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# Polymerization Kinetics of PEO-b-pNIPAAm Block Copolymers

William G. Pitt  
pitt@byu.edu

Yi Zeng

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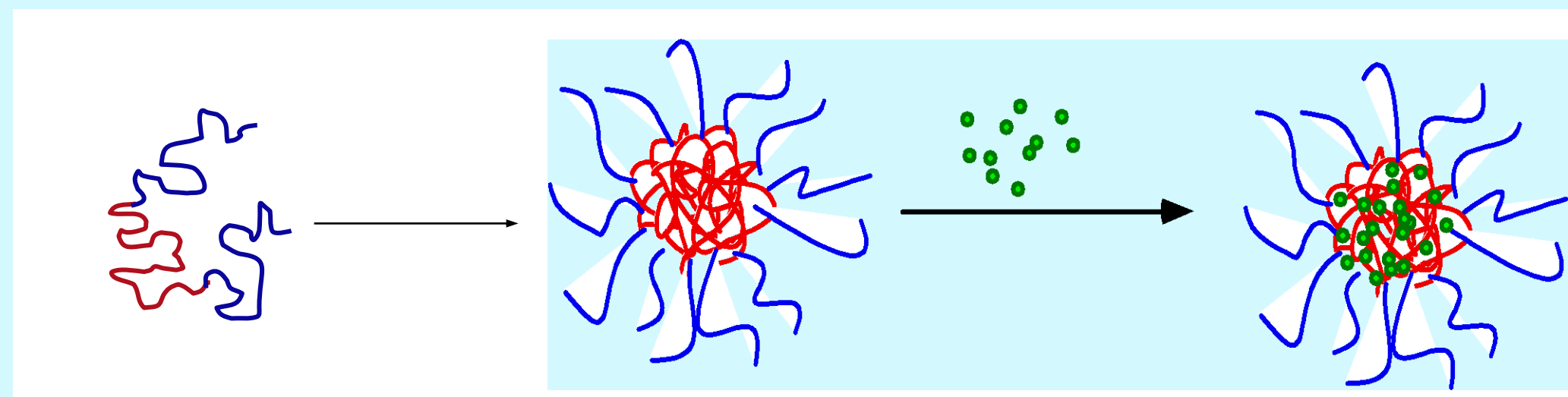


Figure 1. Block copolymers sequester hydrophobic chemotherapeutic drugs in micelles.

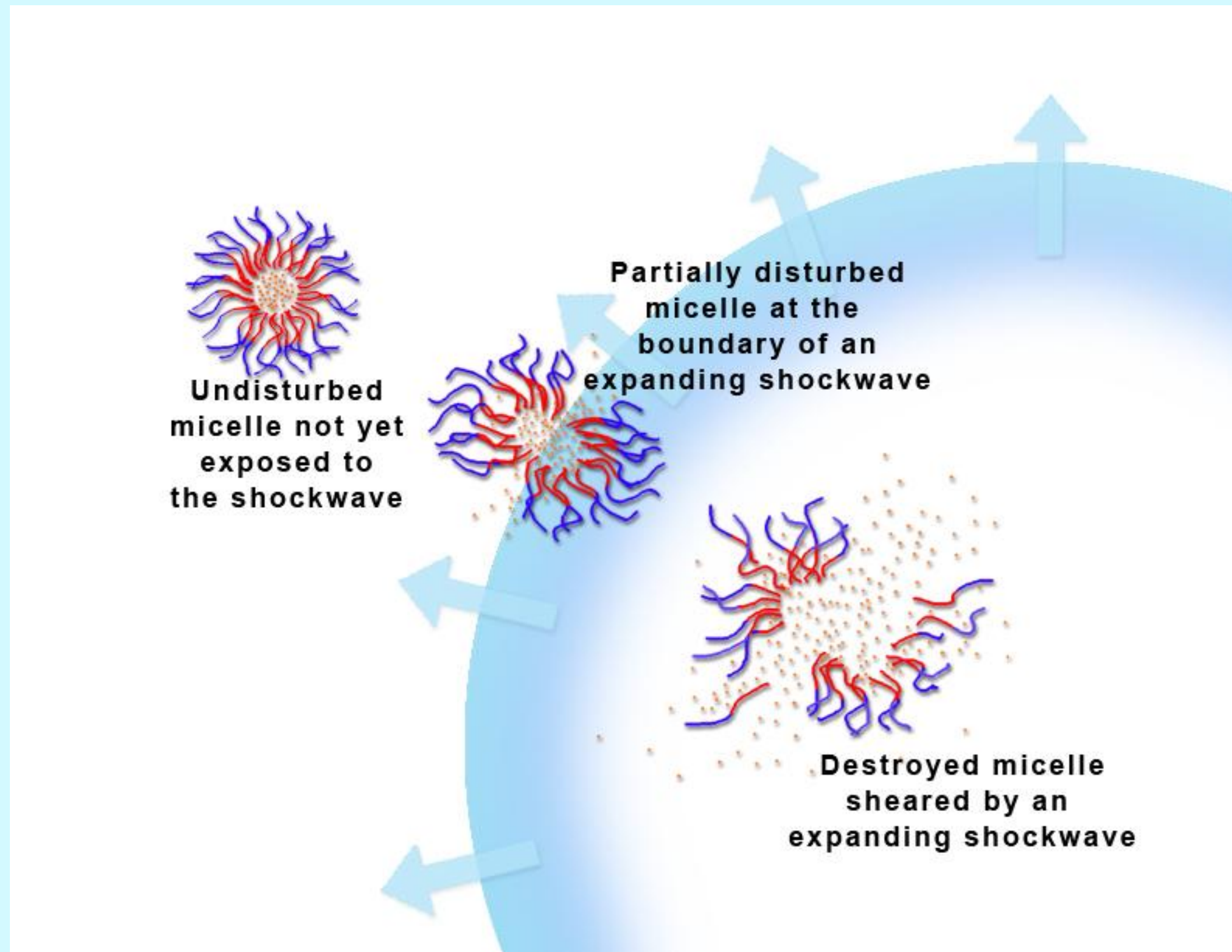


Figure 2. Ultrasonic exposure creates cavitation events that create a shockwave that disrupts micelles containing drug.

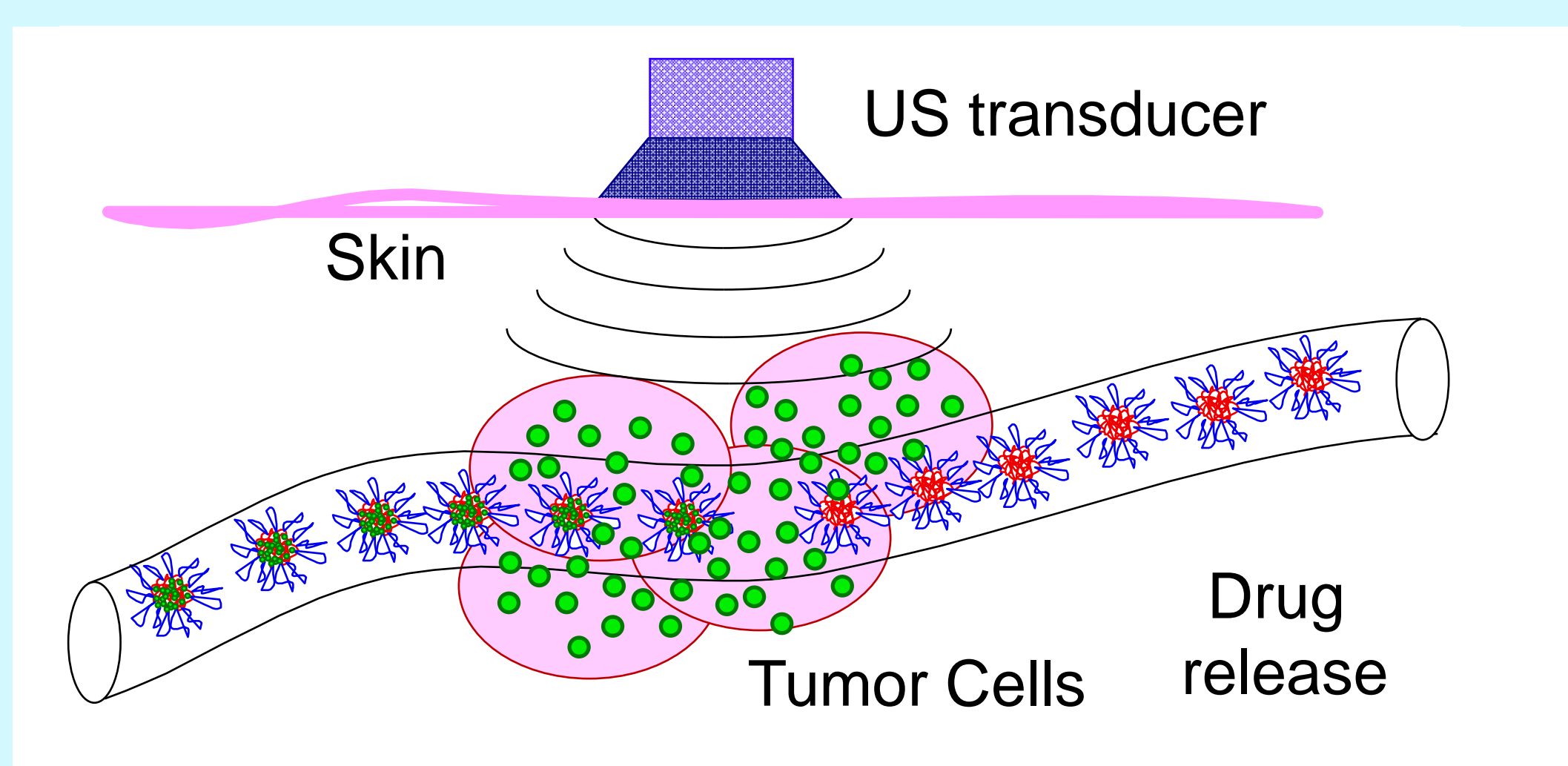


Figure 3. Micelles release the encapsulated drug at the ultrasonically targeted tissue.



Figure 4. Rat with subcutaneous tumors grown on each leg. Rat was given DOX in micellar carriers; ultrasound (70 kHz, 1 W/cm<sup>2</sup>) was applied to the tumor on the left, which grew less than tumor on the right. [4]

**Introduction** Our research in ultrasonic activated drug delivery motivated us to develop polymeric micelles that sequester hydrophobic drugs (Fig. 1) until they are sheared open by cavitation events produced by low frequency ultrasound (Fig. 2). [1] Using this type of drug delivery system, micelles sequestering drug can circulate freely without releasing their drug until they flow through a tumor or other tissue insonated by low frequency ultrasound. There they release part of their drug (Fig. 3). [2,3] This drug delivery technology was used to reduce tumors in a rat model [4] using block copolymers of PEO and PPO. However, we are always seeking better drug-carrying micelles.

This research investigated the polymerization rate kinetics for the production of block copolymers of polyethylene oxide (PEO) and poly(N-isopropylacrylamide) (NIPAAm) that form thermally-reversible self-assembled micelles. Such micelles can be used for ultrasonic-activated drug delivery. The unique polymerization kinetics involves using cerium in the +4 oxidation state, Ce<sup>4+</sup>. The cerium extracts a hydrogen atom from the end of the PEO chains (Scheme 1), which subsequently initiates free radical polymerization. Although this polymerization has been described qualitatively in the literature [5], there are no reports of the polymerization kinetics, which are needed to control the molecular weight of the resulting block copolymers.

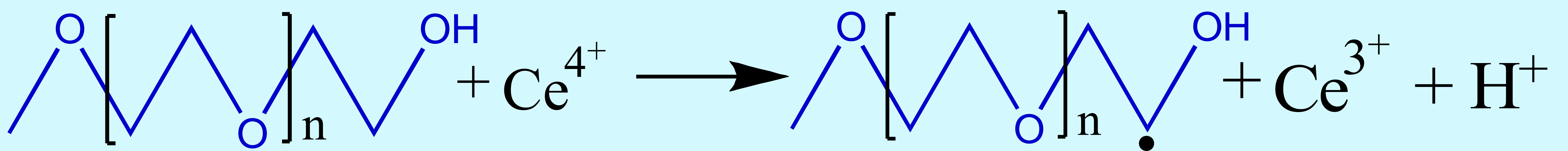
We also studied the assembly of these block copolymers into micelles. Some micelles were further stabilized by copolymerizing with a biodegradable crosslinker N,N-bis(acryloyl)cystamine (BAC).

**Materials and Methods** Methoxypoly(ethylene glycol), N-isopropylacrylamide, ammonium cerium nitrate and N,N-bis(acryloyl)cystamine were purchased from Sigma-Aldrich. Polymerization was done under nitrogen in a round bottom flask. 20 mL of double-distilled water was poured into the flask, stirred magnetically, and purged with nitrogen for two hours at 60°C. One gram of methoxypoly(ethylene glycol), measured amounts of NIPAAm and measured amounts of BAC were added. After 5 minutes purging, ammonium cerium nitrate in 4 mL of 1 M nitric acid was added. After 4 hrs, the solution was cooled to room temperature and 1 M NaOH solution was added to precipitate out the cerium salts. The supernatant (containing copolymer) was centrifuged 0.5 hour (10,000 rpm, Eppendorf 5415C) at 40°C to separate the unreacted PEO. The precipitated copolymer products were dissolved in double-distilled water to form a solution of 2.0±0.1 mg/mL.

To investigate the kinetics of polymerization, the kinetics of Ce<sup>4+</sup> reduction was measured in a UV spectrophotometer by tracking the reduction of the orange color of the cerium. Ce<sup>4+</sup> has strong linearly proportional absorption at 350 nm, while Ce<sup>3+</sup> has no absorption at 350 nm (Figs. 5 & 6). The Ce<sup>4+</sup> reduction kinetics had to be measured in separate experiments in the absence of the NIPAAm because polymerization formed micelles at the high temperature that scattered light and interfered with the spectrometry (Fig. 7).

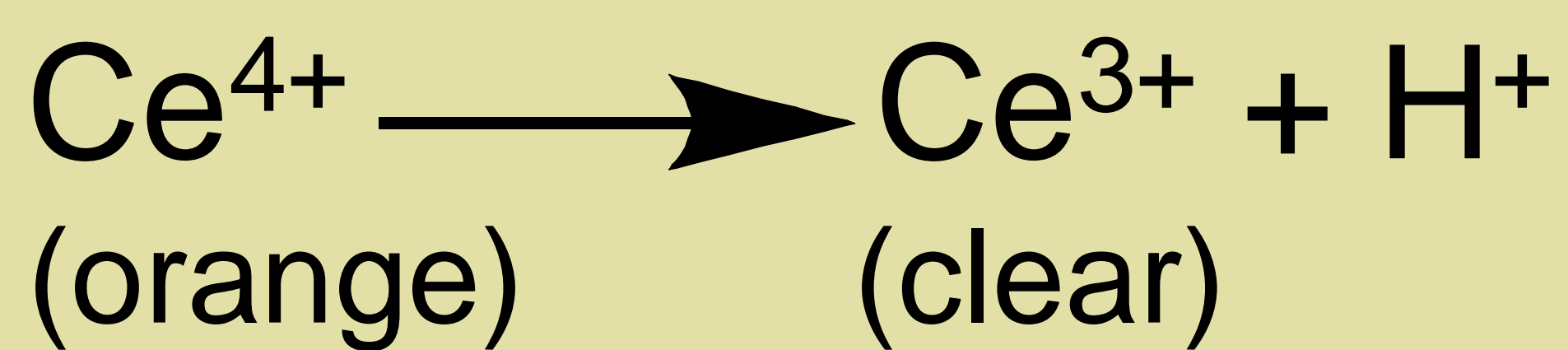
In separate experiments the kinetics of the micelle formation was measured by tracking the turbidity at 600 nm in a spectrophotometer (Fig. 8). Sizes of the micelles were measured by dynamic light scattering.

# Polymerization Kinetics of PEO-b-pNIPAAm Block Copolymers

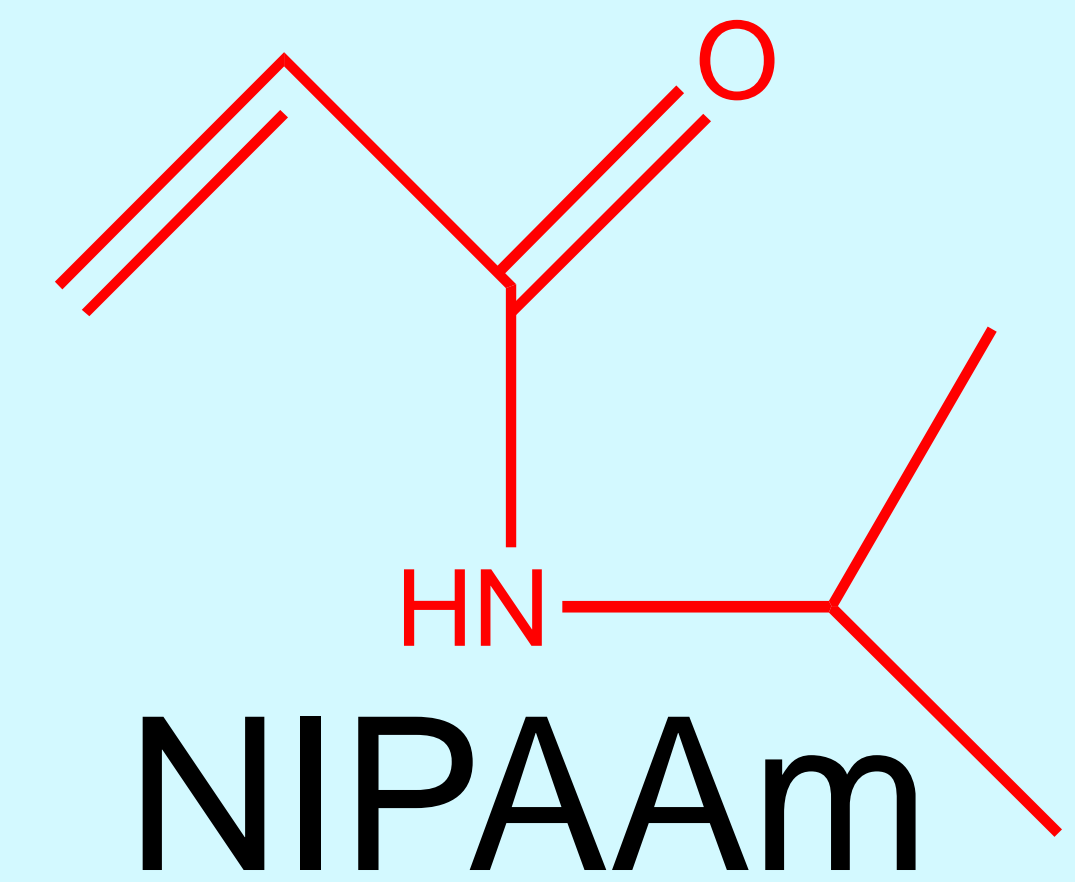
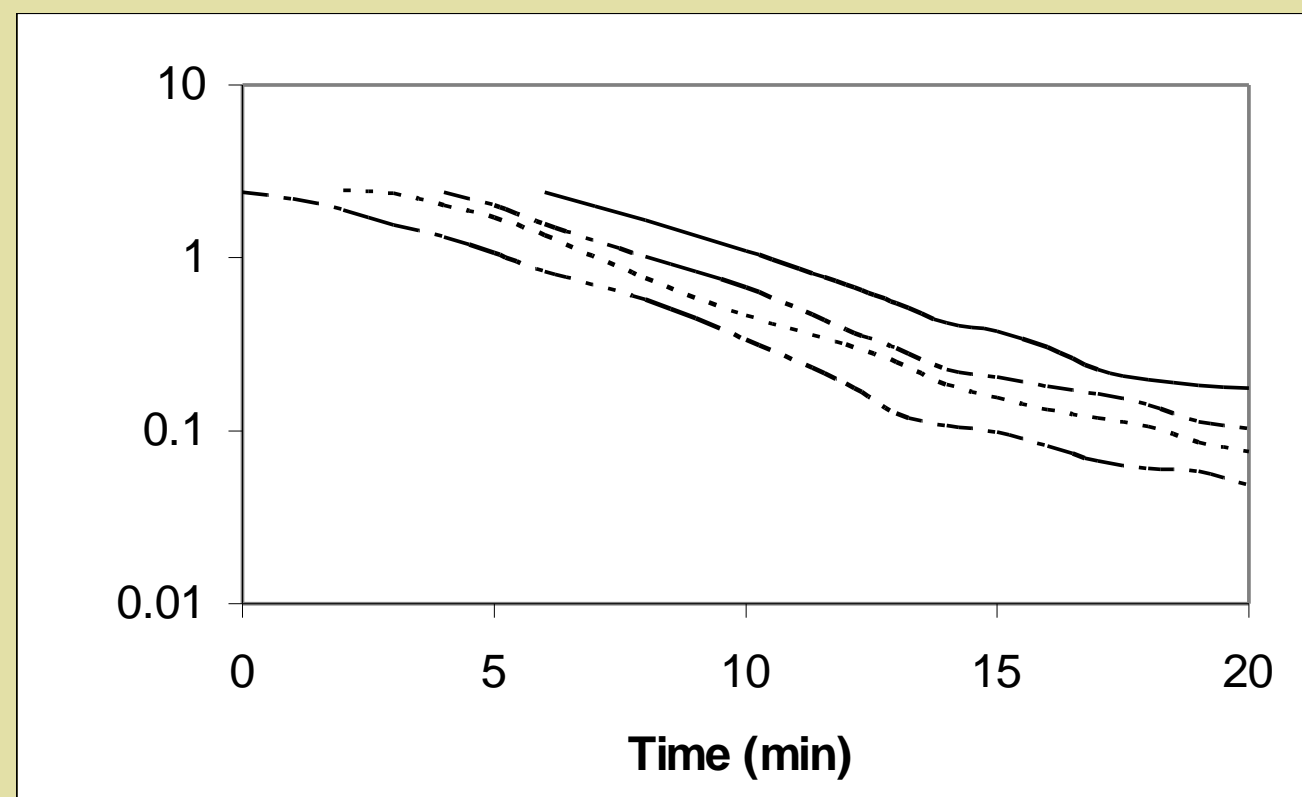


Mono-methoxy-PEO

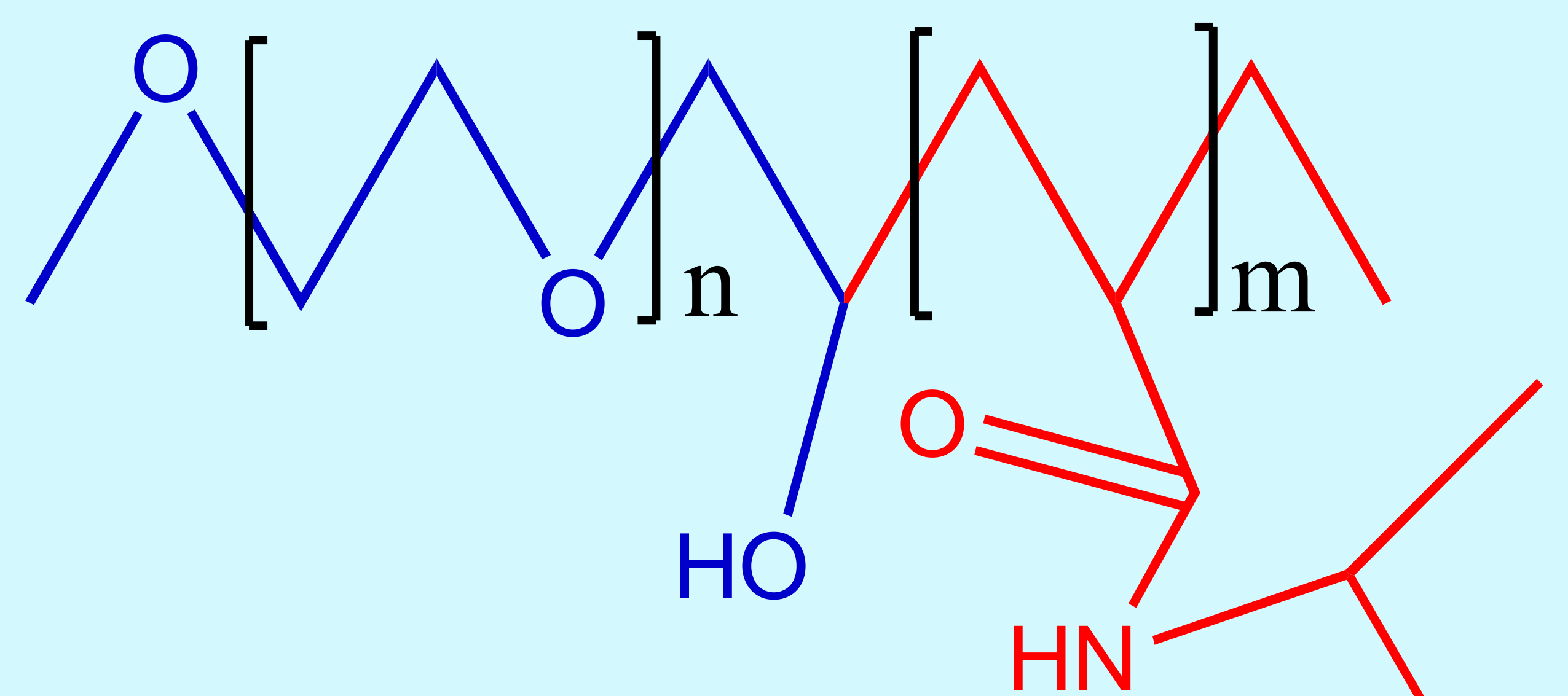
Initiation Kinetics (Radical Formation)



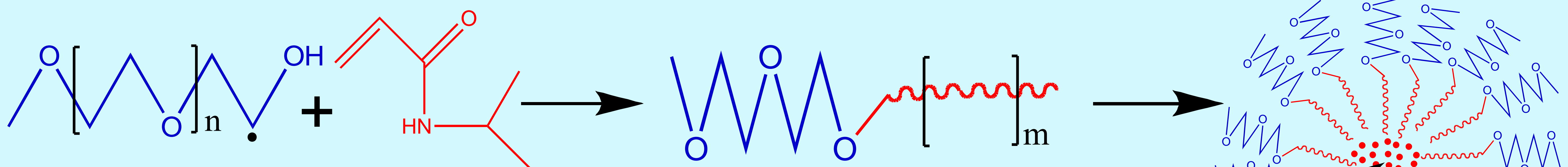
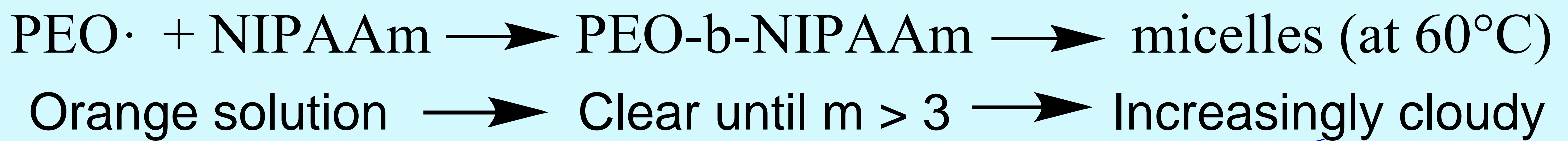
Measured by spectrometer at 350 nm



PEO-b-pNIPAAm

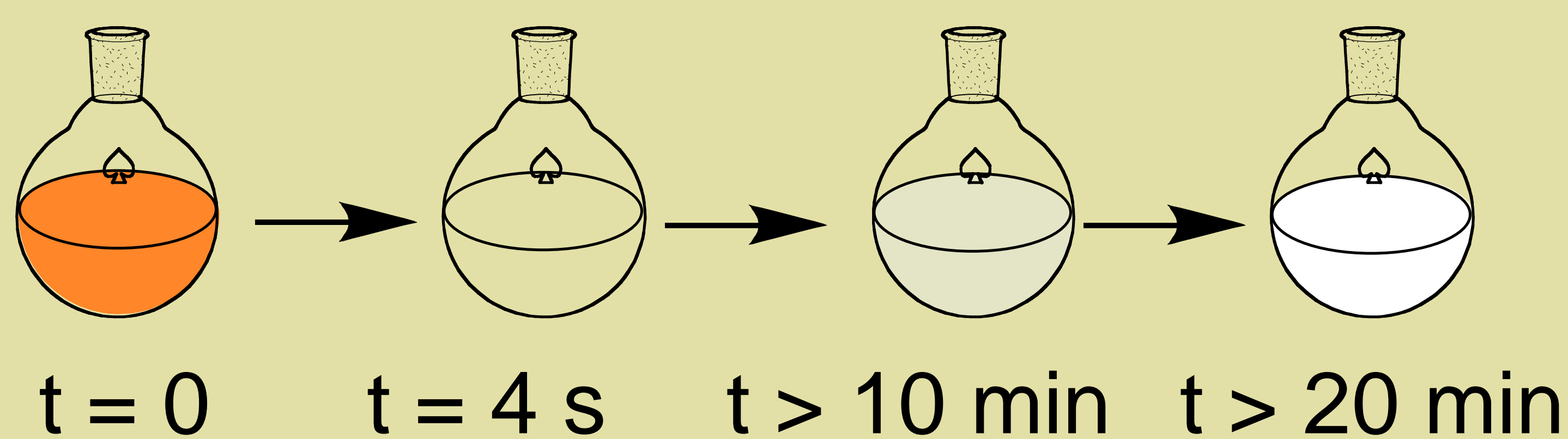


Scheme 1. Polymerization of block copolymer.



## Polymerization Kinetics

Rate of polymerization is measured by the increase in turbidity (at 600 nm) of the emulsion as the hydrophobic pNIPAAm block grows to form new micelles (at 60°C) and densifies existing micelles. The solution changes from orange to clear to slightly milky to white.



NIPAAm inside micelle reacts to lengthen the pNIPAAm block

Eventually all Monomer is converted to pNIPAAm block

Scheme 2. Micellar polymerization.

**Results** Initially in the copolymerization, the orange  $Ce^{4+}$  solution quickly turned clear as PEO radicals formed (Fig. 7). Micelles commenced formation within 3 to 5 minutes, as indicated by a change from clear to white. Because the biodegradable crosslinker BAC is hydrophobic, we assume it was sequestered into micelle cores and was copolymerized with the NIPAAm, thus crosslinking the cores of the micelles. When BAC was present above a concentration of 0.1 wt%, stable micelles were produced that could not be dissolved upon dilution.

Studies of the kinetics of the polymerization showed that the reduction of  $Ce^{4+}$  was first order in PEO concentration and first order in  $Ce^{4+}$  concentration. We assume that the free radical production on the end of the PEO chain was proportional to the  $Ce^{3+}$  production. Fig. 7 shows that the  $Ce^{4+}$  decreased in a first order manner with respect to  $Ce^{4+}$  concentration (log-linear plot) over a wide range of  $Ce^{4+}$  initial concentrations. From this data we proposed a model of

$$\text{Initiation Rate} = \frac{-d[Ce^{4+}]}{dt} = k_{ce} [Ce^{4+}] [PEO]$$

and regressed a rate constant of  $k_{ce} = 5.5 \pm 0.5 \text{ L}/(\text{mol}\cdot\text{min})$

Once the reaction started, the suspension increased in turbidity as the block copolymers formed micelles because the pNIPAAm blocks were above their LCST (Fig. 8). The stability of the micellar particles and the observation that individual micelles were formed (as opposed to a gel) indicates that these micelles sequestered the NIPAAm monomer and BAC effectively. Thus after the first few minutes this reaction should be considered a polymerization within micelles, and not a solution or emulsion polymerization.

The polymerized micellar particles were stable upon dilution, but could be degraded by exposure to beta-mercaptoethanol, indicating that the BAC crosslinker held the micelles together upon dilution below the CMC. They also have potential for ultrasonic-activated drug delivery [7].

**Summary** This study showed that pNIPAAm can be block-polymerized onto PEO oligomers using a cerium redox initiation process in aqueous suspension. The initiation step of the polymerization is first order in PEO and  $Ce^{4+}$  concentration with a rate constant of  $5.5 \text{ L}/(\text{mol}\cdot\text{min})$ . In aqueous media, the polymerization quickly becomes a micellar process that does not follow conventional solution, suspension or emulsion polymerization kinetics.

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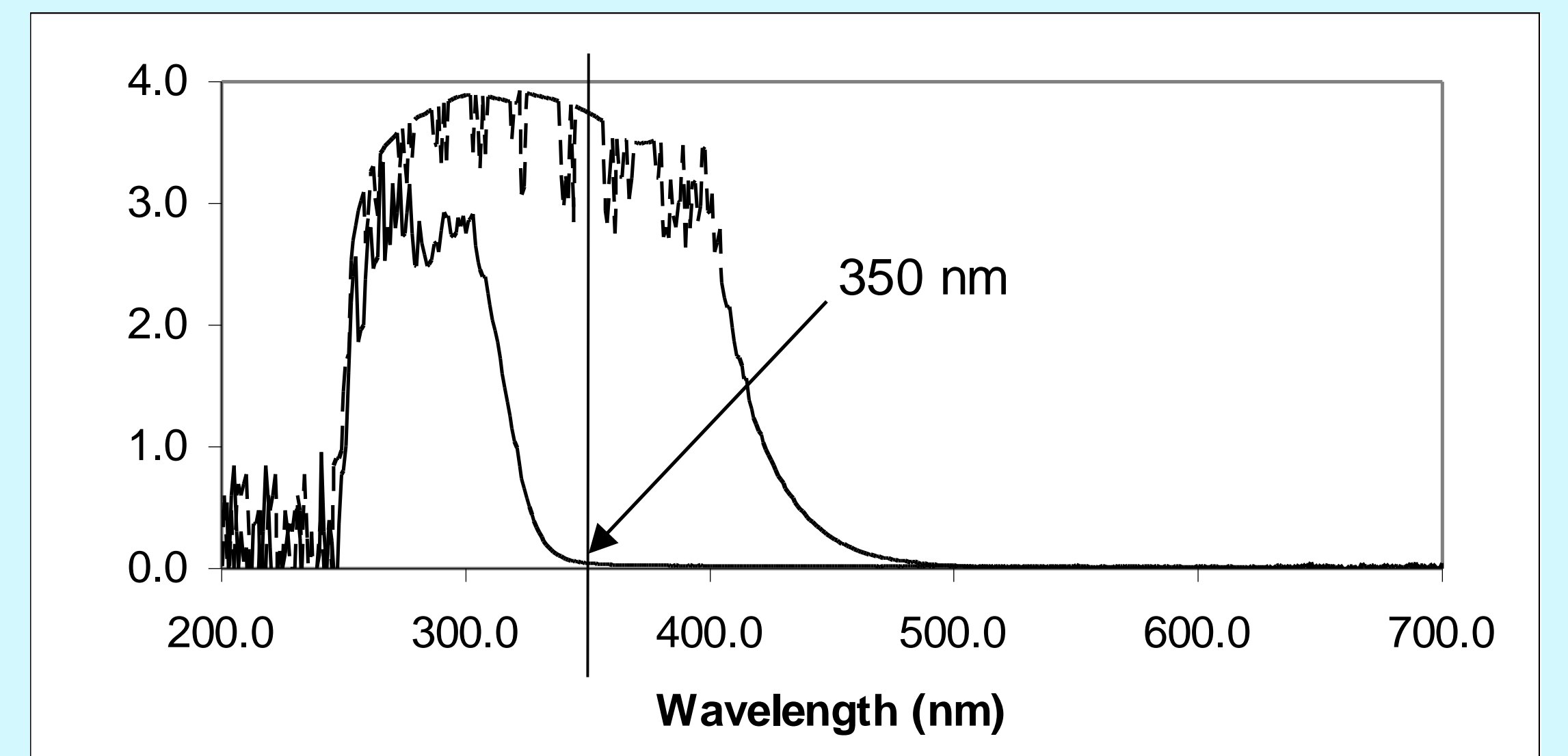


Figure 5. The light absorption spectrum of  $Ce^{4+}$  (dashed curve) and  $Ce^{3+}$  (solid curve) at  $60^\circ\text{C}$ .

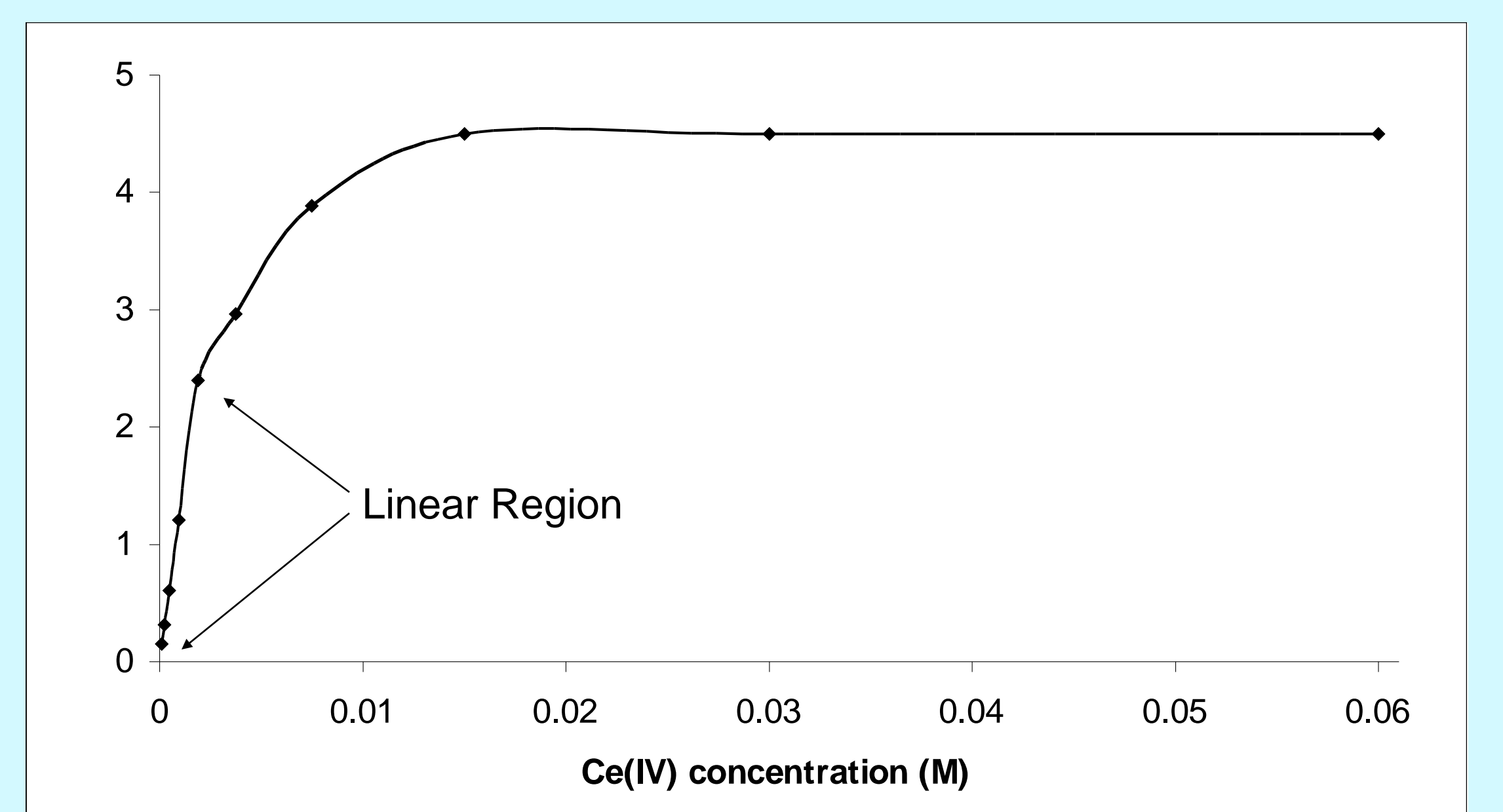


Figure 6. The UV absorption of Ce(IV) aqueous mixture as a function of Ce(IV) concentration at 350 nm. Data were recorded at  $60^\circ\text{C}$ . Data points are  $n = 3$ , and error bars are smaller than the symbol.

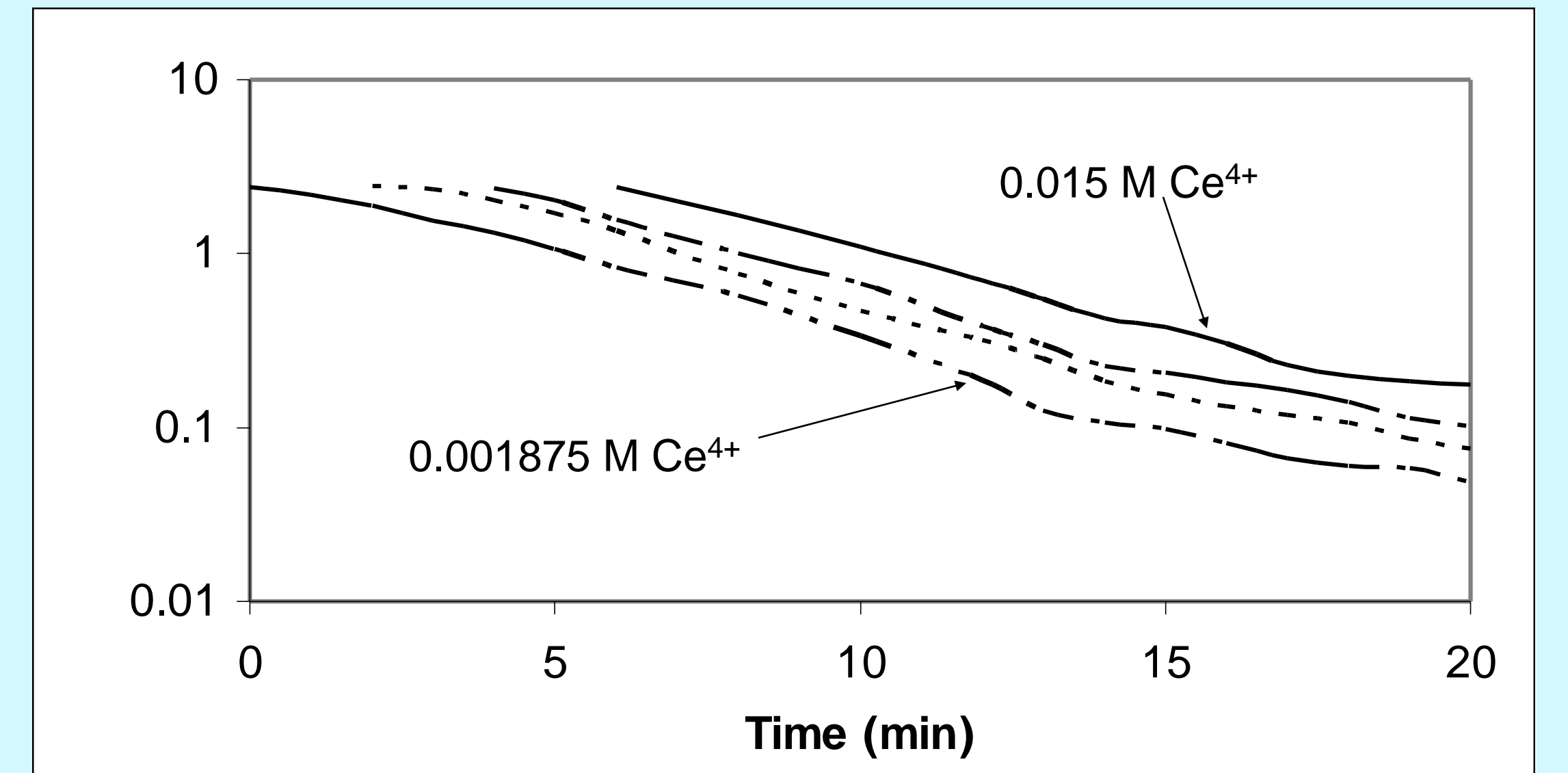


Figure 7. The UV absorption of PEO/Ce(IV) aqueous mixture as a function of time at 350 nm. PEO concentrations were 0.05 M for all four curves. Solid, dashed, dotted and double-dashed lines represent data of solutions at which Ce(IV) concentration equal to 0.015 M, 0.0075 M, 0.00375 M and 0.001875 M respectively. Data were recorded at  $60^\circ\text{C}$ .

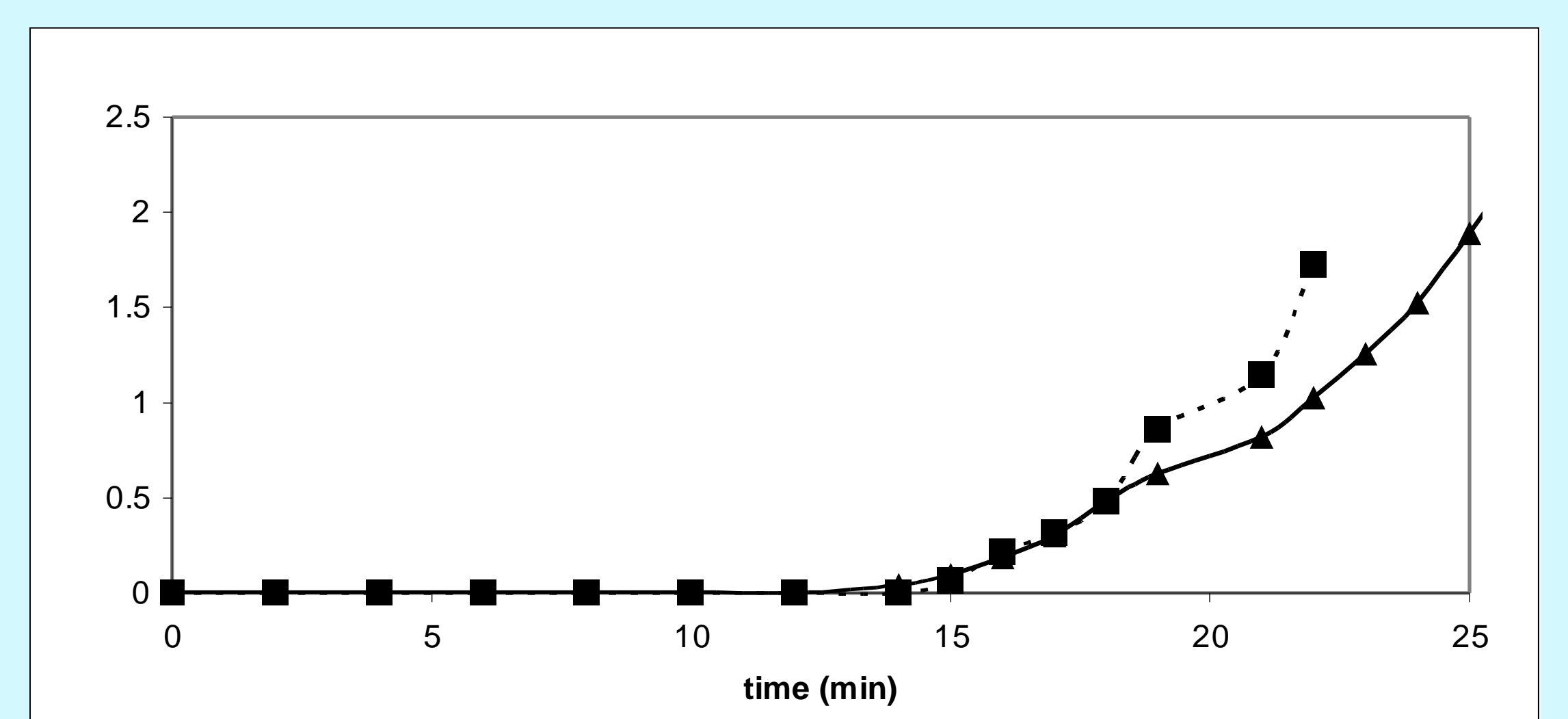


Figure 8. The turbidity of the polymerization system as a function of time at  $60^\circ\text{C}$ . Squares represent data with Ce(IV):PEO = 1.2:1 mol/mol. Triangles represent data with Ce(IV):PEO = 0.9:1 mol/mol. Data points are  $n = 3$ , and error bars are smaller than the symbols.