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RESEARCH ARTICLE

Synthesis and Characterization of Some Capsaicin Derivatives and Study their Pharmacological Hydrolysis

Faris Hamood Mohammed[1*], Sana Hitur Awad[2], Sana Abdul sahib[2]

1. *University of Babylon, College of Science, Department of Chemistry, Iraq.*
2. *University of* Baghdad*, College of Science* for women*, Department of Chemistry, Iraq.*

***Corresponding Author: Email:** *hfarise2009@yahoo.com*

Abstract

One of the alkaloid compounds that were found in the fruit of the Capsicum genus is a Capsaicin, which provides its spicy flavor. Capsaicin extracted directly from fruit and limited use in clinical trials to support the biological activity. In this research, using cationic polymerization were carried out to the synthesis of drug-spacer polymer to obtain more able as hydrolysis proceeded and more convenient for hydrolysis of attachment of the appropriate pendant drugs, through increases the distance between drugs as a bioactive and backbone of the polymer chains. All prepared drug polymers were characterized by FTIR, UV-visible, TGA and ^{1}HNMR techniques.

Introduction

The Capsaicin is found in isomerism cis and trans and consider as a crystalline alkaloid and lipophilic (trans-8-methyl-*N*-vanillyl-6-none amide) ,which has molecular formula $C_{18}H_{27}NO_3$ and molecular weight 305.40 g/mol, and it is fat-, alcohol- and oil-soluble. Tresh in 1876, firstly crystallize capsaicin's molecular structure and named by Nelson and Dawson in 1919 [1].

The Capsaicin is found in trans isomer because the double bond of the longer chain -CH $(CH_3)_2$ on the other side of will be close together in the *cis*-form, , and lead to steric hindrance and repel each other slightly, this does not exist in the *trans* isomer. Also the trans-isomer is more stable than *cis*-isomer because of founding the strain imposed in in cis isomer (Figure 1) [2].

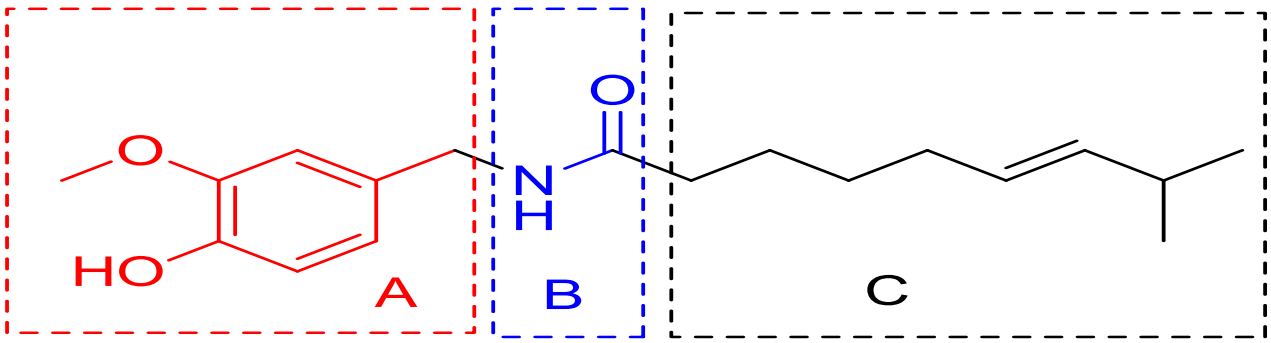


Figure 1: Capsaicin Structure: A (aromatic head), B (amide linkage) and C (hydrophobic tail)

The physical properties of Capsaicin is a hydrophobic ,odourless highly volatile, and colourless alkaloid ,its melting point equal to 62–65 °C, the structurally property it has a vanilloids group and the molecule of capsaicin is dividing into three regions: a vanillyl group (methylcatechol) it found in head group (A-region) , a hydrophobic group which is a aliphatic tail (hydrophobic-C-region), e.g., and a substituted benzyl group which is octyl chain, is required for high potency linked by a central amide bond (B-region) as shown in Figure 1.The lateral chain lengths between 8 and 9 carbons atoms is important for bioactivity of Capsaicinoids as reported by Barbero *et al.*, [5] .Capsaicinoids consider as a natural capsaicinoids ,which are known as amides

formed by the condensation of fatty acids with vanillyl amine of different chain lengths and ,that which depend on the number of branch chain carbons (R) in the presence or absence of unsaturation (Figure 2).These are naturally synthesized from enzymatic condensation of vanillyl amine and elongated by different chains of fatty acid in the placenta of chili fruits.

The capsaicin synthase enzyme (CS) caused the condensation of acting specifically on fatty acid chain length that requires Mg2+, ATP and coenzyme A (CoA) and vanillyl amine. The phenyl propanoid pathway for phenolic portion formed from phenylalanine, while the amino acids valine or leucine forms the fatty acid (Figure2 and 3) [6-10].

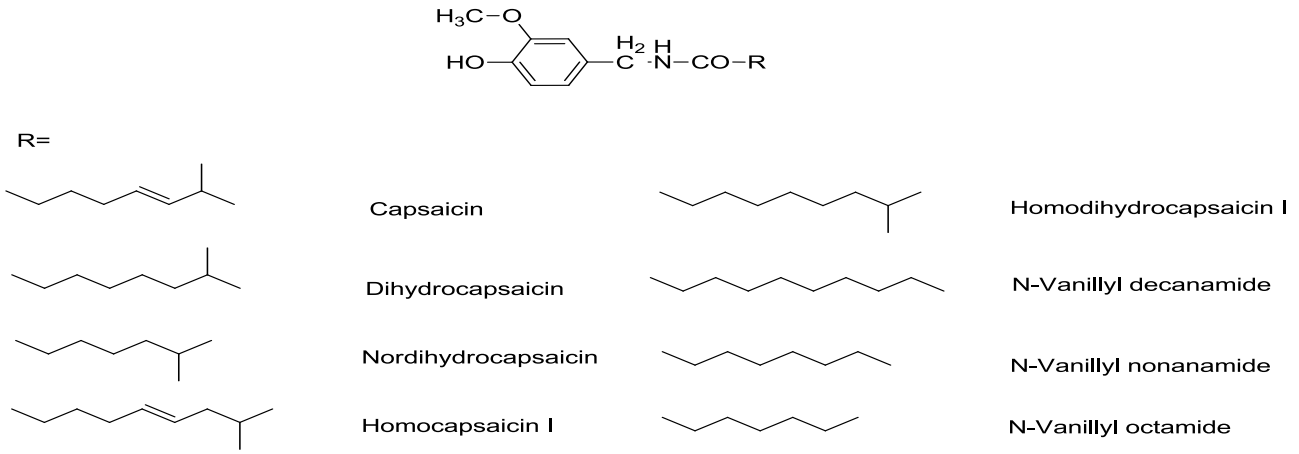


Figure 2: Capsaicinoids Structure with different analogues R

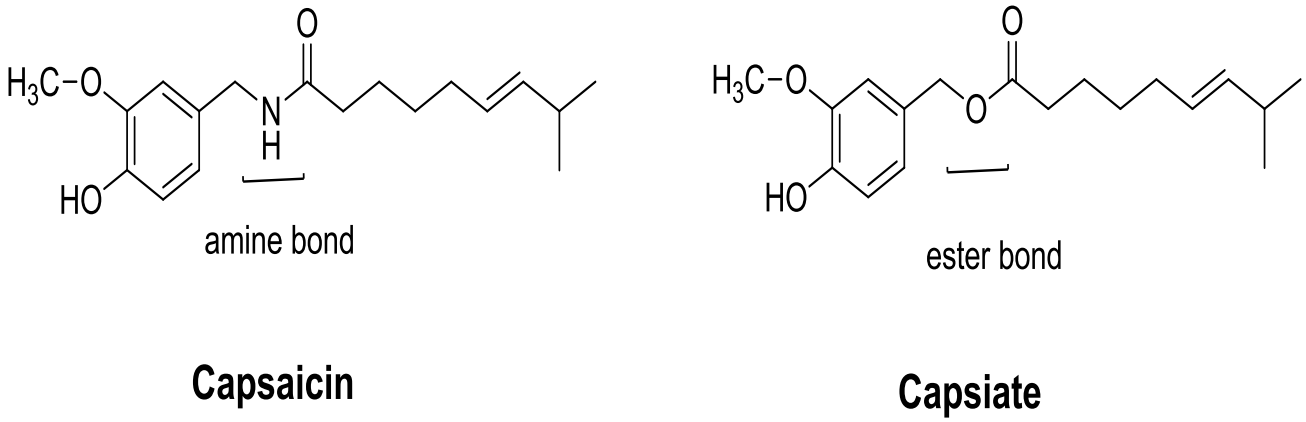


Figure 3: Capsaicin and Capsiate Structures

Capsaicinoids have a structure similarly in changing of length aliphatic side chain and degree of saturation in absence or presence of double bonds through the alkyl side chain region. Capsaicinoids have pharmacological and physiological properties including analgesic, anti-obesity, anti-cancer, anti-oxidant, anti-inflammatory, pain relief, and weight loss [11-15].

Experimental

Materials and Instruments:-

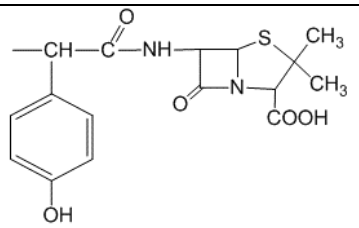
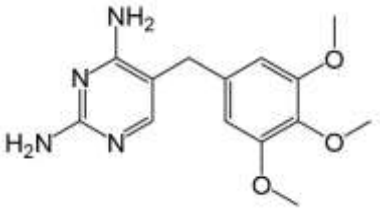
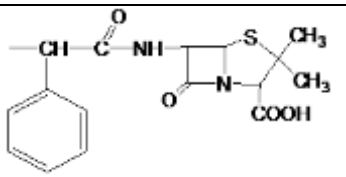
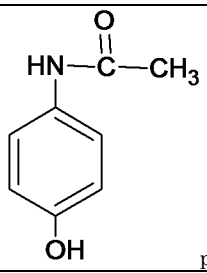
Capsaicin and Dimethyl formamide were supplied from Aldrich and Merck companies respectively. FTIR spectra were recorded by (4000-400cm-1) on a Shimadzu spectrophotometer and ^{1}H-NMR spectra were recorded on a Shimadzu spectrophotometer in Dimethylsulphoxide (DMSO-*d6*).The Melting points were determined on call Enkamp MF B-600 Melting point apparatus.

Synthetic Procedure of Compounds R1-R4

In a 50 ml round bottom flask equipped with condenser provided with magnetic stirring 2 gm of capsaicin was dissolved in 1 ml of DMF and 5ml of acetone added to 1.3gm of succinic anhydride. The mixture was refluxed for 1hr, then cooled .A yellow residue of product was separated, then washed with diethyl ether, derided to afforded compound R1 the melting point was 245^{0}C**.** The product [R1] dissolved in DMF and then added drops of dilute of sulphuric acid to solution, the mixture heating half hour, and the viscous brown

product washed with diethyl ether, dried to yield [R2]. Amoxilline 0.5gm was dissolved in 2 ml acetone and added to the mixture of step 2 [R2], the mixture was refluxed for 1hr then cooled .A yellow residue separated ,then washed with diethyl ether to give [R3] . Similar procedure was used for preparation of compounds [R4-R6] with other antibiotic compounds such as Ampicillin, paracetamol and trimethoprim.

Table 1: Physical properties of prepared polymers (R1-R6)

Pol. No	-Drug	Color	melting point ^{O}C	yield %
R3	 Amoxicillin	Brown	245-253	65
R4		Yellow	243-255	70
R5	 Ampicillin	Reddish Yellow	255-270	66
R6	 paracetamol	Yellow-White	215-220	64

Results and Discussion

This study includes synthesis and polymerization of new derivative compounds of capsaicin, these compounds loading with succinic anhydride as spacer and substituted with different antibiotic. The work including several steps, the first step was including ring opening of succinic anhydride by hydroxyl group of capsaicin to give (trans-8-methyl-*N*-vanillyl-6- none amide) succinate.

Cationic polymerization used in the second step by using dilute sulphuric acid as a cationic initiator with different antibiotic as substitution reaction afforded different drug polymers. The prepared compounds characterized using different techniques [16-20].

FT-IR Spectra of the Prepared Drug Polymers

Table (2) show absorption values of compounds R3-R6, the absorptions at (3230) cm^{-1} due to (NH) stretching vibration, band appeared at (1644) cm^{-1} due to [C=O] stretching vibration, (3466) cm^{-1} due to (-OH) stretching, 1460cm^{-1} due to (C=C) stretching of aromatic ring.

New band appeared at (1745)cm^{-1} due to (C=O) stretching of ester, (-CH_3) absorption appeared at (2854-2960) cm^{-1}, another band appeared at 1379cm^{-1}due to the (C-N) , band at (3055 cm^{-1}) due to the (-CH) aromatic.

Table 2: FTIR data for compounds R3-R6

No.	(O-H) cm^{-1}	(N-H) cm^{-1}	(C-H) cm^{-1} Aro.	(C-H) cm^{-1} Ali.	(C=O) cm^{-1} amide	(C=O) cm^{-1} ester	(C-N) cm^{-1}	(C=C) cm^{-1} Aro.
R3	3466	3230	3008	2854	1644	1745	1379	1460
R4	3460	3350	3070	2856	1639	1737	1369	1531
R5	3444	3238	3051	2856	1670	1736	1372	1544
R6	3421	3230	3007	2854	1677	1737	1359	1562

Proton Nuclear Magnetic Resonance (^{1}H-NMR)

The prepared drug polymers were studied by ^{1}H-NMR spectra using DMSO-d^6 as a solvent with TMS as internal standard. The ^{1}H-NMR spectrum of drug polymer [R3-R6],which indicate the presence of a signal assignments in the corresponding formula, which shows the following peaks: (1.71,S,H, CH_3),(3.25,S,H,CH_2) ,(2.67,S,H,CH_2) ,(2.83,S,NH), (7.61,M,$H_{aromatic}$) (8.05,M,$H_{aromatic}$), (8.19,S,H,OH). The ^{1}H-NMR spectra of prepared polymers (R4-R6) show the following signals:-(1.18,S,H,CH_3), (1.55,S,H,CH_3) (1.61,S,H,CH_2), (1.64,S,CH_2), (1.66,S,H,CH_2), (1.71,S,H,CH_3), (2.75,S,NH), (2.9,d,NH**)**

Antibacterial Activity

Antibacterial activity of some polymer drugs were determined by agar diffusion method at concentration (1mg/mL), DMSO served as control due to this there was no visible change in bacterial growth, different drugs (Allopurinol, Salphamethazol, Amoxilline, procaine, Ciprofloxacin, 4-amino antipyren) were used as a standard antibiotics and the plates were incubated at 37 °C for 24 hours, the inhibition zone measured in (mm). The antibacterial activity of Polymer drugs were evaluated against different bacterial strain**,** *Escherichia coli*, *Pseudomonas aeruginosa* at concentration (1mg/mL). These polymer drugs cause inhibition zones that are determined and listed in Table (3).

Table 3: Antibacterial activity of polymer drugs

Bacteria	Inhibition zone diameter (mm)				
	R3	R4	R5	R6	Positive control gm\ml
E.coli	23	39	26	-	
Pesdomonas aeuroginosa	22	26	27	-	

The Uv- visible Spectra Study of Some Prepared Drug Polymer

The prepared drug polymers are studying by UV-Visible spectroscopy. The maximum absorption of these polymer drugs at (200-355 nm), these absorptions were due to n-π* and π-π* transition as shown in Table 4.

Table 4: UV visible for (R3-R6)

No.of Drug polymer	λ_{max} nm	
	π-π*	n-π*
R3	222	255
R4	225	257
R5	231	310
R6	235	340

Thermal Stability of Polymer Drug

Thermal stability of some selective drug compounds were studied by thermogravtimetric analysis (TGA), including measuring the weight loss as a function of time at constant temperature or as a function of temperature at constant time and heating rate. Several thermal stability parameters were determined from TGA and DSC curves as following:-

- Two type of Decomposition temperature (DT), were determined, the initial and the optimum decomposition temperatures (T_{endo}) ,(T_{exo})respectively .
- From TG curve, we can determine the Weight loss temperature (Ts), at which the sample loss of its total weight.

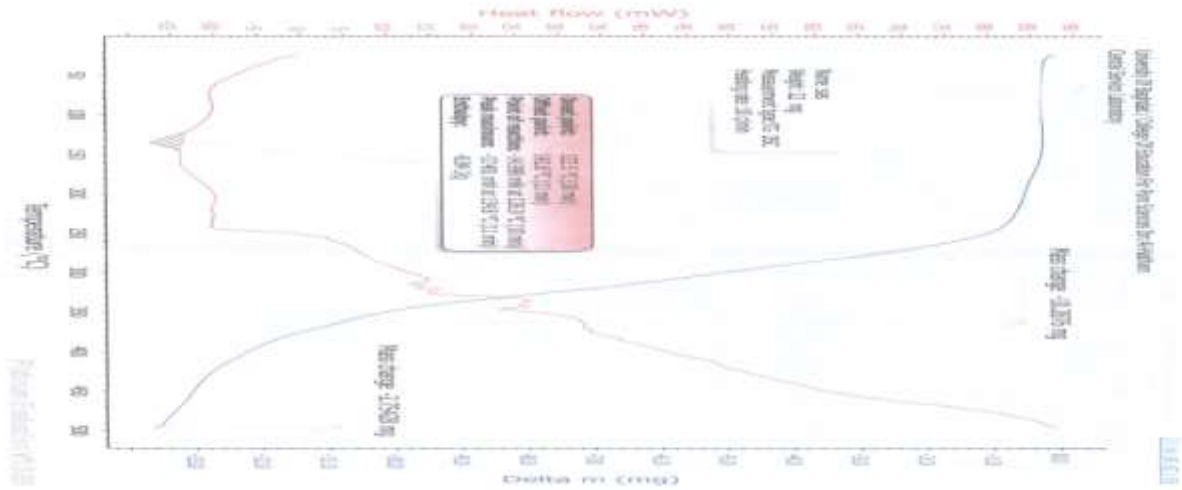
In this study, take 10-20 mg from the prepared polymers and heated at rate of 10 ^{0}C /min. under inert gas (N_2 gas 50ml/min).

Thus the weight-loss vs. temperature thermograms was recorded and analyzed [21-25].

The different parameters for some of the prepared compounds, which were determined, are shown in Table (5) and on the Figures 4 and 5.

Table 5: DSC Analysis of some polymer drugs R3 and R4

No. drug Polymer	Onset Temp. ^{0}C	End set Temp. ^{0}C	Peak Temp. ^{0}C	Heat mj
R3	122.5	142.8	-17.4	-8.84
R4	32.4	114.1	-15.7	-209.14



Figuer 4: DSC spectrum of R3 drug polymer

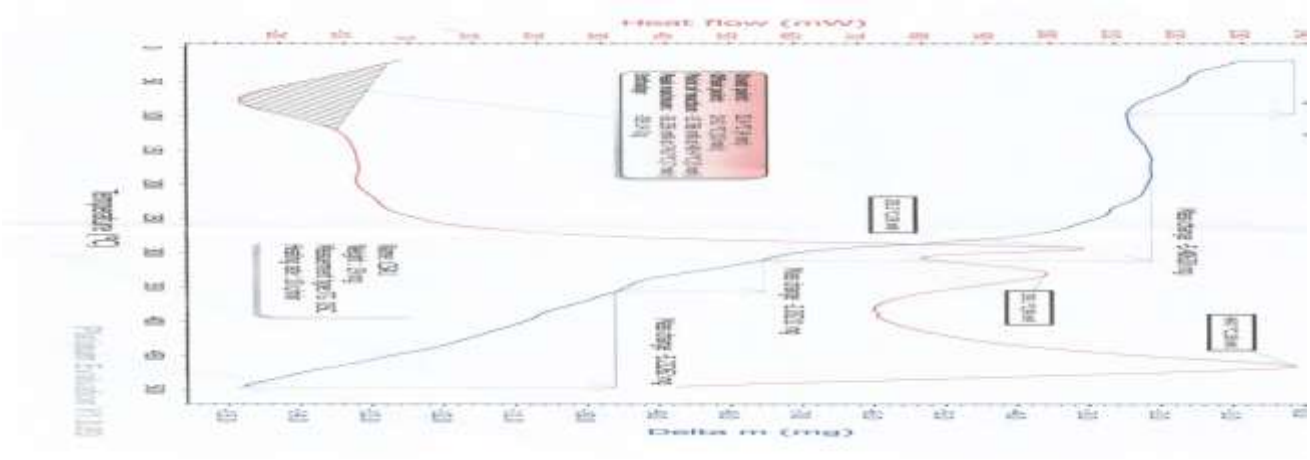


Figure 5: DSC spectrum of R4 drug polymer

Conclusion

A new pro drug Capsaicin polymer was synthesized. The product was modified to the acyl chloride derivative and substitution of amino group of drugs. The synthesized polymers were investigated by FTIR and ^{1}H-NMR techniques the synthesized method of polymer showed good characterized polymers comparing with other known methods. The controlled drug release as drug polymers was studied in DSC and TGA, in addition in basic and acidic medium in different pH values which hydrolyzed due to ester bonds at certain temperature equal to 37℃.

References

1. T Kawada, K Hagihara, K Iwai (1985) "Effects of Capsaicin on Lipid Metabolism in Rats Fed a High Fat Diet," Journal of Nutrition, 116 (7): 1272-1278.
2. YJ Surh, SS Lee (1995) "Capsaicin, a Double Edged Sword: Toxicity, Metabolism, and Chemopreventative Potential (Review)," Life Sciences, 56 (22): 1845-1855.
3. KK Park, KS Chun, JI Yook, YJ Surh (1998) "Lack of Tumor Promoting Activity of Capsaicin, a Principal. Pungent Ingredient of Red Peppers, in Mouse Skin Carcinoens," Anticancer Research, 18 (6A): 4201-4205.
4. YJ Surh, E Lee, JM Lee (1998) "Chemopreventive. Properties of Some Pungent

Ingredients Present in Red Pepper and Ginger," Mutation Research, 402 (1): 259-267.

5. MH Ward, L Lopez-Carrillo (1999) "Dietary Factors and. the Risk of Gastric Cancer in Mexico City," America Journal of Epidemiology, 149 (10): 925-932n.
6. T Watanabe, T Kawada, M Yamamoto, K Iwai (1987) Capsaicin, a Pungent Principle of Hot Red Pepper, Research Communications, 142 (1): 259-264
7. E Lewinson, E Berman, Y Mazur, J Gressel (1986) "Glucosylation of Exogenous Flavanones by Grapefruit (Citrus paradisi) Cell Cultures," Phytochemistry, 25: 2531-2535.
8. M Tabata, Y Umetani, M Ooya, S Tanaka (1988) "Glucosylation of Phenolic Compounds by Plant Cell Cultures," Phytochemistry, 27(3): 809-.813.
9. B Upmeier, JE Thomzik, W Barz (1988) "Nicotinic Acid N-Glucoside in Heterotrophic Parsley Cell Suspension Cultures," Phytochemistry, 27 (11): 3489-3493.
10. T Furuya, M Ushiyama, Y Ashida, T Yoshikawa (1989) "Biotransformation of 2-Phenylpropionic Acid in Root Culture of Panax ginseng," Phytochemistry, 28 (2): 483-487.
11. M Ushiyama, T Asada, T Yoshikawa, T Furuya (1989) "Biotransformation of Aromatic Carboxylic Acids by Root Culture of Panax ginseng," Phytochemistry, 28 (11): 1859-1869.
12. T Suga, T Hirata (1990) "Biotransformation of Exogenous Substrates by Plant Cell Cultures," Phytochemistry, 29 (8): 2393-2406.
13. K Ishihara, H Hamada, T Hirata, N Nakajima (2003) "Biotransformation Using Plant Cultured Cells," Journal of Molecular Catalysis B: Enzymatic, 23 (2-6): 145-170.
14. K Morohoshi, F Shiraishi, Y Oshima, T Koda, N Nakajima, JS Edmonds, M Morita (2003) "Synthesis and Es Trogenic Activity of Bisphenol a Mono- and Di-Beta-D Glucopyranosides, Plant Metabolites of Bisphenol A, "Environmental Toxicology and Chemistry, 22 (10): 2275-2279.
15. S Kwon, K Shimoda, H Hamada, K Ishihara, N Masuoka, H Hamada (2008) "High Production of ß-Thujaplicin Glycosides by Immobilized Plant Cells of Nicotianatabacum," Acta Biologica. Hungarica, 59 (3): 347-355.
16. H Katsuragi, K Shimoda, A Ohiro, H Hamada (2010) "Glycosylation of Capsaicinoids with Panax ginseng Stimulated by Salicylic Acid," Acta Biologica Hungarica, 61 (4): 449-456.
17. K Shimoda, H Hamada (2010) "Synthesis of ß-Maltooligosaccharides of Glycitein and Daidzein and Their Anti-Oxidant and Anti-Allergic Activities," Molecules, 15 (8): 5153-5161.
18. K Shimoda, H Hamada (2010) "Production of Hesperetin Glycosides by Xanthomonascampestris and Cyclodextrin Glucanotransferase and Their Anti-Allergic Activities," Nutrients, 2 (2): 171-180.
19. K Shimoda, H Hamada (2010) "Enzymatic Synthesis and Anti-Allergic Activities of Curcumin Oligosaccharides," Biochemistry Insights, 2010 (3): 1-5.
20. Hoffman A (2008) The origins and evolution of "controlled" drug delivery systems. J Control Release 132:153-163.
21. Reed AM, Gilding DK (1981) Biodegradable polymers for use in surgery – polyglycolic/poly (lactic acid) homo and copolymers:2 In vitro degradation. Polymer 22:494-498(1982).
22. Alonso M.J (1996) Drug and the pharmaceutical sciences V0l.77, Microparticulate systems for the delivery of proteins and vaccines, Marcel Dekker Inc., USA, 203-242.
23. Drobnik J, Saudek V, Vlasak J, Kalal J (1979) Polyspartamide a potential drug carrier, Journal of Polymer Science: Polymer Symposia, 66 (1): 65-74.
24. Puisieux F, Barratt G, Couarraze G, Couvreur P, Devissaguet JP, Dubernet C, Fattal E, Fessi H, Vauthier C (1994) Polymeric Biomaterials, Marcel Dekker Inc., 749-794.
25. Zentner GM, Rathi R, Shih C, McRea JC, Seo MH, Oh H, Rhee BG, Mestecky J, Moldoveanu Z, Morgan M, Weitman S (2001) Biodegradable block copolymers for delivery of proteins andwater-insoluble drugs. J. Control Release 72: 203-215.

