Preparation of Ketoprofen-Loaded High-Molecular-Weight Poly(vinyl alcohol) Gels

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ABSTRACT: High-molecular-weight atactic poly(vinyl alcohol) (a-PVA) gels loaded with (*R,S*)-2-(3-benzoylphenyl)propionic acid (ketoprofen) were prepared from 5, 6, 7, and 8 g/dL solutions of a-PVA with a number-average degree of polymerization of 4000 in an ethylene glycol/water mixture with an aging method to identify the effect of the initial polymer concentration on the swelling behavior, morphology, and thermal properties of a-PVA gels. Then, the release behavior of ketoprofen from a-PVA gels was investigated. As the polymer concentration decreased, the ability for network formation decreased, and the degree of swelling of the a-PVA gels increased. In addition, the enthalpy increased with an increase in the a-PVA concentration, but the melting temperatures of the gels prepared at different initial polymer concentrations were the same; this indicated that tighter gel networks would be formed by a higher polymer chain density. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 3268–3272, 2007

Key words: high-molecular weight; a-PVA gel; ketoprofen

INTRODUCTION

Recently, poly(vinyl alcohol) (PVA) has attracted much attention because of its potential application as replacement fibers for carcinogenic asbestos, as films for polarization, food, and drug packaging, as hydrogels for drug delivery systems, and as barrier membranes.[1,2] Among these, hydrogels are a unique class of polymeric materials that imbibe enormous amounts of water when left in water reservoirs for long times. The underlying property for this unusual behavior of hydrogels is their transition from a glassy state to a rubbery state when they come into contact with thermodynamically compatible solvents. This water sorption property of hydrogels accounts for a great number of biomedical applications. The results reported so far in the literature for drug release from PVA hydrogels suggest veterinary applications. Moreover, many investigations of PVA hydrogels for use in biomedical applications, including implants, soft contact lenses, and artificial organs, have been carried out. In particular, PVA hydrogels have a high solvation degree and biocompatibility, which are needed for the *in vivo* administration of drugs.[1–8]

PVA is a linear semicrystalline polymer, so it can be crosslinked into hydrogels for drug delivery. PVA hydrogels prepared by a low-temperature gelation method have a porous and three-dimensional network structure with strong mechanical strength and high water content. Several methods have been reported for the preparation of PVA hydrogels, including (1) chemical methods using irradiation or bifunctional-group-containing chemical agents such as glutaraldehyde and boric acid, (2) physical methods using complexing agents such as titanium, aluminum manganese, and copper, and (3) radiation methods using X-rays, electron beams, and ultraviolet light. Their water solubility, transparency, and modulus can be modified by the attachment of substituents such as acetates, acetals, or urethanes to some of the secondary OH— groups of the backbone. The remaining alcohol groups act as physical crosslinking sites (via hydrogen bonds) between adjacent polymer chains, forming a three-dimensional network with considerable stability. Moreover, PVA hydrogels prepared by aging methods have shown properties superior to those of hydrogels prepared by other methods.[9–17]

(*R,S*)-2-(3-Benzoylphenyl)propionic acid (ketoprofen), a potent nonsteroidal anti-inflammatory drug that

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inhibits prostaglandin synthetase cyclooxygenase, is used as a peroral treatment for rheumatoid arthritis and other related diseases. Its gastrointestinal side effects could be avoided with transdermal forms. It would be desirable to bring ketoprofen into deeper skin layers to enable it to act at the site of inflammation. Several attempts have been made to enhance the penetration of ketoprofen. One group investigated the effects of fatty acids and urea on the penetration of ketoprofen through rat skin and found 50-fold increased permeation in propylene glycol/water induced by lauric acid. Several researchers[18–21] prepared a supersaturated gel of ketoprofen by heating a mixture of the drug with hydrogenated soybean phospholipid and liquid paraffin and then cooling it. There was a 10-fold increase in the permeation of the heated gel versus that of a gel prepared at room temperature.

In this study, we prepared ketoprofen-loaded high-molecular-weight atactic poly(vinyl alcohol) (a-PVA) gels with various initial polymer concentrations by an aging method and observed their characterizations. That is, the effect of the polymer concentration on the morphology and physical properties of a-PVA gels and the release behavior of ketoprofen were investigated.

EXPERIMENTAL

Materials

High-molecular-weight a-PVA was prepared by the saponification of poly(vinyl acetate) prepared by the solution polymerization of vinyl acetate at 30°C with 2,2′-azobis(2,4-dimethylvaleronitrile).[14] The number-average degree of polymerization and degree of saponification of synthesized PVA were 4000 and 99.9%, respectively. Phosphate buffer solutions (PBSs) were prepared from phosphate buffer powder (Na_2HPO_4/KH_2PO_4). Na_2HPO_4/KH_2PO_4 and ketoprofen were purchased from Wako Co. (Osaka, Japan). Other reagents were purchased from Ducksan Co. (Ansan, Korea).

Preparation of the a-PVA gels containing ketoprofen

a-PVA was dissolved in a mixture of ethylene glycol (EG) and water (6/4 v/v) at 70–90°C for 1 h and was kept there for 30 min to ensure homogenization. Then, the prepared ketoprofen (1 g/dL) in an EG solution was added to the a-PVA solution at room temperature. The prepared a-PVA solution containing ketoprofen was aged at room temperature for 48 h.

Characterization

Electron micrographs of a-PVA gels with different polymer concentrations were taken to observe the effect of the polymer concentrations on the structure of the gels with an S-4100 scanning electron microscope (Hitachi, Tokyo, Japan). The samples were mounted on metal stubs with double-sided adhesive tape and argon-coated *in vacuo* for 120 s. The access voltage was 15 kV.

The degree of swelling of the PVA gels was measured at room temperature. Each PVA gel was placed in 15 mL of diluted water for 24 h at room temperature. The degree of swelling was calculated with the following equation:[22]

$$\text{Degree of swelling} = (W_w - W_d)/W_d \quad (1)$$

where W_w is the original weight of the a-PVA gel and W_d is the dry weight of the PVA gel.

The crystal melting temperature (T_m) of each PVA gel was measured with a TA Instruments DSC 2010 differential scanning calorimeter (New Castle, DE) with a sample weight of 10 mg in hermetically sealed aluminum pans under N_2 at a heating rate of 10°C/min, and the temperature ranged from −20 to 300°C.

Release test of the ketoprofen-loaded a-PVA gels

The prepared a-PVA solution containing ketoprofen was aged at room temperature for 2 days. *In vitro* release rate studies were carried out with the paddle method specified in USP XXIII.[23] Accurately weighted samples of a-PVA gels were used that were calculated to contain 1 mg of ketoprofen. They were placed in pH 7.4 PBS at 37 ± 1°C and rotated at 50 rpm. At designated time intervals, the supernatant (1 mL) from each test basket was withdrawn through a syringe filter, and 1 mL of fresh PBS was added. The released ketoprofen concentration was analyzed by high-performance liquid chromatography (HPLC). The HPLC conditions were as follows: the mobile phase of a solvent consisting of mixed acetonitrile and diluted water, an ultraviolet detector with a 245-nm wavelength, and an operating temperature of 25°C. The cumulative amount of ketoprofen released from the PVA gel was calculated with the following equation:

$$\text{Cumulative amount released } (\%) = M_t/M_{\text{actual}} \times 100 \quad (2)$$

where M_t is the amount of ketoprofen released from the a-PVA gel at time t and M_{actual} is the actual amount of ketoprofen loaded in the a-PVA hydrogel.[24–26] The cumulative amount of ketoprofen released was plotted versus the incubation time. Each data point was calculated on the basis of a calibration curve.

RESULTS AND DISCUSSION

In general, the main factors considered in the preparation of a gel are divided into molecular parameters such as the molecular weight and stereoregularity

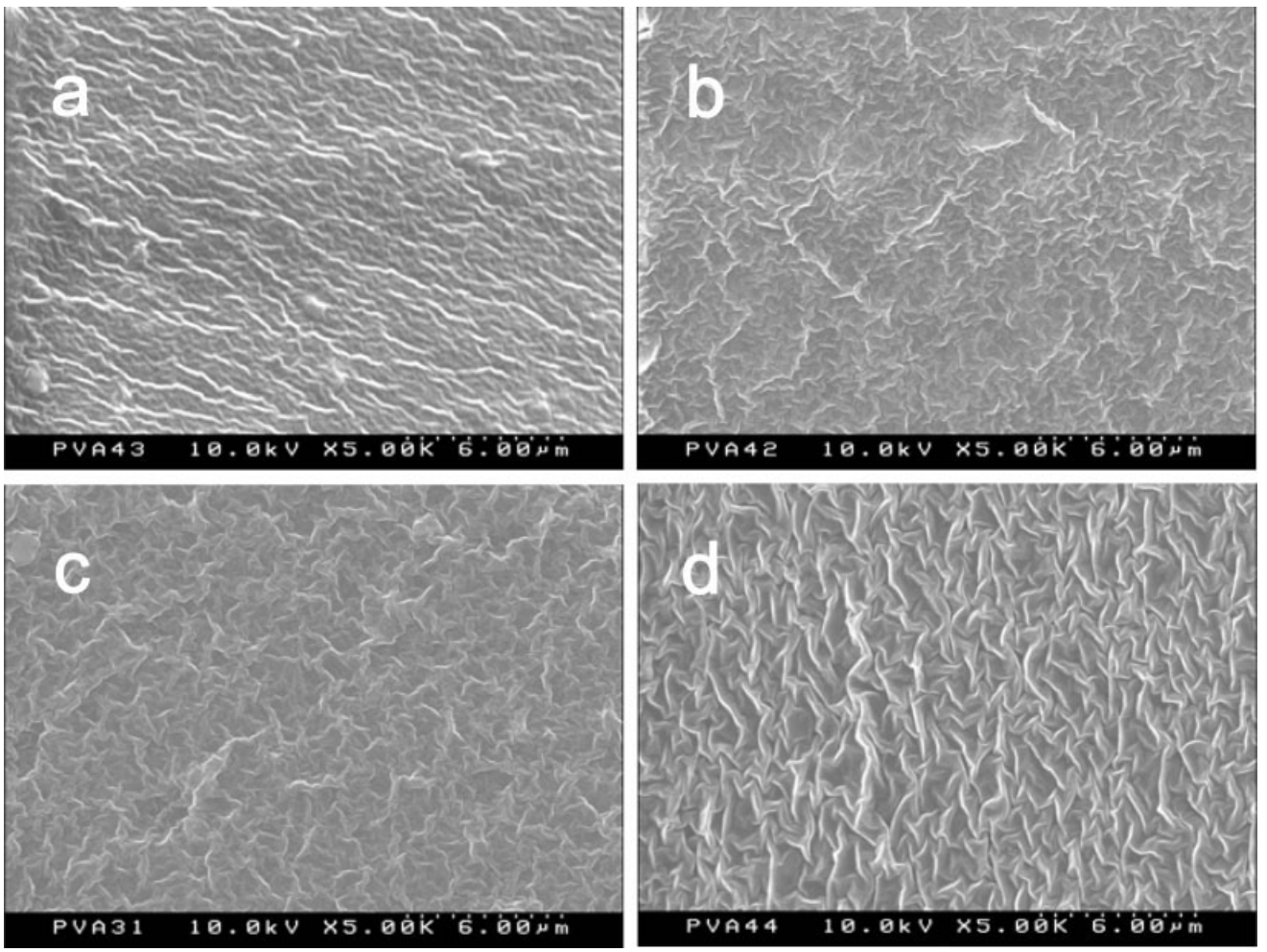

Figure 1 SEM photographs of PVA gels with polymer concentrations of (a) 5, (b) 6, (c) 7, and (d) 8 g/dL.

and processing parameters such as the polymer concentration. Among these, the polymer concentration is most important parameter because the intermolecular attraction can be charged with the polymer concentration. In this study, we mainly checked the effect of the polymer concentration.

Figure 1 shows scanning electron microscopy (SEM) photographs of a-PVA gels with different polymer concentrations. All the gels have a network structure. However, structural distinctions can be observed for the gels from solutions of different initial polymer concentrations. The denser domains are thought to correspond to a PVA-richer solution phase. As shown in Figure 1, more continuous gel skeletons appear at higher polymer concentrations. At the same time, Figure 1(c,d) shows that the gel skeletons become denser and the appearance becomes more distinct. Then, the formation of the PVA crystallites, which act as junction points, is much facilitated, and consequently, the gelation is much enhanced.

The degree of swelling is an important parameter for characterizing the gel because it has a significant influence on the drug release. This can be attributed to the fact that the strong hydrogen-bonding interactions between the polymer and water lead to swelling behavior. It is well established that the hydroxyl groups of PVA form strong hydrogen bonding with water, enhancing the hydrophilicity of the system. The degrees of swelling with respect to the immersion time for four different polymer concentrations are presented in Figure 2. The degree of swelling at equilibrium for the gels decreased from the values of 10.0 and 9.0 to the values of 8.0 and 6.5, respectively. At a higher polymer concentration, the great decrease in the degree of swelling could be attributed to the crystallization of PVA segments. As shown in Figure 2, in the early stage of immersion, the plot can be considered sharply linear. In the linear region, all the gels seem to have a greater rate for absorbing water, and the water absorbed by the gels during this time represented roughly 98% of their water contents. The equilibrium was reached after only 10 h.

Figure 3 shows differential scanning calorimetry (DSC) thermograms of PVA gels with various polymer concentrations, and the data from these

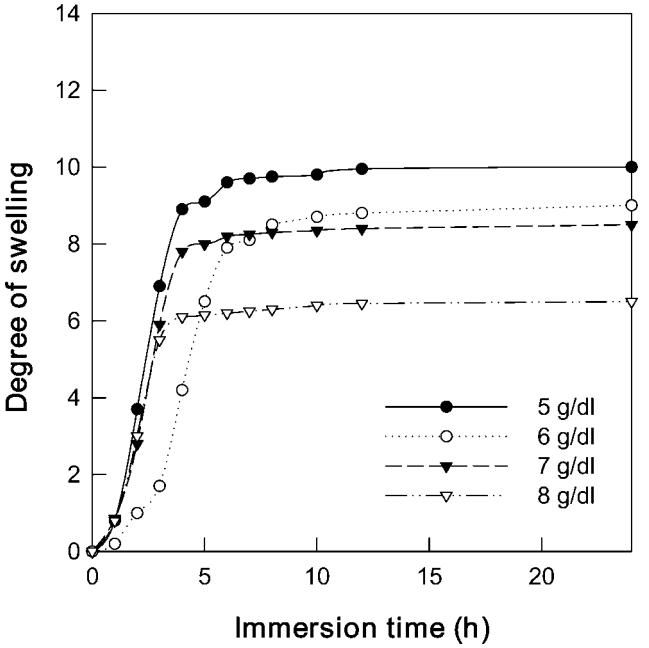

Figure 2 Degrees of swelling of PVA gels prepared at four different initial polymer concentrations versus the immersion time.

measurements are presented in Table I. All the PVA gels had an evaporating point of water during heating, having an endothermic peak at about 110°C. It seems that the introduction of physical crosslinking did not influence T_m in these gels but resulted in a significant increase in the crystallinity, which is expressed in terms of the enthalpy change in Table I. In Table I, it is obvious that the enthalpy of the a-PVA gel tended to increase with an increasing initial polymer concentration, regardless of T_m of PVA.

The drug release from a-PVA gels was studied with a buffer solution under several conditions. Figure 4 shows ketoprofen release profiles from a-PVA gels in PBS. The rate of release decreased with an increase in the initial polymer concentration. The final release amount of ketoprofen of the 8 g/dL gel was larger than those for the 5, 6, and 7 g/dL specimens. Moreover, the lower the polymer concentration was, the higher the release rate was.

CONCLUSIONS

In this study, for the preparation of high-molecular-weight a-PVA gels containing a drug, vinyl acetate was polymerized at 30°C with 2,2′-azobis(2,4-dimethylvaleronitrile), and saponification followed. Stable a-PVA gels were prepared with an EG/water cosolvent for drug delivery systems. Ketoprofen, used as an anti-inflammatory medication, was incorporated into the a-PVA gels. The characterization and drug release behavior with a-PVA gels containing ketoprofen were studied under various polymer concentrations. As the polymer concentration increased, the ability for network formation and the enthalpy of the PVA gels increased. The degree of swelling and the rate of release decreased. On the basis of these results, it is concluded that the initial polymer concentration is an important parameter in preparing PVA gels. In the near future, we will report on the

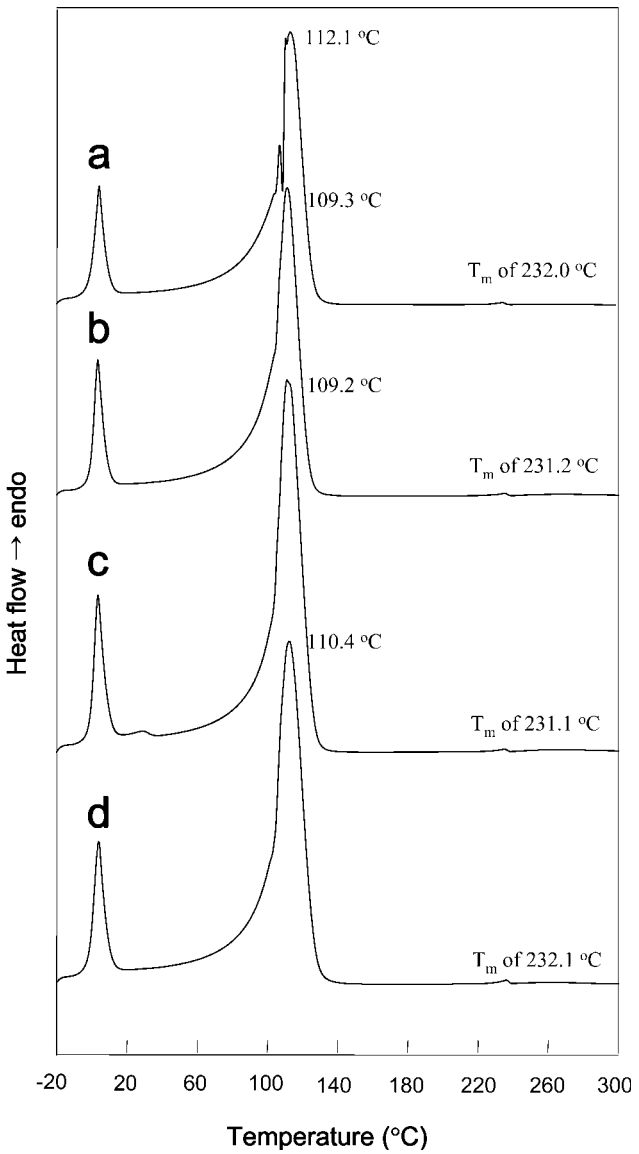

Figure 3 DSC thermograms of PVA gels with polymer concentrations of (a) 5, (b) 6, (c) 7, and (d) 8 g/dL.

TABLE I
Melting Parameters of a-PVA Gels Determined by DSC

Polymer concentration (g/dL)	(ΔH) Enthalpy change (cal/g)	T_m (°C)
5	99.5	232.0
6	136.5	231.2
7	148.6	231.1
8	190.7	232.1

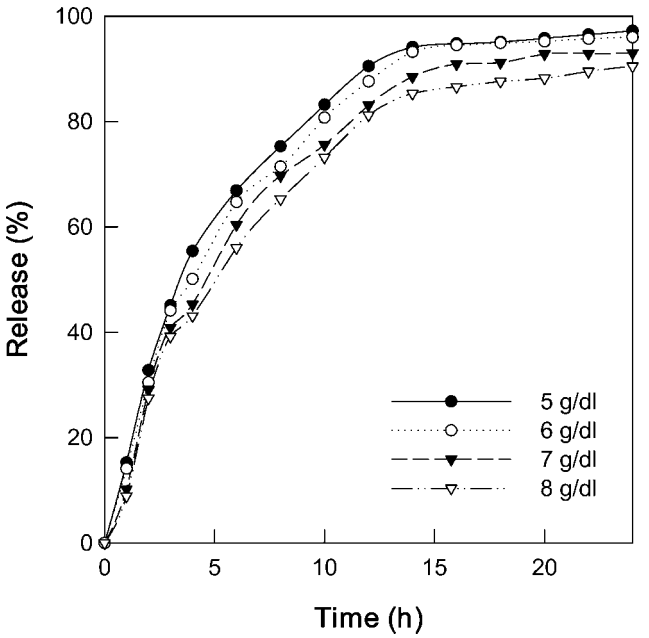

Figure 4 Amount of ketoprofen released from a-PVA gels prepared with four different initial polymer concentrations versus the time.

effects of molecular parameters of PVA such as the molecular weight, degree of saponification, and stereoregularity on the characteristics of PVA gels, including drugs.

References

1. Okaya, T. In Polyvinyl Alcohol Development; Finch, C. A., Ed.; Wiley: New York, 1991.
2. Shaheen, S. M.; Yamaura, K. J Controlled Release 2002, 81, 367.
3. Juang, J. H.; Bonner, W. S.; Ogawa, Y. J.; Vacanti, P.; Weir, G. C. Transplantation 1996, 61, 1557.
4. Chen, D. H.; Leu, J. C.; Huang, T. C. J Chem Technol Biotechnol 1994, 61, 351.
5. Tanigami, T.; Murase, K.; Yamaura, K.; Matsuzawa, S. Polymer 1994, 35, 2573.
6. Basmadjian, D. M.; Sefton, V. J Biomed Mater Res 1983, 17, 509.
7. Colombo, P.; Caramella, C.; Conte, U.; Gazzaniga, A.; Lamanna, A. J Controlled Release 1985, 1, 283.
8. Darwis, D.; Yoshii, F.; Makuuchi, K.; Razzak, M. T. J Appl Polym Sci 1995, 55, 1619.
9. Lyoo, W. S.; Blackwell, J.; Ghim, H. D. Macromolecules 1998, 31, 4253.
10. Tanigami, T.; Yano, K.; Yamaura, K.; Matsuzawa, S. Polymer 1995, 36, 2941.
11. Lyoo, W. S.; Shin, D. S.; Han, S. S.; Noh, S. K.; Kim, J. A.; Choi, H. G.; Yong, C. S.; Kim, J. R.; Kim, J. H. Polym Polym Compos 2006, 14, 39.
12. Lyoo, W. S.; Kim, B. C.; Ha, W. S. Polym Eng Sci 1997, 37, 1259.
13. Lyoo, W. S.; Cho, S. H.; Shin, D. S.; Han, S. S.; Park, C. S.; Kim, J. H.; Noh, S. K. Polym Polym Compos 2006, 14, 47.
14. Kim, S. G.; Lee, W. S.; Jo, S. M.; Kim, B. C.; Lyoo, W. S.; Han, J. R. J Korean Fiber Soc 1999, 36, 354.
15. Cho, J. D.; Lyoo, W. S.; Chvalun, S. N.; Blackwell, J. Macromolecules 1999, 32, 6236.
16. Lyoo, W. S.; Kim, B. C.; Ha, W. S. Polym J 1998, 30, 424.
17. Horiike, S.; Yumoto, K.; Kanbara, K.; Matsuzawa, S.; Yamaura, K. J Appl Polym Sci 2000, 78, 41.
18. Thanoo, B. C.; Sunny, M. C.; Jayakrishnan, A. J Pharm Pharmacol 1993, 45, 16.
19. Carstensen, J. T.; Marty, J. P.; Puisieux, F.; Fessi, H. J Pharm Sci 1981, 70, 222.
20. Tanigami, T.; Shirai, Y.; Yamaura, K.; Matsuzawa, S. Polymer 1994, 35, 1970.
21. Nambu, M. Jpn. Pat. 82-130543 (1982).
22. Gholap, S. G.; Jog, J. P.; Badiger, M. V. Polymer 2004, 45, 5863.
23. Comoglu, T.; Fonul, N.; Baykara, T. Farmaco 2003, 58, 101.
24. Li, J. K.; Wang, N.; Wu, X. S. J Controlled Release 1998, 56, 117.
25. Horiike, S.; Matsuzawa, S. J Appl Polym Sci 1995, 58, 1335.
26. Sugimoto, K.; Yoshida, M.; Yata, T.; Higaki, K.; Kimura, T. Biol Pharm Bull 1998, 21, 1202.