RESEARCH ARTICLE

Discriminatory in vitro dissolution tests of oral dosage forms containing poorly soluble drugs for a Quality by Design approach

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Abstract

The challenge of oral formulations, containing drugs that show pH-dependent solubility, is to increase the dissolution rate in different media that simulate the gastrointestinal conditions, to guarantee their availability for absorption. In this work, some dosage forms containing poorly soluble drugs (diclofenac sodium, ketoprofen and meloxicam) are evaluated in different media: pH 1.0 (simulating fasted state), pH 4.5 buffer (simulating fed state), deionised water and phosphate buffer pH 6.8 or pH 7.5. These last buffers are required by the U.S. Pharmacopoeia monographs. The results obtained in sink and non-sink conditions could show possible critical quality attributes of the drugs and these properties are highly significant for a Quality by Design (QbD) approach. Completely different performances were obtained in the four dissolution media by the products considered. This approach could be useful for the predictive analytics, for the critical risk assessment and control during production, for the design and the development of new drugs in QbD approach.

Keywords: Quality by Design (QbD), Dissolution rate, solid dosage form(s), Solubility, US Pharmacopoeia (USP).

1. Introduction

Quality by Design (QbD) is defined in the International Conference on Harmonization (ICH) Q8 guideline as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[1-2] The quality of pharmaceutical products is evaluated during the lifecycle of the drug allowing the investigation of critical process parameters, which have an impact on critical quality attributes. The entire pharmaceutical product development strategy is based upon the Target Product Quality Profile (TPQP). This parameter determines the design and extent of development. TPQP is the performance based quality attribute that a product should possess in order to meet target product profile.[3-4]

The solubility, the dissolution rate and the biopharmaceutical properties of the drugs are decisive for choosing the excipients in formulation phase, the different dosage forms in development processes and for further studies of the respective products.[5] In vitro dissolution data can be helpful in the evaluation and interpretation of possible risks,[6] especially in the case of immediate release and modified release dosage forms on the food effects that could influence gastrointestinal conditions.[7] A satisfactory in vitro database allows interpreting the pharmacokinetic properties, to improve the design studies and to characterize the pharmaceutical products.[8-9] The in vitro models should pay attention to pH, ionic strength and agitation rate to simulate physiological gastrointestinal conditions.[10-11] In vitro tests should be reproducible, reliable and they are valuable tools to evaluate the behavior of the pharmaceutical products in different conditions simulating gastrointestinal tract. The performances of the product and the different stages of the development process are basic features of the application of Quality by Design approach.[12-13]

The drug should dissolve in the gastrointestinal fluids before it can be absorbed and reach the systemic circulation. Traditionally, the formulations had to satisfy the quality control tests outlined in product specifications. In Quality by Testing, the finished pharmaceutical products are evaluated in sink conditions to test the release of the entire dose and the intra batch reproducibility. If they do not meet the acceptance criteria for approved, are discarded. The products are discarded until the root causes of failure are understood and addressed or FDA approves supplements to revise the acceptance criteria to pass the previously failed batches.[14]

Continuous controls in different phases of the development of drugs could ensure the "real time" quality; understanding the failures allows to improve "step by step" the quality of the obtained products in each stage.[15] Non-sink conditions could let know the critical attributes of the drugs and generally minimize the impact on the finished pharmaceutical product.[16-17-18] The dosage forms should be evaluated in conditions simulating the gastro-intestinal tract since the understanding of the in vitro behavior of the drugs reduces the times of the development, increases the robustness of the process, improves the performance of the pharmaceuti-

cal products and could reduce the clinical trials.[19-20]

The actives chosen for this evaluation are Non-Steroidal Anti-Inflammatory Drug (NSAID) that show pH-dependent solubility, as showed in literature (Table 1): ketoprofen (pKa=4.45), diclofenac sodium (pKa=4.15) and meloxicam (pKa=4.08).

Table 1. Solubility (mg/ml) of diclofenac sodium, ketoprofen and meloxicam in hydrochloric solution pH 1.0/1.2, pH 4.5/5.0 buffer, pH 6.8/7.0 buffer and in water.

	Solubility in different media (mg/ml)			
Drugs	pH 1.0[(25)]/1.2[(21, 23)]	pH 4.5[(21, 23)]/5.0[(25)]	pH 6.8[(21, 23)]/7.0[(25)]	water
Diclofenac Sodium	$1.2 \cdot 10^{-3}$ [(21)]*	$3.6 \cdot 10^{-3}$ [(21)]*	$6.7 \cdot 10^{-1}$ [(21)]*	1.78 [(22)]*
Ketoprofen	$1.3 \cdot 10^{-1}$ [(23)]**	$4.9 \cdot 10^{-1}$ [(23)]**	40.76 [(23)]**	$1.0 \cdot 10^{-2}$ [(24)]*
Meloxicam	$8.6 \cdot 10^{-3}$ [(25)]*	$2.13 \cdot 10^{-3}$ [(25)]*	26.6 [(25)]*	$4.4 \cdot 10^{-3}$ [(26)]*

*solubility values at 25 °C; **solubility values at 37 °C.

These drugs are available in different oral dosage forms: Immediate Release (IR), Extended Release (ER) and Delayed Release (DR). The low solubility of these actives in different media could influence their absorption through the Gastro-Intestinal (GI) tract, while a proper formulation could limit the critical attributes of the active substance. The administration of these anti-inflammatory dosage forms is recommended during or after the meals (as specified in the package leaflet), for this reason, we evaluate them also in a medium that simulates the fed state which pH is within the values of 3.0 and 6.8 (pH 4.5 is used as reference).

In this research IR, ER, and DR dosage forms (both branded and generic) of the three drugs are evaluated, all products are commercially available. The aim of the present paper is to test these pharmaceutical products, in different media: pH 1.0, to simulate fasted state, pH 4.5 buffer, to simulate fed state, deionised water and pH 6.8 or pH 7.5 buffer (as reported in the Pharmacopoeia monography) to evaluate the possible critical issues of the formulations.

The USP Official Monographs of these actives/dosage forms reported the specifications of the in vitro dissolution tests in sink conditions, to actually test the release of the entire drug dose and to verify the results reproducibility as for a final quality control protocol. The dissolution profiles obtained in sink conditions will be compared to those obtained in non-sink conditions (pH 1.0, pH 4.5 and water) for a more realistic comprehension of the drugs/dosage forms performances in more critical conditions that may simulate the in vivo environment.

2. Materials and methods

2.1. Materials

Diclofenac sodium was kindly donated by Dipharma Francis (Milan, Italy), Ketoprofen by Farmalabor (Milan, Italy) and Meloxicam by AMSA S.p.A. (Milano, Italy).

The dosage forms are bought in a pharmacy: Dicloreum® 50 mg (ALFA WASSERMAN, Alanno, Italy); Voltaren® 50 mg (Novartis Farma S.p.A., Origgio, Italy); Diclofenac EG 50 mg (EG S.p.A., Milano, Italy); Diclofenac Hexal 50 mg (Sandoz S.p.A., Origgio, Italy); Diclofenac Angenerico 50 mg (Angenerico S.p.A, Roma, Italy); Ibifen 50 mg capsules (Istituto Biochimico Italiano Giovanni Lorenzini S.p.A., Aprilia, Italy); Orudis® 50 mg and 200 mg capsules (Sanofi S.p.A., Milano, Italy); Ketoprofene EG 50 mg and 200 mg capsules (EG S.p.A., Milano, Italy); Ketoprofene DOC 200 mg capsules (DOC Generici S.r.l., Milano, Italy); Mobic® 15 mg (Boehringer Pharma GmbH, Ingelheim am Rhein, Germany); Meloxicam Mylan Generics 15 mg (Mylan S.p.A., Milano, Italy).

Potassium dihydrogen phosphate are supplied by AppliCHEM PanReac GmbH, Germany; sodium hydroxide by Carlo Erba Reagents, Italy and hydrochloric acid by Sigma Aldrich, USA).

2.2. Methods

The dissolution rate of the pure actives and the release rate from the different products are evaluated in the in vitro dissolution tests in different media within a value range from 1.0 to 6.8 pH at 37 °C. Furthermore, all formulations are tested in in vitro dissolution tests reported by the USP official monographs, in which the acceptance criteria of the dissolved drug are reported too (USP40-NF35) In all cases, the USP Apparatus 2 paddle (Erweka DT-D6, Dusseldorf, Germany) is used. The dissolution media are prepared according to the section "Reagents, Solutions/Buffer solutions".[27]

According to the USP monograph "Diclofenac Sodium Delayed Release Tablets",[28] the dosage units are coated with a polymeric film that should not dissolve in an acid environment. In this way the drug is not released in the stomach, where could cause side effects. Only when the dosage form reaches the small intestine, where the pH is higher, the coating can be dissolved and the drug liberated. For this reason, a pH-change method is prescribed: the tablets of diclofenac sodium are left inside the vessel containing in 900 ml of pH 1.0 solution, with paddle rotation speed of 50 rpm, for 2hrs and then the tablets are transferred into another vessel containing 900 ml of pH 6.8 buffer, maintained at 37 °C. The acceptance criteria reported by the monograph are: in the acid stage the percentage of drug dissolved should not exceeds 10 % of the dose, while after the pH change (pH= 6.8) the amount of drug dissolved should be not less than 75% in 45 mins. To simulate an administration in fed conditions, we modified the first phase as follows: the tablets are initially left in 900 ml of pH 4.5 buffer for 4 hrs and then the pH is adjusted to 6.8.

The IR formulations containing ketoprofen and meloxicam are tested in pH 1.0 hydrochloric solution (to simulate fasted state), in pH 4.5 buffer (to simulate fed state), in deionised water and in pH 7.5 buffer at 37°C. According to the USP monographs, the IR ketoprofen capsules should release not less than 80 % of the dose in 30 mins (in 1000 ml of pH 7.5 buffer at 50 rpm)[29] and the IR meloxicam tablets not less than 70 % of the dose in 30 mins (in 900 ml of the same medium at 75 rpm).[30]

The extended release (ER) products containing ketoprofen are evaluated in 1000 ml of pH 6.8 buffer, apparatus II, 50 rpm, according to USP "Ketoprofen Extended Release Capsules",[29] and the acceptance criteria reported are: the percentage of dissolved drug should be between 10 - 25% of the dose in 1h; 55 - 80% in 4 hrs and not less than 80% of the dose in 8 hrs.[29] The same products were tested also in two different pH-change methods. In both methods the apparatus and the rpm are the same reported by the USP monograph, but the media are changed. In the first pH-changes method, the capsules are left for 2 hours in 750 ml of hydrochloric solution, pH 1.0, for 2hrs (to simulate an administration in fasted state) and then 200 ml of Na_3PO_4 0,2M are added into the vessel to reach pH of 6.8. In the second pH-change method, the first phase and time are modified to simulate an administration in fed conditions. In fact, the products are tested in 950 ml of pH 4.5 buffer for 4hrs and then the pH is adjusted to 6.8.

Six replicates are made for each tests. The concentrations of the dissolved drug are determined by UV absorbance, on filtered portion of the dissolution media. The data are processed through a PC software (Lambda 25 UV Winlab V6 software) connected to the spectrophotometer (Perkin-Elmer, Monza, Italy) to obtain the dissolution profiles.

The pH was monitored, to evaluate possible variation, during all the dissolution tests.

3. Results

3.1. pH variation during the dissolution test

The drugs considered show strong pH-dependent solubility, but, at the same time, the presence of the free acid groups of these molecules would shift the pH of dissolution media especially in deionised water or when the buffering capacity of the media is low. However, in the different buffers tested and in the pH 1.0 solutions, the pH values of the media are constant during all the dissolution tests (data not reported). The salified diclofenac does not influence the pH of water (Fig.1), nor does the 15 mg dose of meloxicam, probably due to the low amount, while ketoprofen shows a decrease of the pH value of water from 6.8 ± 0.13 to 4.8 ± 0.06 in about 120 mins. The same decrease is detected during the tests of the IR products containing ketoprofen in water (see ketoprofen paragraph). Thus, the dissolution rate and the maximum amount of drug dissolved will be clearly dependent on the pH of the medium, and its ability to buffer the NSAID molecules.

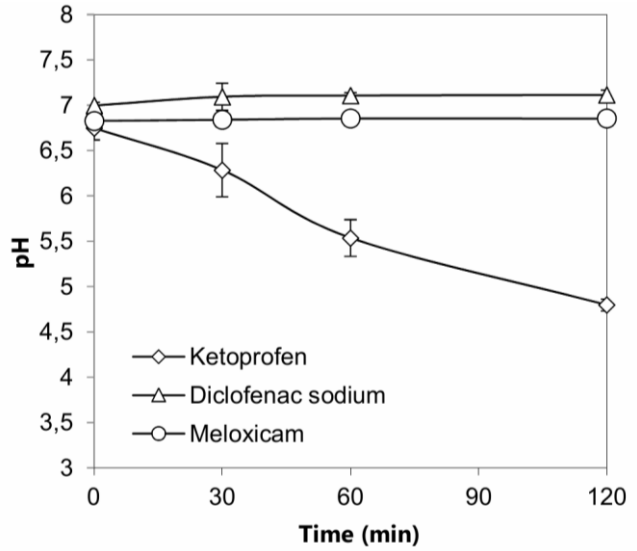

Figure 1. pH variation during the dissolution test of ketoprofen (50 mg), diclofenac sodium (50 mg) and meloxicam (15 mg) in deionised water at 37°C.

3.2. Diclofenac Sodium

Only a very small percentage of the 50 mg dose of pure diclofenac sodium dissolves in 4 hrs of dissolution test at pH 1.0. In phosphate buffer pH 4.5, initially the drug dissolves, but then most of the active precipitates. The re-precipitation of the drugs could be associated to supersaturation of dissolution medium and this transition phase is common for the poorly soluble drugs in non-sink conditions.[31-32] Whereas, 50 mg of pure diclofenac dissolve in few minutes in phosphate buffer pH 6.8 and in water (Fig. 2). The obtained results confirm that the diclofenac sodium solubility strongly depends on the solution pH.

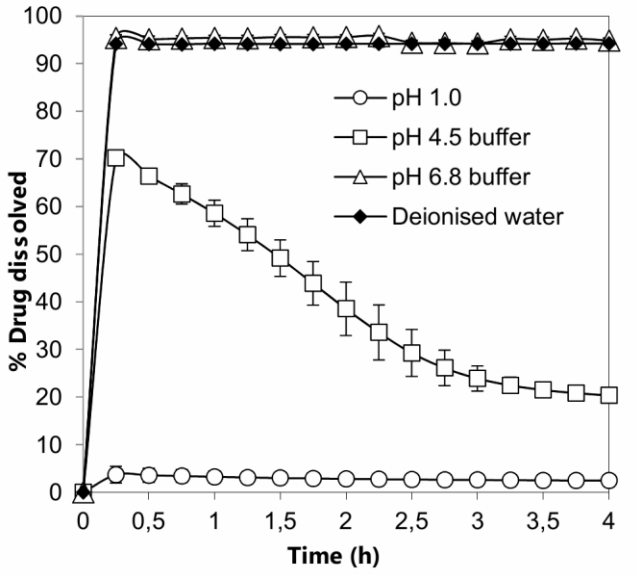

Figure 2. Dissolution profiles of 50 mg of pure diclofenac sodium in 900 ml of pH 1.0 solution, pH 4.5 buffer, pH 6.8 buffer and deionised water.

The gastro-resistant film coated products, containing 50 mg of diclofenac sodium, should not release the drug at pH 1.0 (according to USP, Diclofenac Sodium Delayed-Release Tablets). The coating of all formulations does not dissolve at pH 1.0 in 2 hrs: no drug release is detected. While, at pH 6.8, second phase of the pH-change method, about 90-100% of the dose is released quickly (Fig. 3a).

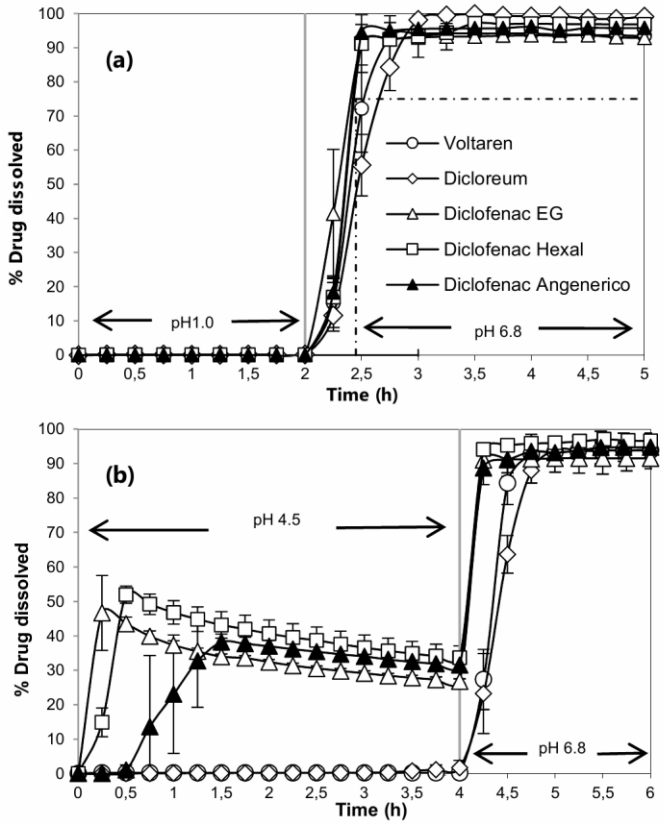

Figure 3. Delayed release tablets containing 50 mg of diclofenac sodium in in vitro dissolution test in two different stages: pH 1.0 and pH 6.8 as from the U.S. Pharmacopoeia. The dashed line shows the dissolution specification of the USP (a). Delayed release tablets containing 50 mg of diclofenac sodium in a pH-change method simulating fed state: pH 4.5 for 4 hs and then pH 6.8 (b).

The same dosage forms show a completely different behavior in pH 4.5 buffer (first phase of the modified pH-change method, fig. 3b). The coating breaks on the edge of the tablets of Diclofenac EG, Hexal and Angenerico, while the coating of Voltaren and Dicloreum tablets does not dissolve at pH 4.5 within 4 hrs of dissolution test. In the pH 4.5 buffer, the Diclofenac EG and Hexal tablets release about 50% of the dose in the first 30 mins and then the dissolved drug tends to precipitate. The same happens to the Diclofenac Angenerico tablets after a lag time of about 30 mins. Finally, for all the products tested, the whole dose is dissolved completely after the pH-change to 6.8.

3.3. Ketoprofen

The 50 mg dose of pure ketoprofen is soluble in the pH 6.8 buffer, in fact, the plateau phase (at 100% of drug dissolved) is

reached in few minutes, while the same amount of drug takes longer times to dissolve in deionised water, in the pH 1.0 hydrochloric solution and in the pH 4.5 buffer (Fig. 4).

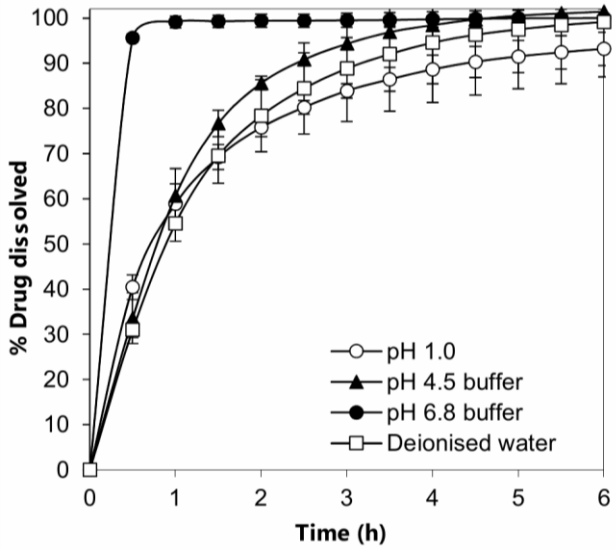

Figure 4. Dissolution profiles of 50 mg of pure ketoprofen in 1000 ml of pH 1.0 solution, deionised water, pH 4.5 buffer and pH 6.8 buffer.

The IR dosage forms, containing 50 mg of ketoprofen, show a different behavior depending on the pH and buffers conditions (Fig. 5). The three different IR products release the entire dose only in the pH 7.5 buffer within 1 hr (Fig. 5c). At pH 4.5 (Fig. 5b) and in deionised water (Fig. 5c) the entire dose is not released in 1 hr. Of course, the initial pH value and the buffering capacity (regulating pH increase/decrease) of the two media are quite different. As reported in fig. 1, the pH of water decreases from 6.8 to about 4.8 in 2hrs, for this reason the dissolution rate of this drug is comparable to that obtained in the pH 4.5 buffer. Furthermore, at pH 1.0, the dissolution profiles are even slower (Fig. 5a).

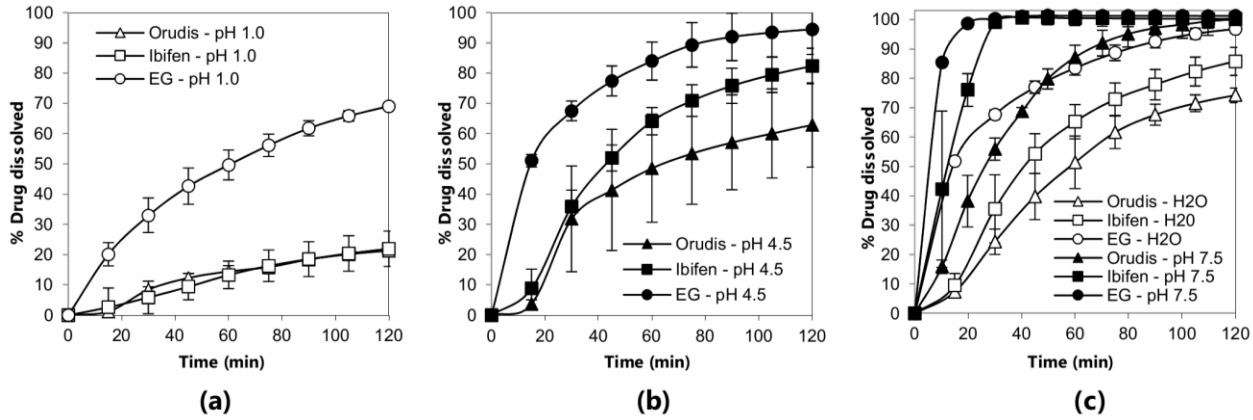

Figure 5. Three different IR products containing 50 mg of ketoprofen, tested at pH 1.0 (a), at pH 4.5 buffer (b), at pH 7.5, buffer and in deionised water (c).

Ketoprofen extended release capsules are tested in a pH 6.8 buffer (Fig. 6a), and in two different pH-change methods (Fig. 6b). The first phases: at pH 1.0 for 2 hrs and at pH 4.5 for 4hrs of the two different pH change methods, are not shown in figure 6b, because none of the products considered releases any drug in the acid conditions (pH 1.0 and pH 4.5). At pH 6.8, an extended release profile is obtained from Orudis capsules. Ketoprofen EG and Ketoprofen DOC show slower dissolution rates in all the conditions considered.

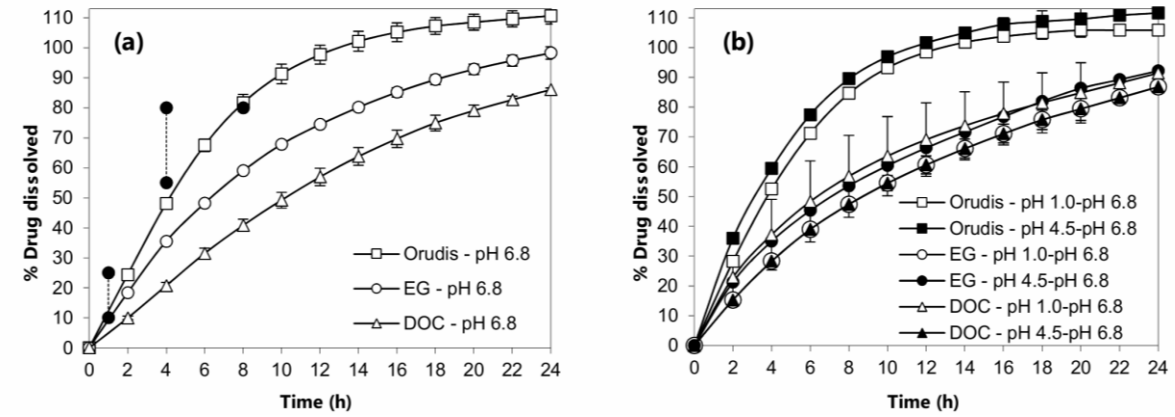

Figure 6. Dissolution profiles of three different extended release products containing 200 mg of ketoprofen. In pH 6.8 buffer, according to the USP method (a), (the black dots indicating the acceptance criteria) and in the second phases of two different pH-change methods, (pH 1.0 for 2hrs, not reported, and then pH 6.8 and pH 4.5 for 4 hrs, not reported, and then pH 6.8) (b).

3.4. Meloxicam

The dose of 15 mg of pure meloxicam is not dissolved in the pH 1.0 solution, in the pH 4.5 buffer and in deionised water, while the solubility increases in the pH 7.5 buffer (Fig. 7a). The results obtained are in good accordance with the solubility values reported in table 1.

Mobic and Meloxicam Mylan, containing 15 mg of meloxicam, show comparable behavior and intra batch reproducibility in the different media, within a pH range from 1.0 to 7.5 (Fig. 7b). The two products release the entire dose in the pH 7.5 buffer in few minutes and in water in about 1 h, at a slower dissolution rate. Instead, in acid conditions, pH 1.0 and pH 4.5, the percentages of drug dissolved is very low.

4. Discussion and conclusions

It may happen that physicians patients or nurses found differences among medicines containing the same drugs in the same dosages. This happens because the dosage form production, the excipients or the physical form of the active molecules may influence to some extent, the in vivo performance of the medicine. Even the different physiological conditions (food, activity, pathology, moods, time of the day) at the moment of the administration may play a critical role in absorption, distribution, effect and metabolism of the drug. The market of generic products is based on the assumption that the same dose in the same dosage form could lead to the same therapeutic effect. This assumption would be supported by a limited in vivo bioequiva-

lence studies on healthy volunteers. Unfortunately, in some cases these studies are not able to discriminate among the so many different conditions that may happen in the real life. Many studies has been conducted to give evidence to the difference between biologic and therapeutic equivalence (i.e.: orange book for the products marketed in the US), but unfortunately, in many other countries a lack of awareness of this critical issue is still evident. This misleading approach can causes many troubles particularly when the patient or the physician switches from one product to another. In this work, we suggest to apply the quality by design approach, not only to optimize the industrial production of the dosage form, but also to study and give evidence to the possible critical issues regarding the administration of the medicine. In particular in the case of the oral administration of drugs showing pH-dependent solubility. These forms should release the active molecule through the gastro-intestinal tract, that exhibits a high variability in terms of pH, and the drug should be in the soluble form for a proper absorption and thus bioavailability.

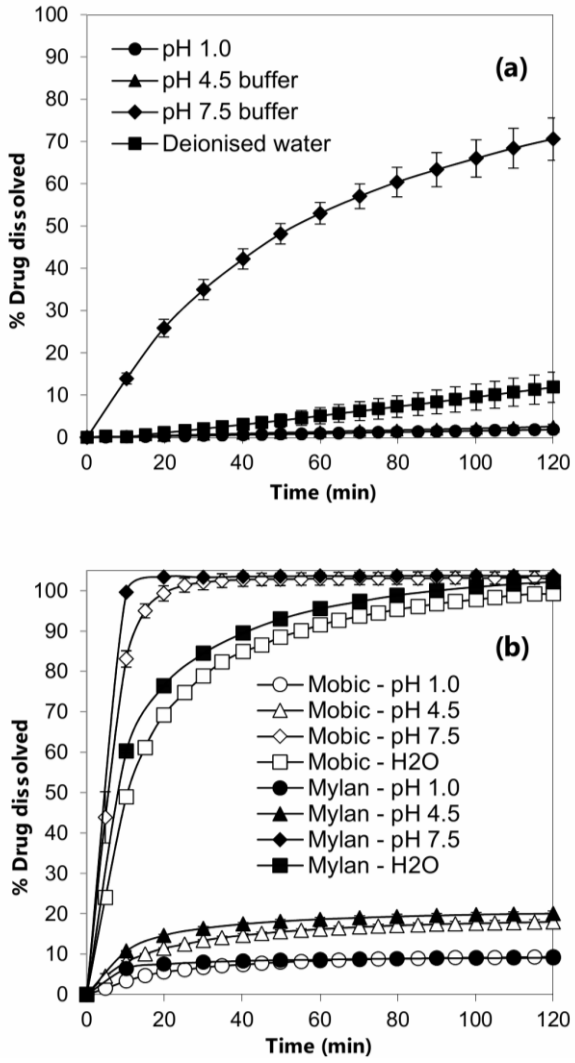

Figure 7. Dissolution profiles of 15 mg of pure meloxicam in 900 ml of pH 1.0 solution, deionised water, pH 4.5 buffer and pH 7.5 buffer (a) and two different IR products containing 15 mg of meloxicam, tested at pH 1.0, pH 4.5, buffer, pH 7.5, buffer and in deionised water (b).

From our study, the oral dosage forms containing the three different drugs, characterized by pH-dependent solubility, show quite different dissolution profiles in the different media and/or pHs tested. These results, in non-sink conditions, suggest possible critical issues in safety, efficacy and quality related to the particular drugs considered. The USP monographs request dissolution tests in sink conditions, but we suggest that more specific conditions, simulating the in vivo environment of the G-I tract, could be useful to better understand the peculiar behavior of these drug. Keeping in mind that both industry and regulatory agency perspectives are still evolving in this relatively new field,[33] we want to underline that, for some oral dosage forms and/or therapy, a QbD approach suggests that the choice of the proper dissolution specifications could be clinically relevant for both IR and modified-release products. A deeper understanding of the possible critical issues through the proper in vitro tests in a QbD approach, could improves the development process, reduces the times to market, increases the robustness of the formulation, reduces the tests for post approval changes and thus improve the overall performance of the pharmaceutical products.

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