# Poly(ethylene glycol-β-cyclodextrin) Gels: Synthesis and Properties

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**ABSTRACT:** A new hydrogel that combines poly(ethylene glycol) and β-cyclodextrin has been synthesized. Both components are linked by using a diisocyanate (HDMI), first by end-capping the poly(ethylene glycol) with isocyanate groups an then reacting it with β-cyclodextrin, forming urethane links. Hydrogels of molar compositions (β-cyclodextrin/poly(ethylene glycol)) ranging from 1/4 to 1/14 have been synthesized. These hydrogels swell quickly and their water contents depend upon temperature. The gels are temperature resistant and show an elastomeric behavior. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 1162–1166, 2006

**Key words:** β-cyclodextrin; hydrogels; poly(ethylene glycol); swelling; thermal properties

## INTRODUCTION

The hydrogels are polymer materials of enormous interest in biomedical applications. In these materials, the biocompatibility of their components and their capacity to retain and to liberate certain substances are fundamental. It is not strange that the poly(ethylene glycol) (PEG), hydrosoluble polymer, with a great chain and chemical stability and high biocompatibility, has frequently been used in the synthesis of biocompatible hydrogels.[1–3] The methods most used for the synthesis of hydrogels based on PEG are based on the reaction of the terminal hydroxyl groups of the chains of PEG with diisocyanates and later reaction with a triol (crosslinker),[4–6] or the direct reaction with a pluri-isocyanate[7] that acts, in the last case, as a crosslinker. In both cases, urethane groups link the different components of the gel. PEG hydrogels are also often prepared by radiation crosslinking of high molar mass poly(ethylene oxide).[8–10]

On the other hand, the capacity of the cyclodextrins for the formation of inclusion complexes[11] is widely applied in separation processes[12,13] (chromatography, waste water treatment) and in the field of the controlled drug delivery, and their application in stimuli-responsive, especially pH- and temperature-responsive, drug release[14] is very well-known.

In these fields, the formation of gels is of great importance. In this sense, among other methods, it has been shown that the cyclodextrins can crosslink with diisocyanates,[15,16] making use of the existence of a high number of hydroxyl groups in their structure.

In this work, we present a new hydrogel type that combines both components, using a diisocyanate. The synthesis is carried out in two stages. The first one takes advantage of the presence of two terminal hydroxyl groups of the PEG to make them react with the diisocyanate, thus obtaining PEG chains with groups located in their isocyanate ends. In the second stage, these modified PEG chains react with the hydroxyl groups of the β-cyclodextrin (βCD), which acts as a crosslinker center for the formation of a hydrogel with urethane-type bonds.

## EXPERIMENTAL

Poly(ethylene glycol) (PEG) (Aldrich), with an average molar mass of 600 g/mol, was dried at vacuum at 65°C for 24 h. Its real molar mass determined by titration of final groups by reaction with the pyromellitic dianhydride[17] (Aldrich) in dimethylformamide (DMF) coincides with the nominal one (617 g/mol).

β-cyclodextrin (βCD) (99.5% of purity) was kindly supplied by Roquette Laisa España S.A., and was dried under vacuum at 100°C for 24 h and stored on a desiccator before use. DMF and toluene (Panreac) HPLC grade were dried over 4A molecular sieves. Hexamethylene diisocyanate (HDMI) and dibutyltin dilaurate (DBTDL) (Aldrich) were used as received. The preparation of the gels is described later (see Synthesis and Characterization section).

Infrared spectra of the gel and pure components were taken with a ReactIR[TM] 1000 Reaction Analysis System (ASI Applied Systems, Mettler-Toledo Corp.) equipped with a light conduit and DiComp (diamond composite) insertion probe, used as a multiple reflection ATR (attenuated total reflection) element. Spectra were taken with resolutions of 4 cm$^{-1}$ and were averaged over 128 scans.

The thermal analysis of gels was done with a DSC Mettler TA4000 and a thermobalance Mettler TG50. Weight samples were about 8 mg in all cases, and scan speed was 10°C/min under nitrogen atmosphere. The glass transition temperature of the gels was determined with the approach of half point of the jump of specific heat.

The conventional method of monitoring swelling kinetics of hydrogels is the weighing technique. The weighing procedure is as follows: hydrogel samples are taken from solution, water is removed on the sample surface by lightly blotting with paper, the hydrogel is weighed using a balance, and finally, the measured weights are recorded.

## RESULTS AND DISCUSSION

### Synthesis and characterization

The preparation of the gels is carried out in two steps. First, two solutions of PEG and HDMI in DMF (molar relationship 1/2) are made to react, at 55°C, in a three-necked flask previously purged with dry N$_2$. The total concentration of reagents is 25 wt % and the reactor contains 0.01 wt % catalyst (DBTDL) with respect to the total weight of the reagents. The resultant reaction is depicted in Scheme 1(a).

The result is poly(ethylene glycol) chains whose terminal hydroxyl groups have been substituted by isocyanate groups, for an end-capped process in which each molecule of HDMI, uses one of their two isocyanate groups to react with a hydroxyl group of the PEG by means of the formation of a urethane group. With this polymerization method, conversions close to 100% were obtained.

The described process is typical in the synthesis of commercial polyurethanes starting from diols and of diisocyanates. In the case of the PEG and the HDMI, the process has been studied using toluene as reaction medium;[18] it is a slow reaction even at high temperatures. Our preliminary tests in DMF showed the same behavior, and we opted to accelerate it with DBTDL. The relative low reaction temperature allows us to avoid secondary reactions in these types of systems such as allophanates formation.

When these reactions are catalyzed, it is difficult to determine their final point.[19] This was determined with the help of a ReactIRTM 1000 probe that allows the reaction to be followed *in situ*. The reaction mon-
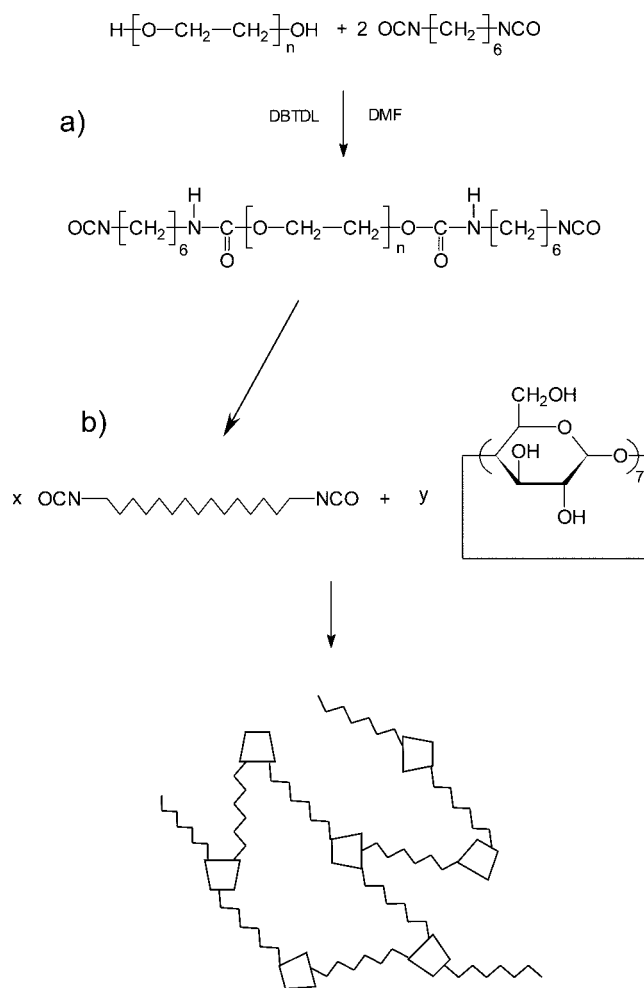


**Scheme 1** (a) End-capping process of PEG with HDMI. (b) Reaction among the end-capped PEG with isocyanate groups and the βCD, together with an idealized outline of the structure of the gel.

itoring was accomplished by following the evolution of the isocyanate band at 2276 cm$^{-1}$, and when the value of the initial absorbance decreased to half, a solution of βCD in dimethylformamide (16.5 wt %) was injected in the flask (second step), in the necessary amount to obtain the desired composition in the gel. The typical time required for the injection of the βCD solution is nearly 60 min. After maintaining the system in agitation during half an hour, the reactive mixture was transferred to a test tube, sealed with septa, and purged with nitrogen. They remained in the stove at 75°C for 7 days. The resulting reaction is summarized in the Scheme 1(b). After this time, the gels were extracted and washed several times, first with DMF and later with deionized water, at room temperature, to remove water-soluble β-cyclodextrin from the samples until less than 1 ppm monomer was detected in the wash solution, during a total of 10 days. Then, the samples were dried at room temperature and finally to a constant weight in a vacuum oven at 50°C.
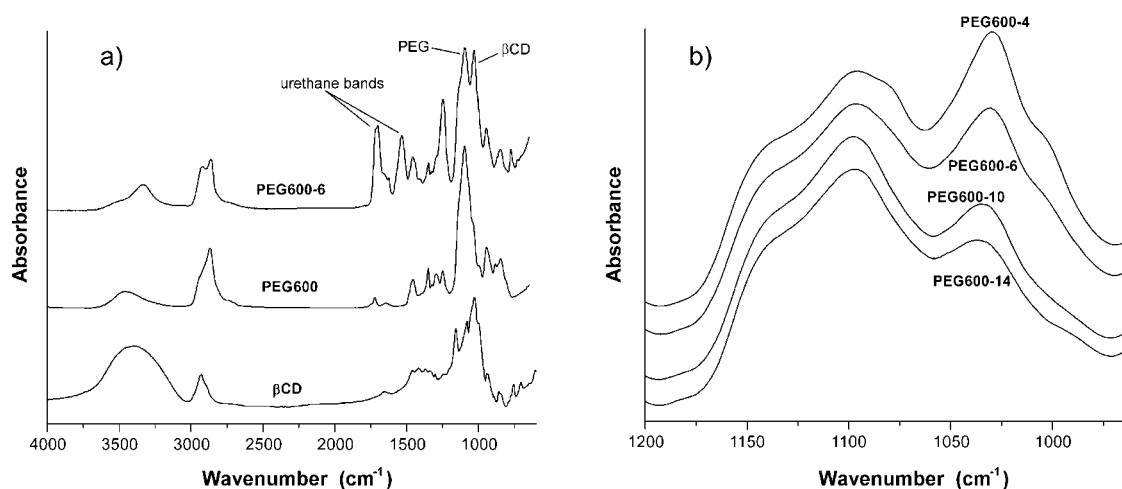
**Figure 1** (a) Infrared spectra of PEG, βCD, and a PEG600-6 gel; (b) ATR Infrared spectra of the different gels in the region 950–1200 cm$^{-1}$.

Following this procedure, gels of molar compositions PEG/βCD: 4/1; 6/1; 10/1; and 14/1 were synthesized. We will denominate to these gels: PEG600-4; PEG600-6; PEG600-10; and PEG600-14. It was not been possible to obtain gels of lower composition than 4/1.

The synthesized gels were characterized by FTIR using the same ReactIR 1000 probe, in the same way as previously described. The elastomeric character of these gels allows good IR spectra to be obtained by means of ATR. Figure 1(a) shows the spectra of the βCD, the PEG600, and a gel PEG600-6. It can be observed that the gel spectrum shows the presence of bands that correspond to PEG and βCD, as well as two clear bands corresponding to the presence of urethane groups: amide I (1708 cm$^{-1}$) and amide II (1536 cm$^{-1}$), which confirm the chemical structure proposed in the Scheme 1(b) for the gel. The differences in composition of these gels can be confirmed starting from the evolution of their infrared spectra. Figure 1(b) shows the evolution of the bands at 1097 cm$^{-1}$ and 1030 cm$^{-1}$, corresponding to the PEG and to the βCD in the gels. Observe that the relative contribution of the last band decreases as the percentage of βCD decreases in the feeding.

## Swelling

The macromolecular networks obtained swell in the typical solvents of PEG, particularly in chloroform,

the most favorable liquid for PEG gels with urethane crosslinking.[4] When water is used, hydrate percentages, $H_p$%, are obtained as:

$$H_p\% = 100 \times \left(\frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}}\right) \quad (1)$$

which is shown in the Table I. It is found that the hydrate percentage varies with the composition of the gel, increasing as the βCD content diminishes. On the other hand, observe that these percentages are notably influenced by temperature. Concretely, in all the gels studied, the $H_p$% value diminishes considerably as the temperature increases, and makes it in a practically linear way, as shown in Figure 2. This
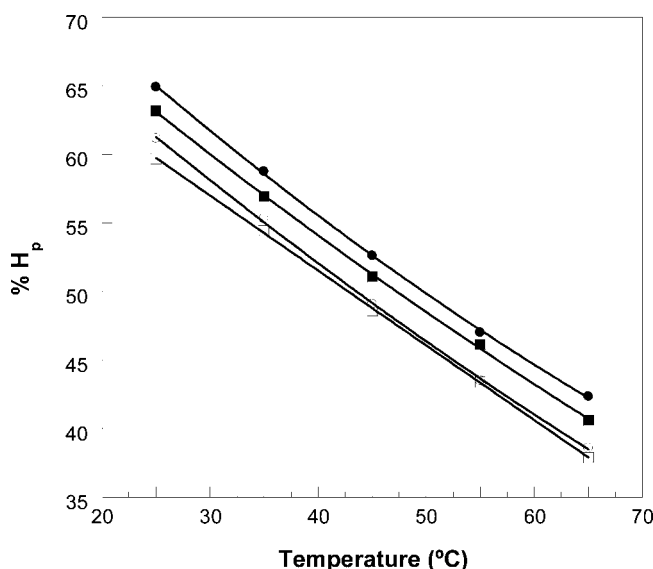
**TABLE I**
**Variation of the Hydrate Percentage with Temperature for Gels PEG600/βCD of Different Compositions**

| Temperature (°C) | PEG600-4 $H_p$% | PEG600-6 $H_p$% | PEG600-10 $H_p$% | PEG600-14 $H_p$% |
|---|---|---|---|---|
| 25 | 64.9 | 63.2 | 61.1 | 59.7 |
| 35 | 58.8 | 57.0 | 55.3 | 54.5 |
| 45 | 52.6 | 51.0 | 49.3 | 48.6 |
| 55 | 47.0 | 45.7 | 43.9 | 43.4 |
| 65 | 42.3 | 41.3 | 38.8 | 37.9 |



**Figure 2** Variation of the hydrate percentage with temperature for the gels: PEG600-4 (●), PEG600-6 (■), PEG600-10 (○), and PEG600-14 (□).
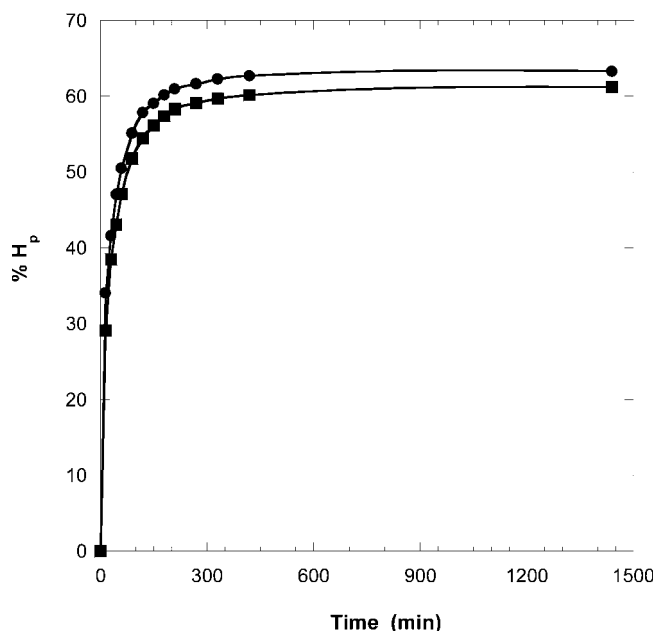
**Figure 3** Variation of the hydrate percentage with time at 25°C for the gels: PEG600-6 (●) and PEG600-10 (■).



**Figure 4** Thermogravimetric curves of PEG, βCD, and a gel PEG600-6.

behavior has already been observed in other PEG-based hydrogels[5] and attributes to the LCST-type phase behavior that this polymer presents in water.

The swelling kinetics of these gels has been followed gravimetrically, starting from samples in the form of disks of similar dimensions. Figure 3 shows the variation of the $H_p\%$ for two of these gels in water at 25°C. It can be observed that their swelling kinetics is fast, and finish in approximately 5 h. Our data shows that it behavior does not seem very affected for the composition of the gel.

## Thermal properties

The thermal behavior of the gels has been studied by means of thermogravimetry. In Figure 4, the degradative behavior of one of these gels and its pure components (βCD and PEG600) in inert atmosphere ($N_2$) can be observed. It is evident that the gels are of a high thermal resistance, since appreciable degradative effects do not appear until temperatures close to 270°C. If we compare, its degradative behavior under the aforementioned conditions turns out to be approximately the sum of the degradative processes of its initial components, when no outstanding contribution of the urethane groups exists. It is worth mentioning that a notable increment of the thermal resistance of the gel takes place with regard to the PEG, which is typical of crosslinked polymers.

The study of these materials, using DSC, allows us to conclude that they are amorphous. This result agrees with recent studies of crystallization of PEG on networks that show that this does not take place
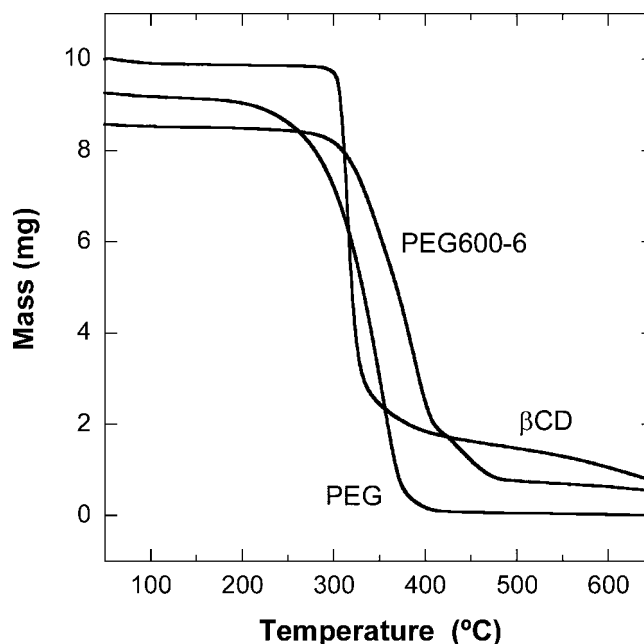
for molar mass inferior to 1000 g/mol.[20] Their glass transition temperature is enough below the ambient temperature so that their behavior is elastomeric. In Table II, the glass transition temperatures are indicated for the different studied gels.

It can be observed that the glass transition temperature of the gels depends of its content in βCD, increasing as the content in βCD rises. This result is not surprising, since a larger content in βCD implies the introduction in the gel of an element that contributes to greater rigidity in the system.

## CONCLUSIONS

We have reported the synthesis of a new hydrogel type based on PEG and βCD whose components offer interesting possibilities in biosciences and/or contamination. The synthesized gels offer a wide interval of compositions in βCD and present a high thermal stability. The hydrate percentages are about 60% and their swelling kinetics are fast. An interesting aspect of its thermal behavior is that they present typical elastomeric states. In these moments, we are using the same technique to synthesize new PEG/βCD gels in

**TABLE II**
**Glass Transition Temperatures of Cyclodextrin/PEG600 Gels**

| Gel | $T_g$ (°C) |
|---|---|
| PEG600-4 | −28 |
| PEG600-6 | −33 |
| PEG600-10 | −35 |
| PEG600-14 | −37 |

which different molar masses of PEG are used as a method of controlling their mechanical and swelling states.

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