# Synthesis and Characterization of PEG-PBS Copolymers to Obtain Microspheres With Different Naproxen Release Profiles

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**Researching for new biomaterials intended for drug delivery systems has considerably intensified in recent years. There is an increasing interest in PBS (poly[butylene succinate]) and its copolymers as biomaterials due to the possibility of synthesis of the PBS from a renewable source. Among these copolymers, PBS-PEG (poly[butylene succinate-co-polyethylene glycol]) is studied for materials that have shape memory and are biodegradable. However, to date, no research into the use of PBS-PEG to prepare microspheres for drugs release has been reported. Herein, PBS-PEGs with three PEG with different chain's length were synthesized by polycondensation reaction and characterized by means of SEC, FTIR, DSC, TGA, and DRX. Naproxen loaded microspheres were prepared by an oil-in-water (o/w) single emulsion technique. The drug release was followed by UV-Vis. The presence of PEG had a marked effect on the in vitro release profiles. The mathematical models employed show that the fundamental mechanism of release is diffusion when PEG is present in the polymer matrix of the particle.**

## 1. Introduction

So-called green polymers have become more important as a result of changing economic and social factors. They can be produced from renewable resources and avoid the use of petroleum-derived reagents. The use of such reagents is disadvantageous, as they are subject to volatile oil prices and increasingly attract criticism from environmental groups. Examples of green polymers include poly(3-hydroxyalkanoates), which are synthesized directly by microorganisms,[1] and poly(lactic acid), which is obtained from glucose fermentation and ring-opening polymerization of the corresponding lactide dimer.[2]

Poly(butylene succinate) (PBS) is another polymer that in recent years has come to be considered as a green polymer. It has been commercially available since 1993 and is obtained from the petrochemical industry.[3] However, one of the necessary monomers for PBS synthesis, succinic acid (SA), is currently produced by fermentation process.[4] The other required monomer, 1,4-butanediol (BD), may be synthesized by reduction of SA.[5] This leads to a complete bio-based PBS.[6]

Traditional uses of PBS have been restricted to environmental purposes, such as mulching films, bags, nonwoven sheets and textiles, catering products, and foams.[3] But recently extensive research has been conducted into potential further applications of PBS as a biomaterial. It is mainly being used as a scaffold in tissue repair,[7–10] although PBS, and especially some copolymers, have also been used as constituents of controlled drug delivery systems.[3] However, in the field of drugs microencapsulation, this polymer and its derivatives are still poorly explored. To the best of our knowledge, only four papers have been published to date.

The first report of using PBS as wall material for encapsulating drugs was done for Park et al. in 2006. Indomethacin was encapsulated using PBS alone or blended with poly (ε-caprolactone).[11] The inclusion of the last polymer made it possible to obtain more closed structures in the particles, leading to a slower release of the drug. The following work, published by Brunner et al. in 2011, shows the effect of experimental conditions on the properties of microspheres made of PBS or the copolymer of it with adipate. The particles prepared using the copolymer differ in morphology and shape to the ones made with PBS but interestingly they enhance the release bovine serum albumin.[12] Mohanraj et al. reported in 2013 on the effect of some encapsulation conditions on the characteristics of levodopa-loaded PBS particles.[13] All of these authors prepared the microspheres by the emulsion—solvent evaporation technique. The most recent work, published by Murase et al. in 2015, explores the usefulness of the electrospray technique for

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preparing PBS microspheres to encapsulated indoles. They found a strong correlation of i) the microparticles structure with the processing variables; ii) the encapsulation efficiency with the chemical structure of the encapsulated substance; and iii) the release profiles with the composition of the receiving fluid.[14]

The obtainment of copolymers of PBS has allowed us to modify and adjust their properties, such as thermal and mechanical behavior or the biodegradability rate. This has increased the use of this polyester. The main synthetic strategy used to obtain PBS-based copolymers is copolycondensation, using titanium (IV) butoxide as a catalyst. Copolymers with butylene dilinoleate,[15] triethylene succinate,[16] α-Amino Acids,[17] and poly(ethylene glycol)[18,19] have been synthesized by this method and the modification of the properties of the new materials have been confirmed. However, these new beneficial characteristics of the PBS copolymers are scarcely used in the drug encapsulation field. In fact, only one copolymer has been tested for this purpose.[12]

One of the most important properties of the release systems, and hence microspheres, is the drug release profiles. It is well known that among other experimental parameters the nature of the polymeric material could be essential in modulating the release rate of any encapsulated substance since it modifies the structure of the microspheres and defines the release mechanisms involved.[20] In particular, the hydrophilic/hydrophobic character of the polymeric matrix could exert a strong influence in the drug release. PBS is basically considered as a hydrophobic material and therefore its modification with hydrophilic polymers could expand the possible applications of this green polymer in the microencapsulation area. In that sense, polyethylene glycol (PEG) could be a good candidate because of its high hydrophilicity that could significantly alter the release rate of the encapsulated substance and specially charged drugs.[21]

The inclusion of PEG in a drug release system has some other advantages since it is a polymer widely used for medical purposes because of its non-toxicity and its chemical versatility. Currently, there are several drugs on the market that include PEG. These range from simple cases like formulations including this polymer as an excipient to more sophisticated cases like liposomes and therapeutic proteins in which the PEG is covalently attached.[22–24] In addition, the PEG moiety might decrease uptake of particles by the reticuloendothelial and mononuclear phagocytic systems, resulting in an increased blood circulation time.[25] Moreover, PEGylation (conjugation to PEG) is an effective method for preventing an unwanted immune response, which would be elicited if the microparticles were sensed as foreign agents.[26]

The synthesis of the PBS-PEG copolymers is a response to research into new materials that have shape memory and are biodegradable.[18] However, to date, no research into the use of PBS-PEG to prepare microspheres has been reported. The aim of this work was to synthesize PBS derivatives using different PEGs in order to prepare microspheres with modified drug release profiles. Naproxen (NPX) was selected as a model drug. It has analgesic, anti-inflammatory, and antipyretic properties and is widely used in rheumatic disorders. However, its clinical effectiveness is affected by i) low solubility; ii) a short half-life; and iii) adverse effects due to being an irritant of the digestive tract.[27] For these reasons, it is a good candidate to be included in a drug delivery system such as microspheres.[28]

## 2. Experimental Section

### 2.1. Materials

All reagents and organic solvents were purchased from Sigma–Aldrich (St Louis, MO, USA). The naproxen was kindly provided by the Center for Research and Development of Medicine, Havana, Cuba.

### 2.2. Synthesis of Polymers

Succinic acid (0.15 mol), 1,4-butanediol (0.15 mol), and PEG (0.76 mmol of PEGs with 3000, 8000, and 20 000 g $mol^{-1}$) were melted and stirred at 140 °C under nitrogen by 2 h. Then a suitable amount of catalyst $Ti(OC_4H_9)_4$was added and polycondensation was carried out at 180 °C by 4 h. The product of the reaction was purified by solubilization in chloroform (200 mL) and precipitation in cold ethanol (600 mL).

### 2.3. Analysis of Polymers

ATR-FTIR spectra of samples were acquired using a Varian model 3100 FTIR Excalibur Series spectrophotometer (Palo Alto, CA, USA). Spectra were recorded at room temperature and a resolution of 4 $cm^{-1}$ and 100 accumulated scans.

Molecular weight and polydispersity index were determined by SEC in a Waters-150C chromatographer with an RI detector (Waters, Milford, MA, USA). Samples (6 mg dissolved in hexafluoroisopropanol [HFIP] at 2 mg $mL^{-1}$) were injected into three Waters Styragel HT-6E columns in series under a flow rate of 1 mL $min^{-1}$ with HFIP as the mobile phase. Polystyrene was used as a standard.

Thermogravimetric analyses were performed with a Perkin Elmer STA 6000 (Waltham, MA, USA). The samples (10 mg) were heated from room temperature to 700 °C under an $N_2$ atmosphere at 10 °C $min^{-1}$.

DSC analyses were made in a DSC7 equipment (Perkin Elmer, Oak Brook, IL, USA). Samples (5 mg) were heated and cooled at a rate of 10 °C $min^{-1}$ from −10 to 200 °C under nitrogen flow (50 mL $min^{-1}$).

X-Ray Diffraction measurements were performed using a Miniflex X-ray diffractometer (Rigaku Corp., Tokyo, Japan) in a 2θ range from 5 to 35°, with a step size of 0.02° at a scanning speed of 4° $min^{-1}$. The radiation used was CuK-α employing a tube voltage and current equal to 40 kV and 20 mA, respectively.

### 2.4. Microparticles Fabrication

Empty and NPX-loaded particles were fabricated using an oil-in-water (o/w) single emulsion technique. Briefly, 200 mg of PBS-PEG copolymer (or PBS as control) and, optionally, 50 mg of NPX were co-dissolved in 2 mL of dichloromethane (DCM) in a

glass tube. The resultant organic solution was added dropwise to 20 mL of 0.1% PVA aqueous solution under stirring at 14 000 rpm (Ultra- Turrax model T10, IKA, Staufen, Germany). Starring was maintained by 3 min. at 25 °C. This emulsion was immediately poured into 80 mL of the same PVA solution and the whole mixture was mechanically stirred (IKA RW 16 basic, Staufen, Germany) in an open beaker at room temperature for 1 h. Microparticles were collected by centrifugation at 11 000 × *g* for 15 min, washed three times with deionized water and freeze-dried by lyophilization.

### 2.5. Microparticles Analysis

Morphological analysis of polymeric particles was completed by an inverted optical microscope Axiovert 40 MAT from Carl Zeiss (Jena, Germany), equipped with Axiocam MRC camera (exposure time: 137 ms), with an objective Epiplan 5x/0.13 HD. One-hundred microliters of microspheres suspensions in distilled water were added onto a microscope slide and were dried by exposure to air. Particle size distributions were measured using a laser diffraction analyzer (Mastersizer 2000, Malvern Instruments, Worcestershire, UK) operated in liquid mode with distilled water as a dispersant. Concentrated suspensions of the particles were pre-treated by sonication during 20 s to help dispersion of microspheres.

A sample of microparticles (50 mg) was carefully weighed in a glass tube and 5 mL of dichloromethane was added. They were maintained under stirring until complete dissolution. An aliquot was properly diluted with DCM and assayed spectrophotometrically at 272 nm to determine NPX content. The wavelength was selected from the spectra of NPX (20 μg mL$^{-1}$) in DCM that showed five peaks (331, 316, 271, 262, 232 nm). The signal at 232 was too intense and it is not very useful when organic solvents are used to prepare the samples. The one at 272 nm was selected to develop a procedure to quantify NPX in samples. A standard curve (slope: 0.0331; $R^2 = 0.999$) was obtained from solutions of NPX in DCM from 1 μg mL$^{-1}$ (Absorbance = 0.0388) to 20 μg mL$^{-1}$ (Absorbance = 0.6646). The concentrations of diluted samples are expected to be around 10 μg mL$^{-1}$. Dissolutions of empty microspheres of each polymeric material were used as blanks.

### 2.6. In Vitro Drug Release

Drug release from NPX loaded microspheres was determined at pH7.4 in phosphate buffer. Microspheres (6 mg) were suspended in 40 mL of dissolution medium in a plastic vial placed in a shaker bath at 50 rpm and 37 °C. Samples were collected at specific time intervals by taking 1 mL that was immediately replaced by an equal volume of fresh dissolution medium. Microparticles from samples were removed by centrifugation and the amount of drug released into the solution was assessed spectrophotometrically at 230 nm to determine NPX content. The wavelength was selected from the spectra of NPX (2 μg mL$^{-1}$) in PBS solution that showed an intense peak at 230 nm, two weaker signals at 260 and 271 nm and other very poor signals at 315 and 330 nm). The one at 230 nm, with an absorbance of 0.6474 was adequate to develop the procedure to quantify NPX in aqueous samples. A standard curve (slope: 0.0331; $R^2 = 0.999$) was obtained from solutions of NPX in DCM (0.2–2 μg mL$^{-1}$). The supernatant of corresponding empty microspheres was used as blanks. Data were analyzed by nonlinear regression analysis using GraphPad Prism 6.0 (San Diego, CA, USA).

## 3. Results and Discussion

### 3.1. Analysis of Copolymers

Obtained copolymers were analyzed by FTIR (**Figure 1**). The spectra show characteristic PBS absorption peaks: a) at 1041 cm$^{-1}$ for the stretching vibration of the O—C—C; b) at 1100–1300 cm$^{-1}$ for the stretching vibration of the C—O—C; and c) the strong signal at 1711 cm$^{-1}$ for carbonyl stretching. Also, PEG absorption bands appear: a) strong ether (C—O—C) antisymmetric stretch absorbance at 1330–1350 cm$^{-1}$; b) stretching vibration of the C—O—C at 1100–1200 cm$^{-1}$; c) C—H asymmetric stretching at 2800–2900 cm$^{-1}$; and d) $CH_2$ wagging motion and rocking vibrations at 915–950 cm$^{-1}$. All spectra show an absorption signal at ≈1100 cm$^{-1}$. This fact has been used by other authors to conclude that the copolymer has been obtained by the polycondensation of PEG, SA, and BD.[19] There is no signal at 1100 cm$^{-1}$ in the spectrum of unmodified PBS.[29] Intensities of C—O—C absorption peaks from ester bond (1200–1300 cm$^{-1}$) were weaker than that of ether (1200–1300 cm$^{-1}$) with PEG MW increase. A similar phenomenon was reported by other authors.[30]

Molecular weights of copolymers were determined by SEC (**Table 1**). No simple relationship was observed between the molecular mass of the PEG and the copolymer. The lower molecular mass of PBS-$PEG_{3k}$ relative to the control PBS could be explained by i) lower reactivity of oligomers including PEG and/or ii) PEG chains affect mass transport in the reaction.

The fact that PBS-$PEG_{8k}$ has even lower molecular mass could be explained by the hypothesis II because in our work the molar relationship between the PEG and the PBS monomers remained constant. So in the reaction with $PEG_{8k}$, there is almost three times as much mass of PEG as in the reaction with $PEG_{3k}$. However, when the reaction was carried out with $PEG_{20k}$ (2.5

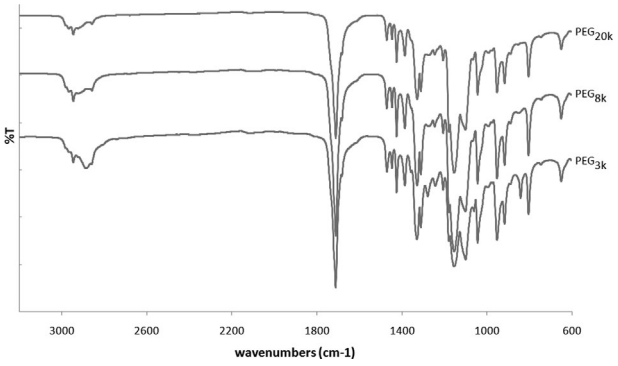


**Figure 1.** FTIR spectra of PBS-PEG copolymers.

**Table 1.** SEC analyses of PBS-PEG copolymers.

| Sample | $M_{n,PEG}$ [$/10^3$ g mol$^{-1}$] | $M_n$ [$/10^4$ g mol$^{-1}$] | PDI |
|---|---|---|---|
| PBS | – | 15.9 | 2.2 |
| PBS-PEG$_{3k}$ | 3 | 11.7 | 1.3 |
| PBS-PEG$_{8k}$ | 8 | 9.2 | 1.2 |
| PBS-PEG$_{20k}$ | 20 | 21.0 | 1.8 |

times more PEG mass than with 8k and almost 7 times more than 3k) the mass of the copolymer was higher than with either of the other two PEGs. This was even greater than the MW of PBS-control (without PEG). These results suggest that there is a very complex relationship between the size of the polymer obtained with the molecular mass and the amount of PEG present in the reaction. It is very likely that the results will be affected by the "transport phenomena."[31] The presence of PEG will substantially affect the viscosity of the reaction mixture. In addition, a variation of viscosity with the temperature depends on the length of the chain.[32] It should be remembered that the polycondensation reaction was carried out at two temperatures; first at 140 °C and then at 180 °C.

Other authors have reported similar results in the synthesis of polyethylene glycol copolymers. Huang et al. obtained the lowest molecular weight of PBS-PEG with PEG$_{6k}$ when they tested different chain sizes (2, 4, 6, and 10k) using a reaction mixture with 30% (w/w) of polyethylene glycol. However, when they used 50% of the polyether in an analogous experiment, the lowest molecular weight was obtained with PEG$_{4k}$.[18] Similar results were obtained by van Dijkhuizen-Radersma[33] and Zhang[30] when they synthesized PEG copolymers with poly(butylene terephthalate) and poly(butylene terephthalate-co-succinate), respectively.

DSC analyses (**Table 2**) showed a decrease in $T_c$ and $T_m$ when the length of the PEG chain increased. Also, the enthalpies of both phase changes diminished which showed a possible decrease in the degree of crystallinity. All these results are from the PBS segments in the copolymer. In our work, the parameters of the PEG segments are almost unobservable due to the low quantity. Huang et al. also did not detect the PEG segments when they analyzed copolymers with 20% (w/w) of the polyether.[18] In our work, the fraction of PEG was lower for 3 and 8k, and only with 20k reached 30%. Similar results for the PBS segments in PBS-PEG copolymers have been reported previously.[34]

Thermogravimetric analysis (**Figure 2**) shows a slight decrease in the degradation temperature, with an increasing MW of PEG. A similar result was reported by D'Antone et al. when they studied the degradation of PEG copolymers with PLGA.[35]

**Table 2.** DSC analyses of PBS-PEG copolymers.

| | $T_c$ [°C] | $\Delta H_c$ [J g$^{-1}$] | $T_m$ [°C] | $\Delta H_m$ [J g$^{-1}$] |
|---|---|---|---|---|
| PEG$_{3k}$ | 72.3 | 38.0 | 112.7 | 60.2 |
| PEG$_{8k}$ | 71.0 | 25,6 | 112.1 | 43.5 |
| PEG$_{20k}$ | 69.4 | 21.2 | 111.7 | 18.0 |

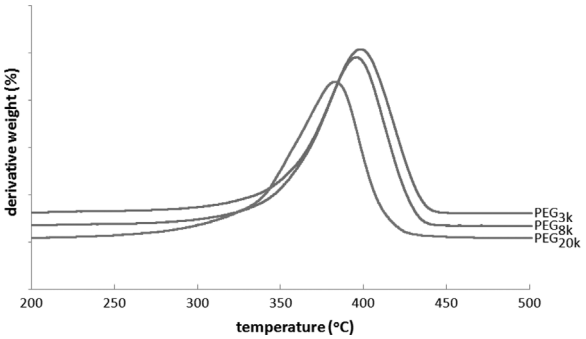


**Figure 2.** DTGA curves of thermogravimetric analyses of PBS-PEG copolymers.

Apparently, all the samples exhibited the same diffraction peaks in XRD analysis (**Figure 3**) indicating that variation in the PEG segment chain length does not modify the crystal structures. We attributed the peaks to a) 19.8°, coinciding with (020) plane of PBS and (120) plane of PEG; b) 22.8°, superimposed of (110) plane of PBS and (032) plane of PEG; and c) 26.2° and 29.1°, (121) and (111) planes of PBS, respectively. The fact that no perceptible change has been found for the 2θ angles with respect to the PEG and PBS diffractograms indicates that each segment crystallizes independently.[18,30] No differences were observed in the height of the peaks. In this work, the copolymers were prepared in the same molar ratio of PEG and PBS. Therefore, the mass fraction of PEG in the copolymer increased with the molecular mass of the polyether. Huang reports an increase in the height of the DRX peaks by increasing the molecular mass of the PEG and a decrease in these peaks when the mass fraction increases.[34] It is considered that in this work both effects were canceled and consequently, no differences in the height of the diffractograms were observed.

### 3.2. Obtaining of Loaded-Microspheres

Naproxen-loaded microparticles were prepared by the emulsification—solvent evaporation method. Naproxen is a very hydrophobic drug that is soluble in organic solvents as DCM and methanol but it is practically insoluble in water.[36] This allows one to obtain the loaded microspheres using a simple

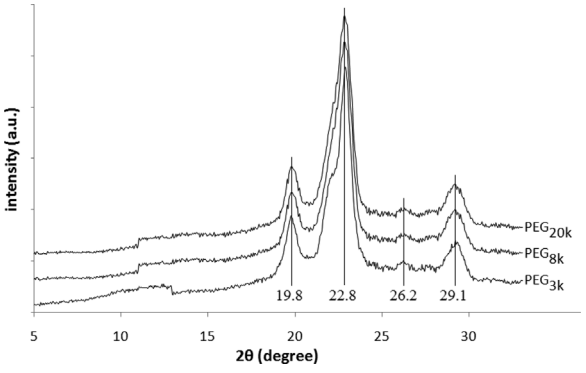


**Figure 3.** XRD analyses of PBS-PEG copolymers.

emulsion. The encapsulation efficiency is usually lower when a double emulsion is needed for hydrophilic drugs because the drug migrates to the external continuous phase during the encapsulation process.[37] Dried microspheres were weighed and naproxen content was determined by UV absorption. Yield, encapsulation efficiency (EE) and drug loading (DL) into particles were calculated (**Table 3**) by the following equations:

$$\text{Yield}\,(\%) = \frac{W_{\text{ME}}}{\left(W_{\text{pol}} + W_{\text{NPX}}\right)} \times 100 \quad (1)$$

$$\text{EE}\,(\%) = \frac{W_{\text{NPXE}}}{W_{\text{NPX}}} \times 100 \quad (2)$$

$$\text{DL}\,(\%) = \frac{W_{\text{NPXE}}}{W_{\text{ME}}} \times 100 \quad (3)$$

Where $W_{\text{ME}}$ is the mass of dried microspheres, $W_{\text{pol}}$ is the mass of added polymer for encapsulation process, $W_{\text{NPX}}$ is the weight of added naproxen for encapsulation process and $W_{\text{NPXE}}$ is the weight of loaded naproxen. Yields were 88–93%. We think that these high yields could be due to the use of a simple emulsion process where the yields are higher than when using a double emulsion. This factor has greater influence than the presence of a hydrophilic moiety. For example, recoveries less than 85% have been reported when obtaining PLGA microspheres by the double emulsion procedure.[38,39] The yield was slightly lower with $PEG_{8k}$. This is possibly due to the lower molecular mass of the copolymer with this PEG. The satisfactory encapsulation efficiencies (>60%) are also in accordance with the simple emulsion procedure and the low solubility of naproxen in the external aqueous phase. When a water-soluble drug is encapsulated by the w/o/w method, leakage to the external aqueous phase can always occur and the amount of drug remaining within the particle is usually lower.[13]

Particles from PBS and PBS-PEG were well-rounded spheres with uniform size distribution under optical microscopy (**Figure 4**). The presence of different chain lengths of PEG in the copolymers did not appreciably change the microspheres morphologies (data not shown). The sizes of the PBS-PEG microspheres were 10–12 μm, with a slight positive effect of the PEG chain length (**Figure 5**). PBS homopolymer particles had a smaller size. The larger particle sizes of microspheres prepared with PBS-PEG copolymers may be due to the high affinity of PEG for water. This polymer has a high hydrodynamic volume since each repeating unit of the PEG is able to join 3–5 molecules of water.[40] A little population of very big (>1 mm) particles was observed when PBS homopolymer was used. Probably, there were small agglomerates of the polymer remained undissolved during the process of obtaining microspheres or any failure during homogenization led to the formation of a little population of larger particles.

**Table 3.** Encapsulation process parameters for naproxen loaded microspheres.

| Sample | Yield [%] | Encapsulation efficiency [%] | Drug loading [%] |
|---|---|---|---|
| PBS | 92 | 67 | 12.2 |
| $PBS\text{-}PEG_{3k}$ | 91 | 62 | 11.9 |
| $PBS\text{-}PEG_{8k}$ | 88 | 61 | 12.5 |
| $PBS\text{-}PEG_{20k}$ | 93 | 64 | 12.3 |

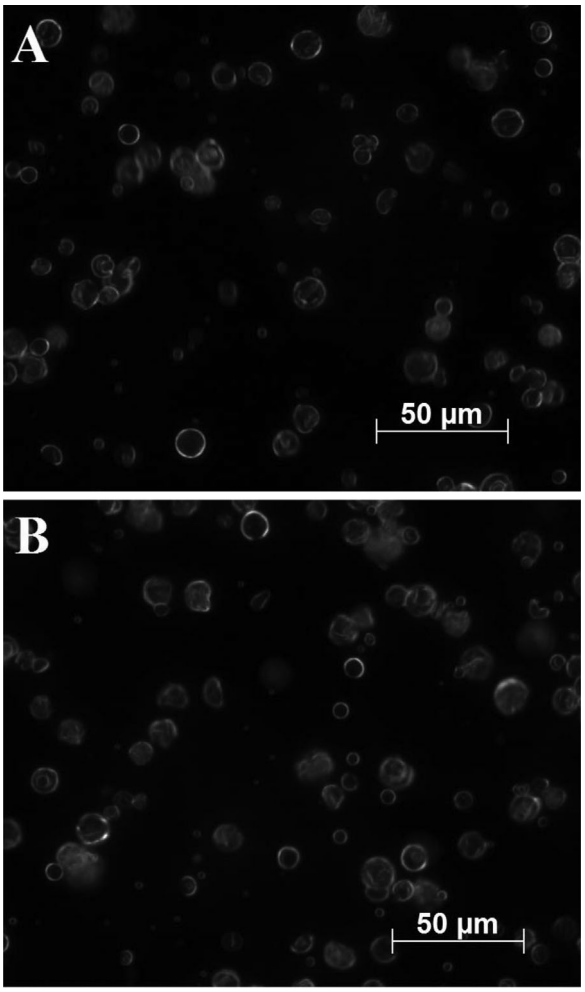


**Figure 4.** Optical micrographs of loaded particles obtained with different matrices: a) PBS and b) PBS-PEG.

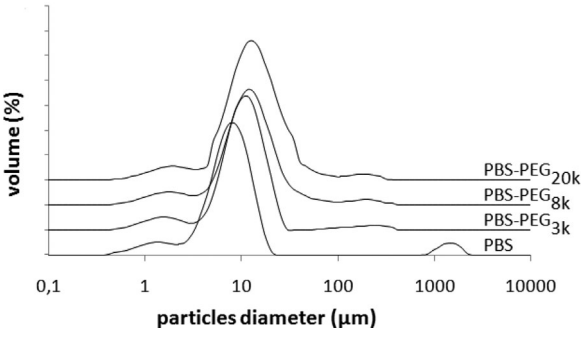


**Figure 5.** Size distributions of loaded particles.

### 3.3. Release Studies

Drugs encapsulated in polymeric microspheres are commonly released following a pattern of three main steps; i) burst release phase, usually occurring during the firsts moments and mainly determined by the drug adsorbed on the surface; ii) slow release phase, usually called the lag phase; and iii) a last phase that comprises a faster release of the drug due to a combination of the drug's diffusion and the erosion of particles.[41] Occasionally, the release can occur in two steps and the profile shows an asymptotic pattern.[42] Other authors prefer a more specific classification separating cases with or without burst, having two or three phases and according to the duration of the lag phase.[43] In our work (**Figure 6**), the release of naproxen from microspheres showed a two-phase profile, with an initial burst (first half hour) followed by a rapid release of the drug, for the three copolymers. The absence of lag phase could be attributed to the presence of PEG in the copolymer that must have favored the entry of water into the pores of the microparticles. Burke et al. found that the lag phase was not present when they used a PEG-PLGA copolymer to encapsulate and slowly release BSA. They also considered that this behavior is strongly related to the presence of PEG, which caused a rapid hydration of particles and the formation of a hydrogel-like structure throughout the particle.[44] PBS microspheres showed a different naproxen release profile. They did not show a burst release and less than 50% of the loaded NPZ went into solution within 72 h of the study.

Results of in vitro release study may or may not be related to the in vivo properties of the drug release process.[45] Nevertheless, in vitro data may be very useful to determine the drug release mechanism and release rates. This knowledge is very important for tuning the desired characteristics of the drug delivery systems.

There are many mathematical models to fit the data obtained from drug release studies.[46] They could be classified into two main groups: mechanistic models and empirical or non-mechanistic models. The models included in the last group are pure mathematical descriptions that are not based on physical, chemical, or biological processes involved in the release of the drug from a pharmaceutical dosage form ref. [43]. However, the mechanistic models have been developed from integral analyses of i) the formulation type (geometry, size, composition, structure, distribution of the drug on the device); ii) the drug properties (molecular weight, solubility, hydrophobic-hydrophilic character); and iii) the processes that affect the drug's transport from the inner or surface of the dosage form to the receiving fluid (water absorption and/or swelling, drug diffusion, polymer degradation, device erosion with a consequent change in the morphology and inner structure, relaxation of the polymeric chains, polymer-drug interactions). In that sense, the last ones could give an idea of the processes that really govern the drug release rate in the system under evaluation and consequently could be easier to control the drug release patterns.

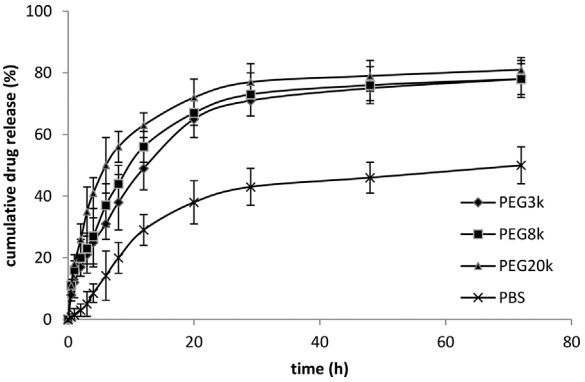


**Figure 6.** Drug release profiles from NPZ-loaded microparticles.

Several mechanistic models have been developed but they should be used conscientiously according to the properties of each particular system. PBS-PEG microspheres released almost all NPX in a relatively short period (72 h). Thus, it is highly probable that the erosion of the polymeric particles has not been started and consequently this process could not affect the NPX release. On the other hand, the presence of PEG into the polymeric matrices helps the water intake which could favor the diffusion process. Considering this, the NPX release data was fitted to the Korsmeyer–Peppas's (Equation (4)) and the Peppas–Sahlin's (Equation (5)) models (**Table 4**):

$$\frac{M_t}{M_\infty} = \mathrm{K}t^n \quad (4)$$

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n} \quad (5)$$

In Equations (4) and (5), $M_t/M_\infty$ is the fraction of drug released, $K$ is a release constant, $n$ is a release exponent indicative of the release mechanism, $k_1$ and $k_2$ are Fickian and relaxational contribution respectively and $t$ is the release time.[47,48] The

**Table 4.** Release kinetics parameters.

| | Korsmeyer–Peppas | | | Peppas–Sahlin | | |
|---|---|---|---|---|---|---|
| Sample | $K$ | $n$ | $R^2$ | $k_1$ | $k_2$ | $R^2$ |
| PBS | 0.020 ± 0.001 | 1.1 ± 0.4 | 0.982 | 0.013 ± 0.002 | 0.0013 ± 0.0003 | 0.997 |
| PBS-PEG$_{3k}$ | 0.143 ± 0.004 | 0.59 ± 0.01 | 0.998 | 0.141 ± 0.002 | 0.0002 ± 0.0001 | 0.999 |
| PBS-PEG$_{8k}$ | 0.17 ± 0.01 | 0.58 ± 0.03 | 0.991 | 0.168 ± 0.006 | 0.0004 ± 0.0002 | 0.992 |
| PBS-PEG$_{20k}$ | 0.227 ± 0.009 | 0.55 ± 0.02 | 0.996 | 0.232 ± 0.006 | −0.0008 ± 0.0007 | 0.996 |

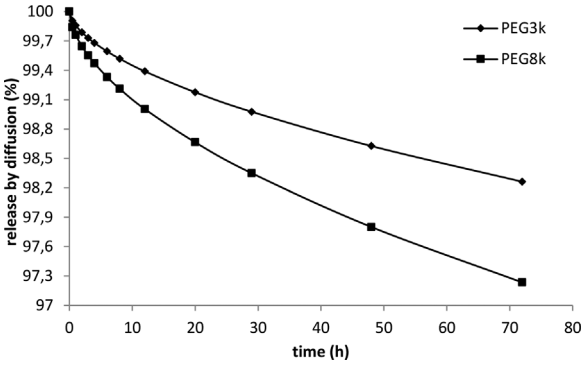


**Figure 7.** Release by a diffusion mechanism.

percentage of drug release at any time due to the Fickian mechanism, $F$, can be calculated by Equation (6).

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^m} \tag{6}$$

$F$ was only calculated for $PEG_{3k}$ and $PEG_{8k}$ (**Figure 7**). The parameter $k_2$ was negative for $PEG_{20k,}$ which is evidence that the release occurs only by diffusion. Even though $k_2$ was positive, its value was very small when compared to $k_1$. This indicates that the release was mainly by diffusion. Figure 7 shows that more than 97% of the release may be attributed to a diffusion process at 72 h. We consider that the high hydrophilicity of PEG allows rapid hydration of the matrix and favors diffusion transport. On the other hand, the fraction of the release that can be attributed to a relaxation mechanism is slightly greater in the copolymer with $PEG_{8k}$. This may be due to the lower molecular mass of this copolymer. A lower molecular mass decreases the relaxation time.[49]

In the case of microspheres made with PBS homopolymer, the model shows that only 50% of the release can be attributed to diffusion during the first 8 h and this fraction decreases to 10% at 72 h (calculations not shown). The hydrophobicity of PBS hinders the transport of water and therefore, affects the diffusion process. So, it is possible to think that relaxation of the PBS is the driving force for the release of NPZ loaded into homopolymer particles.

## 4. Conclusions

Copolymers of polyethylene glycol (PEG) and polybutylene succinate (PBS) were obtained by a polycondensation reaction as confirmed by FTIR analyses. Thermal analyzes showed that the increase in the molecular mass of the PEG moiety slightly decreased the Tc, the Tm, and the degradation temperature of the copolymer. XRD results suggested that an independent crystallization of the two polymer segments was present. Nevertheless, a very complex relationship between the molecular mass and the amount of PEG in the reaction with the resulting size of the copolymer was revealed by SEC analyses.

Naproxen-loaded microspheres were obtained by the emulsion/solvent evaporation method. The particles prepared with the copolymer were larger than with PBS, possibly because of the high hydrophilicity of PEG. The presence of PEG had a marked effect on the in vitro release profiles. The mathematical models employed show that the fundamental mechanism of release is diffusion when PEG is present in the polymer matrix of the particle.

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## Keywords

mathematical models for drug delivery, microencapsulation, naproxen, poly(butylene succinate-co-polyethylene glycol, polycondensation

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