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Development of Acid Sensitive Micelles for Drug Delivery Applications

Ibrahim Youssef[a,b,1], Omer Aydin[a,1], Yasemin Y. Durmaz[a], Gopinath Tiruchinapally[a], I.M.El-Sherbiny[b], AA Fadda[b], Elsayed M Afsah[b] and Mohamed E. H. ElSayed [a,c]*

[a] *University of Michigan, College of Engineering, Department of Biomedical Engineering, Ann Arbor, MI, 48109, USA.*

[b] *Mansoura University, Faculty of Science, Department of Chemistry, Mansoura ET-35516, Egypt.*

[c] *University of Michigan, Macromolecular Science and Engineering Program, Ann Arbor, MI, 48109, USA.*

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Abstract The efficient intracellular anti-cancer drug delivery and control the drug release in tumor tissue but not release healthy tissue as well as during circulation are a vital challenge in advanced prostate cancer treatment. In this study, polymethyl methacrylate-*block*-polyacrylate acid-*block*-polyethylene glycol (PMMA-*b*-PAA-*b*-PEG) triblock polymer were prepared via ATRP polymerizations and 'click' reaction and subsequently self-assembled in aqueous environment into micelles encapsulating anti-cancer drug to be used as a drug carrier. Furthermore, to increase the stability of micelles in aqueous environments, we introduced ketal linkage as a cross-linker that was able to react with COOH functional groups of the PAA block of the copolymer forming acid-labile linkages.

[1] *Equally contributed first Author*

* Corresponding Author: Ahmed Ali Fadda, Ph.D.
E-mail: afadda50@yahoo.com

1. Introduction

Synthesis of shell cross-linking micelles (SCLMs) with a pH sensitive acetal linker to achieve a powerful, biocompatible that can resist the adsorption of serum proteins, and unique nano vehicle that can selectively release hydrophobic drugs in response to endosomal pH. In recent years, substantial studies on pH-sensitive cross-linked nanoparticles was described and focused on the feasibility of shell cross-linked micelle, another example for acid-labile core cross-linked micelle was reported for a pH-triggered release of antitumor drugs*(Li, Du et al.* 2008; Yu, Chang *et al.* 2008). Most of systems were based on nondegradable polymer with limited biocompatibility reported (Ding and Liu 1998; Shanmugananda Murthy, Ma *et al.* 2001; Shuai, Merdan *et al.* 2004; O'Reilly, Hawker *et al.* 2006; Read and Armes 2007; Rijcken, Snel *et al.* 2007; Zhang, Liu *et al.* 2008).

To address this need, we designed and synthesized the amphiphilic [polyethylene glycol-b-polyacrylic acid-b-polymethyl methacrylate] (PEG-*b*-PAA-*b*-PMMA)

triblock copolymer, which encapsulates the drug in the core forming a micelles with an average diameter 43-54 nm.

The hydrophilic Polyethylene glycol (PEG), is one of the most commonly investigated biocompatible polymer because of its high flexibility, high water solubility, low protein adsorption and low cell adhesion to enhance EPR effect (Sinha, Aggarwal *et al.* 2004; Rijcken, Soga *et al.* 2007; Gyenes, Torma *et al.* 2008; Yu, Chang *et al.* 2008). Moreover, the free end of the PEG block can be used to conjugate different types of targeting ligands which will allow the presentation of tunable number of targeting ligands on the surface of the "Smart" micelles to mediate selective binding to cancer cells(Medina, Tiruchinapally *et al.* 2013). The PAA middle shell with carboxylic acid function groups are used for covalent cross-linkage of the polymer chains to form a flexible shell with amine bearing cross-linker [**2,2'-(Propane-2,2-diylbis(oxy))-diethanamine**]. The cross-links not only enhance the micellar stability against the destabilizing condition but also for the protection from extracellular release in physiologic environment (pH 7.4). Within endocytosis, the cleavage of the Acetal cross linker is promoted by an acidic endosomal pH to trigger intracellular drug release. Finally, the PMMA block is designed to facilitate the encapsulation of drug in the micelles' core.

2. Experimental Section

2.1. Materials

Poly (ethylene glycol) monomethylether (**PEG**, Mn: 5000, Sigma-Aldrich), Copper (I) bromide (**CuBr**, Sigma-Aldrich), Tetrahydrofuran anhydrous (**THF**, Sigma-Aldrich), N, N'-Dicyclohexylcarbodiimide (**DCC**, Sigma-Aldrich), N-(2-hydroxyethyl)-phthalimide (Sigma-Aldrich), 2-methoxy propene (Sigma-Aldrich), Benzene (anhydrous, Sigma-Aldrich), 2-propanol (anhydrous, Sigma-Aldrich), P-toluene sulfonic acid (Sigma-Aldrich),Dimethylaminopyridine (**DMAP**, Acros), 4-pentynoic acid (Sigma-Aldrich), Methyl methacrylate (**MMA**), Tert-butyl acrylate (***t*-BA**) , and N, N, N', N'', N''-pentamethyldiethylenetriamine (**PMDETA**) where purchased from Sigma-Aldrich and purified by passing through a basic alumina column to remove the inhibitor,2-bromoisobutyryl bromide (Fluka), N-hydroxy succinimide (**NHS**, Fluka), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (**EDC**, Fluka), Sodium azide (NaN_3, Acros), Trifluoroacetic acid (**TFA**, Acros).

2.2. Synthesis of amphiphilic PMMA-b-PAA-b-PEG polymer

We synthesis our amphiphilic block copolymer via Atom Transfer Radical Polymerizations (**ATRP**) (Matyjaszewski and Xia 2001; He, Li et al. 2004); starting with preparation of poly methyl methacrylate (**PMMA**). We used PMMA as a macro-initiator for the synthesis of the second block poly *t*-butyl acrylate (**P*t*BA**). We functionalize the block copolymer (**PMMA-*b*-P*t*BA-Br**) to azide functional end group to be coupled via click reaction with the last block, which is functionalized poly ethylene glycol (**PEG**) alkyne terminal group (**PMMA-*b*-P*t*BA-b-PEG**). After coupling the polymer, we hydrolysis the second block to be used in forming shell cross-linking micelles (**PMMA-*b*-PAA-*b*-PEG**).

2.2.1. Alkyne functionalization of hydrophilic poly(ethylene glycol) block (1)

Poly (ethylene glycol) monomethylether (**PEG**, Mn: 5000, Sigma-Aldrich) with hydroxyl functional end group (5 g, 10^{-3} mol), 4-pentynoic acid (147 mg, 1.5 x 10^{-3} mol), N, N'-Dicyclohexylcarbodiimide (**DCC**, Sigma-Aldrich) (206 mg, 10^{-3} mol), Dimethylaminopyridine (**DMAP**, Acros) (122 mg, 10^{-3} mol) and 25 mL dichloromethane (**DCM**) introduced in a round bottom flask (Yuksel Durmaz, Vlaisavljevich et al. 2014). The reaction mixture placed at room temperature, and stirred overnight. The mixture was filtered and precipitated in diethyl ether (Yield: 3.86 g) with a functionalization efficiency of 94%. ^{1}H NMR of PEG-alkyne (CDCl3) (500 MHz Varian

Mercury system (Palo Alto, CA) δ : 4.3 (t, 2H, CO-OC*H2*), 3.7 (t, 2H CO-O-CH2-C*H2*-O), 3.7 (bs, 450H, OC*H2CH2*), 3.4 (s, 3H, O-C*H3*), 2.6 (2H, CH2C*H2*-CO-O), 2.5 (2H, CH2C*H2*-CO-O), 2.0 (1H, alkyne proton).

2.2.2. Synthesis of hydrophobic poly(methyl methacrylate) block (2)

The hydrophobic PMMA block was synthesized by ATRP following published protocols (Durmaz, Dag *et al.* 2006). The prepared block copolymers were characterized by Gel permeation chromatography (GPC) measurements were obtained from a Viscotek GPCmax Autosampler system consisting of a pump and Water 2414 refractive index (RI) detector. The molecular weight and molecular weight distribution of final polymers were determined based on their elution volume on an Styragel HR 4E column compared to a series of poly(methyl methacrylate) standards (PolyAnalitik Inc, Canada) using THF as a mobile phase at a flow rate of 1 mL/min at 35 °C. Data were analyzed using Viscotek OmniSEC Omni-01 software. The molecular weight based on GPC ($M_{n,GPC}$: 4855 g/mol), molecular weight distribution (M_w/M_n) or the polydispersity index(**PDI**): 1.27 and the molecular weight based on ^{1}H NMR ($M_{n,NMR}$: 4400 g/mol). ^{1}H NMR ($CDCl_3$) (500 MHz Varian Mercury system (Palo Alto, CA) δ: 4.2 (q, 2H, CH_3-CH_2), 3.6 (s, 3H, CH_3-O), 2.0 (s, 2H, CH_2), 1.9 (s, 6H, 2 CH_3), 1.2 (m, 3H, CH_3-CH_2).

2.3. Synthesis of Poly(methyl methacrylate-b- t-butyl acrylate) azide (PMMA-b-PtBA-N_3) (4)

The PMMA block used as a macro initiator and this extension was done to add the poly tert-butyl acrylate (**P*t*BA**) block using ATRP. Briefly, PMMA (2.22 g, 0.5 x 10^{-3} mol), CuBr (72 mg, 0.5x 10^{-3} mol), PMDETA (104 µL, 0.5 x 10^{-3} mol), , *t*BA (7.32 mL, 0.05 mol) and 18.3 mL Toluene were introduced in a Schlenk tube and the reaction mixture was degassed by three freeze– pump–thaw cycles. The tube was then placed in a thermo-stated oil bath at 80 °C for 6 hours. The polymerization mixture was diluted with THF, passed through neutral alumina column to remove the catalyst, and precipitated in MeOH/Water (9:1) and left in freezer overnight to gives (**3**). $M_{n,NMR}$: 8000 g/mol. $M_{n,GPC}$: 9596 g/mol, M_w/M_n: 1.23 ^{1}H NMR ($CDCl_3$) (500 MHz Varian Mercury system (Palo Alto, CA) δ: 4.1 (m, 2H, -O-CH_2-$^*CH_2$-O-CO- And t, 1H, CH-Br), 3.6(s, 3H, CH_3-O-CO-), 2.2 (m, 1H, -CH-Br), 1.5 (s, 9H, CH_3).

After synthesis the second block Azidation was done by converting the terminal Br groups to azide by reaction with NaN_3 to be coupled to the functionalized PEG alkyne via click reaction. *PMMA-b-PtBA-Br* (1 g, 1.25 x 10^{-1} mmol) and 20 equivalent NaN_3 (0.163 g, 2.5 mmol) were stirred in DMF at 50 °C for overnight. The polymer was dissolved in CH_2Cl_2, extracted with water, the water phase was again extracted with CH_2Cl_2, and combined organic phase was dried over Na_2SO_4. Finally, the organic phase was evaporated to give *PMMA-b-PtBA-N_3* (**4**) functional azide. ^{1}H NMR ($CDCl_3$) ((500 MHz Varian Mercury system (Palo Alto, CA) δ: 3.8 (CH_2CH-N_3), 2.3 (CH_2CH-CO), 1.9 (6H, O-CO-C (CH_3)$_2$), 1.5 (9H, CO-OC (CH_3)$_3$).

2.4. "Click" coupling of PEG-alkyne and PMMA-b-PtBA-N_3 (5)

Coupling of PEG-alkyne to the azide terminal group have been done by cycloaddition reaction (Durmaz, Dag et al. 2006). ^{1}H NMR ($CDCl_3$) ((500 MHz Varian Mercury system (Palo Alto, CA) δ: 1.5 (9H, CO-O-C(CH_3)$_3$), 2.3 (CH2C*H*-CO), 3.7 (bs, 450H, OCH_2CH_2), 7.5 (bs, 1H, triazole ring proton).

2.5. Hydrolysis of tBA groups (6)

To be able to obtain acid functionality in the middle block, tert-butyl groups were hydrolyzed using Trifluoroacetic acid (TFA).enhancing our system by forming shell cross-linked after self-assembly of block copolymer into micelles to protect burst release of the drug. Briefly, (PMMA-*b*-P*t*BA-*b*-PEG) copolymer was dissolved in

dichloromethane and 10 fold excess of TFA (equivalent to tert-butyl group) was added at 0 oC under argon atmosphere. Reaction mixture was stirred 30 min at this temperature and 24 h stirred at room temperature. Dichloromethane and TFA were evaporated with air stream and (PMMA-*b*-PAA-*b*-PEG) was precipitated in methanol.

^{1}H NMR ($CDCl_3$) ((500 MHz Varian Mercury system (Palo Alto, CA) δ: complete reduction in Boc- protons at 1.5, 2.3 (CH_2CH-CO), 3.7 (bs, 450H, OCH_2CH_2), 7.5 (bs, 1H, triazole ring proton) and rest of the backbone protons).

2.6. Synthesis of Amine Bearing Cross-linker [2,2'-(Propane-2,2-diylbis(oxy))-diethanamine]

The synthesis of Amine bearing cross-linker [2, 2'-(Propane-2, 2-diylbis (oxy))-diethanamine] was obtained by two steps literature process (Paramonov, Bachelder et al. 2008; Shim and Kwon 2008; Broaders, Pastine et al. 2011; Lim, Noh et al. 2012). This compound was synthesized according to previous papers with minor alterations. Briefly, N-(2-hydroxyethyl)-phthalimide (5.0 g, 26.15 mmol, 1 equiv.) was completely dissolved in 100 mL of dry benzene and cooled down to 0 °C in ice bath. 2-methoxy propene (2.5 mL, 26.15 mmol, 1 equiv.) was added carefully to the solution along with p-toluenesulfonic acid (50 mg, 0.78 mmol). The reaction mixture was stirred for 1.5 h while keeping the reaction temperature below 0 °C to avoid any loss of the highly volatile 2-methoxy propene (bp:34-36 °C). The flask was then connected to a trap and the mixture was heated to 45 °C under high vacuum to remove the methanol formed during the reaction. As evaporating the solvent, additional benzene was added and subsequently evaporated during 6 h. Finally, the reaction was quenched by adding triethylamine (6.67 mL) and reached room temperature. To further purification, acetic anhydride (1.33 mL) was added to convert any unreacted hydroxyl groups into the corresponding acetate and the mixture was stirred for 18 hours. The reaction mixture was then precipitated by drop wise addition to hexane. The precipitated powder was collected and recrystallized twice from ethyl acetate and obtaining a white solid. Yield: 70%. ^{1}H NMR ($CDCl_3$) ((500 MHz Varian Mercury system (Palo Alto, CA) δ: 1.3 (6H, s, CH_3-C), 3.6 (4H, t, CH_2-O), 3.80 (4H, t, CH_2N), 7.4-7.8 (8H, dt, ArH). Calcd $[M^+H]^+$ ($C_{23}H_{22}N_2O_6$) m/z =422.15; found $[M^+Na]^+$ = 445.1.

2,2'-(Propane-2,2-diylbis(oxy))bis(diethane-2,1diyl)bis(isoindoline-1,3-dione) 400 mg was deprotected in 6 M NaOH (5 mL) by refluxing overnight to obtain 2,2'-(Propane-2,2-diylbis(oxy))-diethanamine. The product extracted by a mixture $CHCl_3$/iPrOH (1/1) three times and dried over anhydrous sodium sulphate. The organic layer was evaporated to obtain amber-colored oil. Yield; 50%. ^{1}H NMR ($CDCl_3$) ((500 MHz Varian Mercury system (Palo Alto, CA): δ)): 1.3 (6H, s, CH_3-C), 2.5 (4H, bs, NH_2), 2.80 (4H, t, CH_2-NH_2), 3.4 (4H, t, CH_2O). 13C NMR (500 MHz, $CDCl_3$) δ (ppm for TMS): 24.8, 41.9, 62.4, and 99.9. Calcd $[M^+H]^+$ ($C_7H_{19}N_2O_2$) m/z = 162.14; found $[M^+H]^+$ = 163.14 and $[M^+Na]^+$ = 185.1.

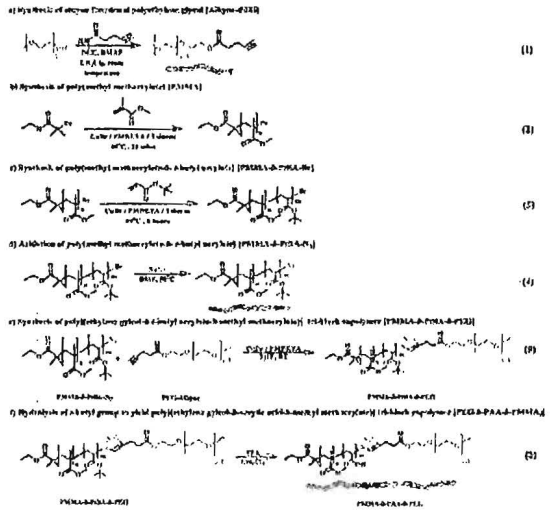
3. Results and Discussion

3.1. Synthesis of Amphiphilic PMMA-b-PAA-b-PEG Copolymer

Amphiphilic block polymers tends to self-assemble into nanosized micelles in which enclosing the hydrophobic quests such as drugs, dyes, or imaging agents the core in *aqua* environment (Yuksel Durmaz, Vlaisavljevich et al. 2014). We have developed tri block copolymers composed of PEG as a corona block, PAA –a middle block-, and a hydrophobic block of PMMA, which were coupled through CuCAAC "click" reactions (Figure 1). All the blocks we preferred are approved by FDA in terms of biocompatibility for biomedical applications. The PEG block of the triblock amphiphilic copolymer provides the hemocompability of the micelles in blood circulation with resisting against adsorption of serum proteins, lack of interaction to blood cells *i.e.* platelets and RBCs. Furthermore, these PEG chains could

be functionalized with targeting ligands and labeled with fluorescence dyes to allow cell specific therapy and imaging.

PMMA and PMMA-*b*-P*t*BA were synthesized via atom transfer radical polymerization (ATRP) and coupled to PEG block with a "click" reaction. First, poly(methyl methacrylate) (PMMA) as a hydrophobic block and a macro initiator was synthesized using ethyl-2-bromoisobutyrate, which is a commercial available initiator. The numbers of MMA units were calculated using the ratio of methyl protons of MMA to initiator protons as 45 units from the ^{1}H NMR spectra (for more synthetic details and characterization see supporting information). The numbers of MMA units are enough to self-assemble of triblock polymers to form efficiently micelles. From bromine groups of this macro initiator, we set up the second ATRP reaction to get copolymer of PMMA-*b*-P*t*BA. This second block is used as a precursor of cross-linkable block aiming 25 repeating *tert*-butyl groups which can easily be hydrolyzed into acid groups that can be functionalized for shell cross-linked after self-assembly of block copolymer into micelles to protect burst release of the drug. Moreover, the bromide group of this two block copolymer can be easily transferred into azide group for following azide-alkyne "click" reaction with alkyne functional PEG block that obtained from commercially available mono hydroxyl end functional PEG reaction with 4-pentynoic acid to give alkyne functional PEG block (alkyne-PEG). The conjugation efficiency was > 95% according to ^{1}H NMR. The Alkyne-PEG was coupled to PMMA-*b*-P*t*BA-N_3 in the presence of CuBr/PMDETA at the room temperature to get the triblock copolymer PMMA-*b*-P*t*BA-*b*-PEG (Fig. 1).



Successful coupling was confirmed with appearance of triazole ring proton in ^{1}H NMR spectrum. Moreover, this reaction was monitored with Fourier transform infrared spectroscopy (FTIR) that did not exhibit any azide or alkyne peaks indicating only existence of block copolymer without precursors. All these results showed that PMMA-*b*-P*t*BA-*b*-PEG copolymer was successfully obtained. Molecular weight and molecular weight distribution of block copolymers were also measured using gel permeation chromatography (GPC). After each block addition, the molecular weights of related block copolymers were shift to lower elution volume, which indicates molecular weight increase. Narrow polydispersity of the curves without a tail indicate that block copolymers were obtained without any impurities such us their precursors.

Finally, *tert*-butyl groups of P*t*BA were efficiently hydrolyzed using trifluoroacetic acid (TFA) to obtain desired triblock copolymer. The success of reaction was monitored using ^{1}H NMR, which showed complete reduction on methyl protons of *tert*-butyl groups at 1.43 ppm for PMMA-*b*-P*t*BA-*b*-PEG copolymers. Furthermore, acid groups of obtained PMMA-*b*-PAA-*b*-PEG were reacted with the amine functional pH sensitive acetal linkage under NHS/EDC coupling conditions. This shell cross-linkage was confirmed by ^{1}H and ^{13}C NMR spectra. The characteristics of all block copolymer and theirs precursor were summarized in Table 1.

	# of Repeating Units	M_{nNMR} (g/mol)	M_{nGPC} (g/mol)	M_w/M_n
PMMA-Br	44	4,603	4,855	1.27
P(MMA-b-tBA)-Br	71	8,063	9,596	1.23
PMMA-*b*-PAA-*b*-PEG	-	11,547	14,860	1.15

3.2. Synthesis of Acetal Linker[2,2'-(Propane-2,2-diylbis(oxy))-diethanamine]

Acid degradable amine bearing cross-linker was synthesized in two steps following modified procedures from the literature (Paramonov, Bachelder *et al.* 2008; Lee, Min *et al.* 2011; Lim, Noh *et al.* 2012). N-(2-hydroxyethyl)-phthalimide was reacted with 2-methoxy propene in the presence of a trace amount of pTSA in the ice bath for first 2 h in the azeotropic distillation system for removing the formed methanol to go forward of the reaction. The intermediate compound was protected in 6 M NaOH solution during reflux to obtain 2,2'-(Propane-2,2-diylbis(oxy))-diethanamine. The product was purified with $CHCl_3$/iPrOH (1/1) extraction. The linker was confirmed by ^{1}H-NMR, ^{13}C-NMR, and MALDI. The ^{1}H-NMR of the ketal cross-linker in $CDCl_3$ showed 4 peaks for H_a-H_d. The two germinal methyl groups (H_a) were observed at δ 1.36 as a singlet. The two CH_2 protons next to oxygen (H_b) observed at δ 3.45 as a triplet, whereas two CH_2 protons (H_c) next to amines were observed at δ 2.81 ppm as a multiplet. The amine protons were observed at δ 1.44 ppm as a broad singlet. The ^{13}C-NMR of the cross linker in $CDCl_3$ showed 4 peaks for C_a-C_d. The germinal 2$\underline{C}H_3$ observed at δ 24.98 ppm. The C_b and C_c carbons observed at δ 62.88 and 42.18 ppm respectively. The quaternary carbon (H_d) observed at 99.79 ppm.

4. Conclusions

We have developed a smart, powerful, biocompatible shell cross-linking micelles that enhance the solubility and efficiency of poorly water-soluble drug.

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تطوير مذيلات حساسة للحامضية لاستخدامها في تطبيقات توصيل الدواء

إبراهيم يوسف[أ،1]، عمر ايدن[1،أ]، د/ ياسمين دورماز[1]، د/ جوبينث توريشنابالي[1]، د/ إبراهيم الشربيني[2]، ا.د/ احمد فضة[2]، ا.د/ السيد عفصه[2]، ا.د/ محمد السيد[3،ج]

[1] قسم الهندسة الطبية الحيوية، كلية الهندسة-جامعة متشجن.

[2] قسم الكيمياء، كلية العلوم-جامعة المنصورة.

[3] برنامج الهندسة وعلوم المركبات الكبيرة، كلية الهندسة-جامعة متشجن.

[أ] يعتبر الباحثين هما المؤلفين الأولين للبحث.

كفاءة توصيل الدواء المضاض للسرطان داخل الخلايا السرطانية والسيطرة على الافراج عن الدواء في نسيج الورم ولكن عدم الإفراج عنه في الأنسجة السليمة، وكذلك خلال الدورة الدموية تشكل تحديا حيويا في علاج سرطان البروستاتا المتقدمة. في هذه الدراسة، من خلال البلمرة بطريقة ATRP تم تحضير (حديد الميثيل ميثاكريلات -متصل ب-حديد حمض الاكريليك-متصل ب-حديد الاثيلين جايكول)، وبعد ذلك تجميعها الذاتي في البيئة المائية في المذيلات التغليف الأدوية المضادة للسرطان ليتم استخدامها باعتبارها الناقل للدواء. وعلاوة على ذلك، لزيادة استقرار المذيلات في البيئات المائية، قدمنا روابط الكيتال لتربط حمض الكربوكسيل مع مجموعه الامين لتكوين رابطة الاميد المحتوية على كيتال .

الكلمات الرئيسية: البوليمر محبة الجهتين، روابط موصله حامضية، المذيلات الحساسة لدرجة الحموضة، وتوصيل الدواء.