Interpenetrating Polymer Networks of Poly(*N*-vinylacetamide) and Poly(acrylic acid) Applied to Novel Amphiphilic Drug Release Substrates with Mechanically Modified Strengths

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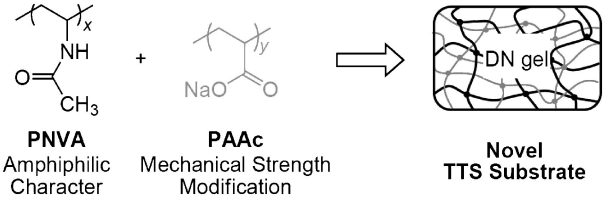
Gels with interpenetrating polymer networks were prepared with *N*-vinylacetamide (NVA) and acrylic acid (AAc) as novel substrates for transdermal therapeutic systems. The gelation of NVA at 1 M in AAc gel sustained the amphiphilic character, and a poorly water-soluble drug was kept in the gel with ethanol as solvent. Mechanical strengths were five times larger in value than those of simple poly(*N*-vinylacetamide) gels.

Transdermal therapeutic systems (TTS) are an attractive approach to drug delivery systems (DDS),[1,2] because percutaneous drug absorption is gentle on patients, compared to injections involving skin penetration or oral administration which induces possible drug inactivation through the liver. The percutaneous absorption mechanism is complicated by drug, substrate, and skin interactions. Thus, novel substrate development, which can support many kinds of drugs, is considered as an important research topic in DDS.

On the other hand, our research group has paid attention to *N*-vinylacetamide (NVA) and its derivatives for decades.[3,4] NVA provides amphiphilic polymer, which is expected for the biomaterial use. It is noteworthy that harmful low molecular weight amines are not generated upon decomposition of amide groups, unlike with poly(acrylamide). In fact, NVA was copolymerized with acrylic acid (AAc) for good skin adhesion, and has been investigated for use in skin patches.[5,6] However, the aforementioned copolymer is sol and mechanical strength remained problematic.

Interpenetrating polymer networks (IPNs) are a promising approach to vary poly(*N*-vinylacetamide) hydrogel (PNVA gel) characteristics without copolymerization. Besides, double network (DN) gels,[7–10] which are a kind of IPN, are known to increase mechanical strengths of hydrogels. However, the aforementioned IPNs were not investigated for patches and TTS substrates.

This study aims to prepare IPNs using NVA and AAc which possess sufficient strengths and suitable amphiphilicity of NVA contained for releasing substrates (Scheme 1). In this letter, we employed simple PNVA gel, poly(acrylic acid) gel (PAAc gel), and two kinds of IPNs. Table 1 summarizes the characteristics of IPNs. $PNVA_{0.37}/PAAc_{0.63}$ gel represents the IPN prepared by the secondary polymerization of 1 M AAc in PNVA gel, which was obtained by the first polymerization of 1 M NVA solution (Table 1, Run 3). The composition of NVA unit in the IPN was 37% calculated with elemental analysis. Similarly, $PAAc_{0.04}/PNVA_{0.96}$ gel shows IPN prepared by the secondary polymerization of 1 M NVA in PAAc gel which was obtained by the polymerization of 1 M AAc solution, containing 96% NVA unit (Table 1, Run 4).



Scheme 1. Preparation of TTS substrate with PNVA and PAAc.

Table 1. Characteristics of gels[a]

Run	Abbreviation	S.R.[b] in water	NVA ratio[c] in gel/%	Swelling with EtOH
1	PNVA gel	24	100	○
2	PAAc gel	400	0	×
3	$PNVA_{0.37}/PAAc_{0.63}$ gel	120	37	×
4	$PAAc_{0.04}/PNVA_{0.96}$ gel	18	96	○

[a][monomer]:[initiator]:[crosslinker] = 100:1:1. [b]The swelling ratio was defined as $(W_s - W_d)/W_d$. [c]Determined by elemental analysis.

A typical procedure for preparing $PNVA_{0.37}/PAAc_{0.63}$ gel was carried out as follows: NVA (0.34 g, 4 mmol), 2,2′-azobis(2-methylpropionamidine) dihydrochloride (V-50; radical initiator) (11 mg, 0.04 mmol), and *N*,*N*-5-oxanonamethylenebis-*N*-vinylacetamide (5ON-bis-NVA) as crosslinkers[10] (12 mg, 0.04 mmol) were dissolved in degassed water (4 mL) at 1 M. The solution was injected between double glass plates that were separated by a silicon gasket (2.0 mm thickness) under a nitrogen atmosphere. After a first polymerization at 37 °C for 8 h, hydrogels were cut into disks (8 mm diameters). Hydrogels were immersed in a second aqueous AAc solution (1 M), containing 1 mol % *N*,*N*-methylenebisacrylamide (MBAAm) as a crosslinker and 0.5 mol % ammonium peroxodisulfate (APS) at 4 °C for 12 h, until equilibrium was reached. Then, 1.1 mol % *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was added and kept at 4 °C for 1 h. A second network was introduced by polymerization at 37 °C for 8 h between double glass plates that were separated by the same silicon gasket (2.0 mm thickness) under a nitrogen atmosphere. Each hydrogel was immersed into a large amount of distilled water to remove reaction residues.

Hydrogel swelling ratios (S.R.) were calculated by the use of the following equation: $(W_s - W_d)/W_d$, where W_s is the weight of the swollen hydrogel at room temperature and W_d is the weight of the dried gel. The amount of AAc units against total weight was estimated by elemental analysis of dried gels. The absorbability of EtOH was tested with dried gels. The stress–strain curve was measured by a compressive tester (EZ Test, Shimadzu, Co.) with a speed of 1 mm·min^{-1}.

Hydrogels were immersed in phosphate buffer saline (PBS) solution with scopolamine (0.5 g·L^{-1}) for 24 h. Hydrogels were

transferred to a UV cell in PBS to monitor the absorbance of released scopolamine at 206 nm. Similarly, the releasing behavior of paclitaxel was measured in EtOH at 228 nm with 0.5 $g \cdot L^{-1}$ in EtOH.

Due to the nonionic property of PNVA gels, polymer chains in hydrogels did not repel and the S.R. values were much lower than those of PAAc gels (Table 1, Run 1 and 2). Thus, depending on which monomer was first gelated, resulting S.R. and AAc contents changed in IPNs, owing to the fact that PAAc gels were able to absorb more of the second monomer solution than that of the PNVA gel. As a result, the amount of the NVA unit in the $PAAc_{0.04}/PNVA_{0.96}$ gel reached 96%, whose amphiphilicity enabled the absorption of EtOH (Table 1, Run 4), while the $PNVA_{0.37}/PAAc_{0.63}$ gel did not associate with EtOH once the gel was dried (Table 1, Run 3). Therefore, swelling abilities with EtOH was not due to the S.R. values with water but more likely to the NVA content in IPNs, even if the same monomer concentrations were employed in gel preparations with different gelation orders.

To add to the amphiphilic character, high mechanical strength is favorable from the view point of TTS substrates. Gong et al. reported that a dramatic mechanical strength improvement was observed when the molar ratio of the second network to the first network is at least ten times, called DN hydrogels,[7] differing from IPNs. In $PAAc_{0.04}/PNVA_{0.96}$ gels, the aforementioned ratio is about 20 times, and is expected to demonstrate strength improvements. The mechanical strength of swollen gels was monitored with a compressive tester, whose stress–strain curves are depicted in Figure 1.

Orders of fracture stress and maximal strains were in good agreement with those of S.R., however, values from $PAAc_{0.04}/PNVA_{0.96}$ gels stood out.[11] The maximal compression strength of $PAAc_{0.04}/PNVA_{0.96}$ gels is about five times as large as that of PNVA gels, while S.R. showed similar values. This tendency was also confirmed with gels swollen in EtOH, implying strength modifications were due to DN gel structures.

Next, drug-releasing profiles from gels were recorded by UV detectors (Figure 2). We selected scopolamine, which is actually commercialized for TTS, and used it as a hydrophilic drug with absorbance monitored at 206 nm in PBS. On the other hand, paclitaxel, which is prescribed as an antitumor, is a target drug that modifies the method of introduction to the body, because of its poor water solubility.[12] Therefore, it was selected in this study as a hydrophobic drug model with absorbance at 228 nm in EtOH. Very little difference was observed in scopolamine release with PNVA gels (Figure 2a), $PAAc_{0.04}/PNVA_{0.96}$ gels

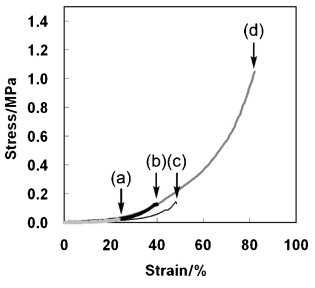


Figure 1. Typical stress–strain charts of PAAc gel (a), $PNVA_{0.37}/PAAc_{0.63}$ gel (b), PNVA gel (c), and $PAAc_{0.04}/PNVA_{0.96}$ gel (d) (EZ test compressive tester).

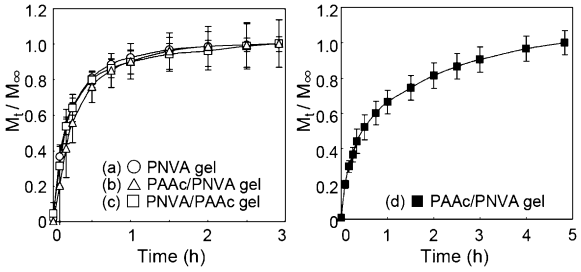


Figure 2. Releasing behavior of scopolamine in PBS with PNVA gel (a), $PAAc_{0.04}/PNVA_{0.96}$ gel (b), and $PNVA_{0.37}/PAAc_{0.63}$ gel (c). Releasing behavior of paclitaxel in EtOH with $PAAc_{0.04}/PNVA_{0.96}$ gel.

(Figure 2b), and $PNVA_{0.37}/PAAc_{0.63}$ gels (Figure 2c). Although the significant difference was not recognized ($n = 3$), when larger amounts of AAc units were introduced into gels (PNVA gel: 0%, $PAAc_{0.04}/PNVA_{0.96}$ gel: 4%, and $PNVA_{0.37}/PAAc_{0.63}$ gel: 63%), a slower release speed was slightly observed, suggesting that electronic interactions between drug and polymer chains increased and nonionic characters became weakened at the same time.

Although $PNVA_{0.37}/PAAc_{0.63}$ gels do not absorb EtOH, $PAAc_{0.04}/PNVA_{0.96}$ gels fully swell in EtOH, which acts as a promoter for TTS as a solvent. Paclitaxel was then easily mounted in gels at 0.5 $g \cdot L^{-1}$, and it was normally released (Figure 2d). More importantly, the releasing behavior sustains characteristics for simple diffusion in EtOH, implying that 4% AAc units in polymer chains do not disturb the releasing behavior, but contribute to the mechanical strength.

In conclusion, DN gels were prepared with AAc (1 M) as first networks and NVA (1 M) as secondary networks, bearing amphiphilicity and increased mechanical strengths, which could not be achieved by copolymerization. Obtained hydrogels sustain releasing properties both from PBS and EtOH. The demonstration in this study could lead to a trailblazing role for novel TTS substrate developments with combinations of huge arrays of drugs. Further research is currently underway.

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