Synthesis of Ibuprofen-PEG Prodrug and Study the Hydrolysis at Different Phosphate Buffers

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Abstract:

The present study is conducted to prepare Ibuprofen as polymeric prodrug to improve its important physiochemical properties, increasing water solubility and decrease its side-effects. The product is characterize by using chemical and spectral methods .Then controlled release of Ibuprofen in from its polymer, in different phosphate buffers (pH =8.5, 7.5 and 1).The result show the percentage release of Ibuprofen was high at basic pH.

Key Words: prodrug, polymeric prodrug, Ibuprofen, PEG.

Introduction:

Drug delivery system should be ideally deliver drug to a specific site at specific time and release pattern.Initialy, constant or sustained drug release were the kinetic pursued by most of drug delivery system (DDS).

In order to avoid the problem associated with conventional administration in chronic treatment, the aspects of DDS covers are the slow release of water soluble drugs, improvement of the bioavailability of low soluble drugs and the delivery of two or more drugs from the same formulation [1]. Polymer carrier control of the release of highly toxic drugs and improvement of the targeting to tissue or cells. Covalent polymer-drug conjugate are special type of DDS where the drug or bioactive compound (peptide, hormone,enzyme….etc.) is covalently linked to the macromolecular backbone through physiological labile bond [2]. The linking of drug to macromolecular chain makes polymeric conjugated system very useful for application not only in relation to medication, but also in field as tissue engineering biosensors and affinity separation. Enzymatic processes cell culture the drug can conjugate directly to the polymer by the covalent bond or indirectly by spacer arm [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually good example for the development of controlled release preparation[3].

Ibuprofen is a drug that belongs to a class of NSAIDs, acting by inhibiting isoforms of cyclo-oxygenase 1 and 2.It treats inflammatory rheumatoid diseases and relieve acute pain. Ibuprofen is readily absorbed orally and plasma peak level is reached with two hrs. of administration. The elimination of Ibuprofen from plasma is first ordered with apparent half life 1.4 to 2.5 hrs [5]. The solubility of Ibuprofen is enhanced when it is given as polymeric prodrug with PEG,because PEG(polyethylene glycol) is water soluble. The solubility depends on various factors such as the method of preparation, carrier weight fraction and molecular weight and the pH of the medium. It was found that the dispersion prepared by the fusion method that gives higher solubilities than those prepared by the solvent technique [6].

Drug delivery system, has been developed to improve the therapeutic availabilities of many pharmaceuticals. One of the effective methods is the use of polymeric prodrug, since polymeric substances are more easily incorporated into target cells.

This drug specificity is originated from the enhanced permeability and retention effect of tissues. Polymeric prodrug of Ibuprofen is prepared by using polymer carrier linked with Ibuprofen, for example polyethylene glycol (PEG)[7], polymethylmeth acrylic acid(MA)[8], β-cyclodextrin(β-CD)[9] and polyvinyl alcohol (PVA)[10].

For reducing the gastrointestinal toxicity associated with Ibuprofen , its carboxylic group is condensed with the hydroxyl group of 1,2,3-trihydroxy propane-1,3-dipalmitate/ stearate to give ester prodrug [11]. PEG is accessible macromolecules with suitable properties for application chemistry, biotechnologies and medicine. The terminal hydroxyl groups of PEG can easily be converted into reactive functional groups by a number of routine reactions of organic chemistry. PEG used as carriers of many low molecular weight as well as high molecular weight medical drugs(in drug delivery system). In the conjugates with drugs their biological activity increases and their toxicity decreases[12].

The aim of study is include preparation polymeric drug conjugate of Ibuprofen as polymeric prodrug. This system has been developed in order to minimize the delivery problems and reduces gastrointestinal side effect by controlling the rate, duration and site of release. This kind of polymeric prodrug has been designed for localized and prolong duration of drug action by parental administration or as dermal prodrugs [13].

Materials:

Dicyclohexyl carbodiimide (DCC) (Fluka CO.),Ethylacetate,Sodium bicarbonate(Riedel-Dehaen CO.), Dimethyl foramide(DMF),Sodium hydroxide. Polyethylenglycol(PEG)(MW 3350)(BDH CO.) Chloroform,Hydrochloric acid (Fluka CO.), cellophane dialysis bag.

Instruments:

- Infrared Spectrophotometer type FT-IR-8400S, Shimadzu (KBr disk) .
-UV Spectrophotometer type UV-1100 Spectrophotometer.
- Melting point Apparatus :Stuart melting point SMP3.
- Hot plate Stirrer: Lab® DAIHAN LABTECH Co.LTD

Methods:

Extraction of Ibuprofen from pharmaceutical formulation in tablet form[14] :

The extraction of Ibuprofen from pharmaceuticals in tablet form has been achieved through the selective dissolution of active ingredient with chloroform. Dry the product and the melting point is obtained at 77.8 C˚. The Ibuprofen is characterized by IR and UV Spectrophotometer.

Preparation of Ibuprofen-PEG[15]:

Mixture Ibuprofen (1.48 gm,$7.1x10^{-3}$ mmol) dissolved in 4 ml DMF and PEG solution (0.22 gm,$5x10^{-3}$ mmol) dissolved in 2 ml DMF,then tripropylamine (0.028 gm,$2x10^{-4}$ mmol) is added with continuous stirring, DCC solution(1.583 gm,$7.75x10^{-3}$ mmol) dissolved in 2ml DMF is added respectively to the reaction mixture with continuous stirring at room temperature. A white precipitate of dicyclourea (DCU) has been formed after 10 min. The precipitate is removed by filtration and the filtrate mixed with ethylacetate (20 ml) and washed with 0.1N HCl, 5% $NaHCO_3$ and distilled water respectively. The solution has been treated with diethylether to precipitate the product that has been isolated by filtration and washed with distilled water three times, the melting point is estimated 152-155 C˚.The product is characterized by IR and UV Spectrophotometer.

Hydrolysis of polymeric prodrug[9]:

The powdered prodrug (20 mg) is poured in 10 ml of aqueous buffer solution (phosphate buffer pH 7.4,8.5 and hydrochloric acid) at 37C˚.The hydrolysis was carried out in cellophane dialysis bag .The bag has been closed and transferred into a flask containing 20 ml of the same buffered solution with continuously stirring at the same temperature. From the buffer samples (3 ml) is removed at selected intervals and 3 ml of new buffer is replaced. The quantityof hydrolyzed was analyzed by means of a UV Spectrophotometer and the amount of the released drug is determined by using the calibration curve under the same conditions at λmax-288 nm.

Results and Discussion:

The prepared final products as polymeric-drug system is characterized and analyzed by various available techniques.

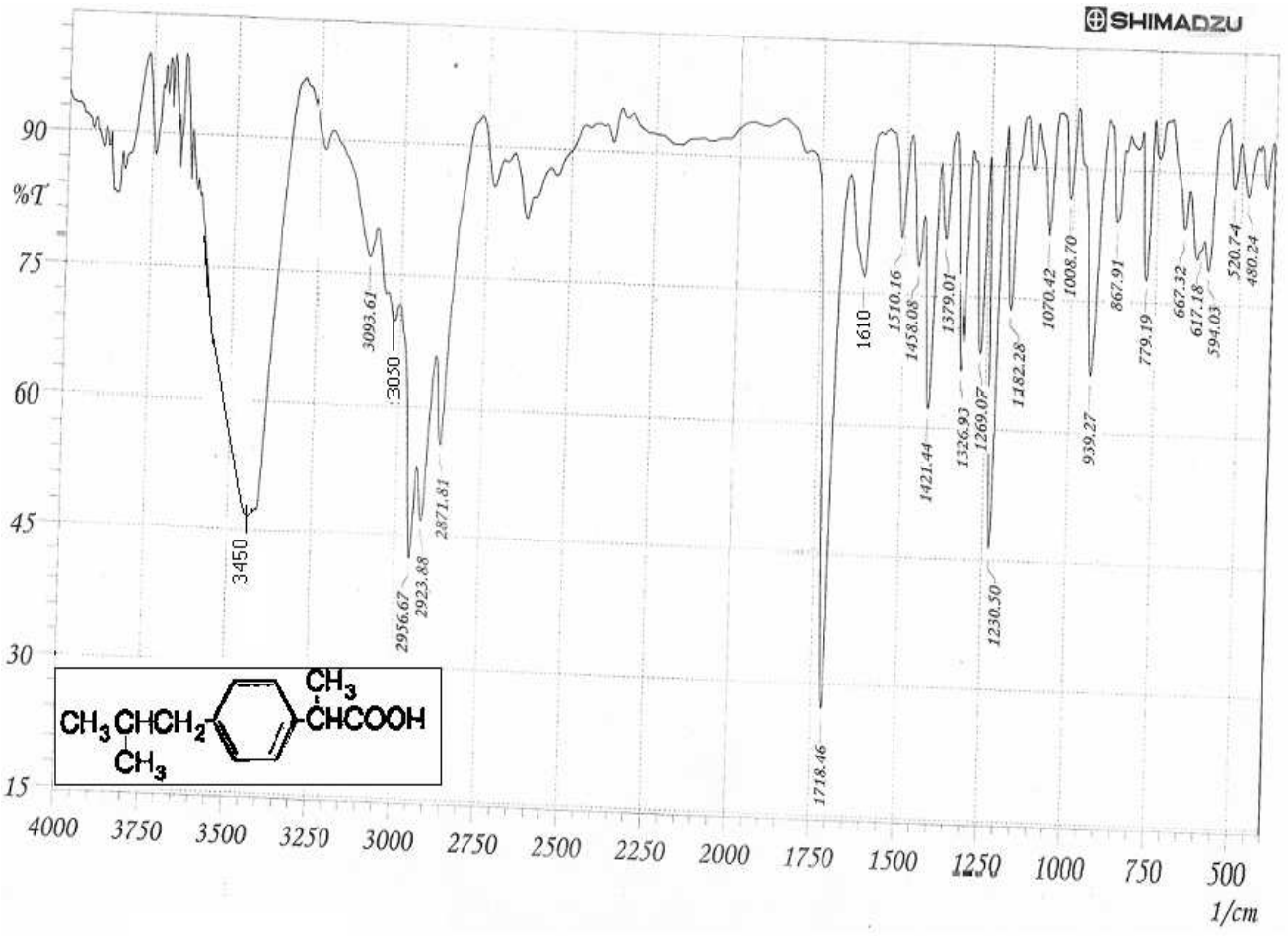
Release gas (CO_2), when treating Ibuprofen by $NaHCO_3$, indicates the presence of the carboxyl group. The appearance of the pink colour of the phenonaphathalene indicator in the presence of an ester in alkaline condition is taken as an indication to the presence for ester group[16].

The chemical test and melting points were estimated the formation of ester linkage. Infrared spectrophotometer was used in the identification of functional groups in Ibuprofen and Polymeric drug conjugate (PEG-Ibuprofen) which are shown in figures (1) and (2) . The absorption band that appeared in Ibuprofen spectrum at stretching vibration (1718 cm^{-1}) blue shifted at stretching vibration (1660 cm^{-1}) in PEG-Ibuprofen this indicates new peak that appeared in relation to ester linkage to confirm the literature [17]. The stretching vibration of C=C in aromatic system was shifted to low vibration due to effect of both polymeric chain and formation of ester linkage (electron attracking) figure (1) show sharp absorbance of carboxyl band. The hydroxyl group of polymer prodrug was shown broad band due to formation of hydrogen bonding. The important absorption bands are shown in Table (1).

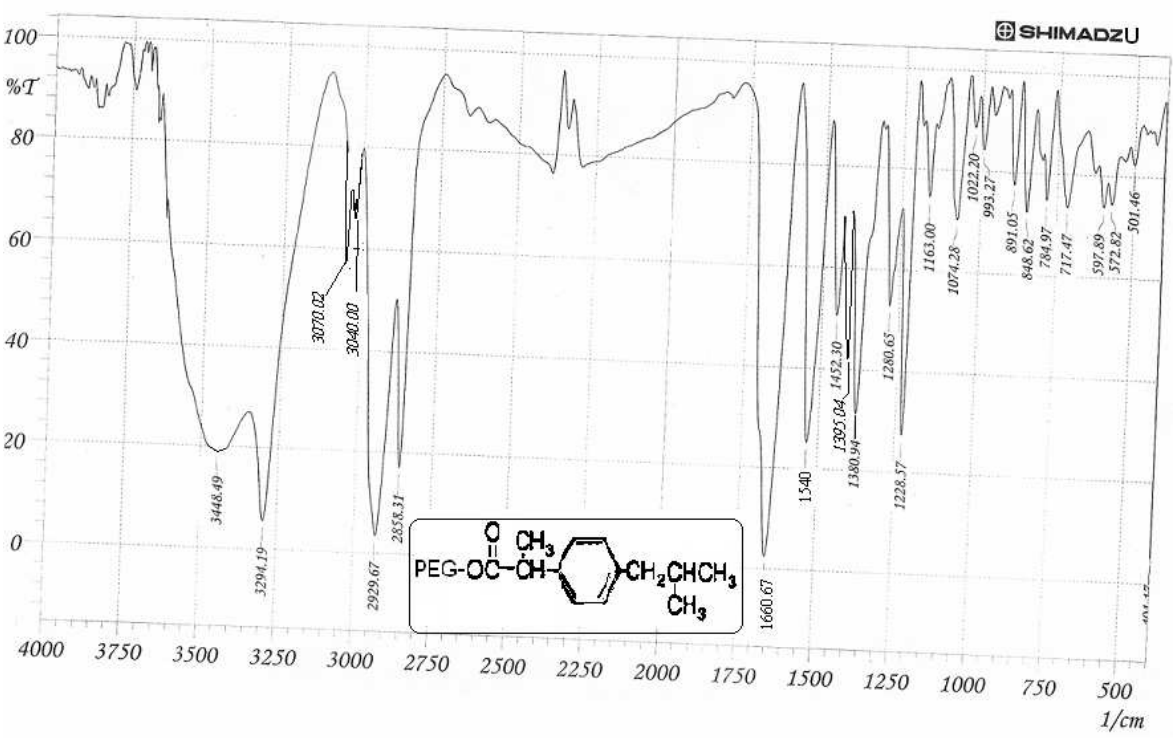
Table (1) Shows the importance stretching vibration bands.

Compounds	C=O *str.*	C-H *Arom.Str.*	$(CH_3)_2CH$ *Str.*	O-H *Str.*	C-O *asymmetrical*	C=C *Arom.Str.*
Ibuprofen	**1718 Sh. (carboxylic)**	**3093 3050**	**1326 1379**	**3450 carboxyl**	**1230 Sh.**	**1610 Med**
PEG- Ibuprofen	**1660 br. (ester)**	**3070, 3040**	**1380 1395**	**3448 Polymer**	**1228 Sh.**	**1540 Sh.**

str.= stretching Arom. = aromatic sh.=sharp br.= broad

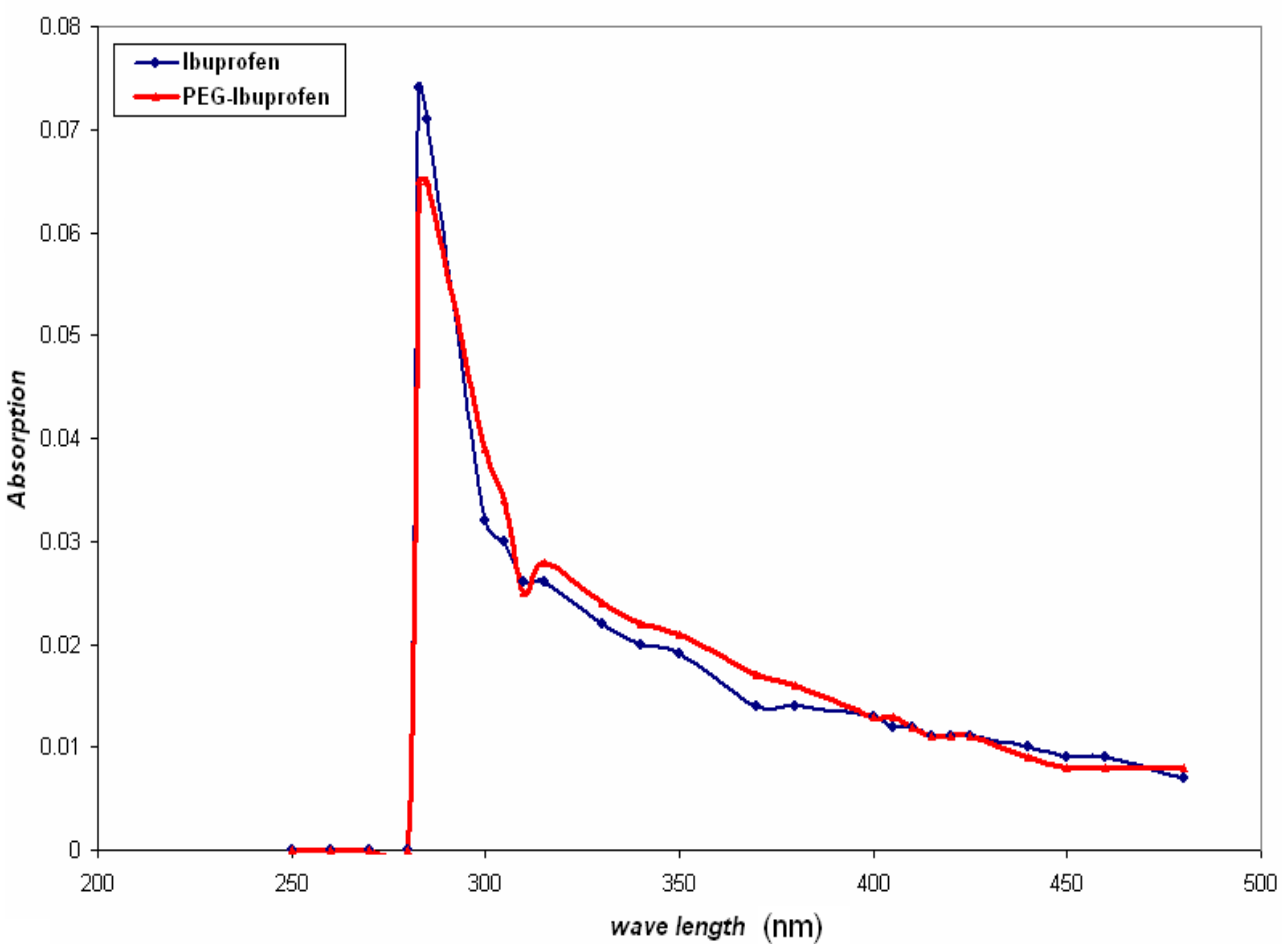


Figure(1): FT- IR Spectra of Ibuprofen.



Figure(2): Shows IR Spectra of PEG-Ibuprofen.

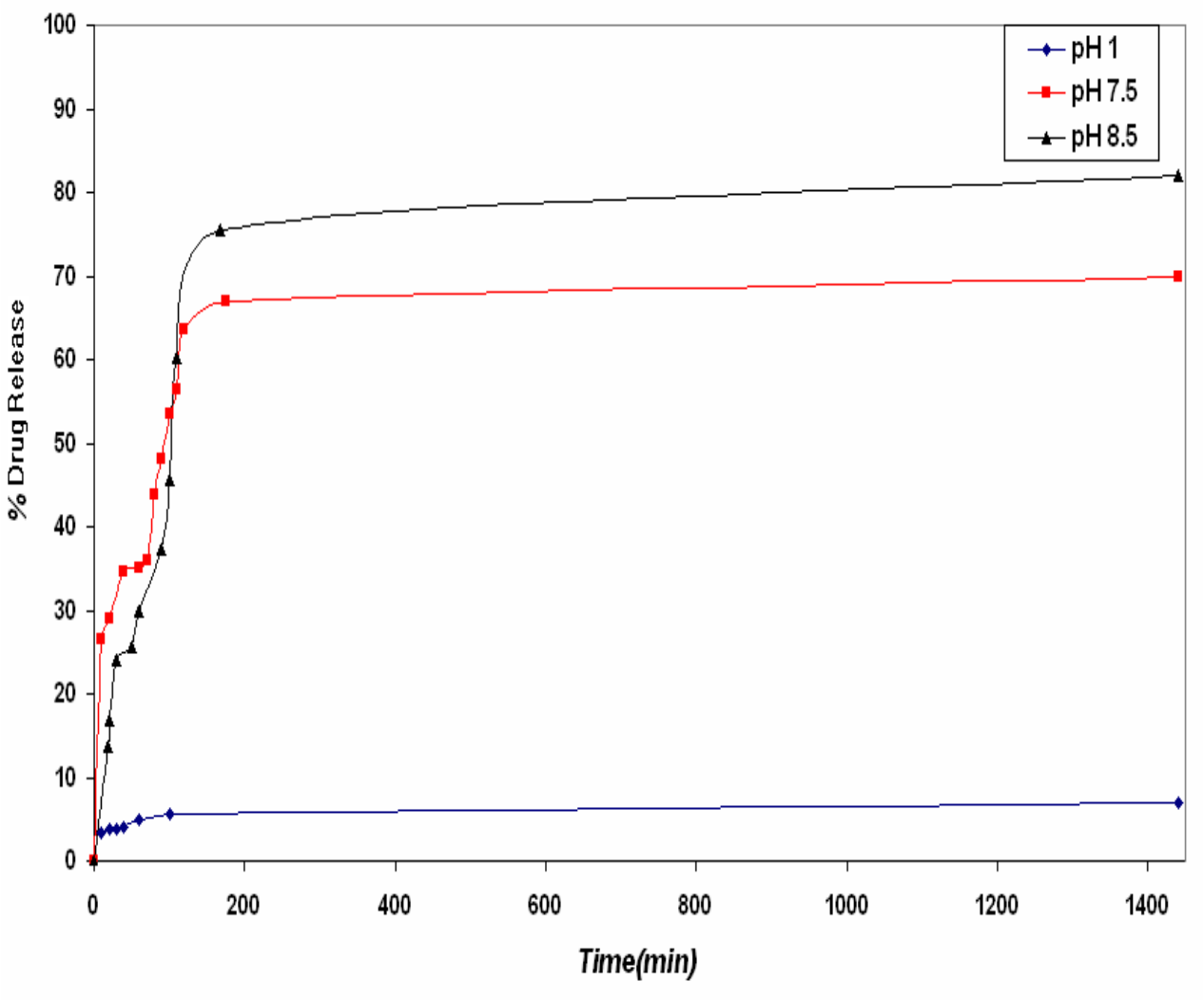
The UV-Vis scan (at position 250-500 nm range) of Ibuprofen shown only two transition bands. The high intenst transition band at 288 nm position(π-----π^*).The low intenst band (shoulder) at 330 nm position (n-----π^*).Also the U.V. spectra of polymeric Ibuprofen shows the same transition bands position at the same condition and solvent (in $CHCl_3$) .From U.V spectral ,can indicate the presence of active drug in polymeric prodrug .[18], as shown in figure(3).



Figure(3) Shows the UV spectra of Ibuprofen and PEG-Ibuprofen in $CHCl_3$.

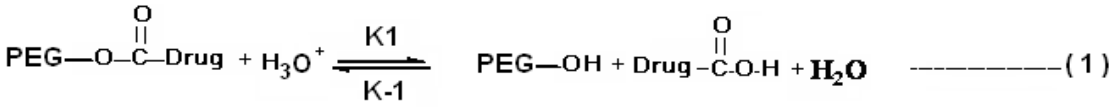
The release of ibuprofen from synthesized polymer prodrugs is carried out *in vitro* by hydrolysis of prodrug in buffer solutions at various pH values. The quantity of the released drug which detected by UV Spectroscopy at 288 nm.

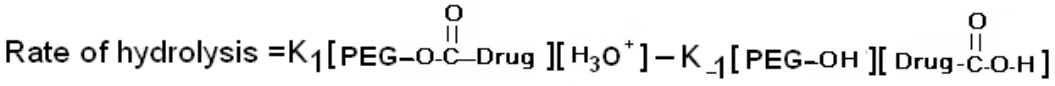
The result shows the release of ibuprofen from the polymeric prodrug at acidic pH is relatively slower compared to the solution of pH 7.5 and 8.5. The hydrolysis of ibuprofen in pH 1 is almost constant at different times, while in pH 7.5 and 8.5 the rate of hydrolysis of ibuprofen increased as a function of time. as shows in figure (4).



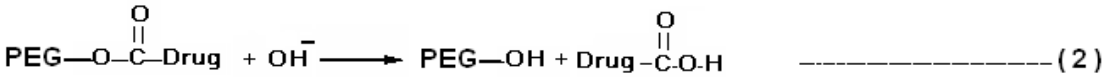
Figure(4): The Release of Ibuprofen from PEG- Ibuprofen prodrug at different pH values.

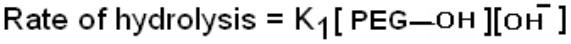
The rate of hydrolysis of ester linkage is pH and time dependant. The hydrolysis of polymeric Ibuprofen in acid pH is reversible.





While the hydrolysis of ester at basic media is not reversible.





For this reason the rate of hydrolysis of polymeric prodrug in basic media is higher than in acid media[8].

Conclusion:

The polymeric prodrug of Ibuprofen has greater potency to inhibit acute inflammatory processes than the free drug over long duration of action [8]. Polymeric prodrug of Ibuprofen enhances the aqueous solubility of Ibuprofen, because Ibuprofen conjugate with polyethylene glycol which is water soluble that leads to increase the release of Ibuprofen. The therapeutic use of non-steroidal anti-inflammatory drugs(NSAIDs) is often restricted by the necessity to deliver the drug to the specific sites of target organ or tissue. The use of NSAIDs is also limited by their irritant side effects on the gastro-enteric mucous and by their frequent poor water solubility. These problems can be solved by the preparation of polymeric prodrugs backbones via hydrolysable bonds.

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تحضير نظام تحميل بولي اثيلين كلايكول–ابوبروفين ودراسة التحلل في محاليل فوسفات منظمة مختلفة

الخلاصة:

يتضمن البحث تحضير دواء ابوبروفين (البروفين) بصيغة البوليمرية وشخصت النواتج بأستخدام الطرق الكيميائية والطيفية, وذلك لتقليل التأثيرات الجانبية المصاحبة عند استخدامه كالقرحه وللتحسين من ذائبيته في الماء بالتالي ممكن السيطرة او التحكم في تحرره في محاليل الفوسفات المنظمة ولقيم حامضية مختلفة. كما درست ظروف تحرر الدواء عند قيم مختلفة من الدالة الحامضية (1 ,7.5 و 8.5) واستنتج بأن نسبة تحرر الدواء عند الدالة القاعدية أكثر من غيرها.