A Study of Some Cellulose Derivatives As Hydrogel For Control Drug Release

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Abstract

Neutral and semi-synthetic hydrophilic polymers are widely used in pharmaceutical technology to formulate as controlled release drugs delivery systems ,cellulose derivatives is biocompatibility, biodegradability , non-toxicity, its is a good candidate as drug carrier. In this study, polymers were used as cellulose derivatives like Methylcellulose (MC) & Sodium Carboxymethylcellulose (NaCMC) as hydrogels for controlled delivery for two kinds of drugs, Cefotaxine & Amoxycilline trihydrate in different media (Distilled water, Normal Saline & Buffer solution PH=2). It has been shown that for sodium Carboxymethylcellulose the drug release rate is more than the Methylcellulose and that the release rate for Amoxycilline trihydrate is more than Cefotaxine.

Introduction

Synthetic hydrogels are used in prosthetic materials, hydrogel lenses, and membranes for controlled drug release because of their compatibility with living tissues (1,2). Hydrogels have been considered as vehicles for the immobilisation, encapsulation and controlled release of many physiologically active substances including, antibiotics anticoagulants, anticancer drugs, antibodies, drug antagonists, enzymes, contraceptives and antibacterial agents (3,4).

The equilibrium water content of a hydrogel is affected by the nature of the hydrophilic monomers used in preparing the polymer or copolymer. The nature and density of the cross-links (the most common cross-linking agent being ethyleneglycol dimethacrylate) and such factors as the temperature, tonicity and PH of the hydrating medium (5). When a water-soluble polymer is formulated as a tablet

and placed in a dissolution medium, a gelatinous layer is formed at the tablet surface that prolongs the release of drugs. Fast hydration would lead to a dispersion of the system, due to the polymer-penetrate interaction and dissolution of water-soluble polymers, increasing drug release. Fast polymer hydration can be reduced by using less water sensitive ingredients. Many polysaccharides possess chemically active functional groups that can be used for further manipulation. Furthermore, development was done on making graft copolymers on polysaccharides as a way of obtaining materials that profit from the particular properties of both natural and synthetic macromolecules (6,7,8) .In this study, some cellulose derivatives already prepared have been used like NaCMC and MC as hydrogel for controlled release of many drugs.

Materials and Methods

Materials

1.Sodium Carboxymethylcellulose(NaCMC),white granules, Aldrich.

2.Methylcellulose (MC), white granules, 29% degree of substitution, obtained from Aldrich.

3.Buffer solution PH=2, G.P.R., Redel-de Haen Ltd-Germany.

4. Normal saline solution, pure, Aqueous solution of sodium chloride 9 gm/L, obtained from Iraqi Local Product.

5.Amoxycillinetrihydrat (ATH) , F.w= C16H19N3O5S.3H2O , M.wt= 419, pure powder, obtained from Sammera Drug Industry (SDI).

6.Cefotaxime (CEF) , F.w= C16H14N5O7S2, M.wt= 452 , pure powder, obtained from Sammera Drug Industry (SDI).

Methods

Swelling Measurement (9).

MethylCellulose and Carboxymethylcellulose was accurately weighed in eppendorfe and placed in stoppered conical flask containing 100 ml distilled water, which was left in a thermostated cabinet at 30±0.1^{0}C for 21 days. After every 24 hrs, excess water was poured off from the eppendorfe, the gel is held for 10 sec. Then dropped in a weighing bottle, which was covered and weighed. The swelling number was calculated as follows:

$$\alpha = \frac{W - Wo}{Wo} \times 100$$

	Buffer Solution (pH = 2)	> Saline Solution	> distilled Water
NACMC	1110	1250	1390
MC	900	1075	1200

The rate of swelling was the highest in buffer solution (pH =2), followed by normal saline and the lowest rate was in distilled water.

The process of swelling in aqueous media that is the interaction energy between aqueous media and (NaCMC or MC) needs to be sufficient to overcome the hydrogen bonding in the interior of (NaCMC or MC). The NaCMC, MC as polysaccharide is hydrolyzed in acid medium.This may be the reason for the highest swelling value in solution of (pH = 2), in this medium the damage of hydrogen bonding will be strong and will allow considerable swelling. In hydrophilic matrices consisting of drug with water gelling polymer (usually polysaccharide) and in vitro drug release occurs by a combination of diffusion through the gel and erosion of the matrix. The proportion of drug released by each mechanism is determined by the properties of the gel and the solubility of the drug (11).

In normal saline there will be interference between hydrogen bonding and ionic species Na^+ and Cl^-, which shield macromolecular chains and weakened hydrogen bonding. Furthermore, normal saline will be more under its own osmotic pressure through pushing water from the aqueous solution of sodium chloride to the matrix, enhancing the extent of swelling than in the presence of water alone (12).

Generally, NaCMC have a higher swelling than MC. These polymers swell more or less in water, depending on the hydrophilicity of the side group. If the hydrophilicity of the side group is insufficient to dissolve the whole molecule in water swelling takes place, as would be expected, a further increase in hydrophilicity leads to water-soluble polymers. The NaCMC swell more in water and contain a large amount of water, which is considered to be better for their bio compatibility for living tissue because the interfacial free energy between water-swollen gel and the aqueous biological environment is very small and the inner water provides a good permeability to oxygen metal ions, and other metabolites (13).

From drug release studies, figures (5) to (12), the following conclusions can be extracted :

1. In all examined media the amount of drug release is increased gradually and then attains equilibrium fixed value at certain concentration. This concentration depends on the medium in which

Where α is the percentage swelling number, W is the weight of equilibrium swelled sample, W0 is the original weight of the polymer

This experiment was repeated again by using pH = 2 buffer solution and normal sallaine instead of distilled water .

U.V. Quantitative Determination of Drugs (10)

200 mg of the pure drug (ATH) or (CEF) was dissolved in 100 ml distilled water. The maximum absorption wavelength was determined for each drug. Different concentrations of each drug were prepared by transferring suitable volume of the mother solution into 10 ml-calibrated flask to cover the working range.

The absorbance of the solution at the specific λmax was measured against the blank. The absorbance was plotted against concentration to obtain a calibration graph. This experiment was repeated again by using pH = 2 buffer solution and normal sallaine instead of distilled water, the data are represented in figure (3)and (4).

Drug Release Studies:

In vitro studies: The release (two replicates) was performed by using methylcellulose and carboxy methylcellulose.

0.1 gm of each of the polymers mentioned above were accurately weighed in eppendorfe, and placed in stoppered vial containing 100 ml distilled water. The vial was kept in a thermostated cabinet at 30±0.1°C for 10 days (the time which required attain maximum swelling). 2 and 6 mg of the drug aqueous solution was dispensed in the swelled polymeric matrix by using horizontal shaker, (ATH) and (CEF) were used. The elution medium was sampled and the content of drug in the samples was measured spectrophotometrically at 278 nm for (ATH) and at 268 nm for (CEF). Sampling was almost carried out every 24 hrs, and the concentration of drug release was calculated from the calibration curve of each drug, the above method was repeated again by using pH = 2 buffer solution and normal saline instead of distilled water, show figures from (5) to (12).

Result and Discussions

The starting point in this work was to study the effect of water, normal saline, and buffer solution (pH=2) on the swelling of two cellulose derivatives, figures (1) and (2).The maximum degree off swelling α can be arranged as follows:

drug release study was carried out .

2. NaCMC is more hydrophilic than MC, Hydrophilicity increased the extent of swelling, NaCMC has higher swelling numbers than MC, this enhances the formation of more voids in the structure of MC; moreover, it induces the formation of new voids.
3. The rate of drug release was highest in Buffer solution of pH=2, lower in normal saline and lowest in distilled water.
4. So it also reaches equilibrium value after 312 hr. Extension of time to 22 days does not increase the amount of drug released. So, it seems that the same factors affecting the release of (ATH) remain affecting release of (CEF) in manner and weight.
5. It was found that the release of (ATH) is faster than that of (CEF)this difference may also be accounted for by
   - The fact that (ATH.) is more soluble than (CEF). (ATH.)solubility is 1gm in 1 ml water, while (CEF) solubility is 1 gm in 4 ml waters.
   - (CEF) size is bigger than (ATH) ,i.e., (CEF) will diffuse slower than (ATH).
   - It proceeds to the position of a more effective factor beside that nature of (NaCMC or MC) and (ATH) is more close than that between (CEF) and (NaCMC or MC), (ATH) is more polar than (CEF) and according to solubility parameter concept,it should be more compatible with (NaCMC or MC), and in this case the polymer will be more permeable to this drug.

Effect of Drug Load:

Increasing initial drug load from 2mg/0.1gm polymer to 6 mg/ 0.1gm polymer, increase of the concentration of drug release, so drug loading was dependent on the concentration of the drug. Factor affecting release depends on the nature the polymer and the permeating agent. The release process is postulated to occur as follows:

1. Absorption of the permeating species into the polymer.
2. Diffusion of the permeating species through the polymer matrix along a concentration gradient.
3. Disruption of the permeating species through the polymer wall and its removal from the surface.

The solubility of the entrant in and its diffusion through the polymer matrix follow Henry's and Fick's laws, respectively. Thus, the type and concentration of the entrant and the molecular state of the

polymer, above or below its glass transition temperature (glassy or rubbery), are important. In the simplest case, where the entrant is a fixed substance and the polymer is above its glass transition temperature, the passage of the entrant through the polymer matrix is proportional to the Fick diffusion constant, and the Henry solubility coefficient.

Permeation also depends upon the nature of entrant. The rate of passage of a permeating species through a polymer matrix is governed by its solubility in the polymer and the relationship between the size of the entrant molecule and interstices in the polymer.

The size of (CEF) is big, the molecular weight is considered here as a measure of the size (452).

Release occurs by outflow of drug from the gel and inflow of water to the gel. Rate of diffusion is explained by Fick's law:

$J = -D \, d \, Cm/dx$

Where: J = flux (gm/cm2 sec).

D = Diffusion coefficient.

Cm = Concentration of the diffusing material.

X = Cross-sectional area, crossed by the drug.

In fact, gross crystalline areas are barriers against permeation and it seems that this reason of attaining maximum release percentages irrespective of increase of drug loading.

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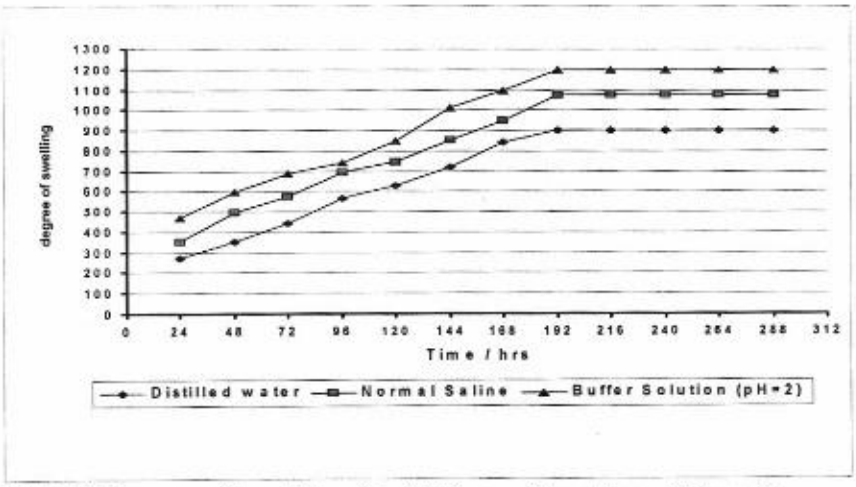

Fig. (1) Degree of swelling for MC as a function of time in different media.

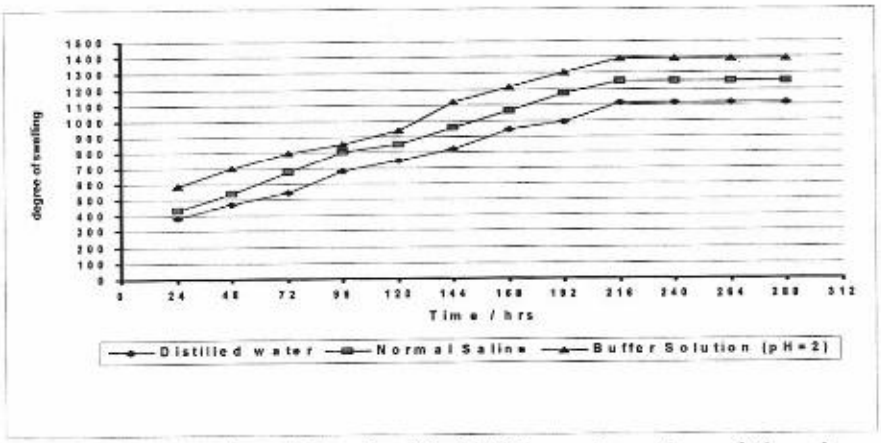

Fig.(2) Degree of swelling for NaCMC as a function of time in different media.

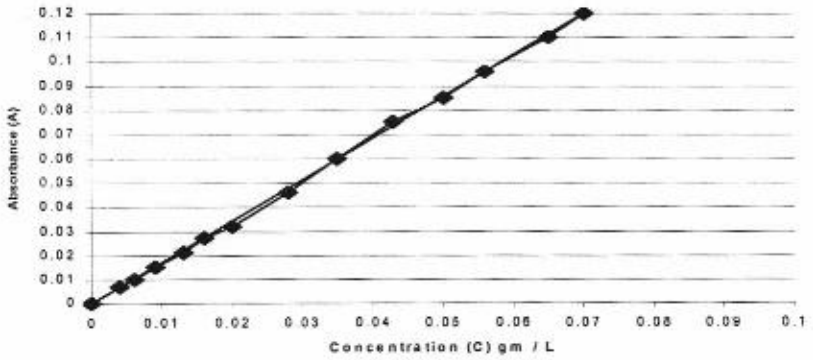

Fig. (3) The working calibration curve for the data of (CEF), (the absorbance in 1 cm cell at λ max = 268 nm).

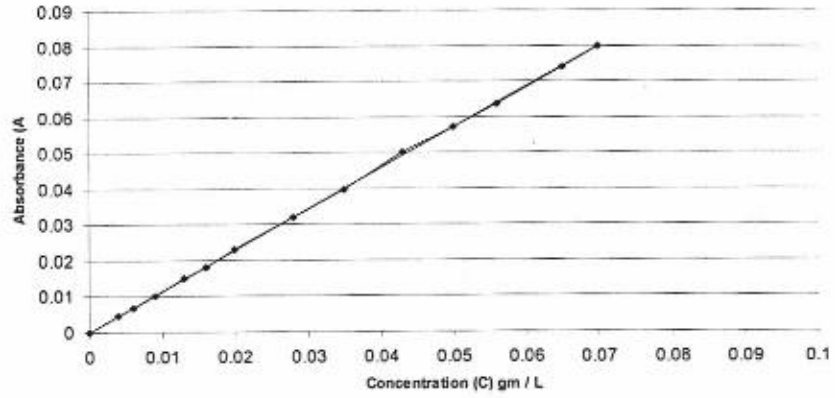

Fig.(4) The working calibration curve for the data of (ATH), (the absorbance in 1 cm cell at λ max = 278 nm).

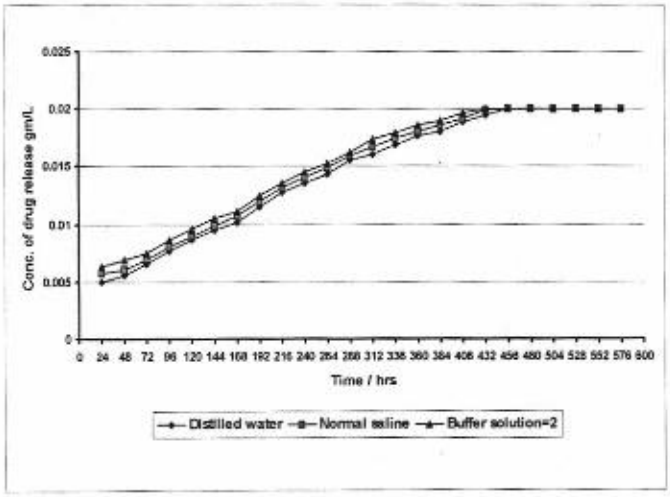

Fig. (5) (CEF) release (load=2mg/0.1 gm NaCMC) as a function of time in distilled water, normal saline and buffer solution (PH=2)

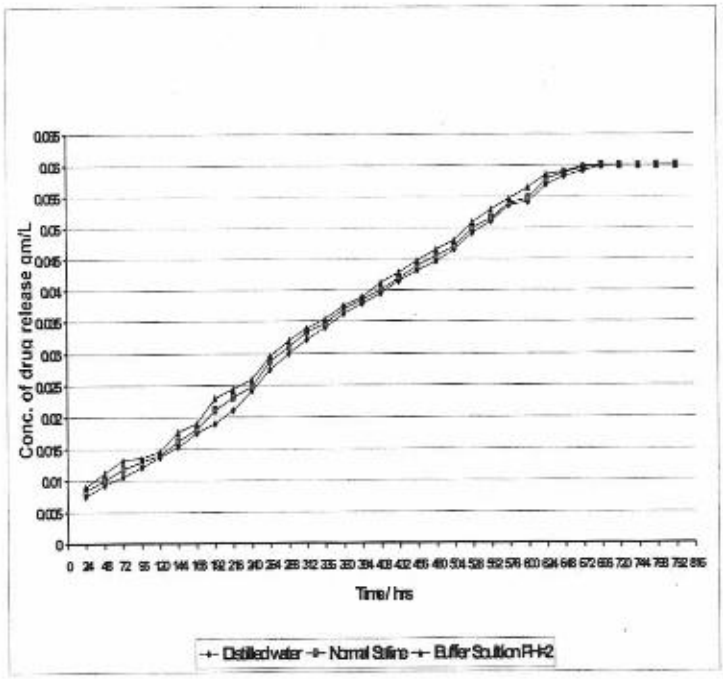

Fig. (6) (CEF) release (load=6mg/0.1 gm NaCMC) as a function of time in distilled water, normal saline and buffer solution (PH=2)

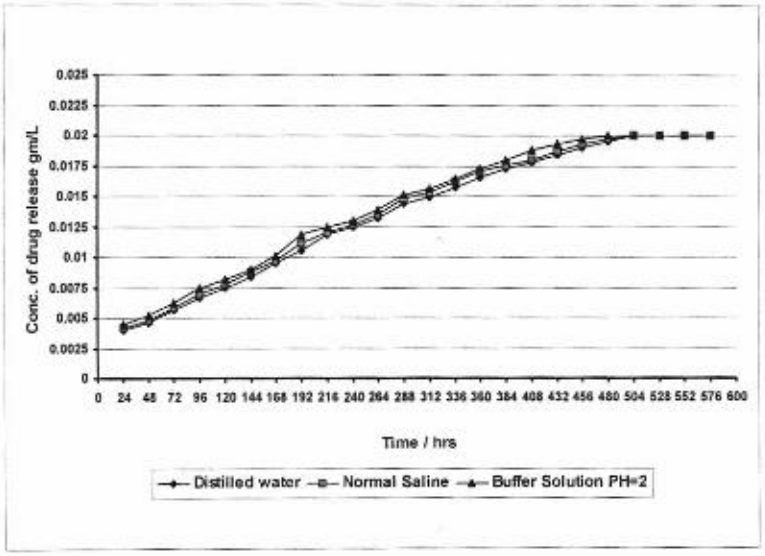

Fig. (7) (CEF) release (load=2mg/0.1 gm MC) as function of time in distilled water, normal saline and buffer solution (PH=2)

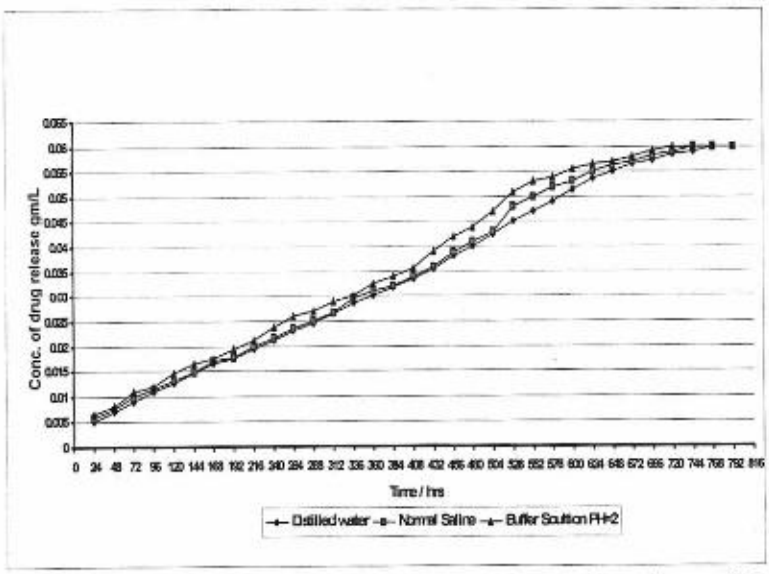

Fig. (8) (CEF) release (load=6mg/0.1 gm MC) as function of time in distilled water, normal saline and buffer solution (PH=2)

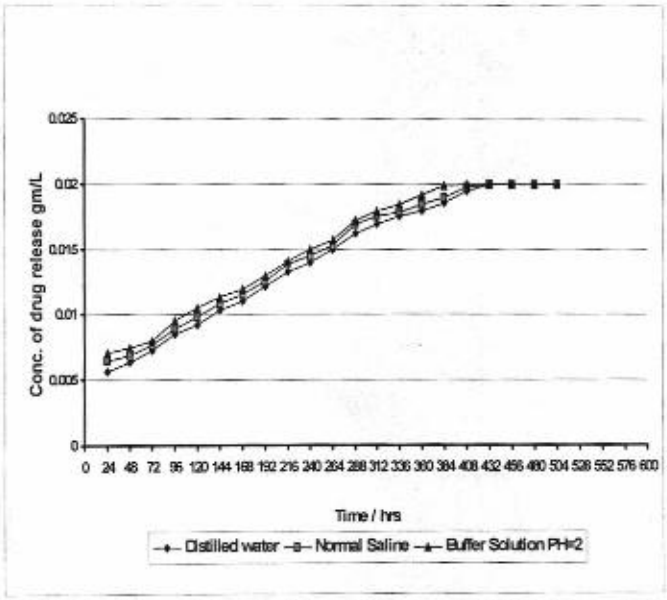

Fig .(9) (ATH) release (load=2mg/0.1 gm NaCMC) as function of time in distilled water, normal saline and buffer solution (PH=2)

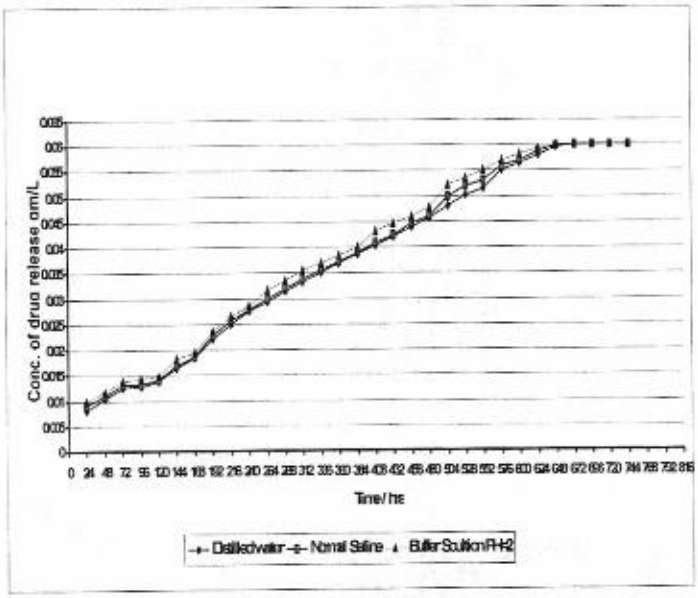

Fig .(10) (ATH) release (load=6mg/0.1 gm NaCMC) as function of time in distilled water, normal saline and buffer solution (PH=2)

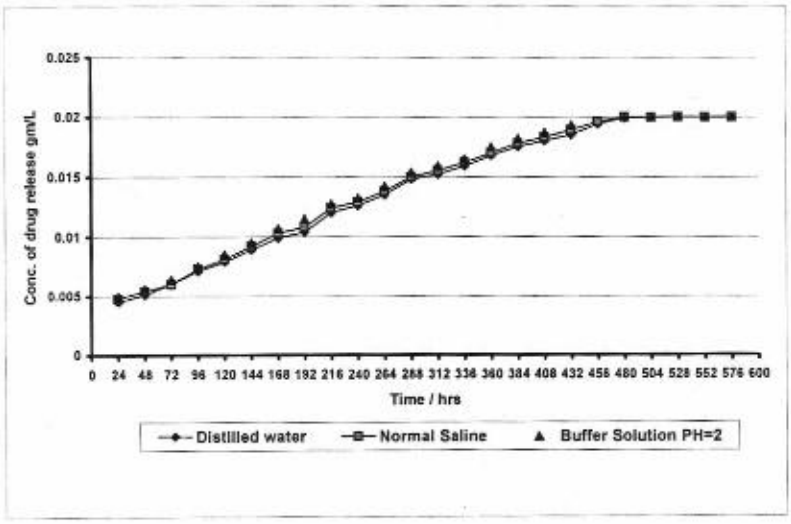

Fig. (11) (ATH) release (load=2mg/0.1 gm MC) as function of time distilled water, normal saline and buffer solution (PH=2)

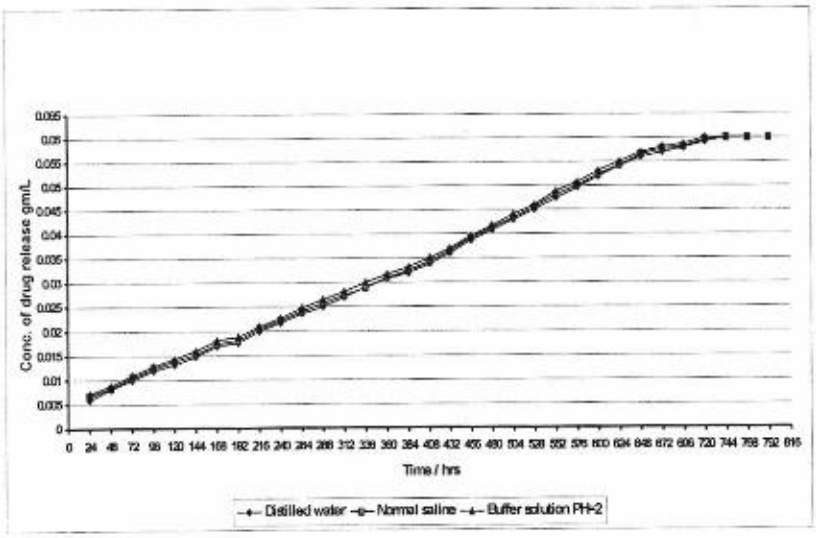

Fig .(12) (ATH) release (load=6mg/0.1 gm MC) as function of time in distilled water, normal saline and buffer solution (PH=2)

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دراسة بعض مشتقات السليلوز كجل يسيطر على كمية تحرر الدواء

محمد عبد المنعم الأزمرلي، عبد الجبار عبد القادر مخلص ، بسام ابراهيم خليل
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الخلاصة

البوليمرات الطبيعية والشبه طبيعية المحبة للماء لها استخدامات واسعة في تكنولوجيا الصيدلة كمواد تسيطر على كمية تحرر الدواء.مشتقات السليلوز هي بوليمرات غير سامة ، لذلك تعتبر مفضلة كمواد حاملة للدواء ،حيث تم في هذه الدراسه استخدام بوليمرات كمشتقات السليلوز مثل(صوديوم كاربوكسي ميثايل سللليلوز) و(ميثايل سليللوز) كهلام للسيطرة على تحرر بعض الادوية المضادة للبكتريا مثل (أموكسلين ثلاثي الماء) و (سيفوتاكسيم) في اوساط مختلفة هي الماء المقطر والمحلول الملحي (0,9%) وأيضا المحلول المنظم ذو الحامضية المساوية إلى 2 ، وقد تبين ان البوليمر (صوديوم كاربوكسي ميثايل سللليلوز) يتحرر منه الدواء أسرع من البوليمر (ميثايل سليللوز) ،وكذلك لوحظ أن سرعة تحرر الدواء(أموكسلين ثلاثي الماء) هي أسرع من تحرر دواء(سيفوتاكسيم) تحت نفس الظروف.