Quality Evaluation of Diclofenac Formulations Manufactured in DR Congo

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Abstract

The purpose of this study was to evaluate the quality of three generics of 50 mg diclofenac sodium (DS) tablets manufactured and marketed in DR Congo in comparison to the original formulation Voltarène® from Novartis Pharma. Drug content and drug release were respectively determined by HPLC and UV spectrophotometry before storage and at 3 and 6 months of storage in the accelerated-aging conditions of temperature (40°C) and relative humidity (75%) recommended by the WHO for tropical climate areas. Before storage, only generic 2 contained the correct amount of active pharmaceutical ingredient (API). Generics 1 and 3 did not comply with established limits for API, one was overdosed (Generic 1) and one underdosed (generic 3). None of the generics resisted to stress conditions with respect to the API content. Moreover, all generics failed the dissolution tests when they were submitted to tropical climate simulation. Differences to explain the different dissolution profiles were searched with ^{1}H NMR that gives a complete profile of the formulation (API and excipients) and infrared spectroscopy which evaluates the overall distribution of the API in the tablets, on the initial samples. Generic 1 contained the acid form of diclofenac instead of its sodium salt, and generic 2 a mixture of acid and salt forms. Generic 3 displayed a poor DS distribution in the tablets. Taken together, our data demonstrated that the three generics analyzed were substandard.

Keywords: Diclofenac sodium; DR Congo; HPLC; ^{1}H NMR; Infrared spectroscopy; Infrared mapping

Introduction

Diclofenac sodium (DS; Figure 1), the first phenylacetic acid derivative developed as an anti-inflammatory agent, is an inhibitor of cyclooxygenase extensively used for its analgesic, antipyretic and anti-inflammatory activities. It is a potent non-steroidal anti-inflammatory drug, extensively used for the treatment of active rheumatoid arthritis and osteoarthritis, ankylosing spondylitis, non-articular rheumatism and sport injuries [1-3]. DS is one of the most consumed drugs by the population in DR Congo [4]. The literature reports few studies on the effect of humidity and temperature on the stability of DS [5,6].

The purpose of this study was to evaluate the quality of three generics of 50 mg DS tablets manufactured in DR Congo in comparison to the original formulation Voltarène® from Novartis Pharma. Drug content and drug release were determined at the time of their collection and at 3 and 6 months during their storage under the accelerated-aging conditions of temperature and relative humidity (RH) recommended by the WHO for climatic zone IVB (40°C/75% RH) [7,8]. The formulation content in active pharmaceutical ingredient (API) and excipients as well as the overall distribution of the API in the tablets were evaluated with ^{1}H NMR and Infrared (IR) spectroscopy on the initial samples.

Materials and Methods

Chemicals and reagents

Three generics of 50 mg DS tablets (generics 1, 2 and 3) manufactured by pharmaceutical industries in DR Congo were collected in pharmacies and wholesalers at Kinshasa. Neither bioequivalence nor bioavailability experiments were done prior to their commercialization. The original formulation Voltarène® from Novartis Pharma also on the Congolese market was used for comparison. All tests were performed within product expiry dates. Blisters were placed in a constant climate chamber (Binder constant climate chamber for

stress testing; Germany) set at 40°C and 75% relative humidity, for a period of six months.

Standard DS (99.9% of purity) was provided by the National Drug Control Laboratory (LNCM; Rabat, Morocco). HPLC grade methanol was from Sigma-Aldrich (Germany). Hydrochloric and phosphoric acids were from Merck KGaA (Germany). Sodium phosphate monobasic was supplied by Riedel-de Haeri (Germany).
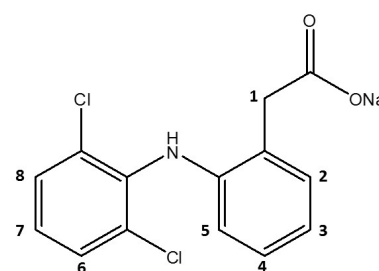

Figure 1: Chemical structure of diclofenac sodium.

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Sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate (TSP) was purchased from Sigma-Aldrich (France) and methanol-d4 (CD_3OD) from Eurisotop (France).

HPLC analysis

Standard solution was prepared by dissolving 50 mg of DS in 100 mL of a 70:30 (v:v) mixture of methanol and water (diluent). After agitation, the solution was diluted to 1/10 with the same solvent.

Sample solutions for HPLC assays were prepared from 20 tablets finely powdered. A quantity of powder equivalent to 20 mg of DS was accurately weighed and dissolved in 100 mL of diluent under stirring. The solution was then diluted to 1/10 with the same solvent. HPLC analysis was performed using a system consisting of a Waters 2695 pump, an auto sampler and a Waters 2998 photodiode-array detector. Data acquisition was carried out with the Empower chromatography data software.

Separation was performed, as described in the USP, by isocratic elution on a Symmetry C18 column (250 × 4.6 mm; 5 μm) at a temperature of 25°C. The mobile phase was composed of methanol and phosphate buffer pH 2.5 in 70:30 (v:v) proportions. Phosphate buffer was prepared by mixing 0.01 M solutions of phosphoric acid and sodium phosphate monobasic and adjusting pH to 2.5 with phosphoric acid. The flow rate was 1 mL/min, the detection wavelength 254 nm and the injection volume 10 μL. Each result is the mean of 3 measurements.

Dissolution test

Dissolution rate studies of the DS tablets were carried out according to the USP paddle method (Apparatus 2) [8,9] with a Hanson SR8-Plus™ Dissolution Test Station (USA). A 50 mg DS tablet was placed in the vessel containing 900 mL of phosphate buffer pH 6.8 at 37°C. The stirring was set at 50 rpm for 45 min. 3 mL aliquots of the medium were removed with a syringe at 10,20,30 and 45 min, filtered through a 0.45 μm filter, and analyzed spectrophotometrically (Perkin Elmer Lambda Series 35 UV-Visible spectrophotometer) at 276 nm. Each time point is the mean of 6 measurements.

To compare dissolution profiles, two factors were calculated: the relative difference factor (f_1) which is a measure of the relative error between the two curves studied and the similarity factor (f_2) that measures the closeness between the two profiles. They are given by the following equations where R_t and T_t are the cumulative percentages dissolved at each of the selected n time points of the reference and test product respectively:

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-1/2} \times 100 \right\}$$

For curves to be considered similar, f_1 values should be ≤ 10 and f_2 values comprised between 50 and 100 [10].

¹H NMR analysis

Sample solutions for ¹H NMR analysis were prepared from a tablet finally powdered. Around 120 mg of powder were dissolved in 2.5 mL of CD_3OD under vortex agitation during 5 min and sonication for 10 min. The suspension was then centrifuged (10 min, 4000 rpm) and 500 μL of the supernatant analyzed after addition of TSP as internal standard.

¹H NMR spectra were recorded on a Bruker Avance spectrometer operating at 400.13 MHz and equipped with a 5-mm Broadband Inverse (BBI) probe. ¹³C-decoupled ¹H NMR spectra were obtained using a GARP pulse sequence. A flip angle of 30°(2.71 μs) was used with a repetition time of 7.4 s and 32K data points for acquisition over a spectral width of 12 ppm (4800 Hz). 2048 scans were collected. The $^1J_{CH}$ delay for GARP decoupling was set at 3.45 ms. Data were processed using the Bruker Top Spin software 2.1 with one level of zero-filling and Fourier transformation after multiplying FIDs by an exponential line-broadening function of 0.3 Hz.

IR analysis

IR spectra were recorded on a Thermoscientific Nexus apparatus using a diamond ATR accessory. The spectral zone analyzed was 4000-650 cm^{-1} with a resolution of 4 cm^{-1}, and the number of scans was 16. The powder from the interior of the tablet was analyzed.

IR mapping was performed with an IN10 MX Thermoscientific apparatus using reflection mode and a MCT detector. Each tablet was cut in half using a razor blade. The wavenumbers scanned were 4000-650 cm^{-1} with a resolution of 8 cm^{-1}, the size of one pixel being 50 × 50 μm^2, every 50 μm. The number of scans was 32. The area scanned contained 900 pixels (30 × 30) corresponding to a scan area of 2.25 mm^2. Two different treatments were performed on the obtained maps. First, the software calculated the correlation coefficient between each measured spectrum and a reference spectrum of pure DS (carboxylate form) in order to determine the distribution of the API in the tablet. This coefficient was visualized using a color code from red (high correlation indicating the presence of DS) to blue (low correlation thus indicating the absence of DS). The second treatment consisted in measuring the absorbance intensity at 1690 cm^{-1} for each measured point in order to detect the presence of the carboxylic form of the API.

Results and Discussion

Three generics of 50 mg DS manufactured in DR Congo were analyzed for drug and excipients content, dissolution profiles and distribution of the API in the tablets and compared to the original formulation Voltarène®.

API content

DS content determination was performed using HPLC before and at 3 and 6 months of storage under accelerated-aging conditions of temperature and relative humidity (40°C/75% RH) on the three generics and the reference formulation. Data are presented in Table 1.

Formulations	mg/tablet (%; mean ± sd, n=3)		
	Before storage	After 3 months of storage	After 6 months of storage
Voltarène®[a]	48.2 ± 0.03 (96.3 ± 0.05)	47.9 ± 0.6 (95.9 ± 1.1)	47.8 ± 0.05 (95.5 ± 0.1)
Generic 1	58.0 ± 0.6 (116.1 ± 1.3)	55.9 ± 0.2 (111.9 ± 0.5)	48.9 ± 0.2 (97.8 ± 0.4)
Generic 2	50.5 ± 0.3 (101.0 ± 0.6)	49.1 ± 0.2 (98.2 ± 0.5)	39.9 ± 0.1 (79.9 ± 0.1)
Generic 3	46.7 ± 0.4 (93.4 ± 0.8)	45.7 ± 0.1 (91.5 ± 0.2)	43.5 ± 0.3 (87.0 ± 0.6)

Table 1: HPLC determination of diclofenac sodium in 50 mg tablets analyzed before and after 3 and 6 months of storage under accelerated-aging conditions of temperature and relative humidity (40°C/75% RH). [a]Reference formulation.

Before storage, Voltarène® and generic 2 were both within the acceptable limits of 95-105% of the advertised dosage required by the FDA for the API. Generic 1 was overdosed while generic 3 was underdosed. Only one of the three generics manufactured in DR Congo (generic 2) fulfilled the standard requirements for drug content. This reflects the non-respect of good manufacturing practices (GMP) at least for two Congolese manufacturers. Similar data were obtained recently with DS sold in Nigeria or in India [11,12], with amoxicillin and acetaminophen produced in DR Congo [13,14] and with other essential drugs marketed in developing countries like Rwanda, Tanzania, Libya and Kenya [15-17].

Data were similar after three months of storage with Voltarène® and generic 2 still within the limits of 95-105% in spite of a slight degradation of DS in the generic formulation, and both generics 1 and 3 outside the limits. The overdosed generic 1 degraded more quickly during the three months of storage than the other preparations.

After six months of storage, only Voltarène® remained in the acceptable limits of 90-110% as recommended in the European Pharmacopoeia [18], the overdosed generic 1 being a particular case. None of the generics manufactured in DR Congo resisted to stress conditions.

The overall level of degradation was negligible for the reference formulation (<1%), and higher for generics 1 and 2 ($\approx$16% and 21%) compared with generic 3 ($\approx$7%).

Dissolution profiles of DS

The percentages of drug release from tablets for the time point of 45 min were 99.8, 77.7, 84.9 and 11.8% for the reference formulation and the generics 1, 2, and 3, respectively (Figure 2A). Based on the USP recommendation (not less than 80% of the labeled amount of DS dissolved in 45 min), the data were correct for reference and generic 2 formulations but not for the two generics 3 and 1. However, the values

found for the relative difference factor (f_1) and the similarity factor (f_2) (f_1=13 and f_2=109) showed that the dissolution profile of generic 2 was not fully equivalent to that of Voltarène®. The poor liberation of API from generics 3 and 1 may be due to the use of excipients not enabling a good release of DS in the dissolving medium at pH 6.8, or to a too high compression on the matrix.

After three months of accelerated degradation at 40°C and 75% RH, the percentages of drug release from tablets for the time point of 45 min were 95.3, 44.9, 52.4 and 5.7% for the reference formulation and the generics 1,2 and 3 respectively. The Figure 2B illustrates that the dissolution profiles of generics 1 and 2 were seriously affected in contrast to that of the reference formulation Voltarène® which was still correct and generic 3 still showing a very poor liberation of DS (Figure 2B).

Only the dissolution profile of the reference formulation was studied after six months of accelerated degradation. The percentage of drug release at 45 min was 93.7% and the dissolution profile was still comparable to those obtained at t_o and after 3 months (Figure 2C).

^{1}H NMR and IR experiments

^{1}H NMR profiles of the four formulations were recorded with a GARP sequence to reduce spectroscopic complexity by removal of carbon satellites and therefore to facilitate the detection of minor signals [19]. Characteristic signals of DS were detected in all formulations (Figure 3) at δ (ppm) 7.36 (d, 8.0 Hz, H6 and H8), 7.19 (d, 7.5 Hz, H2), 7.00 (t, 8.0 Hz, H7), 6.96 (t, 7.8 Hz, H4), 6.82 (t, 7.4 Hz, H3), 6.36 (d, 8.0 Hz, H5) and 3.64 (s, CH_2 1) [20]. A slight variation in the chemical shift of the CH_2 1 signal (+0.06 ppm) was noticed in generic 1. This chemical shift variation is in agreement with IR experiments described below which demonstrated that generic 1 contained the acid form of diclofenac instead of its sodium salt. Some excipients were also detected with NMR. All formulations contained the lubricant stearate that leads to four signals located at 0.89, 1.28, 1.56, and 2.23 ppm with the lowest
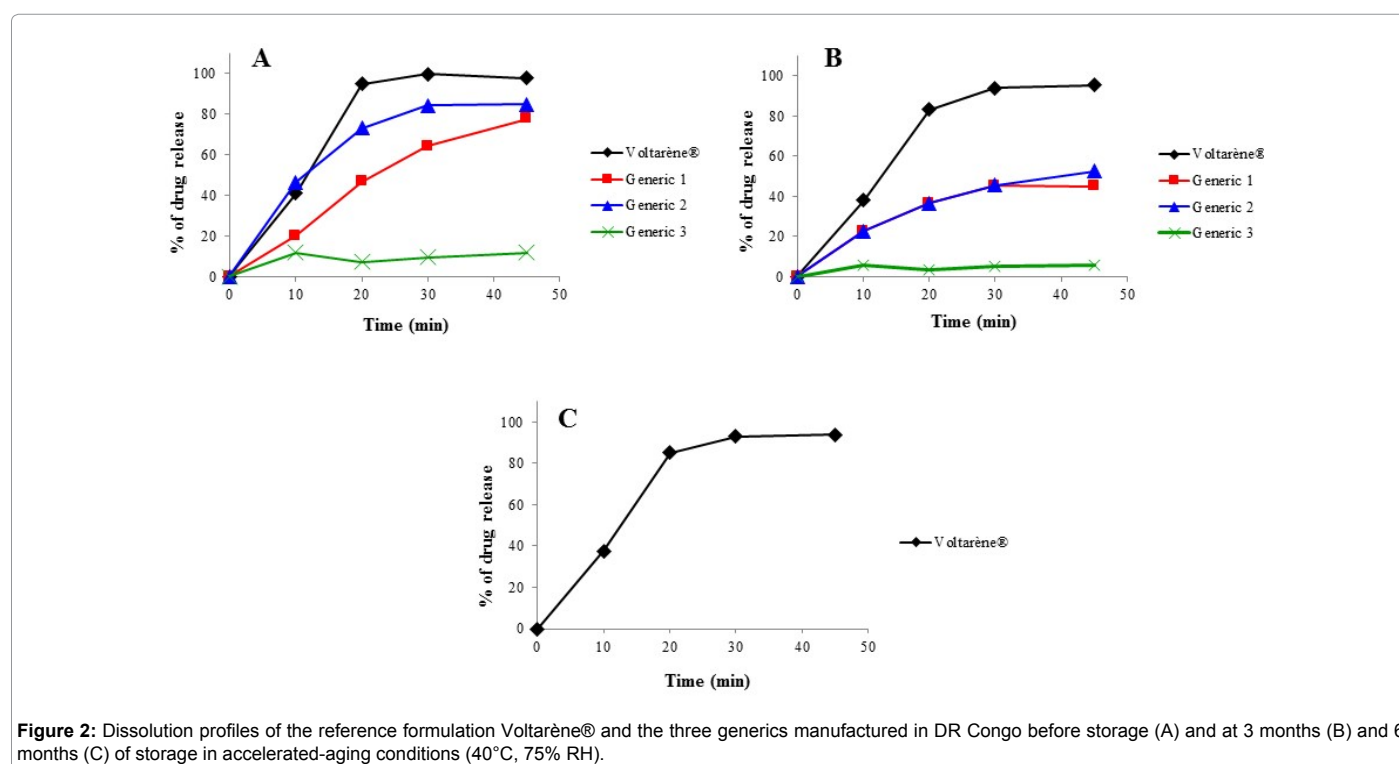

Figure 2: Dissolution profiles of the reference formulation Voltarène® and the three generics manufactured in DR Congo before storage (A) and at 3 months (B) and 6 months (C) of storage in accelerated-aging conditions (40°C, 75% RH).

concentration in generic 3. Lactose peaks (3.20 (t), 3.4-3.9 (m), 4.36 (d), 4.50 (d) and 5.10 (d) ppm) were only identified in the spectrum of the reference formulation Voltarène® that also showed several broad signals (4.10, 2.92 and 2.03 ppm for the most intense) corresponding to cellulose derivatives. Characteristic signals of isopropanol (1.14 (d) and 3.91 (hept) ppm) were observed in generics 2 and 3.

Because ^{1}H NMR spectra of the generic formulations were very similar, differences to tentatively explain the different dissolution profiles were searched with IR experiments. The comparison of IR spectra revealed that the main differences affected the carboxylate function of DS (Figure 4). Indeed the characteristic stretching bands of carboxylate were easily detected in three formulations (Voltarène®, and generics 2 and 3) at 1552 cm^{-1} (asymmetric stretching) and 1383 cm^{-1} (symmetric stretching). A very atypical IR profile was observed for generic 1 with a band at 1690 cm^{-1} characteristic of a carboxylic function and the disappearance of the asymmetric stretching of carboxylate at 1552 cm^{-1} thus demonstrating the presence of the acid form of diclofenac in this formulation. The IR spectrum of generic 2 showed that both carboxylic acid and carboxylate forms seem to coexist as the C=O acid stretching band was detected at 1690 cm^{-1} as a shoulder
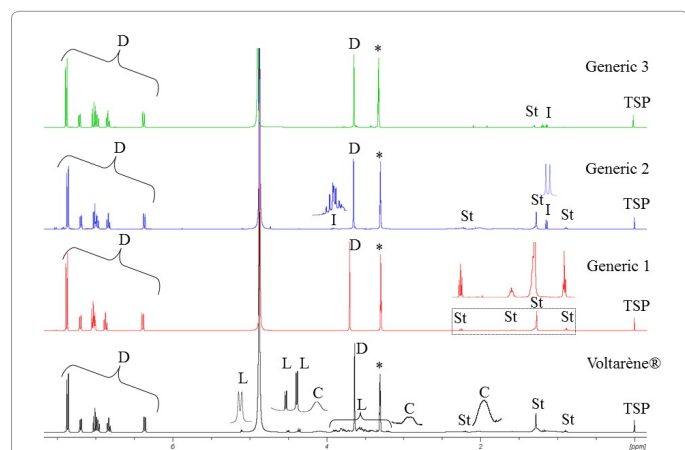

Figure 3: ^{1}H NMR spectra of the reference formulation Voltarène® and the three generics at the time of their collection. Spectra were recorded in MeOH-d4. D: diclofenac, L: lactose, St: stearate, I: isopropanol, C: cellulose derivatives, *: CD$_2$HOD, TSP: internal reference.
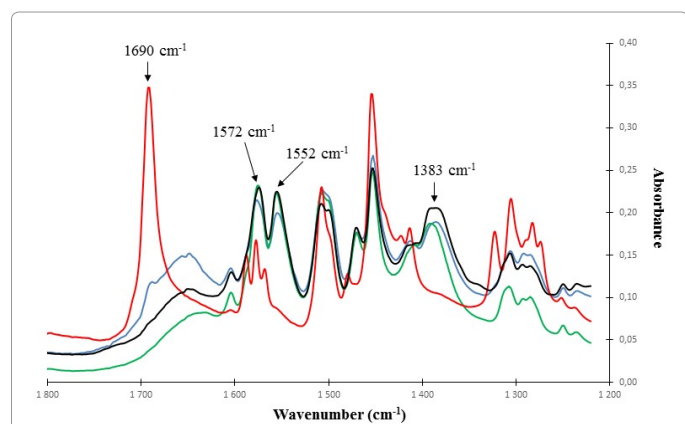
Figure 4: FT-IR spectra (1900-1200 cm^{-1}) of the reference formulation Voltarène® (black) and the three generics 1 (red), 2 (blue), and 3 (green). 1690 cm^{-1} $\nu_{C=O(carboxylic)}$, diclofenac stretching; 1572 cm^{-1} $\nu_{C=O(carboxylate)}$, stearate asymmetric stretching; 1552 cm^{-1} $\nu_{C=O(carboxylate)}$, diclofenac asymmetric stretching; 1383 cm^{-1} $\nu_{C=O(carboxylate)}$, diclofenac symmetric stretching.

of the broad band at 1640 cm^{-1} which could arise from water absorbed by cellulose derivatives [21]. As the tablets analyzed also contained magnesium stearate, we checked the position of the C=O band of this compound and found it at 1572 cm^{-1}.

Microscopy and IR mapping experiments (Figure 5) were then carried out in order to evaluate the distribution and the particle size of the API DS in the tablets [22,23]. The analyses were performed at the core of the tablet and the visible images (magnification 16) allowed us to suppose a more homogenous distribution in the Voltarène® tablet than in the others (Figure 5A). The FTIR images shown in Figure 5B1-5B4 illustrate the distribution of DS in the four tablets because they were obtained by measuring the correlation coefficient of each map spectrum with the reference DS carboxylate form spectrum. The value of this coefficient decreases from red to blue, the red color indicating the presence of DS. The Voltarène® map (Figure 5B1) confirmed the homogeneous distribution of DS in the tablet while the generic 3 map (Figure 5B2) showed a very heterogeneous distribution with a large red area (around 0.2 mm^2) corresponding to a large particle of DS. The distribution was apparently more homogeneous for generics 2 and 1 although the very few red spots observed in generic 1 confirmed the absence of the carboxylate form of diclofenac (Figure 5B4 and 5B3). For generics 1 and 2, we also measured the absorbance intensity of the band at 1690 cm^{-1} attributed to the C=O of the carboxylic form of diclofenac. The color code used for these two images (Figure 5B5 and 5B6) related to the intensity of this band: from red (high intensity indicating the presence of the carboxylic form) to blue (low intensity indicating the absence of the carboxylic form). Generic 1 exhibited a regular distribution and small particle size while generic 2 was more heterogeneous probably due to the presence of both forms of diclofenac.

IR data thus support the results of the dissolution tests. As the distribution of the various constituents in pharmaceutical tablets affects drug dissolution and release [20], the strongly inhomogeneous distribution of DS in generic 3 can explain its very low dissolution (Figure 2). Furthermore, Llinàs et al. [24] have demonstrated that solubility values are lower for the acid form of diclofenac in comparison to the sodium salt form. In our study, generic 1 that contained the acid form of diclofenac had a slower and lower dissolution profile than generic 2 that contained both carboxylate and acid forms and whose dissolution profile was closer to that of the reference formulation at least before storage (Figure 2).

The selectivity of the HPLC analysis and the spectrophotometric assay focusing on the sole API enabled us comparing the reference formulation Voltarène® and three generics manufactured in DR Congo in terms of API content and release before and during storage in accelerated conditions (40°C, 75% RH). To explain these first results, especially those of the dissolutions tests, we called on to ^{1}H NMR and IR, two holistic techniques that provided information on the whole content of the different formulations. If only minor differences were detected with ^{1}H NMR, IR was in contrast particularly informative. Indeed, we easily observed the presence of the acid form of diclofenac in generics 1 and 2 and the inhomogeneous distribution of DS in generic 3 that contribute to decreased API release which in turn may affect the bioavailability of the drug.

Taken together, our data demonstrated that the three generics analyzed were substandard. Generics 1 and 3 did not comply with established limits for API. Generic 1 contained the acid form of diclofenac instead of its sodium salt, and generic 2 a mixture of acid and salt forms. Generic 3 displayed a poor DS distribution in the tablets. All generics failed the dissolution tests when they were submitted to
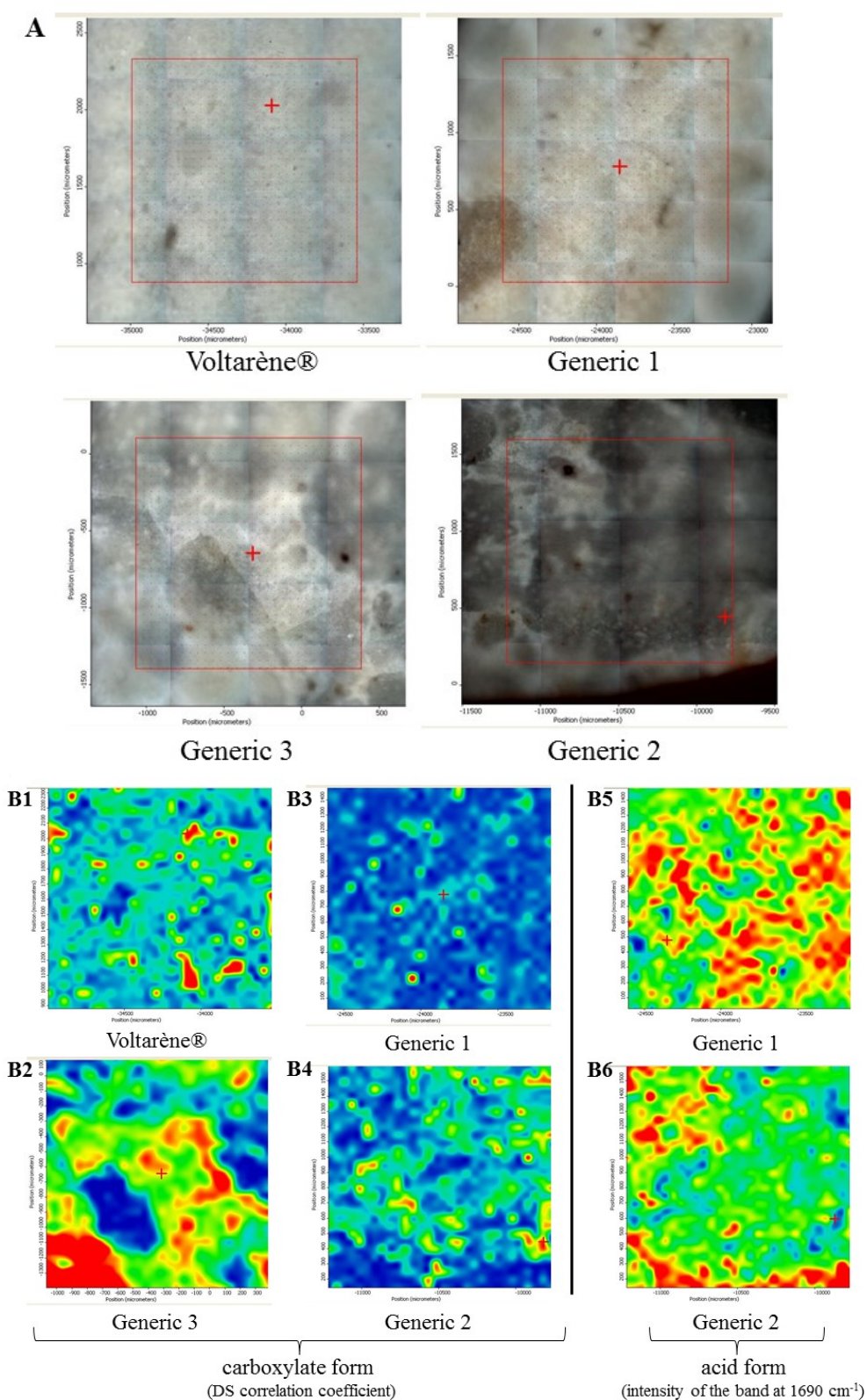
Figure 5: Microscopy (A) and FTIR maps (B) of tablet cross-sections. B1-B4: the color code indicates the correlation between map spectra and standard pure DS spectrum and correlation decreases from red to blue; B5 and B6: the color code represents the absorbance intensity of the band at 1690 cm^{-1}, decreasing from red to blue. months (C) of storage in accelerated-aging conditions (40°C, 75% RH).

tropical climate simulation and generics 1 and 3 even before storage in these stress conditions. This raises the issue of the proposed shelf life that was of three years, obviously a too long period of time to guarantee the quality of these medicines. The root cause of substandard drugs is neglect of GMP and compliance to GMP should be a pre-requisite to granting authorization to market. At least, the manufacturer should prove the good quality of the generic to be commercialized that should be established in comparison with the brand formulation. Ideally, resort to several complementary analytical techniques for a precise and comprehensive characterization of a drug (chemical composition, crystal forms, impurities) is required to fight efficiently against poor quality medicines [25]. However, sophisticated techniques are often not available in developing countries. So, the use of methods simple to implement such as an HPLC assay for quantification of the API and follow up of its stability and/or a dissolution test, could help in marketing good quality generics with an appropriate shelf life.

Conclusion

Three generics of DS tablets manufactured and marketed in DR Congo were analyzed for drug content, dissolution profile and API distribution in the tablets with several complementary analytical techniques (HPLC, UV spectrophotometry, ^{1}H NMR, and IR spectroscopy) and the data compared to those of the original formulation Voltarène® as a reference. All the generics were of substandard quality, which emphasizes the need for GMP application and a constant market monitoring of drug products to ascertain their equivalence to the reference products.

Conflict of Interest

The authors report no conflict of interest, the DR Congo health authorities being aware of the nature of the samples studied and of the results of their analysis.

Acknowledgements

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