

Preparation of Drugs Carrier Vitamin B₂ and Studying their Controlled Drug Release

Firyal Mohammad Ali Al- salami * Khudheyer Jawad Kadem**

*University of Al-mstansiriyah/ College of Science- Department of Chemistry.

Baghdad- Iraq

** Babylon University/ College of Science- Department of Chemistry. Babel- Iraq

E- mail: khudheyer babel@yahoo.com.

Abstract

This study describes modification of Vitamin B₂ as drug derivatives, which were prepared through esterification of some –OH groups of vitamin B₂ with Amoxillinyl or Ibuprofenyl or Cephalexineoyl or Mefenamyl acid chlorides, with different modified ratios. This new idea was applied to improve the prolong delivery of vitamin B₂ with controlling release of bonded antibiotics. The new prepared drug vitamin derivatives were characterized by FT-IR and UV. spectra, and the physical properties were studied; the controlled drug release was studied with different pH values at 37°C, many advantages have been obtained from this new preparation of scientific and therapeutic uses.

Keywords: Vitamin, Drugs Carrier and Controlled Drug Release.

تحضير الادوية المحملة على فيتامين ب₂ ودراسة سرعة التحرر الدوائي

فريال محمد علي السلامي * خضير جواد كاظم**

*الجامعة المستنصرية / كلية العلوم - قسم الكيمياء ، بغداد- العراق

**جامعة بابل / كلية العلوم - قسم الكيمياء ، بابل – العراق

الخلاصة

حضر في هذا البحث وصفت بعض المشتقات للفيتامينات الحاملة للدواء والتي حضرت من استرة بعض المجاميع مع الاموكسيلينيل او الايبوبروفينيل او السيفالكسينيل او الميفناميل ككلوريدات الهيدروكسيلية لفيتامين B₂ وبنسب مختلفة. هذه الطريقة الجديدة التي طبقت لتحسين واطالة العمر الزمني لتحرير الدواء مثل B₂ المضادات الحياتية المحملة على فيتامين شخضت مشتقات الفيتامينات الدوائية بواسطة طيف الأشعة تحت الحمراء والأشعة فوق البنفسجية ، ودرست الصفات الفيزيائية ، ودرست سرعة التحرر الدوائي المحكم في دوال حامضية مختلفة وبدرجة 37 م ، فوائد متعددة تم الحصول عليها من هذه التحضيرات الجديدة ولاستخدامات علاجية

الكلمات المفتاحية: فيتامين ، حامل للدواء ، سيطرة تحرر الدواء.

Introduction

Due to the importance of riboflavin for protein metabolism and energy generation, the intake recommendation depend on the protein and energy content of the diet as well as metabolic rate and body weight, Riboflavin like thiamin and some other B vitamins, is essential for normal development, growth, reproduction, lactation, physical performance, and well-being. It is involved in a wide array of essential biochemical oxidation-reduction reactions, especially those that yield energy. Riboflavin is widely distributed in small amounts in many foods, and milk is one important source. Similar to many members of the water-soluble B-complex family of vitamins, riboflavin is easily lost from grains or vegetables upon milling, canning blanching, and storage. Riboflavin is especially sensitive to light. It is readily absorbed in small amounts from the intestine, and readily excreted through the kidneys (McCormick, 1999). Based on clinical trial data generated after FNB's review (Schoenen *et al.*, 1998), UK EVM tentatively concluded that 400 mg per day produced only minor and infrequent side effects of uncertain significance (Expert Group on Vitamins and Minerals, 2003). Because of the small number of subjects studied at that level of intake undercontrolled conditions, UK EVM assigned the default toxicological UF of 10 and set a supplemental GL at 40 mg, with a total intake GL at 43 mg because intakes of riboflavin from conventional foods are 3.3mg or less Riboflavin,

The alkaline conditions in which riboflavin is unstable are rarely encountered in foodstuffs. Riboflavin

also known as vitamin B₂ of additive E101 (Brahim *et al.*, 2003) is an easily absorbed micronutrient with a key role in maintaining health of humans and animals, it is the central component of the cofactors and is therefore required by all flavoproteins. As such, vitamin B₂ is required for a wide variety of cellular processes. It plays a key role in energy metabolism and for the metabolism of fats, ketone bodies, carbohydrates and proteins (Tu, *et al.*, (2003).

Riboflavin is yellow or yellow-orange in color and in addition to being used as a food coloring, it is also used to fortify some foods. It is used in baby foods, breakfast, cereals, pastas sauces, processed cheese, fruit drinks, vitamin-enriched milk products and some energy drinks. Regarding occurrence and sources of vitamin B₂. Yeast extract is exceptionally rich with vitamin B₂, in addition to liver and kidney which are rich sources of B₂, another important sources of B₂ in diet are wheat bran, eggs, meat and cheese (Malmstadt *et al.*, 2003 and Base *et al.* 1989).

It is difficult to incorporate riboflavin into many liquid products because it has poor solubility in water, hence the requirement for riboflavin-5-Phosphate, a more expensive but more soluble form of riboflavin (Dena. and Reinhart, 2011 and Antti *et al.*, 2003).

Riboflavin is generally stable during the heat processing and normal cooking of foods if light is excluded.

degradation in milk can occur slowly in dark during store in the refrigerator (Hart *et al.* .2006)

Riboflavin has been used in several clinical and therapeutic situations. For over than 30 years, riboflavin supplements have been used as part of the phototherapy treatment of neonatal jaundice, but also the naturally occurring riboflavin within the infants blood, so extra supplementation is necessary (Firyal *et al.*, 2011). A dose of 400mg daily has been used effectively in the prophylaxis of megraines, especially in combination with a daily supplement of magnesium citrate 500mg and in some cases, a supplement of coenzyme Q10 (Mehavar,2008). The structure of vitamin B2 is as shown in Figure (1)

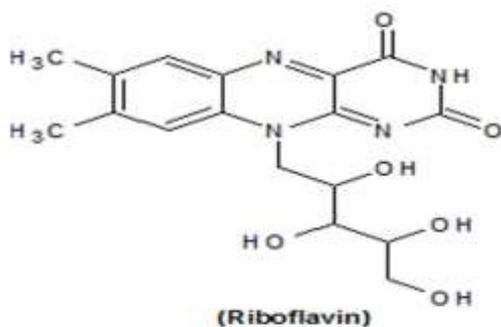


Figure (1)The Structure of Vitamin B2 (Riboflavin)

A prolong castric delivery of vitamin B₂ from a floating drug delivery system an in vitro study at pH 1.2 at 37°C under sink condition were used at different

time intervals and the amount of drug released was determined spectrophotometrically (Gangadhara and Thomas,1998 & Benjamin and Hijji ,2008 and Firyal *et al.*2010). Many studies of riboflavin were carried out such as reduction with UV-light (Agarwal and Yu,2003) and identification of riboflavin and its photoproduct in blood products (Bonartsev *et al.*, 2006).

Materials and Methods

Riboflavin was purchased from BDH, Mefenamic acid, Amoxillin and Cephalexin were obtained from Sumurra Drug Company. Thionyl chloride, Dioxane and DMF were used without further purification.

All other chemicals were used in this research were of analytical grad.

FT-IR spectra were taken on a Shimadzu, Ultra Violet spectra were recorded using Shimadzu UV-Vis recorder.

Thermogravimetric analysis (TGA) study was carried out on a Shimadzu -50 instrument (Japan) at a heating rate of 10°C min⁻¹, under flowing nitrogen of 20ml min⁻¹ over a temperature range from room temperature up to 500°C, C.H.N.S analysis were determined by analyzer type 1106 CarioIrba.

Preparation of Amoxylinyl, Cephalexinyl, Ibuprofinyl and Mefenamyl Chlorides The amoxillin, cephalixin, Ibuprofine, Mefenamic acid were converted to its acid chloride by using thionylchloride with equivalent molar ratio at 0°C..

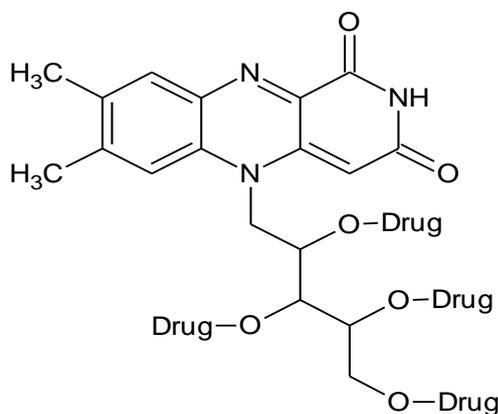
They were introduced in a single neak round bottomed flask containing freshly

dried solvent of dioxin and equipped with a condenser, stirred for 1hr, and then the solvent was evaporated and the residue was washed with ether for several times, finally it was dried under a vacuum until the constant weight was obtained as a deep yellow as a viscose product with 70% yield.

Preparation of Drug Bonded Vitamin B₂

1g, 0.01 mole of dissolved vitamin B₂ in 10 ml DMF and 0.04 mole of some antibiotic such as cephalaxinyl or

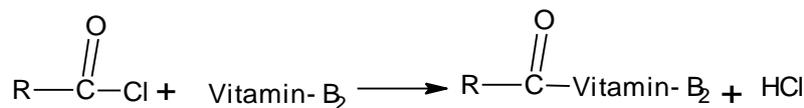
amoxillinyl or Ibuprofenyl or Mefenamic acid chlorides were introduced in a screw capped round bottom flask. The mixture was stirred for 1hr. at room temperature until the deep colored product was formed as drug bonded vitamin with high yield percentage. The product was filtered and washed with ethanol for several times. The drug bonded with vitamin B₂ suggest as was shown in Figure (2) and Table (1) illustrate the Physical Properties of the Prepared Drug Bonded with Vitamin B₂ (A₁, A₂, A₃, A₄)

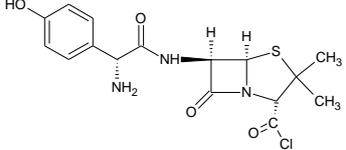
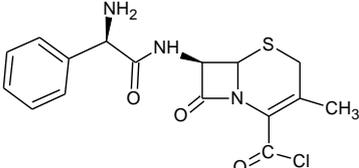
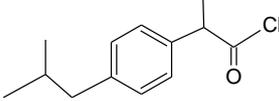
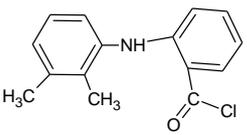


Drug = Amoxillin, Cephalaxin, Ibuprofen, Mefenamic acid, H

Figure (2) Drug Bonded with Vitamin B₂

Table (1) Physical Properties of the Prepared Drug Bonded Vitamin (A₁, A₂, A₃, A₄)



Compound. No.	m.p. °C	Color	Yield%	UV absorption nm
A₁  Amoxicillinyl chloride	220-225	Red	75	280, 330
A₂  Cephalexinyl chloride	230-235	Brown	70	220, 390
A₃  Ibuprofenyl chloride	225-228	brown	78	220, 380
A₄  Mefenamil chloride	200-210	brown	68	215, 320

Drug Release Study

Pre-weight drug bonded vitamin of pH 1.1 CUS pharmacopoeia at 37°C under sink conditions. Aliquots of 3ml were withdrawn at different time intervals

and the amount of drug released was determined spectrophotometrically. The total volume of released medium was kept constant by adding 3ml of fresh buffer after every withdrawal.

Stability Test for Drug Bonded Vitamin B₂

The stability of drug riboflavin was carried out by measuring the absorbance of solution of riboflavin drug ester in HCl solution of pH 1.1 (Artificial

Gastric Fluid) and phosphate buffer of pH 7.4 (Simulating intestinal fluid, SIF at 37°C, after the time interval of every 24 hrs. extended over a period of 6 days.

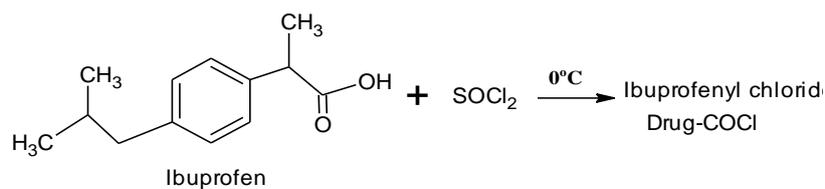
Results and Discussion

In this research the structural modification of riboflavin with some antibiotics were esterified with hydroxyl

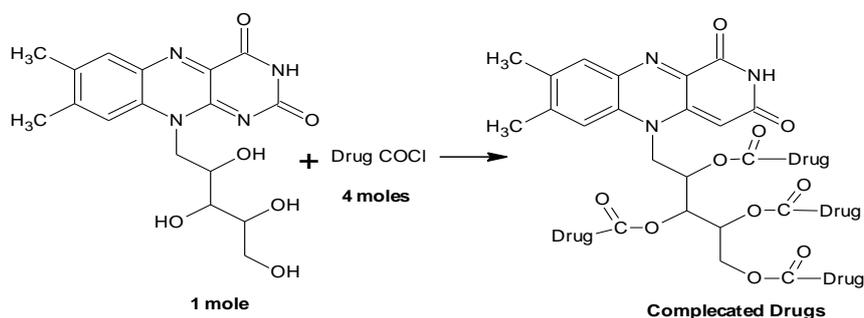
Amoxilline, Cephalexin or Ibuprofen were converted to their acids chloride using thionyl chloride at 0°C, as

groups of vitamin B₂, this is a new idea increases the advantages of two useful drugs, and helps the controlled release with prolonged time of the complicated drugs.

explained in scheme (1) in the following:



Scheme (1) Converted Carboxylic Group in Drug to Acid Chloride

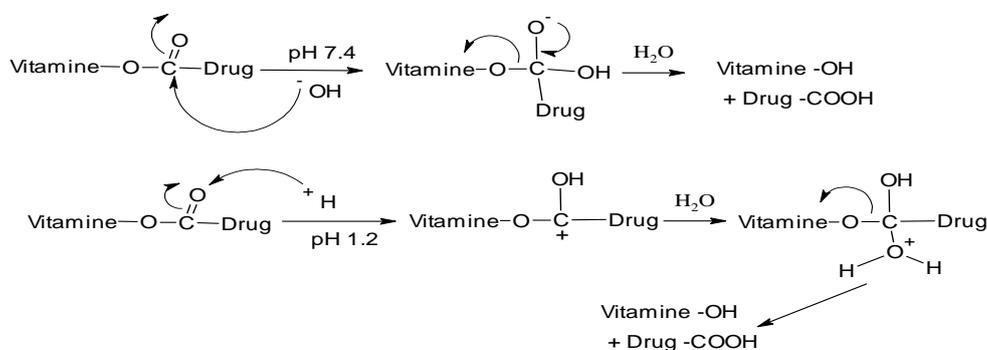


FT-IR spectra of the new prepared complicated drugs vitamin such as A₁, A₂, A₃ and A₄ were shown at figures (5,6,7 and 8), which indicated the disappearance of OH group at 3495cm⁻¹. The CO ester was revealed at 1707cm⁻¹ with comparing with figure (3) of riboflavin and with figure (4)of pure amoxillinyl. Also, the CO ester of cephalixin-vitamin B₂ was observed at

figure 4 of prepared A₂ and figure(7)of prepared A₃, and figure 8 for a₄ preparation with still C=O amide absorption of vitamine B₂ at 1731 cm⁻¹, also the NH amide was observed at

3213 cm⁻¹ with remaining some unreacted OH groups at 3392 cm⁻¹, the disappearance of OH carboxylic acid of corresponding drug. Fig. Figure(9) shows the TGA and DTA of prepared drug vitamin B₂ of A₁compound, which was explained its thermally stable ranged about 223.7°C with 95% weight losses at 404 C. Figure(10) shows the controlled drug vitamin release fwrthremone .

(10) show the rates of controlled drug release through hydrolysis of ester bond in different pH values as shown in the suggested following scheme(2).



Scheme(2) Hydrolysis of Drug-Vitamin in Basic and Acidic Medium

The objective of this study is to modified the vitamin B₂ to drug carrier vitamin to enhanced the sustained delivery system through chemical bond and slowly released under appropriate medium conditions such as

temperature and pH values. After 50 hours we observed the rate release of mefenamic acid was hydrolyzed in pH7.4 higher than pH1.2 which was ranged between 50-52% as a good yield.

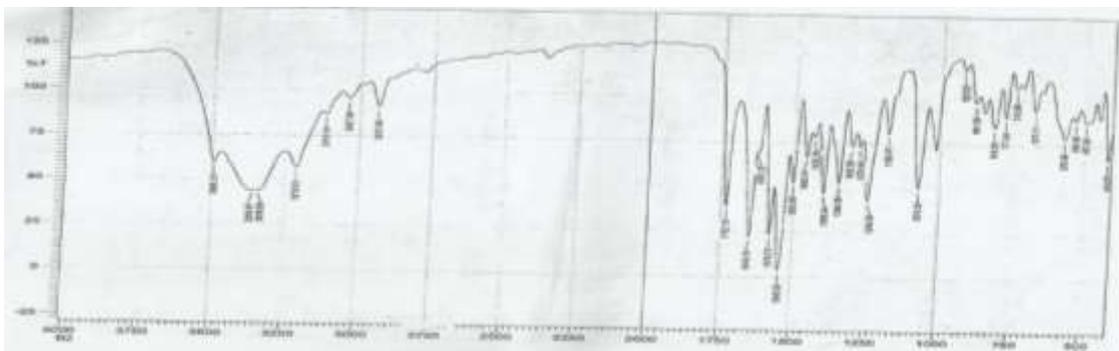


Fig.(3) FTIR Spectra of Vitamin B₂

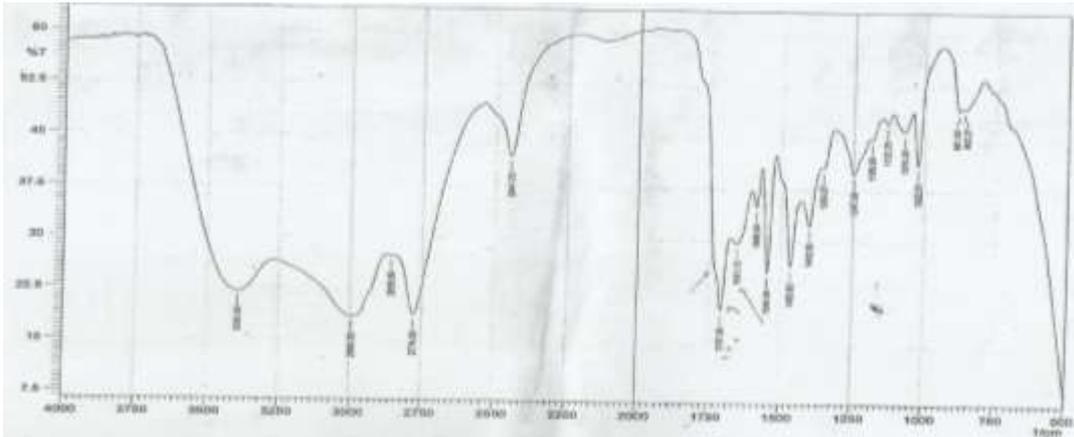


Fig.(4) FTIR Spectra of Amoxicillin

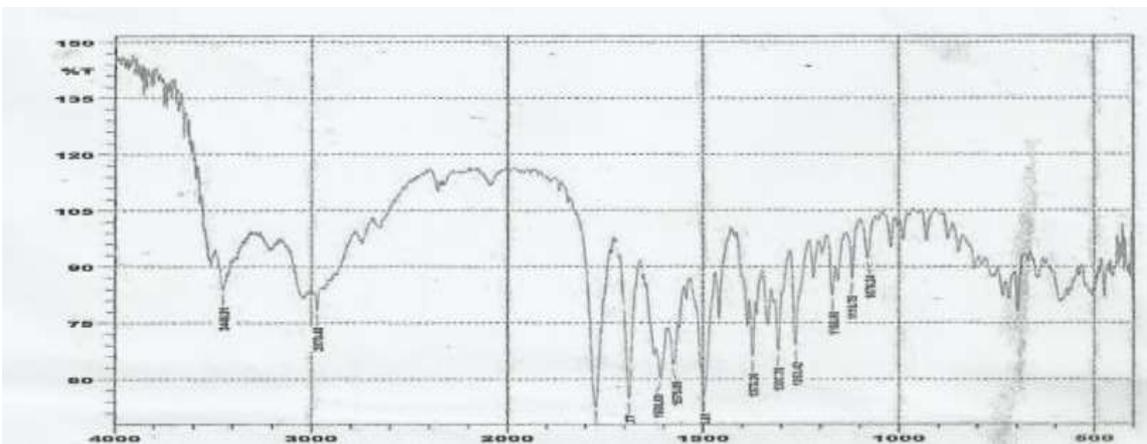


Fig.(5) FTIR Spectra of Amoxicillin Vitamin B₂[A₁]

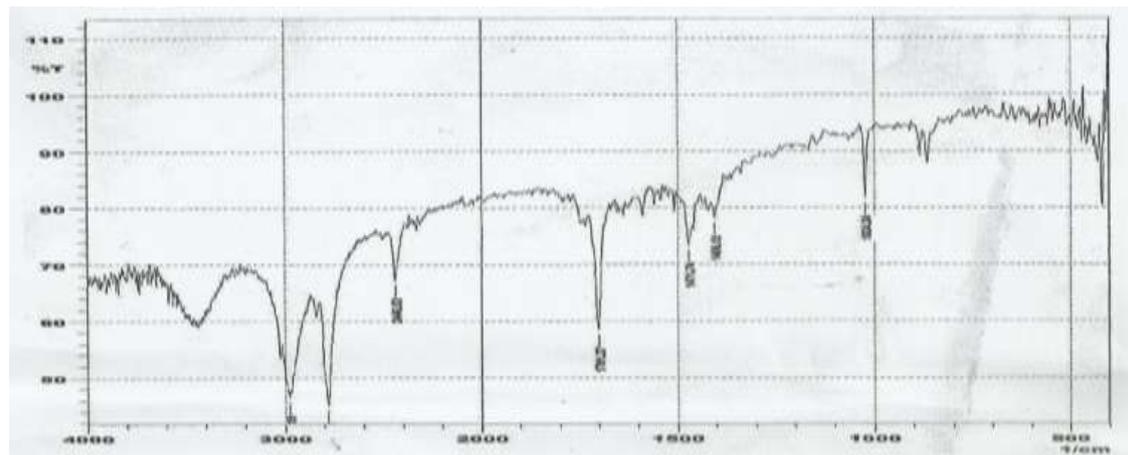


Fig.(6) FTIR Spectra of Cephalexin- Vitamin B₂ [A₂]

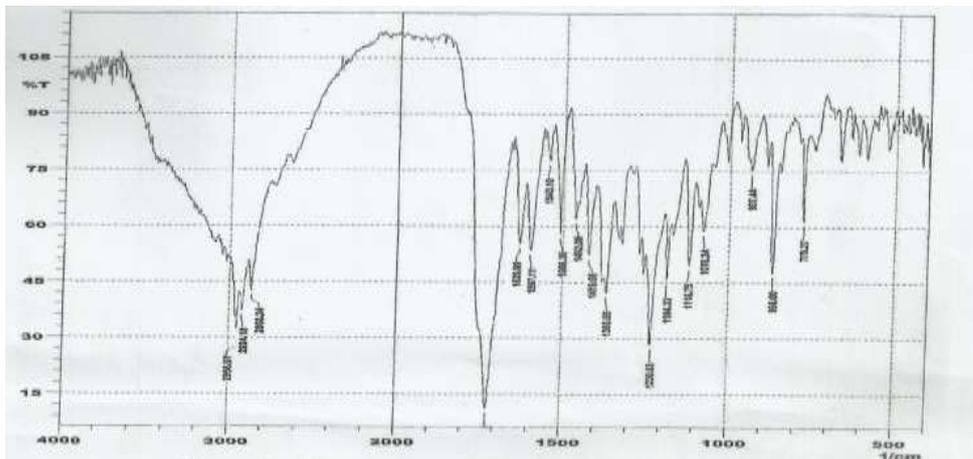


Fig.(7) FTIR Spectra of Ibuprofen-Vitamin B₂ [A₃]

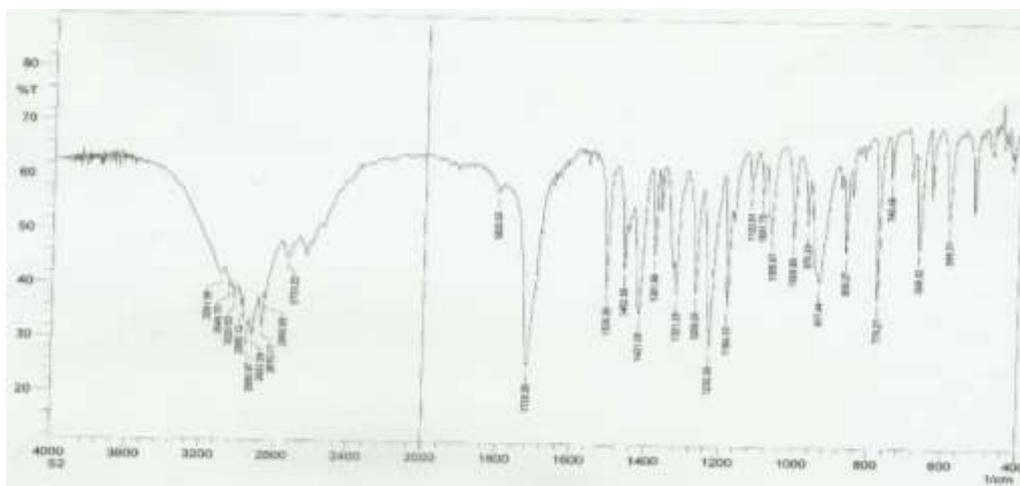


Fig.(8) FTIR Spectra of Mefenamic acid-Vitamin B₂ [A₄]

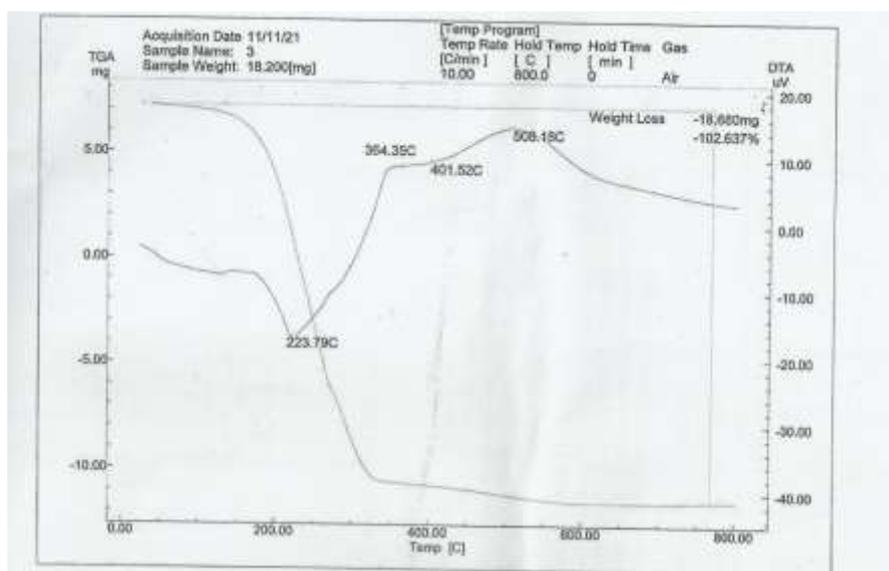


Fig.(9) TGA and DTA of the Prepared Drug-Vitamin B₂ (A₁)

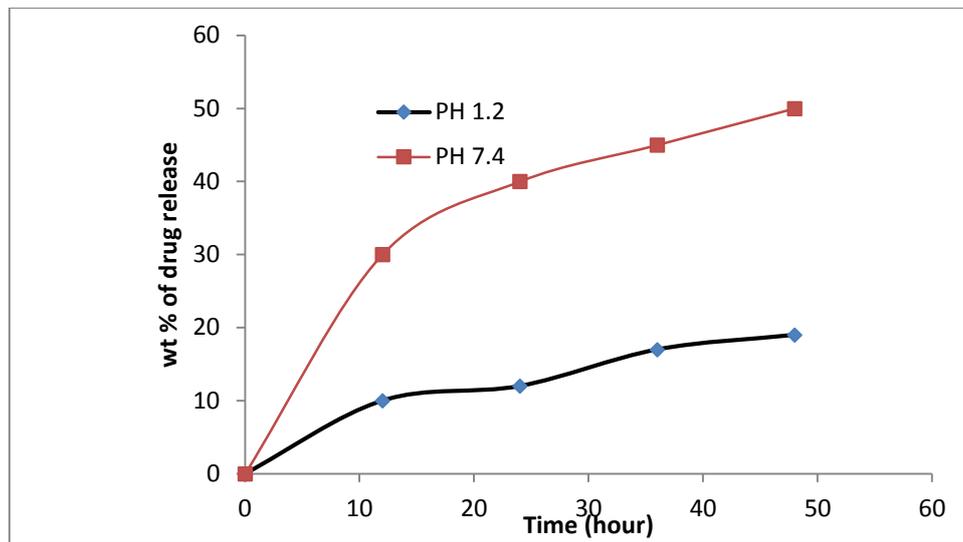


Fig.(10) Controlled Drug Release at 37 °C in pH 1.2, 7.4 of Mefenamic – vitamin(A4)

References

Agarwal, P. and Yu, Q., (2003). Synthesis and Character of Poly Mole Imide, *J. Ind. Eng. Chem. Res.*, 42, 2881-2884.

Antti, O.;Harri, K. and Jukka, V., (2003). Cross linked Poly(ester anhydride) Based on Poly Caprolactone and Polylactide Oligomers, *J. Polym. Science*, 41(23), 3788-3797.

Base, Y.; Okano, T. and Kin, S., (1989). Insulin Permeation Through Thermo Sensitive Hydrolysis, *J. Controlled Release*, 271-278 .

Benjamin, E. and Hajji, Y., (2008). The Synthesis of Cyclic Imides, *J. Molecules* 13, 157-169 .

Bonartsev, A.; Bonartsera, G. and Makhiua, T., (2006). New Poly (3-Hydroxy Buterate)- Based Systems for Controlled Release of Dipyridamole and Indomethacin, *J. App. Biochem. Microb.*, 42, 625-630.

Brahim, S.; Narinesingh, D. and Guisepps, A., (2003). Release Characteristics of Novel pH-Sensitive, *Biomaterials Cromdeules*, 4, 1224-1231.

Dena, M.; Wu, J. and Reinhart, G. (2011). Biodegradable Functional Poly(ester-amide)s with Pendant Hydroxy Functional Groups, *J. Acta. Biomater.*, 4, 1504-1515.

Expert Group on Vitamins and Minerals.(2003) Safe upper level for vitamins and minerals, Food Standards Agency. United Kingdom.

Firyal, M. A.; Abbas, N. M. and Khudheyer, J. K., (2010). Modification of Poly Vinyl Pyrrolidinone with Amoxilline to Drug Polymer, 5th Scientific Conference College of Science University of Babylon. 5, 224-229.

Firyal, M.; Amel, A. and Khudheyer, J. K. , (2011). Preparation of Condensed Polymer of Sulfonated Amino Acids with Benzidine, *J. Education.*, 6,333-343.

- Gangadhara, C.** and Thomas, M., (1998). Synthesis and Characterization of Polymaleimides, *J. Polym. Sci. Part A Polym.*, 36, 2531-2546.
- Hart, K.;** Bisto, A.; Antti, O. and Jukka, V., (2006). Synthesis and Hydrolysis Behavior of Poly Ester Anhydrides, *Macromolecular Bioscience*, 6 (7), 496-505.
- Malmstadt, N.;** Yagek, P.; Hoffman, A. and Styton, P., (2003). A Smart Microfluidic Affinity Chromatography Matric Composed of Poly(N-Isopropyl amide)-Coated Beads, *J. Anal. Chem.*, 175, 2943-2949.
- McCormick, D.B;** Olson, J.A.;Shike, M; Ross, CA.(1999). *Modern nutrition in Health and Disease*, 9th ed. Philadelphia: William & Wilkins,391-399.
- Mehavar, R.,** (2008). Delivery of Therapeutic Agents, *J. Control Release*, 69, 1-25.
- Schoenen, J.;** Jacquy, J.; Lenaerts, M.(1998). Effectiveness of high-dose Rboflavin in Migraine Prophylaxis. A Randomized Controlled Trial. *Neurology*, 50466-470.
- Yu, Y.;** Nakano, M. and Ikeda, T., (2003). Photometric: Directed Bending of a Polymer Film by Light, *Nature J.*, 42, 145-158.