ml)	F
GLM-OX	4.12 ± 0.14	3	9.44 ± 0.53	11.80 ± 0.48	43.15 ± 2.18	2.66
Plain GLM	1.58 ± 0.04	3	7.26 ± 0.38	10.07 ± 0.47	16.20 ± 1.31	

VI. CONCLUSION

In the current study, we successfully prepared GLM-OX co-crystal to improve dissolution rate and eventually enhance oral bioavailability. The solubility study aided in identification of the most appropriate co-former that could be used to prepare co-crystals with maximum solubility potential for GLM. Physicochemical characterization confirmed the formation co-crystal between GLM and OX. In vitro release profiles showed that co-crystallization technique enhance the dissolution rate of GLM in comparison to pure drug. SEM micrographs of GLM-OX co-crystal showed definite shape with crystalline composition. Oral bioavailability of GLM was about 2.66-folds higher in animals administrated GLM-OX than animals received GLM suspension.

REFERENCES

[1] Ahmed, O. A., Afouna, M. I., El-Say, K. M., Abdel-Naim, A. B., Khedr, A., and Banjar, Z. M. (2014). Optimization of self-nanoemulsifying systems for the enhancement of in vivo hypoglycemic efficacy of glimepiride transdermal patches. Expert opinion on drug delivery 11, 1005-1013.
[2] Ammar, H., Salama, H., Ghorab, M., and Mahmoud, A. (2006). Formulation and biological evaluation of glimepiride–cyclodextrin–polymer systems. International journal of pharmaceutics 309, 129-138.
[3] Bahari, N. I., Ahmad, N., Mahmud, M. H., Baharom, M., Amir, S. M., Peng, C. S., Hassan, M. R., and Nawi, A. M. (2022). Issues and Challenges in the Primary Prevention of Type 2 Diabetes Mellitus: A Systematic Review. Journal of Prevention, 1-21.
[4] Basavoju, S., Boström, D., and Velaga, S. P. (2008). Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. Pharmaceutical research 25, 530-541.
[5] Budiman, A., Nurlatifah, E., and Amin, S. (2016). Enhancement of solubility and dissolution rate of glibenclamide by cocrystal approach with solvent drop grinding method. Int J Curr Pharm Rev Res 7, 248-250.
[6] Chaudhari, M. D., Sonawane, R. O., Zawar, L., Nayak, S., and Bari, S. B. (2012). Solubility and dissolution enhancement of poorly water soluble glimepiride by using solid dispersion technique. Int J Pharm Pharm Sci 4, 534-539.
[7] Dixit, A., Singh, R., and Singh, S. (2012). Solid dispersion-a strategy for improving the solubility of poorly soluble drugs. International Journal of Research in Pharmaceutical and Biomedical Sciences 3, 960-966.
[8] Du, B., Shen, G., Wang, D., Pang, L., Chen, Z., and Liu, Z. (2013). Development and characterization of glimepiride nanocrystal formulation and evaluation of its pharmacokinetic in rats. Drug delivery 20, 25-33.
[9] Ganesh, M., Jeon, U. J., Ubaidulla, U., Hemalatha, P., Saravanakumar, A., Peng, M. M., and Jang, H. T. (2015). Chitosan cocrystals embedded alginate beads for enhancing the solubility and bioavailability of aceclofenac. International journal of biological macromolecules 74, 310-317.
[10] Li, H., Ma, L., Li, X., Cui, X., Yang, W., Shen, S., and Chen, M. (2015). A simple and effective method to improve bioavailability of glimepiride by utilizing hydrotropy technique. European Journal of Pharmaceutical Sciences 77, 154-160.
[11] Ning, X., Sun, J., Han, X., Wu, Y., Yan, Z., Han, J., and He, Z. (2011). Strategies to improve dissolution and oral absorption of glimepiride tablets: solid dispersion versus micronization techniques. Drug development and industrial pharmacy 37, 727-736.
[12] Othman, M., Anuar, N., Rahman, S. A., and Taifuddin, N. A. (2018). Corystal screening of ibuprofen with oxalic acid and citric acid via grinding method. Paper presented at: IOP Conf. Ser.: Mater. Sci. Eng.
[13] Rahim, H., Sadiq, A., Khan, S., Amin, F., Ullah, R., Shahat, A. A., and Mahmood, H. M. (2019). Fabrication and characterization of glimepiride nanosuspension by ultrasonication-assisted precipitation for improvement of oral bioavailability and in vitro α-glucosidase inhibition. International journal of nanomedicine 14, 6287.
[14] Reginald-Opara, J. N., Attama, A., Ofokansi, K., Umeyor, C., and Kenechukwu, F. (2015). Molecular interaction between glimepiride and Soluplus®-PEG 4000 hybrid based solid dispersions: Characterisation and anti-diabetic studies. International journal of pharmaceutics 496, 741-750.
[15] Taupitz, T., Dressman, J. B., and Klein, S. (2013). New formulation approaches to improve solubility and drug release from fixed dose combinations: case examples pioglitazone/glimepiride and ezetimibe/simvastatin. European Journal of Pharmaceutics and Biopharmaceutics 84, 208-218.
[16] Vinesh, V., Sevukarajan, M., Rajalakshmi, R., Chowdary, G. T., and Haritha, K. (2013). Enhancement of solubility of tadalafil by cocrystal approach. Int Res J Pharm 4, 218-223.
[17] Wicaksono, Y., Wisudyaningsih, B., and Siswoyo, T. A. (2017). Enhancement of solubility and dissolution rate of atorvastatin calcium by co-crystallization. Tropical Journal of Pharmaceutical Research 16, 1497-1502.
[18] Yadav, S. K., Mishra, S., and Mishra, B. (2012). Eudragit-based nanosuspension of poorly water-soluble drug: formulation and in vitro–in vivo evaluation. AAPS pharmscitech 13, 1031-1044.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY