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**Science Journal of University of Zakho**

Vol. 12, No.4 pp.469–476 October-December,2024

p-ISSN: 2663-628X
e-ISSN: 2663-6298

# ENHANCE THE AQUEOUS SOLUBILITY OF DICLOFENAC THROUGH THE SYNTHESIS OF DICLOFENAC-INOSITOL PRODRUG

Hemn Latif Qader[1*], Omer Abdulrahman Alsheikhly[2], Hewa Abdulla Hamadameen Hama[1], Adnan Burhan Qader[1]

[1] Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq.
Corresponding Author Email: hemn.latif@hmu.edu.krd

Received: 28 Jul. 2024 / Accepted:26 Sep., 2024 / Published: 10 Nov., 2024. https://doi.org/10.25271/sjuoz.2024.12.3.1360

**ABSTRACT:**
Due to limited aqueous solubility, poor bioavailability makes oral dosage formulations difficult to formulate. Chemical alteration of medicinal compounds improves solubility. Prodrug design is a popular molecular modification method that improves solubility and oral bioavailability. This study aims to synthesize a diclofenac prodrug to enhance aqueous solubility. In this study, diclofenac was esterified with inositol to make a prodrug (DIP), which was identified by $^{1}$H-NMR and FT-IR. A computational pharmacokinetic software was used to study DIP's pharmacokinetic profile, and saturation solubility was measured in phosphate buffer (pH 6.8) and 0.1 HCl (pH 1.2) solutions. The ester bands of (C=O) stretch at 1739 $cm^{-1}$ and the elimination of H signals of carboxylic acid at 10-12 ppm in the $^{1}$H-NMR spectrum proved the synthesis of (DIP). Diclofenac solubility increased 827-fold in phosphate buffer solution ($p < 0.05$) from 0.059± 0.0164 mg/ml to 48.8± 0.034 mg/ml, primarily due to polarity change. The solubility of diclofenac and (DIP) in 0.1 N HCl (pH 1.2) was 0.016± 0.0031 and 0.018± 0.002, respectively. The improvement in solubility in the acidic medium was non-significant ($p > 0.05$) due to acid hydrolysis of the ester bond between inositol and the drug. The synthesis of diclofenac prodrug can greatly enhance its water solubility.
**KEYWORDS:** Aqueous solubility, Diclofenac, esterification reaction, inositol, prodrug,

## 1. INTRODUCTION

Due to its ease of use, high patient acceptability, affordability, minimal sterility requirements, and flexibility in dosage form design, oral administration is the most practical and widely used method of drug delivery (Sopan *et al*., 2021). Consequently, a lot of pharmaceutical companies are inclined to create bioequivalent oral medicine products. Essential factors that govern the bioavailability of therapeutic compounds in systemic circulation for optimal pharmacological activity are their soluble and dissolvable state at the site of absorption in the gastrointestinal tract (Yadav *et al*., 2021). However, their low bioavailability is the main barrier to the development of oral dosage forms. The hepatic first-pass effect, permeability through the gastrointestinal wall, drug release in the biological fluid, and water solubility are some factors that affect the bioavailability of medications taken orally (Khan, 2021).

The biopharmaceutical classification system (BCS) divides medicinal compounds into four classes; class II medicines being distinguished by strong membrane permeability and poor aqueous solubility (Daravath *et al*., 2017). Class II medicines have low oral bioavailability and lower pharmacological effects due to rate-limiting phases in the absorption process, namely solubility and dissolving rate (Rubim *et al*., 2014). Drug substance alterations on a physical, chemical, and molecular level are the many categories of solubility improvement techniques. Drug dispersion in carriers, particle size reduction, and drug crystal habit modification are examples of physical modification techniques. Chemical modification strategies, on the other hand, include complexation, pH changes, and drug salt forms (Khatri *et al*., 2022). Prodrug design is a well-known molecular modification technique that aims to optimize the physical, chemical, and biological properties of drugs to decrease toxicity and boost solubility and pharmacokinetic characteristics (Jornada *et al*., 2016).

"Pharmacologically inactive moiety which is converted to an active form within the body" is how Albert initially defined the term "prodrug" (Liu *et al*., 2019). The primary goal of creating a prodrug is to alter the chemical structure of a drug molecule to impart desirable physicochemical and/or pharmacokinetic properties through the use of precursor-based or carrier-linked techniques (Shah *et al*., 2017). One of the first medications to be synthesized as a prodrug to increase its water solubility and bioavailability was phenytoin, a medication which is poor water soluble. A research team under the direction of Valentino J. Stella developed prophenytoin, a phenytoin prodrug that is soluble in water, in 1975. In one of the first and comparatively complete works on prodrugs, the synthesis method, physicochemical characteristics, activity, and pharmacokinetic profile of prophenytoin after oral and parenteral administration were described (Stella, 2020).

Diclofenac is a nonsteroidal anti-inflammatory medication (NSAID) with analgesic, anti-inflammatory, and antipyretic properties that is a member of the phenylacetic acid class (Figure 1) (Kaynak *et al*., 2015). It was selected as the model drug for

* Corresponding author

this study since BCS (Pund *et al*., 2021) indicates that it is classified as a class II drug. As previously indicated, for this category to achieve meaningful bioavailability following oral administration, the solubility must be improved.

A naturally occurring substance, inositol is involved in lipid production, cell development, morphogenesis, and cytogenesis (Bizzarri et al., 2016). Long regarded as a B vitamin (Vitamin B8), inositol is a cyclic carbohydrate with six hydroxyl groups (Figure 1) that controls numerous vital cellular functions, such as neuron activation, secretion, contraction, gametogenesis, and cell proliferation and development (Suliman *et al*., 2022). In numerous trials, including patients with insulin resistance and polycystic ovarian syndrome, inositol has been used as a dietary supplement safely for decades (DiNicolantonio & O'Keefe, 2022). In this study, inositol was added to a novel diclofenac prodrug formulation to improve its oral bioavailability and water solubility, in addition to its clinical applications.

This study aims to enhance water solubility class II drug diclofenac acid through the synthesis of prodrugs with inositol.

## 2. Materials and Methods

### Materials

Diclofenac was kindly gifted from Awamedica Pharmaceutical Company, Erbil. Iraq. The chemical solvents and inositol were received from the commercial suppliers Sigma-Aldrich, Merck, and Alpha. Distilled water was prepared in the laboratory. The chemical structures and the chemical schemes were drawn by the Chemoffice 12 program, the identification of the new products was performed using the FT-IR JASCOFT/IR-4600 spectrometer (Japan) and $^{1}$H-NMR Bruker spectrometer (300 MHz) (Germany).

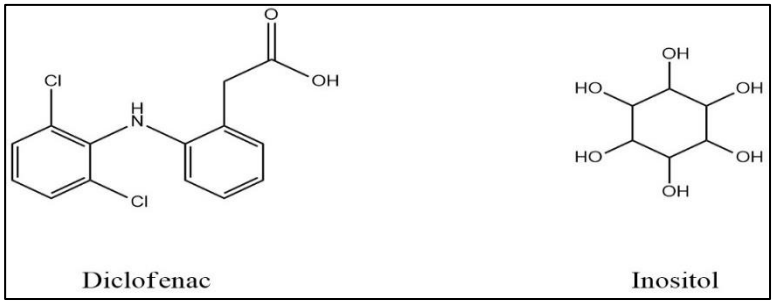



Figure 1: Chemical structure of Diclofenac acid and Inositol

### Methods

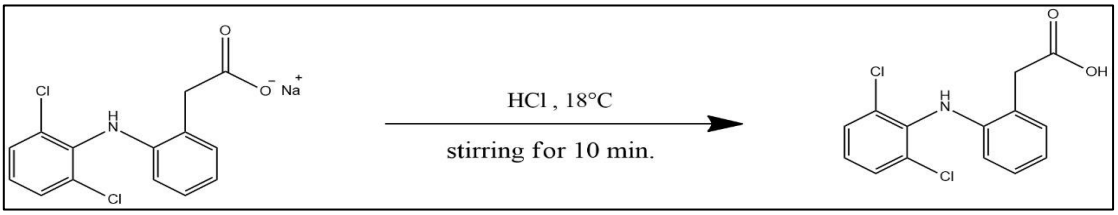
#### Chemical Preparation of diclofenac from diclofenac sodium

The chemical conversion of diclofenac sodium shown in scheme 1, which is one of the methods for chemical preparation of diclofenac according to literature, is accomplished by dissolving precisely 10g of diclofenac sodium in a mixture of absolute ethanol and Tetrahydrofuran (THF) at a volume ratio of 3:1. The mixture was lowered to 18°C. After that, 15 milliliters of 2N HCl were added. After agitating the mixture for ten minutes, 150 milliliters of cold water were added (Hassan & Elias, 2014). The precipitate was filtered and dried without additional purification to produce diclofenac acid, which was used in the next step.

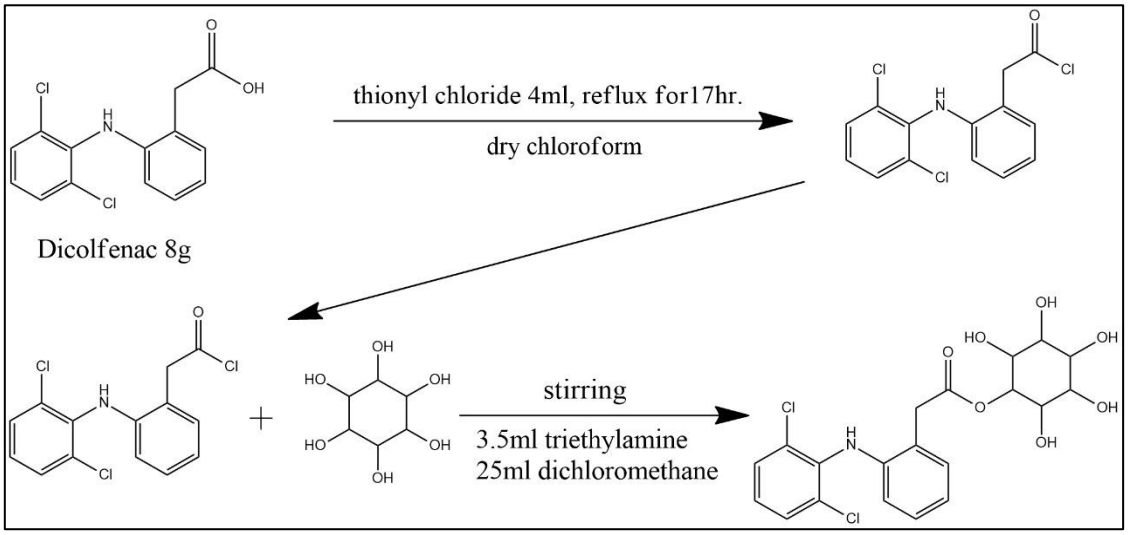
#### Synthesis of diclofenac prodrug

The Diclofenac-inositol prodrug (DIP) molecule was synthesized by dissolving 8g of Diclofenac in 120 ml of dry chloroform scheme 2. The resulting solution was then placed in a round bottom flask and cooled to a temperature of below 0°C, which was maintained throughout the procedure. Exactly 4 milliliters of thionyl chloride were gradually added over 20 minutes while continuously being stirred. Once all of the thionyl chloride had been added, the mixture was subjected to reflux for 17 hours at a temperature of 65°C, with continuous stirring. The solvent was permitted to undergo evaporation, and the
powder was dissolved again in anhydrous chloroform many times to ensure the complete elimination of any remnants of thionyl chloride.

The diclofenac acid chloride was dissolved in 25 milliliters of dry chloroform. The resultant solution was then added to a combination containing 3.5 milliliters of triethylamine, 25 milliliters of dry dichloromethane, and 4.87 g of inositol that had been previously chilled to temperatures below 0°C. The reaction mixture was agitated for an extended period of time, followed by three washes with 20 ml of hydrochloric acid solution with a concentration of 5% volume/volume. Subsequently, it was washed with a 20 ml sodium hydroxide solution with a concentration of 5% weight/volume. Finally, it was rinsed with 5 ml of cooled distilled water and the result (DIP) was dehydrated using anhydrous sodium sulphate (Hassan & Elias, 2014).
The pure compound was obtained using column chromatography with a mobile phase consisting of n-hexane and ethyl acetate at a ratio of 7:1 (Alsheikhly *et al*., 2024).




Scheme 1: Chemical conversion of diclofenac sodium to diclofenac acid




Scheme 2: Synthesis of Diclofenac-inositol prodrug (DIP)

**Identification of the prepared prodrug compound.**

**Fourier transforms infrared spectrophotometry (FT-IR)**

The identification of the prepared prodrug was performed by obtaining FT-IR spectrum in a range of 4000–400 $cm^{-1}$ using JASCOFT/IR-4600 spectrometer (Japan). The main objective of FT-IR study was to detect the formation of ester bond between diclofenac and inositol.

**Proton-Nuclear magnetic resonance ($^1$H-NMR)**

Further identification of the prepared prodrug was performed by obtaining $^1$H-NMR in a range of 1-19 ppm using Bruker spectrometer (Germany).

**Computational pharmacokinetic studies**

The evaluation of pharmacokinetic properties is crucial in the process of drug development, as it facilitates the assessment of the biological components of potential drug candidates. Lipinski's rule of five was employed to assess the suitability of a substance for oral bioavailability. The study focused on examining the ADME characteristics by using the Swissadme program to gain a better understanding of the drug-likeness and pharmacokinetics profiles. The colored portion in the obtained radar image represents the ideal physicochemical conditions for maximizing bioavailability (Unnisa *et al*., 2022).

**Evaluation of Diclofenac acid and Diclofenac prodrug**

**Determination of maximum absorbance (λ max) and calibration curve**

The Maximum absorbance and calibration curve of diclofenac and DIP were determined in two different aqueous media, namely phosphate buffer (pH 6.8) and 0.1 N HCl (pH 1.2). A standard stock solution of diclofenac and DIP was prepared by dissolving a 20 mg of each one in 10% v/v of aqueous methanol solution, which further diluted with phosphate buffer and 0.1N HCl respectively to obtain a total of four standard stock solutions of the drug and the prodrug at a concentration of 200 mcg/ml (Rashid *et al*., 2023). Solutions were prepared by suitable dilution of corresponding stock solution with phosphate buffer and 0.1N HCl: the prepared solutions were scanned using (Lambda 25 double beam UV/Vis spectrophotometer) in the range of 200-400 nm to determine the wavelength of maximum absorbance (λ max) of the drug and the prodrug in both mediums.

For the construction of calibration curves a series of solutions at concentration of 5, 10, 15, 20, 25 and 30 µg/ml were prepared for both drugs in the corresponding mediums by diluting the standard solutions and then the obtained solutions were scanned at the λ max of the drugs (Yilmaz & Ciltas , 2014).

**Saturated solubility studies of Diclofenac acid and Diclofenac prodrug**

Saturated solubility studies were performed to obtain the maximum amount of diclofenac and diclofenac prodrug which could be dissolved per unit volume under specific conditions. Solubility of the drug and its prodrug were obtained in phosphate buffer (pH 6.8) and 0.1N HCl by adding access amount of them to 50 ml graduated conical flasks containing 20 ml of phosphate buffer and 0.1N HCl (pH 1.2) respectively. The solutions were shaken and left for 24 hours with continuous stirring at room temperature, after that the obtained suspension was filtered using Whatman filter paper No.1 (Lobo *et al*., 2013).

Samples were taken from the filtrate for the estimation of drug quantity per unit volume by obtaining absorbance of the samples using a UV-VIS spectrophotometer at the at λ max of diclofenac and diclofenac prodrug. The results are illustrated in Table

**Statistical analysis**

The effect of the new prodrug formulation on the solubility of diclofenac was tested for significance by using paired samples t-test with the aid of the statistical package for the social sciences (SPSS 21) program. The difference was considered statistically significant when (P = 0.005). The calibration curves of diclofenac and DIP in different aqueous media were constructed using Microsoft Excel 2019 program. The correlation coefficient ($r^2$) and standard curve equations for diclofenac and DIP were determined to measure the degree to which the values of x and y are linearly correlated. A correlation coefficient close to 1 shows the strength of the correlation between x and y values. The correlation coefficient was determined using Microsoft Excel 2019 program.

## 3. RESULTS AND DISCUSSION

The FT-IR and H-NMR techniques were performed to identify the possible buildup of prodrug compound through the appearance of the ester bond between diclofenac acid and inositol in the form of evolve of new bands in the IR spectrum and the disappearance of the H signals of carboxylic acid respectively as shown in the Figures (2,3) and Table 1. The FT-IR spectrum for the synthesized compound (DIP) showed the appearance of the ester bands of C=O stretch at 1743 $cm^{-1}$ and the $^1$H-NMR spectrum of compounds (DIP) showed the disappearance of H signals of carboxylic acid at 10-12 ppm as shown in the and this confirm the synthesis of the ester compound (Smith, 2018) (Hamad *et al*., 2022).

The ADMET study is the evaluation of the pharmacokinetics properties of a drug which stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity. According to the results of the computational study, the synthesized compound (DIP) exhibits superior gastrointestinal (GI) absorption in comparison to diclofenac as shown in Figure 4. This indicates an enhanced solubility and bioavailability of the prepared prodrug compound. compounds DIP.

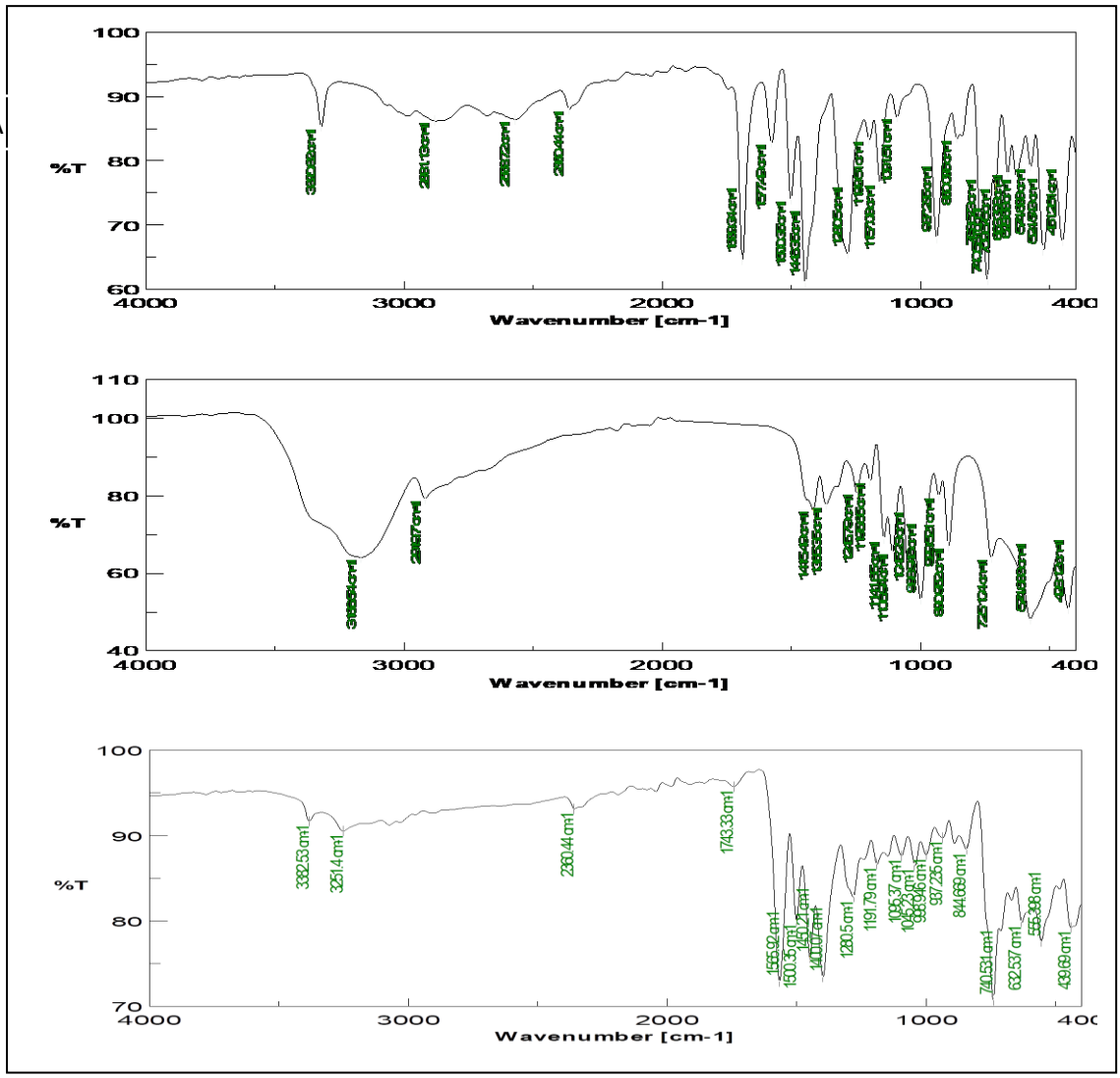



Figure 2: the FT-IR spectrums of Diclofenac (A), Inositol (B) and the prodrug compound DIP (C)

Table 1: The molecular Formula, Chemical name, FT-IR bands and 1H-NMR signals of the compound DIP

| Compound | molecular Formula | Chemical name | FT-IR bands ($cm^{-1}$) | $^1$H NMR signals (DMSO) (ppm) |
|---|---|---|---|---|
| DIP | $C_{20}H_{21}Cl_2NO_7$ | 2,3,4,5,6-pentahydroxycyclohexyl 2-(2-(2,6-dichlorophenylamino) phenyl) acetate | 3382 (N-H) stretching vibration of amine group, 3251 (O-H) stretching vibration of alcohol ,1743 (C=O) stretching vibration of ester group, 1565 (C=C) aromatic stretching | 2.89-2.92 H of methylene group, 3.09-3.7 H of cyclohexane group, 4.62-4.75 H of alcohol group (OH), 6.2-7.44 H of aromatic group |

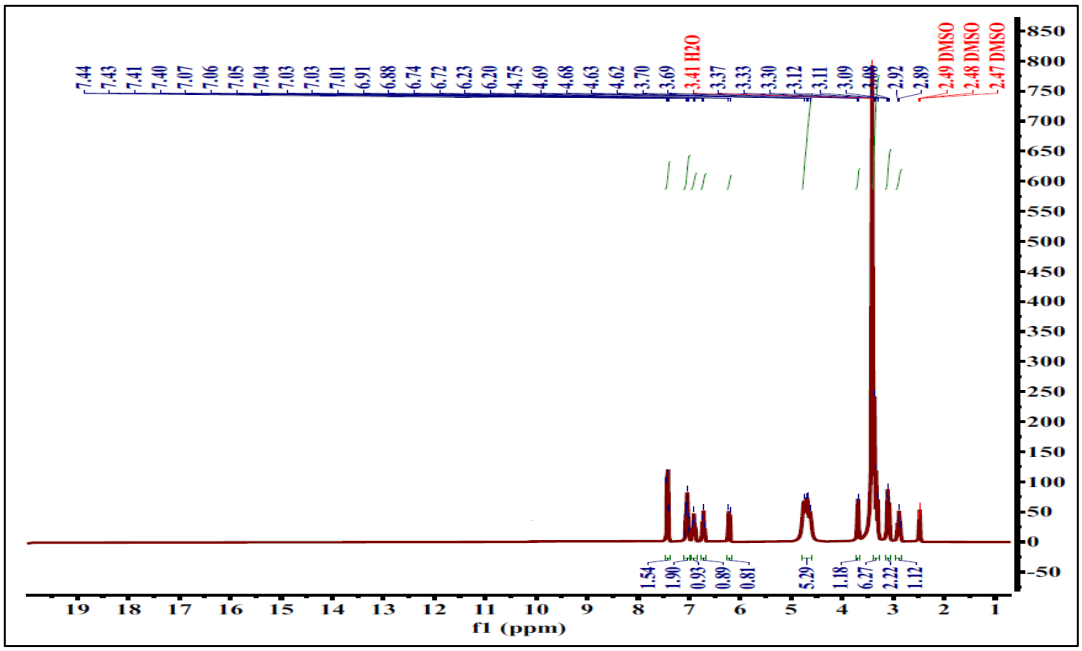



Figure3: $^1$H-NMR spectrum of the synthesized compound DIP

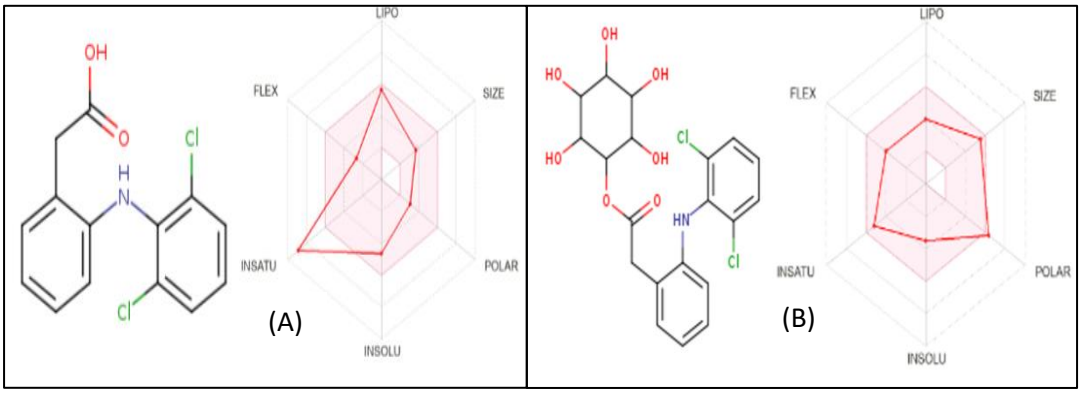



Figure 4: The chemical structures and bioavailability radar images of Diclofenac acid (A) and the synthesized compound DIP (B).

The calibration curves of diclofenac and DIP were constructed by plotting the dissolved amount of diclofenac and DIP in phosphate buffer and 0.1 N HCl (pH1.2) against corresponding absorbance determined at the maximum absorbance of the drugs as shown in Figures 5 and 6. This estimation method was constructed by scanning different solutions at different concentrations ranging from 5-30µg/ml at 278 nm and 276 nm for diclofenac and DIP respectively in phosphate buffer solution. Also, solutions of diclofenac and DIP were scanned at 270 nm and 275nm respectively in 0.1 N HCl against the blank. The standard graphs obtained were linear, with a correlation coefficient of 0.995 and .9951 for phosphate buffer, while the correlation coefficient in 0.1 N HCl solutions was 0.991 and 0.998.

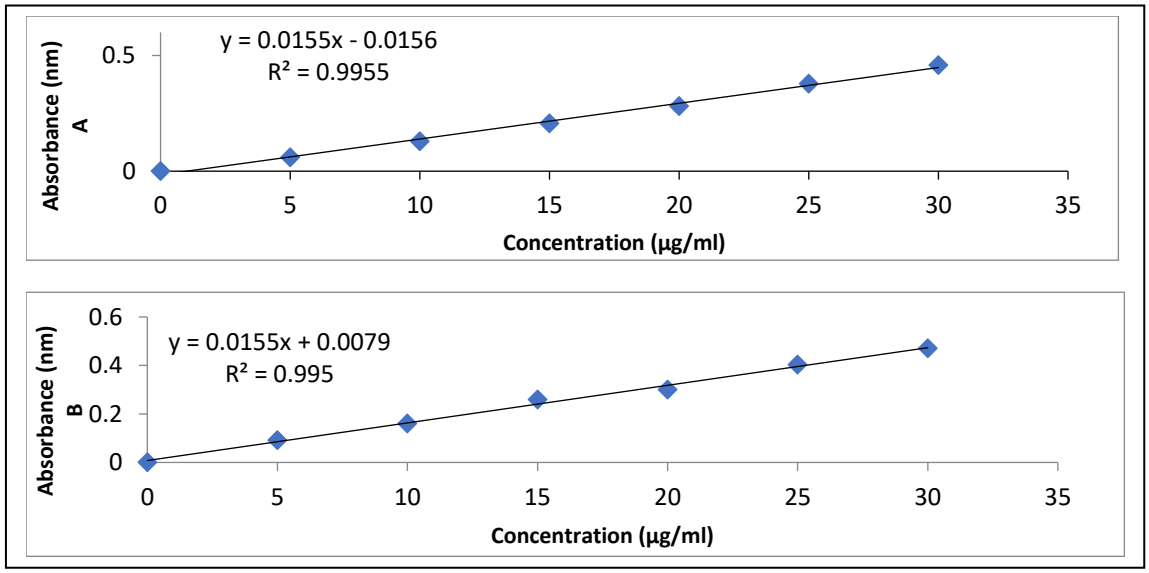



Figure 5: Calibration curve of diclofenac and DIP in phosphate buffer (pH 6.8) solution (A): Diclofenac, (B) DIPml

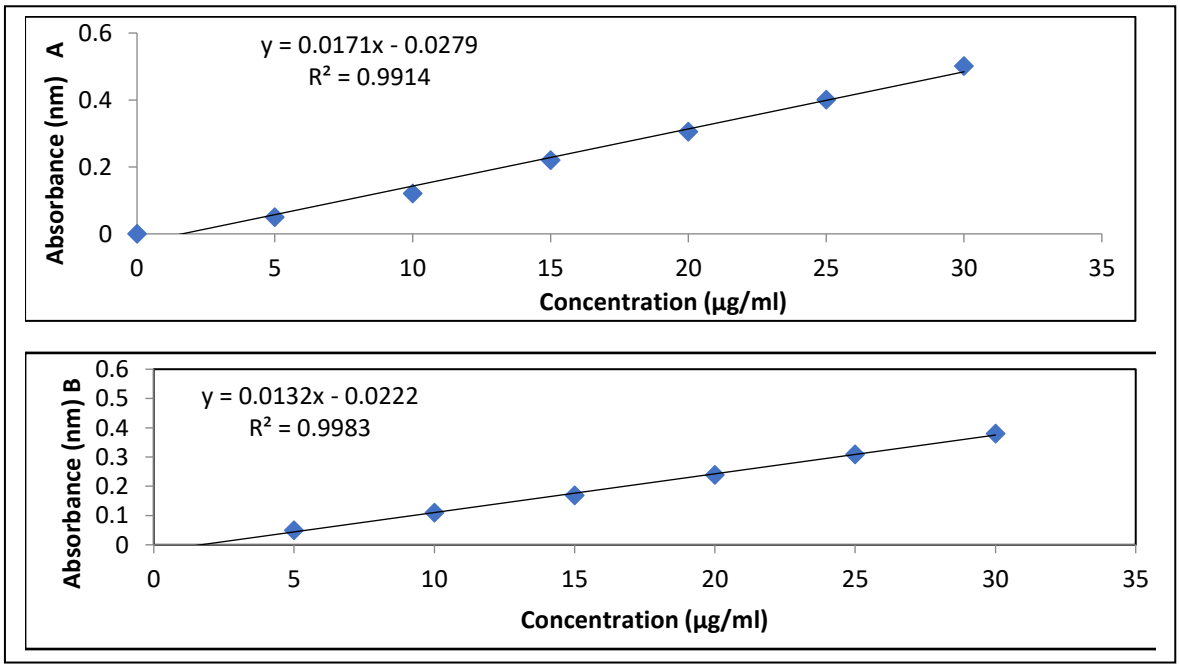



Figure 6: Calibration curve of diclofenacand DIP in 0 .1 N HCl (pH 1.2), (A): Diclofenac, (B) DIP

Saturated solubility studies were carried out for diclofenac and DIP in phosphate buffer and 0.1 N HCl (pH 1.2) solutions at room temperature as demonstrated in Table 2. The solubility data is expressed as mean±SDE (n=3). The solubility enhancement ratio which shows the number of folds increment in the solubility of diclofenac and DIP in different dissolving medium are also shown in Table 3. Comparison and statistical differences in the mean solubility between DIP and diclofenac in the two were shown in Table 3.

According to the results of solubility studies, Diclofenac is considered as practically an insoluble drug with a solubility of 0.059 mg/ml in phosphate buffer and 0.021mg/ml in 0.1 N HCl (pH 1.2) solutions (Mirza, 2021). Enhancement of diclofenac solubility in phosphate buffer was achieved after its preparation as a prodrug with inositol with a solubility of 48.8 mg/ml which is equivalent to (31.5 mg) of pure diclofenac. This enhancement in the solubility is due to modification of drug lipophilicity and the increase in the polarity of the parent drug (Shah *et al*., 2017), while the result of Table 2 indicates that the formulation of prodrug does not affect diclofenac solubility in an acidic medium which is mainly due to the hydrolysis of the basic ester bond between the drug and the career (Wang *et al.*, 2015) Diclofenac solubility also decreased form 0.059 mg/ml in phosphate buffer to 0.016 mg/ml in an acidic medium Table 2, this is because the drug is a weak organic acid that undergoes a partial ionization in an alkaline medium and it will be more soluble in alkaline than in acidic medium (Taylor & Aulton, 2021). The results in Table 3 illustrate the solubility enhancement ratio between the pure

drug and the prepared prodrug in different mediums as well as the statistical difference between them. The result indicates a significant improvement ($p < 0.05$) and 825 folds increase in solubility when the compound DIP is compared with the pure drug in phosphate buffer and 533 folds increase in solubility when the equivalent weight of diclofenac in compound DIP is compared with diclofenac acid. Also, a decrease in the solubility of compound DIP in 0.1N HCl solution was observed when it compared to the solubility in phosphate buffer and this significant change ($P< 0.05$) is due to the breakdown of the ester bond between the drug and inositol in the acidic medium, as mentioned before.

A non-significant improvement ($p> 0.05$) in the solubility between compound DIP and diclofenac in an acidic medium was obtained, as demonstrated in Table 3. This result indicates that this approach of solubility enhancement is preferred in an alkaline medium where the basic ester bond remains stable and efficient to bring the lipid-soluble drug into a solution which finally results an increasing the bioavailability and pharmacological action which is completely consistent with the findings of the earlier study (De Souza *et al*., 2022)

Table 2: Saturated solubility data for diclofenac and the prepared prodrugs

| Formula | Dissolving medium | Solubility mg/ml* |
|---|---|---|
| Diclofenac | Phosphate buffer (pH 6.8) | 0.059±0.0164 |
| DIP | Phosphate buffer (pH 6.8) | 48.8± 0.034 |
| Diclofenac | 0.1N HCl (pH 1.2) | 0.016±0.0031 |
| DIP | 0.1N HCl (pH 1.2) | 0.018±0.002 |

* Mean of three values ± SDE

Table 3: Solubility enhancement ratio between the prepared prodrug and diclofenac acid in phosphate buffer, and the solubility enhancement ratio of the prepared prodrug in two different media

| Formula | Solubility (mg/ml) | Solubility enhancement ratio | P Value |
|---|---|---|---|
| DIP / Diclofenac in (phosphate buffer) | 48.8 mg / 0.059 mg | 827 folds | 0.002 |
| DIP / Diclofenac in (phosphate buffer/ 0.1 N HCl) | 48.8mg/0.012 | 4066 folds | 0.002 |
| DIP / DIP in (phosphate buffer/ 0.1 N HCl) | 48.8 mg/ 0.016 mg | 3050 folds | 0.002 |
| DIP / Diclofenac in (0.1 N HCl) | 0.018mg/0.016mg | 1.12 folds | 0.52 |

## 4.CONCLUSION

The formulation of diclofenac-inositol ester prodrug (DIP) induces a great enhancement in aqueous solubility which may give a higher potency in the inhibition of inflammatory process than free diclofenac or diclofenac salt forms. This approach enhanced the solubility of the drug because the drug is conjugated to the freely water-soluble carrier that modulates the physicochemical properties of the drug and makes it more soluble, effective, and less irritant at the site of absorption.

## 5. RECOMMENDATION

Based on the results of this study, the efficiency and stability of this technique are preferred in an alkaline medium; therefore, a successful oral delivery system containing this prodrug should be coated with an enteric coating solution which improves the stability and allows the drug to be released in the alkaline pH of the intestine.

## REFERENCES

Alsheikhly, O. A., Ganjo, A. R., Abdulrahman, H. S., & Issa, S. Y. (2024). Synthesis of Benzylpenicillin esters and evaluate the change in the anti-bacterial effects by Docking and bacteriological study. Diyala Journal of Medicine, 26(1), 92–105. https://doi.org/10.26505/djm.26017991105

Bizzarri, M., Fuso, A., Dinicola, S., Cucina, A., & Bevilacqua, A. (2016). Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opinion on Drug Metabolism & Toxicology, 12(10), 1181–1196. https://doi.org/10.1080/17425255.2016.1206887

Daravath, B., Naveen, C., Vemula, S., & Tadikonda, R. (2017). Solubility and Dissolution Enhancement of Flurbiprofen by Solid Dispersion Using Hydrophilic Carriers. *Brazilian Journal of Pharmaceutical Sciences*, 53(4). https://doi.org/10.1590/s2175-97902017000400010

De Souza, H. M. R., Guedes, J. S., Freitas, R. H. C. N., Gelves, L. G. V., Fokoue, H. H., Sant'Anna, C. M. R., Barreiro, E. J., & Lima, L. M. (2022). Comparative chemical and biological hydrolytic stability of homologous esters and isosteres. Journal of Enzyme Inhibition and Medicinal Chemistry, 37(1), 718–727. https://doi.org/10.1080/14756366.2022.2027933

DiNicolantonio, J. J., & O'Keefe, J. H. (2022). Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. Open Heart, 9(1), e001894. https://doi.org/10.1136/openhrt-2021-001894

Hamad, H. Q., Taher, S. G., & Aziz, D. M. (2022). Synthesis and Molecular Docking Studies of New Series of Bis-Schiff Bases Thiadiazoles Derived From Disulfides and Thioethers with Potent Antibacterial Properties. Science Journal of University of Zakho, 10(3), 130–139. https://doi.org/10.25271/sjuoz.2022.10.3.932

Hassan, S., & Elias, A. (2014). Synthesis of new diclofenac derivatives by coupling with chalcone derivatives as possible mutual prodrugs. *International Journal of Pharmacy and Pharmaceutical Sciences*, 6(1), 239–245. https://doi.org/10.22159/ijpps.2014v6i1.2320

Jornada, D. S., Fernandes, G. F. S., Chiba, D. E., de Melo, T. J. F., Dos Santos, J. L., & Chung, M. C. (2016). The Prodrug Approach: A Successful Tool for Improving Drug Solubility. Molecules, 21(1), 42. https://doi.org/10.3390/molecules21010042

Kaynak, M. S., Buyuktuncel, E., Caglar, H., & Sahin, S. (2015). Determination of regional intestinal permeability of diclofenac and metoprolol using a newly-developed and validated high performance liquid chromatographic method. *Tropical Journal of Pharmaceutical Research*, 14(1),163–170. https://doi.org/10.4314/tjpr.v14i1.24

Khan, M. A. (2021). Investigating the enhancement of solubility of Poorly Water-Soluble drugs diclofenac sodium by mixed solvency approach. In Book Publisher International (a part of SCIENCEDOMAIN International) (pp. 1–5). https://doi.org/10.9734/bpi/cacs/v6/1926c

Khatri, H., Hussain, S., & Tyagi, S. (2022). Solubility Enhancement Techniques: An Overview. World *Journal of Pharmacy and Pharmaceutical Sciences*,11(5),468–482. https://doi.org/10.22159/wjpps.2022.v11.i5.468

Liu, Y., Chen, Q., Mou, C., Pan, L., Duan, X., Chen, X., Chen, H., Zhao, Y., Lu, Y., Jin, Z., & Chi, Y. R. (2019). Catalytic asymmetric acetalization of carboxylic acids for access to chiral phthalidyl ester prodrugs. Nature Communications, 10(1). https://doi.org/10.1038/s41467-019-09445-x

Lobo, S., Li, H., Farhan, N., & Yan, G. (2013). Evaluation of diclofenac prodrugs for enhancing transdermal delivery. Drug Development and Industrial Pharmacy, 40(3), 425–432. https://doi.org/10.3109/03639045.2013.767828

Mirza, M. A. (2021). Solubility enhancement of diclofenac using solid dispersions. International Journal of Pharmaceutics & Pharmacology, 5(1), 1–6. https://doi.org/10.31531/2581-3080.1000154

Pund, S., Mahajan, N., Gangane, P., & Warokar, A. (2021). Enhancement of solubility of diclofenac sodium by pastillation method. Journal of Drug Delivery and Therapeutics, 11(2), 6–10. https://doi.org/10.22270/jddt.v11i2.4756

Rashid, N. Q. N., Bakir, N. M. H., & Baban, N. S. O. (2023). Spectrophotometric determination of Diclofenac Sodium in pure form and in the pharmaceutical preparations. Tikrit Journal of Pure Science, 21(3), 76–80. https://doi.org/10.25130/tjps.v21i3.999

Rubim, A., Rubenick, J., Laporta, L., & Rolim, C. (2014). Development and Validation of A Dissolution Method Using HPLC for Diclofenac Potassium in Oral Suspension. *Brazilian Journal of Pharmaceutical Sciences*, 50(2). https://doi.org/10.1590/S1984-82502014000200022

Shah, K., Gupta, J. K., Chauhan, N. S., Upmanyu, N., Shrivastava, S. K., & Mishra, P. (2017). Prodrugs of NSAIDs: a review. The Open Medicinal Chemistry Journal, 11(1), 146–195. https://doi.org/10.2174/1874104501711010146

Smith, B. C. (2018). The C=O bond, part VII: Aromatic esters, organic carbonates, and more of the rule of three. Spectroscopy, 33(9), 24–28.

Sopan, P., Nilesh, M., Purushottam, G., & Amol, W. (2021). Enhancement of Solubility of Diclofenac Sodium by Pastillation Method. *Journal of Drug Delivery and Therapeutics*, 11(2), 6–10. https://doi.org/10.22270/jddt.v11i2.4756

Stella, V. J. (2020). Prodrugs: My Initial Exploration and Where it Led. *Journal of Pharmaceutical Sciences*, 109(21), 3514–3523. https://doi.org/10.1016/j.xphs.2020.09.037

Suliman, M., Case, K. C., Schmidtke, M. W., Lazcano, P., Onu, C. J., & Greenberg, M. L. (2022). Inositol depletion regulates phospholipid metabolism and activates stress signaling in HEK293T cells. Biochimica Et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1867(6), 159137. https://doi.org/10.1016/j.bbalip.2022.159137

Taylor, K. M., & Aulton, M. E. (2021). [Aulton's Pharmaceutics E-Book]. *Elsevier Health Sciences*. http://books.google.ie/books?id=H_wqEAAAQBAJ&printsec=frontcover&dq=Aulton%27s+Pharmaceutics&hl=&cd=1&source=gbs_api

Unnisa, A., Huwaimel, B., Almahmoud, S., Abouzied, A. S., Younes, K. M., Anupama, B., Kola, P. K., & Lakshmi, N. V. K. C. (2022). Design, in silico study, synthesis and in vitro evaluation of some N5-(1H-pyrazol-3-yl)-3H-benzo[d]imidazole-2,5-diamine derivatives as potential pancreatic lipase inhibitors for anti-obesity activity. *European Review for Medical and Pharmacological Sciences*, 26(19), 7245–7255. https://doi.org/10.26355/eurrev_202210_29917

Wang, F., Finnin, J., Tait, C., Quirk, S., Chekhtman, I., Donohue, A. C., Ng, S., D'Souza, A., Tait, R., & Prankerd, R. (2015). The hydrolysis of diclofenac esters: synthetic prodrug building blocks for biodegradable Drug–Polymer conjugates. Journal of Pharmaceutical Sciences, 105(2),773–785. https://doi.org/10.1002/jps.24665

Yadav, V., Jain, P., Alex, T., Mirza, M., & Iqbal, Z. (2021). Solubility Enhancement of Diclofenac Using Solid Dispersions. *International Journal of Pharmacy and Pharmacology*, 5(1). https://doi.org/10.31531/2581-3080.1000154

Yilmaz, B., & Ciltas, U. (2014). Determination of diclofenac in pharmaceutical preparations by voltammetry and gas chromatography methods. Journal of Pharmaceutical Analysis, 5(3), 153–160. https://doi.org/10.1016/j.jpha.2014.10.005