

**Invitro evaluation controlled release study for
Metforminhydrochloride polymeric
hydrogel matrixes**

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Abstract

The hydroxyethylcellulose hydrogels were prepared by its chemical crosslinking using glyceraldehyde, and tetramethylolurea resin in the presence of sulfuric acid. Several tablets were prepared as polymeric matrix and polymeric reservoir systems from hydroxyethylcellulose hydrogels, loaded with Metformin hydrochloride in several ratios (25%, 34%, 50% wt/wt). The two polymeric matrix systems were prepared by compression molding and dip coating process respectively.

The release rate of Metformin hydrochloride from polymeric matrix devices was studied by using U.V. technique at constant temperature (37°C). The effect of pH on the release rate of Metformin hydrochloride in (PBS, pH=7.4), SGF , and SIF was studied. The swelling behavior of some prepared samples was also studied , the result showed greater increase in swelling ratio at lower pH values.

تقييم ودراسة الاطلاق المسيطر عليه لدواء الميتفورمين هيدروكلورايد المحمل على شبكة بوليمرية هلامية خارج الجسم الحي

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الخلاصة

تم تحضير هلاميات الهيدروكسي اثيل سيليلوز عن طريق التشابك الكيميائي باستخدام العامل الشباك كليسير الديهايد (Glyceraldehyde)، و حضر راتنج التترامثيلول يوريا و تمت بلمرة هذا الراتنج المثيلولي بإضافة حامض الكبريتيك. حضرت بعد ذلك عدة أقراص على شكل أنظمة شبكية بوليمرية (Polymeric Matrix Systems) و على شكل أنظمة خزان بوليمرية (Polymeric Reservoir Systems) من هلاميات الهيدروكسي اثيل سيليلوز و التترامثيلول يوريا و المحملة بدواء الميتفورمين هيدروكلورايد بنسب تحميل (25%, 34%, 50% w/w). حضرت أنظمة الشبكة البوليمرية بعملية القولبة بالضغط (Compression Molding) و أنظمة الخزان البوليمرية بعملية الطلاء بالتغميس (Dip Coating Process). درس الإطلاق البطيء للميتفورمين هيدروكلورايد من شبكة البوليمر باستخدام تقنية الأشعة فوق البنفسجية (U.V.) عند درجة حرارة ثابتة (37°C). إذ تم دراسة تأثير الدالة الحامضية على نسبة الميتفورمين هيدروكلورايد المتحرر من شبكة الهلام في محلول (PBS, pH=7.4) ، سائل المعدة الافتراضي (SGF)، و سائل الأمعاء الافتراضي (SIF). تم دراسة سلوك الانتفاخ للنماذج المحضرة و أظهرت النتائج ازدياد نسبة الانتفاخ في القيم الواطنة للدالة الحامضية.

Introduction

Hydrgels are three dimensional polymeric network that are capable of absorbing large amount of water, yet are insoluble due to presence of cross-links(Kim &.Peppas 2002) .

Drug delivery system from swellable matrixes for oral administration is usually prepared as tablets by compression molding of hydrophilic micro particulate powders (Colombo et al 1996). When timed release tablets are orally administrated the drug is going to be transferred into a physiological medium with a series of changing pH from highly acidic conditions of the stomach (pH = 1.2) to the slightly basic enteric conditions (pH = 6.8 – 7.4)

then to drop to (pH = 5.5 – 6.8) in the colon (Evan et al 1988) . Therefore , the dissolution behavior must be studied in order to determine how the pH can affect its release characteristics and kinetics (Pena et al 2004) .

Upon contact with water , tablets start to swell , forming a gel layer around the dry core. In general , because the dry core of polymer tablets is glassy , the drug contained in them cannot diffuse unless swelling takes place. on swelling , drug molecules dissolve in water and are released by diffusion . the process of swelling , erosion and drug release can occur simultaneously (Siepmann et al 1999 & Baumgartner et al (2002). In this work , the preparation , swelling properties and release of Metformin hydrochloride in hydroxyethylcellulose matrixes are reported .

Materials and methods

Chemicals

Hydroxyethylcellulose (HEC) was supplied by Aldrich, metformin hydrochloride was supplied by SID company \ IRAQ , glycerinaldehydes was supplied by Fluka and gelatin was supplied by B.D.H.

Preparation of HEC and Gelatin hydroge

HEC and gelatin were dissolved in distilled water then (0 .04 % wt /wt) glycerinaldehydes was added and mixed well then heated at 65C⁰ with stirring by mechanical stirrer for one hour .

Preparation of tetramethylol urea derivatives(TMU)

Tetramethylol urea derivatives (TMU) was prepared via condensation reaction of urea and formaldehyde adopting an experimental procedure which has been described in detail elsewhere (Jabbar et al., 1994) .

Loading of Metformin hydrochloride into HEC hydroge

HEC and Metformin hydrochloride in different ratio were dissolved in distilled water , 0.04 % wt/wt glycerinaldehyde was added and heated at 65 C⁰ with stirring for one hour , then the product was dried at 90 C⁰ .Several

tablets (11 x 8 mm) were prepared from the obtained solid hydrogel by compression molding process to obtained polymeric matrix system . Some tablets were then coated by solution of HEC , Gelatin and (TMU in the presence of sulfuric acid as catalyst) by dip coating process to obtain polymeric reservoir systems . Table 1 shows the quantities of reactants used in the preparation of the metformin hydrochloride loaded into HEC hydrogel tablets.

Table (1): The composition of the prepared polymeric drug systems

Sample No.	HEC (g)	Metformin hydrochloride (g)	Hydrogel used for tablet coating
H1	10	2.5	-----
H2	10	2.5	Gelatin
H3	10	2.5	HEC
H4	10	2.5	TMU
H5	10	3.4	-----
H6	10	3.4	Gelatin
H7	10	3.4	HEC
H8	10	3.4	TMU
H9	10	5.0	-----
H10	10	5.0	Gelatin
H11	10	5.0	HEC
H12	10	5.0	TMU

Result and Discussion

Swelling Study

The dried tablets were allowed to hydrate in the presence of excess amount of Simulated Gastric Fluid SGF (pH 1.2) , Simulated Intestinal Fluid SIF (pH 7.4) and buffer solution (pH 7.4). The weight of the hydrated samples was measured at different time intervals by removing the

tablets from liquid and blotting them to remove the superficial water and weighing them in a closed weighing bottle . The swelling ratio (Q) is determined by the equation :

$$Q = (W_s - W_d) / W_d \quad (\text{g water / g dry gel})$$

Where:

W_s is the weight of the swollen hydrogel and W_d is the weight of the dried hydrogel (Chen and Y. Hsieh 2001 & Chen et al 1999). Figs 1 and 2 showed the swelling ratio of H1 and H2 in different pHs as a function of time .

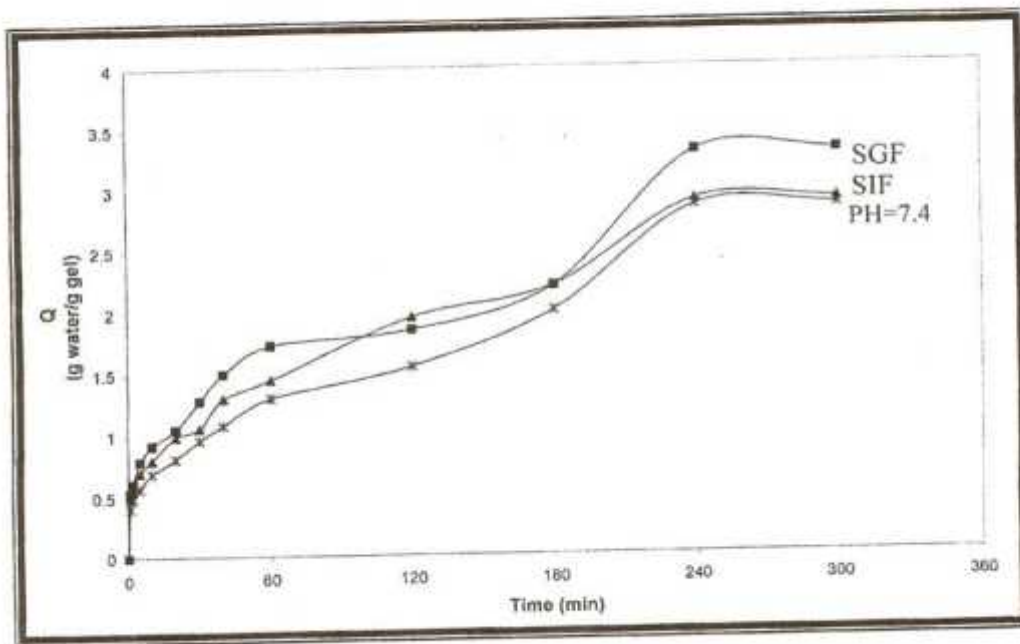


Fig. 1 : Swelling ratio for H1 as a function of time

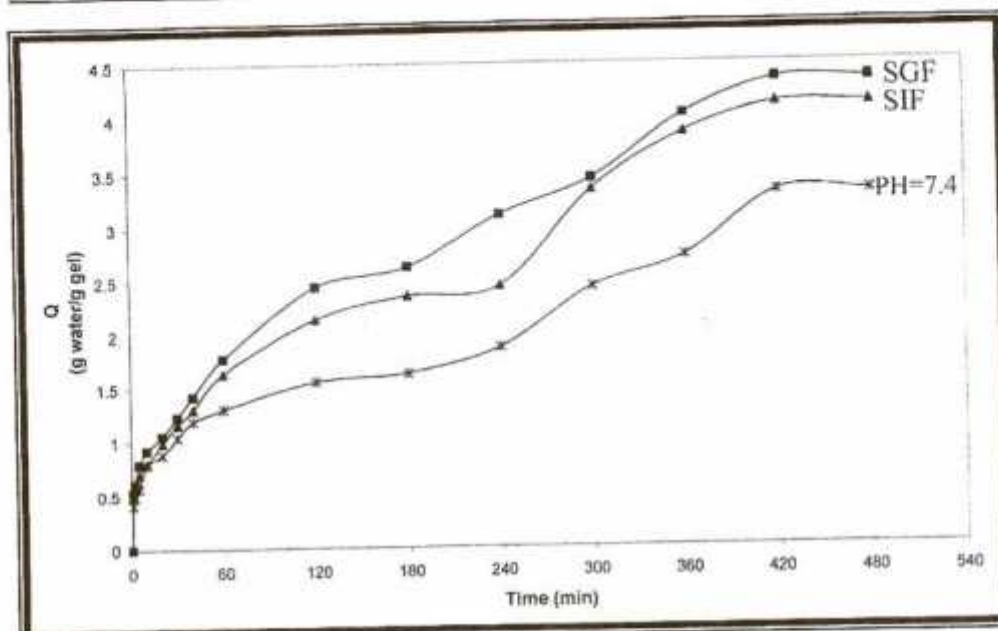


Fig. 2 : Swelling ratio for H2 as a function of time

Releasing study

The tablets were immersed into Fluid SGF (PH1.2), SIF (PH 7.2) and in buffer solution (PH 7.4) . The rate of the drug release was followed by UV spectrophotometer (Helios α V4.60 UV-Visible Spectrophotometer, England).. Fig (3) – (7) shows the release of metformin hydrochloride at 37C⁰ in SGF, SIF and PH= 7.4 as a function of time . The obtained results showed that the drug release proceeds more efficiently at lower pH (SGF) because the swelling ratio in SGF is higher than the swelling ratio in SIF and in pH = 7.4 which mean that the drug can be transferred very easy through polymeric matrix due to large swollen pore size in the swollen hydrogel. The samples H1 , H5 and H9 showed that the drug release proceeds faster than other samples , this behavior can be due to type of the polymer drug delivery system because these samples were prepared as polymeric matrix while the other samples were prepared as polymeric reservoir system. In other wards the drug need more time to release from the polymeric system. Tables2 and 3 show the ratio of Metformin hydrochloride

released from the polymeric system at different time intervals(five hours and eight hours).

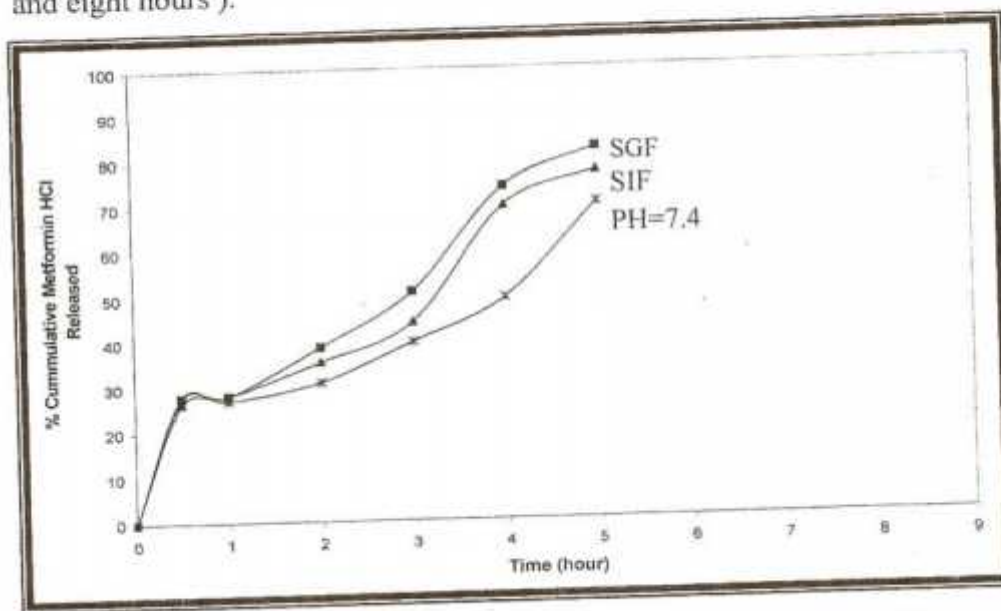


Fig. 3 : shows the release of metformin hydrochloride from H1 at 37C⁰ in SGF, SIF and PH= 7.4 as a function of time

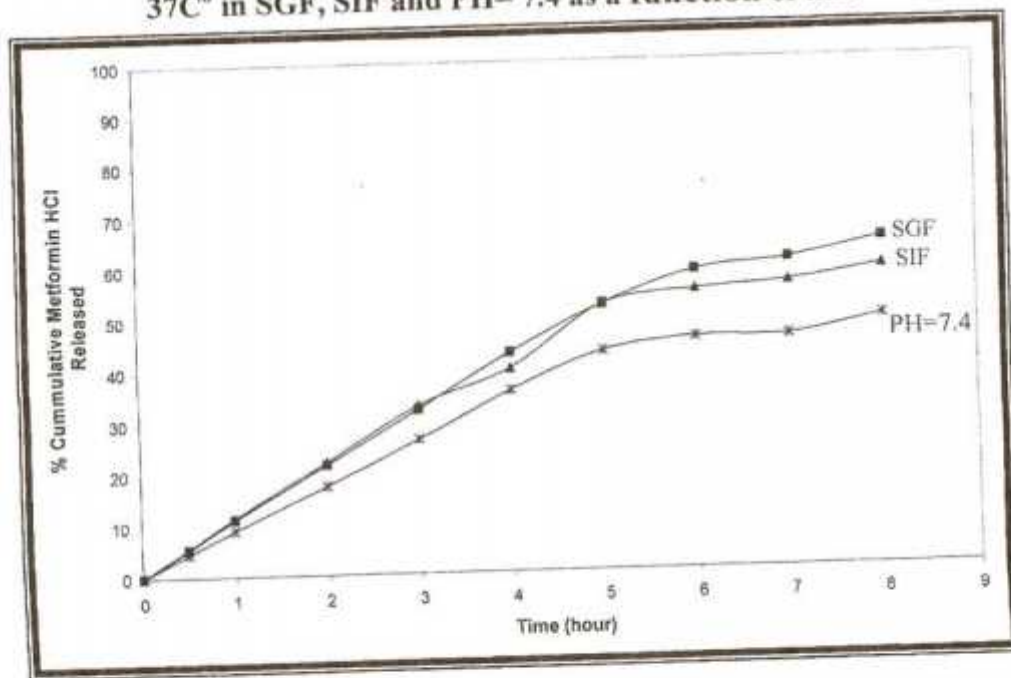


Fig. 4 : shows the release of metformin hydrochloride from H2 at 37C⁰ in SGF, SIF and PH= 7.4 as a function of time

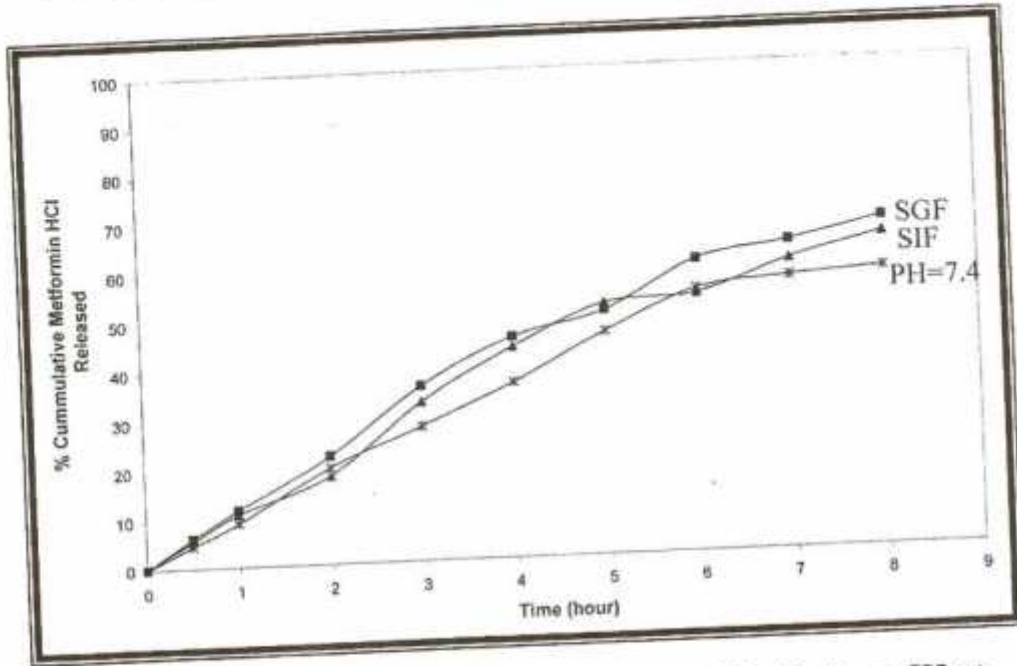


Fig. 5 : shows the release of metformin hydrochloride from H3 at 37C⁰ in SGF, SIF and PH= 7.4 as a function of time

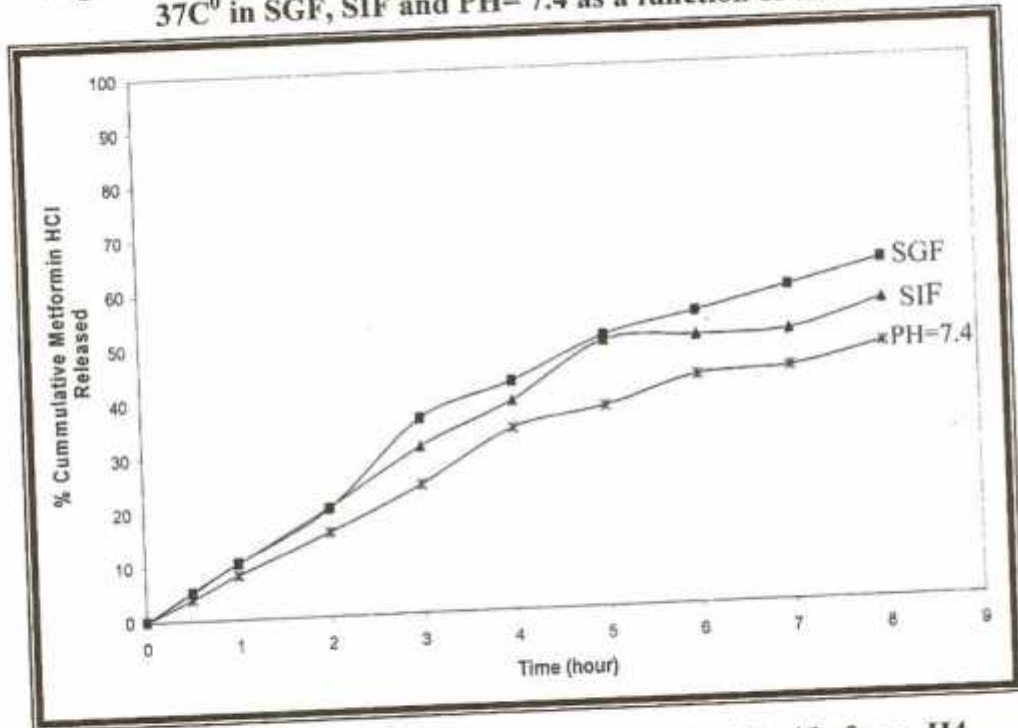


Fig. 6 : shows the release of metformin hydrochloride from H4 at 37C⁰ in SGF, SIF and PH= 7.4 as a function of time

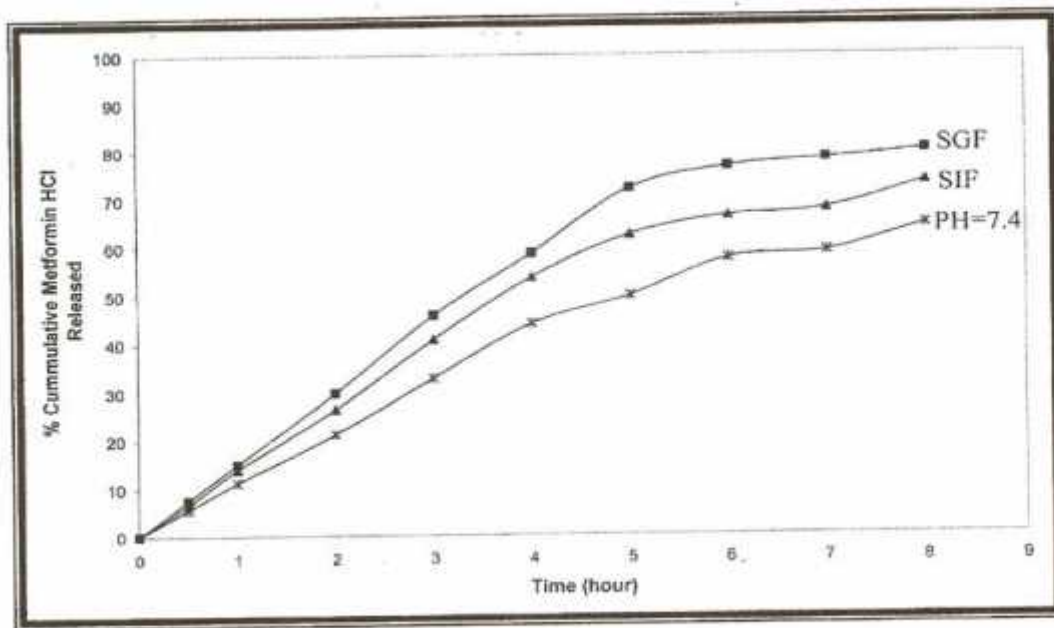


Fig. 7 : shows the release of metformin hydrochloride from H6 at $37C^0$ in SGF, SIF and PH= 7.4 as a function of time

Table (2): shows the ratio of Metformin hydrochloride released from polymeric matrix system at five hour interval .

Sample No.	% cumulated Metformen hydrochloride released		
	pH 7.4	SIF	SGF
H1	70	77	82
H5	78	84	92.3
H9	83.4	92.8	98.2

Table (3): shows the ratio of Metformin hydrochloride released from polymeric reservoir system at eight hour interval.

Sample No.	% cumulated Metformen hydrochloride released		
	pH 7.4	SIF	SGF
H2	49	58.8	64
H3	57	64	67.2
H4	47	55	62.4
H6	64.3	73.3	79.9
H7	69.2	76.4	82.9
H8	60.8	65	74.1
H10	77	87	92.6
H11	82.3	90	94
H12	69	84.7	90.4

The samples shown in Table 2, where prepared by mixing the polymer and drug to get the homogenous system (matrix system). The diffusion in the samples H1, H5 and H9 occurred due to the drug transfer through swollen polymeric matrix to outer environment according to diffusion mechanism. The other samples which are present as reservoir systems, the releasing of the drug was found to be stay constant through the long period of time .

Effect of drug / polymer ratio

Three different ratio from Metformin hydrochloride (25 , 34 , and 50) % to HEC were prepared to study the effect of drug / polymer ratio on the release rate of the drug as a function of time. The highest drug release rate was observed with samples which have highest drug/polymer ratio as shown in fig. 8 . This behavior can be related to the high drug diffusion rate from the polymeric matrix leading to migration of the drug from polymeric matrix.

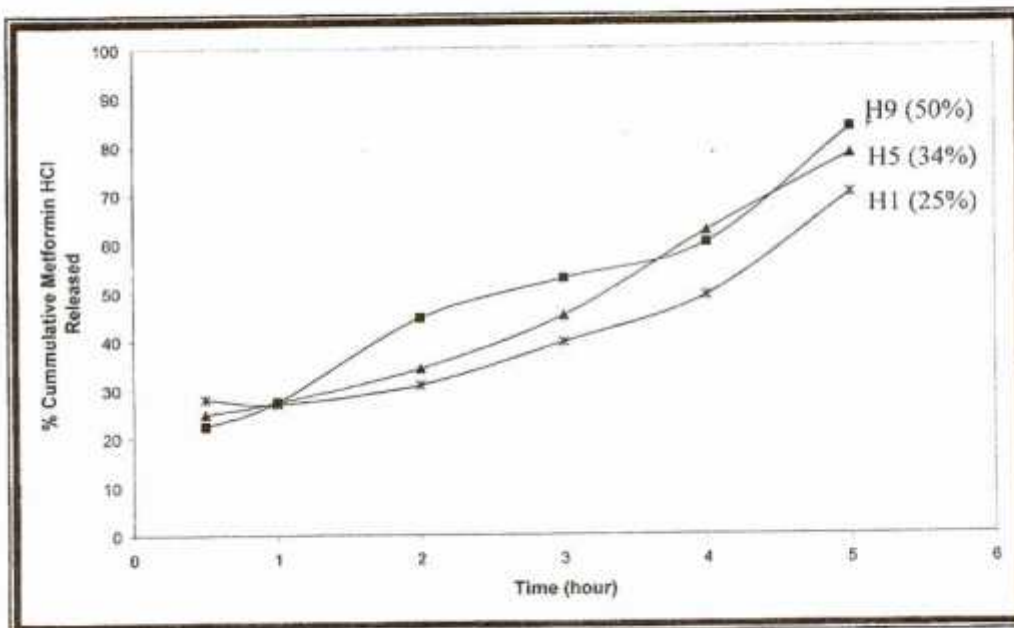


Fig. 8 : The effect of drug constituent on the drug release rate from polymer matrix at pH = 7.4

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