

Microparticles on the Basis of Segmented Polyurethanes for Drug Respiratory Administration

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Abstract

Microparticles based on segmented polyurethane were synthesized by polycondensation of a series of diols having various molecular weight with tolyene-2,4-diisocyanate in water-in-oil emulsion. The resulting spherical microparticles were 6-10 μm in diameter following the Gauss distribution. The size of microcapsules at maximum distribution band increases with growing PEG length. It was observed that with higher length of PEG wall surfaces of capsules become more stable mechanically, however a capsule itself is no more brittle and rough. Some aggregation also occurs for microparticles based on PEG 4200. Since respiratory way of drug administration considers size of particles within 1-10 μm as the most applicable, the resulting PU microparticles could be an ideal candidate as domain for respirable antiTB drug administration.

Introduction

At present there is an increased interest in the preparation and characterization of microparticles prepared by interfacial polycondensation because microencapsulation gives numerous advantages and benefits for application [1,2]. The technique involves the polycondensation of two or more complementary monomers at the interface of a two-phase system carefully emulsified to form small droplets in a suspension medium. Polyurethanes have particular interest, and numerous patents describe their applications in various fields such as medicine, pharmaceuticals, cosmetics, photography and so on. However, academic studies concerning the polyurethane microcapsules are quite scarce [3,4]. In fact, polyurethane microparticles may be produced by two chemical procedures: by polycondensation of a diamine with bischloroformates or by reaction between a diol and a diisocyanate [5]. The last process seems particularly interesting since no secondary reaction products are formed in contrast to the former ones, in which the presence of an acid captor is required.

In this paper, the synthesis and characterization of polyurethane capsules are studied using three dif-

ferent molecular weight diols of two types: poly(ethylene glycol) and poly(propylene glycol). The experimental procedure is derived from the procedures used for the polyamide microcapsule preparation with some modifications [6]. Our main purposes were to modify the way of synthesis as well as to determine the best chemical components for obtaining the capsules with satisfactory size distribution and good mechanical properties. It is quite important to note that the size of polyurethane microcapsules and their distribution are extremely important for their application for targeted delivery by respiratory way. The main point of the pulmonary route of drug administration is a size of the formulation, which should be limited to 1-10 μm [7]. Particles of such size are mainly to be placed in the periphery of the lung and must be phagocytized by alveolar macrophages, the primary site of MTB infection. On account of inevitable absorption of any particles less than 1 μm by the mucous membrane into the blood circulation, the use of only the drug itself is not suitable. Drug ought to be immobilized into a carrier with the appropriate spherical aerodynamic size under 10 μm at least to escape its trapping before it reaches the lung alveoli. Besides, a carrier should possess the other important properties, such as essential drug loadability, non-

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traumatic surfaces, quite compliant biocompatibility, and non-protracted harmless biodegradability. A series of synthetic polymers have been specifically developed for pulmonary drug delivery with a particular attention to lactide and glycolide polymers and their copolymers [7,8]. There are two main reasons why such carriers are less appropriate – complicated techniques to load a required drug amount and relatively rigid surfaces of their particles. Consequently, the objective of the proposed research was to develop a new drug form for the treatment of TB in an effort to alleviate the health problems associated with this disease and epidemic outbreaks in Kazakhstan it could be coped with by their pulmonary administration to the lungs.

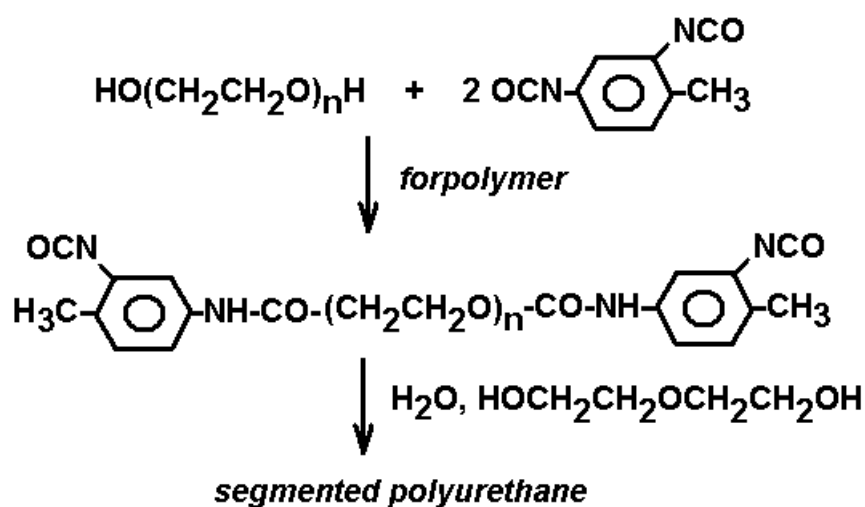
Experimental

All chemicals were used as received and solvents were distilled before synthesis. Poly(ethylene glycol) PEG with various molecular weights 600, 1500 and 4200 (Sigma, USA) - PEG 600, PEG 1500, and PEG 4200 respectively as well as poly(propylene glycol) PPG 1500 were used as diol monomers. Toluene-2,4-diisocyanate (TDI) (Sigma, USA) was applied as a bifunctional monomer for the polycondensation. Polycondensation were realized into a 1 L double-neck flask flushed with nitrogen. Three solutions were prepared separately. In first solution, 45 mg of a suspension stabilizer Tween 40 was dissolved in 450 mL of toluene. In second solution, 20 mmol

of diol were mixed to 45 mL of distilled water. In third solution, 22 mmol of TDI were dissolved in 75 mL of first solution. Second solution was poured into the reactor containing 375 mL of first solution under stirring at 300 rpm and 60°C during 15 min with following 5 min treatment by an ultrasound disintegrator (UH-500W, Germany). Then the stirring was reduced to 200 rpm and third solution added by drop-let. After 5 hrs the polycondensation was stopped by carefully washing by excessive amount of first solution. Scanning Electron Microscopy (SEM) images were recorded by means of an equipment Cambridge F360 with previous covering of samples by gold. Dynamic light scattering analysis was performed using He/Ar 7005H (Mitsumi, Japan) with sample concentration 100 µg/mL in 30 vol.% ethanol aqueous solution. Chemical structure of synthesized polyurethanes was identified making use of ¹H NMR Varian100 Hz (USA) in D₆-DMSO solution.

Results and Discussion

The principle of the microcapsule formation by interfacial polycondensation is described well in different reviews and publications [3,5]. The reaction occurs generally in two steps. The first step is a reaction of one mole of diol with two moles of diisocyanate to produce so-called forpolymer, polydiol with two end isocyanate groups. During the second step the forpolymer reacts with water or diols to condense in a linear macromolecular chain:



In a water-in-oil (W/O) system, an aqueous drop-let suspension containing one monomer is formed in

an immiscible solvent containing a complementary monomer in the presence of a suitable stabilizer. Quite

rapidly the polymer formed precipitates at the organic side of the interface (primary membrane) and the reaction slows down since the polymeric wall restricts the diffusion of monomers. The thickness of the wall increases slowly and the growth occurs on the organic or aqueous side depending on the nature of the membrane and its affinity to the monomers. During the growth, the layer morphology changes and it becomes porous. Pores are formed by the precipitation of polymer at the interface of solvent droplets diffusing through the wall.

The experimental procedure includes three steps. First, a stable initial inverse emulsion is formed by

controlled stirring of an aqueous solution containing one of diols in toluene containing the stabilizer. Second, a final fine emulsion and basically the size of resulting capsules is mainly determined by frequency of the ultrasound treatment, however the amount of stabilizer and the stirring rate are also important. In order to limit the number of parameters and facilitate the optical observations, a fixed frequency 250 MHz, amount of stabilizer (0.5 g/L) and a rate of 300 rpm have been used. This finally leads to capsule diameter within 5-7 μm range. Formation of polyurethane was confirmed with ^{13}C and ^1H NMR analysis (Table 1).

Table 1

Preparation of polyurethane capsules realized at 60°C during 5 hr in the dependence on the type of diol at the same amount of TDI (6.5 mg/L)

Diol type of SPU	Stechiometric content of TDI, wt.%	Content of TDI-chains according to carbamide group numbers by ^{13}C -NMR (145 mp), wt.%
PEG 600	36.7	30.2
PEG 1500	18.8	15.9
PEG 4200	7.7	5.1
PPG 1500	18.6	16.4

Once the emulsion is stabilized, the stirring rate is reduced to 200 rpm and a solution of TDI in toluene is added. The primary membrane is formed immediately, which has been confirmed by SEM microscopy. Finally, the reaction is continued for some hours in order to ensure the wall growth (maturation step). After recuperation and washing, the preparation is analyzed by SEM and optical microscopy. This allows controlling the capsule formation and stability, to estimate their size and size distribution, the ratio of broken capsules and their surface state (Fig. 1).

After the preliminary experiments showing the effective formation of capsules were carried out, the effects of nature and concentration of isocyanate and diols were studied. On the best preparations, the wall structure was analyzed by SEM (Fig. 2) and size distribution by dynamic light scattering analysis (Fig. 3). The results are summarized in Table 2.

The replacement of PPG by PEG tends to increase the yields of reaction. The size of microcapsules at maximum distribution band increases also with the PEG length. Third, one observes that with higher length of PEG the wall surfaces of capsules become

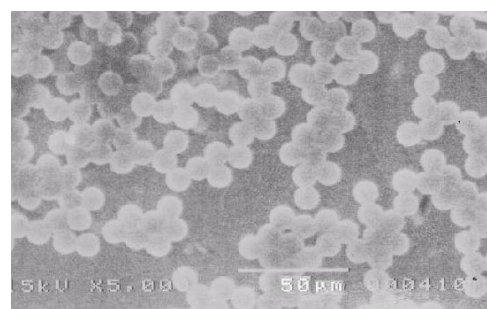


Fig. 1. SEM microphotographs of microparticles of segmented polyurethane based on PEG 1500. Bar is 50 μm .

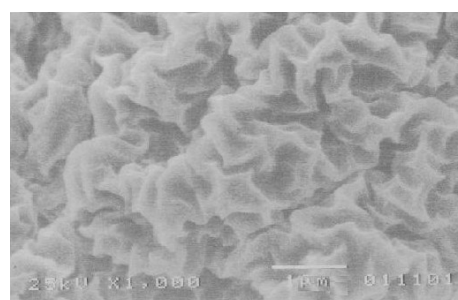


Fig. 2. SEM microphotographs of surface of microparticles of segmented polyurethane based on PEG 1500.

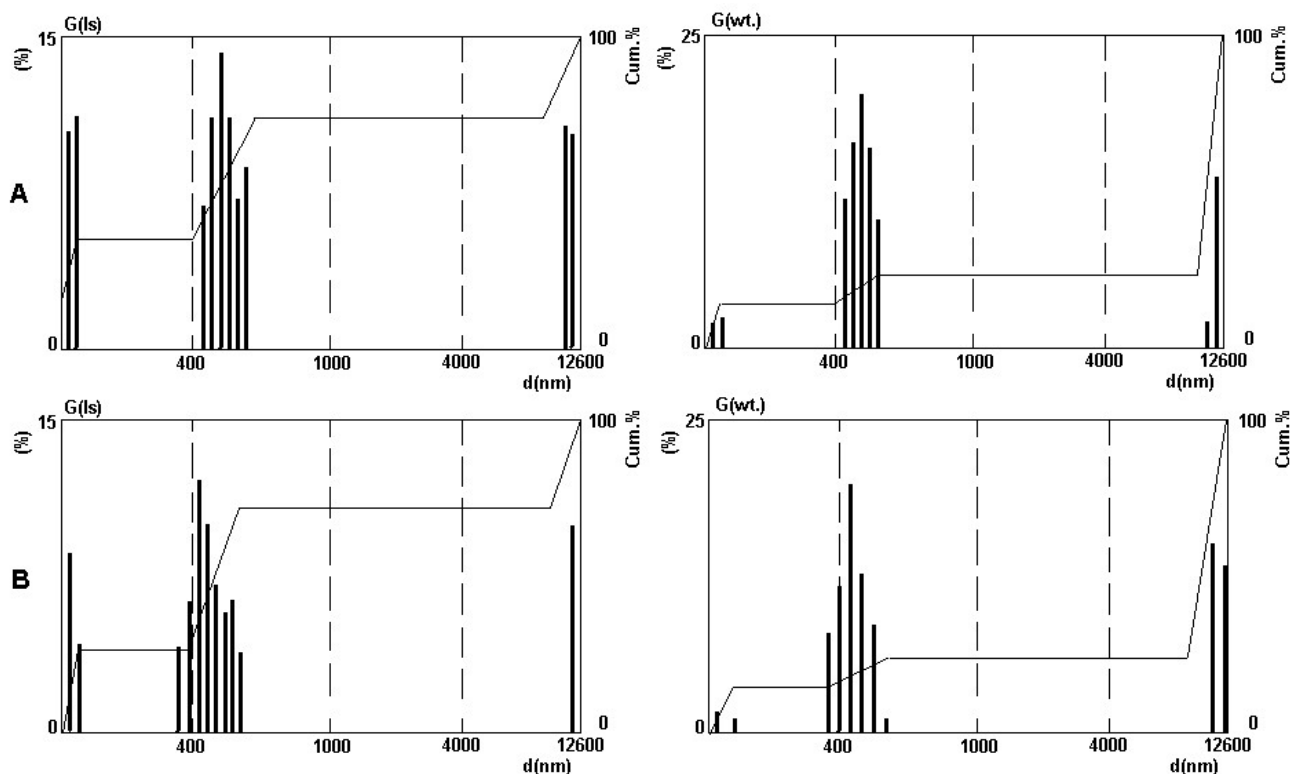


Fig. 3. Number (left) and weight (right) distributions of microparticles based on PEG 600 (A) and PEG 1500 (B) polyurethanes by dynamic light scattering analysis.

Table 2

Preparation of polyurethane capsules realized at 60°C during 5 hr in dependence on the type of diol at the same amount of TDI (6.5 mg/L)

Diol type	Diameter, μm	Yield, %	State and surface appearance
PEG 600	3-5	63	some breakage, rough
PEG 1500	6-8	70	some breakage, spongy
PEG 4200	7-9	79	smooth, spongy, some aggregation
PPG 1500	8-9	51	smooth, very brittle wall

more stable mechanically, however a capsule itself is no longer brittle and rough. With PEG 4200, aggregation also occurs.

Conclusions

The study of preparation of polyurethane capsules from isocyanate and diols shows that by an appropriate choice of the experimental conditions, it is possible to obtain the microcapsules in the range 6-10 μm with good mechanical properties and smooth wall surface. This preliminary work may be extrapolated to the synthesis of microcapsules loaded with antiTB drugs or vaccine, in which such properties

are very important to ensure the encapsulation of the drugs. Since respiratory way of drug administration considers the size of particles within 1-10 μm as the most applicable, the resulting PU microparticles could be an ideal candidate as domain for respirable antiTB drug administration.

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