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Synthesis of a New Co-Polymer and Studying its ability as Drug Delivery System

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Abstract

In this work, a new co- polymer was synthesized from the reaction of pentarythritol with fumaric acid to form the linear co- polymer. Three different moles of acrylic acid monomer (0.5, 1.0 and 1.5 mole), were added to obtain three new co- polymers. Swelling of the polymer samples were measured in the buffer solution in the basic and acidic medium. Five different concentrations (0.05, 0.1, 0.15, 0.2 and 0.25 gm/ml) of albumin protein were loaded onto the co- polymer samples and then the release of the albumin protein was measured in the acid and basic medium.

The results obtained showed that the protein loading and release process in the basic medium were higher than in the acidic medium, indicating that the combined co-polymer is selective in the medium.

Keyword: Hydrogel; Polymer; Co-polymer; Condensation polymerization; Three-dimensional network; Selectivity; Swelling; Buffer solution; Drug delivery system.

INTRODUCTION

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing amounts of water or biological fluids [1] . Due to their high water content, porosity and soft large consistency, they closely simulate natural living tissue, more than any other class of synthetic biomaterials [2] . Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve [3]. They are prepared from materials such as gelatin, polysaccharides, cross-linked polyacrylamide polymers, polyelectrolyte complexes, and polymers or copolymers derived from methacrylate esters [4]. They are insoluble in water and are available in dry or hydrated sheets or as a hydrated gelin drug delivery systems designed for single use [5]. Furthermore, hydrogel can be formulated in a variety of physical forms, including slabs, micro particles, nanoparticles, coatings, and films [6]. As a result, hydrogels are commonly used in clinical practice and medicine with a wide range of applications, including Tissue Engineering and Regenerative Medicine; Diagnostics, Cellular immobilization, Separation of bio molecules or cells, and barrier materials to regulate biological adhesions [7]. These unique physical properties of hydrogels have stimulated particular interest in their use in drug delivery applications [8]. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous the environment in which they are swollen [9]. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at dependent on the diffusion coefficient of a small molecule or a macromolecule through the gel network [10]. Since the polymer cannot dissolve due to the covalent cross-links, water uptakes far in excess of those achievable with hydrophilic linear polymers can be obtained [11]. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic – specifically that a depot formulation is created from which drugs elute slowly; maintaining a high local concentration of drug in the surrounding tissues over an extended period of time, although can also be used for systemic delivery [12]. Hydrogels are also generally highly biocompatible , which may be attributed to the high water content of hydrogel .Biodegradability or dissolution in case of hydrogels may be brought about by enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time frame and location ofthe drug delivery device[13].

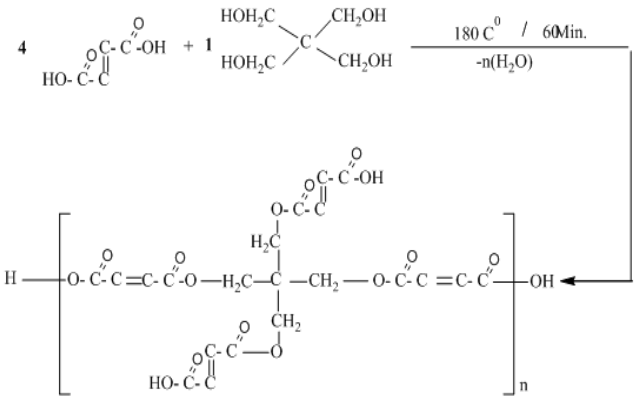
Hydrogels, with high water content as well as tissue like mechanical properties, have been demonstrated to be capable of combining with cells to engineer various tissues in both vitro and vivo [14].

EXPERIMENTAL

1-All chemicals used were produced by companies (B.D.H), (SIGMN), (C.D.H) and (MERCK)**.**

2-Preparation of modified co-polymer [15]

In a 250 ml three-necked round bottom flask, (4.0 mole, 464 gm) of Fumaric acid, and (1.0 mole,136 gm) of Pentaerythritol , were mixed together, this flask was equipped with a thermometer and a mechanical stirrer. The mixture warmed carefully with an electric heating mantel to 140C° until a clear liquor is formed and then about 15 ml of Xylene was added carefully to the reaction flask, in the form of batch (two drops in each batch), withdrawal of water formed in the esterfication process, and the flask was gently heated. Heating was stopped after 60 min. at180 C°, until no more water came off. The flask was allowed to cool to 50C°, and ($1.36x10^{-3}$ mole, 0.147 gm) of Hydroquinone was added to the reaction flask, with stirred by mechanical stirrer. The negative test of $NaHCO_3$ solution proves that the prepared modified polyester resin doesn't contain un-reacted acid. Equation (1), represents the preparation of the modified co-polymer; and at 55C° about (0.5, 1.0 and 1.5 mole) which equal (36, 72 and 108 gm), respectively of Acrylic acid monomer, was added to the modified co-polymer and stirred by mechanical stirrer, until a pourable syrup was formed. Table (1), represents the physical properties of modified co-polymer.



Equation (1): preparation of the modified co-polymer

Table (1): physical properties of the modified resins after addition of acrylic acid monomer

Physical properties	Value
Molecular Weight ($\overline{Mn}$)	Around 1840 gm/mole
Solid content	57 %
Viscosity	21 poise
Gel time	12-16 min at $25C^0$
Acid Value	26
Density	1.3 (gm/cm^3)

3- Preparation of polymeric specimens

The samples of polymeric prepared by add different number of moles of the acrylic acid monomer (0.5, 1.0 and 1.5 mole) to the modified resin prepared in step above with continuous stirrer, and using Methylethylketone peroxide (MEKP), as a hardener (initiator cross-linking process), and cobalt octet 6% (as a accelerator). Three different co-polymers were formed, different between them from where number of moles of the acrylic acid monomer adds to it. After preparation the samples of polymeric molded in matrixes glasses, where hardened resins and measurements (110 x 50 x 3.0 mm) and cutting as a disc in dimensions (thickness=3.0 mm and diameter=10 mm) according to ASTM: D-2849 [15] and the weighted of the xerogel discs was exactly 0.4 gm of all samples were used in the swelling study.

4- Preparation of standard calibration curve [16]

A standard curve for albumin was determined by preparation solutions different concentrations from albumin in the range of (0.025 - 0.25 %). The solutions were prepared, using deionized water as solvent. The absorbance of the resulting solutions was measured at λ_{max} 398.0 nm using deionized water as a blank. Figure (1), showed the linear relationship between the concentration of the albumin and the absorbance.

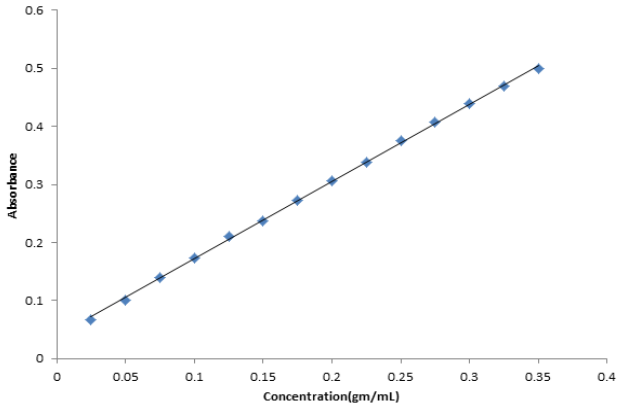


Figure (1): Calibration curve of the albumin (the absorbance in 1cm cell) at λ_{max} 398.0 nm

5- Drug (albumin) loaded

The albumin is a family of globular proteins, is water-soluble, and moderately soluble in concentrated salt solutions, experience heat denaturation, and because the prepared gels are swell extensively in water [17], the albumin was loaded through immersing the xerogel discs in buffer solution pH (pH=2.2 and pH=8.0) containing different weights of albumin and was allowed to loaded for each hour at constant temperature (310 K). After every 1 hr., they were removed from the buffer solution, blotted with filter paper to remove surface water, weighted and the albumin content ratio was calculated by using Equation (2) [18] ; and the same time the absorbance of the albumin concentration in buffer solutions was evaluated by using UV.- spectrophotometer. The measurement was continued until a constant of disc content was repeated for each sample.

$$\text{Swelling ratio (\%)} = \frac{(\text{wt. of hydrogel} - \text{wt. of xerogel})}{(\text{wt. of hydrogel})} \times 100 \quad \text{..... equation (2)}$$

6- Drug (albumin) Release

A loaded hydrogel disc is used in order to determine the amount of albumin released from the hydrogel network. After reaching the equilibrium state of the disc from through a constant of disc content in a buffer solution marinated in it. Loaded hydrogel disc immersed in 50 ml deionized water at temperature (310 K). The amount of albumin release was evaluated each hour. The measurement of release was continued until a stability absorbance was repeated for each sample.

RESULTS AND DISCUSSION

1-preparation of co-polymer

Figure(2), showed the appearance of a strong broad band at about 3338cm^{-1} for stretching carboxylic acid (-OH) with stretching (H-bond), and also showed a weak band at about 2953 cm^{-1} due to the =C-H for carboxylic acid, and the spectrum also showed a weak band at about 2887 cm^{-1} due to C-H aliphatic, and the spectrum also showed a strong band at about 1718cm^{-1} assigned to a stretching band C=O for ester group and also showed a bands at about 1014 cm^{-1} assigned to C-O absorption band. Figure(3), showed the spectrum of ^{1}HNMR, which explain the singlet signal, at 13.24 ppm characteristic of proton in carboxylic acid group furthermore the multiples in the region 7.53- 8.10 ppm back to all protons in aromatic ring, the signals at 6.27-6. 46 ppm for four protons of methylene in the structure of polymer, the multiples at 4.24- 4.50 ppm of methyl protons, but the triplet signal in 3.44-3.62 ppm due to the proton of aliphatic alcohol, so this spectrum was confirmed the structure of ourtarget polymer.

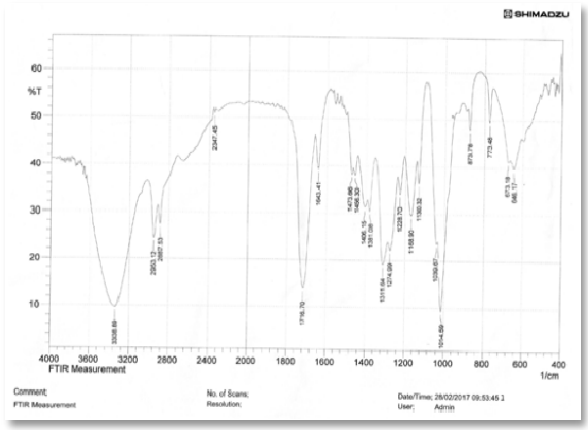


Figure (2): The FT-IR spectrophotometer of the prepared co-polymer

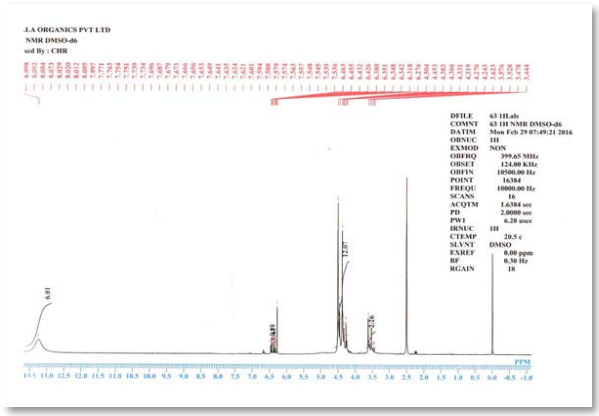


Figure (3): The ^{1}HNMR spectrophotometer of the prepared co-polymer

2-Drug (albumin) loaded

A plot of albumin content (%) versus time (hour), showed the curves of modified resin for three different numbers of moles from acrylic acid (0.5, 1.0 and 1.5 mole), against loaded time (hour) at constant temperature (310 K), as shown in Tables (2) to (4) and Figures (4) to (9) respectively for pH= 8.0 and as shown in Tables (5) to (7) and Figures (10) to (15) respectively for pH=2.2, by using UV-Spectrophotometer and measuring the absorbance of the solutions.

Table (2): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	10.87	0.466	12.89	0.509	14.97	0.544	16.27	0.581	18.91	0.629
2	12.82	0.442	14.88	0.488	16.96	0.528	18.17	0.561	20.87	0.609
3	14.48	0.424	16.65	0.466	18.91	0.508	20.35	0.541	22.81	0.588
4	16.30	0.409	18.35	0.451	20.73	0.489	22.57	0.520	24.91	0.569
5	16.30	0.409	18.35	0.451	20.73	0.489	24.24	0.507	26.90	0.549
6							24.24	0.507	26.90	0.549

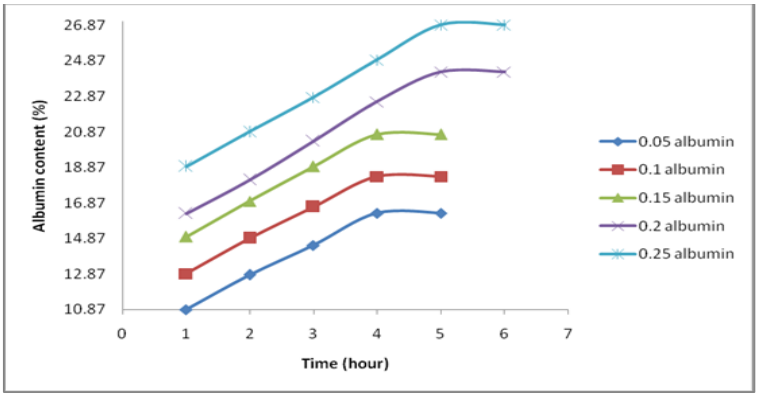


Figure (4): Albumin content (%) curves per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

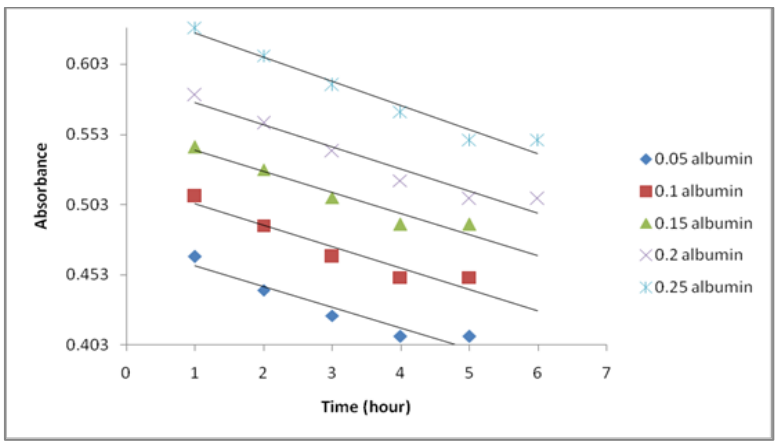


Figure (5): Absorption (Abs.) curves per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (3): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	11.76	0.451	14.27	0.499	16.82	0.538	18.17	0.570	20.70	0.619
2	13.87	0.432	16.25	0.479	18.91	0.519	20.52	0.550	22.74	0.599
3	15.88	0.413	18.35	0.458	20.87	0.499	22.57	0.531	24.84	0.579
4	17.63	0.390	20.27	0.439	22.60	0.477	24.84	0.512	26.97	0.559
5	17.63	0.390	20.27	0.439	22.60	0.477	26.39	0.497	28.56	0.539
6							26.39	0.497	28.56	0.539

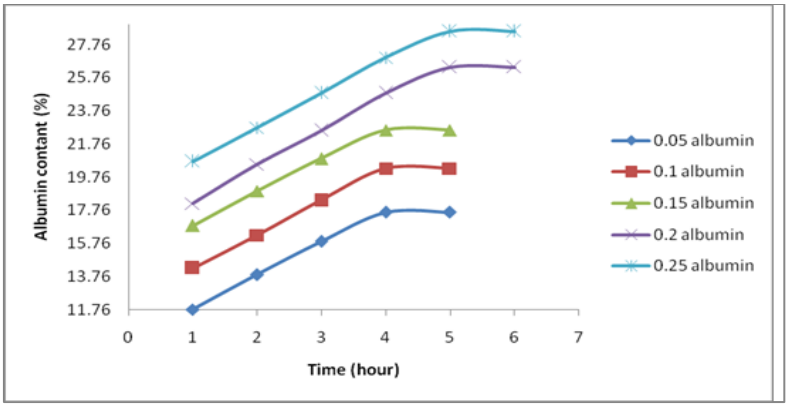


Figure (6): Albumin content (%) curves per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

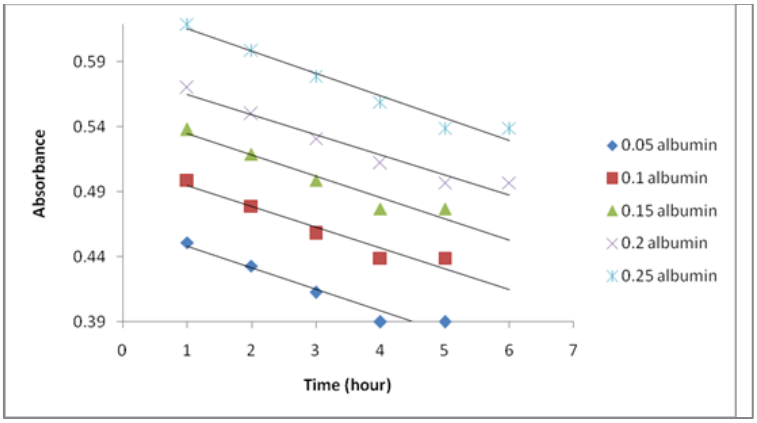


Figure (7): absorption (Abs.) curves per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (4): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	13.66	0.435	16.14	0.478	18.28	0.519	20.00	0.551	22.97	0.599
2	15.68	0.413	18.17	0.458	20.38	0.499	22.07	0.531	24.98	0.577
3	17.53	0.393	20.06	0.439	22.41	0.478	24.20	0.511	26.97	0.559
4	19.31	0.375	22.09	0.419	24.23	0.459	26.23	0.491	28.99	0.539
5	19.31	0.375	22.09	0.419	24.23	0.459	28.56	0.479	30.92	0.519
6							28.56	0.479	30.92	0.519

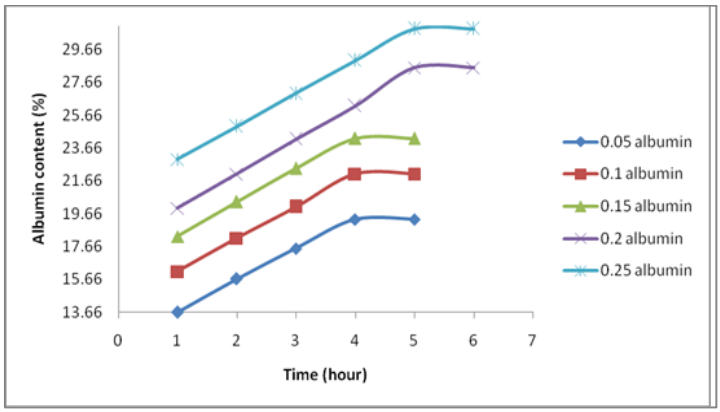


Figure (8): Albumin content (%) curves per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

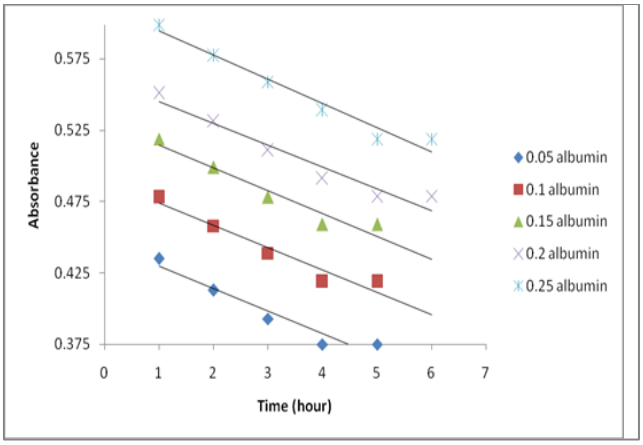


Figure (9): absorption (Abs.) curves per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (5): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	6.10	0.522	8.05	0.569	10.21	0.609	12.61	0.640	14.68	0.689
2	8.09	0.502	10.21	0.549	12.18	0.589	14.27	0.621	16.27	0.669
3	8.09	0.502	10.21	0.549	12.18	0.589	16.65	0.605	18.58	0.649
4							16.65	0.605	18.58	0.649

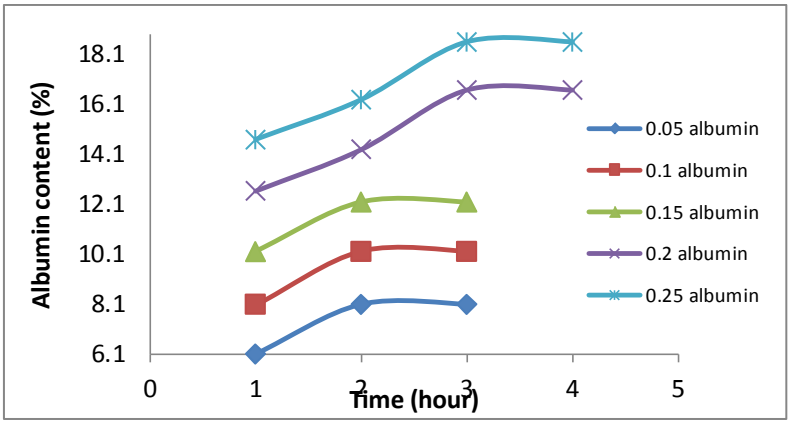


Figure (10): Albumin content (%) curves per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

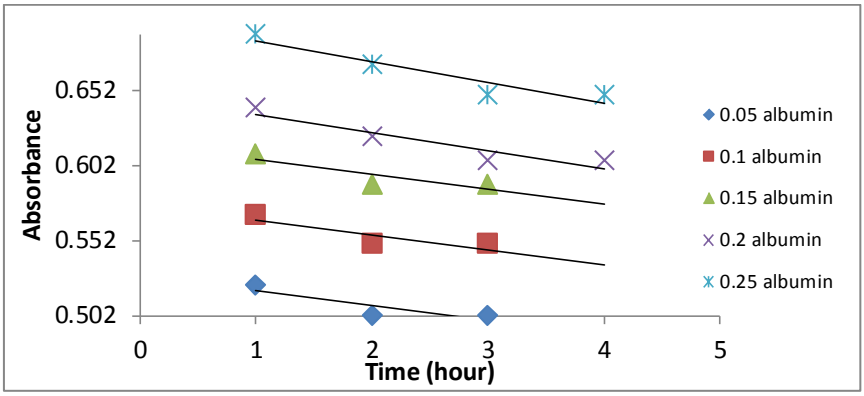


Figure (11): absorption (Abs.) curves per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (6): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	7.08	0.513	9.07	0.559	11.76	0.599	13.02	0.630	15.49	0.679
2	9.13	0.497	11.09	0.538	13.87	0.579	15.88	0.611	17.98	0.659
3	9.13	0.497	11.09	0.538	13.87	0.579	17.81	0.596	19.97	0.639
4							17.81	0.596	19.97	0.639

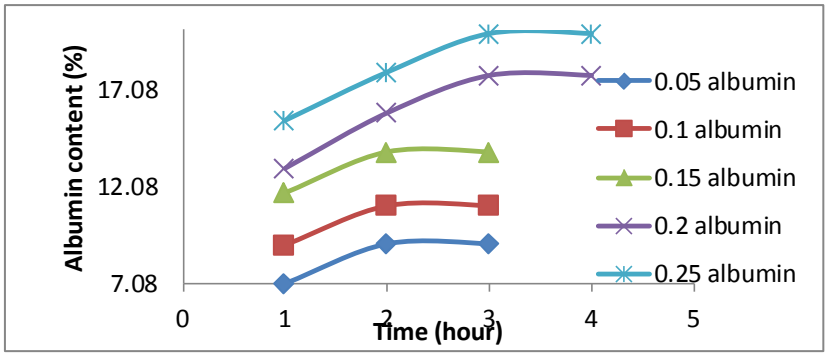


Figure (12): Albumin content (%) per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH= 2.2, Temp.=310K

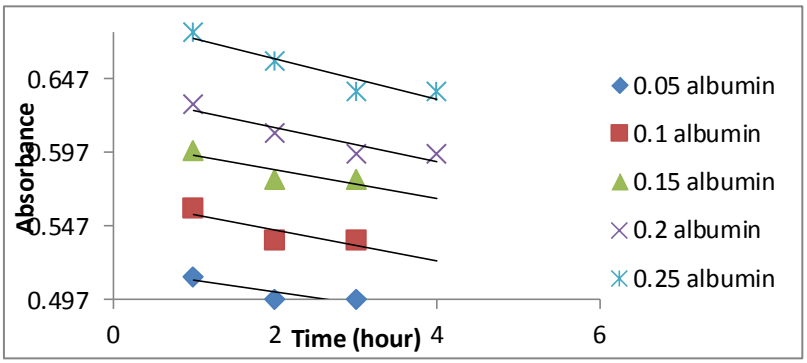
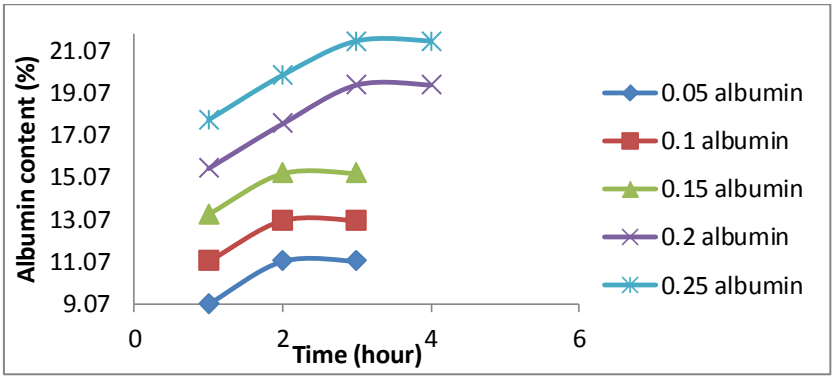


Figure (13): Absorption of solution (Abs.) per hour, of modified resin containing. 1.0 mole of acrylic acid monomer at pH= 2.2, Temp.=310K

Table (7): Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Concentration of albumin									
	0.05		0.1		0.15		0.2		0.25	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	9.07	0.493	11.09	0.538	13.33	0.579	15.49	0.611	17.80	0.659
2	11.09	0.472	13.02	0.519	15.25	0.559	17.61	0.591	19.92	0.639
3	11.09	0.472	13.02	0.519	15.25	0.559	19.45	0.576	21.54	0.619
4							19.45	0.576	21.54	0.619



Figure(14): Albumin content (%)per hour, of modified resin containing. 1.5 mole of acrylic acid monomer at pH= 2.2, Temp.=310K

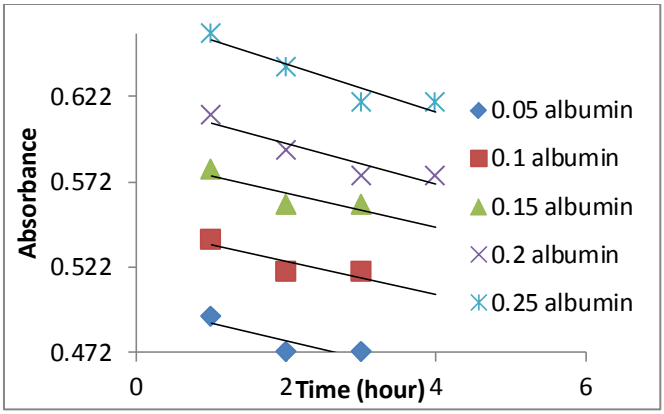


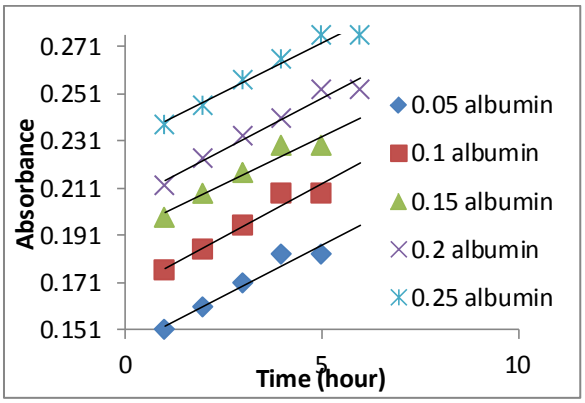
Figure (15): Absorption of solution (Abs.) per hour, of modified resin containing. 1.5 mole of acrylic acid monomer at pH= 2.2, Temp.=310K

3-Release of Drug (Albumin)

Tables (8) to (10) and Figure (16) to (18), respectively, represent the release of albumin drug from the measured samples in the basic medium pH=8.0. Tables (11) to (13) and Figure (19) to (21), respectively, represent release of albumin drug from measured models in the acidic medium pH=2.2. From the results, it can be seen that in the basic medium, the drug is more released than the acidic medium.

Table (8): Release of albumin per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

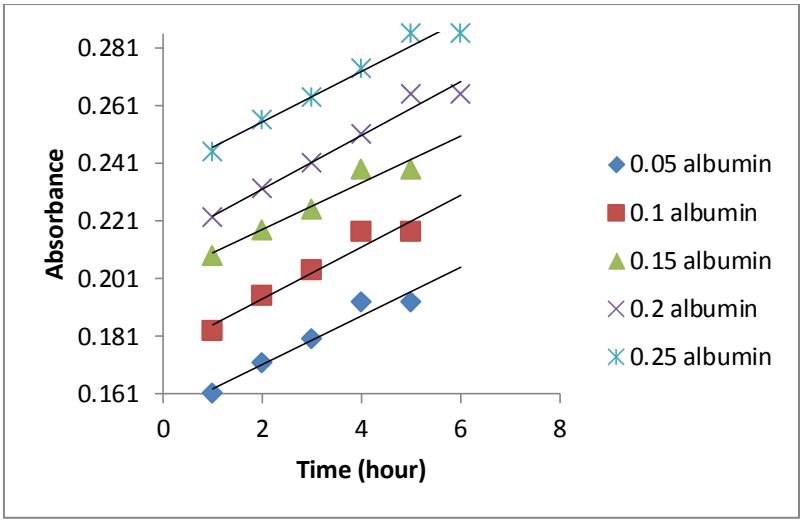
Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.151	0.176	0.199	0.212	0.238
2	0.161	0.185	0.209	0.224	0.246
3	0.171	0.195	0.218	0.233	0.257
4	0.183	0.209	0.229	0.241	0.266
5	0.183	0.209	0.229	0.253	0.276
6				0.253	0.276



Figure(16): Release of albumin per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (9): Release of albumin per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

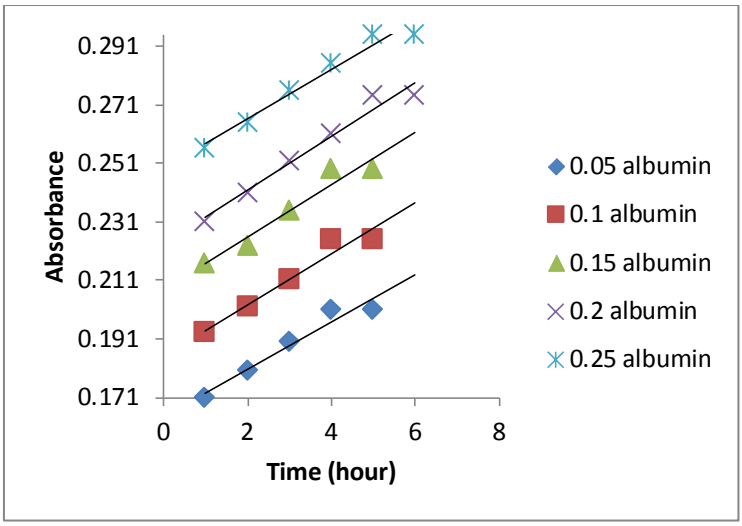
Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.161	0.183	0.209	0.222	0.245
2	0.172	0.195	0.218	0.232	0.256
3	0.180	0.204	0.225	0.241	0.264
4	0.193	0.217	0.239	0.251	0.274
5	0.193	0.217	0.239	0.265	0.286
6				0.265	0.286



Figure(17): Release of albumin per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (10): Release of albumin per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

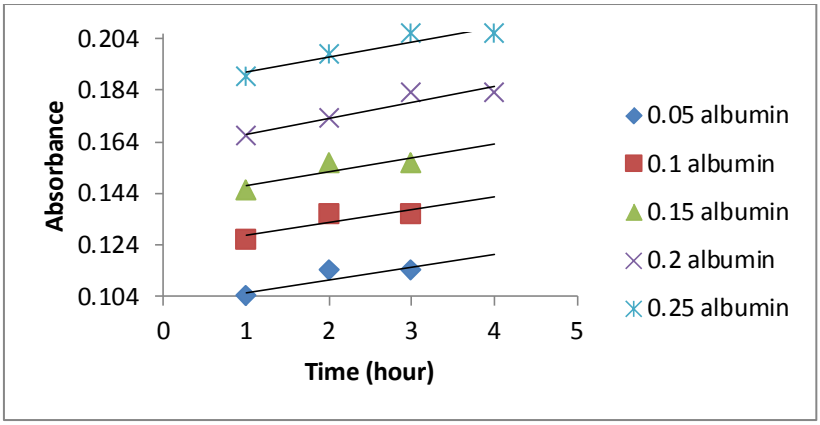
Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.171	0.193	0.217	0.231	0.256
2	0.180	0.202	0.223	0.241	0.265
3	0.190	0.211	0.235	0.252	0.276
4	0.201	0.225	0.249	0.261	0.285
5	0.201	0.225	0.249	0.274	0.295
6				0.274	0.295



Figure(18): Release of albumin per hour, of modified resin containing 1.5mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (11): Release of albumin per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

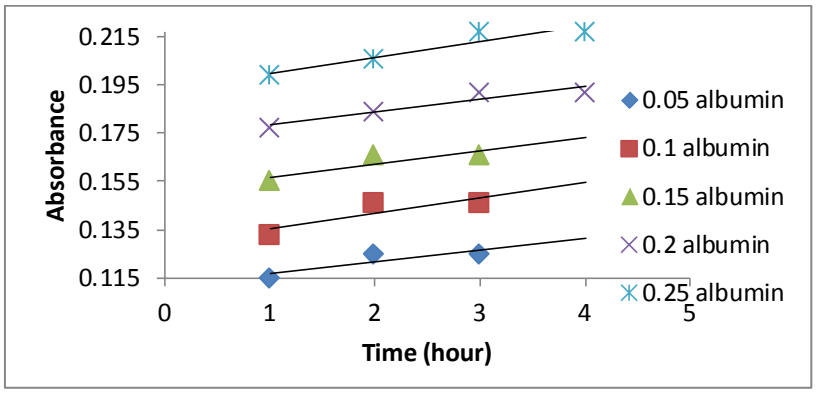
Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.104	0.126	0.145	0.166	0.189
2	0.114	0.136	0.156	0.173	0.198
3	0.114	0.136	0.156	0.183	0.206
4				0.183	0.206



Figure(19): Release of albumin per hour, of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Table (12): Release of albumin per hour , of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

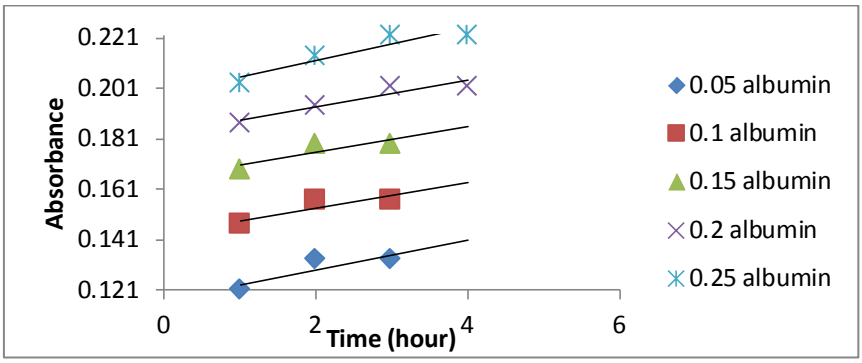
Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.115	0.133	0.155	0.177	0.199
2	0.125	0.146	0.166	0.184	0.206
3	0.125	0.146	0.166	0.192	0.217
4				0.192	0.217



Figure(20): Release of albumin per hour, of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Table (13): Release of albumin per hour, of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Absorbance				
	Concentration of albumin				
	0.05	**0.1**	**0.15**	**0.2**	**0.25**
1	0.121	0.147	0.169	0.187	0.203
2	0.133	0.157	0.179	0.194	0.214
3	0.133	0.157	0.179	0.202	0.222
4				0.202	0.222



Figure(21): Release of albumin per hour , of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

CONCLUSIONS

In this work, a new co- polymer was prepared through the reaction of pentarythritol with fumaric acid to form a linear co- polymer containing four effective sites (double bond) able to bind to the double bond of monomer (acrylic acid monomer) to form three dimensional co- polymer network, and by using three different mole of acrylic acid monomer, bind with linear co-polymer to produce three different co-polymers, that differ among themselves in the number of active sites (double bond). Thus, the density of the cross-linked will vary in these co-polymers. Thus, swelling will be varying, this difference can be observed by loading and releasing of protein (drug), the above measurements can be said: It is possible to observe that the protein loading in the base medium reaches the equilibrium state after five hours of immersion of the sample in the base solution, But in the acid medium, the protein load reaches the equilibrium state after a three hours in a maximum, From this we conclude that loading in the basic medium is more efficient than loading in the acid medium and it can be clearly observed that the process of releasing the albumin protein in the basic medium (pH=8.0) is greater than the process of release in the acid medium (pH=2.2), which indicates the effectiveness of the co- polymer on the release of protein in the basic medium higher than in the acid medium.

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