A Simple Method for Determining Water-Induced Gelling Times of Isocyanate Prepolymers
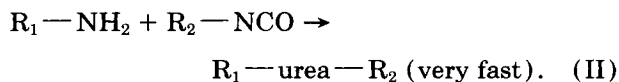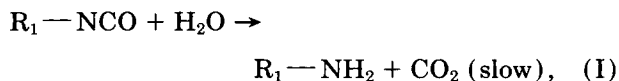
JAMES A. BRAATZ

W. R. Grace & Co.-Conn., Research Division, Department of Mammalian Cell Research, 7379 Route 32, Columbia, Maryland 21044

SYNOPSIS

A spectral assay has been developed that permits reliable determination of polymer gelling times. Water-soluble, isocyanate-containing polyether prepolymers initiate chain extension on contact with water and after some period of time form a semisolid hydrogel matrix. Techniques based on visual observations used to determine the end point for this process generally produce erratic results. By following scattered transmittance of visible light by an aqueous solution of prepolymer during the gelation process, it is possible to obtain a more objective determination of the gelation time. It was empirically demonstrated that the minimum of the first derivative of the scattered transmittance versus time spectrum correlated with the observed gel time over a wide time scale. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

Hydrogels have found numerous applications in the biomedical area as wound dressings, contact lenses, soft tissue replacements, drug delivery matrices, etc.[1] One family of materials of interest in this regard are the polyurethane hydrogels.[2] Polyurethane hydrogels can be prepared from isocyanate-capped prepolymers by reaction with water. These prepolymers can be dissolved in water, then on standing will react with the solvent water according to the following reactions[2]:

$$R_1 - NCO + H_2O \rightarrow$$
$$R_1 - NH_2 + CO_2 \text{ (slow)}, \quad (I)$$
$$R_1 - NH_2 + R_2 - NCO \rightarrow$$
$$R_1 - \text{urea} - R_2 \text{ (very fast)}. \quad (II)$$

The first reaction, conversion of isocyanate to primary amine, is relatively slow. However, once the amine is formed, it reacts rapidly with an isocyanate group to form a urea crosslink. If the prepolymer molecules are multifunctional with respect to isocyanate groups, then as polymerization proceeds, a three-dimensional network will form. If the backbone polyether structure is rich in ethylene oxide units, water will associate with the ether oxygens via hydrogen bonding.[3,4] This structure, together with the bulk-phase water trapped in the network forms a hydrogel, an irreversible, extensively hydrated network of polymer chains. Hydrogels of this type are known to possess excellent biocompatibility properties.[5,6]

In addition to the formation of hydrogels from isocyanate prepolymers, foams can also be generated from related prepolymers that have a higher content of isocyanate and a form of isocyanate that is more reactive with water. Foams result from the rapid production of CO_2 that acts as a blowing agent during the crosslinking process.

The rate of hydrogel formation is dependent on a number of factors, including the concentration of the prepolymer, pH, temperature, etc., most of which can be carefully controlled. At higher pH values, isocyanates crosslink faster due to the higher reaction rate of unprotonated primary amines with isocyanates. The rate also depends on the nature of the isocyanate prepolymer and can vary from batch to batch within the same prepolymer formulation.

During the synthesis of these prepolymers, and for production scale monitoring, various physical and chemical methods are available for monitoring
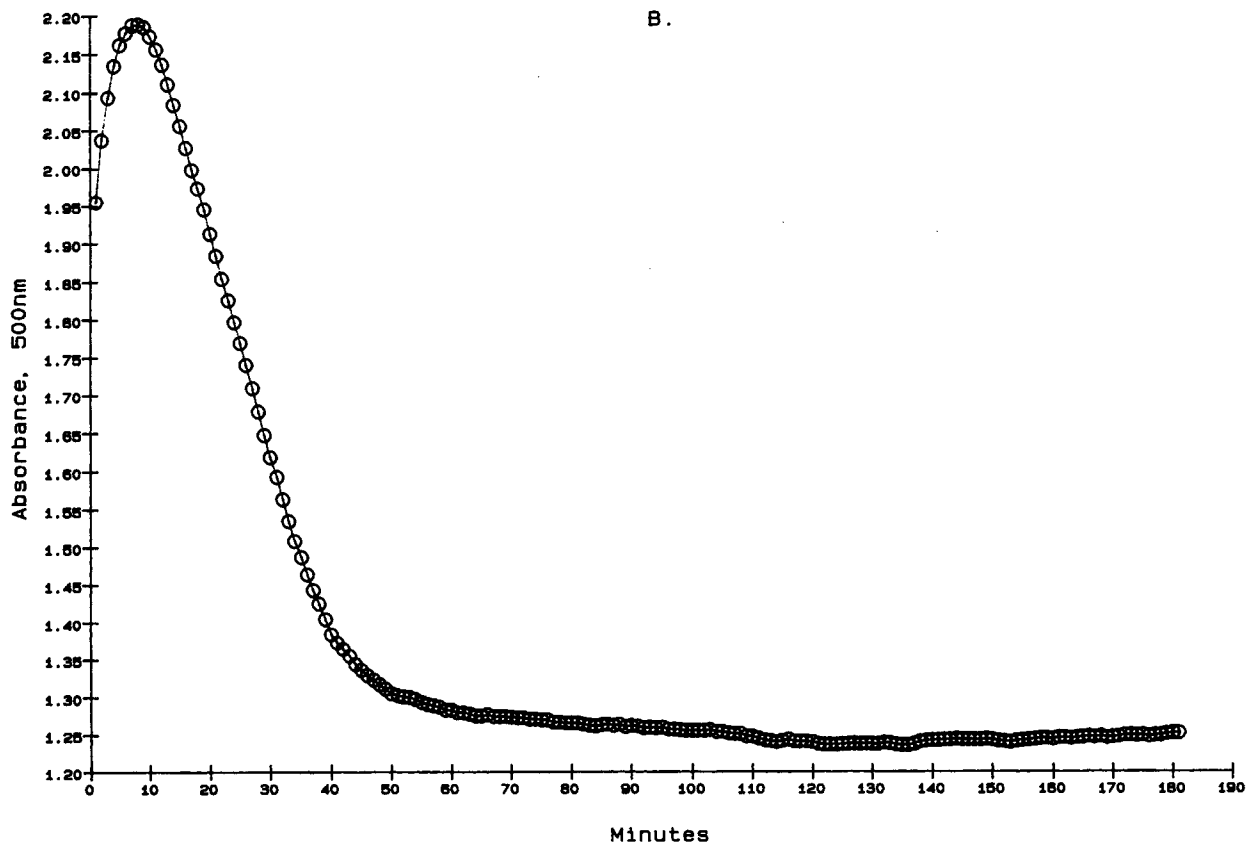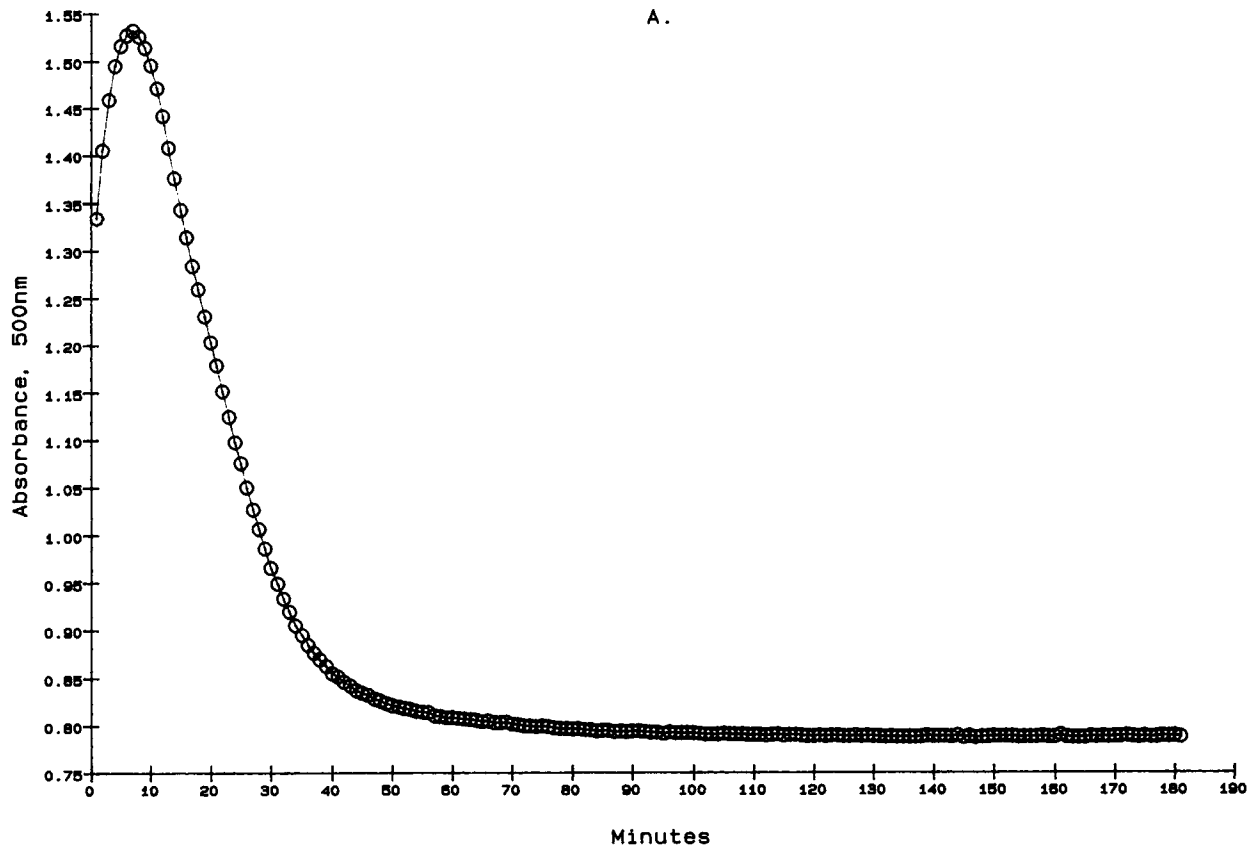
Figure 1 Absorbance changes and first derivative plots during gel formation. Panels A–D are scattered transmittance measurements for four different aqueous solutions of prepolymer and correspond to samples #5, 8, 6, and 2, respectively, from Table I. Panels E–H are the first derivative plots for panels A–D, respectively.
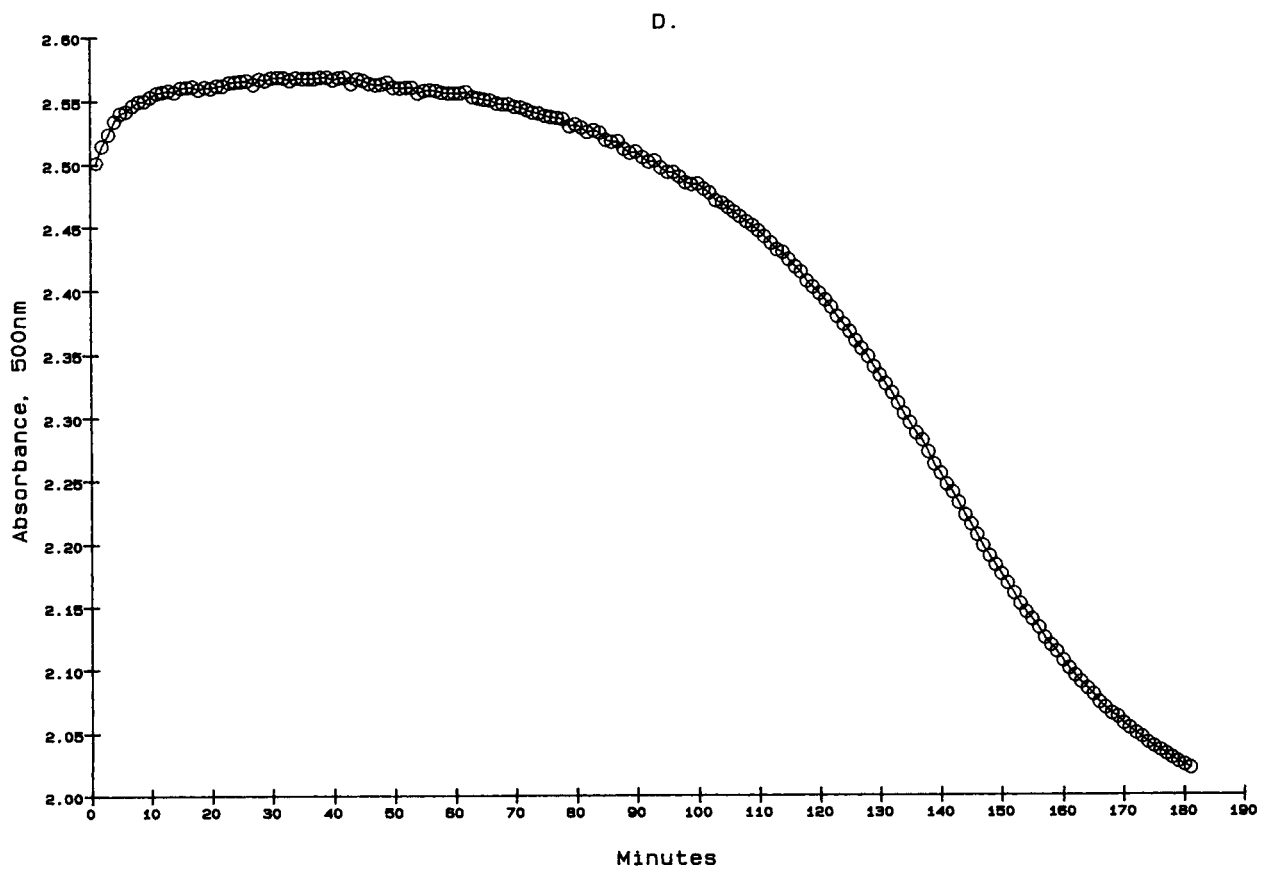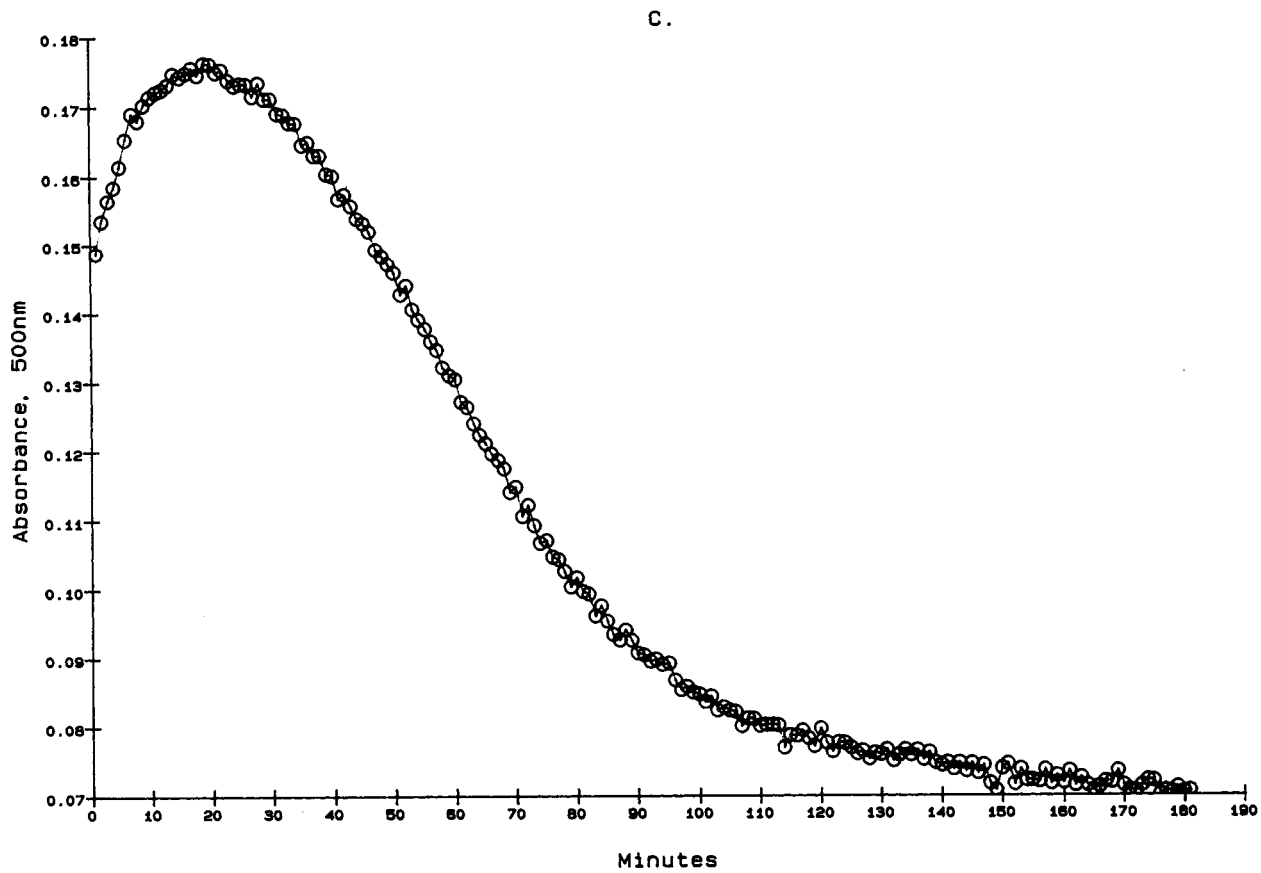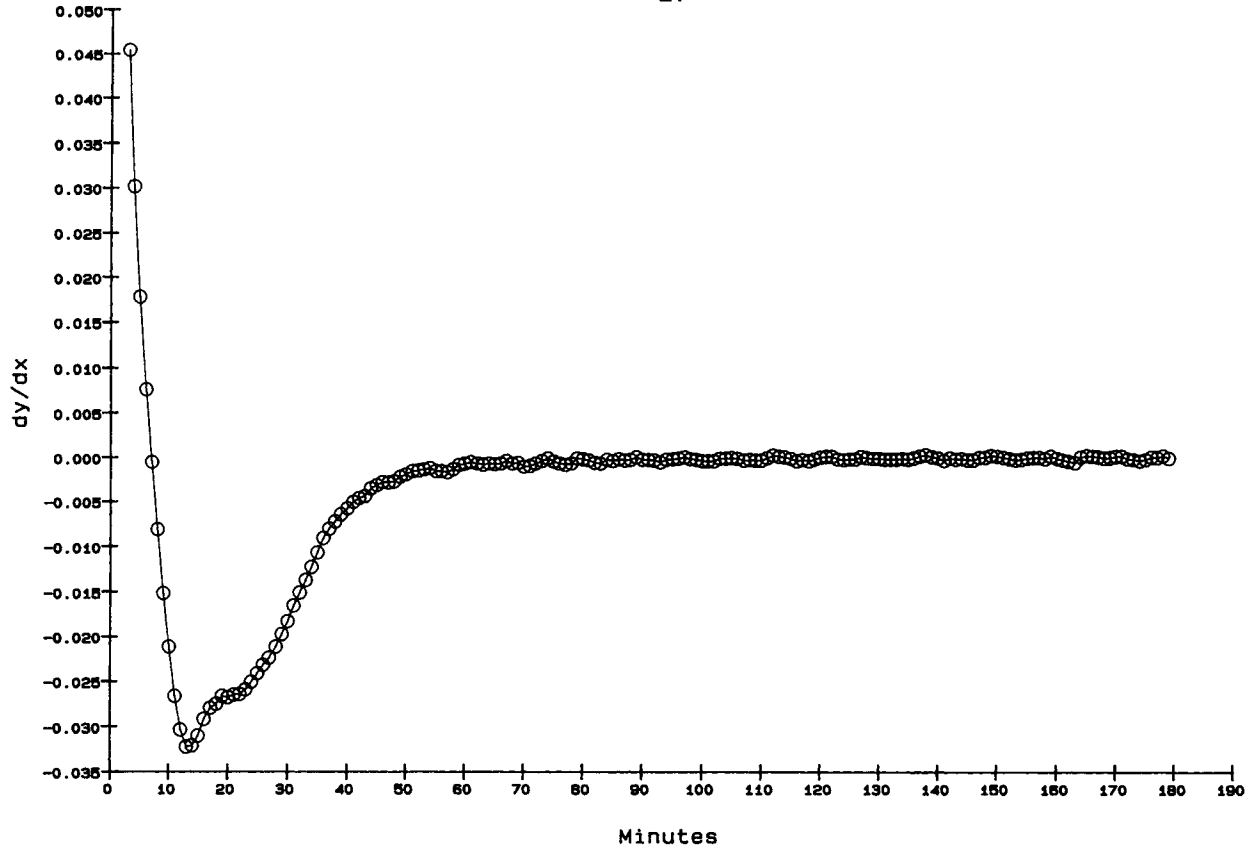
C.

D.

Figure 1   (*Continued from the previous page*)

E.

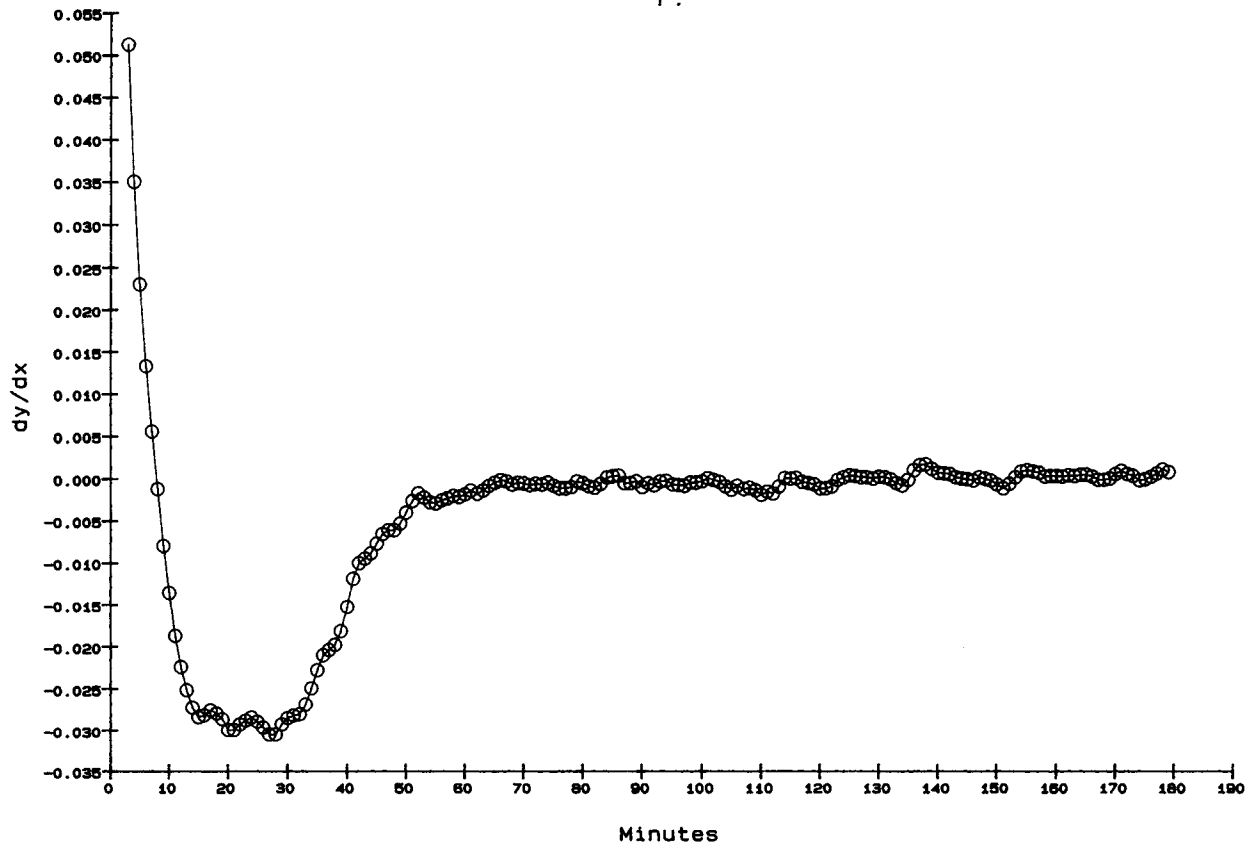
Minutes

F.

Minutes

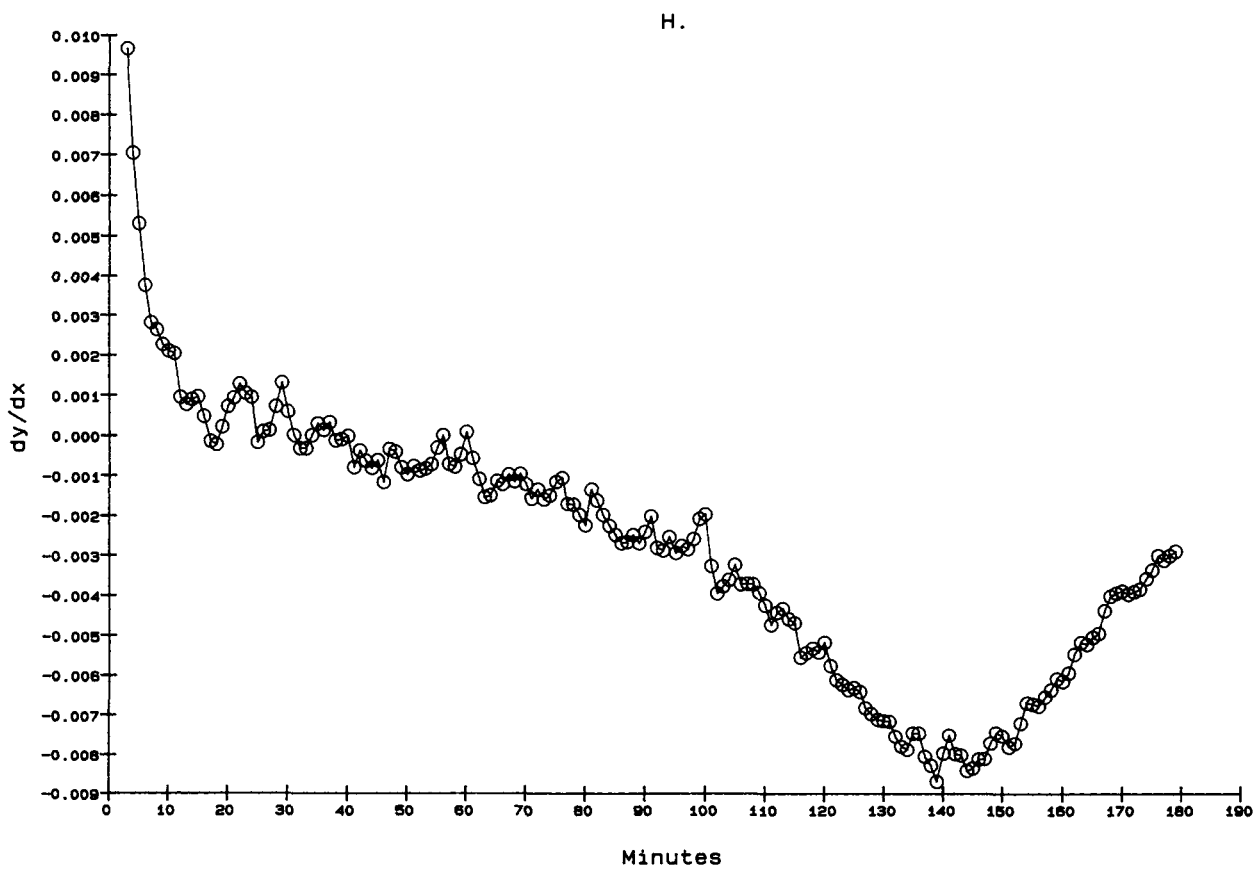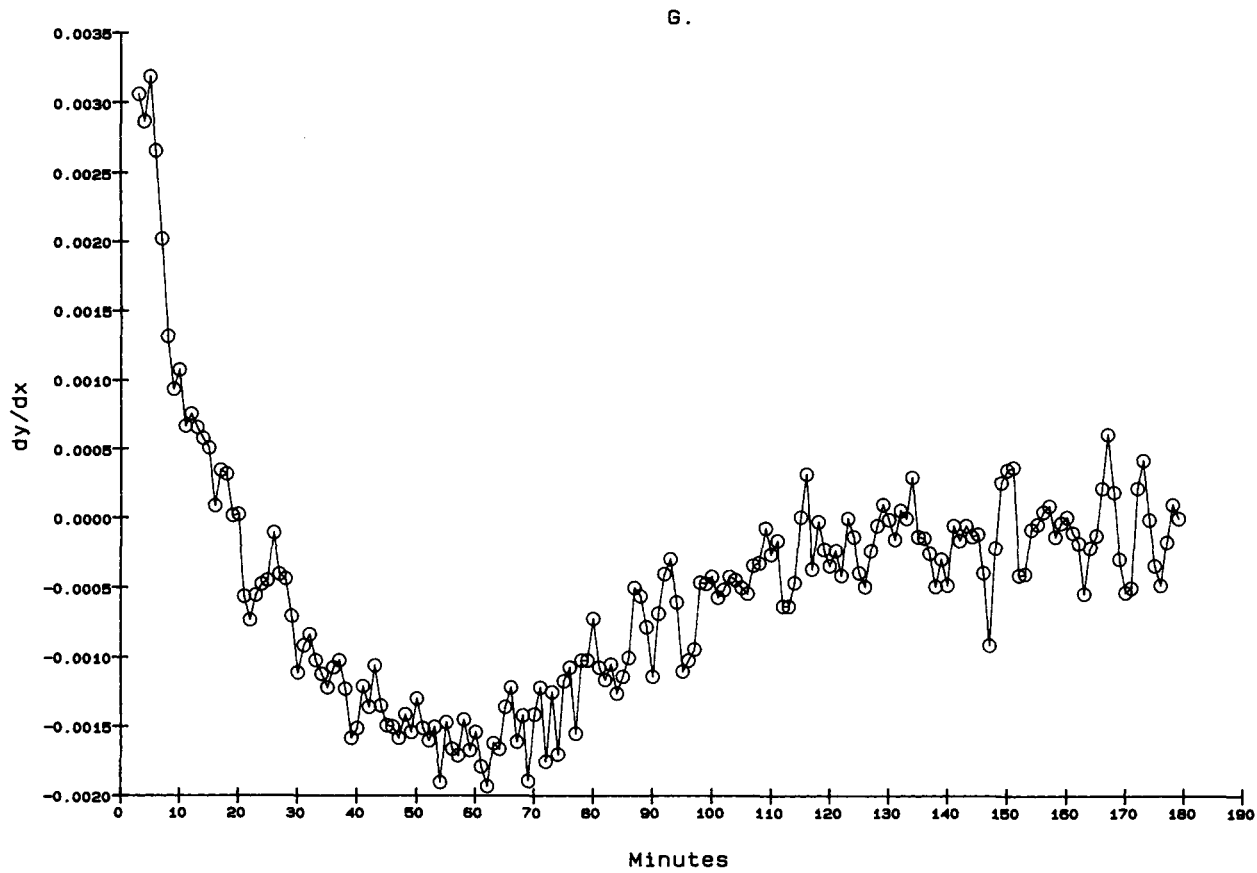**Figure 1**   (*Continued from the previous page*)

Figure 1 (*Continued from the previous page*)

quality or batch to batch variation. Thus, the isocyanate content, molecular weight, and viscosity are useful, quantifiable parameters that can be used to follow the isocyanate capping reaction during the preparation of these materials.

Another test that can provide useful information, one which is more functional in nature, is the time required for gel formation after mixing with water. The gel point of a polymer is a transition state between a liquid and a solid, and its definition and the means for its determination can vary broadly.[7,8] With hydrogel-forming prepolymer, the gelling time can be determined by somewhat subjective methods, such as tilting the mixture and visually observing its flow characteristics. We have found that the gel time for a prepolymer is a good indicator of its performance characteristics; however, the techniques available for measuring this property were unsophisticated and unreliable. The method presented here provides an objective approach to measuring the gel time for these prepolymers.

EXPERIMENTAL

The isocyanate prepolymer used for these studies was HYPOL® XP-5 (Hampshire Chemical Corp., Lexington, MA), a polyetherurethane prepolymer prepared by end-capping a water soluble polyether polyol with an aliphatic diisocyanate.[9] Solutions were prepared by dissolving an amount of prepolymer in distilled water or buffer solution at room temperature at the concentrations indicated in Table I. Immediately after dissolving, the solutions were transferred to semi-micro disposable cuvets (polystyrene, 1.5 mL, 10-mm optical path, VWR Scientific, Bridgeport, NJ). These were placed in a Gilford Response Spectrophotometer (Ciba-Corning Diagnostics Corp., Medfield, MA) that was linked to a VAX computer (Digital Equipment Corporation, Nashua, NH). The instrument was set to record absorbance values at 500 nm every minute for 3 h. Although the spectrophotometer reports absorbance data, the actual measurement being made is the intensity of light that passes through the solution, the remainder of the incident light being lost as a result of light scattering by the solution of polymer in water. The apparent absorbance values might be more properly referred to as "scattered transmittance." These data were transmitted to a VAX computer as an array, then processed with RS/1 software (BBN Software Products Corporation, Cambridge, MA) using the RPL programming language. A listing of the programs used is given in the appendix.

Table I   Gelling Time of Various Prepolymer Solutions

Sample No.	Polymer Batch	Concentration (%)	Solvent Composition	Gelling Time (min)	
				Visual	Spectral
1	A	5	H_2O	> 120	> 180
2	A	10	H_2O	40	140
3	A	20	H_2O	20	80
4	A	5	5 mM NaHCO$_3$	ND	110
5	A	10	0.1M NaHCO$_3$	20	12
6	B	5	H_2O	ND	60
7	B	5	5 mM NaHCO$_3$	ND	35
8	B	10	0.1M NaHCO$_3$	20	20
9	C	10	H_2O	60	95
10	D	5	H_2O	140	70
11	D	10	H_2O	90	60
12	D	15	H_2O	70	40
13	D	20	H_2O	40	30
14	D	30	H_2O	30	19
15	E	5	H_2O	> 180	90
16	E	10	H_2O	60	80
17	E	15	H_2O	20	50
18	E	20	H_2O	15	40

ND, not determined.

RESULTS AND DISCUSSION

As polymerization and crosslinking proceed in freshly prepared aqueous solutions of isocyanate-containing prepolymers of the type described here, the scattered transmittance of visible light was observed to increase briefly, then decrease steadily, finally reaching a constant level. An example of this is shown in Figure 1 (A–D). The nature of this response varied depending on the prepolymer batch, its concentration, and other factors that affect the rate of the reaction of isocyanate with water.

Although the rationale for performing this experiment was that some change in visible light absorption (or scattering) might be observed as the polymer/water mixture changes from a solution to a gel, the actual response of an initial increase followed by a slow decay was not anticipated. A correlation between the gelling time and the generated curve was established by a strictly empirical approach. Thus it was shown that these solutions would form semisolid hydrogel matrices in a time frame that correlated with the midpoint of the descending branch of the experimental curve.

To express this mathematically, a first derivative plot of the curve was generated, producing a minimum at the point of inflection of the curve (Fig. 1 (E–H), each of which is derived from Figure 1 (A–D), respectively. These minima correspond to the flex point of the descending segment of the original curve and allow for a more accurate assessment of that point because the minimum of the first derivative curve is easier to discern than is the midpoint of the original curve.

To validate the correlation between the first derivative minimum and the polymer gelling time, a series of solutions of isocyanate prepolymers were prepared in water under conditions that affected the rate of gel formation. This rate is proportional to prepolymer concentration, and can also be altered
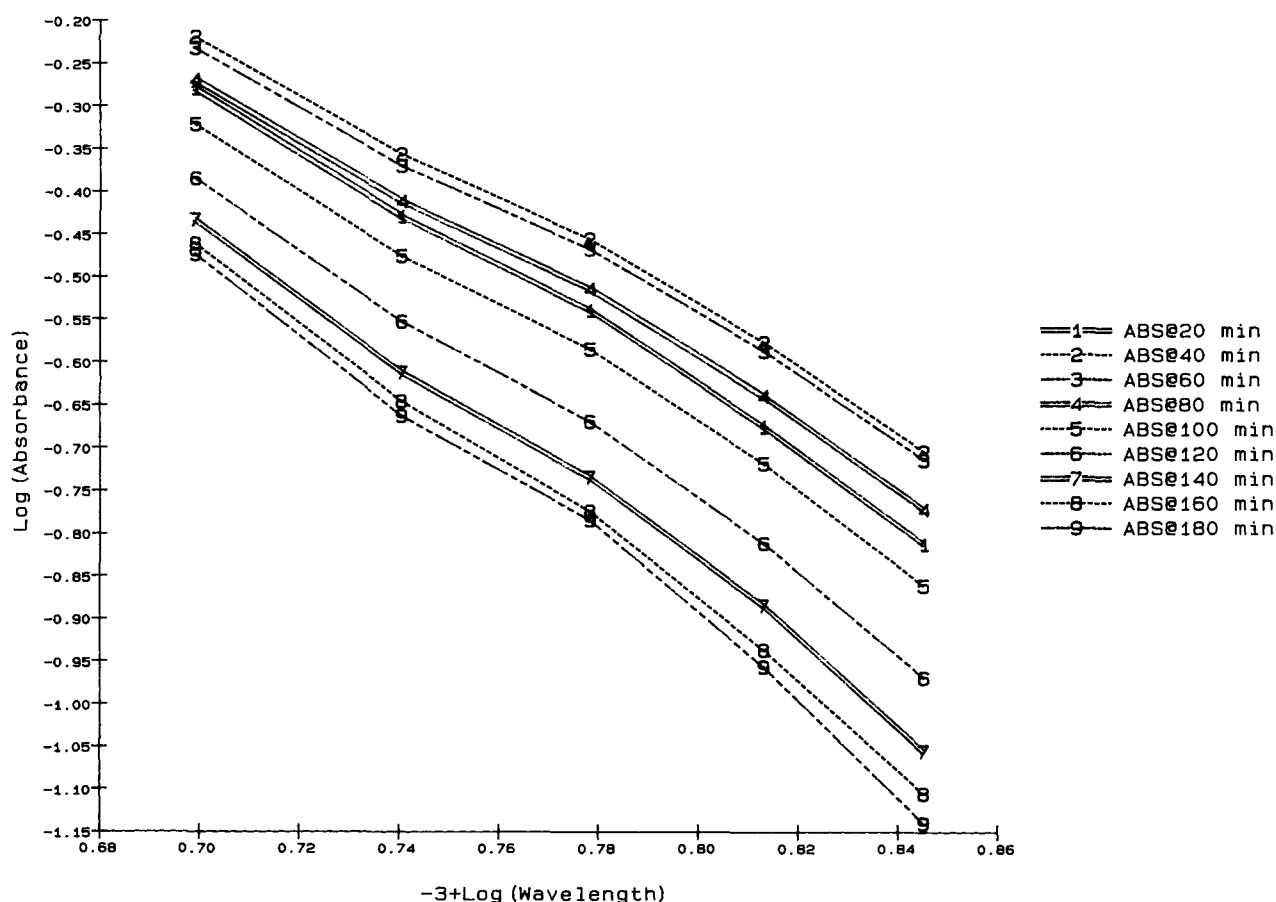
Figure 2   Log of absorbance changes during gel formation as a function of log of wavelength. At 10-min intervals after dissolving the isocyanate prepolymer in water, absorbance readings were taken at 500, 550, 600, 650, and 700 nm. Only half of the curves are plotted here for clarity.

by adjusting the pH of the solution. In this manner a series of experimental gelling times can be measured that vary from a few minutes to several hours. When this was done, each gelling time, as noted by visual inspection, was compared with the value of the first derivative minimum. Table I contains a list of these values generated for comparison. It can be seen that there is reasonable agreement between the two sets of values.

The observed variation in visible light absorbance by aqueous solutions of isocyanate-containing prepolymers can be attributed to light scattering caused by these polymers in solution, and is only indirectly measured as absorbance using a standard UV-VIS spectrophotometer. Nevertheless, the use of absorbance measurements represents a simple and reliable technique for obtaining a more objective estimate of gelling time than visual methods.

There is an initial rise in recorded values during the first 10–20 min after mixing the prepolymer with water, followed by a continual decrease for the next 2–3 h. On mixing with water, the polymer solution becomes visibly turbid, and over the course of the subsequent 3 h very little change can be detected visually.

A related effect has been observed with polyvinyl alcohol (PVA) solutions.[10] When rapidly cooled, PVA solutions have a scattering intensity that gradually increases as the solutions thaw. Turbidimetric measurements as a function of wavelength produced a linear response between 500 and 700 nm. Thus, plots of log D versus log λ produced a family of curves, the slopes of which were related to the particle size.[11] As thawing of the solutions proceeded, the slopes of the curves first decreased, then increased, which corresponded to particles increasing at first, then decreasing in size.

If this approach is applied to the system described here, plots of log D versus log λ can be obtained at varying times during the gelation event. Figure 2
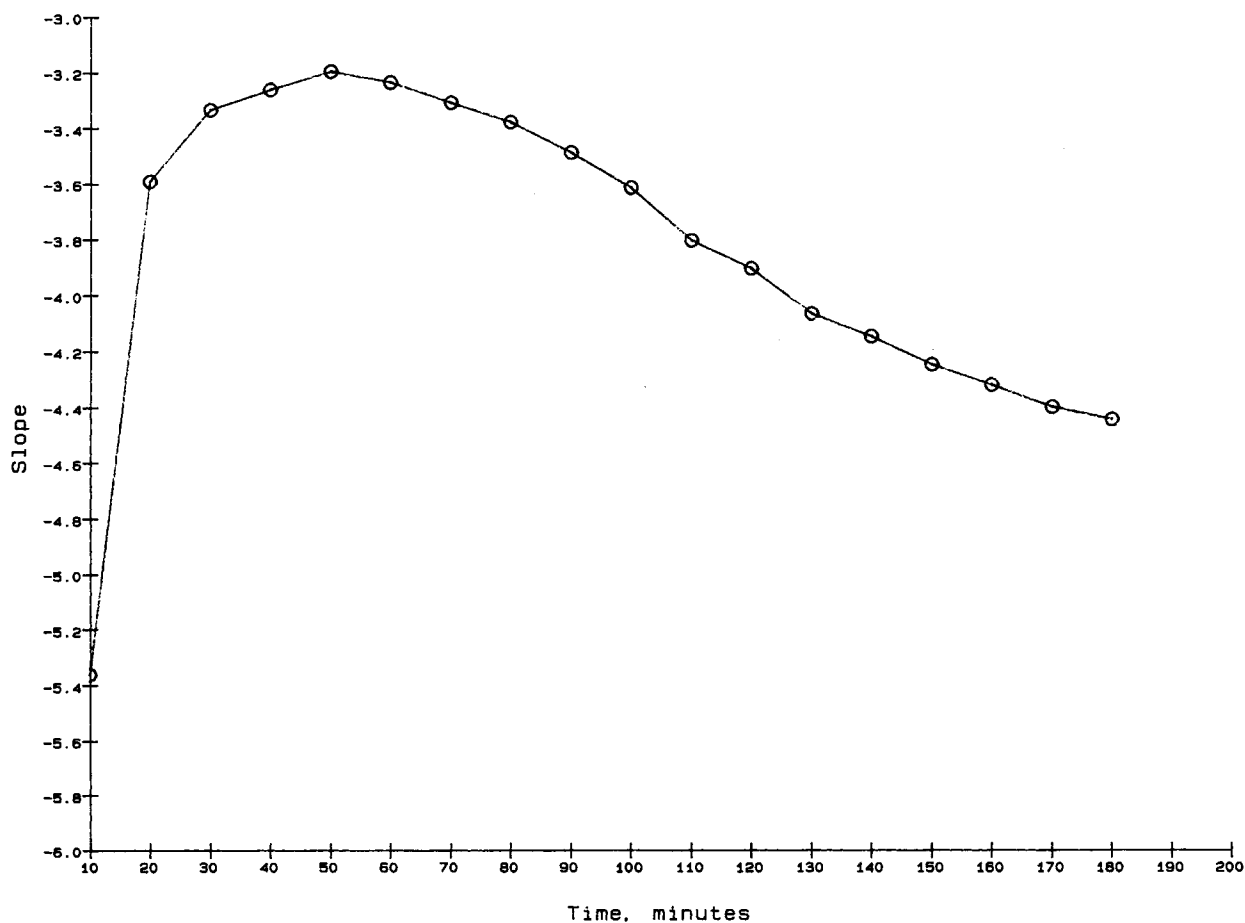
Figure 3 Variation of the slopes of the family of curves from Figure 2 with time. The best fit for each line in Figure 2 was determined by the RSI curve fitting routine. The slopes for each of the 18 lines are plotted here.

shows a family of curves obtained in 10-min increments over a 3 h gelation period. The curves are reasonably linear in this region. If their slopes are plotted over the course of the experiment, as shown in Figure 3, it can be seen that the slope abruptly increases initially, then slowly declines. If the arguments applied to PVA above apply to this system, then the opposite is occurring, that is, the early phase after the polymer is mixed with water produces particles of decreasing size that later are converted to larger particles. If this is the case, we can speculate that solvation of viscous polymer produces smaller particles that more effectively scatter light. As the reaction with water proceeds, the polymer chains crosslink, and smaller particles coalesce to larger particles, until finally a continuous gel phase is reached.

A theoretical treatment of the process of gelation as studied by light scattering measurements in another system has been reported recently. In thermoreversibly gelling polysaccharide models it was shown that slopes of time correlation functions of light scattering plotted against temperature produced a curve with a sharp change of slope. It was speculated that the flex point of this curve was related to the gel point for this system.[12] In a related study, the process of gel formation was found to correlate with gel point based on light scattering measurements.[13]

In block copolymer liquids consisting of polystyrene–polyisoprene, Balsara et al. have demonstrated a simple technique for determining the order-to-disorder transition in the copolymer liquids.[14] They found that static birefringence of these solutions decreased sharply on heating beyond a critical temperature. They attributed this point to the transition between order and disorder, which was confirmed by rheological measurements. Dynamic light scattering studies were also performed in this system at concentrations below and above the order-to-disorder transition and a response was found to correlate with the transition.[15]

CONCLUSION

The method described here can be useful in assessing the quality of gel-forming prepolymers by providing a reliable, reproducible estimate of their gelling time. This property can be used in addition to molecular weight, viscosity, isocyanate content, etc., to monitor batch-to-batch variations. Further, it is a better functional test for evaluating performance charac-

teristics of these polymers using a relatively simple experimental format.

APPENDIX

Gelation Analysis Program (written in RPL):

```
Flexpt
1    procedure;
2    call public $ez_readfile;
3    call tabadj;
4    call geltime;
5    call grapher;
6    end;
```

```
Tabadj
1    /*This procedure adjusts tables of data from
        the
2    /*spectrophotometer to fit the format required
        for RS/1 operation*/
3    procedure;
4    T=gettable("Table name:");
5    del rows 1, last row of table (T);
6    do c = 6 to 2 by -1;
7    set col c of table (T) = col (c-1);
8    end;
9    do i = 1 to last row of Table (T);
10   set col 1 row i of table (T) = i;
11   end;
12   end;
```

```
Geltime
1    /*This procedure calculates first and second
        derivatives*/
2    /*from columns of data using the 5 point
        smoothing*/
3    /*algorithm of Savitzky and Golay[16]*/
4    procedure;
5    t=gettable("Table name:");
6    do c = 2 to 6;
7    do i = 3 to (lastrow(t)-3);
8    x1=col c row (i-2) of table(t);
9    x2=col c row (i-1) of table(t);
10   x3=col c row i of table(t);
11   x4=col c row (i+1) of table(t);
12   x5=col c row (i+2) of table(t);
13   d1=(-2*x1 -x2 + x4 + 2*x5)/10;
14   set col (c+5) row i of table (t) = d1;
15   end;
16   end;
17   end;
```

Grapher

```
1    /*This procedure creates graphs of scattered
     transmittance vs time and first derivative
     plots*/
2    procedure;
3    gname = getgraph ("Name of first graph (Scat.
     Trans. vs Time) to be created:",true);
4    t=gettable("Table name:");
5    make graph (gname) from col 1 of table(t) vs
     col 2;
6    dis graph (gname);
7    gname = getgraph ("Name of first dy/dx graph
     to be created:",true);
8    make graph (gname) from col 1 of table(t) vs
     col 7;
9    dis graph (gname);
10   gname = getgraph ("Name of second graph
     (Scat. Trans. vs Time) to be created:",true);
11   make graph (gname) from col 1 of table(t) vs
     col 3;
12   dis graph (gname);
13   gname = getgraph ("Name of second dy/dx
     graph to be created:",true);
14   make graph (gname) from col 1 of table(t) vs
     col 8;
15   dis graph (gname);
16   gname = getgraph ("Name of third graph (Scat.
     Trans. vs Time) to be created:",true);
17   make graph (gname) from col 1 of table(t) vs
     col 4;
18   dis graph (gname);
19   gname = getgraph ("Name of third dy/dx graph
     to be created:",true);
20   make graph (gname) from col 1 of table(t) vs
     col 9;
21   dis graph (gname);
22   gname = getgraph ("Name of fourth graph
     (Scat. Trans. vs Time) to be created:",true);
23   make graph (gname) from col 1 of table(t) vs
     col 5;
24   dis graph (gname);
25   gname = getgraph ("Name of fourth dy/dx
     graph to be created:",true);
26   make graph (gname) from col 1 of table(t) vs
     col 10;
27   dis graph (gname);
28   gname = getgraph ("Name of fifth graph (Scat.
     Trans. vs Time) to be created:",true);
29   make graph (gname) from col 1 of table(t) vs
     col 6;
30   dis graph (gname);
31   gname = getgraph ("Name of fifth dy/dx graph
     to be created:",true);
32   make graph (gname) from col 1 of table(t) vs
     col 11;
33   dis graph (gname);
34   end;
```

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