History of Medicine, 2023, 9(2): 176–181
DOI: 10.17720/2409-5834.v9.2.2023.027

Synthesis and characterization of some new prodrug polymer based on poly vinyl alcohol and study some application: as a biological model

Wisam Abdul Jaleel Jawad[1].Faris H. Mohammed[2]

[1]*College of science/ Department of chemistry/ University of Babylon. Iraq*
Email: wisamabduljaleel227@gmail.com
[2]*College of science/ Department of chemistry/ University of Babylon. Iraq*

Received: 11 May 2023 **Accepted:** 10 June 2023

Citation: Jawad WAJ, Mohammed FH (2023) Synthesis and characterization of some new prodrug polymer based on poly vinyl alcohol and study some application: as a biological model. History of Medicine 9(2): 176–181. https://doi.org/10.17720/2409-5834.v9.2.2023.027

Abstract

This study was suggested for synthesis a new polymers for polyvinyl alcohol reaction with aspirin and paracetamol as drugs, and these drugs carry carboxylic and amide groups after it's conversation into acid chloride, and all probable techniques were used for identification the product compounds by FT-IR and ^{1}H-NMR spectrums, controlled drug release, swelling, viscosity of polymers and solubility were measured. Finally the thermal analysis and biological activity were studied too.

Keywords:

synthesis, characterization, paracetamol, polyvinyl alcohol, prodrug polymers.

The two activity groups were lead to make benzene ring highly reactivity toward electrophilic aromatic substitution due to their substitutions of both groups on the benzene ring also the conjugation will reduce the basicity of both (the oxygen's and nitrogen atoms), and the hydroxyl group has an acidic characters according to delocalization of charge on benzene ring[(4)]. In constract to Aspirin, no bleeding time and no platelet eggregation of normal subjects or hemophilic patients is affected when paracetamol was introduced as a signal dose for up to six weeks. [(5)]

Aspirin (acetyl salicylic acid) was a popular and oldest drug in in medicine, and as anti-inflammatory drug do main administration route of Aspirin is oral and has poor bio availability [(6-9)]. Moisture is play a key role for physical and chemical stability of dose form [(7)]. Also aspirin is an ester compound and can easily hydrolysis by presence of moisture to form salicylic acid and acetic acid. Reye's syndrome was first noticed in 1963 [(8)], then this syndrome was followed by viral

Biodegradable polymers are classified as one of an important application in medical and industrial fields, and in decreasing of pollution levels.[(1)] Most industry of polymers were reflected as biological inactive and toxic, while other polymers were have a wide area of therapeutic activity[(2)]. Paracetamol contain's benzene ring that substituted by hydroxyl group and nitrogen of an amide group as para position [(3)].

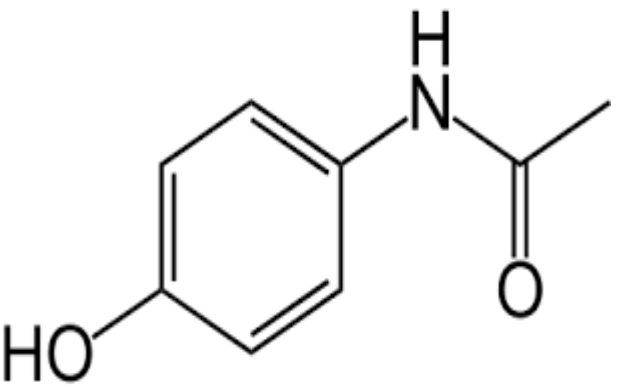
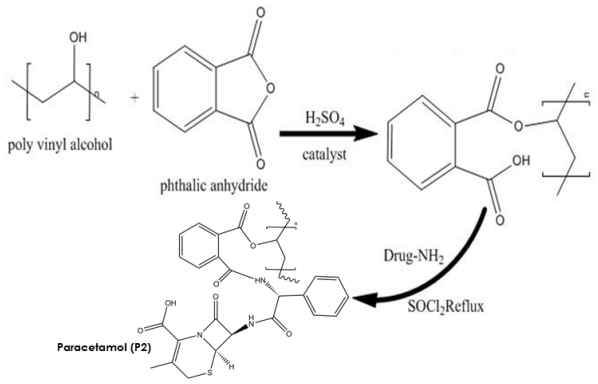


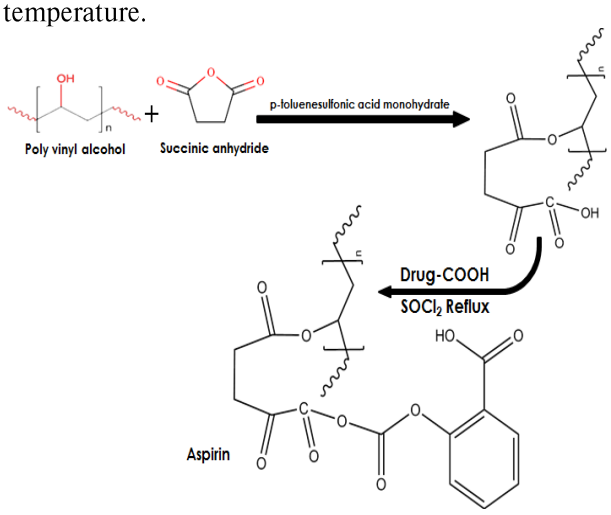
Figure (1) Paracetamol Structure



Scheme (1) Synthesis of polymer A1

Esterification of polyvinyl alcohol and succinic anhydride(15):

(0.5 gram) of polyvinyl alcohol (0.011 mole) was dissolved in distilled water as a small portion and mixed with (0.5 gram) of succinic anhydride (0.004 mole) also the dissolution in a small volume distilled water after that dissolution process all the mixture was heated at (60°C) (45min) and addition of (1 gram) of Aspirin was added the product of heating, then the resulting was filtered and washed many times by diethyl ether for purification product was left for during in a room temperature.



Scheme (2) Synthesis of polymer A2

Results and Discussion

Fourier-Transform infrared (FT-IR) spectrum of A1 shows: 3011.34-3310.25 cm^{-1} stretch (NH amide), 2970.82, 2918.33, 2856.94 cm^{-1} strech (CH aldehyde), (C=O) 1742.85 cm^{-1}. But for ^{1}H-NMR spectrum shows 1.98 ppm for the proton of (OH), 7.58-7.67 ppm and most influenza [9-10]. So Aspirin smell in swelling was like acetic acid (Vinegar) [14-16]

Chemicals:

All chemicals were purchased from commercial sources. 1,4 dioxane, p-toluene sulfonic acid, succinic anhydride company and their purities (98, 99.9, 98, BDH), acetone, acetonitrile, hexane, polyvinyl alcohol (98, 98, 98, 99 purity, Merck). Chloroform, diethyl ether, dimethyl formide (99.8, 98, 98, Chem Lab). While dimethyl sulfoxide, sulphoric acid and thinoyl chloride (98, 98, 98, Alfa). Aspirin and paracetamol were obtained from Samarra company and their purities (99.9 for each one).

Measurements

The Intrinsic viscosity was carried by using distilled water as solvent and Ostwald viscometer was used to complete the measurement. The IR spectrums were recorded through Fourier trans infrared spectro photometer-Bruker, while ^{1}H-NMR was taken by Bruker (400 MHz), Switzerland in DMSO, TMS was used as a reference. Also physical parameters measurement (viscosity, swelling, solubility) were performed in laboratory and finally thermal analysis and biological activity for polymers were studied too.

Experimental:

Synthesis of New functional amino drug polymers(14):

The experiment was done by condensing (0.5gm; 0.0011 mole) of polyvinyl alcohol was added to (0.5 gm, 0.003 mole) of phthalic anhydride to make the mixture, this mixture was refluxed with stirring of one hour (1 hour), after addition (1 gram) of paracetamol drug as an example of amine drugs

The product was collected as powder after it's washing for many times by using di ethyl ether for recrystallization and the product also dried at room temperature.

Figure (4) FT-IR spectrum of polymer A2 Aspirin

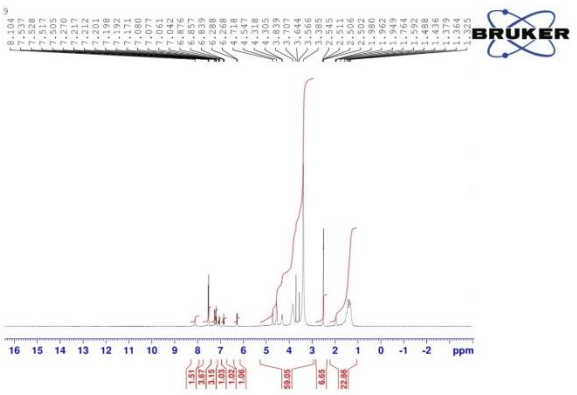


Figure (5) 1H-NMR spectrum of polymer A2 Aspirin

The viscosity measurement of prodrug polymers (A1, A2) was carried in a room temperature (25℃) by using Ostwald Viscometer, also the swelling percentage of same polymers were measured for (24 hours) by using distilled water in the same temperature of room as shown in the table:

Table (1) Values of viscosity and swelling percentage

Polymers	Intrinsic viscosity η dl/g	Swelling %
A1	0.88	12
A2	0.89	14.6

Controlled Drug Release

The controlled drug release for synthesized polymers (A1, A2) was done in three different pH functions (2, 7, 8) as shown in the table:

Table (2) Drug release of polymers A1-A2 at pH (2,7,8) in 37℃

	A1			A2		
Time/Day	pH			pH		
	2	7	8	2	7	8
1	0.131	0.28	1.494	0.83	1.57	1.556
2	0.171	0.277	0.106	2.930	1.36	2.6651
3	0.192	0.281	4.243	1.751	1.66	2.657
4	0.188	0.291	0.1595	2.508	1.45	2.6574

for the proton (H), 9.71 ppm for the proton (CH aromatic).

Fourier-Transform infrared (FT-IR) spectrum of A2 shows: 3310.18 cm^{-1} stretch (OH alcohol) of carboxylic group, 3010.56 cm^{-1} strech (H aromatic), (C=O) 1650.11 cm^{-1}, (C-O) 1162.04 cm^{-1}. While for ^{1}H-NMR spectrum shows 1.43-1.33 ppm for the proton of (OH), (7.72-7.61) ppm for the proton of (H aromatic).

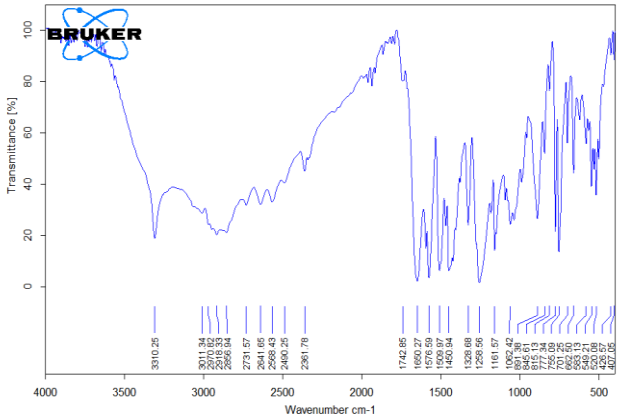


Figure (2) FT-IR spectrum of polymer A1 Paracetamol

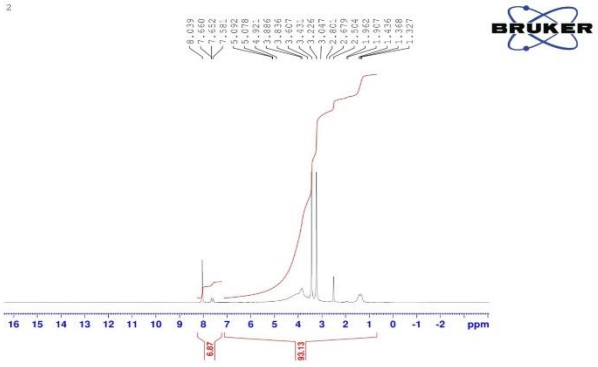
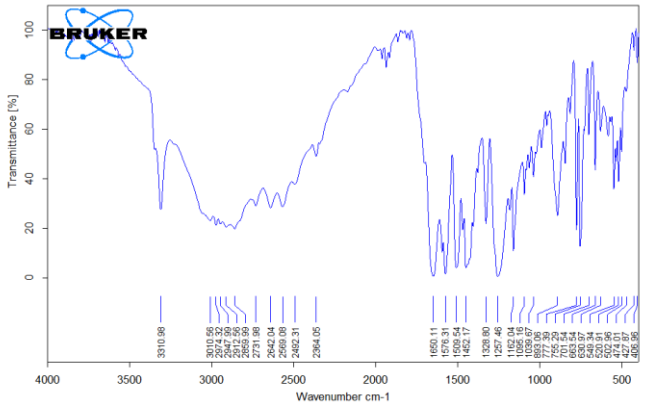


Figure (3) 1H-NMR spectrum of polymer A1 Paracetamol



Thermal analysis of polymers (A1-A2)

Differential scanning calorimetric and thermo gravimetric analysis for synthesized polymers A1-A2 were explained the softening temperature for polymers and the storage ability in suitable temperature (153.64 ℃, 113.56℃) respectively and 95.38 J/g, 32.77 J/g) heat capacity for each polymer.

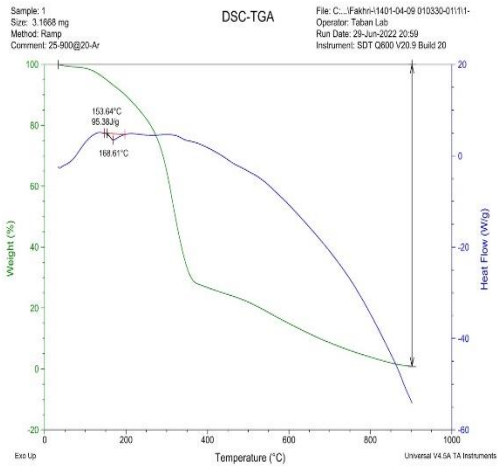


Figure (9) Differential scanning calorimetry and thermo gravity analysis for A1 polymer

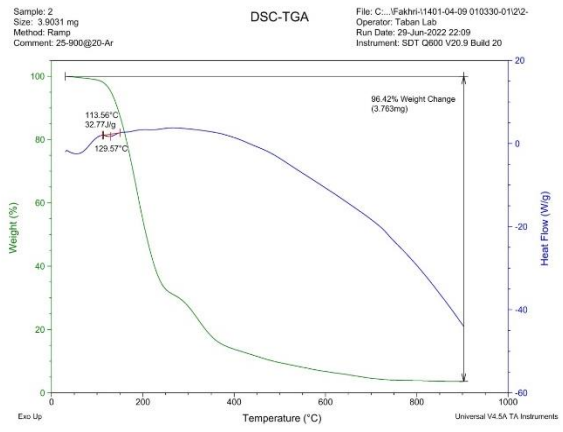


Figure (10) Differential scanning calorimetry and thermo gravity analysis for A2 polymer

Biological Activity

Through biological activity results of polymers (A1, A2) as powdered samples against bacterium types. [16](Escherichia Coli and Staphylococlus aureus) definitely indicate to constant inhibition zones for (A_1) polymer and seemed to be different somewhat for (A_2) polymer according to this table (4):

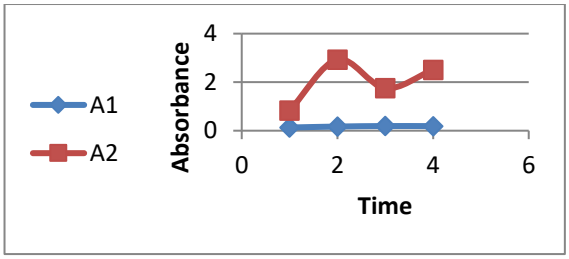


Figure (6) drug release of polymers A1-A2 at pH= 2

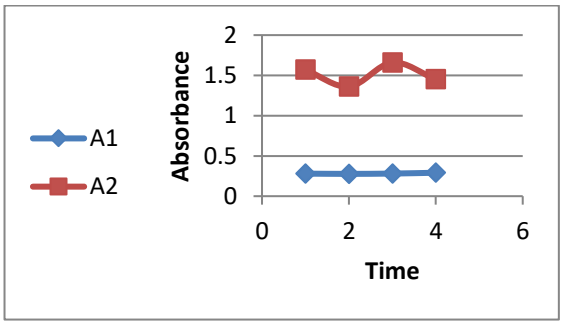


Figure (7) drug release of polymers A1-A2 at pH= 7

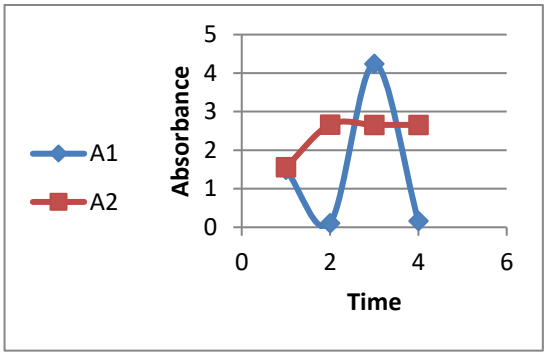


Figure (8) drug release of polymers A1-A2 at pH= 8

Solubility of prodrug polymers in different organic solvent:

The test of solubility for synthesized polymers (A1-A2) was done by taking polar and nonpolar solvents for checking solubility of those polymers.

Table (3) Solubility of A1-A2 polymers

Prodrug polymer	DMF	DMSO	H2O	Acetone	Methanol	Acetonitrile	Hezane	Di ethyl ether	Chloroform	Dioxane
A1	+	+	+	+	+	+	+	+	+	+
A2	+	+	+	+	+	+	+	+	+	+

Table: (4) diameter of inhibition zones (mm) of powdered polymers against different bacteria.

Paracetamol Inhibition zone= mm				
Isolation	(10-1)M	(10-2)M	(10-3)M	(10-4)M
Staphylococlus aureus	0	0	0	0
Escherichia Coli	0	0	0	0
Aspirin Inhibition zone= mm				
Isolation	(10^{-1})M	(10^{-2})M	(10^{-3})M	(10^{-4})M
Staphylococlus aureus	6	0	0	0
Escherichia Coli	18	0	0	0

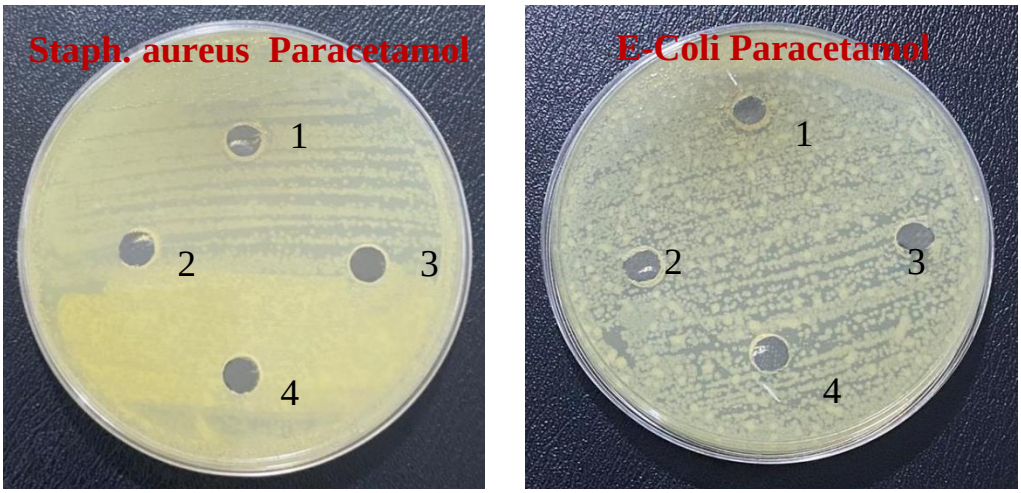


Figure (11) Biological Activity for Paracetamol Prodrug polymer

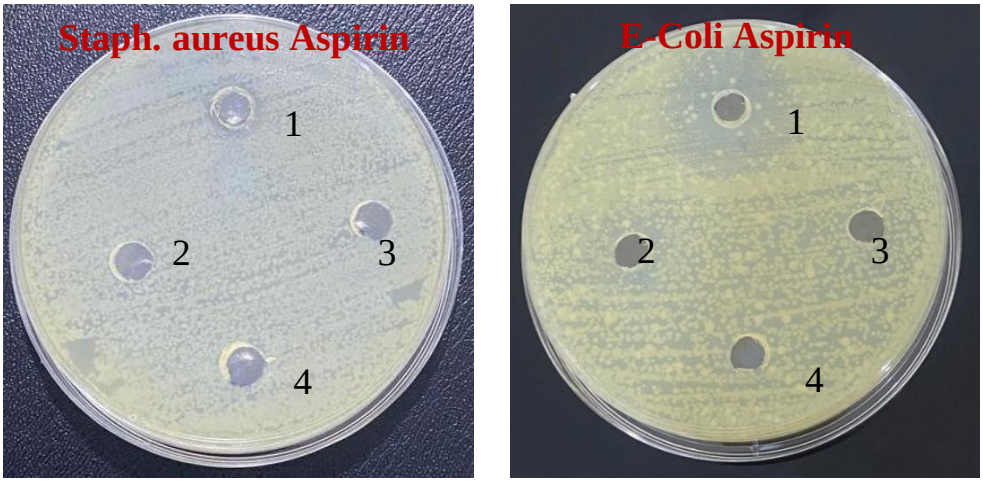


Figure (12) Biological Activity for Aspirin Prodrug polymer

Conclusion

New prodrug polymers were prepared through two different lines reaction (polyvinyl alcohol with phathalic anhydride) with amine drug (paracetamol) , and (polyvinyl alcohol with succinic anhydride) with carboxylic group (aspirin) characterization of these polymers were obtained by different techniques: FT-IR, ^{1}H-NMR, So viscosity, swelling ratio and solubility of polymers, and controlled drug release were measured. Lastly thermal analysis and biological activity analysis were carried too.

References

(1) Gupta, P., & Nayak, K. K. (2015). Compatibility study of alginate/ keratin blend for biopolymer development. Journal of applied biomaterials & functional materials, 13(4), 332-339

(2) Ali, F. M., & Ali, S. M. (2015). Methionine as a Spacer between Poly Acrylic acid and Ampicillin. Baghdad Science Journal, 12(3), 563-571.

(3) Miller J. and Richter A.; "Effects of anticonvulsants in vivo on high affinity choline uptake in vitro in mouse hippocampal synaptosomes". Br J Pharmacol., 84 (1), 19, (1985)

(4) Bales R., Nicholson K. and Sadler P.; "Two-Dimentional proton nuclear magnetic resonance "Maps of acetaminophen metabolites in human urine", Clinical chemistry, 31 (5), 757, (1985).

(5) MIELKE, C.H., HEIDEN, D., BRITTEN, A.R., RAMOS, J. & FLAVELL, P. (1976) Hemostasis, antipyretics and mild analgesics: acetaminophen vs. aspirin. Journal of the American Medical Association, 253, 613.

(6) Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Lowdose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373-83.

(7) Aspirin. Drug Facts and Comparisons . Efacts [online]. 2007 Available from Wolters Kluwer Health, Inc. (accessed 1/11/07).

(8) Reye RDK, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera. A disease entity in childhood. Lancet 1963;2:749-52.

(9) Orlowski JP, Hannah UA, Falls MR. Is aspirin a cause of Reye's Syndrome? A case against. Drug Safety 2002;25:225- 31.

(10) Glasgow JFT. Reye's Syndrome: the case for a causal link with aspirin. Drug Safety 2006;29:1111-21.

(11) Aspirin. Drug Facts and Comparisons . Efacts [online]. 2007 Available from Wolters Kluwer Health, Inc. (accessed 1/11/07).

(12) Monagle P, Chan A, Massicotte P, et al. Antithrombotic therapy in children: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:645S-687S.

(13) Newburger JW, Takahasi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.

(14) Gan B.Bajracharya, RashmiKoju, SarbeshwarOjha, SashisuNayak, SabitaSubedi, HiroakiSasai, synthesis of phthalate esters via $FeCl_3$- catalyzed nucleophilic addition of alcohols to phthalic anhydride, Volume 3, January 2021, 100190. https://www.sciencedirect.com/science/article/pii/S2211715621000953

(15) Zheng-Fa Zhou, Wei-bing Xu, Dian He, Ji-xian Fan, Feng Yu, Feng-Mei Ren, 2006, Solid-State Grafting of Succinic Anhydride onto Poly(vinyl alcohol) Department of Polymer Science and Engineering, Hefei University of Technology, Hefei, Anhui 230009, China Received 6 May 2006; accepted 16 July 2006 DOI 10.1002/app.25190 Published online in Wiley InterScience (www.interscience.wiley.com)

(16) Kenawy, E. R., abdel hay, F.I., El-Shanshoury, A.E. R.R. and El-Newehy, M.H. 202. Biologically active polymers. V. synthesis and antimicrobial activity methacrylate Co-2-hyfroxy ethyl methacrylate) derivatives with quaternary ammonium and phosphonium salts, Journal of polymer science. Part A: polymer chemistry 40, 2.384.2393 .