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Diclofenac sodium multisource prolonged release tablets—a comparative study on the dissolution profiles

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Abstract

The aim of this work was to compare the dissolution behaviour of six diclofenac sodium prolonged release tablets of different brands obtained from the national market. The formulations contain the same amount of drug substance but different types and/or amount of excipients. The influence of these differences in formulation on the release characteristics of the dosage forms was evaluated on the European Pharmacopoeia apparatus 2 (paddle) employing eight different dissolution media in the pH range 1.2–8. Friability and hardness were tested too according to the European Pharmacopoeia.

Dissolution profiles obtained from the studied formulations showed that the release characteristics vary considerably among different manufacturers and that even identical formulations show rather dissimilar release profiles in all the studied media. Use of both SIF without pancreatin and SIF without pancreatin containing 1% (w/v) Tween 20 resulted in strong discrimination among products.

A correlation between friability and hardness and in vitro dissolution was evidenced for two formulations having identical excipient composition.

Keywords: Dissolution test; Friability; Hardness; Prolonged release; Diclofenac sodium; Multisource pharmaceutical products; Interchangeability

1. Introduction

Oral solid dosage forms are the most widely used formulations for new and existing prolonged release products and are still the preferred administration route for many drugs. Prolonged release systems offer many clinical advantages including reduced dosing frequency with improved patient compliance, reduced fluctuations in drug plasma concentrations with lower incidence of side effects and possible enhanced effectiveness.

Diclofenac sodium is a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic and antipyretic properties. It is widely used in the long-term treatment of degenerative joint diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Nevertheless, it produces a relatively high incidence of gastrointestinal side effects due to the physicochemical action on the gastric mucous [1] and the inflammatory action on both small bowel and the colon [2,3]. Due to these adverse effects and its short biological half life [4], diclofenac sodium is an ideal candidate for prolonged release preparations.

Diclofenac sodium has weak acidic properties (pK_a about 4) and its solubility depends on the pH of the medium. It is slightly soluble in water, very slightly soluble in phosphate buffer at pH 6.8 and practically insoluble in hydrochloric acid at pH 1.1 [5–7]. Based on the Biopharmaceutics Classification System (BCS), it can be classified as a Class II drug. BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability,

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Table 1
Excipient composition of the investigated formulations (100 mg diclofenac sodium per tablet)

Formulation	Excipient composition
F1	Colloidal anhydrous silica, cetyl alcohol, magnesium stearate, povidone, sucrose, hydroxypropyl methylcellulose, iron oxide red, polysorbate 80, talc, titanium dioxide
F2	Dextranes, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 3350, titanium dioxide (171), iron oxide red (E 172), carnauba wax, iron oxide yellow (E 172)
F3	Magnesium stearate, iron oxide, talc, polyvinylpyrrolidone, hydroxypropyl methylcellulose, titanium dioxide, mannitol, microcrystalline cellulose, diethyl phthalate
F4	Lactose, hydrogenated ricinum oil, talc, mannitol, polyvinylpyrrolidone, microcrystalline silica, methacrylic copolymers, magnesium stearate, polyethylene glycol 4000, titanium dioxide, iron oxide yellow
F5	Microcrystalline cellulose, lactose, starch, magnesium stearate, polyvinylpyrrolidone, hydroxypropyl cellulose, diethyl phthalate, cellulose acetate phthalate, titanium dioxide
F6	Lactose, hydrogenated ricinum oil, talc, mannitol, polyvinylpyrrolidone, microcrystalline silica, methacrylic copolymers, magnesium stearate, polyethylene glycol 4000, titanium dioxide, iron oxide yellow

the main parameters for influencing rate and extent of absorption of a drug substance through gastrointestinal membranes and having significant influence on its bioavailability [8,9]. Class II drugs are defined as those with high permeability but whose solubility in aqueous media is not sufficient for the whole dose to be dissolved in the gastrointestinal tract. For these substances dissolution is therefore the rate limiting step to absorption. The choice of medium for in vitro dissolution tests is therefore expected to play a very important role in the dissolution of Class II drugs as it can depend on a wide variety of factors such as pH, ionic strength, buffer capacity, presence of surfactants, agitation and medium volume [10].

A medicinal product is composed of drug substance and excipients. The proportion between them, the type of excipients and the manufacturing method of the final product are chosen based on the content, the physicochemical and the bulk properties of the drug and on its absorption properties. Taken as a whole this gives each product certain dissolution characteristics. The quality of a dosage form is continuously improved during the different development phases of a new drug product and dissolution test represents a reliable tool to evaluate formulation and processing variables that may influence the bioavailability of the drug. European Union regulations require the release rate to be tested in vitro during the development phase of controlled release formulations by dissolution analysis under various conditions. For routine control of scale-up and production batches the testing condition with the higher discriminatory power should be chosen to ensure both batch to batch consistency and that the dissolution profiles remain similar to those of pivotal clinical batches. Furthermore, a dissolution test can be used to support the bioequivalence of an essentially similar product [11,12].

The aim of this work was to compare the dissolution behaviour under various experimental conditions of six diclofenac sodium prolonged release tablets of different brands obtained from the national market. The formulations contain the same amount of drug substance but different types and/or amount of excipients such as diluents, disintegrants, lubricants, binders, surfactants. These differences in formulation could influence the release characteristics of the dosage forms playing an important role in the bioavailability of the drug and questioning the interchangeability of the products.

2. Materials and methods

2.1. Materials

Analytical grade potassium dihydrogen phosphate, sodium chloride, sodium hydroxide, hydrochloric acid and methanol were purchased from Sigma-Aldrich (Milano, Italy). Tween 20 was from ICN Biomedicals Inc. (Ohio, USA).

Deionised water obtained from an Ultra Pure Water System Type Integra (SG, Barsbüttel, Germany) was used for the preparation of dissolution media.

Diclofenac sodium reference substance was supplied by Sigma-Aldrich.

Six diclofenac sodium prolonged-release tablet formulations (F1–F6) were obtained from pharmacies in the national market. They all contain 100 mg of diclofenac sodium but greatly differ as concerns the excipient composition. Table 1 summarizes the investigated products.

2.2. Methods

2.2.1. Dissolution test

Selection of the dissolution testing conditions was based on EMEA guidelines (11, 12). For all dissolution tests the European Pharmacopoeia (Ph. Eur.) apparatus 2 was used (paddle method), employing 900 ml of dissolution medium at a temperature of $37 \pm 0.5\,^{\circ}C$ and a rotational speed of 100 rpm.

The dissolution system was fitted with a DISTEK PREMIERE 5100 dissolutor (Distek Inc., New Jersey, USA), an HP 89092A 7-channel peristaltic pump (Agilent Technologies Italia S.p.A., Roma, Italy), PC directed control through the Idis EE software (Icalis Data System Ltd., UK). Released percentages of the active ingredient were automatically measured every 15 min up to 24 h at the maximum absorption wavelength for each dissolution medium (ranging from 276 to 286 nm) using an HP 8452A diode array detector (Ag-

ilent Technologies Italia S.p.A.) equipped with a linear 7-cell transporter. The flowcell pathlength was 1 mm. Filtration of aqueous samples was performed on-line on Whatman GF/C (1.2 μm) filters (Whatman, Kent, England). Check for adsorption to the filters revealed no significant loss of drug.

2.2.2. Composition of dissolution media

The composition of dissolution media was chosen in such a way to cover the physiological pH range. Where appropriate, suitable amounts of surfactant were added to enhance solubility.

- Medium A: simulated intestinal fluid (SIF) without pancreatin (pH 6.8) according to USP 27 [13].
- Medium A_{T1}: medium A added with Tween 20 (1%, w/v).
- Medium A_{T3}: medium A added with Tween 20 (3%, w/v).
- Medium B: phosphate buffer solution (pH 8.0; 0.02 M) (Ph. Eur.) [14].
- Water: deionised water.
- Medium C: phosphate buffer solution, pH 4.5 (Ph. Eur.) [14].
- Medium C_T: medium C added with Tween 20 (1%, w/v).
- Medium D: simulated gastric fluid (SGF) without pepsin (pH 1.2) according to USP 27 [13].

2.2.3. Calibration curves

Calibration curves for diclofenac sodium reference substance were obtained by measuring the absorption in each dissolution medium (A, A_{T1}, A_{T3}, B, C_T) at the maximum absorption wavelength. Due to the low solubility of diclofenac sodium in media C and D, data from the calibration curve obtained in medium A were used. Standards were prepared in the concentration range 0.001–0.17 mg/ml. Absorptivity values were calculated and employed in the analysis software. The linearity of the calibration curves was confirmed over the concentration range 5–150% dissolution of the drug.

2.2.4. Hardness

Hardness was investigated by the "Resistance to crushing of tablets test" according to the Ph. Eur. [15] on a tablet hardness tester (Schleuniger, Thun, Switzerland).

2.2.5. Friability

Friability was investigated by the "Friability of uncoated tablets test" according to the Ph. Eur. [16] on a TAR Tablet Friability Tester (Erweka Italia, Milano, Italy).

3. Results and discussion

3.1. Influence of the rotational speed on the dissolution behaviour

Dissolution profiles of all formulations in medium A obtained at 50 rpm were compared with those obtained at 100 rpm. Some differences in the release were observed, the higher rotational speed providing better discrimination among the dosage forms and a lower variability of the data. All experiments were therefore run at 100 rpm, furthermore preventing the possibility of "coning" which sometimes occurs at lower rpm and whose relevance in vivo is rather questionable [17,18]. The dissolution profiles obtained more accurately reflected the dissolution of the tablets, not system hydrodynamics, and demonstrated a more rugged test procedure.

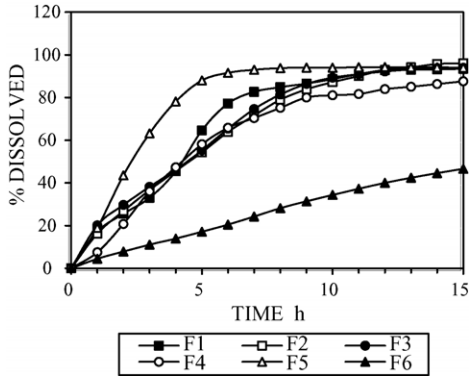

Fig. 1. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in medium A.

3.2. Dissolution profiles

Figs. 1–6 show the mean release profiles for F1–F6 formulations in the selected dissolution media. Each dissolution experiment was performed in triplicate on six tablets. Standard deviations (S.D.) of diclofenac sodium percent release are shown in Fig. 7. Dissolution profiles are presented in the 0–15 h time range.

3.2.1. Dissolution in medium A

All the formulations reached the plateau within 15 h (approx. 85–100% of label strength) with the exception of F6 whose dissolution profile was an almost straight line that did not reach the plateau within 24 h (Fig. 1). Dissolution profiles

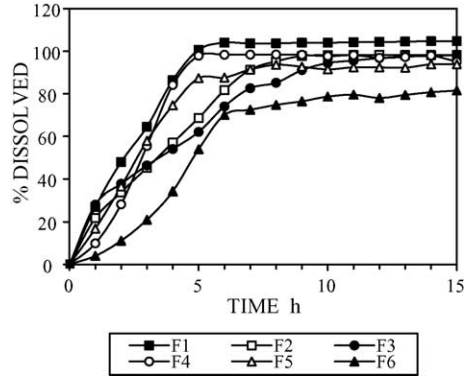

Fig. 2. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in medium A_{T1}.

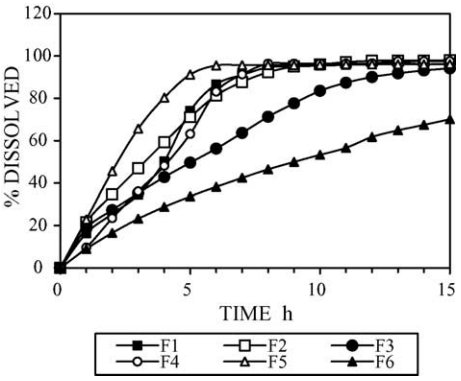

Fig. 3. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in medium B.

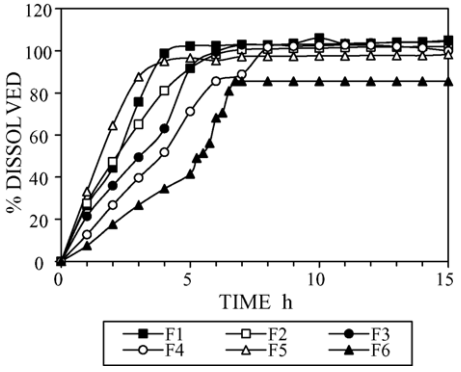

Fig. 4. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in water.

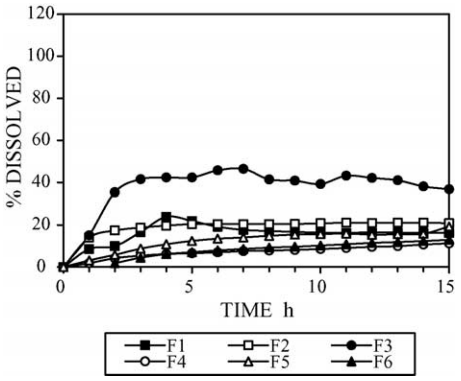

Fig. 5. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in medium C.

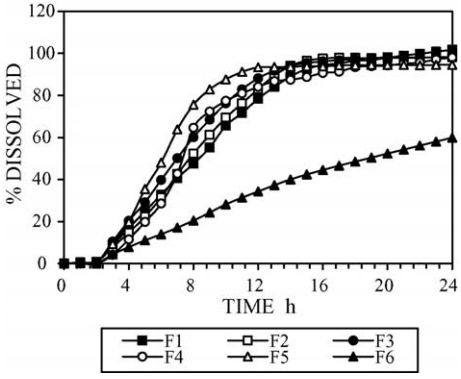

Fig. 6. Mean dissolution profiles of diclofenac sodium from formulations F1–F6 in medium A after a 2 h period in medium D.

for formulations F2 and F3 were similar each other while F4 showed a lower release rate during both the initial and the final tract of the dissolution test. F5 showed a higher release rate reaching the plateau within 6 h (approx. 95% of label strength). The dissolution curve for F1 showed a pronounced sigmoidal shape. Initially, the slope increased up to an inflection point followed by an increase in the slope thereafter. The change of slope occurred during the 3–5 h dissolution time

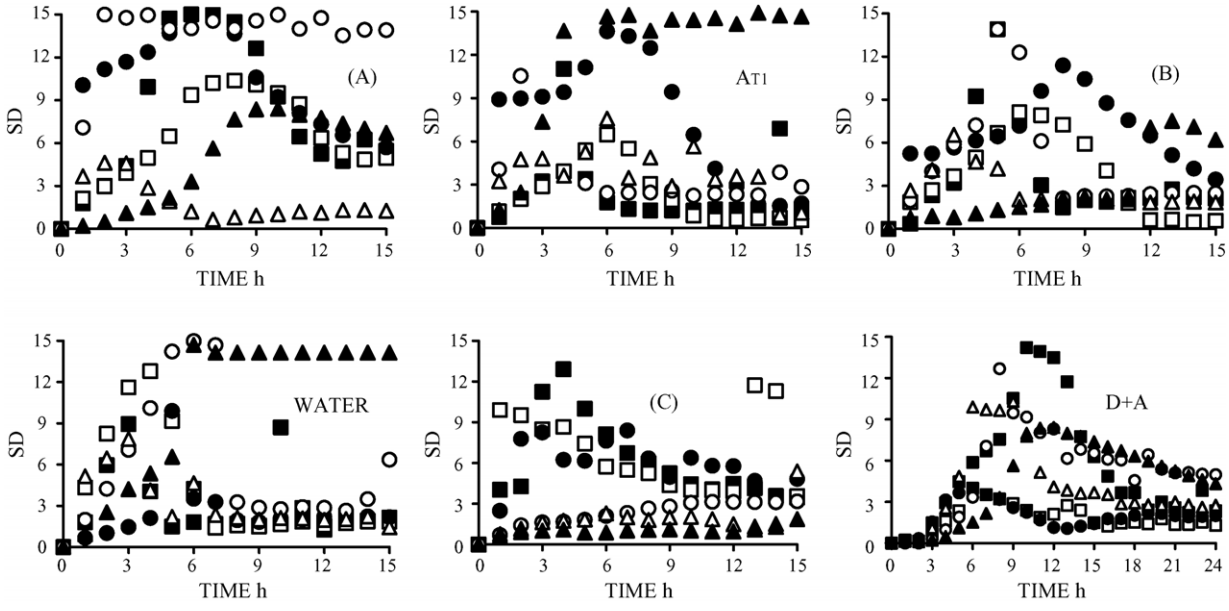

Fig. 7. Standard deviations of diclofenac sodium percent release in the selected dissolution media. Symbols are the same as in Figs. 1–6.

range during which the tablets breakage was observed leading to an increase in the surface exposed to the dissolution medium with a consequent increase in the dissolution rate. The external geometry of the other formulations essentially remained unchanged during the drug release process.

Obtained results showed that medium A provides a good discrimination among the different formulations, particularly as concerns the shape of the dissolution profiles. With the exception of formulation F6, little differences in the release extent were observed at the end of the test. The observed differences in dissolution profiles can be ascribed to a combination of factors: different manufacturing processes, different excipient composition, variability in particle size of the active ingredient. Micronization and surfactants added to the formulation can lead to an increase in the surface area of drug available for dissolution. The behaviour described for formulation F1 was probably due to the presence of polysorbate 80 which enhances the tablet wettability thus leading to a faster solvent penetration and a higher rate of tablet disaggregation [19].

3.2.2. Dissolution in medium A_{T1}

Upon adding a surfactant to the dissolution medium the surface tension is lowered thus improving the penetration process of the tablet by the dissolution medium and enhancing the solubility of the active ingredient. Products showed in fact a higher dissolution rate and extent in medium A_{T1} compared to medium A releasing more than 90% within 10 h (Fig. 2). Even formulation F6, whose dissolution profile in medium A was an almost straight line reaching only 40% dissolution within 10 h, released 80% of label strength within the same time in medium A_{T1}. Only F5 released about the same amount at the same rate as in medium A. As expected, the influence of the surfactant on the release extent increase was more evident for non-matrix formulations F4 and F6. No breakage of the tablets was observed for F1 whose dissolution profile lost the typical sigmoidal shape and showed a higher release rate (100% of label strength within 6 h). In general, the results showed that also medium A_{T1} provides a good discrimination among the different formulations. Nevertheless, dissolution profiles were more similar in shape each other than those obtained in medium A.

3.2.3. Dissolution in medium A_{T3}

By addition of a higher amount of surfactant to the medium a general decrease in the release extent was observed with the exception of F4 and F5 whose dissolution curves remained almost the same (curves not shown). F3 showed a high dissolution rate during the first hour followed by a considerable slowing during the subsequent time. The dissolution curve for F6 was an almost straight line as in medium A.

The decrease in the release extent could be due to the increased medium viscosity with a consequent decrease in the diffusion coefficient of the drug and/or its micellar solubilisation due to the surfactant concentration which is well above CMC value.

3.2.4. Dissolution in medium B

As expected on the basis of solubility data, a general increase in the dissolution rate and extent at pH 8.0 compared to pH 6.8 was observed for all formulations (Fig. 3). Only F3 showed a slight decrease in the dissolution rate and F6 did not reach 100% release within the test period. Formulation F1 showed a sigmoidal profile as in medium A due to the breakage of tablets.

3.2.5. Dissolution in water

The dissolution profiles obtained in water were well separated but similar to each other in shape. All the formulations released between 80 and 100% within 7 h and showed faster releases than those obtained both at pH 6.8 and 8.0 during the first 4 h period (Fig. 4). The presence of steps in the curve for F6 in the 5–7 h time range was due to the breakage of the tablets following their swelling and subsequent impact with paddles.

Water is often used as the dissolution medium but is not always suitable for several reasons: the quality of water can vary depending on the source of water, the surface tension may be variable and depends on the excipients in the formulation and the pH value is inherently difficult to measure because it can vary from day to day and may also change during the run depending on the active substance and excipients [20]. In particular, diclofenac sodium undergoes hydrolysis in water making the pH value raise thus enhancing the solubility of the compound and leading to an increase in the dissolution rate. Consequently, water cannot be considered the ideal medium to give discrimination among the various formulations.

3.2.6. Dissolution in media C and C_T

The behaviour in medium C generally reflected the solubility characteristics of diclofenac sodium. The dissolution rate and extent resulted very low for all the formulations (Fig. 5). The amount released from F2, F4, F5 and F6 varied between 10 and 20% of label strength reaching the plateau within 4 h. Only formulation F3 released about 40% reaching the plateau within 3 h. It was probably due to the physicochemical characteristics of the active ingredient like crystallinity, granulometry and hydration form. F1 showed a characteristic bell-shaped dissolution curve with a maximum release of about 25% within 4 h decreasing below 20% during the remaining test period. The particular shape of the dissolution profile for F1 could be ascribed to formulation factors enhancing the release rate of the drug from the dosage form without increasing the dissolution extent that is mainly controlled by the physicochemical characteristics of the drug substance.

As expected, a general increase in the dissolution rate and extent was observed for all the formulations upon adding a surfactant (medium C_T) but only F1 and F3Sp released between 80 and 100% within 6 h (curves not shown).

Table 2
Friability, hardness and dimensions of the investigated formulations

Formulation	Friability (%, w/w)	Hardness (kp[a] ± S.D.)	Diameter (mm ± S.D.)	Thickness (mm ± S.D.)	
				Min	Max
F1	–	17.35 ± 0.71	9.9 ± 0.1	2.1 ± 0.1	4.1 ± 0.1
F2	–	10.24 ± 0.75	8.6 ± 0.1	1.5 ± 0.1	4.0 ± 0.1
F3	–	8.90 ± 0.78	10.0 ± 0.1	1.2 ± 0.1	4.8 ± 0.1
F4	0.47	6.24 ± 0.42	11.3 ± 0.1	1.5 ± 0.1	5.0 ± 0.1
F5	0.12	3.83 ± 0.75	10.0 ± 0.1	1.5 ± 0.1	3.6 ± 0.1
F6	0.37	5.49 ± 0.84	11.7 ± 0.1	1.1 ± 0.1	5.1 ± 0.1

[a] Kilopounds.

3.2.7. Dissolution in medium D

The amount dissolved in medium D was lower than 1% for all the formulations during the whole test period according to the very low solubility of diclofenac sodium in acid media (curves not shown). When tablets were put for a 2 h period in medium D before undergoing the dissolution test in medium A, all the dissolution curves, with the exception of F6, clustered reaching the plateau within 14 h (90–100% drug released) and showing a dissolution profile similar to that obtained in medium A (Fig. 6).

This behaviour could be ascribed to the initial precipitation of the neutral diclofenac form onto the tablet surface preventing the diffusion of the active ingredient from the inner layers. When the pH reached almost neutral values the molecule regained its original structure and the release extent was similar to that obtained in medium A [21]. The dissolution profile for formulation F1 was shifted to values meaningly lower than those obtained in medium A. It could be ascribed to the presence in the formulation of cetyl alcohol whose hydrophobic properties hinder the penetration of the dosage form by the dissolution medium in this pH-changing system [2].

3.3. Influence of pH on dissolution behaviour

The influence of pH on dissolution behaviour of a pharmaceutical product plays a very important role in the interactions between the drug and the organism. Biological fluids show indeed a high variability in pH values influencing either the amount of drug reaching the circulatory system after oral administration or the place of absorption along the gastrointestinal tract.

The release profile of diclofenac sodium from each formulation at various pH values pointed out that the increase in dissolution rate and extent was directly proportional to the pH increase for all the formulations with two exceptions: F1 showed coincident curves at pH 6.8 and 8.0 and F3 dissolved a little faster at pH 6.8 than at pH 8.0 (Figs. 1, 3 and 5).

Experimental results confirmed that diclofenac sodium is more soluble in the media at pH 6.8 and 8.0, according to its K_a value. On the contrary, it is only slightly soluble or practically insoluble in acid media. At pH values more than 1 unit below pK_a, the compound is mostly in its free acid form, which is even less soluble than the salt [22,23]. Consequently, the solubility of the active ingredient at pH values less than 3 is very low. As the pH value increases, the solubility of the compound increases due to the contribution from the ionised form and the highest solubility is reached in phosphate buffer solution at pH 8.0 [7].

3.4. Friability and hardness of the diclofenac sodium formulations

Friability and hardness data obtained for the studied formulations are reported in Table 2, along with tablet dimensions. Hardness data are the mean of three replicated experiments (±S.D.). Formulations F1, F2 and F3 are coated tablets, consequently the friability test was not performed.

A correlation between friability and hardness and in vitro dissolution can be evidenced for formulations F4 and F6 having identical excipient composition. Friability data for F4 are higher than those obtained for F6. On the other hand, F4 showed a higher resistance to crushing than F6. The compressional force employed in the tableting process greatly influences the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets. There is always a competing relationship between the enhancing effect due to the increase in surface area through the crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, consequently, a decrease in solvent permeability. Nevertheless, the dissolution rate of the active ingredient from a formulation is mainly related to the surface characteristics of the tablet. Consequently, the release rate of the active ingredient from F4 is constantly higher than that observed for F6 in all the studied media, according to friability data.

4. Conclusions

The differences in release characteristics among multisource diclofenac sodium prolonged release tablets suggest likely implications for the bioavailability of the active ingredient thus questioning the interchangeability of the products. Nevertheless, further advice would be needed to determine whether the observed in vitro differences are of any clinical significance.

The dissolution characteristics of poorly soluble drugs like diclofenac sodium are often problematic. The dissolution rate

and extent are in fact influenced both by formulation factors and by the composition of the dissolution medium. The performance of prolonged release formulations greatly depend on the quality of excipients used in manufacturing and on the quality of the process. By their nature, different brands of prolonged release products are more likely not to be equivalent than are different brand of immediate, conventional release products. Consequently, some Drug Regulatory Authorities (DRAs) take the view that such products should never be considered interchangeable, while others define a series of studies that should be conducted, including in some circumstances comparative clinical trials [24].

Acknowledgments

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