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pH- and Thermo-sensitive Hydrogel Nanoparticles

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pH- and temperature-sensitive hydrogel nanoparticles of copolymers of vinylpyrrolidone (VP) and acrylic acid (AA) cross-linked with NN′ methylene bis acrylamide (MBA) of sizes up to 50 nm diameter loaded with marker compound FITC-dextran (mol wt. 19.3 kD) were prepared in the aqueous core of reverse micellar droplets and were dispersed in aqueous buffer. These particles have high entrapment efficiency, and the lyophilized powder can be redissolved in buffer without any significant agglomeration. The release of FITC-dextran from these particles was found to be pH- and temperature-dependent. The release was slow in acid solution, but it increased considerably as the pH of the medium was increased. The release rate was also increased with the increase of temperature.

Key Words: **PVP; hydrogel nanoparticles; pH-controlled release; bioadhesive polymers.**

INTRODUCTION

Oral delivery of drugs can be significantly improved by using nanoparticles as carriers (1–3). The extent and the pathway of uptake of the nanoparticle has been found to be different in different parts of the intestine (4). The phenomenon and the mechanism of orally administered particles into the bloodstream are indeed complex. Investigation of the fate of particles of less than 60 nm in diameter orally administered for delivery into the lymphatic system or blood is expected to come into sharp focus in future studies (5). Since the major pathway of uptake of these particles appears to be via the M-cells and payer's patches in the gut (6), the uptake would increase with increasing hydrophobicity (7) and decreasing particle size (3, 8). Anticipating this, we got interested in the preparation of hydrophilic polymeric nanoparticles of 10 to 100 nm diameter with narrow size distribution (9–11). We used aqueous core of reverse micellar droplets as host nanoreactors to regulate the size of these particles. In addition to drug delivery via uptake of intact particles, enhanced delivery was also observed through a direct interaction of the nanoparticles with membranes (12). Oral drug delivery with nanoparticles, therefore, may be further enhanced by addition of mucoadhesive substances to the nanoparticles (3).

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Among the controlled oral drug delivery systems, hydrogels have been extensively exploited for biomedical applications due to their high water content and excellent biocompatibility (13, 14). The pH-sensitive hydrogels containing pendant acidic or basic groups such as carboxylic acids, sulphonic acids, primary amines, or ammonium salts which change ionization in response to change in the pH have become the subject matter of major interest for use as carriers in oral drug delivery research (15, 16). The extent of interaction, adhesion, and uptake of nanoparticles of broad spectrum sizes after oral administration have been reported to be highest for the smallest particles (11).

In this paper we report the preparation of nanoparticles of up to 50 nm diameter which are co-polymers of biocompatible materials made from vinylpyrrolidone and acrylic acid monomers crosslinked with NN′methylene bis acrylamide and which were prepared in reverse micelles for precisely controlling the particle size. FITC-dextran was used as a marker compound which was entrapped in these nanoparticles. We observed that these smart hydrogel polymers were immensely sensitive to pH and temperature effects on the release of the entrapped marker compound, as has been discussed here.

EXPERIMENTAL

Materials

AOT (Sodium bis 2-ethylhexylsulphosuccinate), N,N,N′,N′ tetramethyl-ethylene diamine (TMED), N,N′methylene bis acrylamide (MBA), and fluorescein isothiocyanate dextran (FITC-Dx) were products of Sigma, USA, and were used directly without further purification. *n*-Hexane (99%), sodium monohydrogen phosphate and dihydrogen phosphate, and Ferrous ammonium sulfate (FAS) were procured from SRL (India). Acrylic acid and vinylpyrrolidone were purchased from Fluka and were used freshly distilled before polymerization. Doubly distilled water was used.

Preparation of Nanoparticles

The nanoparticles of these copolymers were prepared following the methods described in our recent patent and communication (11), the outline of which is described as follows. The surfactant, sodium bis-2-ethylhexylsulfosuccinate, or

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