Preparation of Drugs Carrier Vitamin B_2 and Studying their Controlled Drug Release

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Abstract

This study describes modification of Vitamin B_2 as drug derivatives, which were prepared through esterification of some –OH groups of vitamin B_2 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 B_2 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^oC, 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 بـ 2 ودراسة سرع التحرر الدوائي

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الخلاصة

حضر في هذا البحث وصفت بعض المشتقات للفيتامينات الحاملة للدواء والتي حضرت من استرة بعض المجاميع مع الاموكسيلينيل او الايبوبروفينيل او السيفالكسينيل او الميفنااميل ككلوريدات الهيدروكسيلية لفيتامين B_2 وبنسب مختلفة. هذه الطريقة الجديدة التي طبقت لتحسين واطالة العمر الزمني لتحرير الدواء مثل B_2 المضادات الحياتية المحملة على فيتامين شخصت مشتقات الفيتامينات الدوائية بواسطة طيف الأشعة تحت الحمراء والأشعة فوق البنفسجية ، ودرست الصفات الفيزياوية ، ودرست سرع 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 B_2 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 B_2 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., (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 B_2. Yeast extract is exceptionally rich with vitamin B_2, in addition to liver and kidney which are rich sources of B_2, another important sources of B_2 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, 2011and 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)

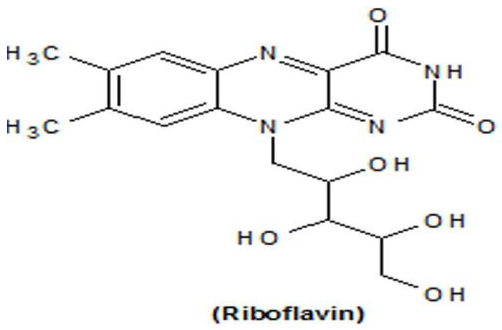


Figure (1)The Structure of Vitamin B2 (Riboflavin)

A prolong castric delivery of vitamin B_2 from a floating drug delivery system an in vitro study at pH 1.2 at 37^{o}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.

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

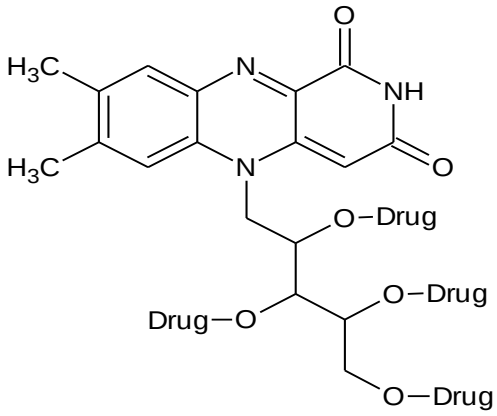
Preparation of Amoxylinyl, Cephalexinyl, Ibuprofinyl and Mefenamyl Chlorides The amoxillin, cephalexin, Ibuprofine, Mefenamic acid were converted to its acid chloride by using thionylchloride with equivalent molar ratio at 0^{o}C..

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 B_2

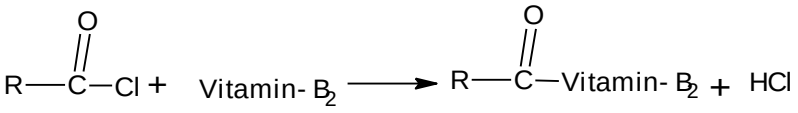
1g, 0.01 mole of dissolved vitamin B_2 in 10 ml DMF and 0.04 mole of some antibiotic such as cephalexinyl or amoxillinyl or Ibuprofenyl or Mefenamic acid chlorides were introduced in a screw capped round bottom flask. The mixture was stirred for 1hr. at room temperature until the deep colored product 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 B_2 suggest as was shown in Figure (2) and Table (1) illustrate the Physical Properties of the Prepared Drug Bonded with Vitamin B_2 (A_1, A_2,A_3, A_4)

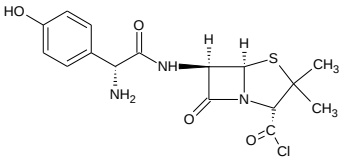
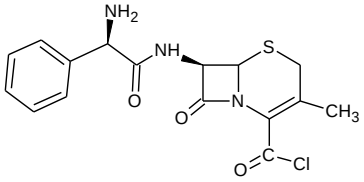
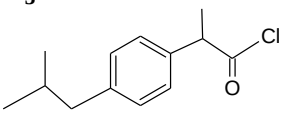
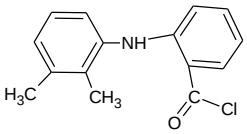


Drug = Amoxillin, Cephalexin, Ibuprofen,Mefenamic acid, H

Figure (2) Drug Bonded with Vitamin B2

Table (1) Physical Properties of the Prepared Drug Bonded Vitamin (A_1, A_2,A_3, A_4)



Compound. No.	m.p. °C	Color	Yield%	UV absorption nm
A_1  **Amoxillinyl chloride**	**220-225**	**Red**	**75**	**280, 330**
A_2  **Cephalexinyl chloride**	**230-235**	**Brown**	**70**	**220, 390**
A_3  **Ibuprofeny chloride**	**225-228**	**brown**	**78**	**220, 380**
A4  **Mefenamyl 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.

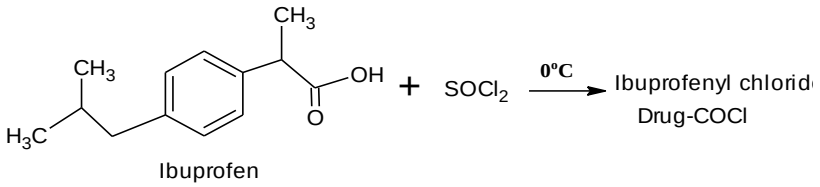
Stability Test for Drug Bonded Vitamin B2

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^{o}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 groups of vitamin B_2, this is a new idea increases the advantages of two useful drugs, and helps the controlled release with prolonged time of the complicated drugs.

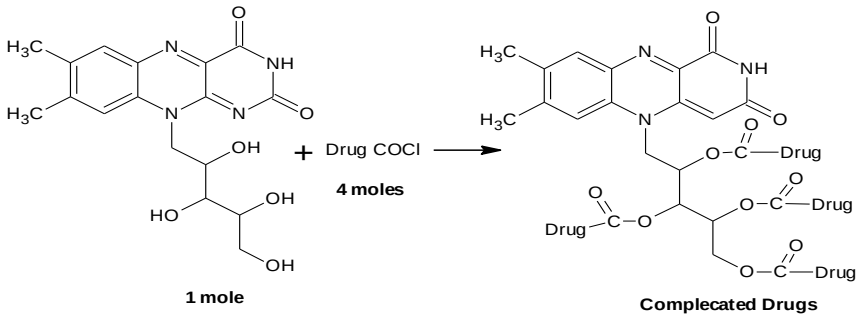
Amoxilline, Cephalexin or Ibuprofen were converted to their acids chloride using thionyl chloride at 0^{o}C, as explained in scheme (1) in the following:



$$\text{Drug COOH} + SOCl_2 \xrightarrow{0^{o}C} \text{Drug -COCl}$$

Drug COOH = (Amoxillin,Cephalexine ,Mefenamic acid)

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

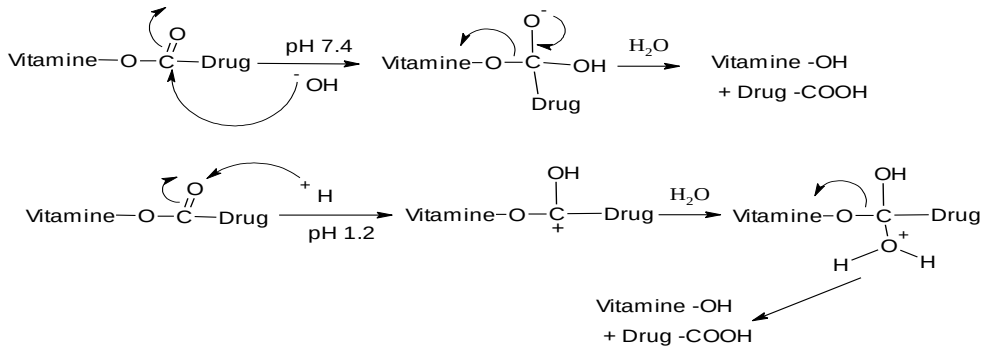


Drug: Amoxillin, Cephalexine, Ibuprofen, Mefenamic acid

FT-IR spectra of the new prepared complicated drugs vitamin such as A_1, A_2, A_3 and A_4 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 cephalexin-vitamin B_2 was observed at

figure 4 of prepared A_2 and figure(7)of prepared A_3, and figure 8 for a4 preparation with still C=O amide absorption of vitamine B_2 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 B_2 of A_1compound, which was explained its thermally stable ranged about 223.7^{o}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 B_2 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.

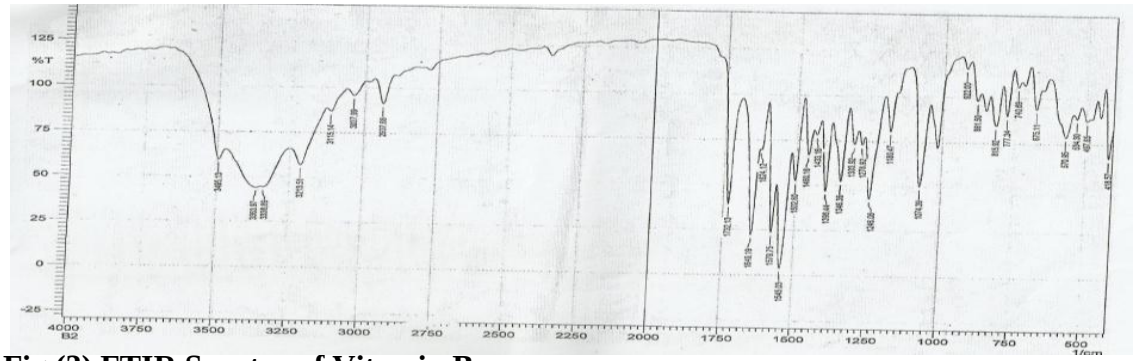


Fig.(3) FTIR Spectra of Vitamin B_2

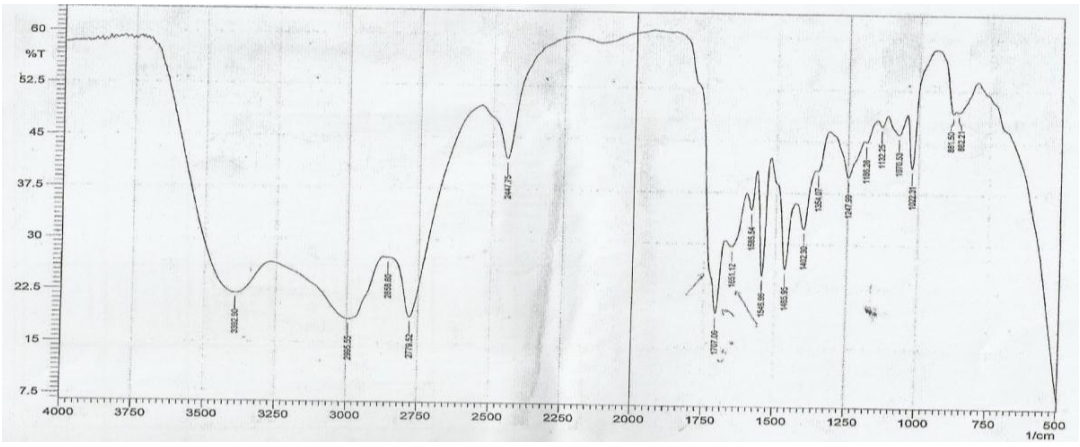


Fig.(4) FTIR Spectra of Amoxilline

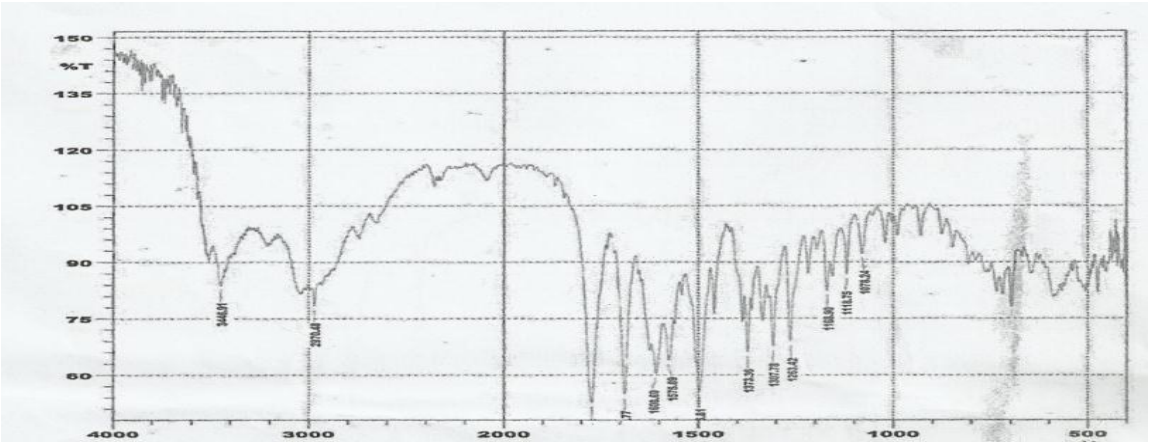


Fig.(5) FTIR Spectra of Amoxilline Vitamine B_2[A_1]

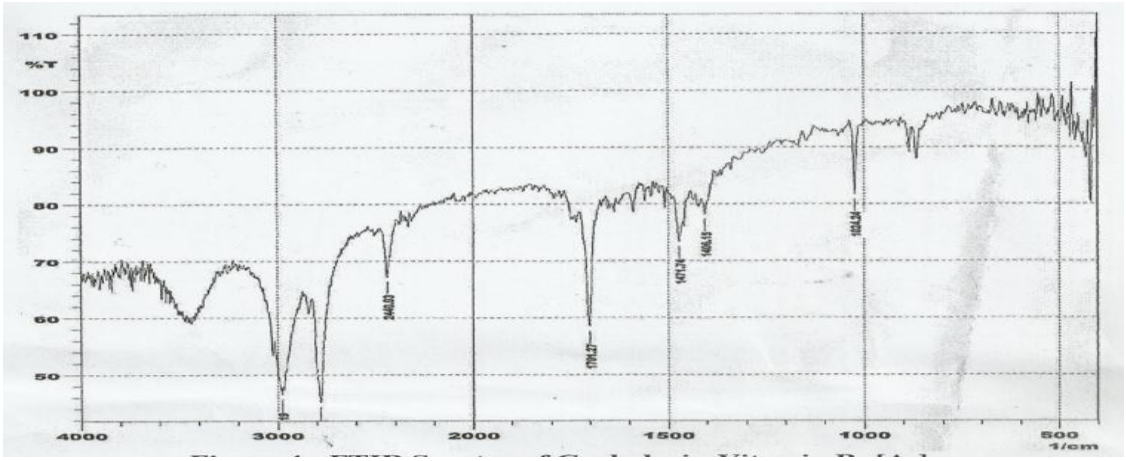


Fig.(6) FTIR Spectra of Cephalexin- Vitamin B_2 [A_2]

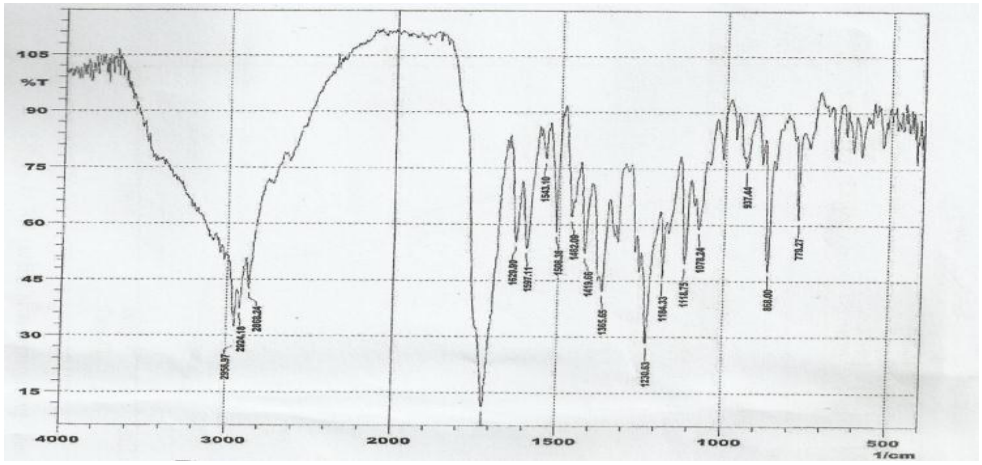


Fig.(7) FTIR Spectra of Ibuprofen-Vitamin B_2 [A_3]

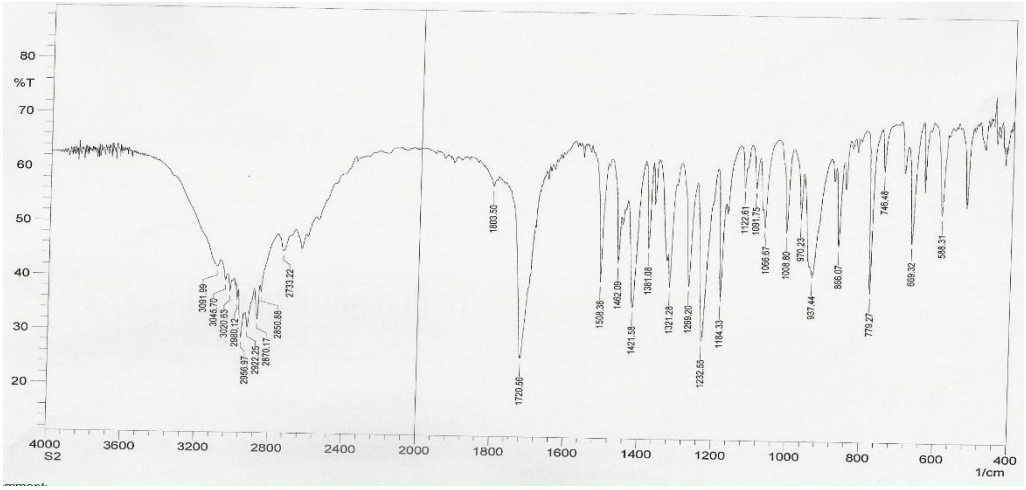


Fig.(8) FTIR Spectra of Mefenamic acid-Vitamin B_2 [A_4]

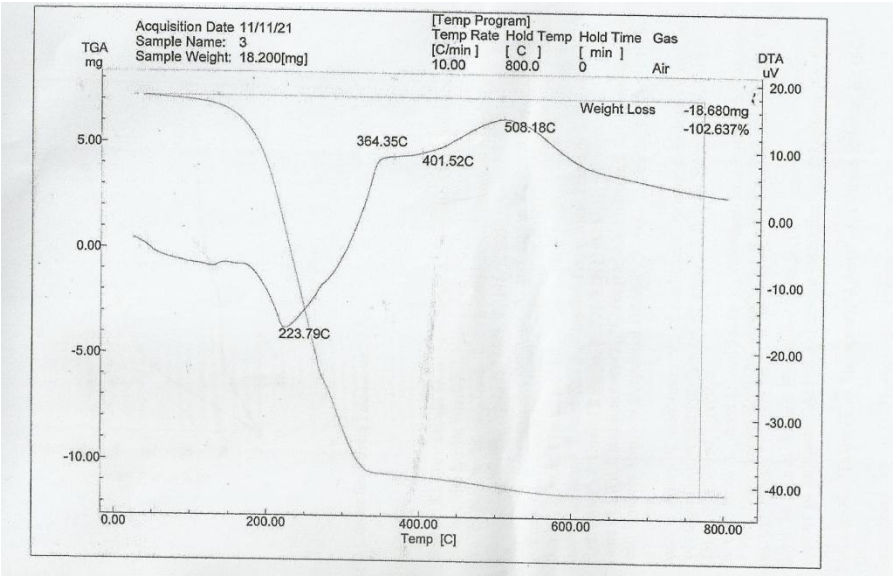


Fig.(9) TGA and DTA of the Prepared Drug-Vitamin B_2 (A_1)

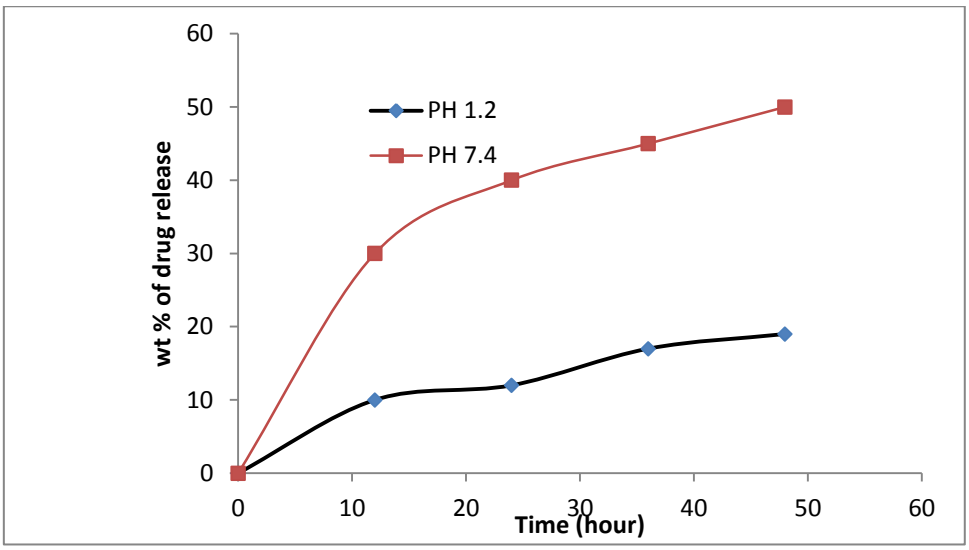


Fig.(10) Controlled Drug Release at 37 ^{0}C in pH 1.2, 7.4 of Mefenamic – vitamin(A_4)

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