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Novel Acrylic Adhesive for Transdermal Drug Delivery

Susumu MARUO, Hiroyoshi MINEMATSU, and Takeyuki KAWAGUCHI

TEIJIN LIMITED, Polymer Research Institute,
2-1 Hinode-cho, Iwakuni, Yamaguchi 740-8511, Japan

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In recent years, transdermal drug delivery(TDD) has been intensively investigated and applied as a practical therapeutic system because of the avoidance of first-pass gastrointestinal and hepatic metabolism, decrease of side effects and improvement of patient compliance. There is a typical case of skin irritation caused by maceration of the skin covered with the adhesives in TDD patch with low water vapor permeability (WVP).[1,2]

To avoid the skin maceration, some modification of acrylic adhesives by introducing hydrophilic group, such as poly(ethylene glycol) groups, into the adhesive molecules has been reported to enhance WVP. Other trials to copolymerize poly(ethylene glycol)acrylates with 2-ethylhexyl acrylate and a small amount of acrylic acid are also reported.[3,4] These trials have been partly successful in that a small amount of poly(ethylene glycol) group was introduced into the adhesive polymer. Bo *et al*. report that poly(ethylene glycol)monomethacrylates easily formed unprocessable cross-linked gels in radical polymerization because of chain transfer reaction.[5]

This study investigates the feasibility of prevention of cross-linking of the adhesives with high WVP by substituent groups at the end of poly(ethylene glycol)moiety. WVP and peel-off strength of the obtained adhesive polymers as the TDD were also studied.

EXPERIMENTAL

Materials

Ethyl acetate, 2-ethylhexylacrylate, tetrahydrofuran (THF) and acetonitrile were purchased from Kanto Chemicals Co., Inc. Acrylic acid was purchased from TOKYO KASEI KOGYO Co., Ltd. Ethyl acetate, 2-ethylhexylacrylate and acrylic acid were distilled before use. 2,2′-Azobisisobutyronitrile(AIBN) was purchased from Wako Pure Chemical Industries, Ltd. Poly(ethylene glycol) acrylate(PEGA), poly(ethylene glycol)methyl ether acrylate(PEGMA), poly(ethylene glycol) butyl ether acrylate(PEGBA), poly(ethylene glycol) octyl ether acrylate(PEGOA), and poly(ethylene glycol) lauryl ether acrylate(PEGLA) were supplied from NOF corporation. Poly(ethylene glycol) phenyl ether acrylate(PEGPA) and poly(ethylene glycol) nonyl phenyl ether acrylate (PEGNPA) were supplied from TOAGOSEI Co., Ltd. The average degree of ethylene glycol polymerization of these monomers was four. The monomers with poly(ethylene glycol)moiety were used for polymerization without further purification.

Polymerization

Polymerization was carried out under the following conditions: monomers(30 g)(see Table I for details), ethyl acetate(30 g) and AIBN(0.3 mol% to monomers) were added to a 200 mL glass flask and the solution was bubbled with nitrogen for 1 h and heated at 70℃ for 2—6 h under nitrogen atmosphere.

Number and weight average molecular weights of the polymers were measured by GPC using Shodex System 11 equipped with GPC column(KF-80 M, SHOWA DENKO) with length of 1.2 m. GPC was operated using THF as eluent and flow rate of 1.0 mL min^{-1} at 40℃.

Preparation of Adhesive Layer

To measure WVP and peel strength of polymers, the adhesive layer was prepared as follows. The ethyl acetate solution obtained after ethyl acetate(5 g) was added to the polymer solution(10 g) obtained above was casted on poly(ethylene terephthalate) (PET) film coated by poly(dimethyl siloxane) at a dry thickness of 40 μm using a doctor blade and dried at 60℃ for 30 min.

Measurement of Water Vapor Permeability (WVP)

The adhesive layers obtained above were transferred to the polyester non-woven fabric substrate with WVP of 8000 g m^{-2} day^{-1}. Each sample was mounted on the glass cup with 38 mm i.d. containing 26 g of $CaCl_2$. It settled down in the thermo-hygrostat(LH 20-11,NAGANO SCIENCE Corporation) at 40℃ with 90% relative humidity for 3 h. WVP was calculated from the weight increase of $CaCl_2$.

Measurement of Peel Strength

The adhesive layers were transferred to the polyester film of 3.5 μm thickness backed with surgical tape(Micropore 1530-3, 3 M Health Care Co.). Each sample was cut into 12 mm×50 mm size and attached to a bakelite plate. After kept at 37℃ for 30 min., they were peeled in the horizontal direction at the speed of 300 mm min^{-1} using the tensile tester(Tensilon RTC-1210 A, ORIENTEC Corporation).

RESULTS AND DISCUSSION

Effect of Substituent Group

To synthesize the adhesive with poly(ethylene glycol) unit, various poly(ethylene glycol) acrylates were copolymerized with 2-ethylhexyl acrylate and a small amount of acrylic acid, which are generally used as the

Table I. Results of copolymerization of poly(ethylene glycol) acrylate derivatives[a]

No.	Monomer (1)	Substitution group (R)	Monomer content / wt% 15	30	45
1	PEGA	-H	Gel	Gel	–
2	PEGMA	$-CH_3$	No gel	Gel	–
3	PEGBA	$-(CH_2)_3CH_3$	–	No gel	No gel
4	PEGOA	$-(CH_2)_7CH_3$	–	No gel	No gel
5	PEGLA	$-(CH_2)_{11}CH_3$	–	No gel	No gel
6	PEGPA	-Ph	Gel	Gel	–
7	PEGNPA	-Ph-*p*-$(CH_2)_8CH_3$	Gel	Gel	–

[a]Comonomers were 2-ethylhexyl acrylate (50—80 wt%) and 5 wt% of acrylic acid. Polymerization time was 6 h.

monomer to give adhesion and cohesion for the TDD adhesive(Scheme I). Poly(ethylene glycol) acrylate easily forms cross-linked gel in radical polymerization by the chain transfer.[5] As shown in Table I, copolymers with high content of poly(ethylene glycol) unit were obtained by copolymerizing butyl, octyl and lauryl substituted poly(ethylene glycol) acrylate monomers. The poly(ethylene glycol) acrylate monomers with phenyl, nonylphenyl and hydrogen substituent easily formed gel at 15 wt% content in the monomers and the monomer with methyl substituent formed gel at 30 wt% content. Butyl, octyl and lauryl substituted monomer did not give a gel even at 45 wt% content. These results indicate that prevention of gel formation decreases in the order of lauryl, octyl, butyl > methyl > phenyl, nonylphenyl and hydrogen.

Although phenyl or nonylphenyl groups are large substituent group like lauryl or octyl, they easily showed gel formation. This indicates that steric effect of substituted group is not important for preventing gel formation.

Electron release of substituent thus appears more effective than steric effect to prevent the gel formation by chain transfer.

Peel Strength and WVP of PEGLA Copolymers

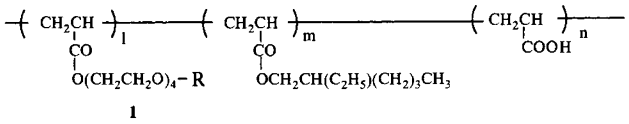
Since solubility of drug is very important for TDD adhesive as well as WVP, we evaluated the properties of PEGLA copolymers which contain surfactant structure. Peel strength and characterization of the copolymers with various PEGLA content(0, 20, 40 wt%) are shown in Table II. The copolymer possesses similar molecular weight(M_w, M_w/M_n) and almost the same peel strength with good cohesion. PEGLA may thus have adhesive properties like 2-ethylhexylacrylate by itself.

WVP of PEGLA copolymers were investigated by

Table II. Characterization and properties of PEGLA[a] copolymers[b]

No.	PEGLA content wt%	M_w[c] (10^{-5})	M_w / M_n	Peel strength (g/12 mm)	WVP g m^{-2} day^{-1}
1	40	3.03	4.8	505	780
2	20	4.33	5.2	558	500
3	0	4.31	4.4	497	390

[a]Poly(ethylene glycol) laurylether acrylate. [b]Comomomers were 2-ethylhexyl acrylate(45—85 wt%) and 15 wt% of acrylic acid. Polymerization time was 6 h except No.3(2 h). [c]Determined by GPC.



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Scheme 1.

measuring increase in weight of $CaCl_2$ covered with adhesive copolymer film. As shown in Table II, WVP increased with PEGLA content. Polymer characteristics (M_w and M_w/M_n) of the PEGLA copolymers were similar. PEGLA copolymers thus increase the affinity to water vapor by introducing PEG unit in the copolymer. WVP of the PEGLA copolymer at 40 wt% PEGLA showed 780 g m^{-2} Day^{-1}. Perspiration from human skin at rest is about 600 $g^{-2}m$ Day^{-1}. Therefore PEGLA copolymer is expected to prevent skin irritation by maceration.

Poly(ethylene glycol) alkyl ether acrylates with long alkyl substituent did not form a cross-linked gel in radical polymerization and the copolymer showed high WVP and good adhesive properties as transdermal drug delivery adhesive.

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REFERENCES

1. T. A. Peterson, S. M. Wick, and C. Ko., in "Transdermal and Topical Drug Delivery Systems", T. K. Ghosh, W. R. Pfister, and S. I. Yum., Ed.,Interpharm Press,Inc.,Buffalo Grove,Illinois, 1997, p 281.
2. T. Sugii, M. Konno, and S. Wada., *Nitto Giho*, **27**, 42(1989).
3. S. Otsuka, T. Yoshikawa, S. Tokuda, and Y. Ito., JP 57-85318, NITTO DENKO Co.(1983).
4. Y. Hosaka, S. Otsuka., JP 01-297068, NITTO DENKO Co. (1989).
5. G. Bo, B. Wesslen, and K. B. Wesslen., *J. Polym. Sci., Part A : Polym. Chem.*, **30**, 1799(1992).