DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(11-13), 2313-2324 (1986)

A PRELIMINARY INVESTIGATION OF A NOVEL SERIES OF SILICA GELS

G. N. Shah and M. J. Groves*

Department of Pharmaceutics, College of Pharmacy,
University of Illinois at Chicago,
833 South Wood Street,
Chicago, Illinois 60612

For Presentation at
5th Pharmaceutical Technology Conference
Harrogate, April 1986

for
subsequent submission to
Drug Development and Industrial Pharmacy

ABSTRACT

Silica gels may be produced by the hydrolytic polycondensation of organic silicates such as tetraethyl ortho silicate (TEOS) under appropriate conditions. These systems are of interest to the ceramic industry for making high purity silicate glasses at low temperatures. These silica gels may have application as drug delivery systems.

---

*Correspondence

0363-9405/86/1211-2313$3.50/0

The gelation rates due to the hydrolytic polycondensation process depend on the concentration of TEOS and water, the temperature, and the presence of acid or base catalysts. A wide variety of polymeric silica gels having different polymeric matrices and pore sizes are possible. Of the alcohols and glycols screened for silica gel formulation, ethanol and glycerol appear to have a unique role in the gelation process although they do not appear to contribute directly to the hydrolytic polycondensation process.

INTRODUCTION

Silica gels may be produced by hydrolytic polycondensation of organic silicates under appropriate conditions. These systems are of significant interest to the ceramic industry since high purity silicate glasses may be made at low temperatures by a sol-gel process[1,2].

Drugs may be incorporated in these silica gels and other investigators have demonstrated the potential application of desiccated silica gels as drug delivery systems[3]. Several drugs have been shown to act as a catalyst in the silica gel formation from an organic silicate, tetraethyl ortho silicate (TEOS)[3].

We are currently investigating the preparation of silica gels from TEOS as inexpensive transdermal vehicles or as oral drug delivery systems. TEOS undergoes hydrolytic polycondensation in the presence of water and ethanol as a mutual solvent under acidic or basic conditions. The sol-gel process can be summarized in three stages as follows:

(1) hydrolysis of alkoxide to form silanols
(2) condensation of the silanols to form siloxane bonds
(3) linking of the polymers to form rigid silica gels.

The relative rates of above stages are very much dependent on whether acid or base catalysts are used, the concentration of water and TEOS, and the temperature. Although all the silica gels formed from TEOS undergo the above three stages, the relative reaction rates and reaction mechanism for acid or base catalyzed gels appear to be entirely different. Hydrolysis and condensation of TEOS in general may be summarized as follows:

$$\equiv\mathrm{SiOEt} + \mathrm{H_2O} \xrightarrow{\mathrm{OH^-\ or\ H^+}} \equiv\mathrm{SiOH} + \mathrm{EtOH}$$

$$2\ \equiv\mathrm{SiOH} \longrightarrow \equiv\mathrm{SiOSi}\equiv + \mathrm{H_2O}$$

A separate reaction mechanism was proposed for acid and base catalyzed reactions by Keefer[4] and by Klein and Garvey[5]. Their proposed mechanisms were also supported by the H' NMR study of these systems by Assink and Kay[6].

EXPERIMENTAL SECTION

MATERIALS

Tetraethyl orthosilicate (TEOS), gold label, Aldrich Chemical Company, Milwaukee, Wisconsin, U.S.A. TEOS is a colorless hygroscopic liquid with a mild ester like odor, boiling point of 168°C, freezing point of -77°C and flash point of 125°F. Prior to use, TEOS was distilled at 168°C and stored under nitrogen.

Glycerol, gold label, Aldrich Chemical Co.

Hydrochloric acid and ammonium hydroxide, Fisher Scientific Co. Ethyl alcohol (95%) and all other chemicals were obtained either from Aldrich or from Fisher.

METHODS

Three types of phase diagrams were prepared.

(A) With water, TEOS and ethanol (95%)

(B) With glycerol replacing portions of water, TEOS and ethanol (95%) and

(C) Using other alcohols such as methyl and isopropyl (in place of ethyl), water and TEOS.

Sample Preparation

Sample preparation involved a single step process in contrast to two step process used by other investigators[3,7,8]. Twenty points were selected (Figure 1) on the miscible region of the phase diagram after initial screening of gel formation in both the miscible and immiscible regions. Compositions were made by weight in a screw capped glass vials. Acid or base catalyst in concentrations of 10^{-2}M to 10^{-4}M were added at the end. Vials were placed in a Fisher Versa bath at 45°C or 70°C and observed for gelation.

RESULTS AND DISCUSSION

TEOS and water are almost completely immiscible with each other. An alcohol as a mutual solvent is required. Phase boundaries using water, TEOS and either methyl, ethyl or isopropyl alcohol were basically very similar and were not changed significantly by the addition of glycerol or other polyhydric glycols (Figure 1).

In the initial studies, the gel formation was observed in the entire region of phase diagram using both acid and base catalysts. In the immiscible region of the phase diagram, either the gels did not form for a long period of time (200 hours), or, if they did, the resulting gels were not

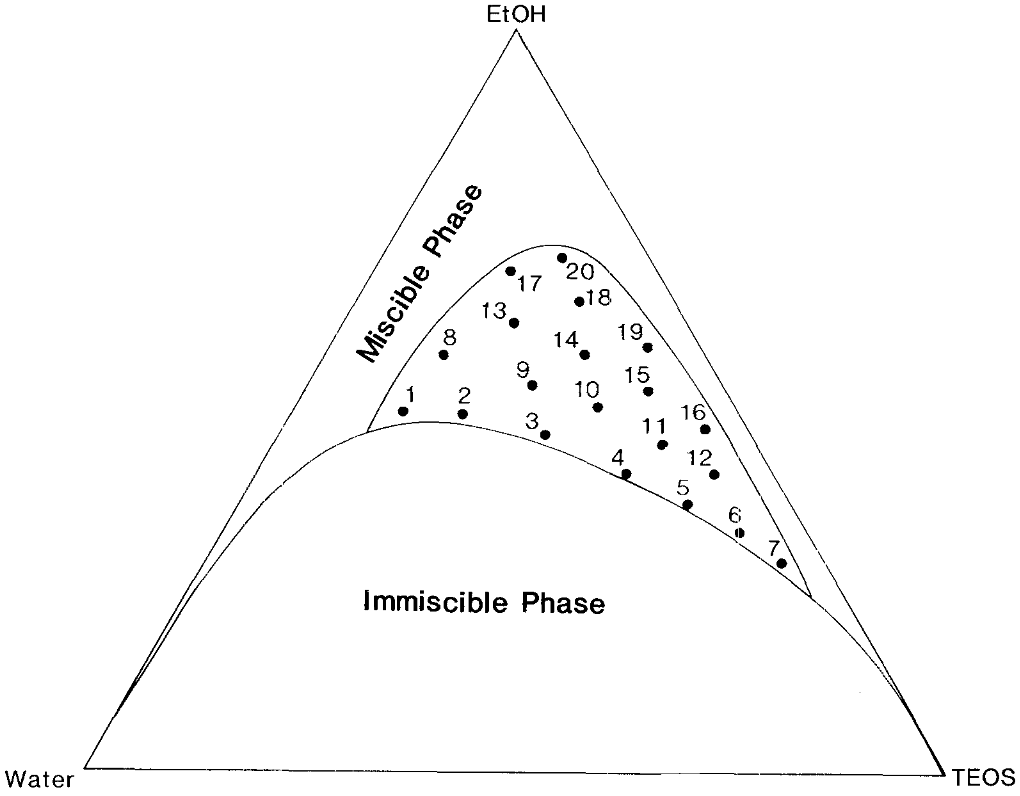

FIGURE 1
Phase diagram for TEOS, water and ethanol system.

uniform. At lower concentrations of either TEOS or water, gelation time in excess of 200 hours was encountered and was not evaluated.

Even though both acid and base catalysis involve hydrolytic polycondensation in general, the resulting gels were quite distinct in appearance. Base catalyzed gels yield branched clusters and generally the polymer does not gel as a unit, large particles sedimenting from solution. Base catalyzed gels are also opaque in nature and are more brittle compared to acid catalyzed gels. Acid catalyzed reactions produce linear polymers and the polymers gel as a complete entity. The resulting gels were less brittle compared to base catalyzed gels, transparent and elegant in appearance. These differences can be attributed to the reaction mechanisms proposed by

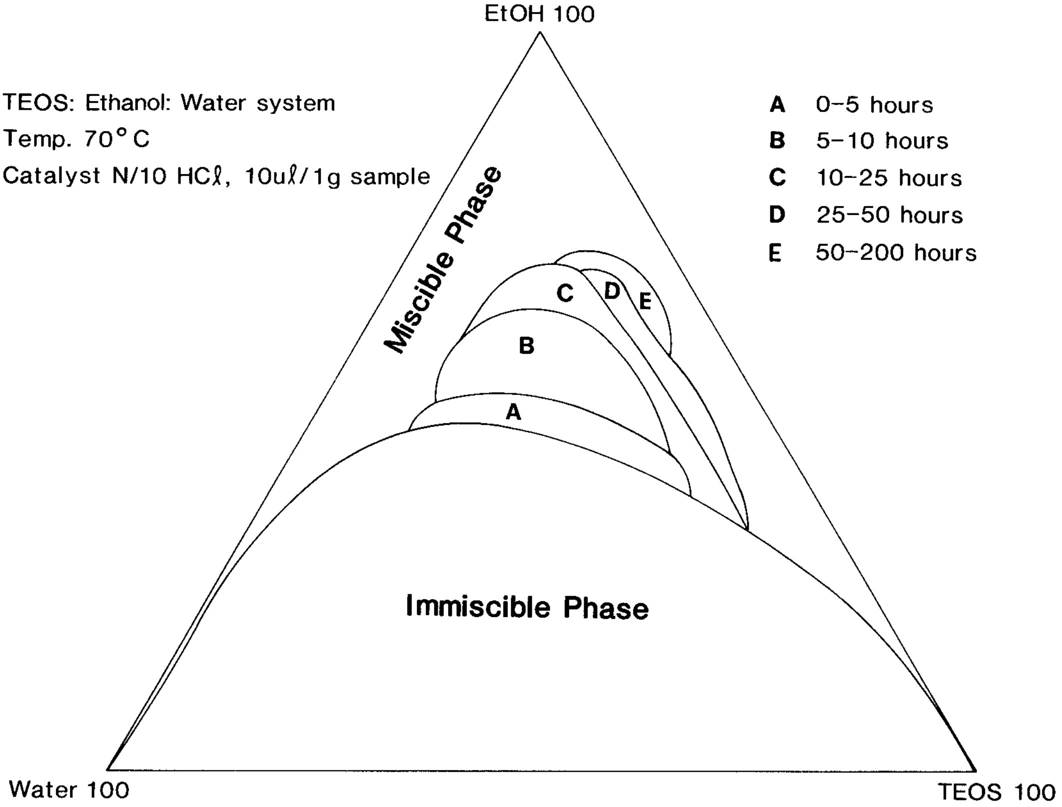

FIGURE 2a.

Gelation time pattern for TEOS, ethanol and water systems in presence of acid catalyst (HCℓ).

Keefer[4], and by Klein et al[5] for acid and base catalysis. According to Keefer[4], alkaline hydrolysis involves nucleophilic attack of the hydroxide ion on silicon whereas acid hydrolysis involves an electrophilic reaction mechanism.

For all of the above reasons, we restricted our investigations to acid catalyzed systems in the miscible region of the phase diagram, Figure 1. Visual gelation times for systems in the miscible region were observed at 45°C and 70°C. Three different concentrations of hydrochloric acid as catalyst were selected for water, ethanol and TEOS systems together with similar systems containing glycerol.

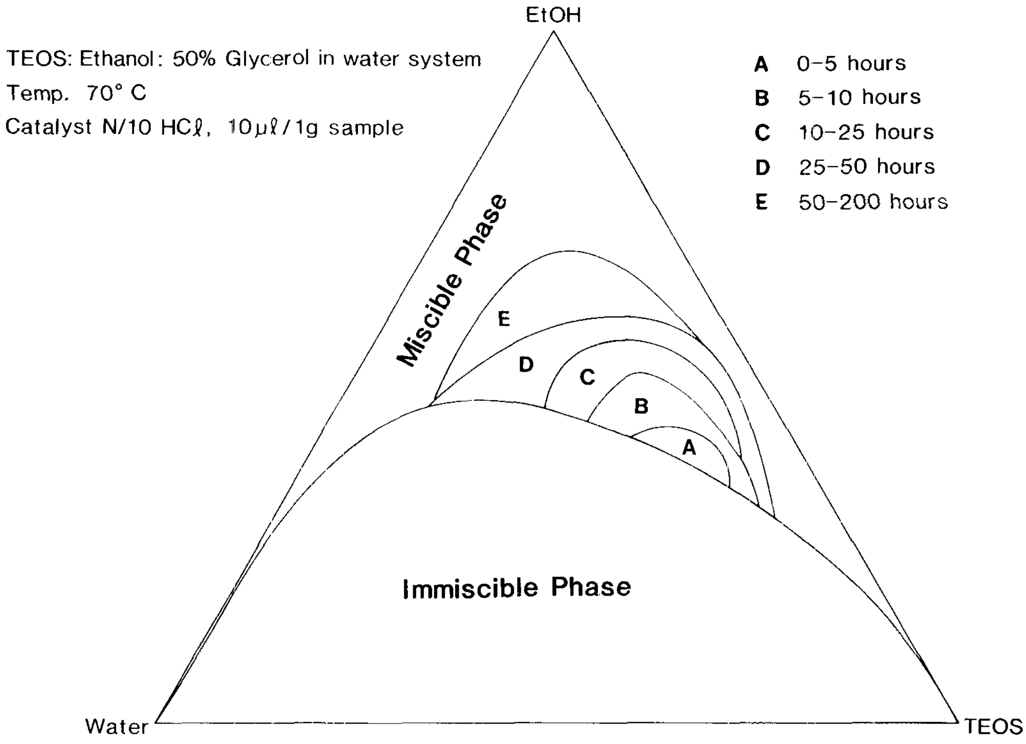

FIGURE 2b.
Gelation time pattern for TEOS, ethanol and water systems containing glycerol in presence of acid catalyst (HCℓ).

Different gelation times and patterns were noted for systems with and without glycerol, Figures 2a and 2b. The boundaries shown for different regions A, B, C, D and E on phase diagram (Figures 2a and 2b) are selected on approximate gelation times.

The presence of glycerol has a significant effect on the gelation time, Table 1. Gels were observed to form faster at low water/TEOS molar ratios in presence of glycerol. In absence of glycerol, gels formed faster at higher water/TEOS molar ratios (Table 1, Figures 2a and 2b).

Gelation times for several polyethylene and polypropylene glycols were also observed, Table 2. Gelation times with glycerol were less than those due

TABLE 1
Gelation Times In Presence And Absence of Glycerol

	SYSTEM A		SYSTEM B		SYSTEM C	
*	WATER/TEOS MOLAR RATIO	GT	WATER/TEOS MOLAR RATIO	GT	WATER/TEOS MOLAR RATIO	GT
1	34.72	5:00	26.04	5:30	17.36	24:00
2	18.52	3:00	13.88	6:30	10.45	11:30
3	8.96	3:15	6.72	4:30	4.48	4:45
4	4.57	4:15	3.43	3:45	2.28	1:00
5	2.67	22:30	2.00	3:30	1.34	1:15
6	1.54	NG	1.15	45:00	0.77	NG
7	1.14	NG	0.65	NG	0.43	NG

*Location on phase diagram in Figure 1

SYSTEM A - TEOS, ETOH and Water System.

SYSTEM B - TEOS, ETOH and (25% Glycerol in water) system.

SYSTEM C - TEOS, ETOH and (50% Glycerol in water) system.

GT - Gelation time in hours and minutes.

NG - No gel formed observed upto 200 hours

CONDITIONS: Temperature 70°C.

Catalyst 0.1N HCl, 10μl/1.0 g sample.

to polyethylene and polypropylene glycols. Some of the gels formed with these glycols were also opague. Some gels cracked and did not have the mechanical strength associated with the glycerol gels.

Gelation times were less at the higher temperature as might be anticipated, Table 3.

Of the three acid catalyst (HCl) concentrations studied, gels formed faster at lower concentrations, Table 4.

TABLE 2
Effect of Other Polyhydric Glycols In Place Of Glycerol

TYPE OF POLYHYDRIC GLYCOL	GELATION TIME HOURS:MIN.
Glycerol	1:00
E - 200	45:00
E - 400	40:00
E - 600	31:00
E - 1000	27:00
E - 4500	22:00
P - 1200	19:00
P - 2000	NG
P - 4000	42:00

SAMPLE: TEOS 43%, ETOH 40%, Water 8.5%, Glycol 8.5%

E : Polyethylene glycol

P : Polypropylene glycol

NG: No gel formed observed upto 200 hours.

CONDITIONS: Temperature 70°C.

Catalyst 0.1N HCl, 10μl/1.0 g sample.

TABLE 3
Effect of Temperature On Gelation Time.

		GELATION TIME HOURS: MINS				
	*→	1	2	3	4	5
TEMP	45°C	37:00	6:30	11:20	20:30	50:00
	70°C	5:00	3:30	3:15	4:15	22:30

* Location on phase diagram in Figure 1.

Conditions: Catalyst 0.1N HCl, 10μl/1.0 g sample.

TABLE 4
Gel Formation At Different Acid Catalyst (HCl) Concentrations

		GELATION TIME HOURS: MINS				
	*>	1	2	3	4	5
CATALYST	I	5:00	3:30	3:15	4:15	22:30
	II	28:00	21:30	10:30	18:00	44:00
	III	53:00	36:00	21:30	20:30	29:00

* Location of sample on phase diagram in Figure 1.

I contains 0.1N HCl, 10μl/1.0 g sample.

II contains 0.1N HCl, 25μl/1.0 g sample.

III contains 0.1N HCl, 50μ/1.0 g sample.

CONDITION: Temperature 70°C.

TABLE 5
Effect of Other Alcohols On Gelation Process

ALCOHOL	GELATION TIME HOURS: MINS
Ethyl	1:00
Butyl	25:00
Pentyl	22:00
Hexyl	20:00
Heptyl	21:00
Octyl	20:00

SAMPLE: TEOS 43%, Alcohol 40%, Water 8.5%.
Glycerol 8.5%

CONDITIONS: Temperature 70°C.

Catalyst 0.1N HCl, 10μl/1.0 g sample.

Replacing ethyl alcohol with other alcohols had a significant effect on gelation process, Table 5. The gelation times were longer with other alcohols and almost all the gels formed were opaque and did not possess the transparency observed in gels made with ethyl alcohol.

It is evident that gelation times have an impact on the nature and properties of the resulting gels. Not only does the concentration of water and TEOS affect the gelation process but so also do the catalyst and temperature conditions. Other additives such as glycerol affect the rate of gelation and the characteristics of resulting gels. In these systems, ethanol and glycerol appear to play unique roles in the gelation process compared to other alcohols and polyhydric glycols. Overall, these silica gels from organic silicates appear to be versatile systems with potential application to the pharmaceutical industry. These systems have the capability to be modified and molded to the specific needs of a desired drug delivery system.

REFERENCES

1. M. Yamane, S. Aso, S. Okano and T. Sakaino., J. Mater. Sci., 14, 607 (1979).
2. B. Yoldas., J. Mater. Sci., 14, 1843 (1979).
3. K. Unger, H. Rupprecht, B. Valentin and W. Kircher., Drug Dev. and Ind. Pharm., 9(182), 69-91 (1983).
4. K. D. Keefer, "Materials Research Society Symposium Proceedings", Vol. 32, Elsevier Science Publishing Co. Inc., p. 15 (1984).
5. L. C. Klein and G. J. Garvey., "Materials Research Society Symposium Proceedings", Vol. 32, Elsevier Science Publishing Co. Inc., p. 33, (1984)
6. R. A. Assink and B. D. Kay., "Materials Research Society Symposium Proceedings", 32, Elsevier Science Publishing Co. Inc., (1984).
7. C. J. Brinker, K. D. Keefer, D. W. Schaefer and C. S. Ashley., J. Non-Cryst. Solids, 48, 47-64 (1982).

8. R. A. Assink, B. D. Kay, C. S. Ashley, C. J. Brinker and K. D. Keefer., J. Non-Cryst. Solids, 63, 45-59 (1984).

9. R. Aelion, A. Loebel and F. Erich., J. Am. Chem. Soc., 72, 5705 (1950).