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RESEARCH ARTICLE

Synthesis of a New Three-Dimensional Network Co-polymer and Studying the Ability of 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. Swellingof the polymer samples were measured in the buffer solution in the basic and acidic medium. The albumin protein was 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.

Keywords: *Hydro gel; Polymer; Condensation polymerization; Three-dimensional network; Selectivity; Swelling; Buffer solution; Drag delivery system.*

Introduction

Hydro gel is 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 bio-materials [2]. Hydro gels 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 poly acr yl amide 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]. Further-more, hydrogels can be formulated in a variety of physical forms, including slabs,micro particles, nanoparticles, coatings, and films[6]. As a result, hydro gels are commonly usedin clinical practice and medicine with a wide range of applications, including Tissue Engineering and Regenerative Medicine; Diagnostics, Cellular immobilization, Separation of bimolecular or cells, and barrier materials to regulate biological adhesions [7].These unique physical properties of hydro gels have stimulated particular interest in their use indrug 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 coefficie nt of a small molecule or a macro- molecule through the gel network [10]. Since the polymer cannot dissolve due to the covalent cross-links, water uptakes far in excess ofthose achievable with hydrophilic linear polymers can be obtained [11]. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic-specific ally 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 attrib-uted to the high water content of hydrogel .Biodegradability or dissolution in case of

hydrogels may be broughtaboutby 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 tissuesin both vitro and vivo [14, 15].

Experimental

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

Preparation of Modified Co-polymer

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. at180C°, 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, untila pourable syrup was formed. Table (1), represents the physical properties of modified co-polymer. Figure (1) represent the FT-IR spectrophotometer of prepared co-polymer and Figure (2) represents the ^{1}HNMR spectrophotometer of prepared co-polymer.

Preparation of Polymeric Specimens

The samples of polymeric prepared by add different number of moles of the acrylic acid monomer (0.5, 1.0and 1.5mole) 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 (110x50x30) and cutting as a disc in dimensions (thickness=3.0 mm and diameter=1.0 cm) 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.

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, usingdemonized water as solvent. The absorbance of the resulting solutions was measured at λ_{max} 398.0 nm using demonized water as a blank.Figure (3) showed the linear relationship between the concentration of the albumin and the absorbance.

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 1hr., 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.

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 hydro gel disc

immersed in 50 ml deionizer 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

Preparation of Co-polymer

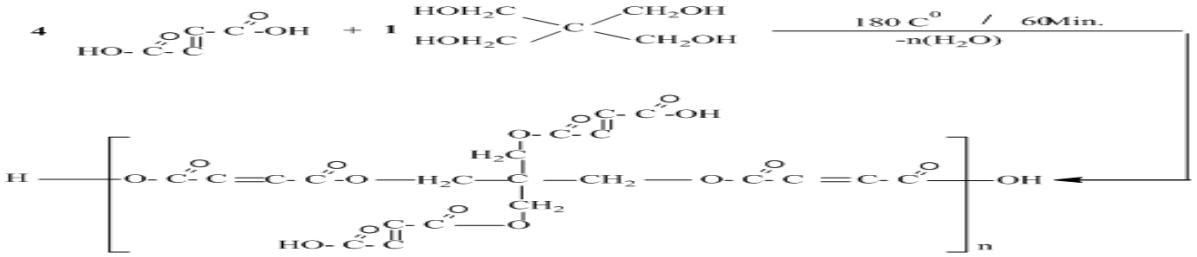
Figure(1), showed the appearance of a strong broad band at about 3338cm^{-1} for stretching carboxylic acid (-OH) with stretching (H-bond), and also showed a weak band at about 2953 cm^{-1} due to the =C-H for carboxylic acid, and the spectrum also showed a weak band at about 2887 cm^{-1} due to C-H 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(2), 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 ethylene 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 our target polymer.

Drug (Albumin)Loaded

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

Release of Drug (Albumin)

Tables (8) to (10), represent the release of albumin from the measured samples in the basic medium pH=8.0. Tables (11) to (13), represent albumin release from measured models in the acidic medium pH=2.2.



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 25C⁰
Acid Value	26
Density	1.3 (gm/cm^3)

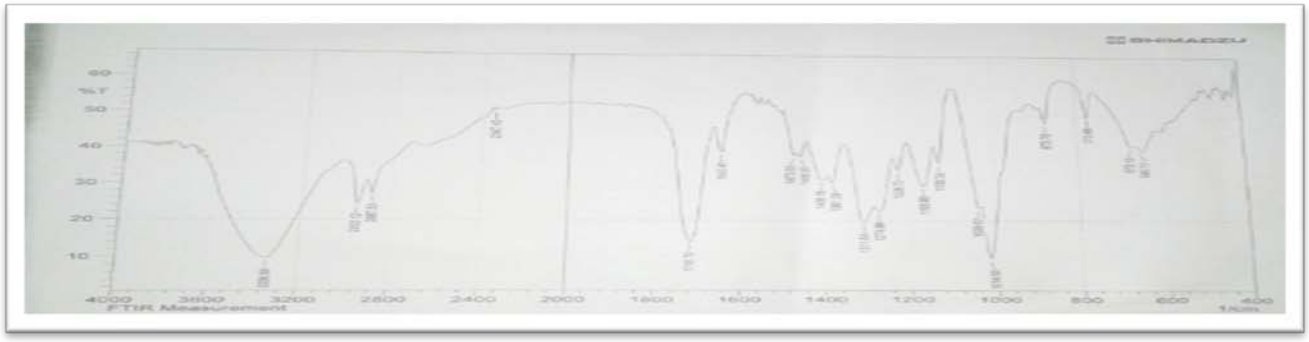


Figure 1: The FT-IR spectrophotometer of the prepared co-polymer

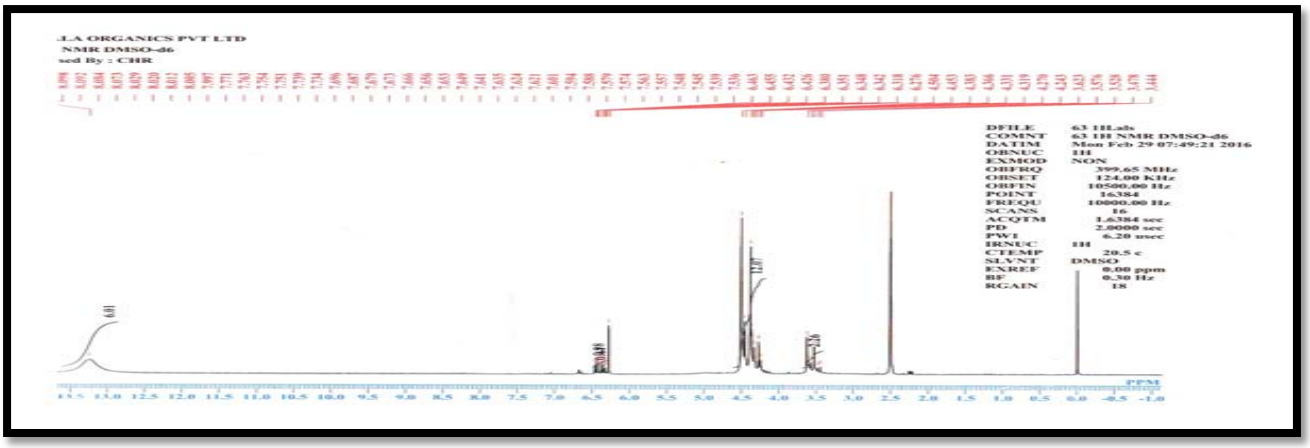


Figure 2: The ^{1}HNMR spectrophotometer of the prepared co-polymer

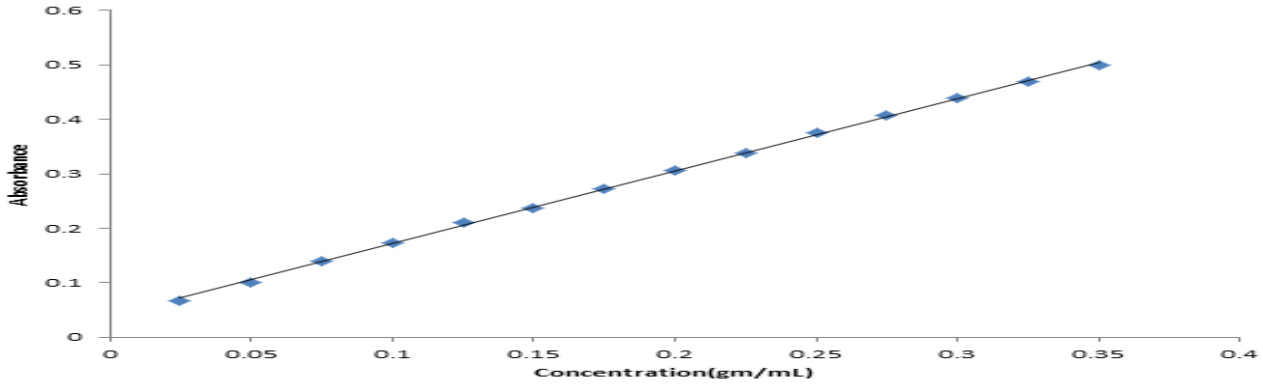


Figure 3: Calibration curve of the albumin (the absorbance in 1cm cell) at λ_{max} 398.0 nm

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

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									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	9.77	0.444	11.99	0.488	13.98	0.528	15.97	0.569	17.42	0.601
2	11.78	0.425	13.90	0.466	15.88	0.509	17.98	0.548	19.63	0.580
3	13.46	0.408	15.56	0.449	17.71	0.488	19.98	0.529	21.80	0.561
4	15.29	0.388	17.27	0.429	19.31	0.471	21.55	0.509	23.88	0.541
5	15.29	0.373	17.27	0.414	19.31	0.460	21.55	0.499	25.48	0.521

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									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	10.43	0.444	13.02	0.477	15.68	0.518	17.98	0.559	19.45	0.592
2	12.82	0.425	15.16	0.458	17.61	0.499	19.98	0.538	21.55	0.571
3	14.68	0.408	17.24	0.439	19.63	0.478	21.91	0.519	23.72	0.550
4	16.58	0.388	19.21	0.419	21.55	0.458	23.55	0.499	25.91	0.531
5	16.58	0.373	19.21	0.409	21.55	0.449	23.55	0.489	27.26	0.511

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									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	12.40	0.411	15.00	0.457	17.04	0.499	19.45	0.536	21.61	0.571
2	14.48	0.395	17.13	0.438	19.27	0.477	21.38	0.519	23.56	0.551
3	16.27	0.373	19.09	0.419	21.10	0.459	23.43	0.499	25.76	0.531
4	18.22	0.355	21.03	0.399	23.06	0.439	25.46	0.479	27.85	0.512
5	18.22	0.344	21.03	0.388	23.06	0.429	25.46	0.469	29.92	0.491

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									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	5.10	0.500	7.06	0.549	9.20	0.589	11.45	0.629	13.66	0.660
2	7.41	0.488	9.32	0.528	11.50	0.569	13.05	0.609	15.29	0.641
3	7.41	0.470	9.32	0.519	11.50	0.559	13.05	0.599	17.64	0.622

Table 6: Albumin content (%) and absorption of solution (Abs.) per hour, of modified resin containing 1mole of acrylic acid monomer at pH=2.2, Temp. =310K

Time (hour)	Concentration of albumin									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	6.01	0.493	8.20	0.538	10.21	0.578	12.61	0.619	14.27	0.652
2	8.15	0.479	10.21	0.517	12.40	0.559	14.66	0.599	16.92	0.630
3	8.15	0.460	10.21	0.509	12.40	0.549	14.66	0.589	18.91	0.611

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

Time (hour)	Concentration of albumin									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	8.15	0.471	10.21	0.519	12.1 8	0.559	14.27	0.599	16.65	0.631
2	10.21	0.455	12.18	0.499	14.07	0.539	16.02	0.579	18.73	0.612
3	10.21	0.440	12.18	0.489	14.07	0.529	16.02	0.569	20.35	0.592

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				
	0.025	0.075	0.125	0.175	0.225
1	0.133	0.166	0.188	0.209	0.223
2	0.144	0.174	0.196	0.219	0.232
3	0.152	0.184	0.206	0.229	0.244
4	0.165	0.196	0.219	0.239	0.252
5	0.165	0.196	0.219	0.239	0.263

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				
	0.025	0.075	0.125	0.175	0.225
1	0.149	0.175	0.195	0.218	0.233
2	0.157	0.183	0.205	0.227	0.243

3	0.163	0.193	0.214	0.237	0.252
4	0.177	0.206	0.227	0.249	0.262
5	0.177	0.206	0.227	0.249	0.276

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				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.159	0.185	0.205	0.228	0.242
2	0.168	0.194	0.213	0.237	0.251
3	0.177	0.201	0.224	0.247	0.263
4	0.189	0.214	0.236	0.259	0.272
5	0.189	0.214	0.236	0.259	0.285

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				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.089	0.115	0.135	0.152	0.177
2	0.099	0.125	0.146	0.162	0.185
3	0.099	0.125	0.146	0.162	0.194

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				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.099	0.125	0.145	0.165	0.187
2	0.109	0.136	0.158	0.174	0.196
3	0.109	0.136	0.158	0.174	0.206

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				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.103	0.136	0.158	0.179	0.195
2	0.116	0.146	0.169	0.188	0.204
3	0.116	0.146	0.169	0.188	0.212

Conclusions

In this work, a new co- polymer was prepared through the interaction 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 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 polymers.Thus, swelling will be vary, this difference can be observed by loading and releasing of protein, 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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