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Preparation and using of acrylamide grafted starch as polymer drug carrier

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ABSTRACT

Starch was modified through chemical grafted of acrylamide on the starch polymer. Various of grafting percentages have been obtained by changing the concentration of initiator. The prepared polymer has been characterized by IR spectroscopy. The gelation of raw material (starch) and modified polymer (acrylamide grafted starch) according to the equilibrium swelling degree has been investigated in different media (distilled water, *n*-saline and buffer solution pH 2). Acrylamide grafted starch shows higher uptake of water compared with starch, suggests more hydrophilicity. In vitro controlled release of (CS: Ceftriaxone Sodium) drug from starch and acrylamide grafted starch hydrogel were studied in three different media (distilled water, *n*-saline and buffer solution pH 2) using ultra violate absorption follow quantities released at different times. The concentrations of drug released increased gradually and then attain affixed value at certain drug load.

1. Introduction

Starch consists of two types of molecules amylose (normally 20–30%) and amylopectin (normally 70–80%). Both consist of polymers of α-D-glucose unit in the $^4C_1$ conformation. In amylose these are linked (1 → 4)- whereas, in amylopectin about one residue in every twenty or fifty is also linked- (1 → 6)- forming branch points. The relative proportion of amylose to amylopectin and (1 → 6)-branch-point both depend on the source of starch. It's a versatile, cheap and has many uses as thickener, water binder, emulsion stabilizer and gelling agent (Li & Yeh, 2001).

Hydrogels are hydrophilic polymers of vegetable, animal, microbial, or synthetic origin. Hydrogels are water-swollen cross-linked polymers (Phillips & William, 2000; Tracy, Phillip, & Annelise, 2003). In water they swell to an equilibrium volume. They posses hydrophilicity due to the preserve of water solubilizing groups, such as –OH, –COOH, –$CONH_2$, –CONH–, –SO_3H, etc. Their relative stability of shape is due to the presence of a three-dimensional network. Their swollen state results from a balance between the dispersing forces acting on hydrated chains and cohesive forces that do not prevent the penetration of water into the network (Mark, Bikals, Overberger, & Menges, 1986). Starch granules are insoluble in cold water, but imbibe water reversibly and swell slightly (Mark & Kirk, 1986). Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care, such delivery systems have numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience (Uhrich, Cannizzaro, Langer, & Shakesheff, 1999). This field of pharmaceutical technology has grown and diversed rapidly in recent years (Cascone et al., 2001; Seung, Seong, & Young, 2000; Stepto, 2000). In this work we report the modification of starch via chemical grafted of acrylamide and study the gelation of starch itself and acrylamide grafted starch (AGS) in three deferent media (distilled water, *n*-saline and buffer solution pH 2). Also we study the Controlled release of (CS: Ceftriaxone Sodium) drug from row material (starch) and (AGS) hydrogels in three different media (distilled water, *n*-saline and buffer solution pH 2) using ultra violate absorption follow quantities released at different times.

2. Experimental

2.1. Materials

All reagents were commercially available (Aldrich Chemical Co.) and were used without further purification. All manipulations in the synthesis of graft copolymers were performed under Nitrogen atmosphere. Solvents used in the syntheses were distilled from the appropriate drying agent immediately prior to use.

2.2. Measurements

2.2.1. Swelling measurement

Starch or (AGS), was accurately weighed in suitable closed thumb and placed in stoppered conical flask containing 100 mL distilled water, which was left in a thermostated cabinet at

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30 ± 0.1 °C for 10 days. After every 24 h. excess water was poured off from the thumb, the gel is held for 10 s. Then dropped in a weighing bottle which is covered and weighed. The swelling number was calculated as follows (Rabek, 1980):

$$\alpha = \frac{W_1 - W_0}{W_0} \times 100$$

where α, is the percentage swelling number.

W_1, is the weight of equilibrium swelled sample.

W_0, is the original weight of the polymer.

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

2.3. Synthetic procedures

2.3.1. Graft copolymerization of starch with acrylamide

The redox method with ceric salt has been used for initiation of grafting of acrylamide onto starch. The reaction was carried out under nitrogen in four necked flask equipped with stirrer, thermometer and reflux condenser and immersed in a constant temperature heating mental at 50 °C.

The procedure was to disperse 8.1 g of starch in the solvent medium (100 mL). Water–DMF (1:1 by volume) was used as solvent medium. A brisk stream of oxygen-free nitrogen was bubbled first into the contents of the dropping funnel and then through the dispersed starch in the reaction vessel before the gas was led out of the system. This continued for 30 min while the temperature in the reaction vessel was kept at 50 °C. The monomer (7.1 g acrylamide) was then added, then after 2 min, the initiator solution was added to the mixture through a dropping funnel. After 3 h the product was separated by filtration and wash with water several times. The resulting product was then extracted with (DMF–acetic acid 1:1 by vol.), to remove any homopolymer (PAN) produced. Extraction continued for 20 h. The extracted product was thoroughly washed by water and left for drying in air. The experiment was repeated again by changing the concentrations of ceric ammonium nitrate initiator in order to obtain the maximum percentage of starch grafted with acrylamide.

2.4. UV quantitative determination of drug

Where only single component in the sample absorbs significantly, the wavelength is chosen to coincide with the center of abroad maximum in the spectrum to minimize wavelength-setting errors. As summing that the linear range for compliance with the Beer–Lambert law has been established and that the drug concentration has been adjusted within the optimum range for the type of instrument concerned, than two approaches to quantification may be employed. If an acceptable standard of the drug in available, and if the calibration graph passes through zero, measurement of replicated of the standard at a comparable concentration, and of the tests are performed in bracketing sequence (i.e. each group of samples is proceeded and followed by the standard). Under identical conditions of solvent and temperature and using the same matched cells. The concentration of the test sample is then found by reference to the results from the standards. Alternatively, the specific absorbance is used to calculate the sample concentration, using the absorbance measured in the specific solvents. 8 mg of the pure drug (CS) was dissolved in 100 mL distilled water. The maximum absorption wavelength was determined for the drug. Different concentrations of the 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 λ_{max} was measured against the blank. The absorbance was plotted against concentration to obtain a calibration graph.

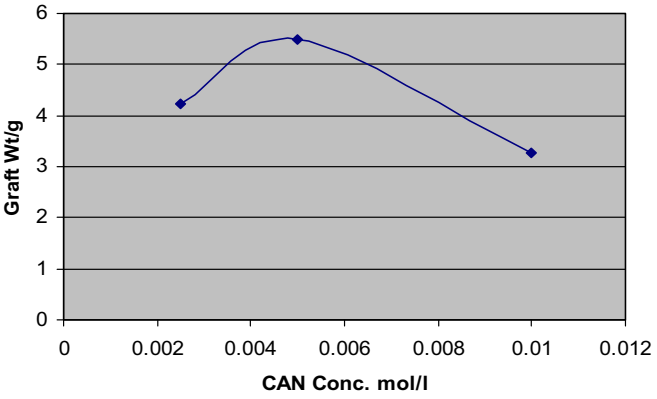


Fig. 1. Effect of CAN concentration on grafting of acrylamide onto starch.

This experiment was repeated again by using pH 2 buffer solution and *n*-saline instead of distilled water.

2.5. Drug release studies

In vitro studies: The release was performed by using starch and (AGS).

0.1 g of starch or (AGS) was accurately weighed in suitable closed thumb, and placed in Stoppard 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 attaining maximum swelling)., 4 and 8 mg of the drug was dispensed in the swelled polymeric matrix by using horizontal shaker, (CS) drug was used. The elution medium was sampled and the content of drug in the samples was measured spectrophotometrically at 240 nm. Sampling was almost carried out every 24 h, and the concentration of drug release was calculated from the calibration curve of drug. The above method was repeated again by using pH 2 buffer solution and normal saline instead of distilled water.

3. Result and discussions

3.1. Effect of concentration of catalyst on the graft copolymerization

The effect of concentration of ceric ammonium nitrate (CAN) on the grafting of acrylamide (AA) to starch is shown in Fig. 1. It can be seen that a significant increase in the degree of grafting was achieved when the CAN concentration was 5.0×10^{-3} M. At higher concentrations the degree of grafting decreased. The amount of homopolymer produced increased slightly as catalyst concentrations was increased. The acrylamide grafted starch which has the highest grafting percentage was used in study of swelling and controlled release of (CS) drug (Table 1).

3.2. FTIR spectrum of AGS

For proper characterization of vinyl-monomer-substituted starch, the infrared method is highly recommended. The potassium

Table 1
Ceric ion-induced grafting of vinyl monomer to starch (reaction time, 3 h at 50 °C).

Catalyst concentration (mol L^{-1})	Starch (wt/g)	Acrylamide (wt/g)	Homopolymer PAA (wt/g)	AGS (wt/g)
2.5×10^{-3}	8.10	7.10	1.10	4.23
5.0×10^{-3}	8.10	7.10	1.65	5.50
1.0×10^{-2}	8.10	7.10	1.79	3.27

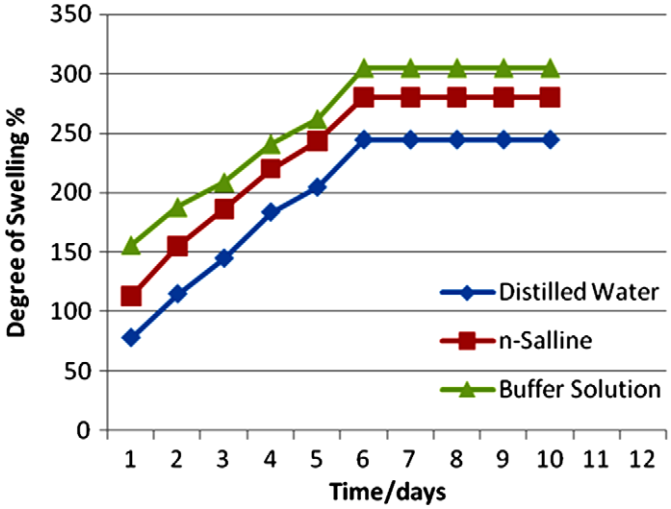


Fig. 2. Degree of swelling % for starch as a function of time in different media.

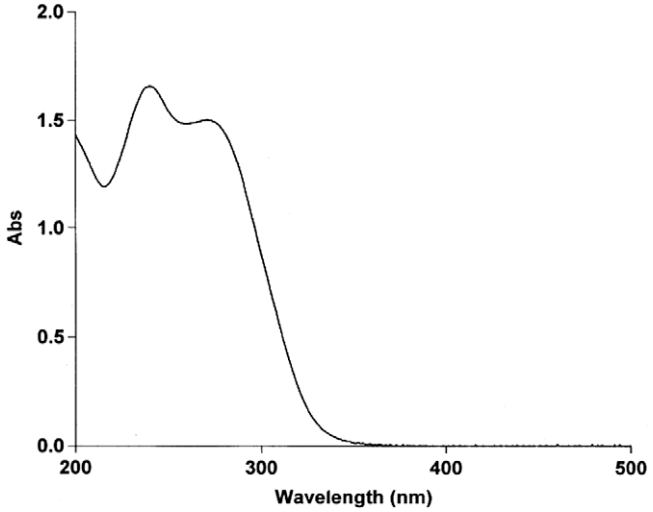


Fig. 4. UV spectrum of (CS) drug.

bromide disk technique offer on ideal method for obtaining infrared spectra of starch and its derivatives, particularly if satisfactory disk can be prepared without excessive grinding. The IR spectrum of acrylamide grafted starch showed distinctive and characteristic absorption bands around (3500–3454 cm^{-1}) for υ (NH_2) and (2931 cm^{-1}) for stretching band of methylene group. The spectrum also exhibited absorption band at (1647 cm^{-1}), which could be assigned to the υ (C=O) group (Silverstein, Webster, & Kiemle, 2005). These bands indicated the formation of acrylamide grafted starch.

3.3. Gelation of starch and AGS

The extensive inter and intramolecular hydrogen bonding among hydroxy groups in starch makes it difficult to dissolve. For this reason starch granules are insoluble in cold water, but imbibe water, and swell slightly. Generally, grafted starch copolymer has a higher swelling than starch itself. This copolymeric material swell more in water and contain large amount of water, which is considered to be better for their biocompatibility for living tissues because the interfacial free energy between water-swollen gel and the aqueous biological environment is very small and the inner water provides good permeability to oxygen metal ions, and other metabolites (Taylor & Bagley, 1974).

The maximum equilibrium swelling was attained after 168 h. in distilled water, normal saline or buffer solution of pH 2. The extent of swelling is as follows:

Buffer solution (pH2) > normal saline > distilled water

This is the same arrangement noticed in starch and (AGS). Typical hydration data of swelling degree against time of starch and (AGS) are graphically represented in Figs. 2 and 3, respectively. The starting point in this work was to study the effect of water, normal saline, and buffer solution (pH 2) on the swelling of starch and modified starch (AGS). The maximum degree of swelling α can be arranged as follows:

Buffer solution (pH2) > saline solution > distilled water

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 starch needs to be sufficient to overcome the hydrogen bonding in the interior of starch granule. The amorphous regions of the granules are solvated first and the granules swell rapidly, eventually many times its original size. During swelling, and as consequence of it, some linear amylase molecules are leached out of the granule into solution. The

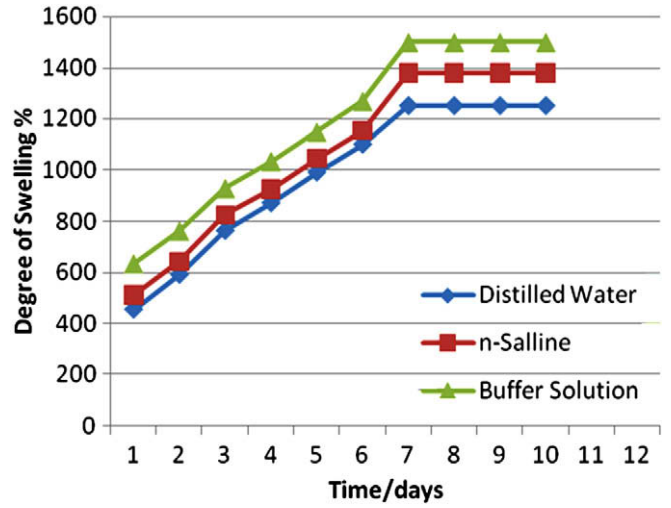


Fig. 3. Degree of swelling % for (AGS) as a function of time in different media.

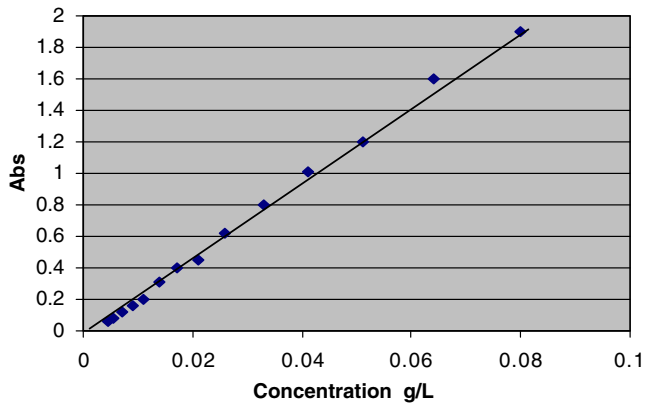


Fig. 5. The working calibration curve for the data of (CS) drug. (The absorbance in 1 cm cell at λ_{max} 240 nm.)

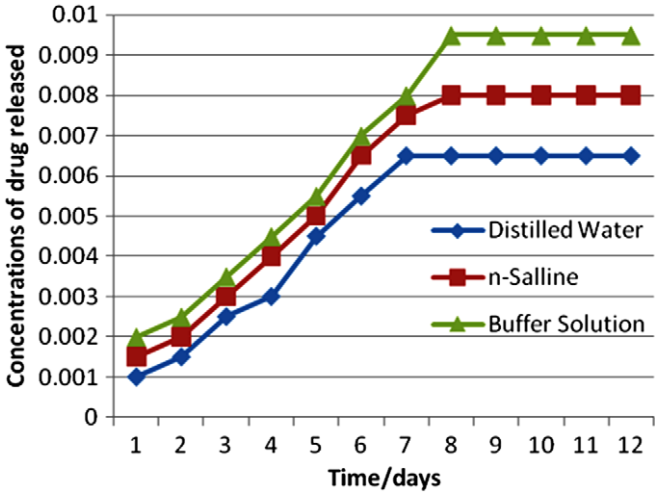


Fig. 6. (CS) drug release as a function of time (load 4 and 8 mg/0.1 starch) in different media.

(CS)

$A = \in bc$

$1.658 = \in 1\ cm\ 9.7 \times 10^{-5}\ M$

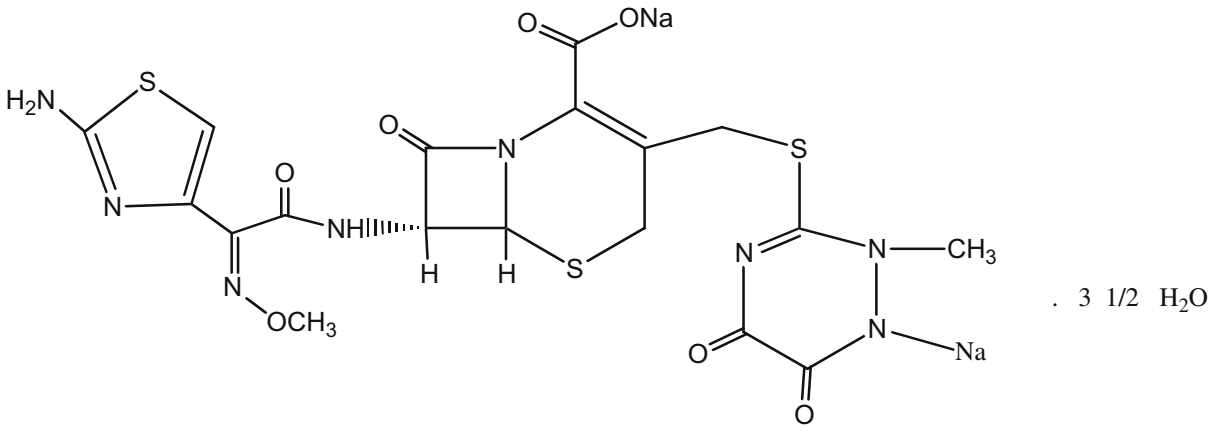
$\in = 17092\ L/mol\ cm$

3.4.1. Calibration curve of (CS) drug

In many but not all cases. Lambert–Beer's low is obeyed during ultraviolet–visible absorption by polyatomic substances. The most straightforward way to use Lambert–Beer's low for quantitative analysis is to measure the absorbance of the sample solution at a wavelength at which the species in solution is known to absorb radiation. A working curve of (CS) drug as a function of concentration is shown in Fig. 5. It is apparent that the slope of the plot should be the product of molar absorptivity and the cell path length. Because the working curve is linear and goes through the origin it can be used to determine concentrations from the measured absorption values (Silverstein et al., 2005).

3.4.2. Controlled release of (CS) drug

Ceftriaxone Sodium (CS) has the following structure,



starch 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 a 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 (Melia, 1991).

3.4. UV analysis

Generally, molecules that absorb in the UV region at a certain wavelength will contain suitable chromophor. The spectrum consisting of a plot of absorbance, percent transmittance, or log of absorbance as a function of wavelength is automatically obtained using scanning spectro-photometer. The absorptivity or molar absorptivity of many substances at specified wavelength is listed in various tables in literature. The UV spectrum of (CS) Fig. 4 was determined and the molar absorptivity of the drug was calculated.

Molar absorptivity which was calculated according to the first method

Formula weight ($C_{18}H_{16}N_8{\cdot}Na_2O_7\ S_3{\cdot}3.1/2\ H_2O$) = 661.59 g mol^{-1}

Ceftriaxone Sodium (CS) represents one of the most antibiotic drugs. It has a broad spectrum activity against Gram positive and Gram-negative bacteria, because it prevents bacteria from building

Table 2
Variation of percentage of drug release concentration with time for (CS) (load = 4 mg/0.1 g starch) in different media (100 mL).

Time/days	Percentage of drug release concentration (%)		
	Distilled water	*n*-Saline	Buffer solution (pH 2)
1	2.50	3.75	5.0
2	3.75	5.0	6.25
3	6.25	7.50	8.75
4	7.50	10.0	11.25
5	11.25	12.50	13.75
6	13.75	16.25	17.50
7	16.25	18.75	20.0
8	16.25	20.0	23.75
9	16.25	20.0	23.75
10	16.25	20.0	23.75
11	16.25	20.0	23.75
12	16.25	20.0	23.75

Table 3
Variation of percentage of drug release concentration with time for (CS) (load = 8 mg/0.1 g starch) in different media (100 mL).

Time/days	Percentage of drug release concentration (%)		
	Distilled water	*n*-Saline	Buffer solution (pH 2)
1	1.25	1.88	2.50
2	1.88	2.50	3.13
3	3.13	3.75	4.38
4	3.75	5.0	5.63
5	5.63	6.25	6.88
6	6.88	8.13	8.75
7	8.13	9.38	10.0
8	8.13	10.0	11.88
9	8.13	10.0	11.88
10	8.13	10.0	11.88
11	8.13	10.0	11.88
12	8.13	10.0	11.88

and maintaining their cell walls. Ceftriaxone Sodium is a yellowish-orange crystalline powder, which is readily soluble in water sparingly soluble in methanol and very slightly soluble in ethanol .The *syn*-configuration of the methoxyimino moiety confers stability to β-lactamase enzymes produced by many Gram-negative bacteria. Such stability to β-lactamases increases the activity of ceftriaxone against otherwise resistant Gram-negative bacteria (Bradley, Wassel, & Lee, 2009). It has an absorption maximal in distilled water at 240 nm. The same λ_{max} was found in normal saline and in aqueous solution of pH 2. After attaining maximum swelling at 30 ± 0.1 °C, the different drug loads were dispensed and the elution medium was sampled every 24 h, where absorptions were measured at 240 nm. The concentrations of (CS) drug released with

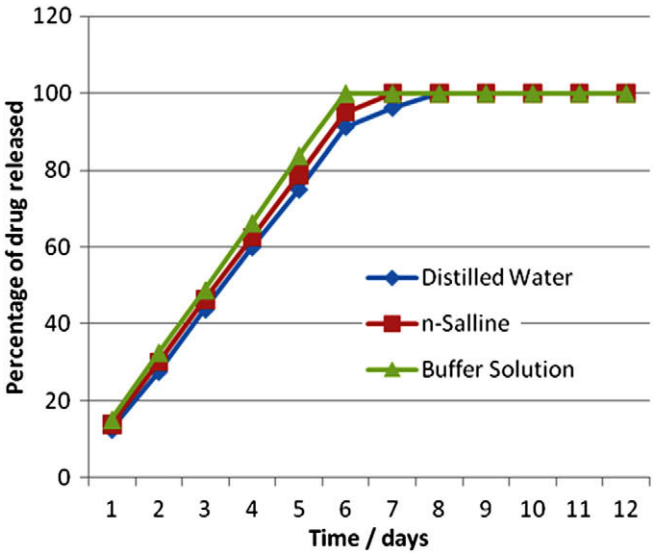


Fig. 7. The percentages of (CS) drug release as a function of time (load 4 mg/0.1 g AGS) in different media.

Table 4
Variation of drug release and percentage of drug release concentration with time for (CS) (load = 4 mg/0.1 g AGS) in different media (100 mL).

Time/days	Distilled water		*n*-Saline		Buffer solution (pH 2)	
	Concentration of drug release (g L^{-1})	Percentage of drug release (%)	Concentration of drug release (g L^{-1})	Percentage of drug release (%)	Concentration of drug release (g L^{-1})	Percentage of drug release (%)
1	0.005	12.50	0.0055	13.75	0.006	15.0
2	0.011	27.50	0.012	30.0	0.013	32.50
3	0.0175	43.75	0.0185	46.25	0.0195	48.75
4	0.024	60.0	0.025	62.5	0.0265	66.25
5	0.03	75.0	0.0315	78.75	0.0335	83.75
6	0.0365	91.25	0.038	95.0	0.04	100.0
7	0.0385	96.25	0.04	100.0	0.04	100.0
8	0.04	100.0	0.04	100.0	0.04	100.0
9	0.04	100.0	0.04	100.0	0.04	100.0
10	0.04	100.0	0.04	100.0	0.04	100.0
11	0.04	100.0	0.04	100.0	0.04	100.0
12	0.04	100.0	0.04	100.0	0.04	100.0

Table 5
Variation of drug release and percentage of drug release concentration with time for (CS) (load = 8 mg/0.1 g AGS) in different media (100 mL).

Time/days	Distilled water		*n*-Saline		Buffer solution (pH 2)	
	Concentration of drug release (g L^{-1})	Percentage of drug release (%)	Concentration of release (g L^{-1})	Percentage of drug release (%)	Concentration of drug release (g L^{-1})	Percentage of drug release (%)
1	0.0085	10.63	0.009	11.25	0.0095	11.88
2	0.0165	20.63	0.0175	21.88	0.018	22.50
3	0.0245	30.63	0.025	31.25	0.0265	33.13
4	0.033	41.25	0.0335	41.88	0.035	43.75
5	0.041	51.25	0.042	52.50	0.043	53.75
6	0.049	61.25	0.05	62.50	0.052	65.0
7	0.0575	71.88	0.0585	73.13	0.06	75.0
8	0.064	80.0	0.067	83.75	0.0685	85.63
9	0.072	90.0	0.075	93.75	0.0775	96.88
10	0.076	95.0	0.0785	98.13	0.08	100.0
11	0.08	100.0	0.08	100.0	0.08	100.0
12	0.08	100.0	0.08	100.0	0.08	100.0
13	0.08	100.0	0.08	100.0	0.08	100.0
14	0.08	100.0	0.08	100.0	0.08	100.0
15	0.08	100.0	0.08	100.0	0.08	100.0

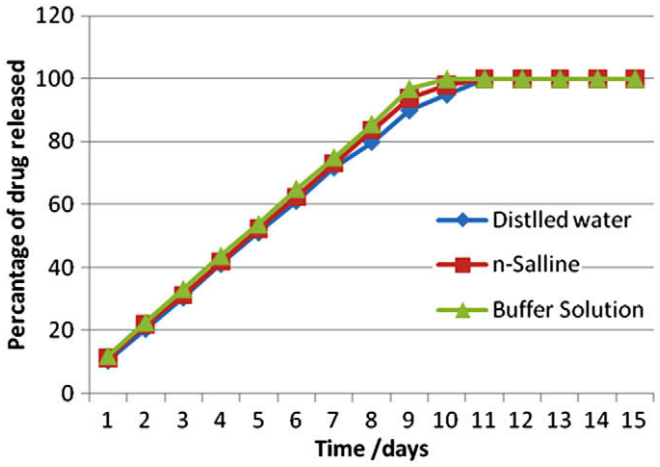


Fig. 8. The percentage of (CS) drug release as a function of time (load 8 mg/0.1 g AGS) in different media.

time from starch hydrogel are graphically represented in Fig. 6. On the other hand, percentages of drug release concentration are collected in Tables 2 and 3.

Starch consists of two types of molecules amylose (normally 20–30%), and amylopectin (normally 70–80%). Amylose and amylopectin are inherently incompatible molecules. Helical amylose structure has hydrogen bonding and amylopectin contain well identified amorphous and crystalline regions. Helical structure in amylopectin give rise to extensive degree of crystallinity. It is a fact that gross crystalline areas are barriers against permeation and it seems that this the reason of increasing the amounts released of drug gradually. In all examined media the amounts of drug release is increased gradually and then attain equilibrium fixed value at certain concentration. This concentration depends on the medium in which drug release study was carried out. Increasing initial drug load to 8 mg/0.1 g polymer, does not increase the concentration of drug release, and if we expressed this in percentage amount as illustrated in Tables 2 and 3, the percentage of drug release will decrease as the original load is increased. Factor affecting release depends on the nature of the polymer and the permeating agent. The percentage of (CS) drug released from (AGS) with time are collected in Tables 4 and 5 and graphically shown in Figs. 7 and 8.

It is clearly seen, from data reported from controlled release of (CS) drug and from swelling measurements of starch, and grafted starch copolymer, that grafted copolymer has the higher equilibrium swelling number, and higher release rate, beside the intrinsic properties of the specific chosen polymer, we have to take into consideration the effect of the microstructure of the final modified polymer on the flux of dispersed biomaterial in the polymeric matrix. The grafting to an existing matrix provides a good way to modify matrix properties. Grafting take place especially in the amorphous parts of the films around crystalline domains and thus offer a great number of diffusion paths for the permeating molecules. This the reason of Polymer before grafting, is not highly swelled by water, while after grafting it more swelled by water and we can expect a higher flux of permeant.

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