Innovative Cross-Linked Polyurethane Networks Based on Cyclodextrins and Polyethylene Glycols: Inclusion Capacity and Potential Use as Controlled Release Carrier for Nifedipine

Márcia Valéria Gaspar de Araújo,[*1] *João Victor Francisco Vieira,*[1] *Thiago Alessandre da Silva,*[1] *Tatiana Kubota,*[1] *Fernanda Malaquias Barboza,*[2] *Paulo Vitor Farago,*[2] *Sônia Faria Zawadzki*[1]

Summary: Polymers derived from cyclodextrins show several biomedical applications. In this paper, six cross-linked polyurethane networks based on β-cyclodextrin (βCD) or hydroxypropyl-β-cyclodextrin (HPβCD) and polyethylene glycols (PEG 400, PEG 1500 or PEG 4000) were synthesized by the usual two-step polymerization method. The polymers were characterized by Fourier-transformed infrared (FTIR) spectroscopy, thermogravimetric analysis (TGA) and X-ray diffraction (XRD). The inclusion capacity was evaluated by the discoloration method of a phenolphthalein solution. In order to explore their potential use as controlled drug delivery systems, dissolution profiles and release behavior of inclusion complexes between PUR/TDI/βCD/PEG4000 or PUR/TDI/HPβCD/PEG1500 and nifedipine (NIF) were investigated. FTIR assignments confirmed the formation of urethane linkages. XRD patterns revealed that the crystallinity decreased mainly due to the crosslinking process. TGA showed three stages of mass loss attributed to water loss, cleavage of urethane bonds and volatilization of decomposition products. The inclusion capacity of cyclodextrins cross-linked with polyurethane was suitably maintained. Dissolution profiles demonstrated that the inclusion complexes PUR/TDI/βCD/PEG4000-NIF and PUR/TDI/HPβCD/PEG1500-NIF are feasible systems for controlling drug release, showing a biexponential release behavior.

Keywords: cyclodextrin; inclusion complex; nifedipine; polyethylene glycol; polyurethane

Introduction

Natural cyclodextrins (CDs) are cyclic oligosaccharide containing six (α-cyclodextrin), seven (β-cyclodextrin) or eight (γ-cyclodextrin) glucopyranose units linked by α-(1,4) glycosidic bonds. The structure of CDs molecules resembles truncated cones with the secondary hydroxyl groups located at the wider edge of the ring and the primary groups on the narrower edge. Therefore, CDs have a relatively hydrophobic cavity, while the outer surface is hydrophilic.[1–3] These CDs can form reversible host-guest inclusion complexes with a wide variety of inorganic and organic molecules in aqueous solution.[4] This property accounts for the great interest in CDs, since the goal of these inclusion complexes is to improve solubility, stability, volatility, flavor, and bioavailability of the guest molecules.[1,5,6]

[1] Laboratory of Synthetic Polymers, Postgraduate Program in Chemistry, Department of Chemistry, Federal University of Paraná, Centro Politécnico Jardim das Américas, 81531-990, Curitiba, Paraná, Brazil
Fax: +55 41 33613186;
E-mail: araujo_mvg@hotmail.com
[2] Laboratory of Pharmaceutical Products, Postgraduate Program in Pharmaceutical Science, Department of Pharmaceutical Sciences, State University of Ponta Grossa, Campus Uvaranas, 84030-900, Ponta Grossa, Paraná, Brazil

Currently, chemical modifications of natural CDs have been extensively reported. Polymers containing CDs have been used to combine synergistically polymer characteristics and inclusion properties of CDs.[7–9] Furthermore, a selective conversion of the hydroxyl groups into other functionalities can also reduce the adverse cytotoxicity of these materials to human erythrocytes.[10] Stable cross-linked network have been synthesized by reacting the hydroxyl groups of CDs with a crosslinking agent. These crosslinking agents can be either bi- or polyfunctional as epichlorihydrin, glutaraldehyde, benzoquinone, dicarboxylic acids, maleic anhydride and diisocyanates.[11,12] In particular, diisocyanates are important compounds usually required to produce polyurethanes. Therefore, cross-linked polyurethane networks can be further obtained by reacting the hydroxyl groups of CDs with a diisocyanate as tolylene diisocyanate (TDI), leading to the formation of the urethane linkage (NHCOO).[13] However, few papers are devoted to study the inclusion capacity of cross-linked CDs into the polyurethane network for pharmaceutical purposes.

Nifedipine (NIF) (Figure 1) is a drug used to treat heart disease, especially hypertension and angina pectoris. It acts by inhibiting the entry of calcium ions across the membrane of cells vascular smooth muscle of the heart, promoting vasodilatation prolonged coronary arteries, increasing the oxygen supplementation and inhibiting the process of muscle contraction. However, this drug is practically insoluble in water and, consequently, exhibits a low bioavailability after oral administration, a fact that affects significantly their efficiency therapeutic.[14–16]

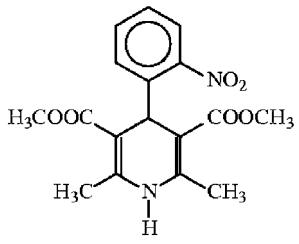

Figure 1.
Nifedipine structure.

The aim of this work is to expand the knowledge about cross-linked polyurethane networks based on CDs for pharmaceutical use as controlled drug delivery system. Polyurethanes using β-cyclodextrin (βCD) or hydroxypropyl-β-cyclodextrin (HPβCD) and different polyethylene glycols (PEG 400, PEG 1500 or PEG 4000) were synthesized and characterized. The inclusion capacity of cross-linked CDs was evaluated. The potential of such polyurethanes for using as controlled release carrier for nifedipine were also investigated.

Experimental Part

Materials

β-cyclodextrin (1135 g mol^{-1}, β-CD, Kleptose, Roquette), hydroxypropyl-β-cyclodextrin (1400 g mol^{-1}, HPβ-CD, Chemyunion), stannous octanoate [Sn(Oct)$_2$, Air Products Brazil], dimethylformamide (DMF, Vetec), and nifedipine (346.34 g mol^{-1}, NIF, Galena) were used as received. Polyethylene glycols (400 g mol^{-1}, 1500 g mol^{-1}, or 4000 g mol^{-1}, PEG, Synth) were dried on a rotary evaporator for 4 h. Tolylene diisocyanate (TDI, Hilax) was distilled under vacuum before use.

Synthesis of Cross-Linked Polyurethane Networks

Six cross-linked polyurethane networks (Table 1) based on βCD or HPβCD and PEG 400, PEG 1500 or PEG 4000 were synthesized by the usual two-step polymerization method.

Briefly, PEG (45.45 mmol of PEG per unit), DMF as solvent, TDI (10.00 mmol), and Sn(Oct)$_2$ (0.74 mmol) were poured into a round-bottom flask to obtain the prepolymer. The system was heated at 50 °C for 90 min under magnetic stirring. After, a previously prepared solution containing CD (1.25 mmol), DMF, and Sn(Oct)$_2$ (0.74 mmol) was added to the prepolymer. This mixture was stirred at 70 °C for a total

Table 1.
Composition of polyurethane networks based on cyclodextrins and polyethylene glycols.

Composition	Cross-linked polyurethane network					
	PUR/TDI/ βCD/ PEG400	PUR/TDI/ βCD/ PEG1500	PUR/TDI/ βCD/ PEG4000	PUR/TDI/ HPβCD/ PEG400	PUR/TDI/ HPβCD/ PEG1500	PUR/TDI/ HPβCD/ PEG4000
Prepolymer						
PEG 400 (g)	2.00	–	–	2.00	–	–
PEG 1500 (g)	–	2.00	–	–	2.00	–
PEG 4000 (g)	–	–	2.00	–	–	2.00
DMF (mL)	10	30	30	10	30	30
TDI (g)	1.74	1.74	1.74	1.74	1.74	1.74
$Sn(Oct)_2$ (g)	0.30	0.30	0.30	0.30	0.30	0.30
Polyurethane						
βCD	1.42	1.42	1.42	–	–	–
HPβCD	–	–	–	1.75	1.75	1.75
DMF (mL)	10	30	30	10	30	30
$Sn(Oct)_2$ (g)	0.30	0.30	0.30	0.30	0.30	0.30

of 8 h. Methanol was then added in excess to obtain a precipitate. The polyurethane was filtered and extensively washed using both acetone and water. Finally, the product was dried in a vacuum oven at 80 °C for 24 h.

Characterization of Cross-Linked Polyurethane Networks

The Fourier-transformed infrared (FTIR) spectra were recorded from 4000 to 400 cm^{-1} on a Biorad Excalibur Series (FTS-3500 GX) IR spectrometer using KBr pellets with 32 scans and resolution of 4 cm^{-1}.

Wide-angle X-ray diffraction (XRD) was performed with a Shimadzu X-ray diffractometer (XRD-6000). The 2θ was increased from 5° to 55° at a scan rate of $2^{\circ}\cdot min^{-1}$ using a Cu-K_α source ($\lambda = 1.5418$ Å) at 40 kV and 40 mA.

Thermogravimetric analyses (TGA) were carried out with a thermobalance (Mettler-Toledo TGA/SDTA 851) using platinum crucibles. The sample (5.0 +,−0.1 mg) was heated from 20 to 700 °C at a heating rate of 20 °C min^{-1} under air purge of 100 mL min^{-1}.

Evaluation of Inclusion Capacity of Cyclodextrins Cross-Linked with Polyurethanes

The inclusion capacity was investigated in triplicate by a previously reported discoloration method of a phenolphthalein alkaline solution.[17] Different amounts (10, 20 and 30 mg) of each cross-linked polyurethane network were added to 10 mL phenolphthalein alkaline solution ($3.75\ 10^{-4}$ mol L^{-1}, pH = 10), placed into an ultrasonic bath and kept in dark for 4 h at 25°C. After, each sample was centrifuged at 3500 rev min^{-1}. The absorbance of the supernatant was measured using a spectrophotometer UV-VIS (Shimadzu UV-2401 PC) at 25 °C and $\lambda_{max} = 552$ nm.

Preparation of Physical Mixtures and Inclusion Complexes Containing Nifedipine (NIF)

Physical mixtures were obtained by homogeneous blending of previously weighted NIF (20% w/w) and PUR/TDI/βCD/PEG4000 or PUR/TDI/HPβCD/PEG1500 in a mortar for 15 min, whereas host-guest inclusion complexes of NIF (20% w/w) and chosen cross-linked polyurethane networks were prepared by kneading.

Kneaded products were obtained by adding small amounts of ethanol in the solid mixtures of NIF and PUR/TDI/βCD/PEG4000 or PUR/TDI/HPβCD/PEG1500 under kneading for 60 min in a mortar. The resulting paste was dried in a vacuum oven at 40 °C for 24 h. Physical mixtures and inclusion complexes containing NIF were pulverized to a fine powder through a 60 mesh sieve.

In Vitro Drug Release

Dissolution rates of NIF as pure drug, PUR/TDI/βCD/PEG4000-NIF physical mixture, PUR/TDI/βCD/PEG4000-NIF inclusion complex, PUR/TDI/HPβCD/PEG1500-NIF physical mixture, and PUR/TDI/HPβCD/PEG1500-NIF inclusion complex were performed with a Nova Ética 299-6 ATTS dissolution tester equipped with paddles (apparatus II) in 900 mL of degassed phosphate buffer solution (50 mmol L^{-1}, pH 6.8) plus 1% (w/v) sodium lauryl sulfate. The surfactant addition can be justified by the poor water solubility of NIF which results in an undesirable dissolution profile. Systems were kept at a thermostatically controlled temperature of 37 (+,−) 0.5 °C and stirred at 100 rev min^{-1}. All experiments were held under dark conditions.

At fixed time intervals, samples were collected, filtered (0.45 μm pore size) and analyzed spectrophotometrically at 338 nm. The dissolution value was obtained from the amount of drug released. A correction factor was applied to the cumulative dilution caused by replacement of the sample with an equal volume of fresh medium.

Analysis of Release Behavior

In order to compare the dissolution profiles of pure NIF, physical mixtures and host-guest inclusion complexes, independent and dependent methods were performed as summarized in Table 2.

As model-independent analysis, dissolution efficiency, the area under a dissolution curve between defined time points,[18] was used to compare release profiles of pure drug, physical mixtures, and inclusion complexes PUR/TDI/βCD/PEG4000-NIF and PUR/TDI/HPβCD/PEG1500-NIF. Dissolution profiles were also investigated by model-dependent methods[19,20] using the MicroMath Scientist 2.01 software. Data were tested to fit first-order, biexponential, zero-order, weibull and monolag equations (Table 2). For selecting the best model was considered correlation coefficient (r), the model selection criteria (MSC) and graphical adjustment.

Table 2.
Mathematical models related to dissolution experiments.

Model	Equation
Dissolution efficiency	$DE = \frac{\int_0^t y.dt}{y_{100}.t} \times 100\%$
First-order	$\%D = 100(1 - e^{-kt})$
Biexponential	$\%D = 100[1 - (Ae^{-\alpha t} + Be^{-\beta t})]$
Zero-order	$\%D = kt$
Weibull	$\%D = 100[1 - e^{-(t/TD)b}]$
Monolag	$\%D = 100[1 - e^{-k(t-x)}]$

Legend: %D = dissolved percentage, b = shape parameter, TD = time interval necessary to release 63.2% of the drug, k, α and β = kinetics constants, t = dissolution time, A and B = initial drug concentrations for the two dissolution stages

Results and Discussion

Cross-linked polyurethane networks based on cyclodextrins and polyethylene glycols were successfully prepared by the proposed two-step polymerization. During synthesis, the first step was a reaction between the hydroxyl groups of PEG and reactive–NCO groups of TDI in which $Sn(Oct)_2$ was used as catalyst. In the presence of cyclodextrin, crosslinking reaction occurred and a three dimensional network of polyurethane was obtained. After drying, these polymers showed powder aspect and pale yellow color.

Fourier-Transformed Infrared (FTIR) Spectroscopy

Figure 2 shows the FTIR spectra of βCD, HPβCD and cross-linked polyurethane networks. These CDs presented a typical −OH stretching band at 3342 cm^{-1} and a C−H stretching band at 2930 cm^{-1}. The C−O−C stretching of anhydroglucose ring was observed at 1157 cm^{-1} in accordance with literature values.[18] The FTIR spectra of polyurethanes showed two bands at 1537–1546 cm^{-1} and 1716–1735 cm^{-1} which can be attributed to C−N−H and C=O stretching of urethane linkage, respectively (Table 3).[22–24] In particular, these bands were not observed in CDs spectra. Therefore, these FTIR assignments confirmed the formation of urethane bonds by reacting

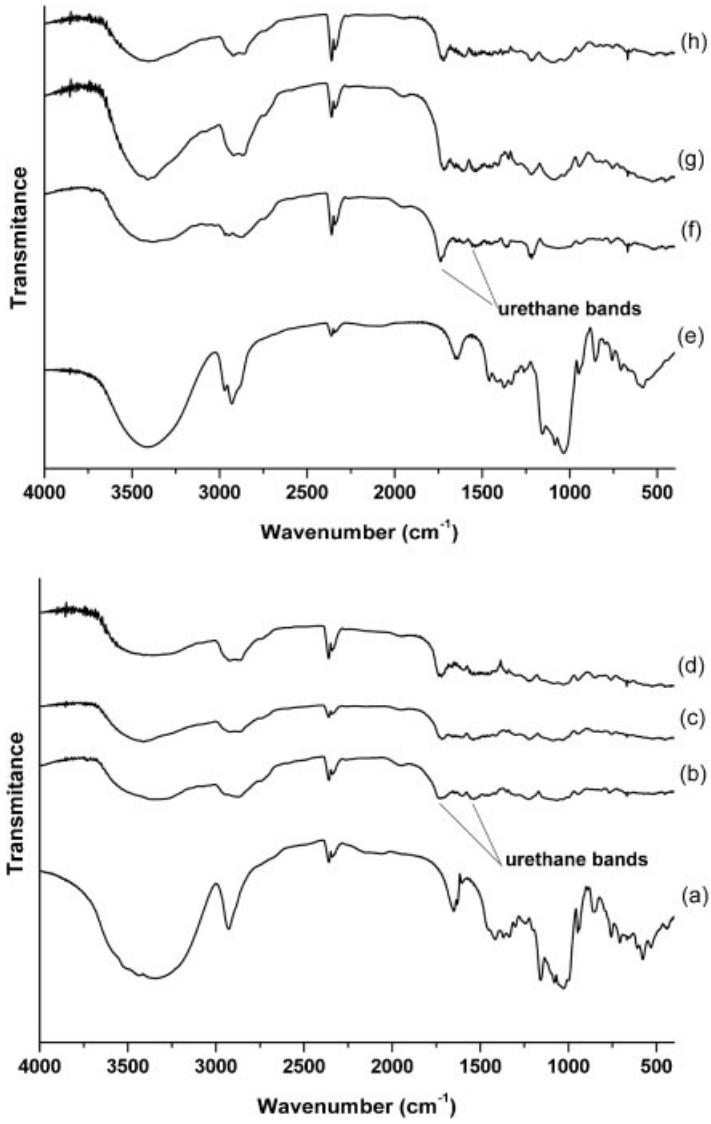

Figure 2.
FTIR spectra of βCD (a), PUR/TDI/βCD/PEG400 (b), PUR/TDI/βCD/PEG1500 (c), PUR/TDI/βCD/PEG4000 (d), HPβCD (e), PUR/TDI/HPβCD/PEG400 (f), PUR/TDI/HPβCD/PEG1500 (g), and PUR/TDI/HPβCD/PEG4000 (h).

the hydroxyl groups of CDs and –NCO groups of TDI.

Wide-Angle X-ray Diffraction (XRD)

Samples of βCD, HPβCD and cross-linked polyurethane networks were studied by XRD in order to evaluate their crystallinity patterns (Figure 3). The diffractogram of βCD presented different peaks related to a crystalline structure.[11] Otherwise, HPβCD showed a non-crystalline structure.

The X-ray diffraction patterns of cross-linked polyurethane networks based on βCD did not have the typical crystalline nature of βCD. Consequently, these XRD data demonstrated that crosslinking process destroyed the crystallinity of βCD, according to the X-ray curves, leading to

Table 3.
Typical bands of urethane linkage observed in cross-linked polyurethane networks.

Polymer	Assignments
PUR/TDI/βCD/PEG400	1535- ν(CNH), 1730- ν(C=O) urethane
PUR/TDI/βCD/PEG1500	1543- ν(CNH), 1716- ν(C=O) urethane
PUR/TDI/βCD/PEG4000	1544- ν(CNH), 1722- ν(C=O) urethane
PUR/TDI/HPβCD/PEG400	1539- ν(CNH), 1735- ν(C=O) urethane
PUR/TDI/HPβCD/PEG1500	1544- ν(CNH), 1720- ν(C=O) urethane
PUR/TDI/HPβCD/PEG4000	1546- ν(CNH), 1722- ν(C=O) urethane

formation of non-crystalline polymers. Although HPβCD had already revealed a non-crystalline structure, cross-linked polyurethane networks based on HPβCD showed changes in this initial pattern, resulting in diffractograms quite similar to those observed for the cross-linked polyurethane networks based on βCD and also related to non-crystalline materials. Thus, it is possible to suggest that the crystallinity of CDs was destroyed mainly due to the crosslinking process that was used for obtaining the polyurethane networks.[11]

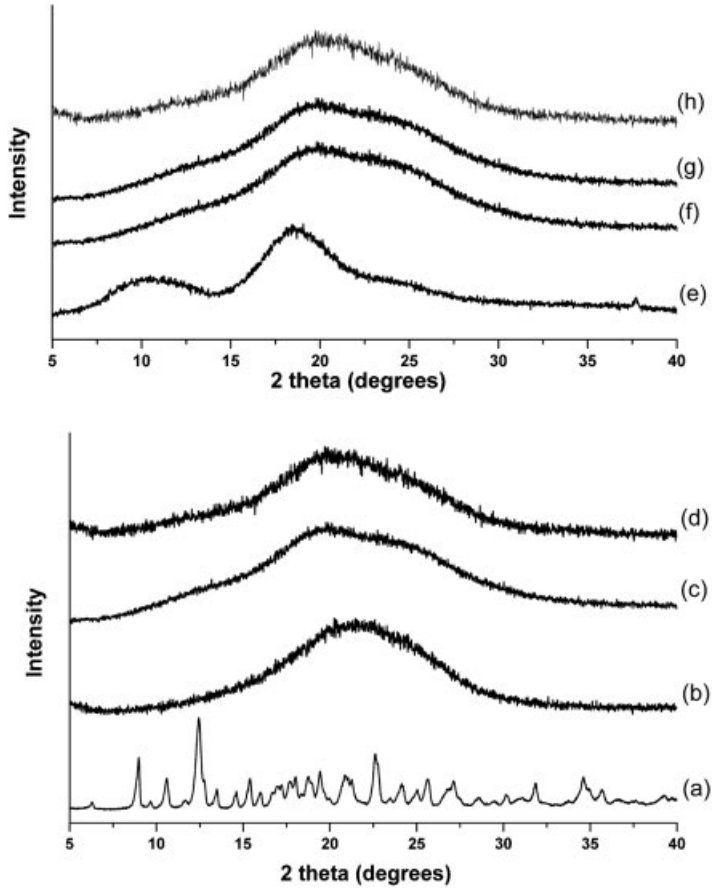

Figure 3.
Diffractograms of βCD (a), PUR/TDI/βCD/PEG400 (b), PUR/TDI/βCD/PEG1500 (c), PUR/TDI/βCD/PEG4000 (d), HPβCD (e), PUR/TDI/HPβCD/PEG400 (f), PUR/TDI/HPβCD/PEG1500 (g), and PUR/TDI/HPβCD/PEG4000 (h).

Thermogravimetric Analysis (TGA)

Table 4 summarizes the stages of thermal decomposition verified for cross-linked polyurethane networks and the Figure 4 the TGA curves. All polymers displayed similar degradation profiles, suggesting that changes in CD (βCD or HPβCD) and PEG (PEG400, PEG1500 or PEG4000) did not significantly alter the mechanism of thermal decomposition.

All cross-linked polyurethane networks showed three-stage thermal decomposition profiles. The first stage of mass loss was associated to water loss. The second and third stages were attributed to cleavage of urethane bonds and volatilization of decompositions products, respectively.[22,24]

Moreover, the TGA curves indicated that the onset decomposition temperature of all these cross-linked polyurethane networks was above 240 °C under air purge. This result suggests a suitable thermal stability, considering their potential use for pharmaceutical purposes as controlled drug delivery system.

Evaluation of Inclusion Capacity of Cyclodextrins Cross-Linked with Polyurethanes

In order to explore whether the crosslinking process had influence on inclusion capacity of CDs, discoloration method of a phenolphthalein solution was performed for pure CDs and cross-linked polyurethane networks as shown in Figure 5.

Regardless of the amount used, cross-linked polyurethane networks based on βCD showed similar absorbance values to those observed for pure βCD due to phenolphthalein that remained in solution. The same behavior was verified for cross-linked polyurethane networks based on HPβCD when compared to pure HPβCD.

In addition, it was possible to observe that the inclusion capacity of βCD, HPβCD, and the related cross-linked polyurethane networks was proportional to the amount of sample used, since the increase of mass from 10 to 30 mg provided an improved inclusion capacity of phenolphthalein and led to a progressive discoloration of its solution (Figure 5). Therefore, inclusion capacity of CDs cross-linked with polyurethane was suitably maintained in relation to the native CDs used as precursors.[25,26] Moreover, the effect of polymerization process on inclusion capacity of CDs can be considered negligible.

Furthermore, it is possible to suggest that cross-linked polyurethane networks based on βCD and HPβCD can be used to form reversible host-guest inclusion complexes with a wide variety of inorganic and organic molecules including drugs as nifedipine.

In Vitro Drug Release

In order to investigate the potential use of these cross-linked polyurethane networks as controlled drug delivery systems, PUR/TDI/βCD/PEG4000 and PUR/TDI/HPβCD/PEG1500 were chosen to further evaluations due to their highest inclusion capacity among the previously synthesized polyurethanes. For this purpose, physical mixtures and inclusion complexes containing

Table 4.
Stages of thermal decomposition of cross-linked polyurethane networks.

Polymer	Thermal decomposition					
	1st stage (°C)	mass loss (%)	2nd stage (°C)	mass loss (%)	3rd stage (°C)	mass loss (%)
PUR/TDI/βCD/PEG400	83	4.1	313	68.7	497	25.6
PUR/TDI/βCD/PEG1500	101	4.4	316	74.2	485	21.4
PUR/TDI/βCD/PEG4000	119	6.1	341	64.5	509	27.7
PUR/TDI/HβBCD/PEG400	99	5.4	314	71.5	498	22.2
PUR/TDI/HPβCD/PEG1500	116	4.8	320	75.2	490	18.7
PUR/TDI/HPβCD/PEG4000	97	4.7	343	71.8	492	21.3

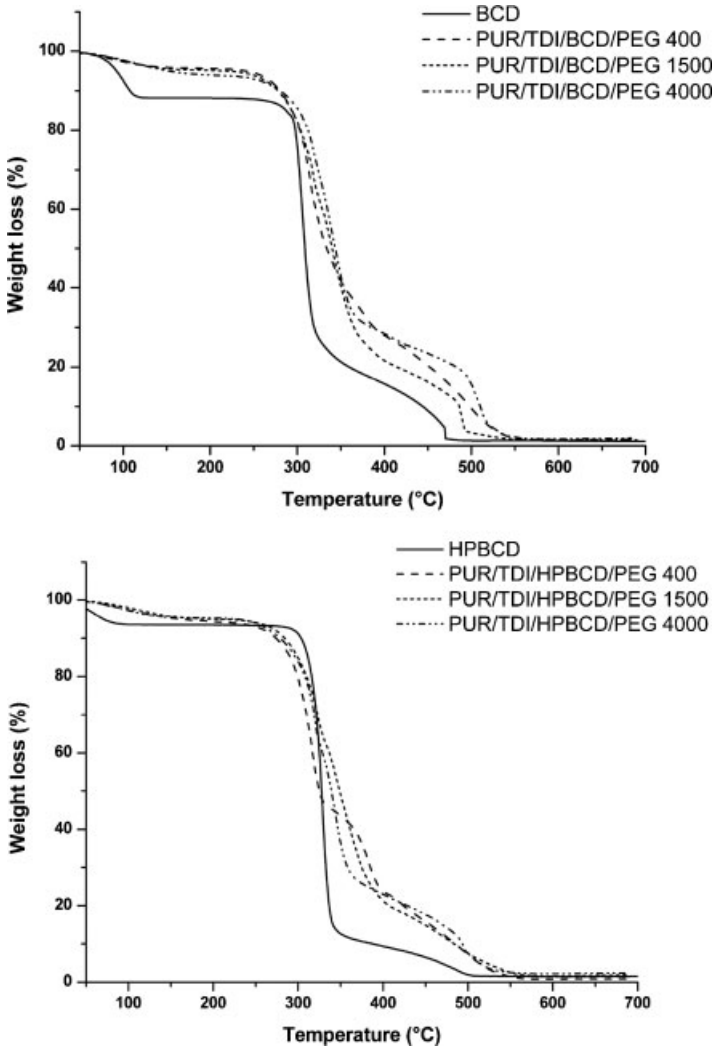

Figure 4.
TGA curves of the polyurethanes based in CDs.

nifedipine (NIF) were prepared as previously described. In this work, NIF was also chosen as model drug due to its wide use as a calcium channel blocker for treating heart diseases such as hypertension and angina.[27] Furthermore, many controlled delivery systems containing NIF have been currently studied in order to improve its bioavailability.[28–30]

The dissolution profiles of NIF, PUR/TDI/βCD/PEG4000-NIF physical mixture, PUR/TDI/βCD/PEG4000-NIF inclusion complex, PUR/TDI/HPβCD/PEG1500-NIF physical mixture, and PUR/TDI/HPβCD/PEG1500-NIF inclusion complex are shown in Figure 6. By the performed dissolution test, the mean time for 80% release of pure NIF was 3.62 h. However, physical mixtures demonstrated mean dissolution times of 6.44 h (PUR/TDI/βCD/PEG4000-NIF) and 6.01 h (PUR/TDI/HPβCD/PEG1500-NIF) for 80% drug release. For inclusion complex, a value of 80% drug release was achieved in mean dissolution times of 11.89 and 9.42 h for PUR/TDI/βCD/PEG4000-NIF and PUR/

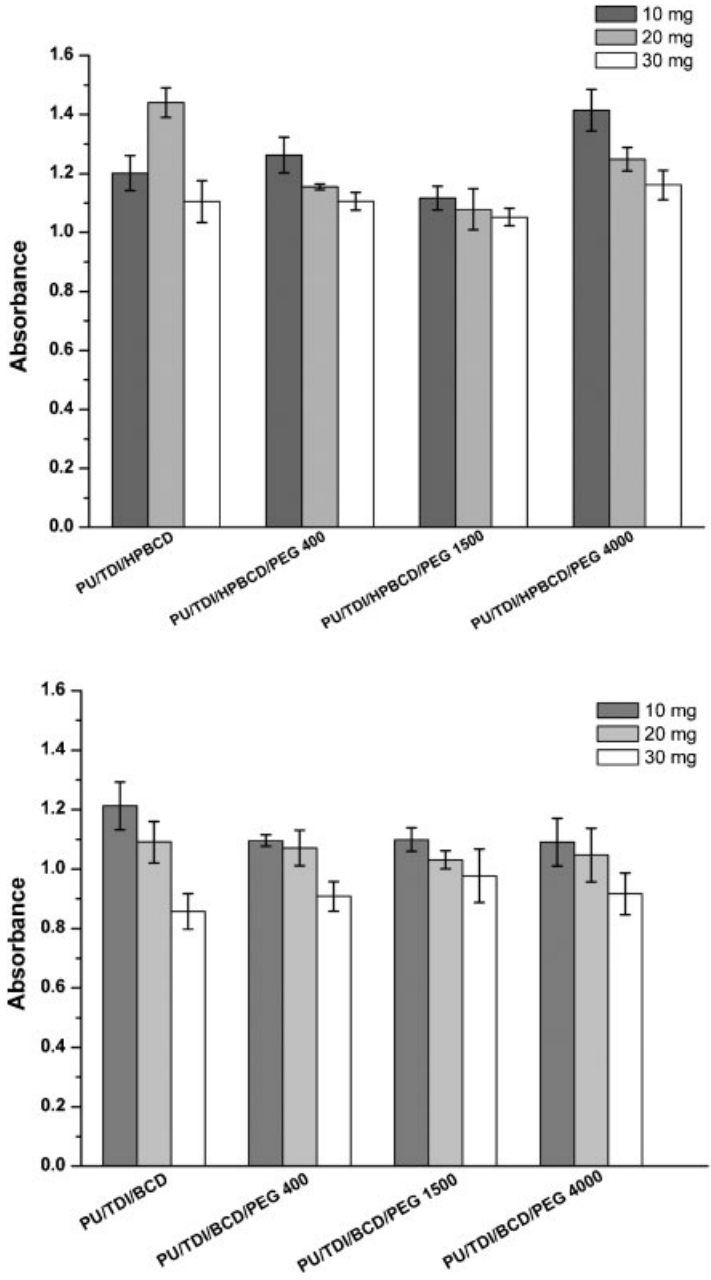

Figure 5.
Absorbance values of a phenolphthalein alkaline solutions at 552 nm obtained in evaluation of inclusion capacity of βCD, HPβCD, and cross-linked polyurethane networks.

TDI/HPβCD/PEG1500-NIF, respectively. Therefore, inclusion complexes between cross-linked polyurethane networks and NIF exhibited a remarkable slower dissolution rate than pure drug.

When comparing the dissolution rates for physical mixtures and inclusion complexes, the host-guest complexes had a great effect on prolonging the drug release. These results indicate that the preservation

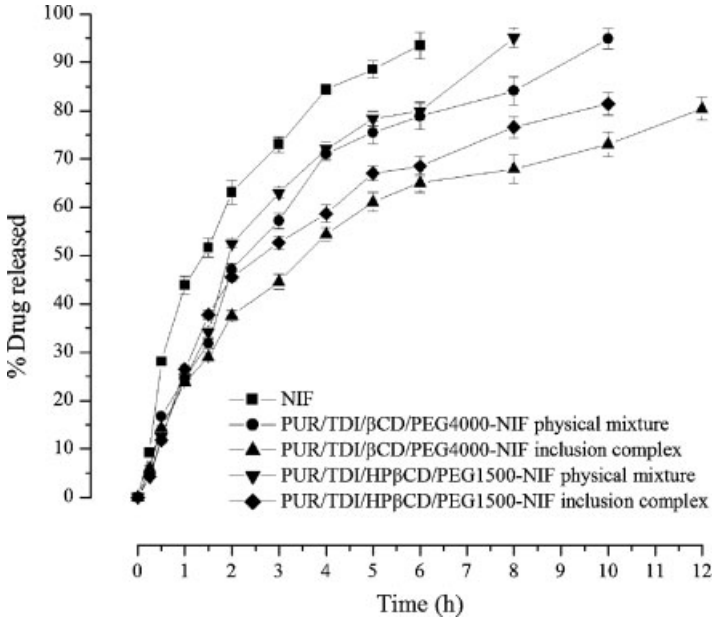

Figure 6.
Release profiles of pure drug, physical mixtures and inclusion complexes performed in degassed phosphate buffer solution (pH 6.8) plus 1% sodium lauryl sulfate.

of inclusion capacity combined with the formation of host-guest complexes between cross-linked polyurethane networks and NIF played an important role on the delay of drug dissolution.

Nevertheless the chemical properties of both CDs and PEGs that were used for obtaining the polyurethane networks may have affected these dissolution profiles. The solubility in water of βCD is relatively low (1.8%) whereas HPβCD has a higher aqueous solubility at room temperature (above 60%).[31] Therefore, this more hydrophilic behavior of HPβCD may have provided the formation of various hydrogen bonds with water molecules resulting in faster dissolution rates for NIF. For PEGs, the solubility decreases with increase in molecular weight.[32] Thus, PEG1500 may have caused a more hydrophilic environment than PEG4000 which also improved the drug dissoluton rate.

All these data support that host-guest inclusion complexes between cross-linked polyurethane networks and NIF can be used as a feasible oral drug delivery carrier for controlled release purposes.

Analysis of Release Behavior

Whereas the pure drug presented dissolution efficiency (DE) of 82.55% along 12 h, physical mixtures showed DE of 70.92% (PUR/TDI/βCD/PEG4000-NIF) and 74.83% (PUR/TDI/HPβCD/PEG1500-NIF). Considering host-guest inclusion complexes, DE of 56.80 and 63.03% was obtained for PUR/TDI/βCD/PEG4000-NIF and PUR/TDI/HPβCD/PEG1500-NIF, respectively. The decrease in DE for physical mixtures and inclusion complexes reinforces the influence of cross-linked polyurethane networks on the delay of dissolution profile of NIF and is indicative of a controlled release behavior.

The release profiles were fitted to mathematical models and the selection of the best model considered the correlation coefficient (r), the model selection criteria (MSC) and the graphic adjustment. Both NIF as pure drug and inclusion complexes

Table 5.
Release data obtained by fitting the dissolution profiles of NIF, physical mixtures and inclusion complexes to the mathematical models.

Materials	release parameters and kinetic constants				
	MSC	r	k (min^{-1})	α (min^{-1})	β (min^{-1})
NIF	5.29	0.9990	–	4.9198	0.4043
PUR/TDI/βCD/PEG4000-NIF physical mixture	4.67	0.9964	0.2872	–	–
PUR/TDI/βCD/PEG4000-NIF inclusion complex	4.30	0.9979	–	0.8285	0.7093
PUR/TDI/HPβCD/PEG1500-NIF physical mixture	4.47	0.9957	0.3186	–	–
PUR/TDI/HPβCD/PEG1500-NIF inclusion complex	4.76	0.9979	–	0.7413	0.1232

were better fitted to the biexponential equation, whereas physical mixtures were better fitted to the monolag equation. The kinetic constants for NIF, PUR/TDI/βCD/PEG4000-NIF physical mixture, PUR/TDI/βCD/PEG4000-NIF inclusion complex, PUR/TDI/HPβCD/PEG1500-NIF physical mixture, and PUR/TDI/HPβCD/PEG1500-NIF inclusion complex are reported in Table 5.

These results demonstrated that host-guest complexes between cross-linked polyurethane networks and NIF reduced the drug dissolution rate, nevertheless without changing its biexponential release model. According to this mechanism, the first stage of release is rapid (burst effect) whereas the second stage of release is slow (controlled release).[33] The burst release can help to reach the effective concentration of NIF rapidly in plasma, whereas the controlled release would maintain the suitable concentration of drug in plasma for a long time.

Otherwise, both physical mixtures between cross-linked polyurethane networks and NIF provided dissolution profiles better fitted to the monolag equation. Concerning this mathematical model, the dissolution is explained by a first order kinetic preceded by a lag time. The first order equation describes a dissolution process in which the drug release rate is dependent of its concentration. The lag time is defined as a time delay prior to the commencement of dissolution process.[33] Therefore, physical mixtures can be also used as controlled release carrier for NIF, particularly as delayed release dosage forms.

Conclusion

Cross-linked polyurethane networks based on CDs and PEGs were successfully prepared. FTIR assignments confirmed the formation of urethane linkages. XRD patterns demonstrated that the crystallinity disappeared mainly due to the crosslinking process. TGA showed three stages of mass loss attributed to water loss, cleavage of urethane bonds and volatilization of decomposition products. The inclusion capacity of CDs cross-linked with polyurethane was maintained. Dissolution profiles showed that the inclusion complexes PUR/TDI/βCD/PEG4000-NIF and PUR/TDI/HPβCD/PEG1500-NIF were suitable approaches for prolonging the drug dissolution according to a biexponential release model. These results support an experimental basis for the use of cross-linked polyurethane networks based on CDs and PEGs as a feasible oral drug delivery carrier for controlled release of NIF.

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