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# Influence of phosphated cross-linked high amylose on *in vitro* release of different drugs

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ABSTRACT

The influence of structural characteristics of high amylose cross-linked at different degrees on the release of drugs with important molecular differences, namely sodium diclophenac (SD) and nicotinamide (NI), was assessed *in vitro* from non-compacted systems. The release profiles were related with classical kinetic mathematical models for better understanding of the release mechanism. An increase in polymer cross-linking degree resulted in longer release time for both drugs, although SD generally was released slower than NI. SD release from samples cross-linked at 2% of basis was driven mainly by Fickian diffusion, while from samples cross-linked at 4% of basis follows anomalous mechanism. Inversely, anomalous mechanism was responsible for NI release from 2% samples and Fickian diffusion from 4% samples. Results suggest that the performance of cross-linked high amylose as excipient for controlled drug release not only depends on cross-linking degree but also is highly influenced by structural characteristics of the drug.



## 1. Introduction

There has been a continuous interest of the pharmaceutical industry in the research and development of sustained or controlled drug release. Polymers are almost indispensable to prepare oral drug delivery systems and, among them, polysaccharides play an important role due to their biocompatibility and biodegradability. In 1991, high amylose cross-linked with epichloridrin was introduced as excipient, assuring a teophyline sustained release of about 20 h (Lenaerts, Dumoulin, & Mateescu, 1991).

In fact, different cross-linking degrees could be obtained by varying the epichloridrine to amylose ratios, but it was found that the maximal drug release time occurred with high amylose cross-linked at lower degrees (Dumoulin, Alex, Szabo, Cartilier, & Mateescu, 1998). This non-monotonous relation between release time and cross-linking degree is a particular property that differs high amylose from other polymers, for which, generally, the increase in cross-linking degree results in slower drug release (Dini, Alexandridou, & Kiparissides, 2003; Kurkuri & Aminabhavi, 2004; Vandelli, Rivasi, Guerra, & Forni, 2001).

Several cross-linking degrees of high amylose resulted from the process proposed by Cury, Klein, and Evangelista (2008), in which the temperature and the original amounts of polymer and sodium trimetaphosphate (STMP), a non-toxic cross-linker, were kept constant, but the contact time with sodium hydroxide (NaOH) and the base strength were varied. Thus, eight samples at 0.5, 1, 2 and 4 h reaction times and at base strengths of 2 and 4% were prepared and characterized by C and H elemental analysis, IR, SEM and solid state NMR, as well as their structures could be predicted (Cury et al., 2008).

Furthermore, these cross-linked polymers were used as excipient for the preparation of non-compacted solid systems (physical mixtures) for drug delivery purposes and the influence of the cross-linking degrees on the physical characteristics (particle size distribution, swelling degree and rheological properties) of these systems as well as on the *in vitro* release behavior of sodium diclophenac were evaluated (Cury, Castro, Klein, & Evangelista, 2009).

In this work, the sodium diclophenac and nicotinamide *in vitro* release from phosphated cross-linked high amylose non-compacted matrix were compared in order to evaluate the influence of drug properties on the release process. Besides, the explanation of the drug release mechanism from the polymeric matrix was attempted by fitting the experimental data to well known mathematical kinetics models, such as the Higuchi, first order, Hixson–Crowell, Peppas and Weibull. The best performing models were correlated to the mechanism of drug release from phosphated cross-linked high amylose.

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**Table 1**
Applied release models.

| Model | Equation[a] |
|---|---|
| Baker–Londsdale | $\frac{2}{3}\left[1-\left(1-\frac{F}{100}\right)^{\frac{2}{3}}\right]-\left(\frac{F}{100}\right)=k_{BL}t$ |
| First-order | $F=100(1-e^{k_1 t})$ |
| Higuchi | $F=k_H\sqrt{t}$ |
| Hixson–Crowell | $F=[1-(1-k_{HC}t)]^3$ |
| Peppas | $F=k_P t^n$ |

[a] $F$ = amount of drug released at time $t$; $k_{BL}$, $k_1$, $k_H$, $k_{HC}$ and $k_P$ = release rate constants for the different equations; $n$ = release exponent.

## 2. Materials and methods

### 2.1. Raw materials

Acetone and hydrochloric acid (Synth – Diadema – Brazil), purified water (Milli-Q Plus System Millipore), high amylose (HYLON VII, National Starch and Chemical, 70% amylose, 30% amylopectin – New Jersey – EUA), nicotinamide (Henrifarma – São Paulo – Brazil), sodium diclophenac (Henrifarma – São Paulo – Brazil), sodium hydroxide (Grupo Química – Rio de Janeiro – Brazil), trisodium trimetaphosphate (Sigma–Aldrich Co – St. Louis – USA) were used as purchased.

### 2.2. Preparation of cross-linked high amylose

High amylose was cross-linked as described earlier (Cury et al., 2008). Briefly, eight samples with different cross-linking degrees were obtained by reacting high amylose in aqueous medium alkalinized by NaOH (2% or 4%) at four different times (0.5, 1, 2 and 4 h). The amount of the cross-linker STMP was kept constant at 30% and the polymer pre-gelatinization step was skipped. The samples were labeled as 2% (2% 0.5 h, 2% 1 h, 2% 2 h and 2% 4 h) and 4% (4% 0.5 h, 4% 1 h, 4% 2 h and 4% 4 h).

### 2.3. In vitro drug release

Samples were prepared by manually mixing 50 mg of sodium diclophenac with 230 mg of each type of high amylose (cross-linked at different degrees). These physical mixtures were poured into n° 0 hard gelatin capsules, which were placed in a Hanson Dissolution Test Station SR8-Plus (Chastworth – USA). The tests were performed with three replicates, in 900 mL distilled water at 37 °C and stirring set at 50 rpm by using apparatus 1 (US Pharmacopeia XXVI, 2003). Drug release was followed by measuring the absorbance of the samples at 276 nm or 262 nm, for sodium diclophenac or nicotinamide, respectively.

### 2.4. Analysis of kinetic models

The various models describing drug release listed in Table 1 were fitted to the dissolution data using linear and non-linear regression analysis (Sigma Plot 10.0 software). All equations were fitted to the whole release curves, except for Peppas equation fitted only up to 60% of drug release. The fitting results are given in Tables 2 and 3.

## 3. Results and Discussion

### 3.1. In vitro drug release

Figs. 1 and 2 show drug release profiles in which can be observed that nicotinamide, generally, was released faster than sodium diclophenac. In respect of sodium diclophenac release profiles presented by samples 2% 0.5 h and 2% 1 h, no difference was observed in the total release time of the drug (Fig. 1a and b). However, in the first 5 h of the release process, the samples 2% 0.5 h allowed a slower drug release, which can be attributed to the lesser swelling capacity of these samples (Cury et al., 2009), that must result in fewer interactions among the hydrophilic matrix, water and drug (Colombo, Bettini, Santi, & Peppas, 2000), slowing down the release process. After 1 h, the 2% 0.5 h matrices must have absorbed enough water to hydrate the polymer matrix, resulting in a gel of good physical stability, which leads up to an almost constant drug release shown in Fig. 1a.

It is also interesting to observe that the release profiles of the 2% samples (Fig. 1) shows a decrease of drug release rate as the cross-linking reaction time increases. In this way, samples produced at shorter reaction times released ca. 80% of the drug between 7 and 9 h while the $t_{80\%}$ for 2% 4 h sample was reached only after 18 h.

This behavior indicates that the effects of swelling and gel formation are important factors for the drug release from samples synthesized up to 2% 2 h. For the other samples synthesized under stronger conditions, the size of the polymer meshes produced during the synthesis is perhaps the most important factor influencing a slower and controlled drug release, since the samples 2% 4 h were those that showed the lowest complex viscosity (Cury et al., 2009),

**Table 2**
Release rate coefficients for sodium diclophenac *in vitro* release data fitted with different release models (bold values indicate the best fits).

| Release models | | Samples | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2% 0.5 h | 2% 1 h | 2% 2 h | 2% 4 h | 4% 0.5 h | 4% 1 h | 4% 2 h | 4% 4 h |
| Baker–Londsdale | $k$ | 0.0209 | 0.0377 | 0.0233 | 0.0067 | 0.0154 | 0.0108 | 0.0109 | 0.0064 |
| | $r^2$ | 0.9624 | 0.9608 | 0.9439 | 0.7726 | 0.8000 | 0.8183 | 0.8233 | 0.7464 |
| Higuchi | $k$ | 27.6104 | 31.4099 | 24.0549 | 17.1029 | 26.3593 | 21.1281 | 21.2297 | 17.2412 |
| | $r^2$ | **0.9943** | 0.8389 | 0.7381 | 0.8389 | 0.8627 | 0.8862 | 0.8898 | 0.8008 |
| Peppas[a] | $k$ | 25.8656 | 49.4104 | 44.4484 | 0.9660 | 11.3651 | 6.7325 | 5.2647 | 4.0227 |
| | $r^2$ | 0.9735 | **1.0000** | **0.9734** | 0.9938 | **0.9914** | 0.9509 | 0.9527 | 0.9503 |
| | $n$ | 0.5141 | 0.2431 | 0.2076 | 1.6773 | 1.0028 | 0.9198 | 1.0965 | 1.0634 |
| First-order | $k$ | 0.2155 | 0.4640 | 0.2732 | 0.0738 | 0.1808 | 0.1115 | 0.1132 | 0.0790 |
| | $r^2$ | 0.9805 | 0.9781 | 0.8114 | 0.9175 | 0.9326 | 0.9336 | 0.9409 | 0.8893 |
| Weibull | $k$ | 118.5543 | 113.6770 | 109.0297 | 113.0913 | Not converge | 106.8484 | 100.5798 | 123.5478 |
| | $r^2$ | 0.9922 | 0.9886 | 0.9829 | **0.9983** | Not converge | **0.9972** | **0.9960** | **0.9919** |
| | $b$ | 0.8127 | 0.4491 | 0.4675 | 1.3082 | Not converge | 8.5017 | 1.5003 | 16544.0039 |
| Hixson–Crowell | $k$ | 0.0575 | 0.1091 | 0.0625 | 0.0211 | 0.0520 | 0.0312 | 0.0316 | 0.0232 |
| | $r^2$ | 0.9707 | 0.7722 | 0.7122 | 0.9485 | 0.9592 | 0.9632 | 0.9686 | 0.9184 |

[a] Release exponent evaluated for <60% of drug released.

**Table 3**
Release rate coefficients for nicotinamide *in vitro* release data fitted with different release models (bold values indicate the best fits).

| Release models | | Samples | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2% 0.5 h | 2% 1 h | 2% 2 h | 2% 4 h | 4% 0.5 h | 4% 1 h | 4% 2 h | 4% 4 h |
| Baker–Londsdale | $k$ | 0.0714 | 0.0548 | 0.0176 | 0.0195 | 0.0202 | 0.0263 | 0.0269 | 0.0227 |
| | $r^2$ | 0.9588 | 0.9373 | 0.7959 | 0.8892 | 0.9344 | 0.9712 | 0.8989 | 0.9673 |
| Higuchi | $k$ | 48.0966 | 44.4395 | 27.9155 | 28.0258 | 28.2793 | 31.5513 | 32.3741 | 28.6588 |
| | $r^2$ | 0.9777 | 0.9780 | 0.8598 | 0.9463 | 0.9834 | 0.9866 | 0.9572 | 0.9803 |
| Peppas[a] | $k$ | 49.9570 | 20.4770 | 8.1305 | 15.4948 | 25.9549 | 35.5783 | 26.9404 | 33.3576 |
| | $r^2$ | **1.0000** | **1.0000** | 0.9839 | **0.9974** | **0.9929** | **0.9979** | **0.9921** | **0.9748** |
| | $n$ | 0.9540 | 1.1231 | 1.3564 | 0.8583 | 0.5006 | 0.3556 | 0.4360 | 0.3643 |
| First-order | $k$ | 0.6996 | 0.5443 | 0.2012 | 0.2081 | 0.2122 | 0.2754 | 0.2765 | 0.2275 |
| | $r^2$ | 0.9955 | 0.9788 | 0.9321 | 0.9822 | 0.9635 | 0.9248 | 0.9556 | 0.9193 |
| Weibull | $k$ | 112.9541 | 5732.2589 | 96.4943 | 116.2778 | 170.4861 | 111.1304 | 236.4028 | 113.0636 |
| | $r^2$ | 0.9995 | 0.9917 | **0.9918** | 0.9972 | 0.9900 | 0.9686 | 0.9797 | 0.9658 |
| | $b$ | 0.7090 | 0.4197 | 2.1134 | 1.3413 | 0.7875 | 0.7081 | 4606.0994 | 0.6639 |
| Hixson–Crowell | $k$ | 0.1876 | 0.1444 | 0.0578 | 0.0575 | 0.0583 | 0.0741 | 0.0759 | 0.0591 |
| | $r^2$ | 0.9949 | 0.9762 | 0.9599 | 0.9955 | 0.9659 | 0.8952 | 0.9704 | 0.8962 |

[a] Release exponent evaluated for <60% of drug released.

a factor that had been pointed out earlier to force a shortening, not a lengthening, of drug release times (Ford, Rubistein, & Hogan, 1985; Sung et al., 1994; Espinoza, Hong, & Villafuerte, 2000; Roy & Rohera, 2002).

The lesser sustained release exhibited by 4% samples suggests that the formation of smaller sized meshes does not allow the adequate attachment of the drug and this factor must be predominant in controlling drug release under these stronger conditions (Fig. 2a–d). The shorter release times observed for nicotinamide can be attributed to the fact that its smaller molecule is not adequately attached in the polymeric meshes, favoring the faster drug release. The 2% 0.5 h and 2% 1 h samples showed the same total release time (5 h) while for 2% 2 h and 2% 4 h samples the release time were about 11 h. This behavior suggest that the samples with lower cross-linking degrees (0.5 and 1 h) have a reduced ability for the attachment of the drug molecules due to these samples present

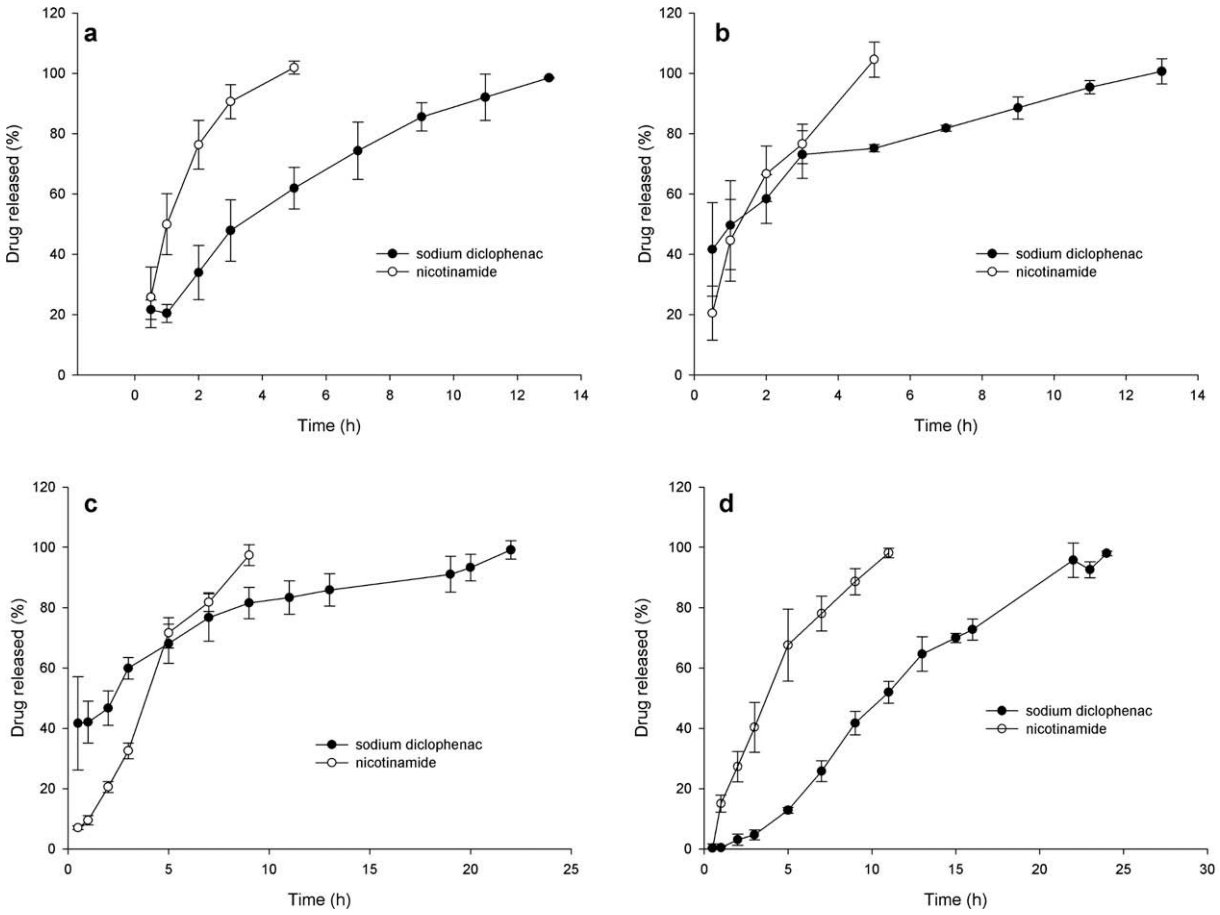


**Fig. 1.** *In vitro* drug release profiles from 2% samples: (a) 2% 0.5 h; (b) 2% 1 h; (c) 2% 2 h; (d) 2% 4 h.

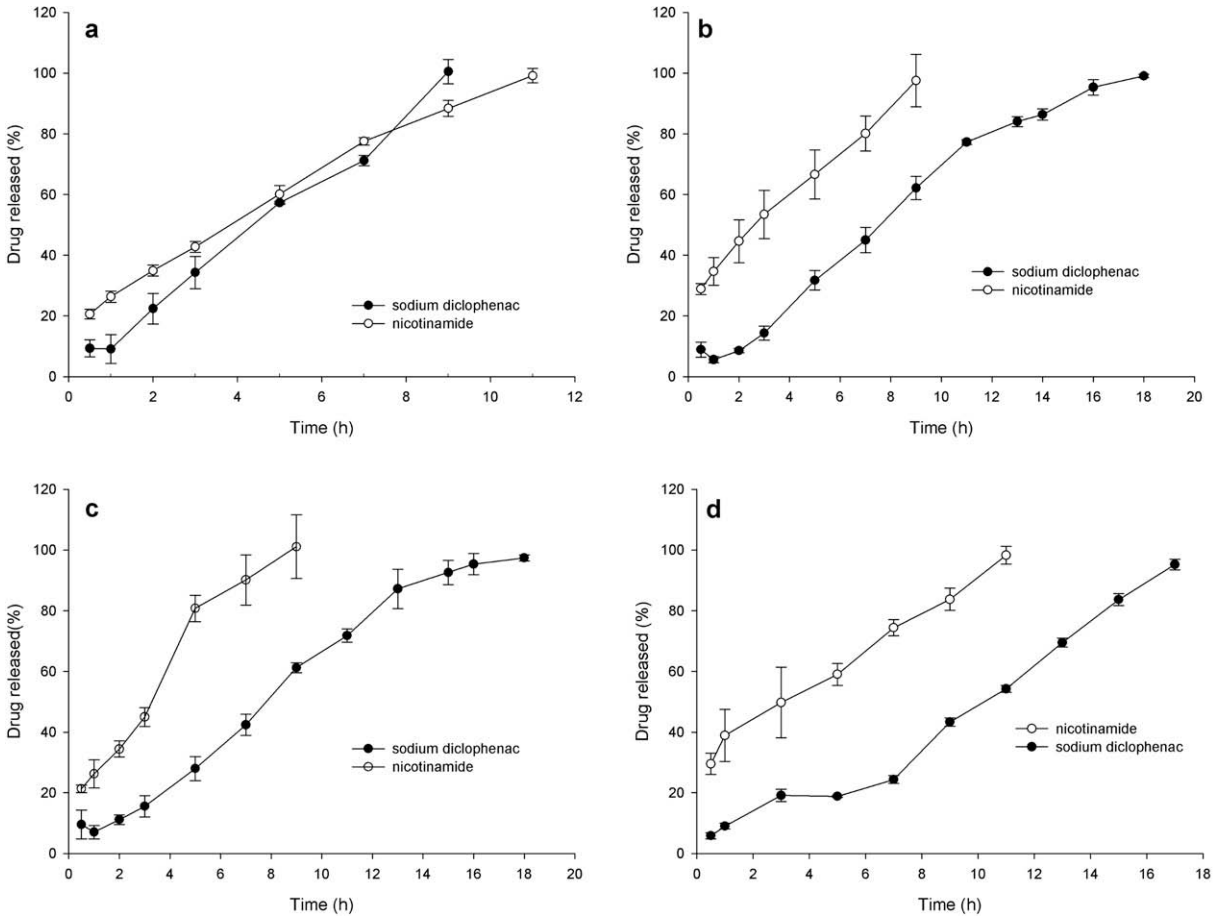


**Fig. 2.** *In vitro* drug release profiles from 4% samples: (a) 4% 0.5 h; (b) 4% 1 h; (c) 4% 2 h; (d) 4% 4 h.

meshes of bigger size than those samples with higher cross-linking degrees (2 and 4 h). This trend was previously observed in sodium diclophenac release results.

The samples at 4% base strength (Fig. 2) showed release times close to that presented by 2% 2 h and 2% 4 h samples (Fig. 1c and d), indicating a trend of increasing of release time as the cross-linking degree also increases and points out to the influence of the mesh size on drug imprisonment, as observed for sodium diclophenac.

These findings indicate that the prolongation of release time does not occur only as function of a physical factor, namely a mechanical imprisonment of molecules in polymer meshes, but it must be also influenced by the chemical nature of the drug. In this way, sodium diclophenac must behave as an anionic molecule in aqueous media, allowing the establishment of hydrogen bonds with the pendant hydroxyl groups of the polymer, which must be broken for drug removal by water from the matrix. On the other hand, nicotinamide must behave as a neutral molecule in aqueous media building weaker linkages, as van der Walls type, which are broken down more easily, facilitating the drug removal and favoring drug release.

### 3.2. Evaluation of drug release kinetic

The data of *in vitro* sodium diclophenac release fitted with different equations as well as the parameters calculated for these models are showed in Table 2. It can be observed that, in most cases, the better fits were found for Peppas or Weibull equations (higher $r^2$). Generally, in spherical matrices, if release exponent of Peppas equation, $n$, is 0.43, a Fickian diffusion (case-I) is applicable; when $0.43 < n < 0.85$, a non-Fickian (anomalous) transport takes place and if $n \geqslant 0.85$, a case-II transport (zero order) dominates the drug release mechanism (Cox, Khan, Munday, & Sujjaareevath, 1999; Green et al., 2009; Siepmann & Peppas, 2001; Yu, Zhang, Cheng, Zhuo, & Li, 2006). On the other hand, for Weibull equation, $b$ values $\leqslant 0.75$ indicate a release by Fickian diffusion, $0.75 < b < 1.0$ corresponds to Fickian diffusion associated to Case-II, and $b > 1.0$ a complex release mechanism (Papadopoulou, Kosmidis, Vlachou, & Macheras, 2006).

The data obtained for 2% 0.5 h sample correlated better with Higuchi equation, indicating that the release occurs by classical Fickian diffusion of the drug through polymeric matrix due to a concentration gradient (Costa & Sousa Lobo, 2003). The drug release from 2% 1 h correlated better with the Peppas model, while 2% 2 h and 2% 4 h samples follow the Weibull equation.

Although these samples correlated better with different mathematical models, the $n$ values of Peppas and $b$ values of Weibull equations, 0.24 and 0.46, respectively, presented by 2% 1 h and 2% 2 h samples, both indicate a drug release by Fickian diffusion of drug, suggesting that release occurs by diffusion through the swollen matrix. These findings are in agreement with the explanation of *in vitro* drug release, since these samples generally presented a great swelling ability and polymeric meshes with bigger sizes than other samples synthesized under stronger conditions (Cury et al., 2008). These factors must contribute for the diffusion of drug molecules to be the main mechanism involved in drug release since the beginning of the release process. For the 2% 4 h sample, the $b$ value (1.30) pointed to a complex mechanism of

release, in which the relaxation of chains and erosion of polymer may be occur simultaneously during drug release.

This result seems to be consistent, since this sample presented lower swelling ability than previous samples, as well as smaller meshes size (Cury et al., 2008). In this way, the swelling and, consequently, chains relaxation must be imperative for the release of drug entrapped in the polymer network.

The same trend can be observed for 4% samples series, for which, except for 4% 0.5 h, which fits better with Peppas equation with $n \approx 1$ (Case-II), all samples follow Weibull equation with the $b$ values > 1.0 indicating a complex mechanism of release, probably due to the similar structural characteristics of these samples with 4% 2 h sample, as was previously proposed by Cury et al. (2008).

The data of *in vitro* nicotinamide release from 2% samples series showed a better fit with Peppas equation (Table 3), except for the 2% 2 h sample. The higher $n$ values of 0.95 and 0.85 exhibited by 2% 0.5 h and 2% 4 h, respectively, pointed to an anomalous release mechanism, while the $n$ value of 1.12 for 2% 1 h sample indicates a super case-II mechanism.

Despite of 2% 2 h samples have shown better fitting with Weibull equation, the $b$ value (2.11) also corresponds to a complex mechanism. Considering that 2% samples present higher swelling ability and originate a more elastic gel than 4% samples (Cury et al., 2009), the relative small nicotinamide molecules can be retained in the resultant swollen elastic mass. Thus, the drug release must have been highly dependent on relaxation of polymer chains, which, in turn is dependent on swelling process.

This behavior can be supported by the initial nicotinamide release rate. This was generally lower than for sodium diclophenac as evidenced by percentual drug release after 0.5 h of dissolution test. By this time the percentage of drug release from 2% 0.5 h, 2% 1 h and 2% 2 h samples were 23, 41 and 21%, respectively, for sodium diclophenac, while for nicotinamide these numbers were 21, 25 and 7%. For the 4% samples, the $n$ values of Peppas equation (0.36–0.50) suggest that the nicotinamide release process is occurring mainly by diffusion, fact that seems to be consistent, since these samples present lower swelling ability than others and origin less elastic gels (Cury et al., 2008). Thus, the diffusion of the small molecules of nicotinamide can initially occur through pores and channels filled with water before the polymer significantly swells and latter throughout the swollen matrix.

## 4. Conclusions

The results presented in this work demonstrate that besides of polymer cross-linking degree, the structural characteristics of the drug, mainly its chemical nature and its molecule size can alter the drug release profiles as well as the release mechanism of drug incorporated into phosphated cross-linked high amylose.

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