Drug-Release Behavior of Polyurethane Microspheres

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SYNOPSIS

Polyurethane (PU) microspheres were prepared by a novel and simple method using the condensation polymerization technique. Microspheres of different morphological characteristics were prepared using tolylene 2,4-diisocyanate (TDI) and methylene diphenyl diisocyanate (MDI). These microspheres were fully characterized by thermal analysis, scanning electron microscopy, and spectral techniques. MDI-containing microspheres were found to be more porous as compared to TDI-containing microspheres. The infrared spectra indicated the complete utilization of the isocyanate groups in the synthesis of microspheres. Bromothymol Blue (BTB) was used as a model drug for the *in vitro* release studies from the spheres. The results indicated that BTB released much faster using the MDI spheres as compared to the TDI spheres. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

Polyurethanes constitute one of the major classes of polymers that have found widespread application as biomaterials. Polyurethane elastomers are very useful in developing many biomedical devices due to their excellent biocompatibility and tensile strength.[1-3] Polyether polyurethanes are one of the possible matrices for drug-delivery systems due to their high mechanical strength, resistance to calcification and infection, and sufficient blood and biocompatibility.[4-8] Various segmented polyurethanes (PUs) are being used as matrices for drug-delivery systems.[9,10] Although PUs in various forms have been exploited for their potential in the biomedical field, the development and application studies on PU microspheres is a relatively virgin area. Even though few papers[11,12] dealing with the release of pesticides using PU microspheres are available, the work is mostly in patented form. However, the literature using the PU microspheres as controlled-release systems is scanty.

In the present study, we attempted to develop a novel and simple method for the preparation of PU microspheres and their application as a drug-delivery system. These microspheres were characterized by various techniques such as infrared spectroscopy (IR), scanning electron microscopy (SEM), optical microscopy, particle-size analysis, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Bromothymol Blue (BTB), an aqueous marker, was entrapped as a model drug. The *in vitro* release studies of BTB were carried out under physiological conditions.

EXPERIMENTAL

Materials

Polyvinylpyrrolidone (PVP) was obtained from SRL, India. Tolylene 2,4-diisocyanate (TDI) (Fluka) and methylene diphenyl diisocyanate (MDI) (Merck) were used as supplied. 1,4-Diazabicyclo-[2,2,2]octane (DABCO) (Aldrich), BTB (BDH, UK), and poly(ethylene glycol)-1000 (PEG-1000) (SDS, India) were used as obtained.

Methods

Preparation of PU Microspheres

To 90 mL of a 1% aqueous solution of PVP taken in a round-bottomed flask was added 10 mL of a 1% aqueous solution of DABCO, which was then stirred vigorously using a mechanical stirrer at 40°C. PEG and TDI or MDI in an appropriate ratio were mixed

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and added dropwise while stirring. The temperature was increased to 60°C and stirred for another 1 h. At the end of the reaction, the microspheres were filtered and they were washed with distilled water and dried in an air oven. Figure 1 shows the schematic representation for the preparation of PU microspheres.

Entrapment of BTB in PU Microspheres

BTB was employed as a model drug to study the *in vitro* release profile. The chemical structure of BTB is given in Figure 2. BTB was dissolved in the aqueous solution of PVP before the addition of DABCO and stirred thoroughly for 10 min. At the end of the reaction, the BTB incorporated spheres were filtered off and washed to remove the BTB adhered to the spheres. The filtrate and washings were collected and absorbance was read at 620 nm. The amount of BTB entrapped was calculated by subtracting from the amount of BTB originally taken into the PVP dispersion medium.

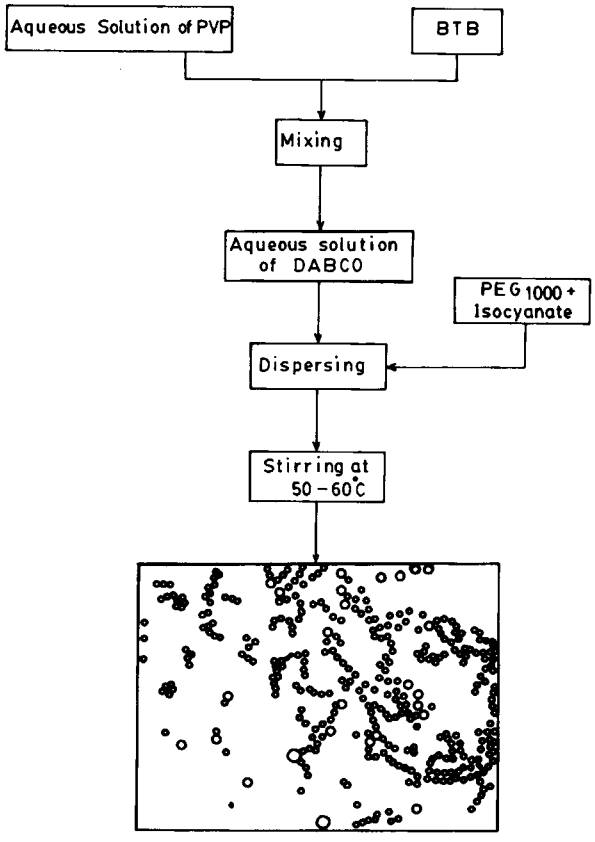

Figure 1 Schematic representation for the preparation of PU microspheres.

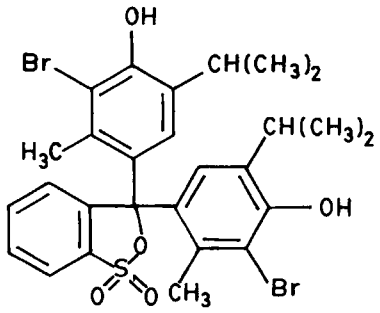

Figure 2 Chemical structure of BTB.

Characterization of PU Microspheres

Instrumentation

IR spectra were obtained on Shimadzu-470 spectrophotometer. DSC was carried out using a DuPont 2000 instrument in nitrogen at a heating rate of 10°C/min. The sample weight taken was 13 mg and the temperature range was from −100 to 400°C. TGA was carried out on a Perkin-Elmer Series −7 in a nitrogen atmosphere at a heating rate of 10°C/min. The sample weight taken was 15 mg and the temperature ranged from 50 to 600°C. SEM was carried out on a Cambridge Stereoscan S-150 scanning electron microscope. The samples for the SEM analysis were prepared by sprinkling the microspheres onto one side of a double adhesive tape stuck on an aluminum stub. The stubs were then coated with gold using an Edwards E-306 sputter coater to a thickness of 20–30 nm. The optical micrographs of the microspheres were also taken using a Hertel & Reuss optical microscope. The particle size was analyzed using the Malvern Mastersizer/E.

In Vitro Release Studies

A known weight of the microspheres were placed in 100 mL of phosphate buffer of pH 7.4 and kept at 37°C to study the release behavior. Aliquots were taken at regular intervals and assayed for the amount of BTB released at 616 nm on a Shimadzu UV/visible spectrophotometer.

RESULTS AND DISCUSSION

PU microspheres were prepared by dispersing the mixture of PEG and TDI in aqueous medium containing PVP as the suspension stabilizer. This method is an elegant and simple method developed in our laboratory as compared to the complicated

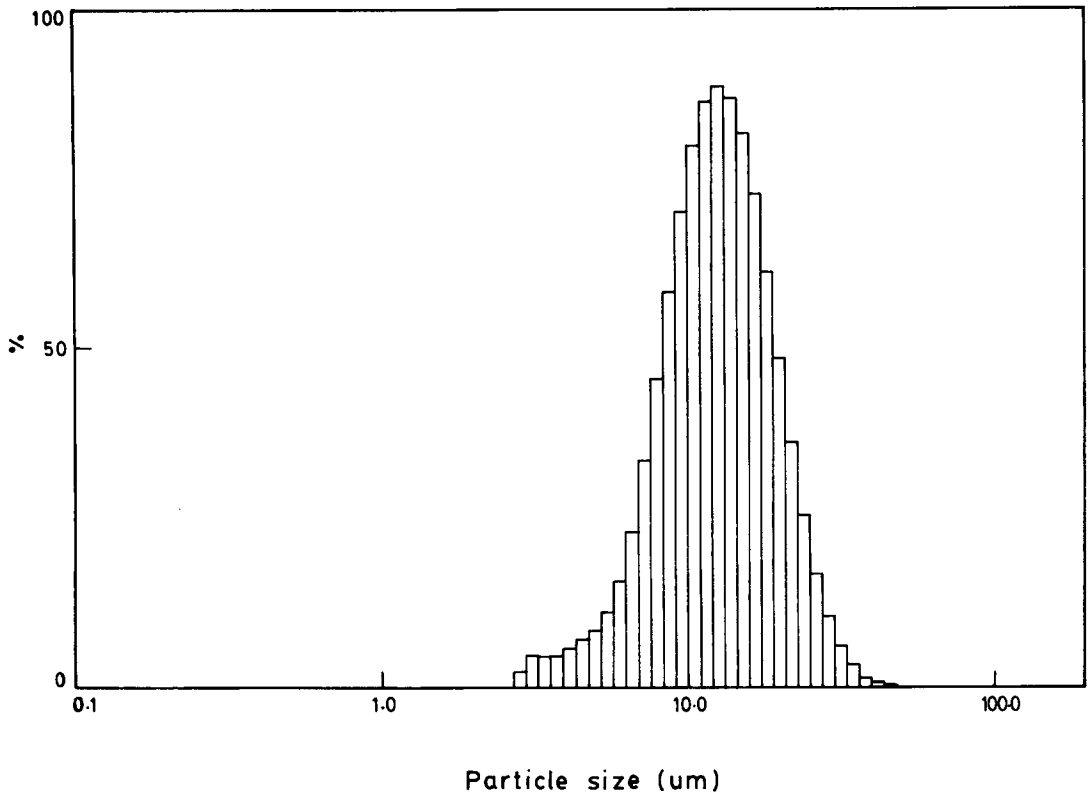

Figure 3 Particle-size distribution of TDI-based PU microspheres.

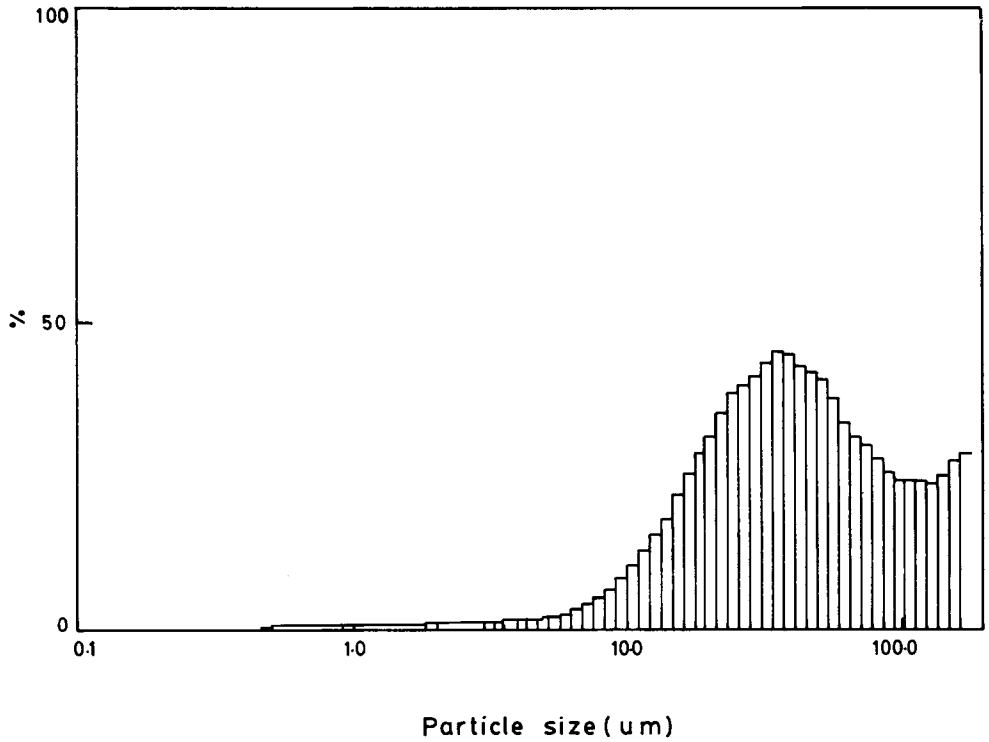

Figure 4 Particle-size distribution of MDI-based PU microspheres.

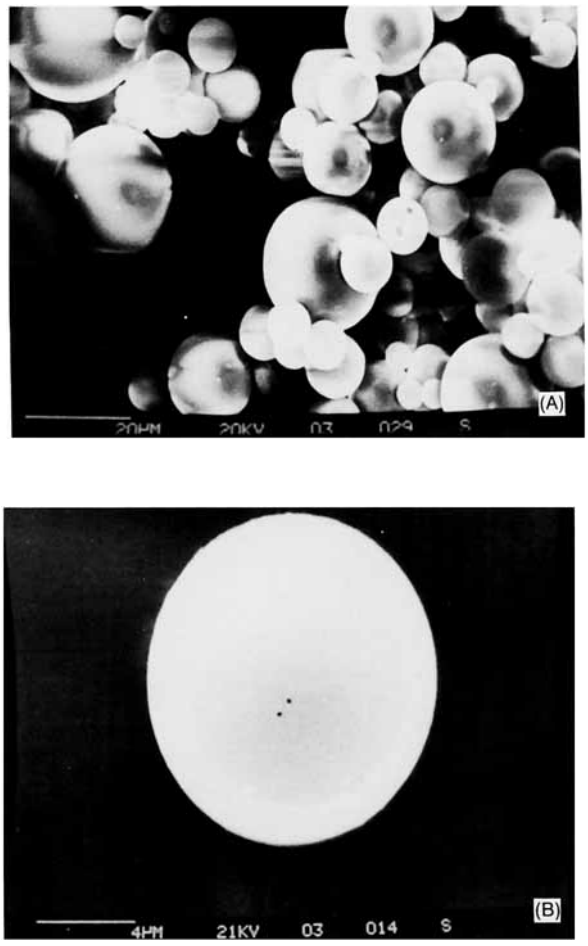

Figure 5 Scanning electron micrographs of TDI based PU microspheres: (a) lower magnification; (b) higher magnification.

methods reported earlier. DABCO was added to the dispersion medium even before the introduction of the PEG + TDI mixture and this prevented the agglomeration of the microspheres. DABCO acts as a catalyst for the formation of the spheres. The PEG + isocyanate mixture was added dropwise into the dispersion and there may be cross-linking at the surface due to the presence of DABCO in the medium. The formation of urethane will take place inside each droplet, resulting in beads with a regular spherical geometry and excellent mechanical properties.

Characterization of Microspheres

Infrared Spectroscopy

The IR spectrum of a typical PU usually centers on three spectral regions: the N—H stretching region (3450–3300 cm^{-1}) and the carbonyl stretching regions (1740–1690 cm^{-1} or 1695–1620 cm^{-1}) in a PU urea. In our study, the IR spectra showed bands at 1740 and 1700 cm^{-1} for the carbonyl stretching of urethane and also bands at 1690 and 1650 cm^{-1} for urethane urea formation. The N—H stretching was observed at 3300 cm^{-1}. The IR spectra also indicated the completion of the reaction between isocyanate and polyol by the disappearance of the NCO absorption band at 2270 cm^{-1} and the appearance of the N—H and carbonyl absorption bands. C—C stretching in the phenylene ring at 1600 cm^{-1} and C—H stretching at 2850 cm^{-1} were also observed. The C—O—C stretching at 1100 cm^{-1} and C—H bending absorptions at 880 and 750 cm^{-1} were the other peaks observed.

Particle-size Distribution of Microspheres

The particle-size distribution of both the TDI- and MDI-based microspheres were measured. In the case

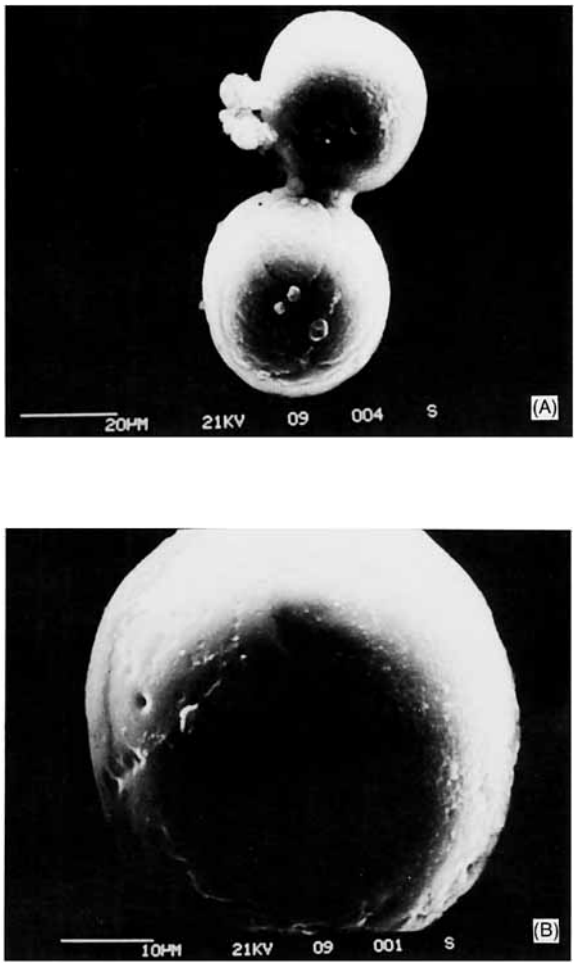

Figure 6 Scanning electron micrographs of MDI-based PU microspheres: (a) lower magnification; (b) higher magnification.

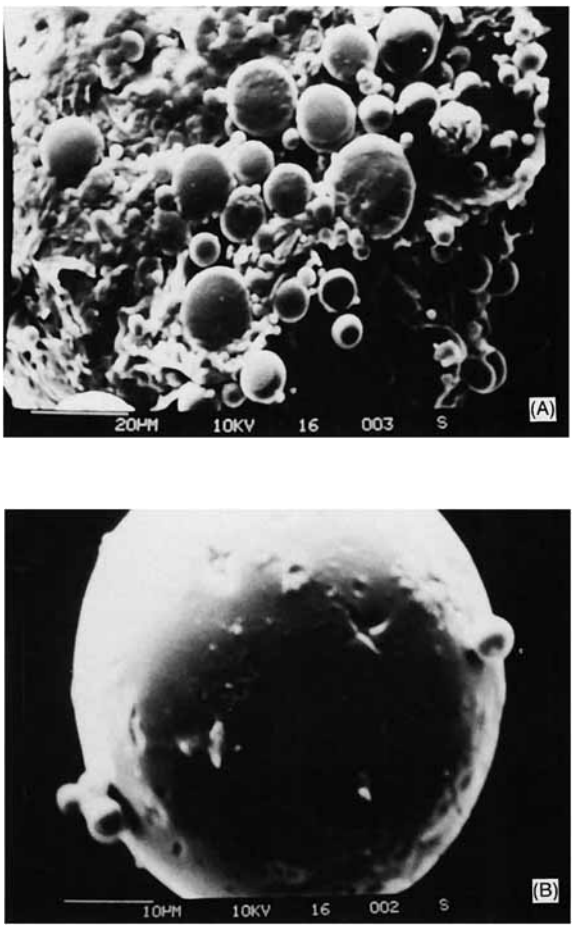

Figure 7 Scanning electron micrographs of TDI-based microspheres after the release of BTB: (a) lower magnification; (b) higher magnification.

of the MDI-based PU, about 50% of the microspheres had an average mean particle size of 35 μm, whereas with TDI, 50% of the spheres obtained had a mean particle size of 12 μm. Figures 3 and 4 show the distribution pattern of spheres using two different isocyanates. The particle-size distribution does not seem to be affected greatly by the change in the ratio of the dispersed phase to dispersion medium.

Optical Microscopy

The spherical geometry of the obtained PU particles was established by optical microscopy. TDI-based PU spheres were spherical with a smooth external surface. The MDI-based spheres also exhibited regular sphericity, but were found to be bigger in size than the TDI-based spheres. The PU microspheres were kept for about 1 month in a phosphate buffer of pH 7.4. Swollen aggregates and some spheres with distorted geometry were observed.

Scanning Electron Microscopy

Figure 5 shows the scanning electron micrograph of the blank PU microspheres based on TDI. These spheres have a smooth external surface with spherical geometry and are compact in nature. These microspheres had a mean particle diameter of 12 μm. Microspheres based on MDI exhibited somewhat porous external surface but were spherical. About 50% of the MDI-based spheres were in the range of 30–35 μm (Fig. 6). The morphology of the BTB-incorporated spheres of TDI and MDI was not much different from the blank PU microspheres. At a higher magnification, the highly porous nature of the MDI-based spheres was clearly seen. Figures 7 and 8 show the microspheres after completion of the release study of the incorporated BTB. This shows the spheres with distorted shapes and also the formation of aggregates after the release. In the case

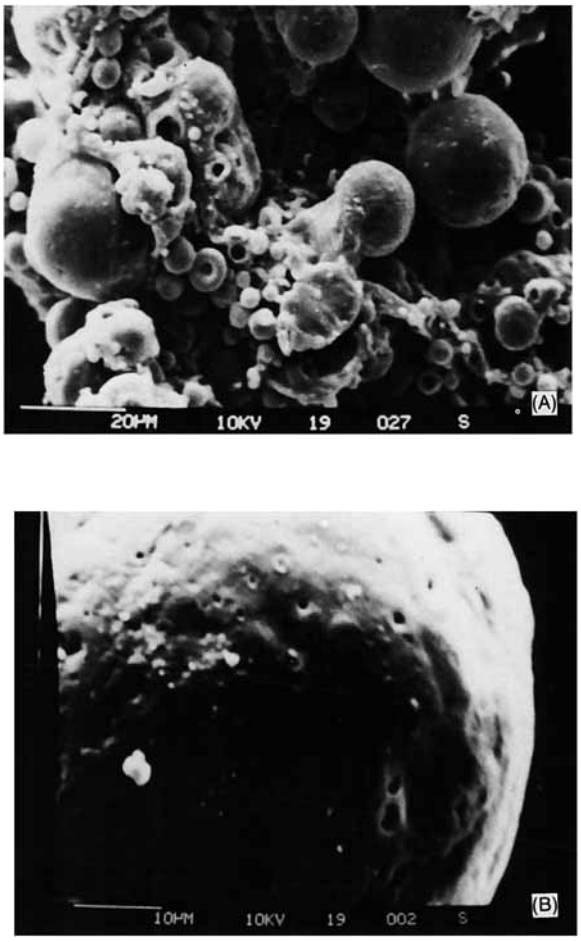

Figure 8 Scanning electron micrographs of MDI-based microspheres after the release of BTB: (a) lower magnification; (b) higher magnification.

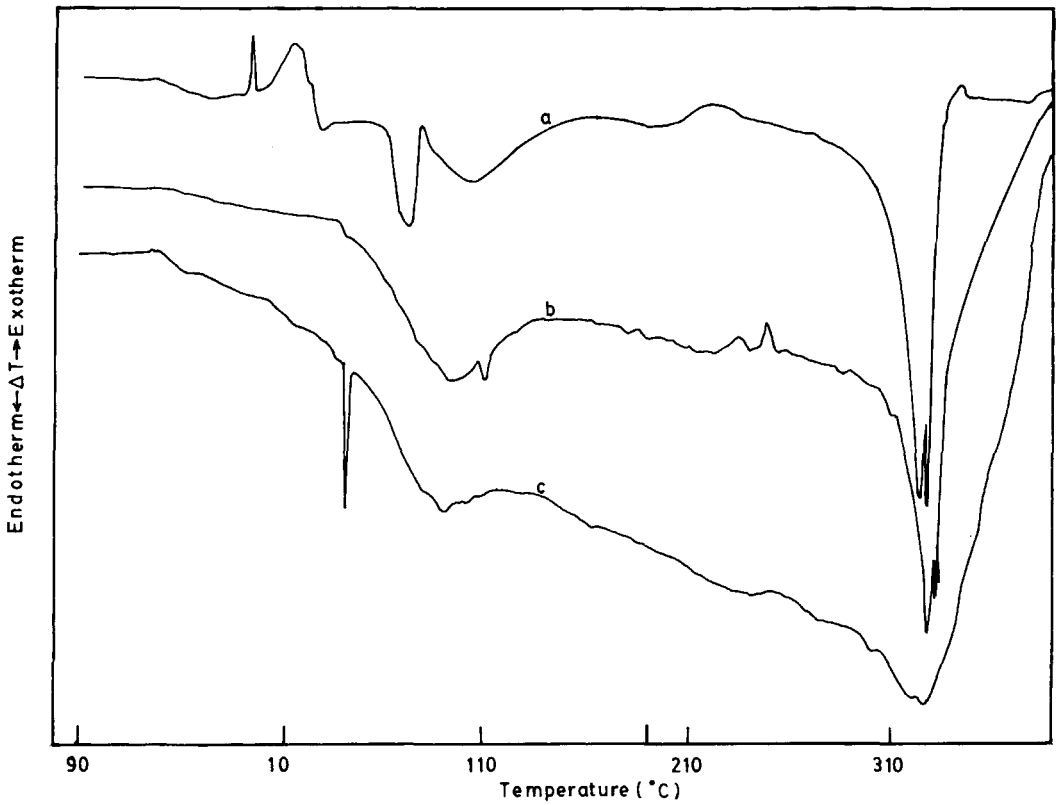

Figure 9 DSC thermogram of (a) TDI-based PU microspheres; (b) BTB-loaded microspheres; (c) MDI-based PU microspheres.

of BTB-loaded spheres based on MDI, the surface seems to be very rough and with crenalations on the exterior, which may result due to the very fast release of BTB.

For a clear understanding of the morphology of the spheres and their porosity, cross sectioning of the spheres is needed. However, it was very difficult to cut the microsphere using a microtome due to the somewhat elastic nature of the PU.

Thermal Analysis by DSC and TGA

Figure 9 shows the typical DSC thermograms of the PU microspheres. The thermogram of the TDI-based spheres showed a glass transition at −43°C and displayed three endothermic transitions at 75, 100–110, and 340°C [Fig. 9(a)]. The first endotherm at 75°C may correspond to the melting phase of the soft segment in the PU. The endotherm at 100–110°C may be due to the evaporation of the absorbed water, whereas the third endotherm corresponds to the melting transition of the hard segment. The TGA of the same blank microspheres showed the onset of weight loss at about 286°C and there was 45% weight loss that continued up to 313°C [Fig. 10(a)]. The second stage of degradation starts at 340°C and continues up to 410°C with the onset at 361°C and weight loss was up to 48%. The DSC thermogram of the microspheres with incorporated BTB did not show any glass transition very clearly, but the endotherms at 85, 110, and 335°C were almost coinciding with those of blank microspheres [Fig. 9(b)]. The TGA of the BTB-incorporated spheres [Fig. 10(c)] showed a weight loss of 60% with the onset at 230°C and the weight loss continued up to 325°C. The second stage of degradation ranges between 330 and 425°C with about 25% weight loss and the onset of degradation was at about 355°C. A typical DSC thermogram of the PU microspheres based on MDI is shown in Figure 9(c). This essentially shows three main features: a gradual transition at −45°C; a more sharply defined endotherm at about 35°C, which may be due to the melting of the polyol soft segment; and a broader transition at 85°C that may correspond to soft-segment crystallinity. The melting endotherm of the

hard segment at 335°C was also a broader transition when compared to that of the TDI-based PU spheres. The broadening of the hard-segment endotherm may be due to the disruption of larger hard-segment domains into smaller size hard-segment domains. The TGA of the PU microspheres based on MDI [Fig. 10(b)] shows the onset of degradation at about 301°C and undergoes 42% weight loss that continued up to 447°C. The above data clearly indicate the presence of microdomains in PU microspheres.

Release Studies of BTB

The *in vitro* release studies of BTB entrapped in both the TDI- and MDI-based spheres were carried out in phosphate buffer of physiological pH 7.4 and at 37°C. About 65% of the BTB was entrapped into the spheres based on TDI, whereas the percent entrapment in the case of MDI-based spheres was only 33%. Figure 11 shows the release curve for BTB-incorporated microspheres based on TDI. The release takes place in a three-phased manner. In the first phase, there was an initial boost release, followed by a slow release up to 10 days in a zero-order pattern. In the final stage, the BTB release was much slower and the release has continued for 23 days. About 25% of the incorporated drug was released within 23 days. The release of BTB was very fast in the case of MDI microspheres. There was an initial

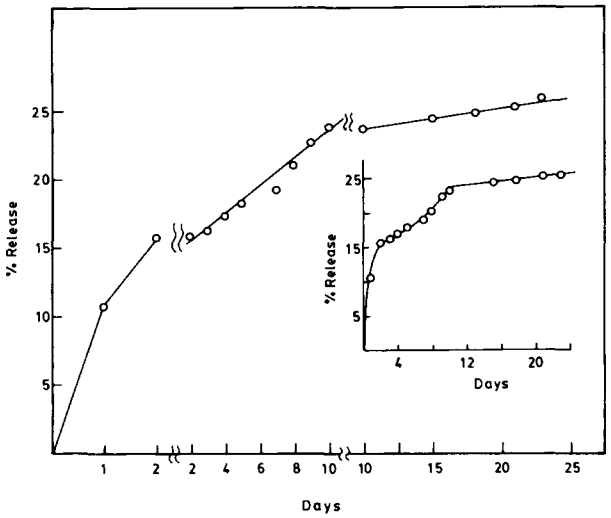

Figure 11 *In vitro* release profile of BTB loaded in TDI-based PU microspheres.

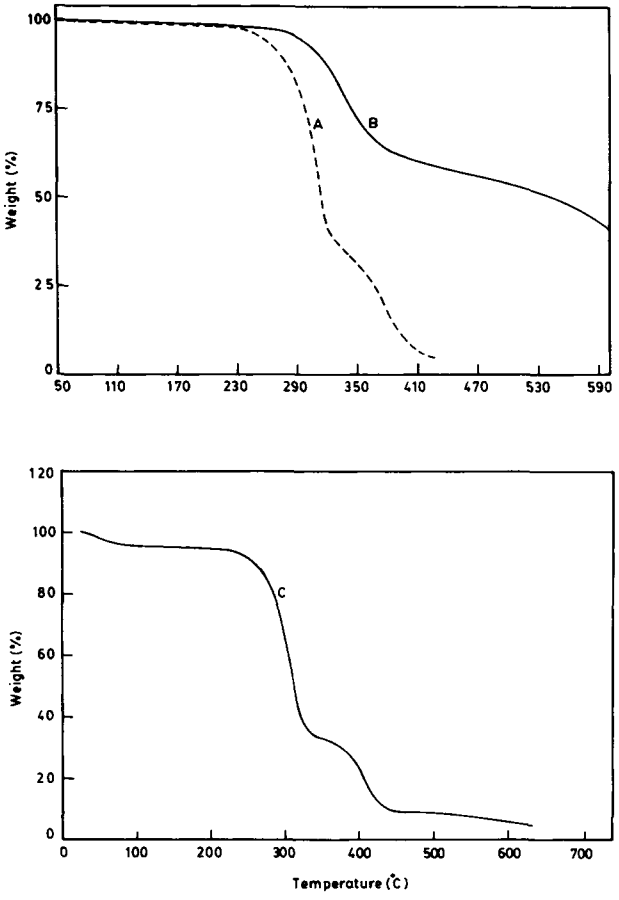

Figure 10 TGA thermogram of (A) TDI-based PU microspheres; (B) MDI-based PU microspheres; (C) BTB-loaded microspheres.

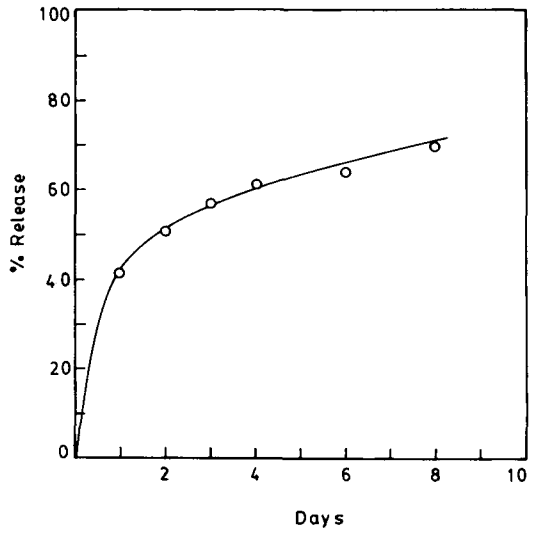

Figure 12 *In vitro* release profile of BTB loaded in MDI-based PU microspheres.

boost release up to 42% within 24 h, and, thereafter, the release followed a regular pattern of zero-order release. This pattern was followed up to 8 days by releasing about 69% of the incorporated BTB (Fig. 12). This faster release of BTB from the MDI microspheres may be attributed to the porous nature of MDI microspheres. On the other hand, the TDI microspheres released BTB in a much slower fashion and the release was about 25% even after 23 days. This is in agreement with the compact morphological structure of the TDI microspheres.

CONCLUSION

A novel and elegant method was developed for the preparation of the PU microspheres using the condensation polymerization technique. PVP was employed as the suspension stabilizer with DABCO as the catalyst in aqueous medium. The microspheres were fully characterized for their morphology, particle size, and thermal behavior using different isocyanates. BTB, a model drug, was entrapped in these microspheres and its release characteristics were studied at physiological conditions. These studies opened up new avenues for PUs as drug-delivery systems. Efforts are in progress in our laboratory in this direction.

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