Evaluation of Biocompatible Films using Copolymers of *N*-Vinylbenzamide with Cationic Moieties by Hydrolysis of *N*-Vinylformamide

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Abstract

Biocompatible materials using poly(*N*-vinylamide) derivatives were developed via a recently designed synthetic route. *N*-Vinylbenzamide (NVB) was synthesized as typical hydrophilic *N*-vinylamide monomer, then copolymerized with *N*-vinylformamide (NVF) by free radical polymerization, which can convert to cationic polyvinylamine unit by hydrolysis. Cell toxicity on the surface of copolymer films was investigated, revealing that poly(*N*-vinylamide) derivatives showed biocompatibility regardless of the cationic ratio.

Introduction

Poly(*N*-vinylamide) derivatives have been investigated extensively for a variety of polymer materials.[1-5] *N*-vinylacetamide (NVA) is one of the typical monomers of poly(*N*-vinylamide) derivatives, the industrial synthesis route of which was reported by M. Akashi et. al. in 1990.[6] This route[6] was capable of synthesizing various new *N*-vinylamide monomers. Currently, a more facile synthetic route for *N*-vinylamides starting with a_*N*-vinylformamide (NVF) and acyl chlorides has been reported, making it easy to obtain and use various *N*-vinylamides.[7] The *N*-vinylamides are unconjugated vinyl monomers, which can be polymerized themselves with a radical initiator. Recently, the living radical polymerization has been achieved by organotellurium-mediated radical polymerization[8] and RAFT.[9] However, these monomers are difficult to polymerize by ionic polymerization.[10] Vinyl acetates are also un-conjugated monomers, which can be copolymerized with *N*-vinylamides as gradient copolymers.[11] Furthermore, one of the specific characteristics of poly(*N*-vinylamide) derivatives is the structure in which a nitrogen atom of the amide group is directly connected to the vinyl group, conferring the amphiphilicity and a cationic precursor. In particular, poly(*N*-vinylformamide) (PNVF) can change to poly(vinylamine) by hydrolysis in both alkaline and acid conditions.[12] On the other hand, poly(*N*-vinylacetamide) (PNVA) can only change in an acid condition.[13,14] Thus, the composition ratio of cationic groups of poly(*N*-vinylamide)

copolymers can be controlled.

Poly(*N*-vinylamide) derivatives have been used as various polymer materials. For example, thermal responsive properties have been studied, such as in the copolymer of *N*-vinylcaprolactam[15,16] . Copolymerization with *N*-vinylamides is one of the most commonly used approaches for preparing thermosensitive hydrogels.[17] When an acyclic *N*-vinylamide was used, it could also be applied to pH responsive materials due to the presence of a polycation after hydrolysis, such as in a thermal and pH responsive hydrogel.[18] Poly(NVA-*ran*-NVF) gel could be changed to Poly(NVA- *ran*-vinylamine) gel which has pH sensitive behavior.[19] A surface poly ion complex (sPIC) gel was reported as a pH responsive drug delivery carrier, which could switch between two kinds of drug release by pH.[20] Furthermore, it can be used in a loading function for a fluorescent compound.[21]

Recently the biocompatibility and biomaterial application of poly(*N*-vinylamide)s have also been investigated. Poly(*N*-vinylamide)s were conjugated with D-octaarginine and oligoarginines, in order to protein drug delivery.[22,23] as well as to investigate cell adhesion and proliferation on poly(*N*-vinylamide) hydrogels.[24] Moreover, conjugation with biological interfaces is an important approach to creating novel biocompatible materials. For example, poly(*N*-vinylamide)s were conjugated with a natural compound

to produce biohybrid nanogels by direct coupling between reactive copolymers and protein.[25] In another example, a copolymer with a polycation and fluorine polymers were coated on fluorine polymers to introduce peptide on the surface.[26]

On the other hand, polyphenylalanine is known as a biocompatible polymer. It has been used as the solid phase of HPLC[27] and peptide-like polymers.[28,29] The hydrophobicity of polyphenylalanine has been used for various applications, such as the graft modification to hyperbranched polyethyleneimine to use gene transfection,[30] oligo(L-phenylalanine) conjugate,[31] copolymers for drug delivery,[32-34] and imaging.[35] The basic structural analysis and property of polyalanine has been studied.[36] We were therefore, motivated to develop poly(*N*-vinylbenzamide) (PNVB) as a biocompatible polymer material, because it is a structural isomer of polyphenylalanine.

In this study, we synthesized PNVB and its copolymer to evaluate their biocompatible behaviors. The PNVB films were prepared by spin-coating and the hydrophilicity and cell adhesion on their films were investigated.

Experimental.

Materials

N-vinylformamide (NVF), benzoyl chloride and 1-bromopropane were purchased

from Tokyo Chemical Industry Co. Ltd. Sodium hydride (NaH) 60% in oil, sodium hydroxide (NaOH), Triethyl amine (TEA), magnesium sulfate ($MgSO_4$), dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were purchased from Nacalai Tesque Inc. Azobisisobutyronitrile (AIBN), sodium chloride (NaCl) and ethyl acetate were purchased from Wako Pure Chemical Industries. Hexane, ethanol, tetrahydrofuran (THF), methanol and diethyl ether were purchased from AZBIO Corp. Mouse fibroblast NIH3T3 cells were obtained from the Riken BRC Cell Bank (Tsukuba, Japan). Fetal bovine serum (FBS) was purchased from Biowest (Nuaillé, France). Dulbecco's modified Eagle's Medium was purchased from Sigma-Aldrich (St. Louis, MO, USA). Cell Counting Kit-8 was purchased from Dojindo Molecular Technologies (Kumamoto, Japan).

Analyses

^{1}H NMR spectra was measured by a JEOL JNM-GMX400 system. The number-average molecular weights and their distribution were measured by size exclusion chromatography (SEC). ChromNAV system (Shimadzu Corporation, Japan) using AS-2055 and RI-2031 was employed with polystylane standards at room temperature. The column (TSKgel α-M) was used, and DMF (1 mg/mL) was used as an eluent at 0.6

mL/min.

Synthesis

In a glass flask, NaH (4.32 g, 180 mmol) was placed and washed with anhydrous THF (15 ml) twice under nitrogen, and 90 mL of anhydrous THF was introduced. NVF (12.8 g, 180 mmol) was slowly added at 0ºC after some minutes then temperature was increased to 40ºC. After stirring for 4 h at 40ºC benzoyl chloride (24 g, 171.4 mmol) was slowly added by syringe at 0ºC. After some minute the reactor was warmed up to room temperature and stirring continued for 2 h. Water was introduced into the reaction mixture to terminate the reaction, and the mixture was extracted into 500 mL of dichloromethane and 400 mL of water, washing the organic layer successively with water. After washing, the organic layer was evaporated. In glass flask, this product was placed at 0ºC and NaOHaq (5M, 220ml) was slowly added into the product solution at 0 ºC after some minutes then temperature was increased to room temperature. After stirring for 2 h at room temperature, ethyl acetate was slowly added into solution at 0ºC and strongly then stirred some minute. The mixture was extracted into 500 mL of dichloromethane and 400 mL of water, washing the organic layer successively with water. The organic layer was combined and dried with anhydrous $MgSO_4$ and then further purified on a silica gel

column chromatography using hexane/ethyl acetate as eluent. The pure product of NVB was obtained as a solid (4.6 g, 32.6 mmol 18% yield).

Polymerization

A, B and E were synthesized according to previous research.[5] The procedure of synthesis of E is selected as a typical method as follow. Into a 20 mL glass tank, NVB (0.59 g, 4 mmol), toluene (10 ml) and AIBN (0.018 g 0.125 mmol) were combined. The reactor was capped with septa, then N_2 bubbling was carried out for 2 min. The reaction mixture was heated up to 60 ºC to start polymerization. After 24 hours, it was cooled down to room temperature, and the reaction mixture was poured into 10 mL of methanol. The polymer was twice washed by poor solvent of 500 ml diethyl ether and recovered by centrifugation. The obtained polymer was dried under vacuum at 30 ºC over 12 hour.

Hydrolysis

In a glass flask, polymer (200 mg) was placed, and 20 ml of 2M NaOH methanol was introduced. The mixture was heated up at 40 ºC to start hydrolysis. After 24 h, it was cooled down to room temperature, and the mixture was poured into dialysis tube. Its tube

was packed and then dipped into 500 ml of methanol for 3 days, the solvent was changed to the flesh methanol one time per day. After 3 days, mixture was dried under vacuumed at 30ºC over 12 hour.

Polymer reaction

In a glass flask polymer (0.1 g) and DIEA (0.028 g, 0.22 mmol) were placed and dissolved in 0.8 ml of anhydrous DMF. 1-Bromopropane (8.9 g, 125 mmol) was slowly added into mixture at room temperature after five minutes then temperature was increased to 80ºC. After stirring for 20 hr, it was cooled down to room temperature, and the reaction mixture was poured into 2 mL of methanol. The polymer was twice washed by poor solvent of 50 ml water and recovered by centrifugation. The obtained polymer was freeze dried under vacuum over 12 hour.

Cell experiment

The seven kinds of polymers were dissolved in methanol at the concentration of 10 mg/mL. Polymer films were fabricated by spin-coating of the 20 mL polymer solution at 4000 rpm for 30 sec onto round cover glass (15 mm diameter), under the assumption of

the similar surface morphologies among all of the polymer samples. The cover glasses were put into 24 well plates. A total of 1.0 x 10^4 cells in serum-containing medium was plated in the 24-well plate and then incubated at 37 ºC in a humidified 5% CO_2 atmosphere. After 48 h, the medium was replaced to fresh medium. Following further 48 h-incubation, a solution containing 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt (WST-8) and 1-methoxy-5-methylphenazinium methylsulfate was added to each well at a 10-fold dilution. After 3 h incubation for 37 ºC, 200 mL of the supernatant of each well was transferred to a 96-well plate. The absorbance was measured at 420 nm using a plate reader (Multiskan JX, Thermo Fisher Scientific, Waltham, MA, USA). The viability was calculated using the following equation:

$$\%\ \text{cellular viability} = \frac{A_{420\,nm}\ (\text{with polymer coating}) - A_{420\,nm}\ (\text{blank})}{A_{420\,nm}(\text{without polymer coating}) - A_{420\,nm}\ (\text{blank})} \times 100$$

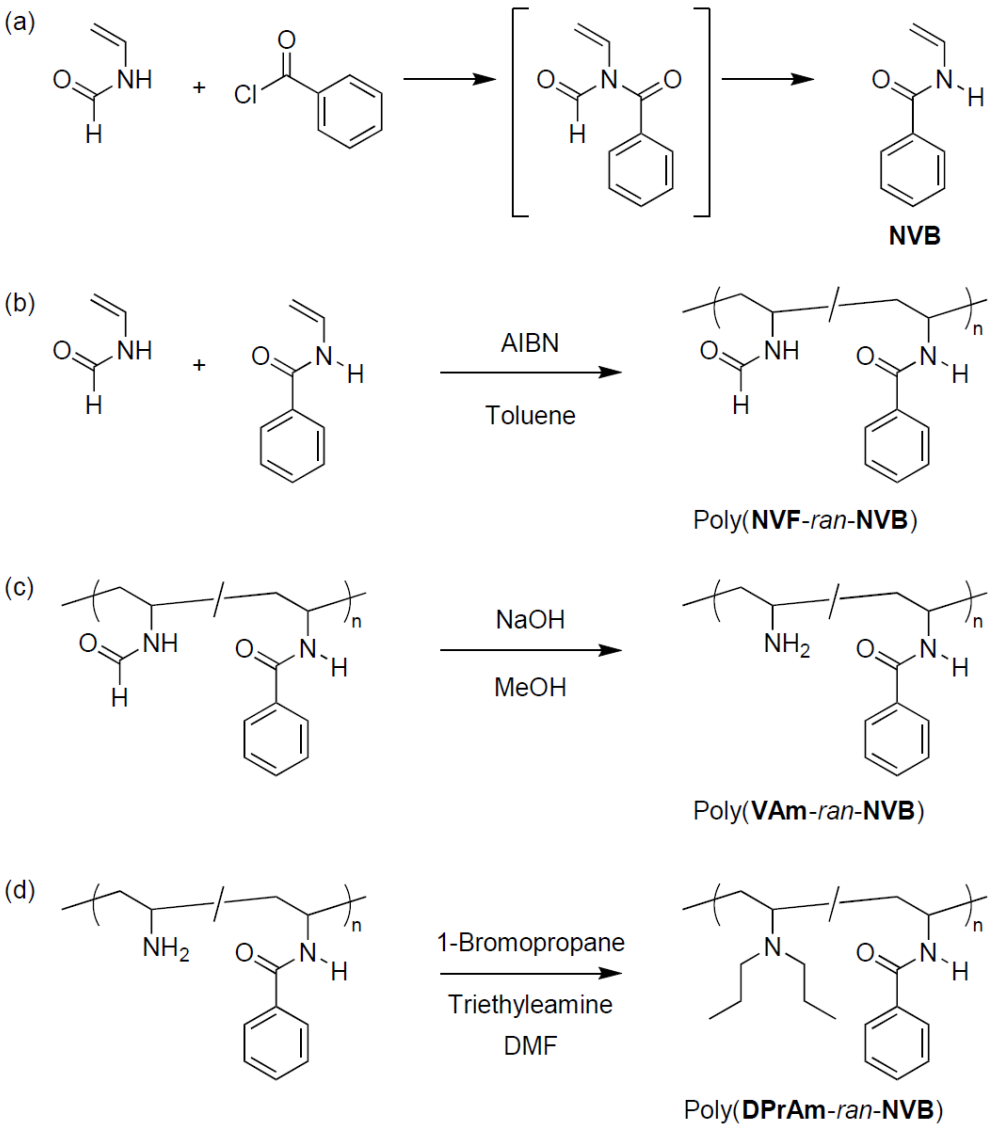
, where $A_{420\ \text{nm}}$ (with polymer coating) is the absorbance at 420 nm after culture on the polymer-coated cover glass, $A_{420\ \text{nm}}$ (without polymer coating) is the absorbance at 420 nm after culture on the bared cover glass, and $A_{420\ \text{nm}}$ (blank) is the absorbance of medium containing WST-8 reagent at 420 nm.

Contact angle measurement

The polymer-coated cover glasses were prepared by the same procedure as the above. The contact angle measurement of the polymer-coated cover glass was performed using a DMe-200 (Kyowa Interface Science Co., Ltd., Japan). Deionized water (1 μL) was dropped on the polymer-coated glass, and the contact angle was measured.

Results and Discussion

To develop the biocompatible materials, poly(*N*-vinylamide) derivatives were synthesized via new synthetic route. We selected PNVB as the first choice for material development as it is a typical hydrophobic compound that is easy to synthesize in organic solvents. Initially, a novel monomer, NVB, was synthesized following a previously reported method by S. Tu and C. Zheng,[7] (Scheme 1a). The yield of NVB was low (18%) although the monomer can be obtained without great energy expenditure, above 200 ℃. This synthetic method enhanced the chances of monomer synthesis of *N*-vinylamide derivatives.



Scheme 1. Monomer and copolymer syntheses in this study.

NVB was copolymerized with NVF by free radical polymerization (Scheme 1b). Table 1 shows analytical data for the synthesized polymers. The molecular weight given is the apparent molecular weight with polystyrene standards. There were no significant differences for yields, molecular weights or $Đ$ between each batch due to the very similar

monomer ratios. The values for yield and molecular weights were both higher than in previously reported results.[6] The hydrophobicity and solubility of NVB probably influenced the radical reactivity during polymerization.

Table 1. Copolymer compositions with NVB units and their molecular weights.[a]

Entry	Sample ID	Polymer	NVB unit in feed	NVB unit in polymer	Yield[b]	M_n[c] kDa	$Đ$[c]
1	**A**	Poly(**NVB**)	100	100	78	15.1	2.3
2	**B**	Poly(**NVF**-*ran*-**NVB**)	95	89	87	19.0	1.9
3	**C**	Poly(**NVF**- *ran* -**NVB**)	83	82	87	16.6	3.4
4	**D**	Poly(**VAm**- *ran* -**NVB**)	ND	89	ND[d]	ND[d]	ND[d]
5	**E**	Poly(**VAm**- *ran* -**NVB**)	ND	82	ND[d]	ND[d]	ND[d]
6	**F**	Poly(**DPrAm**- *ran* -**NVB**)	ND	89	ND[d]	ND[d]	ND[d]
7	**G**	Poly(**DPrAm**- *ran* -**NVB**)	ND	82	ND[e]	ND[e]	ND[d]

[a] Polymerization conditions: Solvent=toluene, Initiator=AIBN, Temp.=60°C. [b] Diethyl ether insoluble part. [c] Determined by SEC with polystyrene standard in DMF. [d]Not determined.

The obtained copolymers were hydrolyzed under alkaline conditions to obtain the cationic polymers (Scheme 1c). The formamide group of poly(*N*-vinylamide) derivatives can be hydrolyzed in both alkaline and acid conditions but, their acetamide group can only be hydrolyzed in an acid condition. Thus, the ratio of cation units can be controlled by the initial ratio of comonomers.

Figure 1 shows the time-dependent ^{1}H NMR spectra of poly(*N*-vinylamide) derivatives during hydrolysis in the alkaline condition. The peak intensity derived from

the formamide group decreased as time passed due to the hydrolysis of the formamide group, and changed to an amine group. On the other hand, there was no concomitant decrease in peak intensity derived from the phenyl group. This result indicated that the benzamide group is not degradable but only the formamide group is hydrolyzed in the alkaline condition. Furthermore, the kinetics of hydrolysis were observed by the calculation of the integral intensity of the ^{1}H NMR spectra (Figure 1a-1d). Most of the decomposition (84%) is completed after 12 hours, then almost all of the formamide groups (97%) are hydrolyzed after 2 days. This result gave us important knowledge that the complete decomposition of the formamide group could not be demonstrated by 1H NMR analysis after 2 days and it took a week, although the benzamide group was stable for an extended period of 7 days in the alkaline condition.

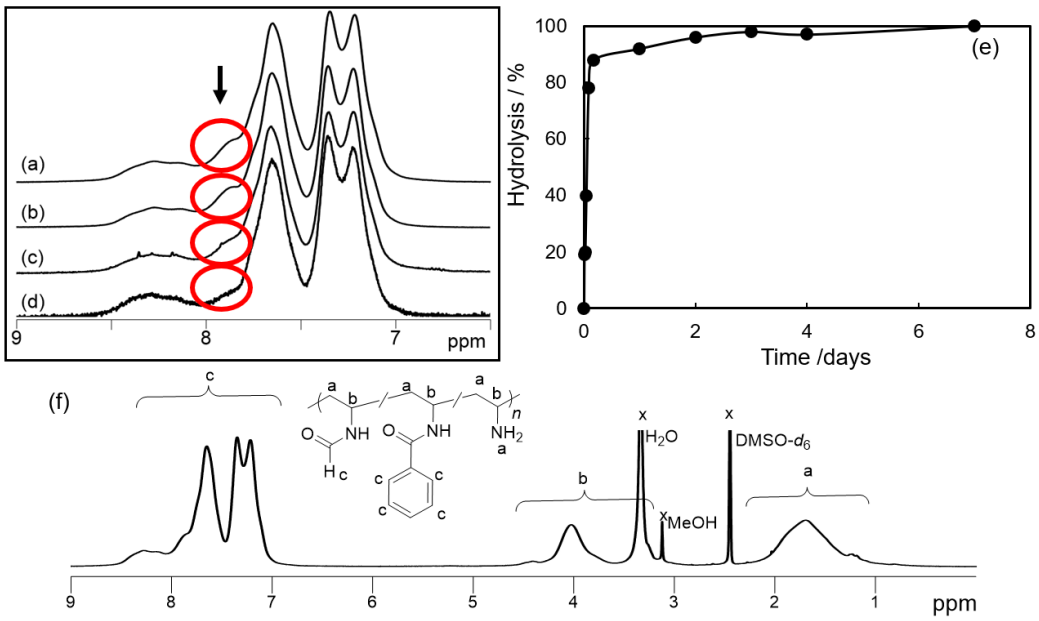


Figure 1. ^{1}H NMR spectra of poly(NVF-*ran*-NVB) after hydrolysis for 10 min. (a) and (f), 4 hours (b), one day (c), and one week (d) (In DMSO-d_6, 400MHz, r.t.). The hydrolysis ratios against time (e).

A small alkyl group, a propyl group, was introduced to the poly(vinylamine-*ran*-NVB) to control the biocompatible properties of the copolymers (Scheme 1d). The cationic groups have an antimicrobial property and sometimes cell toxicity. So, the ratio of the units of "vinylamine", which would produce cationic moieties, is one of the important factors of these properties. The alkyl groups are typical hydrophobic compounds, but the long alkyl groups give copolymers too much behavioral variation. We therefore tried to control the biocompatible properties using moderate variation by introducing the small alkyl group. Next, we prepared the film using seven kinds of polymers and their biocompatibility was then evaluated (Table 1).

The polymer films were prepared by spin-coating in methanol (10mg/ml) and the surface behavior was then assessed by observing the water contact angle. Polymer A, PNVB homopolymer, showed the most hydrophilic surface compared with the other copolymers (Figure 2a). The phenyl group might be assembled in methanol and the amide group came on the surface. On the other hand, all of the copolymers contained the formamide or amine or the alkyl amine groups, which probably made it easier for the phenyl group of each to appear on the surface.

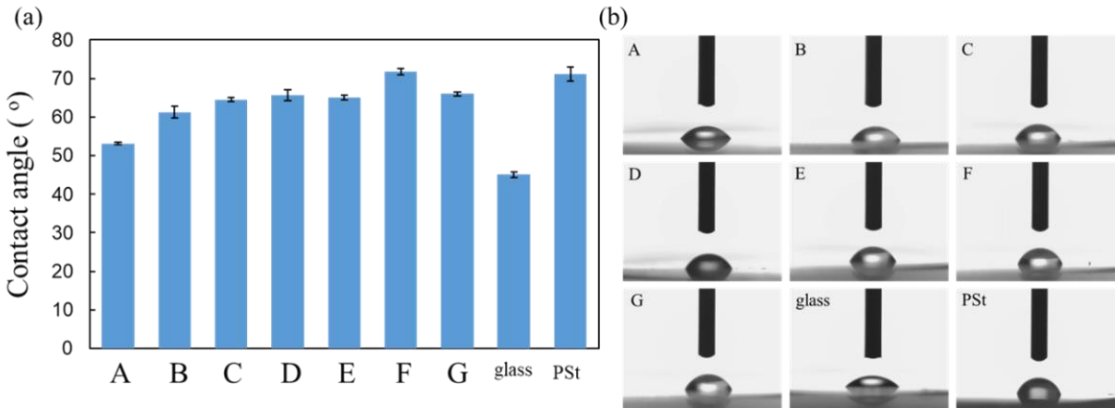


Figure 2. Contact angles of water droplet on the copolymers on the substrates (a), and their photos.

The biocompatibility of the synthesized polymers was evaluated by WST test using the spin-coat films (Figure 3). Some polymers contained a cationic group, but every sample showed high biocompatibility and high cell viability. The surfaces of these polymer films were hydrophobic and their contact angles were similar with polystyrene substrate. Probably, the cationic group was not so apparent on the surface of films, so the contact angles were similar with PSt substrate and the cell viability ratios were a high percentage. Furthermore, the homopolymer, A, looked to possess the highest cell viability. The difference in chemical structure between A and PSt is only the presence or absence of the amide group. It is possible the amide group of A influenced on the polymer film surface, causing the higher cell viability.

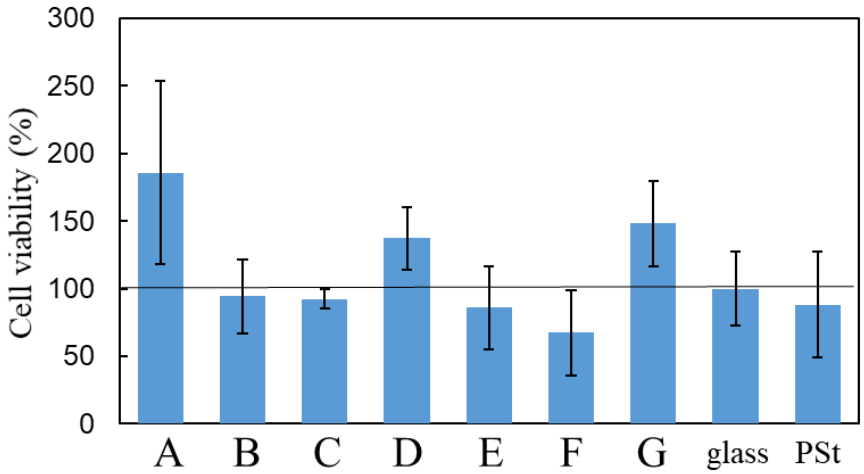


Figure 3. Cell viability on the various polymer films and substrates after 48 hr, evaluated by WST-8.

Conclusion

We synthesized poly(*N*-vinylamide) derivatives bearing a phenyl group at the acetamide position. According to a previous report, the modification of poly(*N*-vinylamide) derivatives at the acetamide position allows for easier synthesis. The cationic group was introduced to their polymers by hydrolysis. It was revealed that the benzamide group is not decomposed by hydrolysis in an alkaline condition which is the same as in hydrolysis of the acetamide group. It is important to control the ratio of cationic groups of poly(*N*-vinylamide) derivatives. Furthermore, the polymer films were prepared by a spin-coating method using methanol and the surface behaviors were then investigated. The homopolymer, A, showed mild hydrophilic behavior on the surface compared with other polymers. It was surmised that the amide group came to the surface as a result of

the phenyl group probably due to the solubility difference with methanol. The cell viability of the homopolymer, A, showed a high value compared with the other polymers. This might also be the effect of the amide group on the surface of a polymer film. Finally, we developed a material using novel poly(*N*-vinylamide) derivatives as the polymer film. These results indicated that the surface behavior of the films might be controlled by the chemical structures and solvents when using a spin-coating method.

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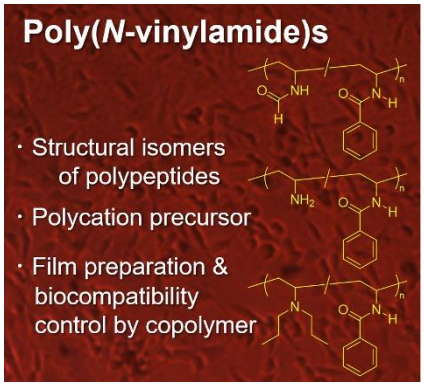

Poly(*N*-vinylbenzamide) and its copolymers were designed and synthesaized. They were selected as structural isomers of polypeptides and their biocompatibilities were evaluated, depending on the introduction of polycationic moieties after the hydrolysis of *N*-vinylformamide moieties. The spin coated films on glass were used for contact angle of water droplet and cell adhesion.