INFLUENCE OF DISSOLUTION CONDITIONS ON THE DISSOLUTION RATE AND RELEASE MECHANISM OF KETOPROFEN FROM EXTENDED RELEASE HYDROPHILIC MATRIX SYSTEMS

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Abstract

Development of a hydrophilic matrix based extended release system involves the appropriate selection of polymer type, excipients and active ingredient with suitable physicochemical properties in order to obtain the desired release profile. Considering the multivariate nature of factors affecting the dissolution rate from hydrophilic matrix tablets, this study evaluates the effect of dissolution media, device type and stirring rate on the dissolution rate and release mechanism of ketoprofen from hydroxyethylcellulose and hydroxypropylmethylcellulose K4M matrices. The results show that dissolution media type influenced the release rate mostly by limiting solubility, but also by influencing polymer hydration time and solubility. The effect of stirring rate was dependent on device type, dissolution media and product type. Results also show that the selection of device type is an important step in the development of an appropriate dissolution test considering the sticking properties of hydrophilic matrices. Using multivariate data analysis, by developing O2PLS models, the systematic variation between dissolution profiles, kinetic parameters and dissolution conditions was integrated, highlighting joint and unique sources of variations. O2PLS results show that drug release mechanism is mostly influenced by media type, followed by stirring rate and at last by product type.

Rezumat

Dezvoltarea unui sistem de eliberare cu cedare prelungită de tip matriță hidrofilă implică selectarea adecvată a tipului de polimer, a excipienților și a substanței medicamentoase, cu proprietăți fizico-chimice potrivite pentru a obține profilul de eliberare dorit. Având în vedere natura multivariată a factorilor care afectează cedarea din comprimate de tip matriță hidrofilă, acest studiu evaluatează efectul mediului de dizolvare, tipul dispozitivului și vitezei de agitare asupra vitezii de dizolvare și mecanismului de eliberare a ketoprofenului din matrițe de hidroxietilceluloză și hidroxipropilmetilceluloză K4M. Rezultatele au evidențiat o influență a mediului de dizolvare, în principal prin limitarea solubilității, dar și prin influențarea timpului de hidratare a polimerului și a solubilității acestuia. Efectul vitezei de agitare a fost dependent de tipul dispozitivului, mediul de dizolvare și tipul de produs. De asemenea, s-a identificat importanța selectării tipului de dispozitiv în dezvoltarea unui test de dizolvare adecvat, având în vedere proprietățile de lipire ale matrițelor hidrofile. Folosind metode de analiză multivariată, prin dezvoltarea de modele O2PLS, a fost integrată variația sistematică între profilurile de dizolvare, parametrii cinetici și condițiile de dizolvare, identificând surse comune și unice de variații. Modelul O2PLS arată că mecanismul de eliberare a medicamentului este în mare parte influențat de tipul de mejun, urmat de viteză de agitare și în cele din urmă de tipul de produs.

Keywords: dissolution testing, tablets, extended release, release kinetics, multivariate data analysis
induced dependent on their solubility [6]. The drug release is highly dependent on the interaction between water, polymer, excipients and drug particles, the dissolution process being governed by a combination of diffusion and erosion [5]. Dissolution testing is an official pharmacopoeial quality testing method that was introduced in order to evaluate the in vitro profile and to predict in vivo performance of solid oral products [15].

The purpose of dissolution testing is found either in the development and optimization of pharmaceutical formulations when a characteristic release profile is wanted or in quality control when the consistency of the product quality is tested across different batches. Dependent on the two main area of applications, a dissolution method should have a discriminating power in quality control in order to identify changes in formulation, raw material attributes and manufacturing that might affect the product’s performance [3, 7]. However, for the estimation of in vivo performance, the dissolution test should be highly predictive of bioavailability, and not a highly discriminatory power [3]. A discriminatory dissolution test is developed considering bioavailability studies and clinical trials, and its power should rely on identification of formulation and process deviations that translate into a change in the in vivo profile [14].

In the case of conventional immediate release dosage forms, the dissolution test can prove the bioequivalence between two products, in specified conditions without the need of in vivo data. Although in the case of modified release systems the discriminatory power of a dissolution test should be considered on the basis of in vivo - in vitro correlations. Due to a large number of factors that affect the in vivo performance building a correlation with in vitro data becomes difficult, therefore in most of the cases specification limits are selected considering the dissolution test applied on the product used in the bioavailability studies [14]. The development of a bioequivalent product should be accompanied by comparative dissolution testing under various conditions of the generic and innovator product, considering the differences between the extended release systems [15].

Therefore, the objective of the present study is to evaluate the influence of dissolution testing parameters on the release profile and of two hydrophilic matrix extended release formulations with ketoprofen, considering the reference product Profenid® LP 200 mg (RP) and an experimental formulation (EF). The EF was developed to have similar release profile by means of design of experiments, in a previous preliminary study (data not shown). Considering the multivariate nature of factors that affect the dissolution from hydrophilic matrix systems, this study investigates the effect of dissolution media, the device type and stirring rate over the release profile of two different formulations. The RP is formulated using hydroxyethylcellulose (HEC) and an insoluble filler, calcium phosphate, whereas the EF has another cellulose derivate hydroxipropylmethylcellulose (HPMC) K4M, and a soluble filler, lactose. Even though the EF was developed using QbD principles to have similar dissolution profile in certain conditions, the two products could behave differently under various dissolution conditions. Multivariate data analysis is applied to evaluate the influence of dissolution conditions on the release mechanism by means of two-way orthogonal partial least squares (O2PLS), as a method that enables an overview of the data sets and identifies information overlaps between input variables represented by dissolution conditions and output variables, such as dissolution profiles and kinetic constants.

Materials and Methods

Materials

The materials used in this study were: ketoprofen (Sims, Italy), microcrystalline cellulose – Avicel PH 102 (JRS Pharma, Germany), lactose monohydrate – Tabletop 80 (Meggle, Germany), polyvinyl pyroliodine – Kollidon25 (BASF, Germany), lactose DC – FlowLac100 (Meggle, Germany), hydroxipropylmethylcellulose – K4M (Colorcon, UK), colloidal silicium dioxide – Aerosil200 (Rohm Pharma, Germany), magnesium stearate – Emprove (Merck, Germany), Profenid® LP 200 mg (Sanofi Aventis, France), sodium hydroxide (Chemical Company, Romania), monobasic potassium phosphate (Chemical Company, Romania), sodium acetate trihydrate (Chemical Company, Romania), acetic acid (Sigma-Aldrich, USA), hydrochloric acid (Chemical Company, Romania). All materials were of analytical grade.

EF preparation

The EF tablets were prepared by wet granulation method using a high shear granulator (Erweka AR400, Germany) by pulverizing a 10% aqueous PVP solution over a homogenous mixture consisted of ketoprofen, lactose monohydrate and microcrystalline cellulose. The wet granulate was passed through a 1.2 mm sieve, then dried at a temperature of 40°C for 24 hours followed by dry calibration using the same sieve. Granulate was efficiently mixed with the correspondent quantities of directly compressible lactose and HPMC K4M. The homogenous mixture was passed through a sieve before Aerosil and magnesium stearate was added. The final mixture was compressed using a Korsch EK-0 tableting machine equipped with 9 mm punches. The weight of each tablet was 430 mg. The EF is a non-coated product, developed by compressing a mixture of granules of the active ingredient with HPMC and a soluble diluent, whereas the RP has a core made of active ingredient, HEC and an insoluble diluent, coated with an enteric coating.

API solubility studies
The selection of dissolution media for the present study was based on the pH range from 1.2 to 7.5 for extended release oral formulations according to USP [11]. The solubility of the API was evaluated using at four different dissolution media as follows: 0.1 M hydrochloric acid (pH 1.2), acetate buffer (pH 5.4) containing 5.76 g/L NaC₂H₃O₂ + 3 H₂O and 3.85 mL/L CH₃COOH 2 N, 0.05 M phosphate buffer (pH 6.8) containing 0.89 g/L NaOH and 6.80 g/L KH₂PO₄; 0.05 M phosphate buffer (pH 7.4) containing 1.56 g/L NaOH and 6.80 g/L KH₂PO₄. An excess of ketoprofen was added into the dissolution vessel filled with 900 mL dissolution medium at 37ºC for a period of 24 hours under continuous stirring. Stability of the solutions was evaluated for a 24 h period in all dissolution media.

**In vitro dissolution studies**

The dissolution profiles were evaluated using a Pharma-Test WS 100 dissolution tester using various experimental setups. The dissolution studies were carried out using USP1 and USP2 type devices at two different stirring rates, 50 rpm and 100 rpm, in four different dissolution media. The volume of the dissolution media was 900 mL.

The sampling protocol included the outtake of 5ml dissolution medium at 1, 2, 3, 4, 6, 8, 10 and 24 hours, with each volume being replenished in order to ensure a constant volume during the experiment. The quantification of the released API was done on a UV-Vis Jasco V530 spectrophotometer (Jasco, Japan) at 259 nm using validated methods. Each formulation was tested in 6 replicates. Dissolution profiles were obtained by plotting the average percentage of drug released versus time.

The comparison of the two products in 0.1 M hydrochloric acid is not relevant to the two products performance, but instead to the two matrix systems. The RP is coated with cellulose acetate phthalate, therefore for a comparison of the two matrix systems.

**Comparison of dissolution profiles**

Similarity of dissolution profiles was evaluated using a model-independent approach, by calculating f2 (Eq. 1), the similarity factor. The formula takes into account the number of samples (n), the mean percentages of dissolved API by the reference and tested product (R, T) [10].

\[
f_2 = 50 \times \log \frac{100}{1 + \left( \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{1/2}}.
\]

**Kinetic release estimation**

Kinetic release parameters were calculated by fitting the dissolution profiles to mathematical equations that describe the drug release mechanism using Sigma-Plot 11 (Systat Software, USA). As mathematical models, the equations proposed by Peppas and Korsmeyer (Eq. 2), respectively by Peppas and Sahlin (Eq. 3) were applied. The SS residuals, the number of model parameters and the number of samples were used for the calculation of Akaiake Information Criterion (AIC).

\[
\frac{M_t}{M_{\infty}} = 1 - e^{-kt^n}, \quad \text{Eq. 2,}
\]

where, M/M∞ – fraction of drug released at time t; k – kinetic constant; n – diffusion constant.

\[
\frac{M_t}{M_{\infty}} = \frac{k_1 t^m}{M_t} + k_2 t^{2m}, \quad \text{Eq. 3,}
\]

where, M/M∞ – fraction of drug released at time t; k₁ – kinetic constant for diffusional release; k₂ – kinetic constant for relaxation release; m – Fickian diffusion exponent.

For the Fickian diffusion exponent a value of 0.45 was selected, based on data found in literature on hydrophilic matrix tablets with cylindrical geometry prepared using various cellulose derivates [5, 11].

**Multivariate data analysis**

SIMCA 14 (MKS Umetrics, Sweden) was used to develop O2PLS models which, unlike conventional partial least squares models, address the data integration issue. An O2PLS model consists of two data blocks and divides the information overlapping between the two datasets and the information that is unique to one specific dataset. The algorithm uses a flexible model structure incorporating three types of components, expressing the overlapping information and information what is unique to X and Y, respectively [9].

In the present case, the O2PLS models were applied to evaluate the covariance between the X data block represented by product type, device type, dissolution media pH, stirring rate, API solubility and the Y data block represented by kinetic release parameters and dissolution profiles. Product type and device type variables were not scaled, whereas all other variables were scaled to unit variance.

**Results and Discussion**

**API solubility studies**

Ketoprofen (2-(3-benzyolphenyl)propionic acid) is a BCS class 2 molecule with low solubility and high permeability [24]. Due to its short plasmatic half-life and poor aqueous solubility, is an appropriate candidate
for controlled release formulations. Patient compliance is improved by means of a low frequency of administration and due to the low incidence of side effect \[21, 27, 28\]. Being a weak acid (pKa = 4.45), its aqueous solubility increases with the increase of pH to the basic domain. The solubility values obtained were: 0.159 mg/mL in hydrochloric acid 0.1 M, 3.845 mg/mL in acetate buffer, 7.884 mg/mL in phosphate buffer (pH 6.8) and 11.658 mg/mL in phosphate buffer (pH 7.4).

**Influence of dissolution media**

A first objective of this study was to evaluate the effect of the dissolution media type on the release of the active ingredient from prolonged release tablets. In the case of RP, the release of the API in different media was in line with its solubility. The highest release rates were obtained in the case of pH 7.4, where the solubility is the highest, followed by the other media in function of their pH. The differences in the released percentage are more visible when the dissolution test is carried out using USP1 compared to USP2 (Figures 1a and 1b). The effect of the pH is more obvious in the case of USP1, affirmation sustained by the values of the similarity factor obtained by comparing dissolution profiles of the RP using the same device type at different values of pH (data not shown). The higher values of f2 in the case of USP2 show that the improved hydrodynamic conditions ensured by the device is able to reduce the differences, reducing the effect of the pH.

The dissolution profiles of the EF obtained in different media showed smaller differences, especially considering pH 7.4, 6.8 and 5.4 (Figures 1c and 1d). Despite the device type the lowest release rate is found in hydrochloric acid media.

**Influence of stirring rate (50 rpm/100 rpm)**

The experimental runs conducted on the two products in phosphate buffer pH 7.4 using USP1 at two stirring rates resulted in similar dissolution profiles (Figure 2a). Due to the high solubility at this pH, the differences in the hydrodynamics ensured by USP1 at the two stirring rates, doesn’t influence the release of the active ingredient.

In the case of USP2 the release of ketoprofen is lower especially in the case of the EF at a stirring rate 50 rpm (Figure 2b). This phenomenon was also observed in the case of the RP but at a smaller extent. Using two stirring rates with USP2, contributed to the generation of different hydrodynamic conditions, highlighting differences between RP and EF.

A similar effect of the stirring rate is observed when dissolution testing is done in phosphate buffer pH 6.8. Using USP1, the stirring rate has no influence over the percentage of API released at each time point, all profiles are similar according to the value of f2 (Table I). Using USP 2 at 50 rpm, the lowest release is found in the case of the EF (Figure 2d).

**Figure 1.**

Dissolution profiles of RP ((a) and (b)) and EF ((c) and (d)) at different values of pH and a stirring speed of 50 rpm with USP1 and USP2.
Release of ketoprofen under different hydrodynamic conditions at pH 7.4 ((a) and (b)) and pH 6.8 ((c) and (d)) using USP1 and USP2

Table I

<table>
<thead>
<tr>
<th>Product</th>
<th>Device</th>
<th>Stirring rate (rpm)</th>
<th>pH 7.4</th>
<th>pH 6.8</th>
<th>pH 5.4</th>
<th>pH 1.2</th>
<th>f2-comparison 50 - 100 rpm</th>
<th>f2-comparison USP1-USP2</th>
<th>f2-comparison RP-EF</th>
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<tr>
<td>RP</td>
<td>USP1</td>
<td>50 - 100</td>
<td>73.65</td>
<td>86.82</td>
<td>52.26</td>
<td>47.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>USP1</td>
<td></td>
<td>65.45</td>
<td>83.56</td>
<td>53.43</td>
<td>67.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>USP2</td>
<td>63.75</td>
<td>59.33</td>
<td>81.13</td>
<td>53.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>USP2</td>
<td>49.66</td>
<td>46.57</td>
<td>47.88</td>
<td></td>
<td>62.41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dissolution testing carried out using USP1 in media with pH of either 5.4 or 1.2 show that the release of ketoprofen is higher when using 100 rpm stirring rate (Figures 3a and 3c). The similarity factor values determined at these values of pH in case of USP1 are near the lower limit of the acceptance interval or below it, demonstrating the effect of hydrodynamic conditions.

The same results can be observed in the case of USP2 at pH 1.2, the higher the stirring speed, the faster the release of the active pharmaceutical ingredient. However the differences between the dissolution profiles in case of experimental runs carried out on RP in pH 5.4 with USP2 device at two different stirring rates show small differences, having an f2 value near 80. In the case of the EF the different hydrodynamics ensured by USP2 at pH 5.4 leads to dissimilar profiles.
Figure 3.
Release of ketoprofen under different hydrodynamic conditions at pH 5.4 ((a) and (b)) and 1.2 ((c) and (d)) using USP1 and USP2.

Figure 4.
Release of ketoprofen using USP1 and USP2 type devices in pH 7.4 at 100 rpm (a) and 50 rpm (b)
Influence of the device type

Due to the increased solubility of ketoprofen at pH 7.4 and a high stirring rate (100 rpm), the type of device used doesn’t influence the dissolution rate. Although at 50 rpm, in the case of the EF, when USP2 is used, the percentage of released API is lower due to the greater sticking of HPMC to the bottom of the dissolution vessel. The lowest value of f2 (53.40) was obtained by comparing the profiles of the EF using USP1 and USP2 at 50 rpm. Experimental runs carried in pH 6.8 media, using 100 rpm stirring rate lead to higher release in the case of USP2 for both products. By judging the f2 values at 100 rpm, the differences in dissolution profiles are higher compared to pH 7.4 (Table I). At 50 rpm in the case of the RP, the f2 value (98) is also high, which demonstrates that the type of device doesn’t influence the dissolution profile of this product when using a low stirring rate.

In the case of the EF the differences between the dissolution profiles are slightly higher when 100 rpm is used, although the profiles are similar. The type of device used doesn’t influence the release profile despite the type of the product or the stirring rate used at a pH value of 5.4 of the dissolution medium.

Considering the acetate buffer media, the use of 100 rpm stirring rate highlights the differences between the RP and EF, whereas at 50 rpm profiles tend to be more similar (Figures 5a and 5b).

The effect of the device type can be better observed in 0.1 N HCl (pH = 1.2) as dissolution medium, at both 50 rpm and 100 rpm. The highest differences in release rate are found in the case of the RP, having f2 values very close to 50. The comparison in hydrochloric acid media a strictly related to the matrix systems and not the products performance.

Similarity of RP and EF

The calculated f2 values under various dissolution setups are presented in Table I. In phosphate buffer pH 7.4 and pH 6.8 the highest differences could be observed using USP2 at 50 rpm due to the sticking tendency of the hydrophilic matrix based prolonged release tablets. These differences are smaller when a stirring rate of 100 rpm is used due to the higher hydrodynamic conditions that level out the differences between formulations.

In acetate buffer (pH 5.4), similarity factor values are closer to the lower edge of the interval. At pH 1.2 the f2 values reflect only the behaviour of the matrix systems and not of the product.

In all cases the f2 values regardless of the type of dissolution medium (excepting pH 1.2), the device type (USP1 and USP2) or the stirring speed (50 rpm, 100 rpm) the two pharmaceutical products are similar.
Dissolution kinetic evaluation

The kinetic release parameters along with the AIC for each experimental run is presented in Table II. Based on the AIC values both models fit with good approximation the dissolution data.

<table>
<thead>
<tr>
<th>Experimental run</th>
<th>Peppas and Sahlin</th>
<th>Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td>k1</td>
<td>k2</td>
<td>AIC</td>
</tr>
<tr>
<td>pH 7.4/100 rpm/USP1-RP</td>
<td>6.78</td>
<td>2.77</td>
</tr>
<tr>
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<td>4.90</td>
<td>3.17</td>
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<td>7.33</td>
<td>2.53</td>
</tr>
<tr>
<td>pH 7.4/100 rpm/USP2-EF</td>
<td>2.88</td>
<td>3.55</td>
</tr>
<tr>
<td>pH 7.4/50 rpm/USP1-RP</td>
<td>6.82</td>
<td>2.35</td>
</tr>
<tr>
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<td>2.96</td>
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<tr>
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<td>2.68</td>
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<td>3.81</td>
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<tr>
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<td>2.00E-08</td>
<td>2.16</td>
</tr>
</tbody>
</table>

Developing O2PLS models allowed a more comprehensive evaluation of dissolution testing parameters and product type influence over the kinetic release mechanism. An overview of the O2PLS model and loading column plots of the two predictive components are presented in Figure 6.

Effect of dissolution media

Drug release rate from extended release hydrophilic matrix systems can be modelled by diffusion and erosion. The two processes occur simultaneously, however diffusion controls the release rate of the dissolved drug, whereas erosion of the matrix controls the release of the poorly soluble drugs [12]. Therefore, the changes in drug’s solubility in function of the media’s pH, leads to a change in the significance of the involved processes that control the release rate.

In a different study conducted on hydrophilic matrix tablets with ketoprofen, an increase of dissolution rate occurred when the pH of the medium was increased. However not only the swelling property of the polymer, but also its hydrophobicity and tablet hardness had an important influence [22].

The presence of soluble drugs reduces the water required for polymer hydration, whereas poorly soluble molecules could affect polymer hydration by reducing the hydrogen bond network and reducing the amount of bound water [23]. Excipients included in the hydrophilic matrix can lead to different effects based on their solubility. A soluble excipient will increase the rate of water uptake due to an osmotic gradient, however not necessarily affecting the rate of polymer disentanglement. Insoluble excipients will produce lower osmotic pressure, reducing the solvent diffusion rate. The effect of insoluble excipients over polymer disentanglement is controversial, by influencing the integrity of gel it makes the matrix more erodible but also reduces the phenomenon by limiting the water uptake [25].
As the pH of the dissolution media decreases, erosion of the matrix becomes predominant over the diffusion. The erosion rate of the system is related to the molecular weight of the polymer, the composition of media and to the characteristics of the incorporated excipients and active ingredients [9]. Out of the media constituents, it has been demonstrated that phosphate ions can mitigate the hydration of HPMC by reducing its solubility, therefore the swelling front is growing towards the centre of the tablet at a slower rate, also reducing the release rate [13, 20]. This can be the reason behind the smaller differences seen in the case of the EF considering higher values of pH (7.4 and 6.8).

Dissolution rate from HEC matrices follows a non-Fickian behaviour, including drug diffusion, polymer swelling and erosion processes, that constantly modify the diffusion path and release of the active ingredient [21, 22].

Compared to HPMC, HEC is more polar, considering the nature of substituents and degree of substitution of the cellulosic backbone. HEC is more hydrophilic due to the shorter alkyl chain lengths that facilitate
the interaction with water molecules and chain disentanglement [5]. HPMC K4M has a slow self-diffusion coefficient that implies a low water mobility within the matrix, affecting the hydration rate of the polymer and the diffusion of the drug through the system [8]. This explains the use of a soluble filler in the EF, whereas in RP an insoluble diluent is used to avoid a rapid release considering the faster hydration and swelling of HEC.

The faster hydration of HEC matrices leads to the formation of a thicker gel layer compared to HPMC K4M, meaning that HEC chains relax quickly making the tablet more susceptible to erosion, ensuring a more rapid release of the active ingredient [4]. The hydration time of HEC is mainly influenced by pH and temperature. The highest hydration time at 35°C is found between a pH 4 - 5, and it drops as the pH increases or decreases, having significantly lower times at pH6.8 and pH 7.4 [2]. Besides the pH dependent solubility of the API, the pH dependency of the hydration in the case of the RP may exert an effect in differentiating the release profiles using different media. Hydration of the polymer is associated with an increase of the viscosity, followed by its dissolution. The time needed for complete dissolution is affected similarly by pH and temperature. Even though the hydration time below pH 5.4 is smaller the dissolution rate in hydrochloric acid is smaller, due to the considerably reduced solubility of ketoprofen. The effect of pH on the hydration rate of HEC can be observed on the dissolution profiles conducted on the reference product using USP1 that generates a less efficient flow dynamics of the media (Figure 1a). In this case the separation between the dissolution profiles starting from the first time points is the greatest. pH intervenes in two ways by influencing both the structure of the hydrating gel, and the solubility of ketoprofen.

Stirring rate

By varying the stirring rate the robustness of the two formulations can be evaluated. It is considered that a high influence of stirring rate makes the matrix system more susceptible to dose dumping in vivo situations due to the mechanical stresses in the gastrointestinal tract. Therefore, it is desirable that the prolonged release formulations to be less influenced by this parameter [10].

Dissolution testing conducted on EF in phosphate buffer pH 7.4 using USP2 lead to a reduction in release rate because of the tendency to stick to the bottom of the dissolution vessel. This way the surface of the tablet that is exposed to the dissolution medium is significantly smaller, limiting the release from the EF, especially at 50 rpm. Using USP2 at 100 rpm the EF has similar profile with RP, because of the improved hydrodynamic conditions ensured by the more efficient stirring and due to the high solubility of ketoprofen in this media. HEC also forms a gel barrier, but its viscosity is reduced compared to HPMC, considering its faster water uptake and polymer disentanglement.

Comparing the dissolution profiles of the EF using USP2 at the two stirring rates the similarity factor is below 50 (f2 = 49.66), therefore are not similar. To avoid these limitations caused by the sticking tendency the use of USP1 is recommended, although the tablet can stick to the bottom of the basket a higher surface of the tablet is exposed to the dissolution medium compared to the situation when USP2 is used [17]. Differences in the sticking tendencies of the two products can be explained considering the differences in the amount of hydrophilic polymer used in the formulations and due to the type of excipients. Although the amount of HEC included in RP is not known, it is possible that the overall viscosity of the gel layer is smaller compared to HPMC K4M. The EF is formulated using a soluble filler that during its dissolution could contribute to an increased adherence of the tablet, by increasing the contact area of the gel layer with the bottom of the dissolution vessel. In the case of RP, using an insoluble diluent the overall sticking surface area is smaller, because the excipient will not dissolve.

At pH 6.8 and 7.4, in most of the cases the influence of the hydrodynamics over the release of ketoprofen is not highlighted due to the high solubility at these values of pH, therefore having f2 value between 50 and 100. The major difference in the f2 value at the two phosphate buffers is found in the case of the EF evaluated using the USP2 at 50 and 100 rpm. At low stirring rates the release of ketoprofen is retarded more in the EF because of the stronger sticking, making the media hydrodynamics more critical for drug dissolution.

As the pH value of the dissolution medium decreases the solubility decreases, therefore the influence of the hydrodynamic conditions over the release profile could be highlighted.

Device type

Out of the several device types described in the USP, apparatus number 1 and 2 are most widely used for oral solid dosage forms [3, 7]. According to some authors USP1 is not recommended for dissolution testing of hydrophilic matrix based extended release products because the swelled matrix clogs the orifices of the basket. Although using a high stirring rate for USP1 allows a better contact compared to the paddle apparatus, due to a higher surface exposed to the media and better hydrodynamics [7]. Although it was expected that USP2 would lead to a higher release rate, this effect was not observed throughout all conditions due to the sticking of the hydrophilic matrix system. Only in hydrochloric acid 0.1 M the effect of device type was observed in the case of both stirring rates.
Generally, the viscosity of cellulose derivatives is affected in conditions with pH under 3 [2]. Due to the instability of HEC at pH 1.2, the hydration capacity of the polymer may be affected and the pharmaceutical form doesn’t stick entirely to the bottom of the dissolution vessel, having a higher surface exposed for drug release. Therefore the different hydrodynamic conditions ensured by the two devices used become obvious at both stirring rates, especially using 50 rpm, when f2 value is under 50.

**Dissolution kinetics**

Several mathematical models have been proposed to gain a better insight into the drug release mechanisms. Korsmeyer and Peppas developed a mathematical model for kinetic analysis of dissolution data controlled by various mechanisms as follows: Fickian diffusion (n = 0.5), non-Fickian or anomalous transport (0.5 > n < 1) and swelling controlled release (n = 1), dependent on the value of the diffusion constant [18]. In the case of an anomalous transport, both diffusion and erosion contribute to the release mechanism of the active ingredient.

Peppas and Sahlin developed an empirical model that takes account of the diffusion and polymer relaxation processes that allows the determination of each process’ contribution and relevance to the overall drug release [5]. The dissolution testing conditions, API solubility, kinetic release parameters and the dissolution profiles were included in the multivariate data analysis. The objective of O2PLS stands in the integration of the data from X-Y blocks, by grouping the systematic variability into predictive and orthogonal components in each data set. The predictive components represent the joint variation of the two data sets, whereas the orthogonal components describe unique variability [9]. The developed O2PLS with two predictive components explained 95.6% of Y data block variance with 63.7% of variance from the X data set (Figure 6a).

The first predictive component describes 77.6% of dissolution profile and mechanism variability through 41.9% of X data variance, representing the major component. From the loading plot of the first predictive component it can be concluded that de pH value of the dissolution media and the solubility of the API are the two major factors that influence the kinetic release parameters and consequently the involved mechanism that describes the release of the drug (Figure 6b). An increase in the pH of the dissolution media has a positive effect over the kinetic constant for diffusional release (k1) and also reduces the difference between the kinetic constants (k2-k1), increasing the importance of diffusion. This affirmation is confirmed by the inverse correlation with the diffusion constant (n).

In a study conducted by Baumgartner et al. it was concluded that in the case of HPMC K4M matrices the kinetic constant for diffusional release is much larger compared to the relaxational kinetic constant, while in the case of HEC based matrices the two constants presented similar values. The hydrophilic matrices contained water soluble drug molecules [5]. In the present study the k1 and k2 kinetic constants were determined for HEC and HPMC K4M based tablets in different media, that influenced the solubility of the drug. In case of RP, the diffusional kinetic constant is higher in the case when phosphate buffer with pH 7.4 was used, meaning that ketoprofen is mainly released by diffusion due to its increased solubility in this media. In the case of phosphate buffer with pH 6.8 the two constants have more similar values, showing that the drop of solubility reduces the importance of diffusion, offering similar significance to the two mechanisms. In acetate buffer the kinetic constant for diffusional release from the HEC matrix loses its significance having a close to zero value, making the matrix erosion the main mechanism for drug release. This affirmation is also available in the case of hydrochloric acid 0.1 M media.

Understanding the effect of dissolution media on release kinetics and the mathematical description of dissolution process is of main importance for the process of selection of appropriate dissolution conditions and for efficient product development [1, 19].

In the case of EF, the kinetic constant for diffusional release has higher values compared to the constant for erosional release only when dissolution testing was conducted in phosphate buffer pH 7.4 with USP1 despite of the stirring rate. Using USP2, the sticking of the tablet to the bottom of the dissolution vessel reduced the surface area for the diffusion process, therefore making the polymer relaxation more important for drug release. However, at pH 7.4, k1 has significantly higher values compared to the other media used. At lower values of pH the decreased solubility and due to the sticking of the tablet the importance of diffusion is reduced, and drug release will be controlled by erosion.

The second predictive component has a lower importance compared to the first component, but still describes a moderate value of 18% variation of the dissolution profiles and release mechanism using 21.9% variation of dissolution parameter variance. The second component’s loading shows a moderate influence of the product type over the release mechanism, considering k1 and k2 kinetic parameters (Figure 6c).

The drug release mechanism in the case of the EF is associated with higher significance of the kinetic constant for erosional release, while in the case of the RP a smaller importance of this mechanism is found across all experimental runs. The stirring rate has a higher influence compared to the product type, and directly influences the value of erosional kinetic constant and the percentage of the API released at the last time points. A higher stirring rate increases the erosion of the matrix through improved hydrodynamic conditions that fastens the polymer chain relaxation phenomenon.
From the loadings of the two predictive components, the pH and solubility of the API influenced at a greater extent the release of ketoprofen in the first 6 hours and its decreasing gradually at higher time points. The product type and stirring rate apparently is not influencing the release in the first 8 hours and then it has a gradually increasing significance over the release at 10 and 24 hour time points.

Other effects of dissolution parameters over the dissolution profiles were not observed using O2PLS methodology, because they manifested an influence only under certain conditions, meaning that O2PLS-Class analysis should’ve been applied to observe their effect. However, the development of O2PLS models within a certain class for example at a specific pH and stirring rate or type of product, includes the use of a reduced number of dissolution profiles, therefore not depending on the means of multivariate analysis, making the use of profile comparison methods more suitable.

Conclusions
This study evaluates the effect of dissolution conditions on the dissolution rate and release mechanism of ketoprofen from two different hydrophilic matrix systems. It was demonstrated that the type of dissolution media mainly influenced the release rate by limiting the solubility of the active ingredient, and by a smaller extent the behaviour of the polymers. The stirring rate had an influence over the release rate, but the extent of its effect was dependent of the device type, dissolution media and the type of product tested. At higher levels of pH (7.4 and 6.58), the effect of stirring rate was highlighted in the case of both products when USP2 was used. However the differences in the case of EF were slightly higher, due to the higher sticking of the product to the bottom of the dissolution vessel. At lower levels of pH (5.4 and 1.2) the effect of stirring rate was demonstrated despite the type of product, due to the lower solubility of ketoprofen.

Prolonged release products based on cellulose derivates directly influence the choice of the type of device that should be used when conducting dissolution testing, due to their tendency to stick to the bottom of the dissolution vessel.

By means of O2PLS models the influence of dissolution conditions over the kinetic release mechanism were highlighted. Out of all factors the type of dissolution media had the major effect over the release mechanism, by influencing the significance of diffusion and erosion processes. The next factor, the stirring rate increased the kinetic constant for erosional release by increasing the polymer relaxation phenomenon. The type of product used had a moderate influence over the release mechanism, in the case of the EF the significance of erosion being higher throughout all dissolution tests compared to the RP.

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Conflict of interest
The authors declare no conflict of interest.

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