PolySciTech Division of
AKINA, INC.
1291 Cumberland Avenue
West Lafayette, IN 47906-1385
Tel: (765) 464-0501; Fax: (765) 464-0820 www.polyscitech.com
John Garner, Sarah Skidmore

White Paper: Thermogel Mixtures Impact on Rheology

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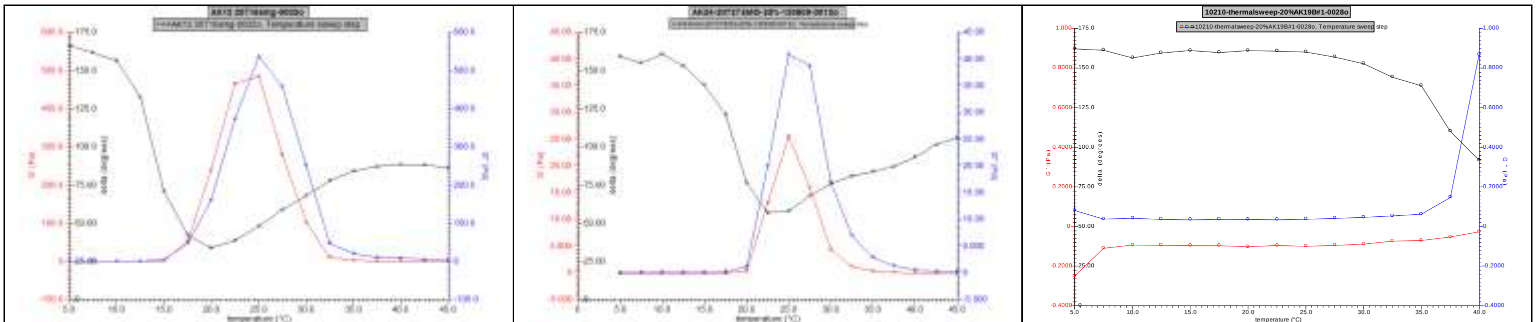
Background

Currently the varying thermogel PLGA-PEG-PLGA products available at Akina have distinct gelation set-points. Notably AK12 (PLGA-PEG-PLGA Mw ~1000-1000-1000 1:1 LA:GA) and AK24 (PLGA-PEG-PLGA Mw ~1100-1000-1100 3:1 LA:GA) have a gelation point in the 17-25° C (lower than body temperature) range with precipitation at higher temperatures whereas AK19 (PLGA-PEG-PLGA Mw~1500-1500-1500 1:1 LA:GA) has a gelation point with onset ~40-45° C (higher than body temperature) (Fig. 1). The purpose of this research is to determine if gelation properties of these materials can be tuned by combining them together in aqueous solution.



A. PolyVivo AK12 Thermogelation | B. PolyVivo AK24 Thermogelation | C. PolyVivo AK19 Thermogelation

Figure 1. Rheology charts 20% w/v solutions of each PLGA-PEG-PLGA polymer (AK12, AK24, AK19) from prior batches separately.

Method

Each polymer (PolyVivo AK19-B#2, PolyVivo AK12-B#4, PolyVivo AK24-Lot# 20727SMG) was dissolved first in cold (~4° C) water with shaking at a preset 20% w/v concentration. Dissolution was achieved by shaking cold for at least overnight. The solutions were combined while cold at the below indicated values as volume:volume ratios (e.g. “3:1”, is 1.5 ml + 0.5 ml of each respective part etc.). Each solution was mixed and shaken together at cold temperature for at least 5 minutes prior to rheology testing. In addition to these AK12 and AK24 samples were co-dissolved with PEG-2000 Da however these samples were observed to precipitate the polymer and as such were not carried forward.

Rheology

Rheology was performed on an AR550 (TA instruments) with 60 mm 2 degree cone on 20% w/v polymer solution in dissolved water. Viscosity of solution at 0.1 (sec-1) and 5C was measured (1minute peak hold 5 second test intervals). Rheology performed by oscillating at constant 6.283 rad/s, 0.1% strain, in increments of 2.5° C ranging from 5-45° C with 3 minutes of temperature equilibration at each point.

Results

Rheology Charts

The charts below show the relationship between the varying mixtures in terms of the rheological properties at each increment. Note X-axis is ° C with red axis indicating G’ and blue axis indicating G”.

AK12:AK19

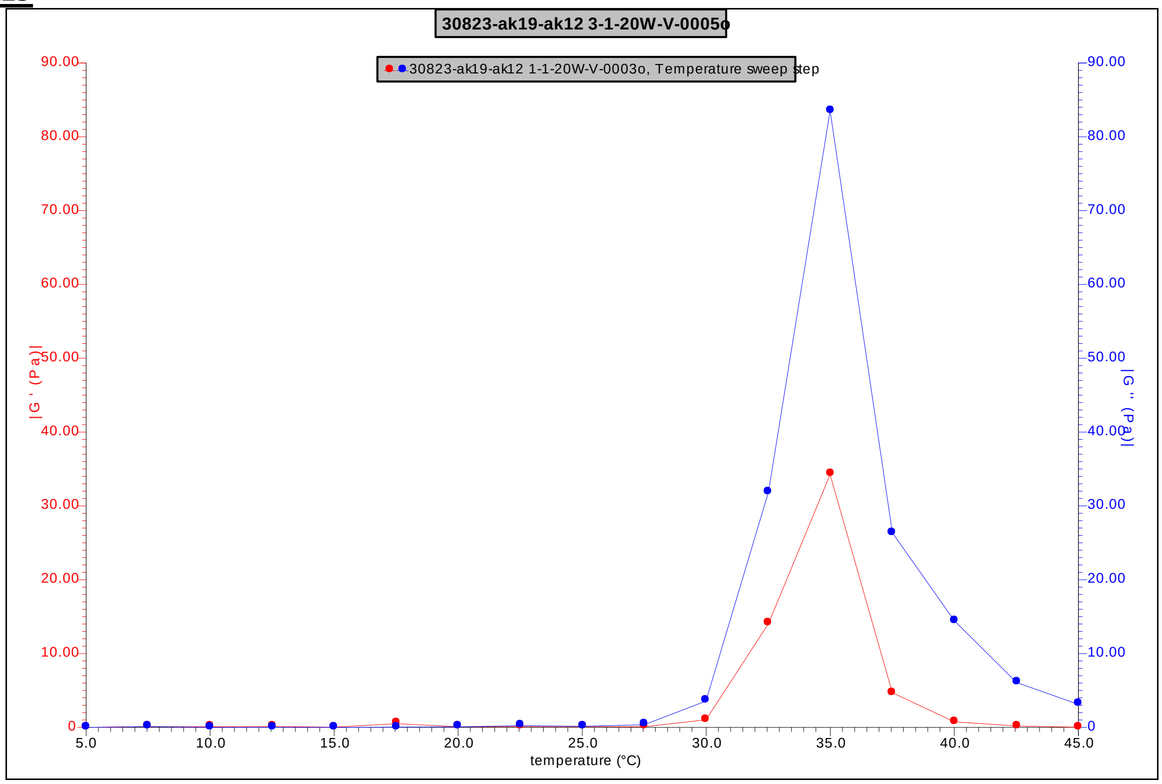


Figure 2. Mixed solution 1:1 AK12:AK19 20% w/v in DI H2O.

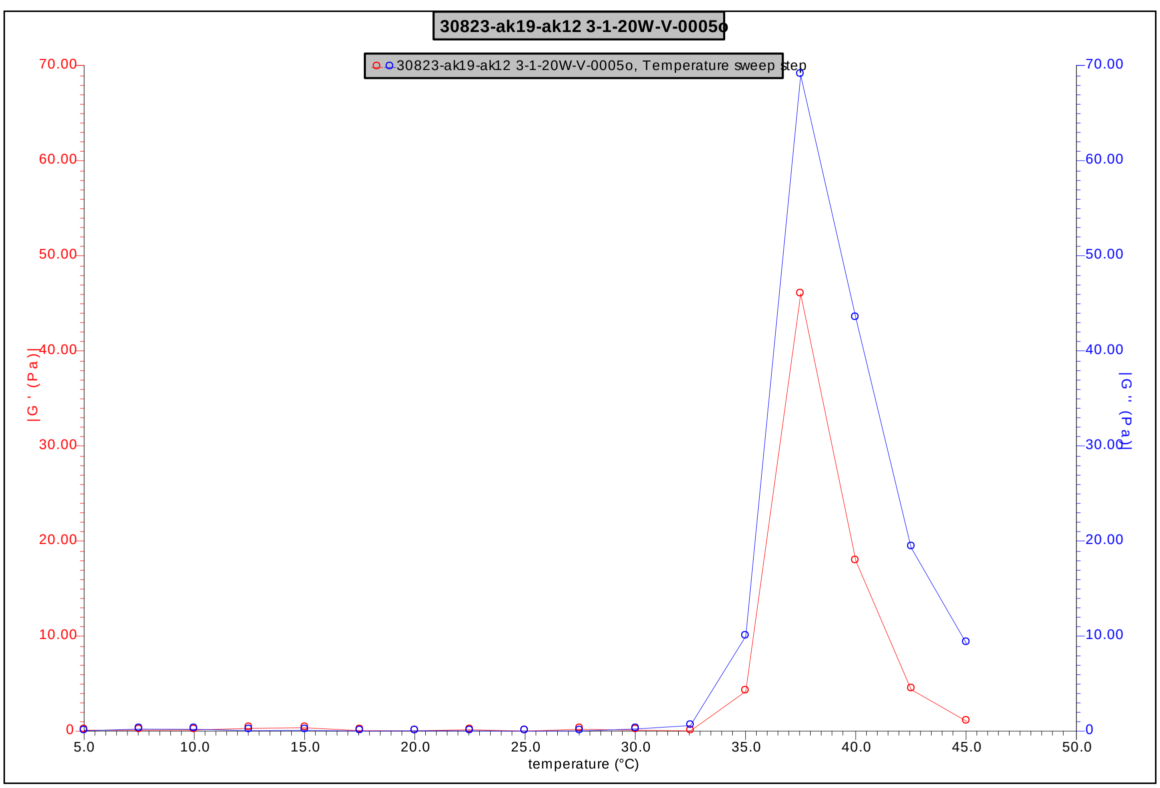


Figure 3. Mixed solution 1:3 AK12:AK19 20% w/v in DI H2O.

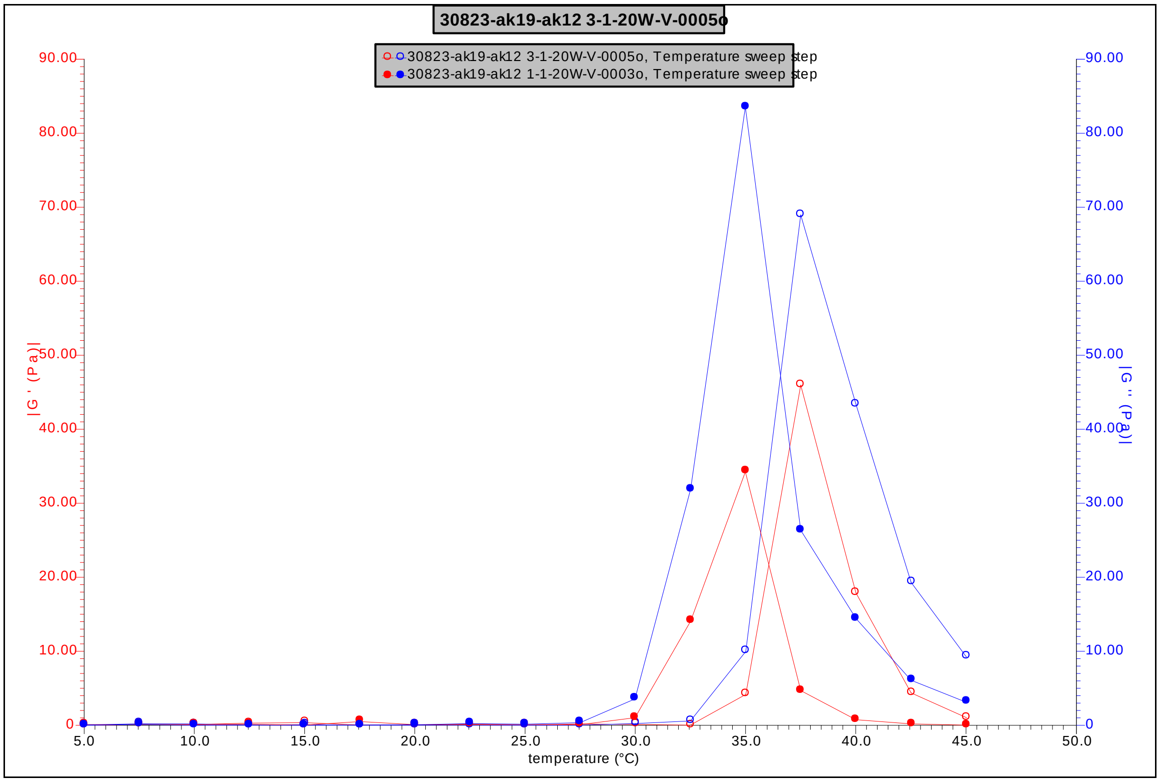


Figure 4. Overlay 1:1 (open dots) and 3:1 (filled dots) AK19:AK12 mixed solutions.

The viscosity of the 3:1 AK19:AK12 was also tested at 5C and was found to be 0.1274 Pa. The 1:1 mixture was below detectable limit for viscosity. Visually these solutions flowed similar to water at this cold temperature.

AK24:AK19

The same test was performed with AK24 and AK19.

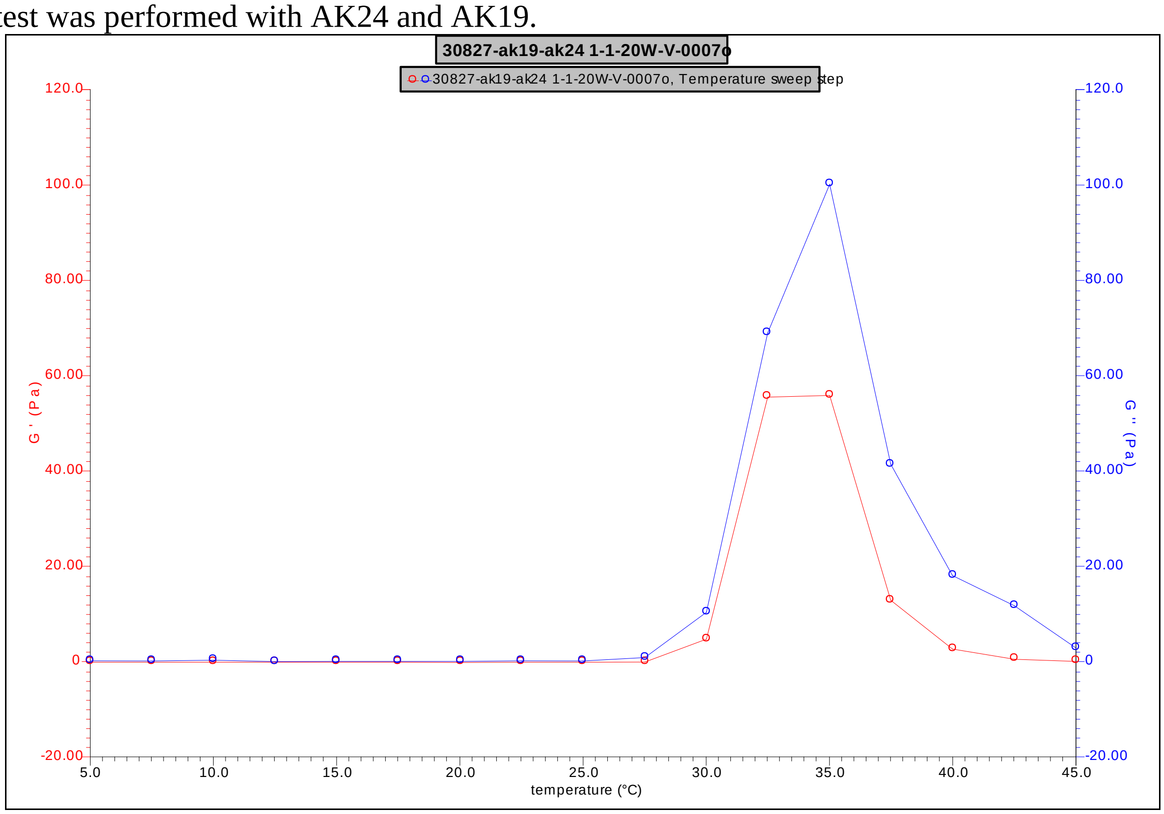


Figure 5. Mixed solution 1:1 AK24:AK19 20% w/v in DI H2O.

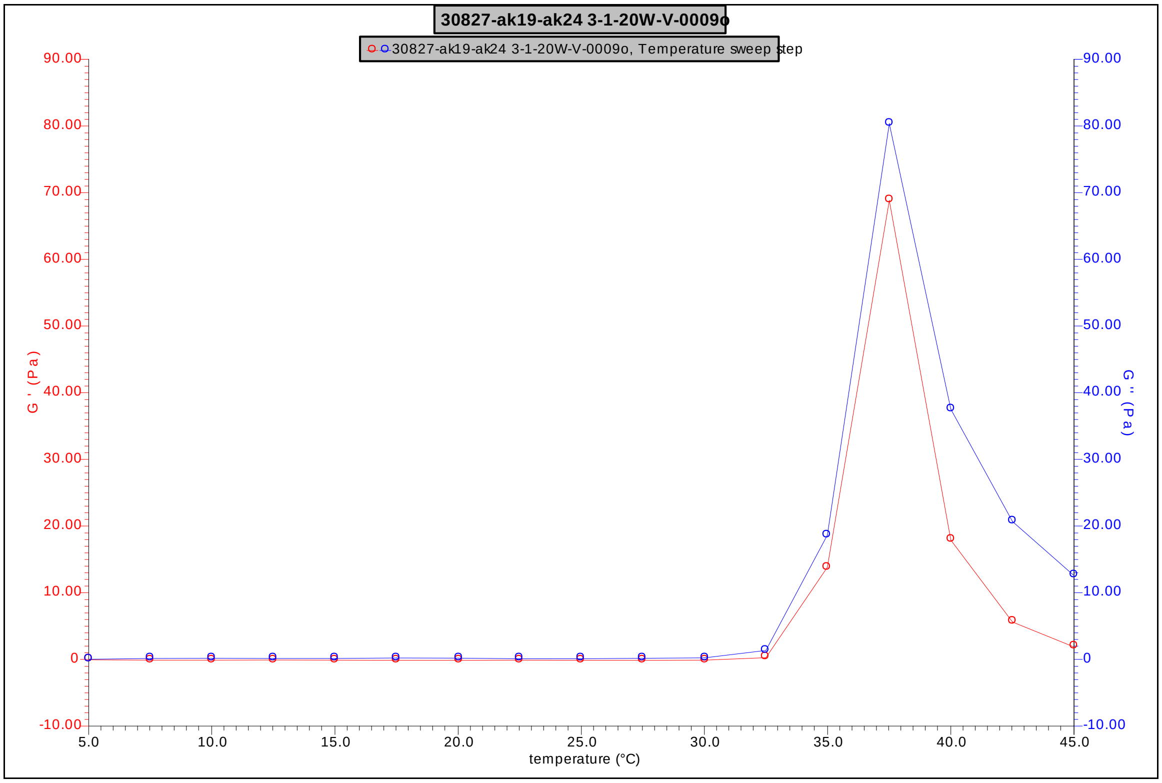


Figure 6. Mixed solution 1:3 AK24:AK19 20% w/v in DI H2O.

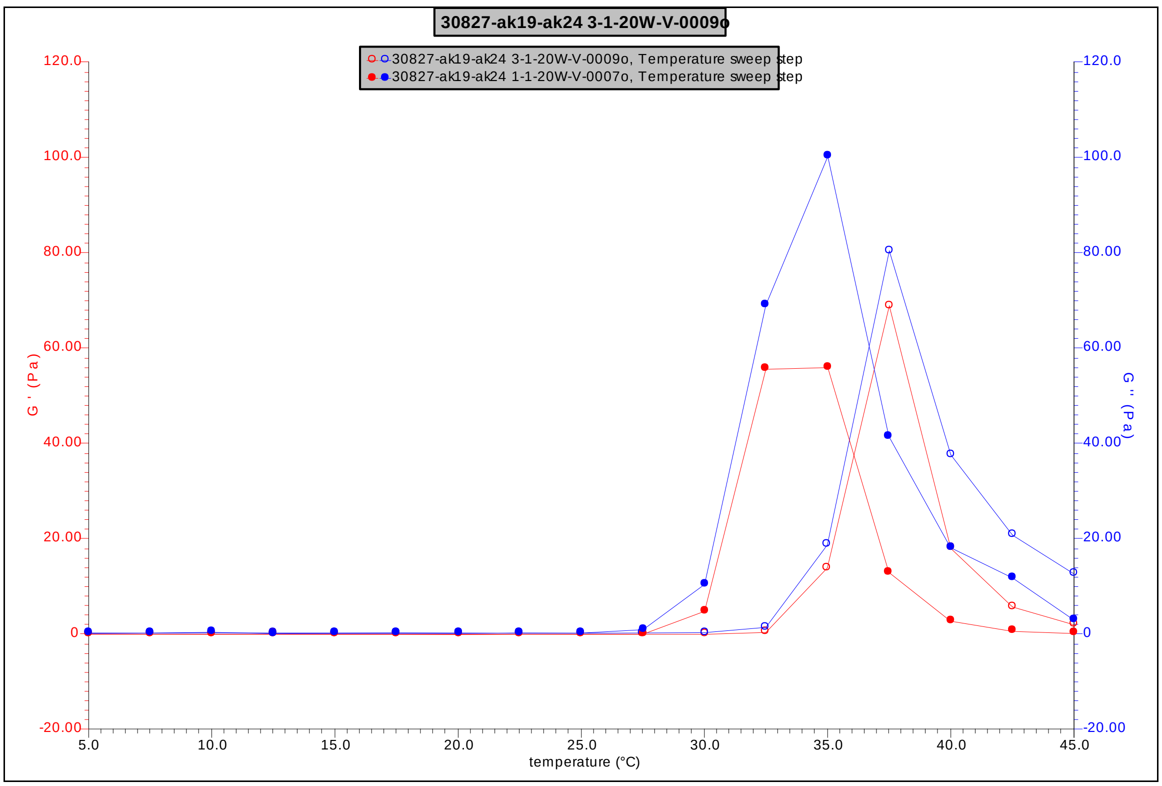


Figure 7. Overlay 3:1 (open dots) and 1:1 (filled dots) AK19:AK24 mixed solutions.

Empirical Study

Two solutions were prepared 1ml each of 3:1 AK19:AK24. One was left at room temperature while the other was warmed to 37° C in an incubator. The rheology results were confirmed by the "tube tip test" and results are shown in Figure 8.

Figure 8. Results of tube tip test 3:1 AK19:AK24 solution at 37C (left) and 20C (right) respectively. Note solution flows easily at 20° C but is a gel at 37° C.

Set 1ml portions of 1:1 and 1:3 AK24:AK19 were set aside and allowed to equilibrate to 37° C over 2 days. These were pictured and are shown in Figure 9. Note there is polymer phase separation in 1:1 but not in 1:3.

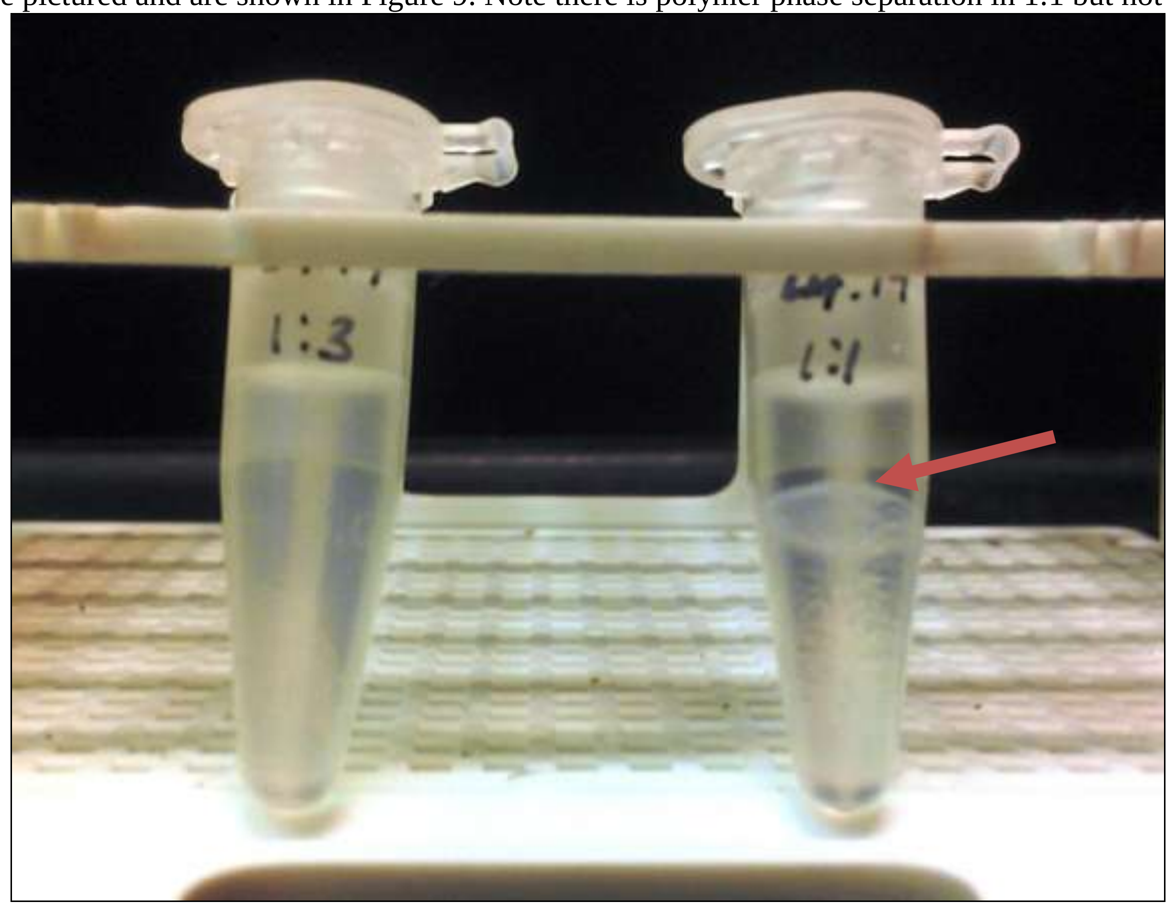


Figure 9. AK24:AK19 mixtures 1:3 (left) and 1:1 (right) after equilibrating over 2 days at 37° C. Note phase separation present in 1:1 (red-arrow) but not 1:3 mixtures.

The lack of phase separation and success in tube-tip test indicates that a 1:3 mixture of AK24:AK19 creates a stable gel at 37° C suitable for injectable delivery of drugs.

Conclusion

Thermogelation properties of varying PLGA-PEG-PLGA polymer solutions can be adjusted by altering the mixed solution of each thermogel. In this test 3 parts AK19 to 1 part AK12 or 1 part AK24 yielded an optimal gelation near 37° C, respectively.