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Evaluation of Sodium Diclofenac Release Using Natural Rubber Latex as Carrier

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Sodium Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and, as an analgesic, reduce pain. Although this drug is widely used in the general population, properties such as the short half-time and some side effects restrict its clinical use. The most common side effects are: gastric irritation, gastritis, peptic ulcer and bleeding. Studies involving biomaterials as carrier for drug release have been proving their efficiency in overcoming those problems and better controling the release rate and targeting of the drug. Natural rubber latex (NRL) has been proven excellent for its biocompatibility and ability to stimulate angiogenesis, cellular adhesion and the formation of extracellular matrix, promoting the replacement and regeneration of tissue. In this work, a NRL membrane is used to deliver sodium diclofenac. Sodium diclofenac (NaDic) was found to be adsorbed on the NRL membrane, with little or no incorporation into the membrane bulk, according to energy dispersive Scanning Electron Microscopy with X-Ray microanalysis (SEM-EDS) spectroscopy. In addition, FT-IR shows that there is no molecular-level interaction between drug and NRL. Already, the X-Ray Diffraction (XRD) of NaDic-NRL shows a broader one spectrum than the sharper halo (amorphous characteristic XRD spectrum) of pure NRL. More importantly, the release time of diclofenac in a NRL membrane *in vitro* was increased from the typical 2-3 h for oral tablets to ca. 74 h. The kinetics of the drug release could be fitted with a double exponential function, with two characteristic times of 0.899 and 32.102 h. In this study, we demonstrated that the interesting properties provided by NRL membranes combined with a controlled release of drug is relevant for biomedical applications.

Keywords: *membranes, natural rubber, sodium diclofenac, drug delivery system, biomaterials*

1. Introduction

Diclofenac sodium (NaDic) is a non-esteroidal anti-inflammatory, analgesic and antipiretic drug (NSAID) (Figure 1). It is a sodium salt of an aminophenyl acetic acid[1] which is rapidly absorbed after oral administration, having a short biological half-time between 1-2h and high solubility above pH 5[2]. Although this drug is widely used in the treatment of tendinitis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, properties such as the short half-time and some side effects restrict its clinical use[1]. The most common side effects are: gastric irritation, gastritis, peptic ulcer and bleeding[3]. Recent researches are being developed to improve drug release such as use of tabletted microspheres[2], acetate butyrate microparticles (a kind of polymer)[3], nanoparticles and many other. Studies involving biomaterials as carrier for drug release have been proving their efficiency in overcoming those problems and better controling the release rate and targeting of the drug.

When drugs are injected intravenously only one part in ten thousand reaches its final target, in appropriate concentrations to cause the expected therapeutic effect[5,6]. This proportion is due to many anatomical, chemical and biological obstacles verified between the local administration of the drug and the target organ or tissue.

Therefore controlled drugs release is an important pharmacology subject. This technique can provide the creation of optimized systems that ensure the controlled release of these drugs to a specific site.

One candidate already described in literature[7-11] as a potential carrier is the natural rubber latex (NRL) from *Hevea brasiliensis.* The NRL membrane is an important inductor of the healing process of wounds, being used in several medical applications like prosthetics and bone grafts[12-16]. In addition, the treatment of diabetic and phlebopathic ulcers with these membrane leads to a faster healing process due to a vascular growth factor found in the latex and due to a physical blockage of the entrance of new infectious agents in the treated site[17,18]. NRL membrane has some interesting characteristics such as: easy manipulation, low cost, can stimulate natural angiogenesis and cellular adhesion, is a biocompatible material and presents high mechanical resistance[19,20]. The aggregation of sodium diclofenac in drug-delivery systems (DDS) aimed at drug-

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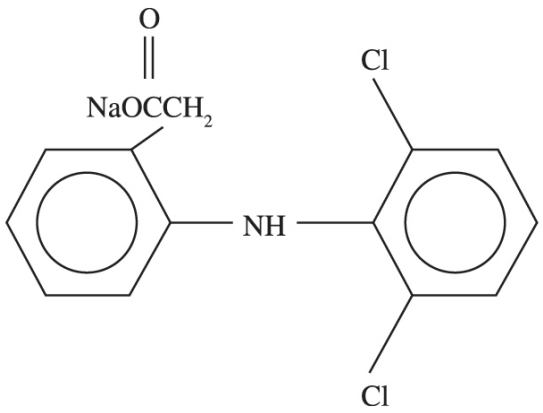


Figure 1. Molecular structure of sodium diclofenac[4].

membrane interaction, for further optimization of the located anti-inflamation, avoiding some complications.

In this work, it is propose a novel release system based on the encapsulation of diclofenac in NRL membrane for a sustained and controlled delivery of the drug, possibly being a future application in medicine as surgical bandage for bone and tissue regeneration. Results showed that the NRL membrane can release sodium diclofenac for up to 74 hours. In addition, the X-Ray Diffraction (XRD) and Scanning Electron Microscopy with X-Ray microanalysis (SEM-EDS) showed that sodium diclofenac properties and structure are preserved while incorporated in the membrane, which is relevant for possible biomedical applications. FT-IR spectra shows that there is no molecular-level interaction between drug and NRL. More importantly, the release time of sodium diclofenac in a NRL membrane *in vitro* was increased from the typical 1-2 h for oral tablets to ca. 74 h. The kinetics of the drug release could be fitted with a double exponential function, with two characteristic times of 0.899 and 32.102 h.

2. Material and Methods

Natural rubber latex (NRL) used in the present study was commercial high-ammonia natural rubber latex (BDF Latex, Guarantã/SP, Brazil) of about 60% dry rubber content (DRC). After extraction, ammonia was used to keep the latex liquid. NRL was performed by centrifugation at 8,000 g[7,8] to reduce the protein content related with allergies.

Sodium diclofenac ($C_{14}H_{11}Cl_2NO_2$) was purchased from CALLITHEA Pharmaceutics Ltd., Brazil. Diclofenac was incorporated by mixing 6 mL of natural rubber latex with 3 mL of diclofenac solution (3 mg.mL^{-1}). These membranes were prepared by pouring the latex + diclofenac solution in a stainless steel plate with 5.00 ± 0.05 cm diameter and 234.40 ± 5.00 μm thick. Typically, the membranes were left for 2 days to fully polymerize before use. For the study of the diclofenac release, latex membranes were placed in 300 mL of an aqueous solution in triplicate, from which aliquots were collected during an interval ranging from 0 to 250 hours. The diclofenac released into the solution was monitored by measuring the UV–VIS spectra with a BEL ENGINEERING SF200 ADV spectrophotometer, as diclofenac has a maximum absorption at 276 nm.

The membranes were characterized by X-ray powder diffraction (XRD), using a Siemens D5005 X-ray diffractometer and a graphite crystal as monochromator to select Cu Kα1 radiation (1.5406 Å), in a step of 0.02° s^{-1}. The surface morphology of the NRL membrane was observed using a Scanning Electron Microscopy (SEM) model Zeiss® EVO 50 (20 KV) and a take off angle of 35°.

The FT-IR spectra of the pure diclofenac, Natural Rubber Latex (NRL) and NRL + diclofenac (3 mg.mL^{-1}) were obtained to prove the chemical integrity of the drug in the polymer. The samples were measured directly by Attenuated Total Reflection (ATR) method, which is an excellent method for obtaining infrared information for the powder sample surface. The membranes were characterized using a VERTEX 70 (Bruker, Germany) (4000-500 cm^{-1}) with a resolution of 4 cm^{-1}.

In Figure 2 shows the absorbance intensity as a function of diclofenac concentration in solution. This calibration curve is important because to make one relationship between absorbance and the diclofenac concentration. For this experiment several dciclofenac concentrations from 0.01 to 0.1 mg.mL^{-1} were made. After this, it was measurement your absorbance. Each drug concentration (point) were made in triplicate, where the estimated error was minor that 5%.

3. Results and Discussion

The goal of controlled-release delivery systems is to provide desirable delivery patterns so that predictable plasma drug levels can be achieved, which requires the characterization of the basic pharmacodynamic and pharmacokinetic properties of a drug/extract. For sodium diclofenac studied here, it has been found that it absorbs at 276 nm.

As can be seen in Figure 3, the absorbance intensity of diclofenac increase in function as time. We can observed that diclofenac is encapsulated in natural latex membranes, where the NRL membrane allows a gradual release of diclofenac from the aqueous solution. We observed that the release profiles for sodium diclofenac in a NRL matrix is similar from our previous work[8], but the saturation point is different and the inclination of bi-exponential function. In this work, the points to saturation at approximately 74 hours. Its release control can be due biomembrane hydrophobicity[21].

These results were also obtained by Giri et al.[22] which acrylic acid grafted guargum-nanosilica biomembrane provided excellent control over diclofenac releases, as well as by Pulat et al.[23] that showed that PU (hydrophobic) membranes had a slower release than hydrophilic ones. This may be due hydrophobic membranes do not lead to void volume between molecules, hampering the diffusion through membrane.

In this work, it was used the method proposed by Herculano et al.[24], that is, to mix the drug (diclofenac) with the polymer (latex) in a colloidal state, in order to create a membrane that works as a delivery system.

Upon analyzing the profiles, we concluded that the first, fast step of burst release corresponded to the diclofenac near

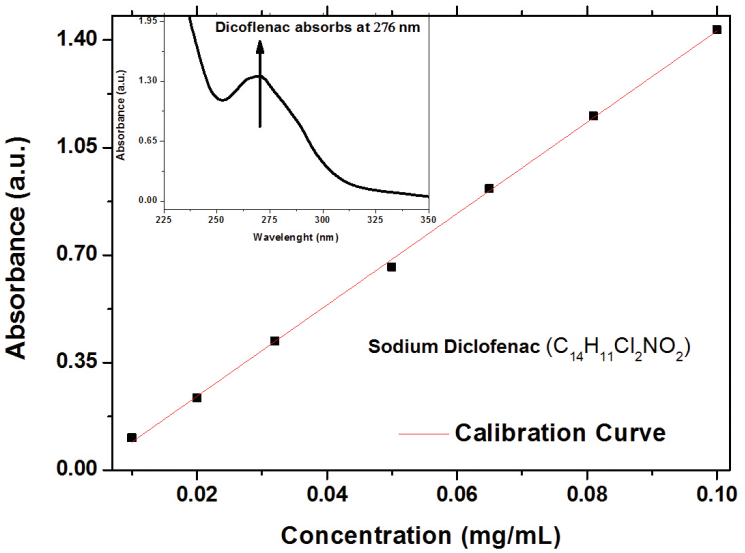


Figure 2. Absorbance instensity as a function of sodium diclofenac concentration in solution. Notice that the insert graph shows a typical spectrum of sodium diclofenac.

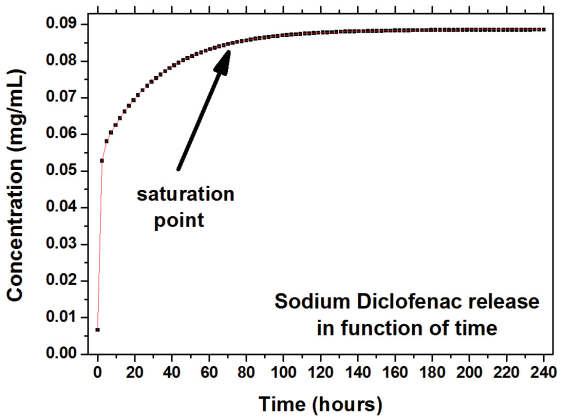


Figure 3. Sodium diclofenac release as a function of time for the NRL membrane. Notice that the diclofenac concentration reaches a plateau after approximately 74 hours. Each point refers to triplicate measurement.

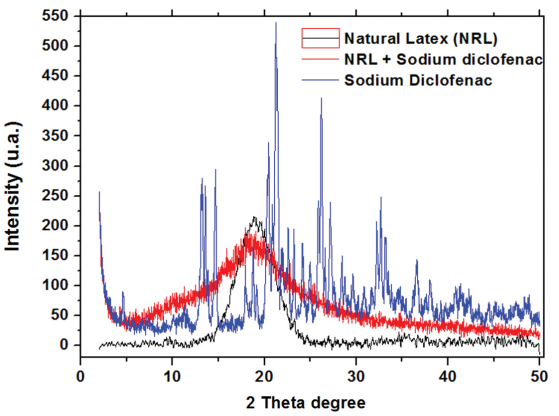


Figure 4. X-ray diffraction pattern of NRL (black line), sodium diclofenac powder (blue line), NRL membrane prepared with 3 mg.mL^{-1} of sodium diclofenac (red line).

or on the surface of the NRL membrane. Therefore, the slower release process would be associated with diclofenac diffusing slowly through the matrix. The experimental data in the Figure 3 were fitted using a bi-exponential function (A).$y(t)=y_0+A_1e^{-t/\tau1}+A_2e^{-t/\tau2}$, where, y(t) was the amount of sodium diclofenac in the NRL at a given time, t, y_0 is the initial content of diclofenac, A_1 and A_2 are constants, equal to –0.047 and –0.035, respectively, the characteristic times are τ_1 = 0.899 hours and τ_2 = 32.102 hours.

Upon integrating the curve until 74 h, the total amount of diclofenac released by the membrane in the 300 mL aqueous solution was 5.37 mg (59.62%).

The X-ray diffraction (XRD) pattern for the NRL membrane, sodium diclofenac powder (NaDic) and NRL membrane prepared with 3 mg.mL^{-1} of sodium diclofenac (NaDic-NRL) is shown in Figure 4, which indicates the amorphous nature of NRL, as expected, at 19° at 2θ[21]. In contrast, sodium diclofenac powder exhibits a XRD pattern of a crystalline material with no amorphous component, with peaks appearing at 14.70, 20.48, 25.96, 26.40 and 27.20° at 2θ values[25]. The absence of crystallinity in the NaDic-NRL membrane indicates that NaDic is amorphous or molecularly disperse within the microparticles[25,26].

Amorphous NaDic has also been found by Li et al.[27], Manjunatha et al.[28], Lopes et al.[29] and Maiti et al.[30] showed barely irritant to rat skin.

Although NaDic-NRL shows a broader XRD spectrum than the sharper halo (amorphous characteristic XRD spectrum) of pure NRL, FT-IR shows that there is no chemical interaction between NaDic and NRL, since there is no new absorption peaks.

The IR spectra of the sodium diclofenac, natural rubber latex (NRL) and NRL + diclofenac are portrayed in Figures 5, 6 and 7. The IR spectra of diclofenac sodium

(Figure 5) exhibited distinctive peaks at 3381.57 cm^{-1} due to NH stretching of the secondary amine, 1572.66 cm^{-1} owing to –C = O stretching of the carboxyl ion and at 745.35 cm^{-1} because of C-Cl stretching[27].

FT-IR spectra of natural rubber is presented in Figure 6. The cis-1,4-polyisoprene absorption band of strong amplitude corresponding to =CH out of plane

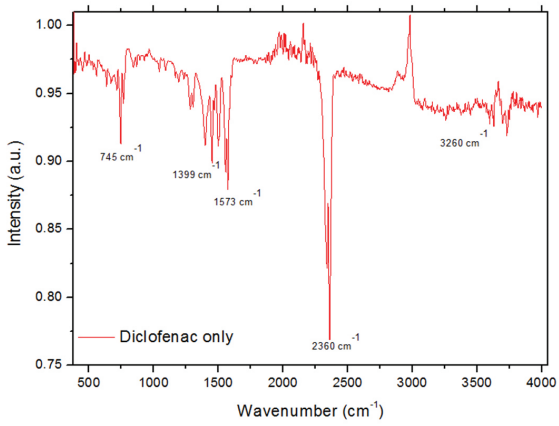


Figure 5. FT-IR spectra of sodium diclofenac in ATR method.

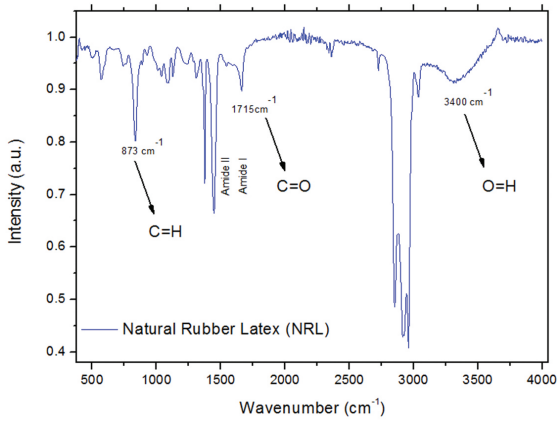


Figure 6. FTIR spectra of natural rubber membranes in ATR method.

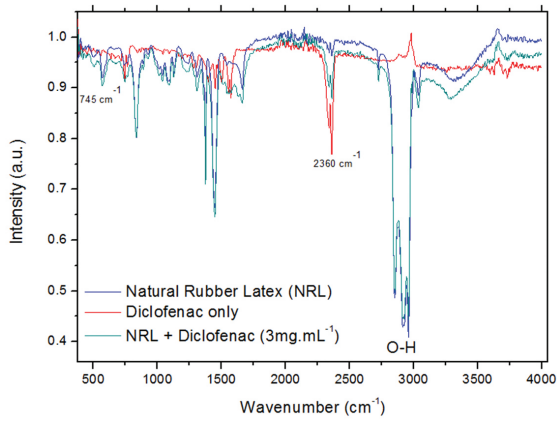


Figure 7. FTIR spectra after of incorporation of sodium diclofenaci in natural rubber membranes.

bending is observed at 873 cm^{-1}; the trans isomer has no absorption at this wavelength. A closer inspection of the infrared spectra reveals that it has absorbance bands at 1240 cm^{-1}, corresponding to O-P-O asymmetric stretching of phospholipids indicating the presence of associated phospholipids at the rubber chain.. The absorptions bands at 1375 cm^{-1} (CH_2 deformation), 1394 cm^{-1} and 1432 cm^{-1} and 1494 cm^{-1} are characteristics of CH_2 deformation. The absorption band at 1647 cm^{-1} correspond to C=C stretching in cis-1,4-polyisoprene. The CH_2 symmetric stretching vibrations are observed at the region 2852 cm^{-1}-2925 cm^{-1}. The CH_3 asymmetric stretching in FT-IR of NRL membranes is observed at 2961 cm^{-1}. These FT-IR correlations for NRL are consistent with the earlier works[24,31]. In addition, Figure 6 also shows a broad peak at approximately 3200-3500 cm^{-1}. This absorption band might be related to the presence of a hydroxyl group, which appears to be generated after the hydrolytic ring opening of epoxy group‘s formed during the casting of NRL membranes[24,32].

In the IR spectra of the polymer and drug (Figure 7) was not altered after immobilization in the latex membrane, indicating no chemical interaction between the drug and the polymer.

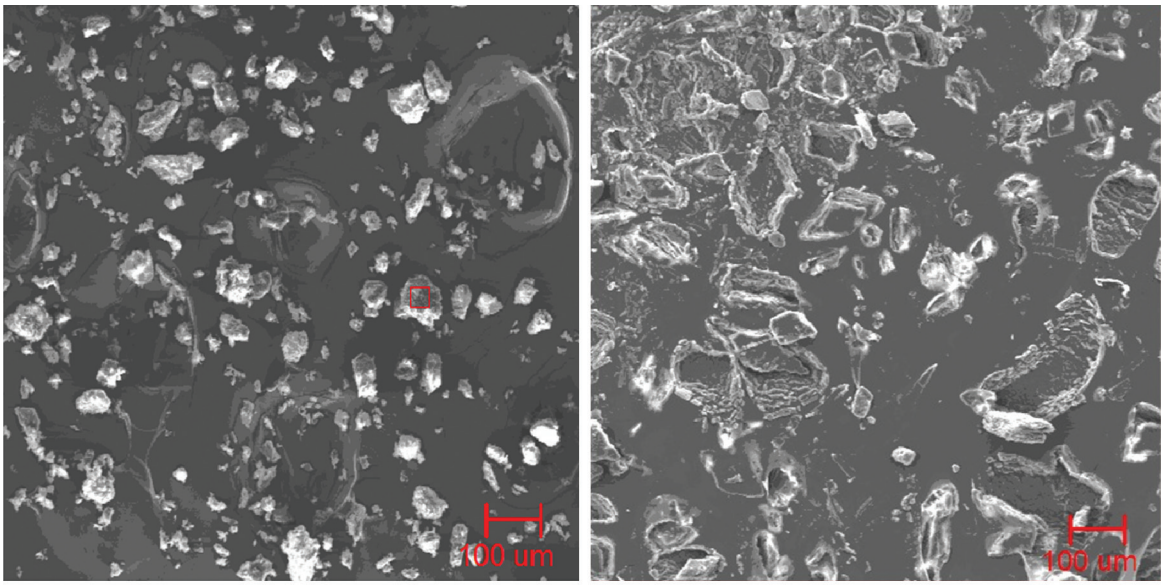
Figure 8a is an SEM-EDS image of the sodium diclofenac powder (NaDic) and Figure 8b is SEM-EDS of Natural rubber membrane + sodium diclofenac (NaDic-NRL). Notice that sodium diclofenac is aggregated in surface polymer reinforcing that burst release corresponded to the drug on the surface of the NRL membrane.

The controlled release of drug is of interest for medical applications, since the dose can be adjusted according to the necessity of the patient. Löbler et al.[33] developed a device based in polyhydroxyalkanoates (PHA) for implantation of a glaucoma drainage system. In this study, polyhydroxyalkanoates (PHA) based on hydroxybutyric acid were tested in terms of their potential suitability to manufacture mechanically stable tube components of drug delivery drainage systems and in terms of biocompatibility.

Several procedures are used to control the release of substances by polymers. For example Woo et al.[34] used a combination of 3 different biodegradable microspheres of poly(D,L,-lactide-co-glycolide (PLGA)), using different molecular weight and terminal endings of the polymeric chain (hydrophilic or hydrophobic) to determine the best delivery system of BMP. They conclude that the best bone healing results were achieved using high dose and slow delivery rate systems.

Herculano et al.[7,8,35] proposed a drug release system based on natural rubber latex (NRL) for the sustained and controlled delivery of metronidazole (MET), Bovine Serum Albumine (BSA) and *Stryphnodendron sp* extract. They concluded that the release time of MET, BSA and *Stryphnodendron sp* in *in vitro* tests were very promising for the kinetics of release.

Wang et al.[36] prepared uniform-sized chitosan microspheres by membrane emulsification technique. Uniform chitosan microspheres were further used as a carrier of protein drug (BSA). They observed that BSA loading efficiency was highest when pH value was 8.09, and it decreased with an increase of the crosslinking degree.



(a) (b)

Figure 8. SEM-EDS of spectra of: a) Sodium diclofenac powder; b) Natural rubber membrane + sodium diclofenac. Notice that the diclofenac is present on surface.

Some biomaterial have been developed to diclofenac delivery. Guargum (natural polymer) have showed good diclofenac delivery, it showed a fast release, 81% of the content in 20 hours; but the acrylic acid grafted guargum-nanosilica membrane showed a slower release due its hydrophobicity[22]. Biomembranes of polyethylene glycol 400 (PEG 400) with hydroxypropylmethylcellulose (HPMC) for ophthalmic uses with diclofenac-loaded particles released 50% in 12 hours[37].

The release time of sodium diclofenac in a NRL membrane *in vitro* was increased from the typical 1-2 h for oral tablets to ca. 74 h. Our results indicate that with very simple changes in preparation of NRL membrane, 59.62% of the initial diclofenac content inside NRL was released in 3 days, with a slow release rate.

4. Conclusion

It has been demonstrated that diclofenac can be encapsulated in NRL membranes, lying mostly on the membrane surface, as inferred from energy dispersive X-ray spectroscopy. FTIR indicate that NaDic did not interact chemically with the membrane. The XRD shows the absence of crystallinity in the NaDic-NRL membrane indicates that NaDic is amorphous or molecularly disperse within the microparticles.

Results indicate that with very simple latex preparation it is possible to control diclofenac release up to 3 days, or in other words with a slow release rate.

We have observed that 59.62% of the initial diclofenac content inside NRL was released in 74 hours. The SEM-EDS and the release behavior indicated that diclofenac remains close or on the surface of the membrane. The drug is not found in the inner portion of the membrane, thus making them promising materials for drug release in *in vivo* applications

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