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Synthesis of some network polymers with siloxane units as a drug delivery system

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Abstract

New biodegradable network polymers containing siloxane-linked polymeric prodrugs of 5-ammino-2-hydroxybenzoic acid (5-ASA) in the main chain were prepared by terpolymerization of methacrylic acid; (MA), 2-hydroxyethylmethacrylate (HEMA), and bis (trimethylsilyloxy) methylsilane (VBM) in the presence of some new cross-linking agents. The monomers and polymers were characterized by FT-IR and ^{1}H-NMR spectroscopy, and studied by DSC analysis. The hydrolysis of them was carried out in cellophane membrane dialysis bags containing aqueous buffer solution at 37ºC. Detection of the hydrolysis product by UV spectroscopy showed that attaching of siloxane units in these hydrogels modified this drug delivery system.

Keywords: Cross-linking; siloxane; methac rylate; vinylsilane; drug loading.

Introduction

It is essential that device makers looking for delivery materials understand the chemical and structural properties of silicones. The chemistry of silicone and silicone materials and their interactive characteristics indicate the suitability of these materials for drug-delivery devices [1,2]. These materials are already used extensively in the healthcare industry and in existing drug-delivery applications. Evaluating these factors shows the versatility of silicone and how this versatility can benefit drug delivery. The interactions between drugs, release-enhancing agents, and silicone systems are all important factors when considering

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silicone materials. Medical device industry manufacturers and their suppliers are in a unique position to leverage their expertise to provide delivery technologies. From system design to the materials used to build those systems, the medical device industry has already addressed many of the challenges the pharmaceutical industry faces as it develops drug-delivery systems.

Silicones, for example, are widely used in the medical device industry. These materials have a long history in medical devices and offer drug-delivery product engineers versatility and biocompatibility. A silicone system can also be tailored to fit a specific application. Already, manufacturers of drug-delivery devices are incorporating silicones in products that require a matrix, whereby the device is then capable of elution or ion release of an active additive or component. This article discusses the chemical properties of silicone and organosilicon systems, which are the key to silicone's flexibility and use in drug-delivery systems.

Silicones expanded into healthcare and medical applications in the 1950s after extensive use in the aerospace industry in the previous decade. Within 20 years, a considerable body of work established that silicone oils and cross-linked siloxane systems did not give rise to harmful consequences when performing subcutaneous, intracutaneous, and intramuscular administrations. In 1954, J. D. B. McDougall reported the cultures of various tissues of warm-blooded animals known to be extraordinarily sensitive to foreign influences showed no deviation from the usual growth pattern on contact with liquid, semisolid, and rubberlike silicone products [3]. Silicones have been characterized as biologically and toxicologically inert [4].

Many applications, such as pacemaker leads, hydrocephalus shunts, heart valves, finger joints, and intraocular lenses, use silicone materials.

Commercial applications such as Norplant (Wyeth Pharmaceuticals; Madison, NJ) and Femring (Warner Chilcott; Rockaway, NJ) are examples of clinically successful drug-delivery applications that involve silicone materials. The patent cites a number of agents that could be used in drug-eluting applications. The drugs cited include antidepressants, anxiolytics, vitamins B6, D, and E; antifungals, opioid analgesics, nonopioid analgesics, and antiviral compounds [5, 6].

Experimental Section

Synthesis of monomers and copolymers were carried out under argon to exclude oxygen and moisture from the reaction system. All solvents were dried by standard methods.

Materials

The solvents and reagents were purchased from Merck and Fluka Co. THF was dried by a standard method and 5-amino-2-hydroxybenzoic acid (MZ), Et_3SiCl and $Me_2(CH_2{=}CH)SiCl$ used as received.

2-Propenoic acid, 2-methyl-, 2-hydroxyethyl ester (HEMA), and methacrylic acid (MA) were distilled under reduced pressure. Initiator 2, 2'-azobisisobutyronitrile (AIBN), and allylmethacrylate (CA_3) was purified by recrystallization from methanol.

Measurements

^{1}H-NMR spectra were recorded on a Bruker 400 AC spectrometer in $CDCl_3$.The IR spectra were recorded on a Shimadzu FT-IR-408 spectrophotometer. The DSC curves were obtained on a TGA/SDTA 851 calorimeter at heating and cooling rates of 10ºC/min in the air.

Monomer synthesis

1-1- Synthesis of triethylsiloxyethylmethacrylate (TES-EMA)

A mixture of 3 g (0.02 mol) HEMA and 3.5 g (0.03 mol) triethylamin in 50 mL dried THF was treated in a drop wise manner with a solution of 6g (0.04 mol) triethylchlorosilane in 10 mL of THF under argon, at room temperature. After (6 h) stirring at room temperature the reaction mixture was filtered. The THF was removed under reduced pressure to produce a nearly colorless oily residue. The solution of residue in n-hexane and ethyl acetate with ratio of 7:1 was chromatographed over silica gel to yield (60%) of TES-EMA.

IR (neat, cm^{-1}) :2940, 1722, 1640, 1257, 840.

^{1}H-NMR (CDCl3, *ppm*): 0.06 (q, 6H, -CH2), 0.9 (t, 9H, -CH3), 1.9 (s, 3H, -CH3), 3.82 (t, 2H, -OCH2), 4.2 (t, 2H, -COOCH2), 5.53 (s, 1H, CH2=), 6.1 (s, 1H, CH2=).

1-2-Synthesis of dimethylvinylsilyloxyethylmethacrylate (CA_1)

A mixture of 3 g (0.02 mol) HEMA and 3.5 g (0.03 mol) triethylamin in 50 mL dried THF was treated in a drop wise manner with a solution of 4.8g (0.04 mol) dimethylvinyl chlorosilane in 10 mL of THF under argon, at 0 ºC temperature. After (8 h) stirring at room temperature the reaction mixture was filtered. The THF was removed under reduced pressure to produce a nearly colorless oily residue. The solution of residue chromatographed by CH_2Cl_2 over silica gel to yield (50%) of CA_1 [7].

IR (neat): ν =2930, 1739, 1407, 1253,830.

1H-NMR ($CDCl_3$): δ= 0.18 (s, 6H, $SiCH_3$), 1.92 (s, 1H, CH_2=), 3.8 (t, 2H, CH_2O), 4.20 (t, 2H, CH2COO), 5.55 (m, 1H, SiCH=), 5.71 (d, 1H, CH_2=), 6.05 (d, 1H, CH_2=), 6.10 (d, 2H, CH_2) ppm.

1-3-Synthesis of 1, 2 bis (vinylphenyl) ethane (CA_2)

6.10g (40 mmol) 4-chloromethylstyrene dissolved in 30 mL THF was added to 1.07g (44 mmol) magnesium turning under argon gas at 37°C for 2h to produce Grignard reagent. Then 6.01g (40 mmol) 4-chloromethylstyrene dissolved in 15 mL THF was added drop wise to Grignard solution and stirred at the same temperature for 2 h. The precipitated was filtered, the THF was removed under reduced pressure, and the residue was choromatographed over silica gel by n-Hexane to yield 1, 2-bis (vinyl phenyl) ethane (BVPE) [8], Scheme 3.

IR (neat, cm-1): 3083, 2920, 1629, 1509, 1348, 912, 829.

^{1}H-NMR (CDCl3, ppm): δ= 2.96 (s, 2H,-CH_2), 5.25-5.28 (d, 1H, =CH_2), 5.75-5.80 (d, 1H, =CH2), 6.72-6.79 (q, 1H, CH=), 7.18 (d, 2H, C-H Ar), 7.38 (d, 2H, C-H Ar).

Table1. The molar composition of monomers, cross-linking agent, and Tg of polymer

Hydrogel	TES-EMA : MA : VBM : % CA_1	Tg (˚C)
H_1	1 : 1 : 0 : % 5	56
H_2	1 : 1 : 1 : % 5	49
H_3	1 : 1 : 2 : % 5	48
H_4	1 : 1 : 3 : % 5	47

Hydrogel Synthesis

2-1-Polymerization of (TES-EMA), (MA), vinyl bis (trimethylsilyloxy) methylsilane (VBM), and CA_1 as a cross-linking agent (H_1-H_4)

In a Pyrex glass ampoule a mixture of TES-EMA (0.58 g, 2 mmol) and MA (0.24 g, 2 mmol), with specific mol percent of CA_1 (5%) and VBM with various ratio (Table 1) using AIBN as initiator. ([I] = 0.01 M), were frozen and degassed under vacuum. The

freezing and degassing procedure were repeated three times, and the ampoules were sealed. The solution was polymerized at 60°C for 48 h. Then the viscous solution was poured from the ampoule in to cold methanol, the precipitate was collected and washed several times with methanol, dried under vacuum at room temperature to give product (Table 1).

2.2. Polymerization of (TES-EMA), (MA), vinyl bis (trimethylsilyloxy) methylsilane (VBM), and CA_2 as a cross-linking agent (H_5-H_8)

In a Pyrex glass ampoule a mixture of TES-EMA (0.58 g, 2 mmol) and MA (0.24 g, 2 mmol), with specific mol percent of CA_2 (5%) and VBM with various ratio (Table 2) using AIBN as initiator. ([I] = 0.01 M), were frozen and degassed under vacuum. The freezing and degassing procedure were repeated for three times, and the ampoules were sealed. The solution was polymerized at 60°C for 48 h. Then the viscous solution was poured from the ampule into cold methanol, the precipitate was collected, and washed several times with methanol, dried under vacuum at room temperature to give the product (Table 2).

Table 2. The molar composition of monomers, cross-linking agent, and Tg of polymer

Hydrogel	**TES-EMA : MA : VBM : % CA_2**	**Tg (˚C)**
H_5	1 : 1 : 0 : % 5	76
H_6	1 : 1 : 1 : % 5	69
H_7	1 : 1 : 2 : % 5	57
H_8	1 : 1 : 3 : % 5	44

Table 3. The molar composition of monomers, cross-linking agent, and Tg of polymer

Hydrogel	TES-EMA : MA : VBM : % CA_3	Tg (˚C)
H_9	1 : 1 : 0 : % 5	87
H_{10}	1 : 1 : 1 : % 5	56
H_{11}	1 : 1 : 2 : % 5	55
H_{12}	1 : 1 : 3 : % 5	44

2-3-Polymerization of (TES-EMA), (MA), vinyl bis (trimethylsilyloxy) methylsilane (VBM), and allylmethacrylate (CA_3) as a cross-linking agent (H_9-H_{12})

In a Pyrex glass ampoule a mixture of TESiEMA (0.58 g, 2 mmol) and MA (0.24 g, 2 mmol), with specific mol percent of allylmethacrylate (CA_3) (5%) and VBM with various ratio (Table 3) using AIBN as initiator. ([I] = 0.01 M), were frozen and degassed under vacuum. The freezing and degassing procedure were repeated three times, and the ampoules were sealed. The solution was polymerized at 60° C for 48 h. Then the viscous solution was poured from the ampule into cold methanol, the precipitate was collected and washed several times with methanol, dried under vacuum at room temperature to give the product (Table. 3).

2-4-Synthesis monomer of para-Dimethylvinylsiloxy-Benzoic acid

To a mixture of 2.76 g (0.02mol) para-Hydroxy-Benzoic acid, 50 mL THF, 2 g (0.025mol) pyridine as a base, 4.8 g (0.04mol) Dimethyl chlorovinylsilane was poured. The mixture was mixed for 10 h in 0° C. The reaction was monitored by T.L.C. Then the precipitated was washed by Hexane for several times. The solution was filtered to obtain product (30%).

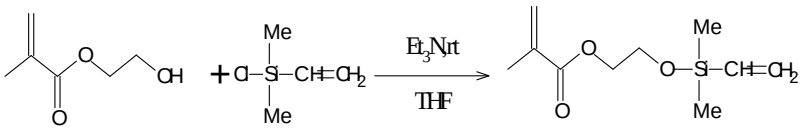
2-5-Synthesis poly para-Dimethylvinylsiloxy-Benzoic acid

In a Pyrex glass ampoule a mixture of para-Dimethylvinylsiloxy-Benzoic acid 0.22g (0.1 mmol), AIBN as initiator. ([I] = 0.01 M), were frozen and degassed under vacuum. The freezing and degassing procedure were repeated three times, and the ampoule was sealed, and polymerized at 60° C for 48 h. Then the viscous solution was poured from the ampule into cold methanol, the

precipitate was collected and washed several times with methanol, dried under vacuum at room temperature to give the product.

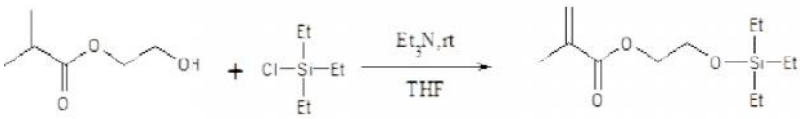
Results and discussion

For preparing of network polymers, first monomers were synthesized. Dimethylvinylsilyloxyethylmethacrylate (DVS-EMA) (CA_1) was synthesized from the reaction of HEMA with dimethylvinyl chlorosilane in the presence of triethylamine at room temperature (Scheme 1). This compound is a cross-linking agent that have silyl group in the chain.



Scheme 1. Reaction of HEMAwith chlorodimethylvinylsilane

In a similar way triethylsiloxyethylmethacrylate (TES-EMA) was synthesized (Scheme 2).



Scheme 2. Reaction of HEMA with chlorotriethylsilane

Cross-linking of 1, 2 bis (vinyl phenyl) ethane (BVPE) (CA_2) was synthesized from the coupling of chloromethyl styrene with its Grignard reagent (Scheme 3). All of monomers and cross-linking agent were characterized by instrument methods, such as FT-IR, and NMR. A typical NMR spectrum was showed in Figures 1 and 2.

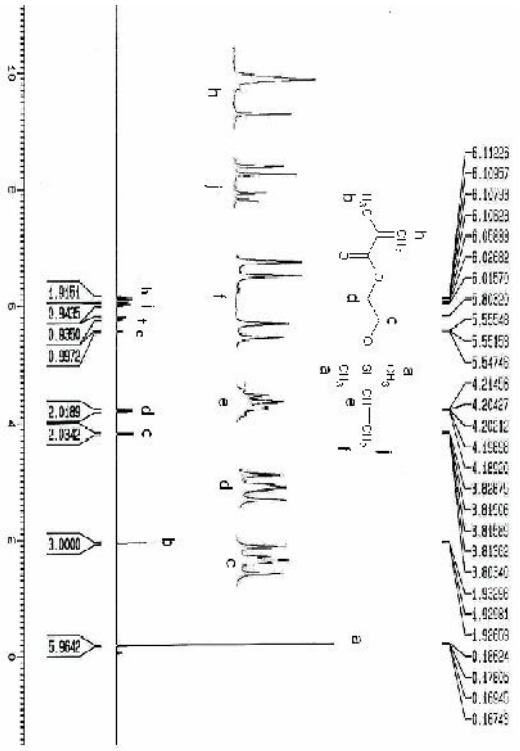


Figure 1. FT-^{1}H-NMR of dimethylvinylsilyloxyethylmethacrylate (CA_1)

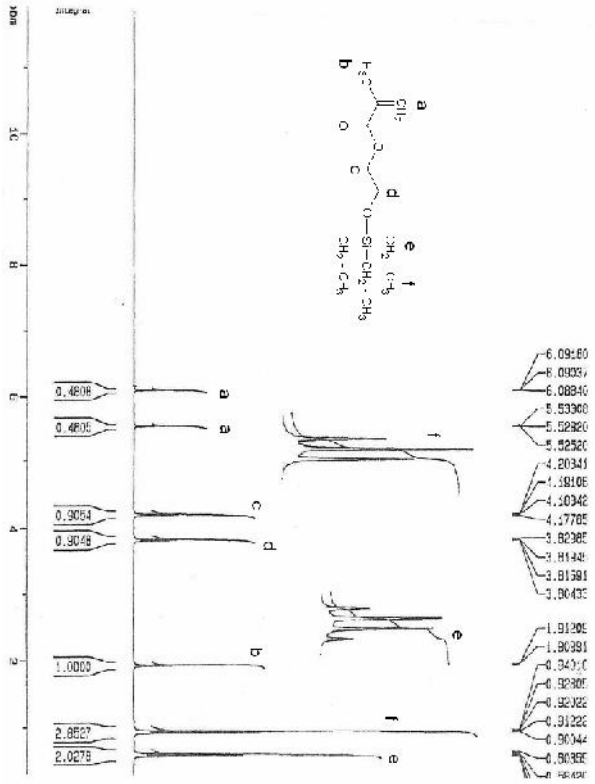
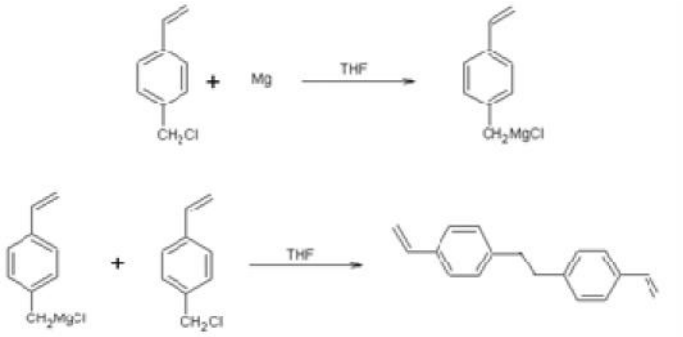


Figure 2. FT-1H-NMR of TES-EMA

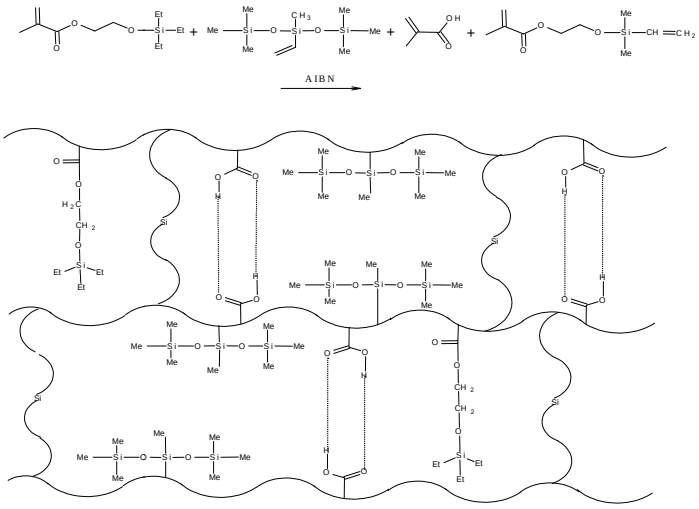
Differential scanning calorimetry (DSC) for the network polymers was evaluated. We determined the glass-transition temperature (Tg) for all modified polymers by DSC analyses. The DSC analysis indicated that with incorporation of siloxane groups in the chains of polymer, the glass transition temperature of copolymer decreases. It would increase the flexibility of the chains and the ability of the chains to undergo segmental motion [9, 10].



Scheme 3. The coupling reaction for preparing of BVPE (CA_2)

Hydrogel Synthesis

Hydrogels were synthesized from the reaction of TES-EMA, MA, and VBM as monomers and CA1, CA2 as cross-linking agents. In these hydrogels mol compositions of siloxane monomer are 1 to 4. Incorporation of siloxane in polymers causes some interesting modifications for example; it increases lipophilic properties of some drug that have hydrophilic moiety (Scheme 4). Therefore, these drugs can be released simply from lipid barrier and this property cause to increase the activity of them.



Scheme 4. Preparation of cross-linked copolymer containing siloxyl groups

Drug loading in hydrogels

70 mg of hydrogels (H_1… H_{12}) was placed in 10 mLof 5-ammino-2-hydroxybenzoic acid (5-ASA) to suck up the total amount of the drug solution. After approximately 60 min, the completely swollen hydrogels loaded with 5-ASA were placed in desiccators and dried under vacuum at room temperature.

In vitro release studies

The copolymers (10mg) were poured into 3mL of aqueous buffer solution (SGF: pH 1 or SIF: pH 7.4).The mixture was introduced into a cellophane membrane dialysis bag. The bags were closed and transferred to a flask containing 20 mL of the same solution maintained at 37°C. The external solution was continuously stirred, and 3mL samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. The sample of hydrolyzed was analyzed by UV spectrophotometer [11].

All of the samples (H_1-H_{12}) were hydrolyzed in above condition. Released curves (Figure 1) showed that it is good selectivity for releasing of this drug in pH=7.4 in which the release in this pH is maximum and in pH=1 is minimum. Also, it is good released percentage in pH=7 where molar composition of siloxane in network polymers increases. These data show that attaching of siloxane in these hydrogels modified drug delivery system. Therefore, it can be a candidate for colonic delivery system. The drug-release profiles indicated that the amount of drug released depended on the molar composition of siloxane in hydrogels. Colonic drugs delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon, but also for its potential for the delivery of proteins and therapeutic peptides [12].

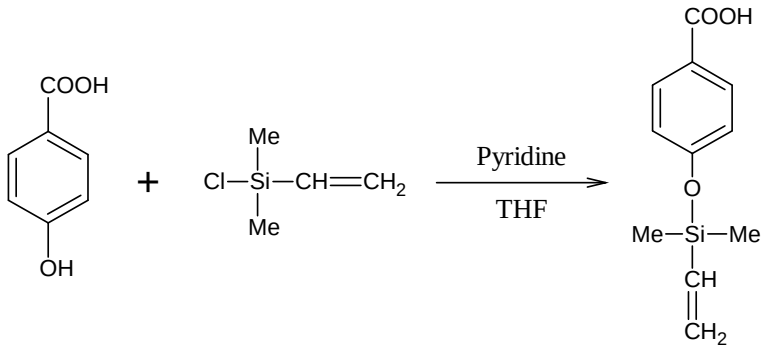
Identification of network polymers

In the FT-IR spectra of network polymers, absorption of C-Si bond appeared in the region of 1258-1270 and 837-900 cm-1 that is referred to stretching, and bending vibration respectively, absorption at 1730 cm-1 is referred to stretching of carbonyl bond. Also absorption in range of 3400-3500 cm-1 is referring to OH stretching vibration of methacrylic acid. In this way we characterized presence of silyl groups, HEMA, and methacrylic acid in cross-linked copolymers Therefore, one of the important properties of these hydrogen is the amount of drug release not only depends on its degree of swelling and cross-linking, but also mol composition of siloxcane units [13, 14].

Monomer of benzoic acid

This monomer was synthesized by reaction of para-hydroxy benzoic acid with

dimethylchlorovinylsilane in the presence of pyridine as a base (Scheme 5). In most hydrogels that used in drug delivery systems one of the important polymer is HEMA. Because it is biodegredeble, and pH sensitive. One of the important factors that cause this new polymer pH sensitive is refer to COOH group. In this monomer that we synthesized presence of COOH, and silyl group also can be convert this monomer to a drug delivery system similar to HEMA. Therefore poly para-Dimethylvinylsiloxy-Benzoic acid can be used as an alternative to HEMA in drug delivery system.



Scheme 5. Preparation of para-Dimethylvinylsiloxy-Benzoic acid

Conclusion

Monomer of vinyl dimethylsilyl HEMA was synthesized. Then with various cross-linking agents such as: dimethylvinylsilyloxyethylmethacrylate (CA_1), 1, 2 bis (vinylphenyl) ethane (CA_2), allylmethacrylate (CA_3) network polymer were synthesized. Incorporation of silyloxy in HEMA as a drug delivery system modified it. Released curves for drug showed that it has good selectivity for releasing of this drug in pH=7.4. Also, it has good released percentage in pH=7 where molar composition of siloxane in network polymers increases. Also, we synthesized monomer of dimethylvinyl silyloxy of para-benzoic acid. This monomer and its polymer can be candidated for drug delivery system instead of HEMA.

Acknowledgement

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References

[1] M. G. Assadi and N. Golipour, Designed Monomers and Polymers, **2007**, 1–11

[2] M. Mahkam, M.G. Assadi, and R. Mohammadzadeh, *Macromolecular Research*, **2006**, *14*, 1, 34-37 (2006).

[3] K. Malcolm, "Influence of Silicone Elastomer Solubility and Diffusivity on the In Vitro Release of Drugs from Intravaginal Rings," *Journal of Controlled Release*, **2003**, *90*, *2*, 217–225.

[4] M. Ghannam, K. Tojo, and Y. Chien, Kinetics and Thermodynamics of Drug Permeation through Silicone Elastomers (I) Effect of Penetrant Hydrophilicity (New York: Marcel Dekker., **1986**, 303–325.

[5] S Nabahi. *Intravaginal drug-delivery device. U.S. Patent.*, **1998**, *6,039,968*, 22, and 2000, *issued July 9*.

[6] C. Passmore et al. *Intravaginal drug-delivery devices for the administration of testosterone and testosterone precursors.* , **2000**, *6,416,780*, filed May 1.

[7] Suh YW, Kung MC, Wang YM. *JACS.* **2006**, *128*, *9*, 2776-2777.

[8] M. Cazacu, C.Racles, A. Airinei, *Degaradable polymers. Siloxanes in hydrolitically degradable polymeric* structures Material Plastice., **2005**, *42*, *1*, 12-16.

[9] S.Brahim, D.Narinesingh, A. Guiseppi-Elie, *BIOMACROMOLECULES*. 2003, *4*, *5* 1224-1231.

[10] M. Kajihara, T. Sugie, A. Sano, K. Fujioka, Y. Urabe, M. Tanihara and Y. Imanishi, *Chemical and Pharma Bulletin*., **2003**, *51*, 11-14.

[11] K. Malcolm et al, *Journal of Controlled Release*, **2003**, *90*, *2*, 217–225.

[12] L. Ren, A. Osaka, B. Yu, *Bioactive gelatin-siloxane hybrids as tissue engineering scaffold. Science and Technology of Hybrid Materials Book Series: Soild State Phenomena.* **2006**, *111*, 13-18.

[13] Passmore and Clare and Gilligan and Clare, *U.S. Pat*., **2002**, *6,416*,780.

[14] S.M. Xing, Y.L. Wang, *Synthetic Techniques of Organic Silicon and Application of Its Products, Chemical Industry Press*, **2001**, 382.