Purity of crosslinkers for polymeric hydrogel preparation

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Chromatographic procedures are described for purifying and assessing the purity of two crosslinking agents commonly used in the preparation of polymeric hydrogels. Densities and refractive indices at different temperatures are reported for these materials.

Keywords Chromatography; purification; crosslinking; hydrogel; thin layer chromatography; column chromatography; ethylene glycol dimethacrylate

Introduction

Polymeric hydrogels find extensive biomedical application, e.g. for soft contact lenses. They must satisfy several stringent requirements including that of elasticity in the swollen state. This particular facet is influenced by the concentration of crosslinking agent used in the polymerization (or, more usually, the copolymerization or terpolymerization). Although the chemical nature of the crosslinker is of much less significance than its concentration, the precise role of the former is not yet wholly resolved. In the authors' laboratory the hydrogels are prepared at 100% conversion *via* the γ-irradiation of outgassed mixtures comprising crosslinker and monomer(s).

Polyfunctional acrylate and methacrylates are among the most frequently used crosslinking agents in this field. This is presumably associated with their failure to introduce incompatibility in the final product, at least at the low concentrations employed (*ca.* $\leqslant 1\%$ wt.). Much effort has been expended on attaining high levels of purity in the monomers, but the literature indicates otherwise with regard to the crosslinking agents. Certainly, purification by vacuum distillation of such very high boiling and readily polymerizable materials can be both difficult and inconvenient.

In this communication we describe a simple mode of purifying two important crosslinkers, one being tetrafunctional and the other hexafunctional, viz. ethylene glycol dimethacrylate (EDMA)* and 1,1,1-trimethylolpropane trimethacrylate (TPT)** respectively. The procedure should be readily applicable to similar substances. Some physico-chemical data obtained on the purified products are also presented.

Procedure and Results

(*a*) *TPT.* Two commercial samples of TPT were examined, one from ICN Pharmaceuticals Inc., Plainview, New York, U.S.A., denoted here as ICN, and the other from Ancomer Ltd., Manchester, England, for which the makers' designation of ATM-11 is adopted here. (Sample ATM-11 is the same as the product marketed as SR-350 by the Sartomer Company in U.S.A.) In each instance *ca.* 0.5 g of TPT was deposited on preswollen silica gel (Hopkin and Williams, type M.F.C., 60–120 mesh) in a glass tube of length 50 cm and diameter 2 cm and eluted at a flow rate of 0.2 ml min^{-1}. The eluant consisted of a 1:1 (vol) mixture of diethyl ether/n-hexane in which the n-hexane had been purified beforehand by passage through a similar column, dried with anhydrous $MgSO_4$ and distilled at atmospheric pressure. About thirty eluted fractions (each 1 ml) were collected and monitored by thin layer chromatography (t.l.c.). The first half contained only eluant, whilst pure TPT, as evidenced by a single t.l.c. spot, was present in the next 4–5 fractions. Pure TPT was isolated from the latter by rotary evaporation of the mixed solvents.

For t.l.c., a Polygram Sil G/UV$_{254}$ plate, 20 × 5 × 0.025 cm was used (Macherey–Nagel, W. Germany) and the eluant was the same as that used for column chromatography. The spots were revealed (yellow on a purple background) by spraying the plate with a 0.2% w/v solution of $KMnO_4$ in acetone. *Figure 1* shows that t.l.c. is able to reveal the presence of six impurities in the original ICN and four impurities in the original ATM-11. For the

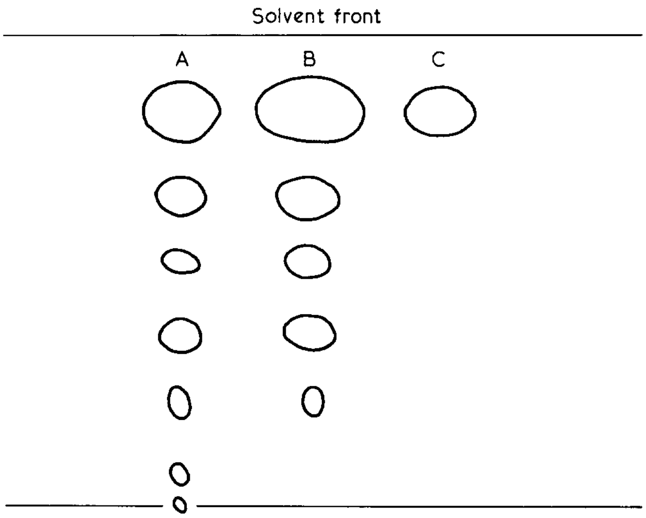

Figure 1 Thin layer chromatograms of (A) ICN, (B) ATM-11 and (C) pure TPT

Systematic names:
* Ethane-1,2-diyl-bis-2-methyl-2-propenoate
** 2-ethyl-2-{[(2-methyl-1-oxo-2-propenyl)oxo]methyl}-1,3-propandiyl-bis-2-methyl-2-propenoate

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Table 1 Properties of commercial and purified crosslinkers

	TPT			EDMA	
	ICN	ATM-11	Purified	BDH	Purified
n^D at 20°C	1.4760	1.4761	1.4751	1.4548	1.4545
$-10^4 \cdot dn^D/dT$ (deg^{-1})	–	–	4.62	–	5.30
ρ at 20°C (g cm^{-3})	1.0711	1.1937	1.0199	1.0559	1.0137
$-10^4 \cdot d\rho/dT$ (g cm^{-3} deg^{-1})	–	–	8.37	–	9.30

purified TPT alone as well as for TPT in ICN and ATM-11, the R_f value of TPT under the specific t.l.c. conditions here was 0.75. To obtain sufficient pure TPT (*ca.* 2 cm^3), about six separate isolations (each using *ca.* 0.5 g impure TPT) were made by the column chromatography method. The infra-red spectrum was superimposable exactly with the literature spectrum[1]. In particular the –OH peaks[2] at 3430 cm^{-1} and 3530 cm^{-1}, present for ICN and ATM-11, were not evident in the purified sample.

(*b*) *EDMA*. One commercial sample (from B.D.H., Poole, England) was used. It is designated here as BDH. The procedures employed in column chromatography and t.l.c. were as in (a) above with the following slight differences: (i) it was possible to effect efficient separation by column chromatography starting with a larger quantity of BDH (*ca.* 2 ml) and (ii) to obtain good separation in both column chromatography and t.l.c. it was necessary to use a diethyl ether/n-hexane composition of 2:3 (vol) [instead of 1:1 (vol.)]. Six impurities were shown by t.l.c., the R_f value being 0.78 for EDMA alone and for EDMA in BDH. To obtain a yield of *ca.* 2 ml pure EDMA only two separate column separations were necessary.

(*c*) *Properties.* At several temperatures between 14° and 45°C, densities ρ were measured in previously calibrated dilatometers, and refractive indices n_D at a wavelength *in vacuo* of 589 nm were read on an Abbé refractometer. Results are given in *Table 1*. Infra-red spectra were run on a Perkin-Elmer 297 spectrometer.

Discussion

The mode of purifying TPT described here is convenient, since the b.p. is reported[3] to be >200°C at 1 mm pressure. We have been unable to locate any published physico-chemical data on the pure compound and so the properties listed in *Table 1* should prove useful to others as corroborative evidence of purity.

Provided certain mixed halides are added to prevent polymerization,[4,5] vacuum distillation of EDMA (b.p. 84°C at 1 mm pressure and 90°C at 4 mm pressure) is not only simple, but also removes the major impurities. However, Brinkman *et al.*[5] used similar but not identical conditions to isolate EDMA by preparative t.l.c. and observed one impurity remaining after distillation; a single spot was obtainable only *via* t.l.c. purification. We note that a reasonably large yield of pure EDMA is obtainable by column chromatography as described here. With regard to the properties of EDMA a cautionary note is advisable. In certain publications[5,6] literature values of n^D, ρ and b.p. have been tabulated. Unfortunately, due to a minor oversight, these collations do not appear to be wholly reliable, e.g. in some instances the values in the cited references are either slightly different or are not mentioned at all. Accordingly it is only possible to make unambiguous comparison on the basis of n^D_{20} for which the present value of 1.4545 lies between those of 1.4549 and 1.4533 obtained by Kopecek *et al.*[7] and Walling[8] respectively.

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