The Use of Poly(*N*-isopropylacrylamide) Latices as Novel Release Systems

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The uptake and temperature-controlled release of two samples of fluorescein-labelled dextran from swollen crosslinked latex particles has been studied and the reversibility of the process demonstrated.

The controlled uptake and subsequent release of materials, including macromolecules, is of considerable importance in the pharmaceutical and agrochemical industries. Methods used to take up and transport materials in a controlled manner include encapsulation systems *e.g.* cyclodextrins,[1] microemulsions[2] and vesicles.[3] In this paper the use of a colloidal dispersion of microgel particles swollen in water at 25 °C by solvent molecules is described as a potential uptake and delivery system. By careful manipulation of temperature it is shown that such microgel particles can be used as novel release systems for water-soluble macromolecules. Particles of poly(*N*-isopropylacrylamide) can be envisaged as sponge-like structures with the interstitial spaces filled with solvent when dispersed in water at 25 °C. On heating, however, the particles shrink (reversibly) to become hard sphere-like in nature, whilst simultaneously releasing solvent molecules.

Poly(*N*-isopropylacrylamide) (NIPAM) particles were prepared by the free radical polymerisation of NIPAM in water at 70 °C, in the presence of *N*,*N*′-methylene-bisacrylamide [$(CH_2{=}CH{-}CO{-}NH)_2CH_2$; from BDH Chemicals] as a crosslinking agent, following the procedure described by Pelton *et al.*[4] Following dialysis against distilled water, transmission electron micrographs showed the particles to be monodisperse spheres having a mean diameter of 460 ± 9 nm. Two narrow molecular mass samples of fluorescein isothiocyanate (FTIC)-labelled dextran (M_w 69 000 and 140 000) were purchased from Sigma Chemicals Ltd.

The temperature dependency of the particle diameter of poly(NIPAM) latex was determined by photon correlation spectroscopy using a Malvern instruments type 7027 dual LOGLIN correlator equipped with a krypton ion laser (λ = 530.9 nm). Fig. 1 illustrates the decrease in particle diameter of the poly(NIPAM) latex particles on heating. On cooling the particles reexpanded to their original size. This procedure was found to be fully reversible over a number of heating and cooling cycles, with no hysteresis. The decrease in particle diameter with increasing temperature is a consequence of the increase in the Flory[5] interaction parameter (χ) for poly(NIPAM) in water with increasing temperature. This facilitates more polymer–polymer contacts; hence the particles contract, forcing out solvent from the interstitial spaces.

The UV spectrum of aqueous solutions of FTIC dextran was measured against a reference of distilled water and an absorption maximum found at 491 nm. The mass of FTIC dextran absorbed into the particles was measured by placing 2.5 cm^3 of 0.08% FTIC dextran, 2.5 cm^3 of 0.4% poly(NIPAM) and 3 cm^3 of distilled water in a screw-top glass vial and allowing it to tumble overnight. A further 2 cm^3 of a 100 ppm solution of Alcofood 2315 (Allied Colloids Ltd) was then added. This caused the poly(NIPAM) to flocculate by the mechanism of charge-patch flocculation described by Gregory.[6] The supernatant was then removed and the absorbance at 491 nm measured and compared with that of similar solutions prepared without poly(NIPAM). The supernatant material could not be obtained by centrifugation as this resulted in the absorbed material being forced out of the microgel particles as a result of the particles been squeezed under the action of the centrifuge. The mass of polymer absorbed was calculated from previously constructed calibration curves and found to be 40 mg g^{-1} for the 69 000 molecular mass sample and 55 mg g^{-1} for the 140 000 sample.

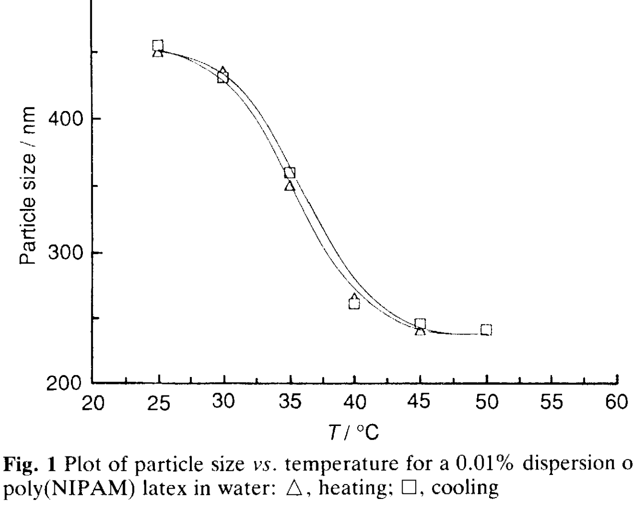

Fig. 1 Plot of particle size *vs.* temperature for a 0.01% dispersion of poly(NIPAM) latex in water: △, heating; □, cooling

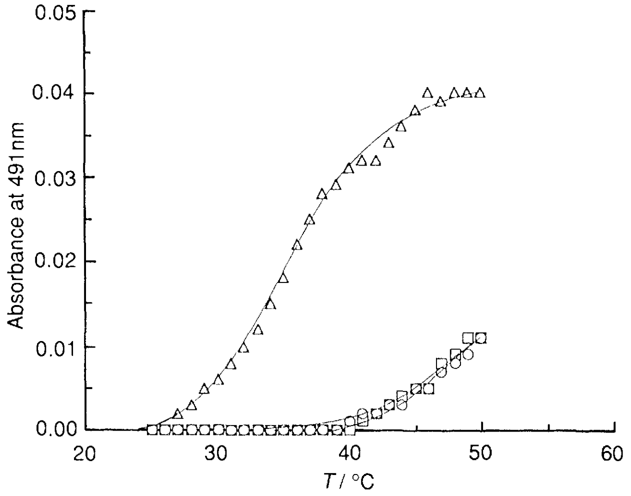

Fig. 2 Plot of absorbance *vs.* temperature for two samples of FTIC dextran in a dispersion of poly(NIPAM) measured against a reference of poly(NIPAM): △, heating (148 000); □, heating (70 000); ○, cooling (70 000)

The uptake and subsequent release characteristics of the FTIC dextran were determined as follows. 0.2% m/m dispersions of poly(NIPAM) containing 0.02% FTIC dextran solutions were prepared in water at pH 7. Similar dispersions containing poly(NIPAM) only were also prepared. The initial absorbance of the poly(NIPAM)/FTIC dextran sample was measured at 491 nm, using a UVIKON 940 spectrophotometer, against a reference of the poly(NIPAM) dispersion at the same concentration. The samples were then allowed to tumble over 24 h and the absorbance was redetermined. The decrease in absorbance after tumbling was recorded.

The absorbance at 491 nm of the poly(NIPAM)/FTIC dextran was arbitarily set to zero relative to the reference of a poly(NIPAM) dispersion at the same particle concentration. This was to enable any changes in absorbance in the sample cell relative to the reference cell to be quickly recognised. The two samples were then heated to 50 °C in the spectrophotometer using an external water bath and the increase in absorbance resulting from the release of absorbed FTIC dextran was recorded (Fig. 2). The process was found to be fully reversible, with the polymer being reabsorbed on cooling. This is illustrated in Fig. 2 for the 69 000 molecular mass sample of FTIC dextran. The absorbance spectrum of dextran in water does not change over the temperature range studied. The increase in absorbance in the dispersion containing FTIC dextran/poly(NIPAM) relative to the reference must therefore be due to the polymer molecules being displaced from the interstitial pores as the particles collapse. The volume of the microgel particles decreases by twentyfold on heating from 25 to 50 °C and approximately 65% of the absorbed polymer molecules were found to be rereleased into solution following heating with 100% secondary uptake on recooling the dispersion.

The preliminary results of a series of experiments to illustrate the use of poly(NIPAM) microgels as potential release and delivery systems are reported here. It is hoped in the near future to describe experiments which show a number of different commercial macromolecules being successfully absorbed, and subsequently released, under controlled heating conditions. It is further hoped to show that the absorbed material will remain within the microgel over an extended shelf life period with no adverse effects on the release behaviour.

The author thanks B. Vincent for useful discussions and BP Research, Sunbury, for financial assistance.

Received, 9th March 1992; Com. 2/01263D

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