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Poly (Butylene Succinate)-g-Poly(Hydroxypropyl Methacrylate) as a New Meloxican Delivery System

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The use of biopolymer-based drug delivery systems is increasing in the pharmaceutical area due to them biodegradable and biocompatible properties. In this work, a poly (butylene succinate) (PBS) grafted with poly (hydroxypropyl methacrylate) (PHPMA), PBSgPHPMA, is prepared using maleic unsaturations inserted in the PBS chain during its synthesis. Several characterization techniques are used to study the homopolymers and the grafted material. Among them, Fourier Transform Infrared (FTIR), Thermogravimetric analysis (TGA) Differential scanning calorimetry (DSC), and X-ray diffraction (XRD) allowed inferring the obtaining of the aimed materials. Also, the copolymer is used to prepare microparticles containing Meloxicam by emulsification and solvent evaporation method. These microparticles are tested as drug delivery systems under pH 8.5 (gastrointestinal) and pH 5.5 (skin). The primary results allowed inferring that the grafted material can be used as a drug delivery system, showing that the release rate at pH 5.5 allowed the slower delivery rate among tested materials.

1. Introduction

Biopolymers are materials characterized by its biodegradability and biocompatibility properties.[1] Those properties allow them to be used in the distinct applications, such as packaging or structures, replacing petrochemical polymers.[2] Besides that, since these biomaterials mostly do not generate byproducts harmful to the human body, they are also can be used in the medical area, especially in drug delivery applications.[3–6]

Among green polymers, the poly (butylene succinate) (PBS) is obtained by the polycondensation of 1,4-butanediol and succinic acid.[7–13] PBS is an aliphatic, thermoplastic, and crystalline polyester with excellent thermal and mechanical properties.[14] Also, due to new biotechnological routes used for the preparation of the succinic acid, this polymer is considered as future platform material.[15,16] Nowadays, succinic acid is efficiently produced from renewable biomass, such as crop stalks wastes, by batch fermentation[17] helping to remove CO_2 from the atmosphere.[18] Despite poly (hydroxypropyl methacrylate) (PHPMA) petrochemical nature, this polymer also presents biocompatibility.[19] Also, due to its hydroxyl groups, PHPMA presents an intense interaction with polar molecules.[20] Thus, PHPMA could be used as an alternative to Polyethylene Glycol (PEG) acting as a hydrophilic phase useful to the biomasking.[21]

Meloxicam is a non-steroidal anti-inflammatory drug, used for the long-term treatment of chronic diseases such as osteoarthritis and rheumatoid arthritis.[22] This drug presents as the main advantage the small damage to the gastrointestinal mucosa.[23] Thus, its application by skin route is beneficial since it can reduce side effects.[24] Among poorly soluble drugs, Meloxicam is considered as a drug model.[25]

The primary goal of the present work is to synthesize a graphitized PBSgPHPMA copolymer aiming to generate materials with hydrophilic and hydrophobic characteristics. In this context, the hydrophilic phase would be responsible for the biomasking while the hydrophobic one will entrap and carry the Meloxicam. Also, to the best of our knowledge, the PBSgPHPMA is reported here for the first time. Finally, the obtained results showed that the release under the transdermal pH is slower than the one achieved using the gastrointestinal conditions.

2. Experimental Section

2.1. Materials

2-Hydroxypropyl methacrylate (2-HPMA) was purchased from Evonik Degussa Brasil Ltda.; Deutereted Chloroform was purchased from Cambridge Isotope Laboratories; Meloxicam was purchased from Pharmanostra Ltda. All the other reagents were purchased from Sigma–Aldrich, Brazil. All chemicals were used as received.

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2.2. Preparation of the Polymers

2.2.1. Poly (Butylene Succinate)

Synthesis of the PBS was performed as described by our group elsewhere.[26] Firstly, 39 mL of 1,4-butanediol, 47.3 g of succinic acid and 2.79 g of maleic anhydride (responsible for the unsaturated portions of the polymer chain) were inserted in a three-necked flask, where they were kept for 4 h at 130 °C under constant stirring and N_2 atmosphere. A condenser was used to retrieve water from the system. In the second step, 0.140 mL of tin(IV) tert-butoxide was added, and the temperature was increased up to 150 °C under vacuum. The constant stirring was kept, and the reaction followed during another 6 h, totalizing 9 h of reaction. To purify the sample, it was diluted with chloroform and poured into a beaker. Then ethanol was added, and the sample rested during 48 h. After that, the sample was decanted, filtered and kept in an oven set at 40 °C for 24 h.

2.2.2. 2Poly (2-Hydroxypropyl Methacrylate)

Synthesis of PHPMA was performed using 10 g of its monomer 2-hydroxypropyl methacrylate (2-HPMA) into a three-necked flask under constant stirring and N_2 atmosphere. The temperature was increased up to 85 °C, and then 0.194 g of benzoyl peroxide and 6.1 µL of dodecyl mercaptan were added to the system. Benzoyl peroxide acted as an initiator while n-dodecyl mercaptan is the chain-transfer agent. The reaction lasted for 1 h. The sample was then filtrated, washed using distilled water and kept inside an oven set at 40 °C for 24 h.

2.2.3. Poly(Butylene Succinate)-g-Poly(Hydroxypropyl Methacrylate)

The PBSgPHPMA was prepared using a procedure adapted from Abdel-Bary.[27] In the first step, 2 g of PBS were swollen into glycerin warmed up at 120 °C for 1 h. In the second step, 200 mL of distilled water, and 1.03 mL of 2-HPMA were added to the system, and the medium was stirred for 1 h at room temperature. In the third and last step, the temperature was increased up to 85 °C, and a then 10 mL of a solution at 78 g L^{-1} of benzoyl peroxide in toluene was added to the system, reacting for 4 h. All the three steps were performed under constant stirring and N_2 atmosphere. The sample was then filtrated, washed using distilled water and kept in an oven set at 40 °C for 24 h.

2.3. Preparation of the Microparticles

In a typical procedure, 200 mg of the copolymer and 10 mg of the drug were diluted in 4 mL of chloroform. Then, the solution was separated into two equal parts. Soon afterward, each sample was slowly dropped into 8 mL of a 1% PVA solution while an IKA ULTRA TURRAX T10 dispersant was turned on inside the solution to produce the particles. The sample was then placed into a rotary evaporator for 30 min aiming to remove the chloroform. Finally, the sample was centrifuged into a Boeco Germany C28A centrifugal for 40 min at 6000 rpm.

2.4. In Vitro Drug Delivery Tests

The microparticles samples were deposited into an acetate film and kept in contact with a borate buffer (pH equal to 8.50). The same procedure was performed using a phosphate buffer (pH equal to 5.5). These solutions were chosen to mimic the gastrointestinal,[28] and skin pH,[29] respectively. The liberation tests were performed in duplicate during 48 h. Samples were collected at 1/4, 1/2, 1, 2, 3, 24, and 48 h. Samples were studied using the UV-Vis spectrometry at 364 nm, following a procedure described by Nemutlu and Kir.[28] The description of the drug delivery system is shown in **Figure 1**.

2.5. Characterization

Fourier Transform Infrared (FTIR) was used to study the prepared materials. Materials were studied using a Varian model 3100 FTIR Excalibur Series spectrophotometer (Japan). Samples were macerated with potassium bromide (1 mg/100 mg samples/KBr). Then, the FTIR spectra of the samples were recorded at room temperature, using a resolution of 4 cm^{-1}.

X-Ray Diffraction (XRD) was also used to characterize the copolymers, the samples prepared and the drug. The equipment used was a Rigaku Miniflex X-ray diffractometer in a 2θ range from 2° to 80° by the method FT (fixed time). The steps were equal to 0.05° s^{-1}, using a tube voltage and current equal to 30 kV and 15 mA, respectively. The radiation used was CuKα = 1.5418 Å.

Thermogravimetric (TGA) and Differential Scan Calorimetry (DSC) studies were performed using a Parkin-Elmer STA 6000. Samples were heated from 25 to 700 °C using a heating rate of 20 °C min^{-1} under nitrogen flow (40 mL min^{-1}).

2.6. Optical Microscopy

Optical Microscopy was made using a Carl Zeiss Axiovision microscopy with a 200x lens. Data treatment was performed using ImageJ® and LibreOffice Calc®.

UV/Vis spectrophotometry was performed using a Varian Cary 100 Spectrophotometer. Analyses were made at 364 nm using a glass bucket and a deuterium lamp. Calibration curves

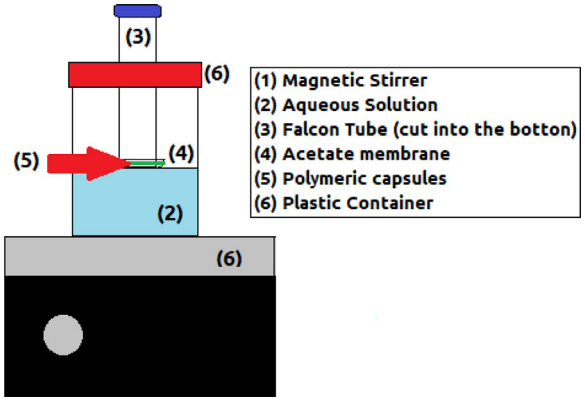

Figure 1. In vitro drug delivery system.

were performed using chloroform, Borate buffer 8.5 pH and phosphate buffer 5.5 pH at 0, 1, 5, 10, 15, and 20 g L^{-1}.

2.7. Microparticles Formulation Yield and Encapsulation Efficacy

The yield was calculated by the following equation:

$$\text{Yield}(\%) = \frac{\text{Me}}{\text{Mb}} \times 100 \quad (1)$$

where Me is the mass at the end of the formulation and Mb is the mass at the beginning of the formulation.

The Encapsulation Efficacy (Emx) was calculated by the following equation:

$$\text{Emx} = \frac{\text{Me}'}{\text{Mb}'} \times 100 \quad (2)$$

where Me′ is the sample mass at the end of each process, while the Mb′ is the sample mass at the beginning of each process.

2.8. Drug Release Modeling

Several models were tested for the calculation of the drug release kinetics. They are: the 1) Zero Order model, which describes drug dissolution from dosage forms that do not disaggregate and release the drug slowly (see Equation 3); 2) Higuchi model, which is frequently used to describe the drug release from planar, geometric, or porous systems (see Equation 4); 3) the Korsmeyer–Peppas model, which is used to describe the solute release based on a combination of drugs diffusion (Fickian Transport) and Case II transport (non-Fickian, controlled by the polymeric chains' relaxation) mechanisms (see Equation 5); 4) First Order model, useful to describe adsorption and/or elimination of some drugs (see Equation 6); and 5) Hixson–Crowell, used to describe release systems where there is a change both in surface area and in diameter of particles or tablets (see Equation 7).[30]

The tested models are shown in Equations (3–7).

$$Q_t = Q_0 - K_0\, t \quad (3)$$

$$Q_t = Q_0 - K_H\, t^{1/2} \quad (4)$$

$$Q_t = Q_0 - K_t^n \quad (5)$$

$$\text{In}Q_t = \text{In}Q_0 - K_1\, t \quad (6)$$

$$Q_t^{1/3} = Q_0^{1/3} - K_c\, t \quad (7)$$

In Equations (3–7), "t" is time; "Q_t" is the drug released at time t; Q_0 is the initial drug release at time 0; and K_0, K_H, K^n, K_1, and K_c are the release constants of First Order, Higuchi, Korsmeyer–Peppas, First Order, and Hixson–Crowell models, respectively.

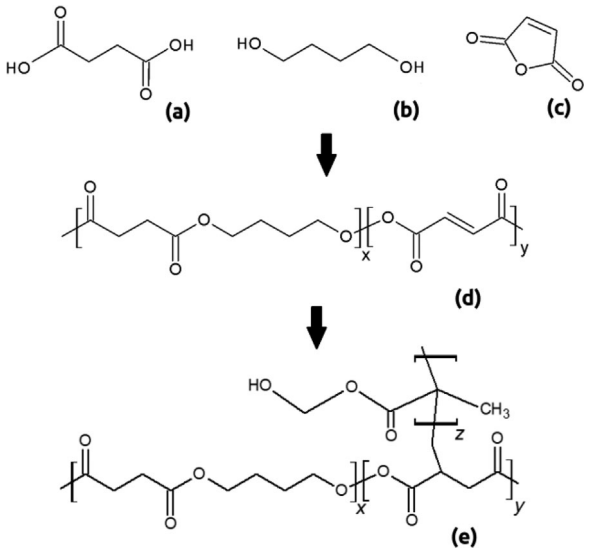

Figure 2. Chemical structures of succinic acid (a), 1,4-butanediol (b), maleic anhydride (c), unsaturated PBS (d), and PBSgPHPMA (e).

3. Results and Discussion

Maleic anhydride (b) inserts itself in PBS chains (a) while they were growing, resulting in an unsaturated PBS (c). After the initial reaction, the PHPMA polymer can attack the double bond, adding itself to the polymer structure, resulting in the graft copolymer PBSgPHPMA (d). The proposed mechanism is shown in **Figure 2**.

FTIR spectra of the prepared materials are shown in **Figure 3**.

The PBS sample, shown in Figure 3a, presented the $-CH_2$ bands at 1330 and 2945 cm^{-1}; the C—O—(C=O) ester group bonds at 1145 and 1265 cm^{-1}; the C=O ester band at 1711 cm^{-1}; and the O—C—C bonds at 1045 cm^{-1}. The PHPMA sample, shown in Figure 3b, presented the OH band at 3445 cm^{-1}; the

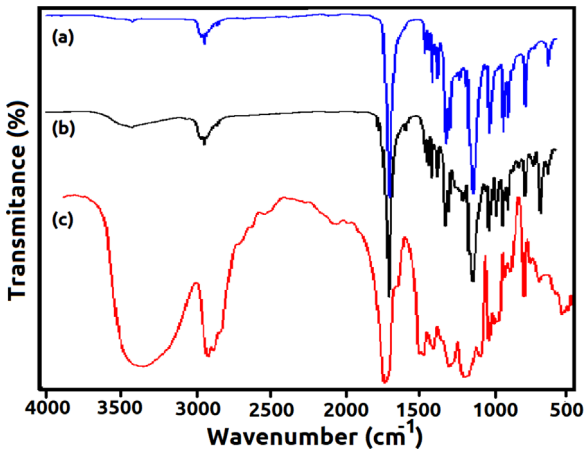

Figure 3. FTIR spectra of PBS (a), PBSgPHPMA (b), and PHPMA (c).

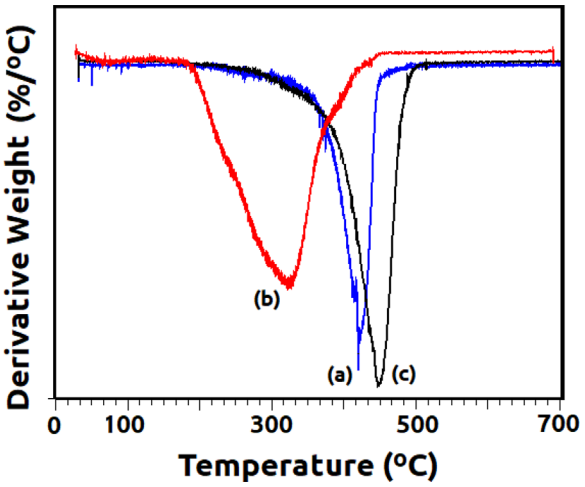

Figure 4. Derivative TGA results of the PBS (a), PHPMA (b), and PBSgPHPMA (c).

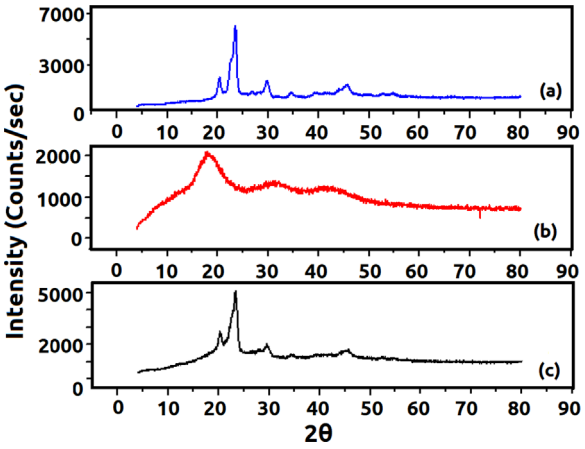

Figure 5. XRD patterns of PBS (a), PHPMA (b), and PBSgPHPMA (c).

C═O bond of the ester portion of the polymer at 1731 cm^{-1}; the band of the main chain CH_2 at 1465 cm^{-1}; the CH_3 portion of the polymer chain at 1390 cm^{-1}; the peak of the C—O bonds at 1265 and 1180 cm^{-1}. In turn, the PBSgPHPMA presented a stronger signal from the PBS portion of the copolymer, since the signal of this polymer is very characteristic. The C—O—C═O characteristic bands of the two polymers at 1200 cm^{-1}; the C═O band at 1700 cm^{-1}; and the CH_2 bands at 3000 cm^{-1}; the OH groups around 3500 cm^{-1}. These results prove the insertion of the PHPMA chains in the unsaturated PBS.

Results in the derivative TGA (see **Figure 4**) allowed inferring that, among tested materials, PHPMA is the polymer with the lowest thermal stability.

PHPMA main degradation peak is centered at 322 °C, while the one from PBS is at 406 °C. This phenomenon is due to the depolymerization of the PHPMA under higher temperatures.[31] In turn, the PBSgPHPMA copolymer presents a degradation peak around 410 °C, showing increased thermal stability compared to the homopolymers, since it has a degradation peak higher than its both homopolymers, specially PHPMA. This is possibly due to the cross-linking side-reactions between the PHPMA portions of the sample, which made the copolymer more thermally stable.

The DSC thermal transitions results are shown in **Table 1**.

The DSC results are in agreement with the derivative TGA ones. For instance, the enthalpy during the degradation of PBS is higher than that of the copolymer, demonstrating a more natural degradation of the copolymer, since less energy is needed to degrade it (167.9 J g^{-1} needed to degrade the copolymer against 277.8 J g^{-1} needed for the referred homopolymer). Thus, the insertion of the PHPMA in the PBS decreased the energy needed to start the thermal degradation of the copolymer.

Table 1 also shown the crystallization degree (CD) of the tested materials. Calculations were performed based on the literature, according to which, the theoretical heat of fusion of 100% crystalline PBS is equal to 200 J g^{-1}.[32] Pure PBS presents a higher CD (50.5%) than copolymer (26.1%). This result indicates that the graft of the PHPMA chains to the PBS makes harder the organization of the new material, proving again the obtaining of the copolymer.

Table 1. Melting and degradation enthalpy and degree of crystallization of the prepared materials.

	Samples		
Properties	PBS	PHPMA	PBSgPHPMA
Melting (J g^{-1})	101	25.9	52.2
Degradation (J g^{-1})	277.8	339.9	167.9
Degree of crystallization (%)	50.5	12.9	26.1

Table 2. Crystal size, inter-planar distance, and number of crystalline planes for PBS and PBSgPHPMA.

	Crystal size [Lc]	
Crystalline plane	PBS [nm]	PBSgPHPMA [nm]
(020)	2.36	1.46
(021)	2.07	1.55
(110)	3.08	2.60
(111)	1.75	1.03
	Inter-planar distance [d]	
Crystalline plane	PBS [nm]	PBSgPHPMA [nm]
(020)	0.2677	0.2657
(021)	0.2964	0.2964
(110)	0.3059	0.3039
(111)	0.3822	0.3804
	Number of crystalline planes [Lc/d]	
Crystalline plane	PBS	PBSgPHPMA
(020)	9	6
(021)	7	5
(110)	10	9
(111)	5	3

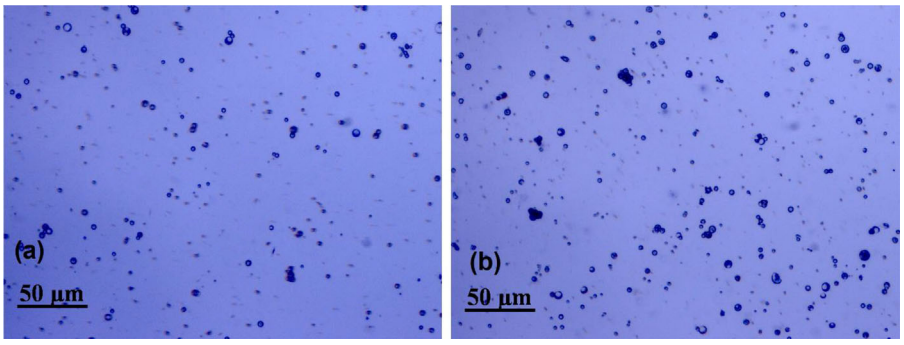

Figure 6. Optical Microscopy images from the PBS (a) and PBS filled with Meloxicam (b).

XRD patterns of prepared materials are shown in **Figure 5**. The presence of the characteristic peaks of the PBS (Figure 5a) can be seen. These peaks are centered 19.8° (020), 22.0° (021), 22.6° (110), and 29.8° (111). The data are in complete agreement with the literature.[32] In turn, PHPMA (Figure 5b) does not show crystalline peaks mainly due to the presence of the methacrylate group, which does not allow the formation of organized structures, keeping the material amorphous.[33]

The PBSgPHPMA (Figure 5c) presents the same crystalline structures of the homopolymer PBS. However, the PBSgPHPMA's amorphous area grows as proved by the decrease of the crystallite sizes (Lc) shown in **Table 2**. This decrease takes place due to the difference between the hydrophobic and hydrophilic characteristics of the PBS (Figure 5a) and PHPMA (Figure 5b), respectively. This different nature produces, in the grafted material, the reduction of the staked crystalline planes, as proved by the relationship Lc/d, also shown in Table 2. The decrease in the number of crystalline planes is directly related to the peak enlargement of the peaks and reduction of the crystalline degree.

The optical micrographs of the samples, before and after the insertion of the drug, are shown in **Figure 6**. The copolymer presented an average diameter equal to (6.0 ± 0.2) µm. The insertion of Meloxican produced a particles set with an average diameter equal to (7.1 ± 0.6) µm. Despite statistically different, particle sizes remained similar. This size allows the material to be deposited on the skin to act as a transdermal patch, releasing the material at a slow rate.

The formulation yield was calculated according to Equation (1), and the obtained result was equal to 77%. After the dissolution of the particles in chloroform, the efficacy of encapsulation was calculated following Equation (2), and the result was equal to 79%. Both results are positive, showing that only a small part of the materials used was lost during the preparation steps.

The Meloxican released from borate and phosphate media along experimental time is shown in both **Table 3** and **Figure 7**.

Results showed in Table 3, and Figure 7 allowed inferring that the release speed is media dependent. Specifically, the release from the borate medium (pH = 8.5) was faster than the release in phosphate medium (pH = 5.5), releasing around 3.6 times more Meloxicam than the one released from phosphate medium. This phenomenon can be explained due to the better interaction of the drug with alkali media.[34] This is substantial evidence of the usefulness of this material as a transdermal patch since copolymer can be applied on the skin (pH = 4.2 to 5.6)[29] for days without the complete release of the drug.

Several models were tested for the calculation of the drug release kinetics. As shown in **Table 4**, several models showed high correlations values to one or both liberations.

However, the Higuchi model presented a very high correlation for both samples (highest R^2 value for phosphate and second highest for borate), being the best model for describing this liberation. So, as Higuchi equation is usually used to describe transdermal release systems,[35,36] the obtained result indicates that tested materials could be suitable for use as transdermal patches.[37]

Table 3. Meloxicam release in Borate pH 8.5 and Phosphate pH 5.5 buffer.

Time [h]	Borate [%]	Phosphate [%]
0.25	1.85 ± 1.10	0.18 ± 0.09
0.5	4.19 ± 3.08	0.60 ± 0.28
1	8.67 ± 11.20	1.53 ± 0.49
2	17.50 ± 9.25	2.99 ± 0.68
3	23.71 ± 12.71	3.97 ± 0.79
24	47.90 ± 13.71	11.15 ± 3.95
48	60.75 ± 5.69	16.86 ± 1.41

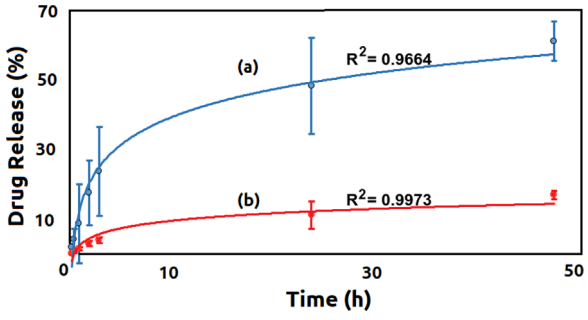

Figure 7. Meloxicam released from borate pH 8.5 (a) and phosphate pH 5.5 (b) media and respective Higuchi's fittings.

Table 4. Linear fitting analysis for the drug delivery systems in both media.

	Borate pH 8.5			Phosphate pH 5.5		
Model	$\log Q_0$	Log Kt	R^2	$\log Q_0$	Log Kt	R^2
Zero order	10.4503	1.1609	0.8787	1.533	0.3371	0.9616
Higuchi	−0.0643	0.1071	0.9664	0.3664	0.3921	0.9973
Kors–Peppas	−0.4461	0.0368	0.9776	−0.2670	0.1289	0.9233
First Order	1.9536	−0.0080	0.9487	1.9935	−0.0016	0.9693
Hixson–Crowell	0.1652	0.0243	0.9222	0.0235	0.0055	0.9669

4. Conclusions

The copolymerization of PBS with PHPMA generates a copolymer useful to the preparation of microparticles by emulsification and solvent extraction method, which presented good encapsulation efficiency. Besides that, the release tests allowed concluding that the kinetics in the alkali medium (intestine) was around 3.6 times faster than the one in the acid medium (skin), indicating the potential application of these release systems as transdermal patches.

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Keywords

copolymerization, drug delivery systems, graft copolymer, PBSgPHPMA, polyesters

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