Alicia Aliena-Valero, Enrique Alborch, Germán Torregrosa, Juan B. Salom, Francisco J. Miranda, (2017),” Mechanisms involved in the increased sensitivity of the rabbit basilar artery to atrial natriuretic peptide in diabetes”, European Journal of Pharmacology, S0014 - 2999 (17) 30659.3.

39- George Liamis, Evangelos Liberopoulos, Fotios Barkas, Moses Elisaf, (2014),” Diabetes mellitus and electrolyte disorders”, World J Clin, 2(10): 488 - 496.

40- Liamis G, Milionis H, Elisaf M (2008) A review of drug-induced hyponatremia. Am J Kidney Dis 52: 144 - 153 .

41- Liamis, G., Tsimihodimos, V., Doumas, M., Spyrou, A., Bairaktari, E., & Elisaf, M. (2007). Clinical and laboratory characteristics of hypernatraemia in an internal medicine clinic. Nephrology Dialysis Transplantation, 23(1), 136 - 143 .

29- C Jaiganesh and S Subramanian,(2017), "Metformin-3hydroxyflavone, A New Schiff Base Complex Modulates the Activities of Carbohydrate Regulatory Enzymes in High Fat Diet Fed - Low Dose Streptozotocin Induced Type 2 Diabetes in Experimental Rats", Journal of Chemical and Pharmaceutical Research, 9(6): 90 - 100.

30- Farswan, M.; Papiya Mitra Mazumder, V.; Percha, (2009)," Protective effect of Cassia glauca Linn. on the serum glucose and hepatic enzymes level instreptozotocin induced NIDDM in rats". Indian J. Pharmacol, 1(41): 19 - 22.

31- Bruckert E.,Giral P., RatziuV., PoynardT. Chapman, M.J, (2012), "Opolon, P. and Turpin,G: Aconstellation of cardio vascular risk factors is associated with hepatic enzyme elevation in hyperlipidem. Metabolism"; 51(8) 118 - 125.

32 – عبد الواحد. فاتن عبد الواحد مجيد، (2005)، «دراسة مقارنة لأنواع اليرقان وتأثيرها على بعض مكونات الدم في مدينة تكريت «، رسالة ماجستير، كلية التربية للبنات، جامعة تكريت..

33- Evliyaoglu O., Kibrisli E., Yildirim Y., Gokalp O. and Colpan L., (2011), "Routine enzymes in the monitoring of type 2 diabetes mellitus", Cell Biochem Funct., 29(6): 506 - 512 .

34- Muragundla, A.; Kanwaljitquercetin, C. an anti - oxidant bioflavonoid, 2004.

35- Firas Sh. Abdul Razzaq, Ayad S. Hameed, Noori M. Aziz,(2017)," Synthesis, characterization and biochemical study of novel ester prodrugs containing aspirin and ibuprofen",Tikrit Journal of Pharmaceutical Sciences,12(2).

36- Ul Amine, N.; Mahmood, T. R.; Asad, M.J.; Zafar, M. et al., (2014),"Elvaluating urea and creatinine levels in chronic renal failure pre and post dialysis a prospective study",12(2).

37- KFoo,NSekhri,ADeaner,CKnight, A Suliman, K Ranjadayalan, A D Timmis,(2015)," Effect of diabetes on serum potassium concentrations in acute coronary syndromes", Heart 2003; 89: 31–35.

38- Mikahela A. López-Morales, José M. Centeno, Teresa Jover Mengual, Vannina G. Marrachelli, María C. Burguete, María Castelló Ruiz,

18- Al-Jabouri .Nemah H. Mahdi. (2013)," Effects of Oral Hypoglycemic Drugs on Serum Lipid Profile in Hyperlipidemic Rats", Medical Journal of Babylon, 10(1): 245 - 256.

19- Senzana, S.; Gordana, Z., Aleksandra , N.; Senzana , B. and Salvinca , M. (2008),"Quantitative analysis of acetylsalicylic acid in commercial pharmaceutical formulations and Human control serum using kinetic spectrophotometry", Acta chem solv, 55: 508 - 515.

20- Suresh , K. S.; Latif , D. and Prashant , B. (2010),"Analytical method development and Validation for Aspirin", international Journal of chemtech Research,2(1):389.

21 – كاظم، محمد جواد الطبية»، (2010)، « تأثير الأسبرين على صفة الإنتاج في فروج اللحم «، مجلة جامعة بابل للعلوم الصرفة والتطبيقية، مجلد 1(2):53-66.

22- Langley R.E., Ward V., Trevor and Anor ,(2011)," Aspirin and cancer: has aspirin been overlooked as anadjuvant therapy", Brit. J Cancer, 105: 1107 - 1113.

23- Anthony C., Moffat M., David O. and Brian W. C.,(2005),"Analysis of Drugs and Poisons",Pharmaceutical Press.107

24 – الجميلي تحسين سليمان سعيد، (2010)، « دراسة بايوكيمياوية لبوليمرات الكيتين والكيتوسان المستخلصة من قشور الروبيان والمحملة دوائياً»، رسالة ماجستير، كلية العلوم، جامعة تكريت.

25- Nicole S.F., Noel J.C., Anthong R.C., Gareth D. and Graham A.J.,(2001) ,"Effect of aseries of novel sulphonyl thioureas on glucose tolerance in the obese falfa zuker rat",Clinical and Experimental Pharmacology and Physiology, 28: 386 - 391.

26- Shatha,Hani Mohamad. (2011), "Effects of repaglinide vs glimepiride on serum glucose concentrations, HbA1c and body weight in patients with type 2 diabetes mellitus", Tikrit Medical Journal, 17(2): 109 - 115.

27- Sazan, D. S.; Kassim, J.S. and Ansam, N.H. (2012),"Comparative study between Metformin, Glibenclamide and their combination in newly diagnosed diabetic (type II) patients in Hawler City", AJPS, 12(2): 61.

28- Kohei, K.A.K.U. "Pathophysiology of type 2 diabetes and its treatment policy. " JMAJ 53.1 (2010): 41 - 46.

6-Abu-jaish A., Jumaa S., Karaman R., (2014), Prodrugs Overview in Prodrugs Design – A New Era, Karaman R. (editor), Nova Publisher, USA: 77 - 102.

7- H. Surgya, R. Prakash, (2003),” Capping drug :development of prodrug resonance “, Resonance , 8 (2): (19 - 27) .

8- H. Hyo-Kyung L. Gordon, (2000), “Targeted prodrug design to optimize drug delivery”

9- World Health Organization ,(2017) ,”global report of diabetes mellitus”, p2- 4.

10- Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death,(2018),” reactive oxygen species (ROS) and diabetic complications”, Cell Death Dis., 9(2): 119.

11- Esraa A. Hussein ,1 , Dheyaa J. Kadhim,and Tawfeeq F. Al-Auqbi,(2017),» Belief About Medications Among Type 2 Diabetic Patients Attending the National Diabetes Center in Iraq», Iraqi J Pharm Sci, Vol.26(2).

12- Leslie RD, Palmer J, Schloot NC, Lernmark A.,(2016),” Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment”, Diabetologia, 59:13–20.

13- American Diabetes Association, (2017),” Report of the Expert Committee on the Diagnosis and classification of Diabetes Mellitus” , Diabetes Care,40(1):S11–S24.

14- Otávio Augusto Chaves, Bijo Mathew, Monu Joy, Krishnakumar K. Lohidakshan, Akash Marathakam, José Carlos Netto-Ferreira, (2018),” Introduction of fluorinated environment on metformin. Evaluation of its serum-albumin interaction with molecular modeling studies”,Journal of Molecular Liquids, S0167-5-30394 (18)7322.

15- An H, He L., (2016),” Current understanding of metformin effect on the control of hyperglycemia in diabetes”, J Endocrinol , 228(3):R97 - 106.

16- A.M. Elinashar, (2011), “ The role of metformin in ovulation induction: Current status”, Middle East Fertil. Soc. J. 16,175 - 181.

17- Aggarwal, S., & Phadke, S. R. (2015). Medical genetics and genomic medicine in India: current status and opportunities ahead. Molecular genetics & genomic medicine, 3(3), 160.

The results showed that the hydrolysis at basic pH were faster than acidic pH, so it mean that the most hydrolysis will obtain at intestine not at stomach.

Conclusions

Inhibitory effect in (G3 and G4) groups compared with the control group, and more strongly inhibition than the parent drugs. A significant decrease in the activity of levels of liver enzymes of ALP, AST and ALT compared with the control group. significant increase in the concentration of Insulin compared with the control group. significant decrease in the concentration of GLU, Urea, creatinine, sodium, and potassium compared with the control group. The release of the drug associated in the basic medium faster than the release in the acidic medium, which that mean the prepared derivatives reduce the side effects of aspirin and metformin and their toxicity at stomach.

REFRENCES

1- Saikat S.,and Raja C.,(2017), Revival modernization and integration of indian traditional herbalmedicinein clinical practice: importance, challenges and future, J. Trad. Compl. Med., 7: 234244.

2- Karaman, R.; Fattash B. & Qtait A., (2013), The future of prodrugs – design by quantum mechanics methods, Expert Opinion on Drug Delivery,10:713–729.

3- Kengo Hanaya, Shohei Yoshioka, Shinya Ariyasu, Shin Aoki, Mitsuru Shoji, Takeshi Sugai, Development of a novel sulfonate ester-based prodrug strategy, (2016), Bioorganic & Medicinal Chemistry Letters, 26: 545– 550.

4- Yang, Y. H., Aloysius, H., Inoyama, D., Chen, Y., & Hu, L. Q. (2011), Enzymemediated hydrolytic activation of prodrugs. Acta Pharmaceutica Sinica B, 1(3): 143159-.

5- Alaa Abu-Jaish1, Gennaro Mecca, Salma Jumaa1, Ameen Thawabteh, Rafik Karaman, (2015), Mefenamic acid prodrugs and codrugs - two decades of development, World Journal of Pharmaceutical Research, 4(6):24082429.

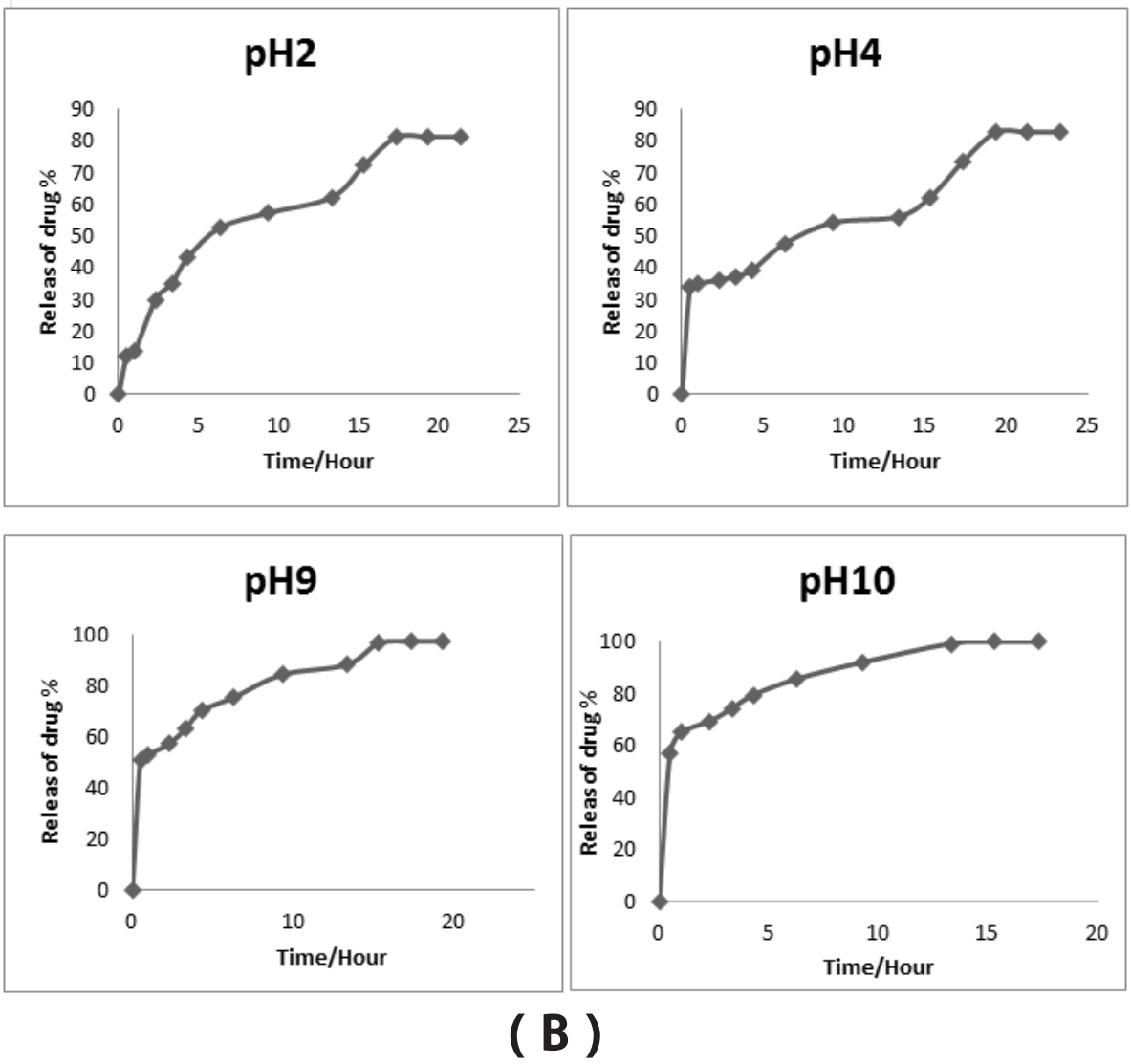
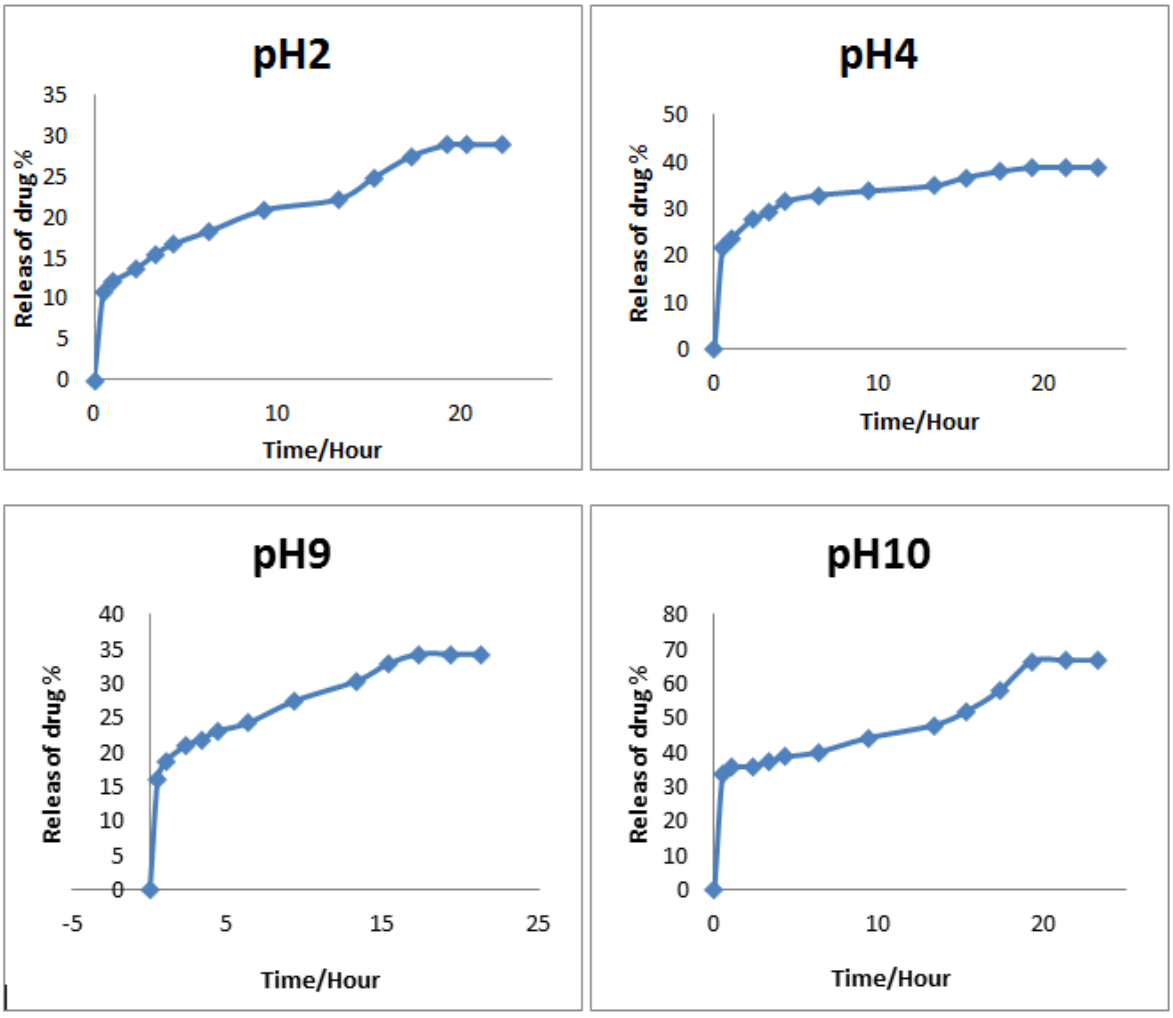


Fig.(4):- Releasing of prodrugs derivatives(AM) at different pH for: (A): Aspirin ,(B): Metformin

hyponatremia even in people with diabetes[40]. We note the high sodium level in the second group infected, there is a study between the high sodium, due to diabetes, which is poorly controlled in the development of increased sodium blood[41].

The ratio of drug releasing has been calculated by using spectrophotometric methods, the releasing of drug follow up by UV-Visible at λ max =265 nm for aspirin and λ max = 232 nm for metformin , figure(4) show the percentage hydrolysis at different pH



(A)

Table (4):- Groups, mean ± SD, of Potassium, and Sodium

Parameters	Group	N	Mean ± SD
K^+ mmol\L	G1	8	**5.22±0.62^b**
	G2	8	**6.52±0.70^a**
	G3	8	**5.21±0.55^b**
	G4	8	**5.71±0.33^b**
Na^+ mmol\L	G1	8	**136.00±5.12^b**
	G2	8	**155.13±14.22^a**
	G3	8	**144.75±7.08^{ab}**
	G4	8	**144.00±16.86^{ab}**

Difference letters vertically means that there is significant difference between the groups, $P \leq 0.05$

The potassium results of table(4) shows the values for G1,G2,G3,G4, (5.22 ± 0.62), (6.52 ± 0.70), (5.21± 0.55), (5.71 ± 0.33) mg\dL, respectively. We found a significant decrease in the potassium level in the third group G3 that dose the prepared derivative(AM) and this ratio is similar to the G4 dosed with the drug separately because there was no significant difference for both groups[37]. In the second group with diabetes, we notice a slight increase in the level of potassium, A study investigated the effect of alloxan induced diabetes on the role of potassium channels in diabetes[38]. Insulin deficiency is involved in the development of hyperkalemia[39].

The sodium results of table(4) shows the values for G1,G2,G3,G4 (136.00 ± 5.12) , (155.13 ± 14.22) , (144.75 ± 7.08), (144.00 ± 16.86) mg\ dL respectively. We find a significant decrease in the level of sodium in the group G3 which the dose of the prepared derivative(AM) and this ratio is similar G4 dosed with the drug separately because there was no significant difference for both groups, Medications are a common cause of

Table (3):- Groups, mean ± SD, of Urea, and Creatinine

parameters	Group	N	Mean ± SD
Urea mg\dL	G1	8	**42.12±6.26^{b}**
	G2	8	**75.12±27.31^{a}**
	G3	8	**45.68±4.60^{b}**
	G4	8	**50.06±1.78^{b}**
Creatinine mg\dL	G1	8	**1.013±0.203^{b}**
	G2	8	**2.125±0.580^{a}**
	G3	8	**1.181±0.226^{b}**
	G4	8	**1.331±0.088^{b}**

Difference letters vertically means that there is significant difference between the groups, P≤0.05 .

The Urea results of table(3) shows the values for G1,G2,G3,G4, (42.12 ± 6.26) ,(75.12 ± 27.31) , (45.68 ± 4.60) ,(50.06 ± 1.78) mg\dL respectively. We note that the results of G3 were better in lower urea level than G4 and the concentration of urea in the third group was almost the same as normal level in G1 due to the use of the prepared derivative(AM). We note the high concentration of urea in the infected G2[34].

The Creatinine results of table(3) shows the values for G1,G2,G3,G4, (1.013 ± 0.203) , (2.125 ± 0.580) , (1.181 ± 0.226), (1.331 ± 0.088) mg\ dL respectively. It was noted that G3 results were better in lower creatinine level than in group G4 and creatinine concentration in G3 was close to the normal level in G1 due to the use of the prepared derivative(AM) About the original medicine. This finding is consistent with (Firas)[35]. Note the high concentration of creatinine in the infected G2[36].

Table(3) show the effect of derivatives on Potassium and Sodium:

The AST results of table(2) shows the values for G1,G2,G3,G4, (41.61 ± 5.93), (52.51 ± 5.93), (44.41 ± 4.83), (48.66 ± 3.89) U/L respectively. It was noted that the G3 group was better in the inhibition of the enzyme (AST) than the group G4, which represents the original drugs separate and may indicate that the prepared derivative(AM) with the proposed less harmful heart muscle or liver cells. As for the second group infected we note the rise of the enzyme (AST) due to insulin deficiency and thus affect the liver tissue causing damage in the liver cells due to the essential role of the hormone insulin from the control of many metabolic processes within the liver cells such as building fat and proteins and decomposition of Glycogen so the liver function can be affected When a defect in the proportion of insulin in the blood[30].

The ALT results of table(2) shows the values for G1,G2,G3,G4, (38.65 ± 4.36), (51.76 ± 4.41),(40.49 ± 3.46), (46.52 ± 3.54) U/L respectively. An increase in the level of ALT was observed in the diabetic G2, mainly due to the breakdown of hepatocytes, usually accompanied by high enzyme levels[31]. It was noted that the G3 group was better in the inhibition of the enzyme (ALT) than the group G4, which represents the original drugs separate and may indicate that the prepared derivative(AM) with the proposed less harmful heart muscle or liver cells[32].

The ALT results of table(2) shows the values for G1,G2,G3,G4, (178.25 ± 22.73), (283.87 ± 27.17), (187.18 ± 33.16), (204.50 ± 42.78) U/L respectively. It was observed that the results of the fourth group G4 less enzyme inhibition (ALP) than the third group G3, which led to the inhibition of the enzyme (ALP) at the level of effectiveness of the group G1, which shows less side effects of the prepared derivative(AM) with the original drug. The second group G2, where diabetes leads to changes and complications on the liver[33].

Table(3) show the effect of derivatives on Urea and Creatinine:

The Insulin results of table(1) shows the values for G1,G2,G3,G4, (11.10 ± 1.45), (7.06 ± 0.91), (12.43 ± 1.37), (9.80 ± 1.27) µU/mL respectively. We note that insulin levels in the second group with diabetes significantly decreased when compared with the controlled group G1, which is consistent with (Kohei) study, which concluded through his study that insulin hormone decreases in patients with type 2 diabetes due to high glucose Fats negatively affect beta-pancreatic cells as they gradually begin to fibrosis and thus decrease their insulin secretion[28], While these significantly altered levels were improved in the diabetic G3 treated with the prepared derivative(AM), This proved the effectiveness of the derivative prepared from metformin, This corresponds to the results of a previous study[29].

Table(2) show the effect of derivatives on AST, ALT and ALP:

Table (2):- Groups, mean ± SD, of AST, ALT and ALP

parameters	Group	N	Mean ± SD
AST U/L	G1	8	**41.61 ± 5.93^{c}**
	G2	8	**52.51 ± 5.93^{a}**
	G3	8	**44.41 ± 4.83^{bc}**
	G4	8	**48.66 ± 3.89^{ab}**
ALT U/L	G1	8	**38.65 ± 4.36^{c}**
	G2	8	**51.76 ± 4.41^{a}**
	G3	8	**40.49 ± 3.46^{c}**
	G4	8	**46.52 ± 3.54^{b}**
ALP U/L	G1	8	**178.25 ± 22.73^{b}**
	G2	8	**283.87 ± 27.17^{a}**
	G3	8	**187.18 ± 33.16^{b}**
	G4	8	**204.50 ± 42.78^{b}**

Difference letters vertically means that there is significant difference between the groups, $P \leq 0.05$

2- Biochemistry part

After the preparation of derivatives , and gave the written doses as shown at the used animals and samples collection part, the effect of these derivatives on the measured parameters were shown at the table (1,2,3,4) :

Table(1) show the effect of derivatives on Glucose (Glu) ,and Insulin (Ins):

Table (1):- Groups, mean ± SD of GLU ,and Insulin

parameters	Group	N	Mean ± SD
GLU mg\dL	G1	8	114.75 ± 23.26^{b}
	G2	8	180.63 ± 15.43^{a}
	G3	8	89.00 ± 32.37^{c}
	G4	8	131.00 ± 20.68^{b}
Insulin µU/mL	G1	8	11.10 ± 1.45^{b}
	G2	8	7.06 ± 0.91^{c}
	G3	8	12.43 ± 1.37^{a}
	G4	8	9.80 ± 1.27^{b}

Difference letters vertically means that there is significant difference between the groups, $P \leq 0.05$

The Glucose results of table(1) shows the values for G1,G2,G3,G4, (114.75 ± 23.26), (180.63 ± 15.43), (89.00 ± 32.37), (131.00 ± 20.68)mg\ dL respectively. It was noted that the level of glucose in (G3) was lower than the level of glucose in (G4) This is an indication that the prepared derivative (AM) G3 worked to reduce the level of glucose more than G4 with the control groups G1 and G2, This corresponds to the results of other studies on rabbits in the effectiveness of the preparation of a Prodrug with metformin with aspirin[25]. The results of the study showed that metformin reduced blood glucose level and this is consistent with the results of previous studies (Shatha)[26] and the results (Sazan et al)[27].

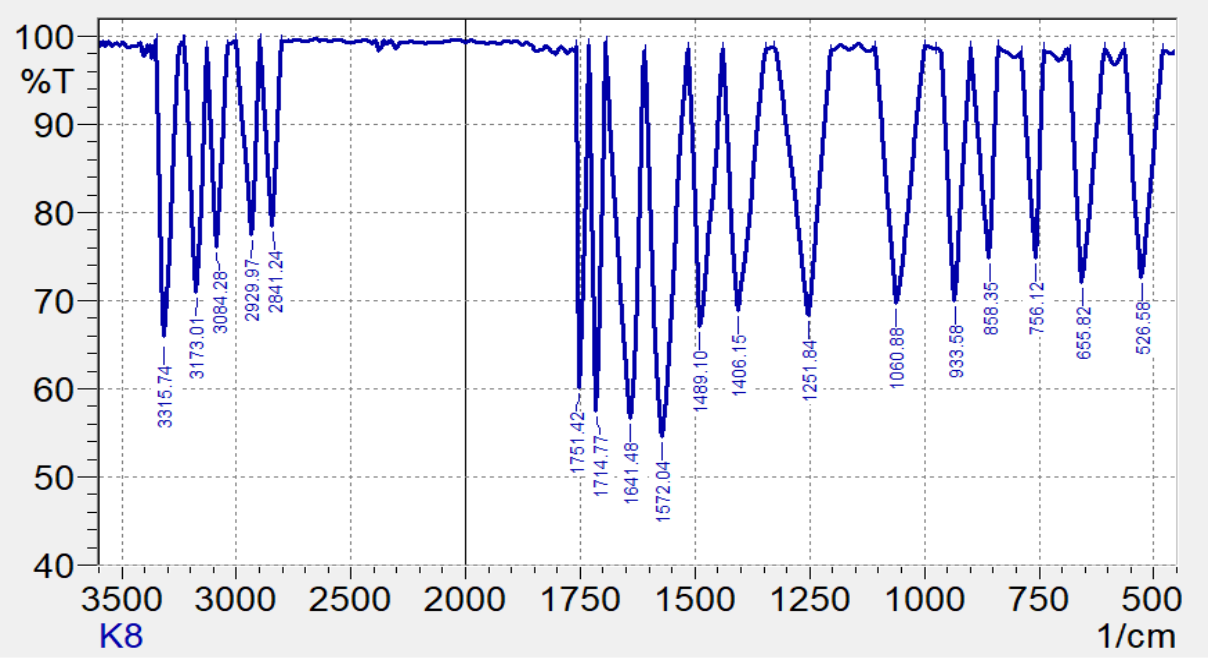


Fig. (2): - FT- IR spectrum for Prodrug (AM)

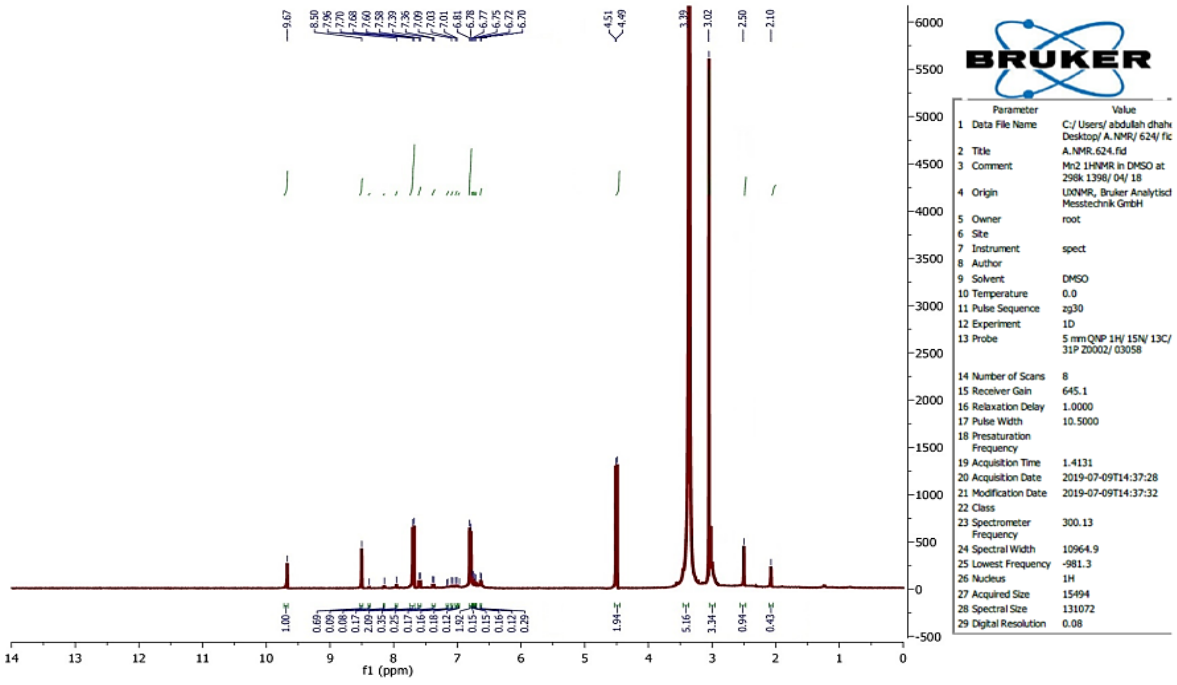


Fig (3) H[1]NMR of Prodrug (AM)

Estimation of Sodium Concentration in serum

Used kit equipped by the German company Human where sodium is deposited with the magnesium-uranyle acetate compound, uranyl ions remain stuck in the filtrate and form a yellow complex with thiocyclic acid.

Estimation of Potassium Concentration in Serum

Used kit equipped by the German company Human Where the potassium ion reacts with sodium tetraphenylboron (TPB-Na) in an alkaline medium to form potassium tetraphenylboron (TPB-K) which is foggy.

Results and Discussion

1- Organic part:

Preparation of prodrug derivative

The synthesis of the derivative has been obtained according to the reaction below:

The derivative was purified by Thin layer chromatography (aluminum coated silica gel as stationary phase and mixture of benzene and ethyl acetate as a mobile phase) and follow up by TLC. The characterization of the derivative (prodrug) was accomplished by measuring spectral data FT-IR, which showed the presence of the absorbance band at, while the results of ^{1}HNMR:

TLC ,Rf (0.693) (**Benzen : Ethyl acetate**) (1:1); **IR(Film)** (cm^{-1}), **1251 (C-O)**, 1489 (C=C) aromatic, 1641(C=N) azomethene, 1714 (C=O) ester,1751 (C=O) ester, 2841 - 2929 (C- H) aliphatic, 3084 (C-H) aromatic, **^{1}HNMR** ,(2.10)ppm (s, H, NH), (2.5) ppm (H,solvent), (3.02) (d ,6H ,2CH3), (3.39) (d ,6H ,2CH3), (4.50)ppm (s, CH2), (6.72) ppm (CH), (6.81)ppm (d, CH), (7.50) ppm (m, 4H ,aromatic) ,(9.69)ppm (s,1H,C=NH) .

Estimation of alanine aminotransferase activity

It was used Kit by the Spanish company Linear Chemicals. Colorimetric method for estimating the enzyme ALT activity. According to the following reactions:

$$\text{L-Alanine} + \text{2-Oxoglutarate} \xrightleftharpoons{\text{ALT}} \text{Pyruvate} + \text{L-Glutamate}$$

$$\text{Pyruvate 2,4-D.N.P.H} \longrightarrow \text{Pyruvate} + \text{2,4 DNPH}$$

Estimation of Aspartate amino transferase activity

It was used Kit by the Spanish company Linear Chemicals. The kit was used by the Spanish company Linear Chemicals. Based on the Colorimetric method to estimate the effectiveness of the activity of the amino transfusion AST. According to the following reactions:

$$\alpha\text{-ketoglutarate} + \text{L-Aspartate} \longrightarrow \text{L-Glutamate} + \text{Oxaloacetate}$$

$$\text{Oxaloacetate} + \text{2,4-d.n.Ph} \longrightarrow \text{Oxaloacetate Dinitrophenylhydrazone}$$

Estimation of Urea in serum

The urea concentration was measured by the diagnostic kit manufactured by the Spanish company Linear by enzymatic Colorimetric reaction . According to the following reactions:

$$\text{Urea} + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$

$$NH_4^+ + \text{Salycilate} + \text{NaClO} \xrightarrow{\text{NITROPRUSSIDE}} \text{indophenol} + \text{NaCl}$$

Estimation of Creatinine in serum

Serum creatinine concentration was measured using a diagnostic kit manufactured by the Spanish company Linear by Colorimetric reaction (Jaffe reaction). According to the following reaction:

$$\text{Creatinine} + \text{Pricic acic} \xrightarrow[37^\circ C]{ph > 12} \text{Red addition complex}$$

2- Biochemistry part

In this study, (32) rabbits proximate in the weight and divided into four groups, every group contain (8) rabbits. the first group used as a control group and the second group Diabetes Mellitus group (deals with alloxan 150 mg/kg), the third group treated with synthesized compound (AM) at a concentration of (68.431 mg / ml) ,and the fourth group dosed with metformin at a concentration of (160.71 mg / ml),and aspirin at a concentration of (42.85 mg / ml) and glyceraldehyde at a concentration of (111.9 mg / ml), separately, for five days. After 2 hours, blood was taken from all groups, the serum was separated, Keeped at (-20 C) for the purpose of conducting its own enzymatic biochemical tests.

Estimation of biochemical parameters in serum

Measuring the hormone insulin

Measuring the hormone insulin by ELISA Kit From company Labor Diagnostika Nord (LDN) Germany, Based on the principle of sandwich.

Determination of serum glucose

It was used Kit by the Spanish company Linear Chemicals. Serum glucose concentration was determined by the use of the Enzymatic Colorimetric method. According to the following reactions:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOD}} \text{Gluconate} + H_2O_2$$

$$2H_2O_2 + \text{phenol} + 4\text{AAP} \xrightarrow{\text{POD}} \text{Quinoneimine} + H_2O$$

Estimation of alkaline phosphatase activity

It was used Kit by the Spanish company Linear Chemicals. Depends on the Colorimetric method to estimate the effectiveness of alkaline phosphatase ALP. According to the following reaction:

$$\text{Phenylphosphate} \xrightarrow{\text{ALP}} \text{Phenol} + \text{phosphate}$$

clear solution to a reddish and leaving the mixture stirring for 24 hours to complete the reaction. gelatinous deposition was obtained after dissolving it with absolute ethanol, precipitite it with water several times, then leaving the precipitate to dry and obtaining bright crystals that were slanted to the dark brown of the resulting composite

Preparation of 3- ((N- (N, N-dimethylcarbamimidoyl) carbamimidoyl) imino) propane -1, 2-diyl bis (2-acetoxybenzoate) (AM)

In a round bottomed flask (0.3748 gm) of ester was dissolved at 10 ml of absolute ethanol, and(0.149 gm) of metformin (dissolved in 10 ml of absolute ethanol) was added, the mixture refluxed in a water bath with stirring for 12 hours.

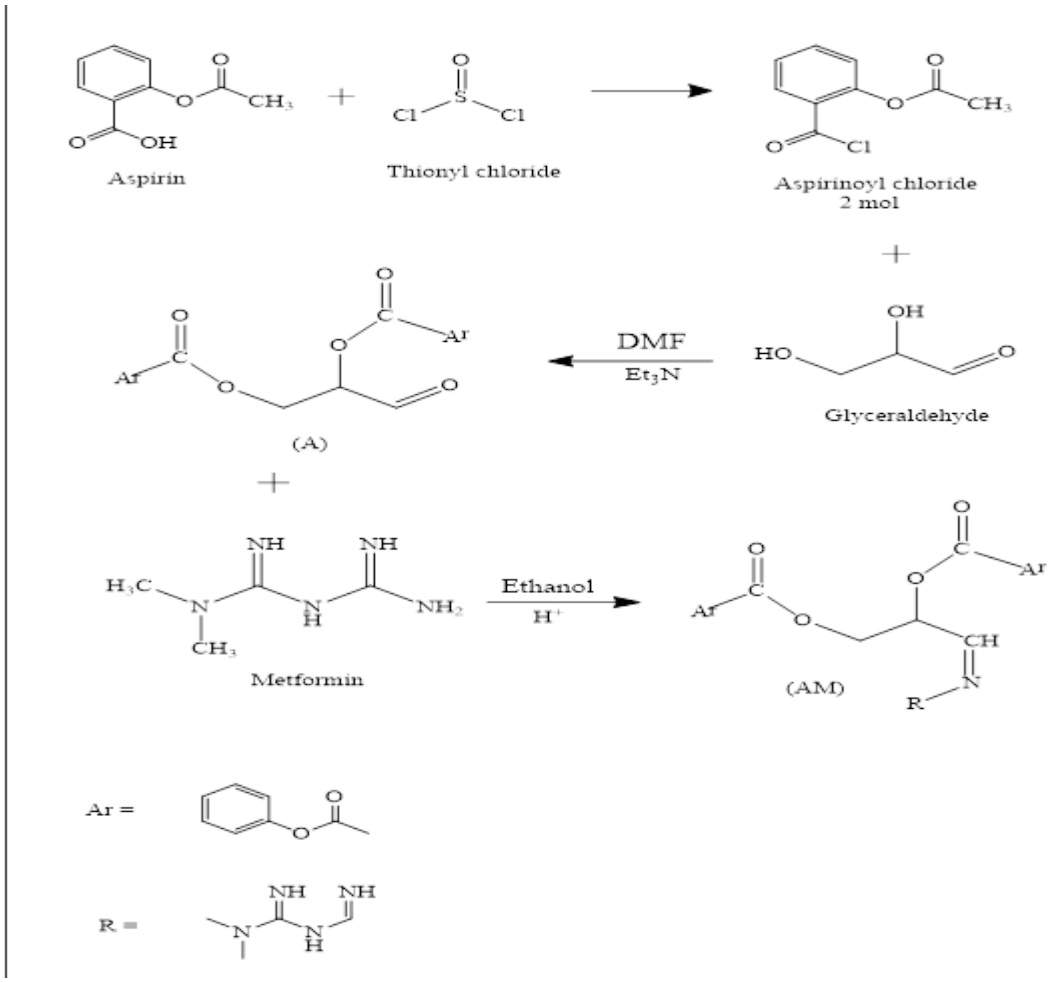


Fig. (1): Synthesis of the prodrugs (AM)

particular, people who are overweight and obese and who have abnormal renal function[13,14]. Metformin is an important major drug, which reduces the high blood glucose by lowering glucose production in the liver[15]. Its chemical composition (N, N - dimethyl biguanide hydrochloride)[16], and molecular formula ($C_4H_{11}N_5$. HCl). The metformin crystals are white and easily soluble in water, and practically in-soluble in acetone, ether, chloroform[17]. Al-Jubouri[18] confirmed that metformine was the most beneficial drug to reduce the risk of arteriosclerosis when compared with (rosemmitazone and acarbose), when the three properties were studied for their effect on blood levels of blood.

Aspirin

Aspirin is [2-(acetyloxy) benzoic acid][19], German pharmacists on acetylsalicylic acid first called aspirin for the first time in 1899[20], is one of the most famous drugs in the world that has saved millions of people from fever, arterial blockage, heart attacks, brain and rheumatic pain. It is still a distinct alternative treatment for blood clotting[21] and its effects on cancer[22], The molecular formula of the aspirin is $C_9H_8O_4$ and It is in the form of white crystalline powder, which dissolves easily in water, alcohol, ether, glycerol, and also in acetic acid[23]. Al-Jumaili[24] said that taking aspirin tablets before bedtime benefit patients with diabetes because it activates the pancreas to secrete insulin, which converts sugar to energy and reduces resistance to cells and increase its sensitivity to insulin.

Materials and Method

1- Organic part:

Preparation of acid chloride (acetyl salicylic acid)

(5.9 gm) from thionyl chloride was added to (4 gm) of aspirin, then the mixture was refluxed for two hours by a water bath. The excess of thionyl chloride was decreased by using the Excessive pressure. A yellow material was obtained.

Preparation of 3-oxopropane-1,2-diyl bis (2-acetoxybenzoate) (A)

Dissolve (1.1538 gm) of glyceraldehyde in 2 ml of DMF with a little heating and add 2.5 ml of triethylamine, then The acid chloride solution was added (5.088gm) to glyceraldehyde solution drop by drop with vigorous stirring by a separating funnel until the color changed from a

INTRODUCTION:

Prodrug:

Generally, a drug is characterized by its biological and physicochemical properties. Some of the used drugs have undesirable properties that result in an inefficient delivery and unwanted side effects. The physicochemical, biological and organoleptic properties of these drugs should be improved in order to increase their usefulness and their utilization in clinical practice[1,2], utilizing the prodrug approach might improve the physicochemical properties of a drug and hence increase its bioavailability and therapeutic efficiency[3,4]. The prodrug have been extensively and successfully used as a chemical tool for modification of the physicochemical, pharmacokinetic as well as pharmacodynamic characteristics of commonly used drugs and new drugs[5]. In most cases, prodrugs contain a promoiety (linker) that is removed by enzymatic or chemical reactions, while other prodrugs release their active drugs after molecular modification, such as an oxidation or reduction reactions[6], Most drugs have some certain unwanted physical, chemical and biologic properties, so the drug can be improved and increased drug efficiency by eliminating or reducing undesirable traits while maintaining desired traits[7], the concept of prodrug includes a powerful, effective and multi-use drug design[8].

Diabetes mellitus

Diabetes mellitus is a chronic metabolic disease characterized by high blood sugar levels, caused by defects in the secretion of pancreatic insulin and / or insulin action on target tissues, which over time leads to serious damage to the heart, blood vessels, eyes, kidneys and nerves. Blood to the death of about 4 million people every year [9,10], Diabetes is a common health problem worldwide, with around 1.2 million cases in Iraq in 2015[11]. According to the current classification, there are two main types: Type I (T1DM) insulin-dependent diabetes mellitus and Type II (T2DM) non - insulin - dependent diabetes mellitus[12].

Metformin

Is a topical anti - diabetic drug (Biguanide) given orally, and is the first line of choice prescribed for the treatment of type 2 diabetes, in

doi.org/10.52866/esj.2020.05.16.12

Journal of Education and Scientific Studies Chemistry Science
JESCS Vol. 16, No. 5, August 2020, ISSN 2413 - 4759

Preparation and biochemical study of one of glyceraldehyde derivative as a Possible prodrug

Kamal-aldeen Hussein Ali*, Hanaa Kaain Salih*, Firas Shawqi Abdul-AL-Razzaq**
* Tikrit University / College of Science - Dept. of chemistry
** Tikrit University / College of Pharmacy - Dept. of chemistr

Abstract:

This study included synthesis of 3-((N-(N,N-dimethylcarbamimidoyl)carbamimidoyl)imino) propane-1,2-diyl bis(2-acetoxybenzoate) (AM) afforded by reaction of glyceraldehyde as an alcohol carrier of aspirin and metformin drug by reactive esterification, and Schiff bases respectively . The purification of the synthesized derivative was established by (TLC), while the structure suggesting was confirmed by (FTIR, 1H-NMR), and the result obtained given good evidence for structure proposed to their compound and using through the study groups , and take (32) rabbits proximate in the weight and divided into four groups contain of (8) rabbits . the first group used as a control group and the second group Diabetes Mellitus group, the third group dosed with synthesized compound (AM) at a concentration of (68.431 mg / ml) ,and the fourth group dosed with metformin at a concentration of (160.71 mg / ml),and aspirin at a concentration of (42.85 mg / ml) and glyceraldehyde at a concentration of (111.9 mg / ml), separately, for five days. After 2 hours, blood was taken from all groups, the serum was prepared to study it with biochemical and enzymatic Parameters , Statistical data analysis revealed significant decreases in the levels of: Alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) And a significant increase in the hormone insulin (INS) by effect of the prepared compound and significant decreases in the concentration of Glucose (GLU), creatinine, urea, potassium and sodium,by effect of the prepared compound as compared with the Infected control group, and this study included the hydrolysis of compound at different pH (pH 2,4,9,10) and the results showed that the compound hydrolyzed at basic medium faster than acidic medium.

Keywords: Prodrug, Diabetic, Metformin, Aspirin

خلاصة :

تضمنت الدراسة تحضير المركب [3-((N-(N،N-dimethylcarbamimidoyl)carbamimidoyl)imino) propane-1،2-diyl bis(2-acetoxybenzoate)] (AM) من خلال مفاعلة الكليسير الديهايد كحامل للكحول مع دواء الاسبرين والميتفورمين بواسطة تفاعل الاستره وقواعد شف على التوالي. إذ تم تنقية المركب المحضر بواسطة تقنية TLC)) ، وتم التأكد من الصيغة التركيبية المقترحة باستخدام الطرق المتاحة (FTIR، 1H-NMR) وقد دلت النتائج المستحصلة على صحة التركيب المقترح. تم أخذ (32) أرنبا متساوية تقريبا في الوزن وقُسمت الى اربع مجموعات، كل مجموعة تحتوي على (8) أرانب، المجموعة الاولى مجموعة السيطرة، المجموعة الثانية مجموعة السيطرة المصابة، المجموعة الثالثة جُرعت بالمركب المحضر AM)) بتركيز (68.431 mg / ml) والمجموعة الرابعة جُرعت بدواء المتفورمين بتركيز (160.71 mg / ml) الاسبرين بتركيز (42.85 mg / ml)، والكليسر الديهايد بتركيز (111.9 mg / ml) على التوالي لمدة خمسة ايام، بعد مرور ساعتين من تجريعها تم سحب عينة الدم من كل أرنب وفصل المصل منها وأجريت عليها دراسة للمتغيرات الكيموحيوية والانزيمية. أظهرت نتائج التحليل الإحصائي انخفاض معنوي في فعالية كل من انزيم الفوسفاتيز القاعدي (ALP)، اسبارتيت امينوترانسفيريز (AST)، الانين امينوترانسفيريز(ALT) و ارتفاع معنوي في هرمون الانسولين INS)) بتأثير المركب المحضر، وكذلك اظهرت الدراسة وجود انخفاض معنوي بتركيز كل من الكلوكوز (GLU)، كرياتنين، يوريا، البوتاسيوم والصوديوم، بتأثير المركب المحضر وبالمقارنة مع السيطرة المصابة. تم دراسة تأثير الاس الحامضي على تحلل الدواء في المركب المحضر في أوساط حامضية مختلفة (pH=2،4،9،10) حيث لوحظ ان الوسط القاعدي يسبب تحرر الدواء اسرع من الوسط الحامضي.