© 2023 Journal of Pharmacy & Pharmacognosy Research, 11 (4), 585-594, 2023
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1641_11.4.585

Original Article

In vitro pharmaco-equivalence analysis of diclofenac potassium oral film-coated tablet relative to marketed generics

[Análisis de farmacoequivalencia *in vitro* del comprimido oral recubierto de diclofenaco potásico en relación con los genéricos comercializados]

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Abstract

Context: Diclofenac potassium, a potent member of the non-steroidal anti-inflammatory drugs (NSAIDs) that is commonly used for acute analgesia and multiple inflammatory conditions, has various marketed tablet brands available. However, quality parameters of tablet dosage forms may vary across different brands.

Aims: To evaluate critical quality attributes, including *in vitro* dissolution characteristics of four diclofenac potassium immediate-release (IR) tablet brands (labeled A–D) collected from Saudi Arabia market.

Methods: All brands were tested for conformity with the United States Pharmacopoeia, through evaluation of weight variation, hardness, friability, disintegration, and dissolution. Dissolution profiles were compared using model-dependent and-independent approaches relative to the innovator A.

Results: Data showed that the samples were compliant in terms of weight variation, hardness and friability. Disintegration time (DT) for brands B and D was below USP specifications whereas that of brand C was higher. Brand B and D had higher dissolution efficiency (DE) and similar mean dissolution time (MDT) compared with innovator. Brand C had lower DE and greater MDT compared with innovator. Weibull model of drug-release kinetics was found to be the best fit for all samples.

Conclusions: In summary, brand C, unlike brands B and D, appears to relatively undermine the purpose of a diclofenac IR formulation, given its longer DT, lower DE and slower dissolution release compared with the innovator. These differences are potentially attributable to variations in tablet additives and manufacturing processing across different pharmaceutical industries.

Keywords: diclofenac potassium; drug dissolution; Saudi generic brands; USP tablet testing; Weibull drug kinetics.

Resumen

Contexto: El diclofenaco potásico, un potente miembro de los antiinflamatorios no esteroideos (AINE) que se utiliza habitualmente para la analgesia aguda y múltiples afecciones inflamatorias, dispone de varias marcas comercializadas de comprimidos. Sin embargo, los parámetros de calidad de las formas farmacéuticas en comprimidos pueden variar entre las diferentes marcas.

Objetivos: Evaluar los atributos críticos de calidad, incluidas las características de disolución *in vitro* de cuatro marcas de comprimidos de diclofenaco potásico de liberación inmediata (IR) (etiquetados A-D) recogidos en el mercado de Arabia Saudí.

Métodos: Se comprobó la conformidad de todas las marcas con la Farmacopea de Estados Unidos, mediante la evaluación de la variación de peso, la dureza, la friabilidad, la desintegración y la disolución. Los perfiles de disolución se compararon utilizando enfoques dependientes e independientes del modelo en relación con el innovador A.

Resultados: Los datos mostraron que las muestras eran conformes en términos de variación de peso, dureza y friabilidad. El tiempo de desintegración (DT) de las marcas B y D fue inferior a las especificaciones USP, mientras que el de la marca C fue superior. Las marcas B y D presentaron una mayor eficacia de disolución (ED) y un tiempo medio de disolución (TMD) similar en comparación con el innovador. La marca C tuvo una ED menor y un MDT mayor que el innovador. El modelo de Weibull para la cinética de liberación del fármaco fue el que mejor se ajustó a todas las muestras.

Conclusiones: En resumen, la marca C, a diferencia de las marcas B y D, parece socavar relativamente el propósito de una formulación de diclofenaco IR, dada su DT más larga, su DE más baja y su liberación de disolución más lenta en comparación con el innovador. Estas diferencias son potencialmente atribuibles a variaciones en los aditivos de los comprimidos y en el proceso de fabricación en las distintas industrias farmacéuticas.

Palabras Clave: diclofenaco potásico; disolución del fármaco; marcas genéricas saudíes; ensayo de comprimidos USP; cinética farmacológica de Weibull.

ARTICLE INFO
Received: March 24, 2023.
Accepted: July 1, 2023.
Available Online: July 18, 2023.

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Abbreviations: AIC: Akaike Information Criteria; α: time dependence scale parameter; ANOVA: analysis of variance; API: active pharmaceutical ingredient; AUC: area under the curve; BCS: biopharmaceutical classification system; β: dissolution curve shape parameter; COX: cyclooxygenase; DE: dissolution efficiency; f1: dissimilarity factor; f2: similarity factor; IR: immediate release; K_0: zero-order release constant; K_1: first-order release constant; K_h: Higuchi drug release constant; Khc: Hixson-Crowell drug release constant; Kkp: Korsmeyer drug release constant; kp: kilopond; MDT: mean dissolution time; M_∞: amount of drug at equilibrium state; Mt/M∞: fraction of drug released; n: drug release exponent; NSAIDS: non-steroidal anti-inflammatory drugs; PB: phosphate buffer; Q and M: amount of drug; Q_0 and M_0: initial amount of drug; Q_t and M_t: amount of drug released over time; r^2: determination coefficient; RS: reference standard; SGF: simulated gastric fluid; SFDA: Saudi Food and Drug Authority; T: lag time; t: time; USP: United States Pharmacopeia.

INTRODUCTION

Diclofenac, a phenylacetic acid derivative, is a recognized member of the non-steroidal anti-inflammatory drugs (NSAIDs). It has marked anti-inflammatory, analgesic, and antipyretic properties, making this drug a potent agent with a comparable to superior efficacy relative to other NSAIDs (Chuasuwan et al., 2009). Pharmacologically, diclofenac action is based on the inhibition of the cyclooxygenase (COX) enzyme, which consequently reduces the autocoids' prostaglandins and thromboxane syntheses (Joshi and Rapoport, 2017). There are two important COX isoforms: COX-1, being expressed in almost all tissues to mediate physiological processes, and COX-2, which is expressed in inflammatory cells to mediate pathological response, with the inhibition of these culminating in NSAIDs' adverse and therapeutic effects, respectively (Hinz and Brune, 2002). Interestingly, diclofenac induced-COX inhibition is rated 3-1000 times greater than other NSAIDs and carries a 4-fold higher selectivity to COX-2 compared with COX-1, hence justifying its potency, medical usability, and high therapeutic index (Chuasuwan et al., 2009).

Therapeutically, oral diclofenac is commonly available in two salt forms: sodium- or potassium-salt formulations. The older diclofenac sodium form was first marketed under the brand name Voltaren in 1973 (Altman et al., 2015) as delayed- and extended-release formulations to provide a convenient, once-daily dosing for anti-inflammatory and chronic pain management in conditions such as osteo-rheumatoid arthritis and ankylosing spondylitis (Chuasuwan et al., 2009). In contrast, the newer form, diclofenac potassium, was introduced under the brand names Cataflam or Voltaren Rapid in the early 1980s (Altman et al., 2015) as immediate-release (IR) tablets, soft gelatin capsules or powder dosage forms, which primarily promoted faster absorption and rapid onset for acute analgesia in conditions such as dysmenorrhea, dental and migraine pain management (Altman et al., 2015; Chuasuwan et al., 2009). Notably, most dispersible dosage forms of diclofenac contain sodium salt, whereas most plain tablets contain potassium salt as IR (Altman et al., 2015; Chuasuwan et al., 2009). Relative to diclofenac sodium enteric-coated tablets, diclofenac potassium IR given as a single dose orally can provide a significantly faster pain relief (Joshi and Rapoport, 2017).

Chemically, diclofenac is 2-[(2,6-dichlorophenyl) amino] benzene acetic acid, which is present in salt forms such as monosodium or potassium salt (Fig. 1) (Altman et al., 2015; Chuasuwan et al., 2009). Diclofenac potassium is soluble in water, whereas the sodium salt is sparingly soluble in water (Chuasuwan et al., 2009). The solubility of diclofenac potassium is pH dependent, with insoluble behavior seen at pH 4.5, very slightly soluble at pH 6.8 and slightly soluble at pH 7.4 (Chuasuwan et al., 2009).

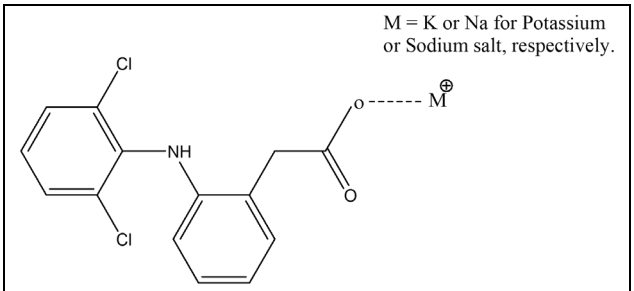

Figure 1. Chemical structure of diclofenac (brand's active pharmaceutical ingredient).

While extensive literature is available on diclofenac sodium salt (Su et al., 2003; Altman et al., 2015), a few have been conducted on the diclofenac potassium form (Hammami et al., 2020). Pharmaceutically, with respect to the IR dosage form containing diclofenac potassium as an active pharmaceutical ingredient (API), the biopharmaceutical classification system (BCS) classifies it as a class II drug (Chuasuwan et al., 2009). However, if the IR form of the drug product available in a salt form has a reported measurable therapeutic use, high therapeutic index, known pharmacokinetic and excipient properties, and bioavailability (Chuasuwan et al., 2009), then a biowaiver or *in vitro* testing can be of a substantial use (Chuasuwan et al., 2009; Alwadi et al., 2022). Capitalizing on this notion, performing *in vitro* testing of oral dosage form can save money and time, avoid involvement of research subjects, forecast *in vivo* bioavailability (Alwadi et al., 2022), and lastly, provide to pharmaceutical regulatory bodies continuous monitoring and quality control data for medicines that are available in the market after their approval (Alwadi et al., 2022). Consequent to the presence of various

branding of innovators and generics of drug manufacturing, the financial and economic competition is highly sophisticated between these pharmaceutical firms (Alwadi et al., 2022). Many of these have been flourishing and growing in Saudi Arabia, witnessing major ongoing economic and pharmaceutical services revamp according to its strategic plan of Vision 2030 (Alwadi et al., 2022). Interestingly, oral diclofenac products have been among the top-selling drugs in Saudi Arabia in recent years (AlKhamees et al., 2018) with >30 formulations including tablets, capsules, sachets, granules, suspensions, solutions, patches, ophthalmic drops, injectables, suppositories, gels and creams currently listed under the Saudi Food and Drug Authority (SFDA) (SFDA, 2022). Specific to diclofenac potassium, oral dosage form is available in 25, 50, 75, and 100 mg strength of API, many of which are manufactured and marketed as a NSAID product under the Saudi formulary (SFDA, 2022). Additionally, there are currently 12 oral diclofenac potassium formulations registered under the local SFDA (SFDA, 2022).

In recent years, more emphasis has been placed on quality parameters testing within the pharmaceutical industry and correspondingly, by regulatory authorities (Alwadi et al., 2022). Thus, for tablet dosage forms, any chemical breakdown or interaction between tablet components may alter their physicochemical properties, thereby potentially affecting the bioavailability of a tablet system (Lachman et al., 1976). Therefore, the tablet dosage form must contain the designated API within a narrow range of the labeled strength, and be fabricated to withstand chipping, abrasion, and breakage (Burlinson and Pickering, 1950). These properties can be assessed using the friability, hardness, and uniformity of dosage unit tests (Alwadi et al., 2022; Burlinson and Pickering, 1950; Webster and Van Abbé, 1955). The prediction of *in vivo* bioavailability of most oral drug formulations depends greatly on *in vitro* dissolution studies (Alwadi et al., 2022). As such, these dissolution studies are imperative during the drug development stages and data derived from these quality control measures can be used to correlate between drug release and absorption and serve as a valuable tool for marketing approval (Shah, 2001). Practically, the *in vitro* dissolution process can be exploited to serve the analysis of tablet release quality via 3 main methods (Alwadi et al., 2022; Petrone et al., 2014): Firstly, statistical ANOVA-based analysis that uses the dissolution data in their native form to show the differences between dissolution profiles level and shape, which in turn help to recognize dissolution mechanism differences. Secondly, model-independent method, which uses the dissolution data in their native form, and thirdly, model-dependent method, which uses numerical values in different mathematical functions in order to describe the dissolution profile, which ultimately aids in identifying the best fit model for drug release (Petrone et al., 2014).

With the enhanced dissolution and drug kinetics of diclofenac potassium that led to the development of several products of this NSAID (Altman et al., 2015), and the availability of various generic products of this widely used medicine in Saudi Arabia, the manufacturing quality standards might not be frequently examined and thus queried. Accordingly, this study has the following aims; to provide an up-to-date investigation of the *in vitro* quality parameters of 4 commercially available diclofenac potassium brands of 50 mg dosage strength obtained from pharmacies in Saudi Arabia; namely Cataflam (innovator), Rapidus, Fast-Flam and Joflam (generics), and evaluate their conformity with the United States Pharmacopeia (USP) standards, as these generics might vary in tablet quality relative to the innovator or essentially deviate from the pharmacopeial standards. Furthermore, to explore the drug-release kinetics and describe the yet-to-be-explored dissolution profiles of these selected dosage forms, using model-dependent and independent approaches, as this can help to determine the tablet-release behavior of these medicines in solution. Data generated from this study can support the ongoing evaluation of marketed products, help in public health and individual patient protection, and provide surveillance feedback to regulatory bodies like the SFDA to take actions on medicines that have been already registered and marketed.

MATERIAL AND METHODS

Chemicals and reagents

Diclofenac potassium reference standard (RS) was a donated gift from Hikma Pharmaceuticals (Riyadh, Saudi Arabia). Potassium dihydrogen phosphate, disodium hydrogen phosphate and sodium hydroxide are chemicals of analytical grades, were purchased from Sigma-Aldrich, USA. Special PS micro 2 mL cuvettes for UV were obtained from LP Italiana SPA, Italy and 5 mL syringes were bought from Bu Kwang Medical Inc., Korea.

Tablet samples

Four diclofenac potassium brands of 50 mg dosage strength were procured from different retail pharmacies in Riyadh, Saudi Arabia. These marketed brands were as follows: Cataflam (branded medicine) (LOT: KFK52, EXP: 02/2025, Novartis, Switzerland), Rapidus (generic) (LOT: 1MX716, EXP: 10/2024, Tabuk Pharmaceuticals, Saudi Arabia), Fast-Flam (generic)

Table 1. Characteristics of 50 mg diclofenac potassium tablet formulations.

Brand code	Price[b]	Appearance	Diameter (mm)	Thickness (mm)
A[a]	8.43	Orange; round	8.79 ± 0.03	4.95 ± 0.11
B	7.74	Orange; round	8.01 ± 0.03	4.02 ± 0.04
C	5.70	White; round	8.00 ± 0.00	3.40 ± 0.00
D	3.30	Orange; round	7.90 ± 0.00	3.99 ± 0.03

Data represent mean ± standard deviation, (n = 20). Data were analyzed by one-way ANOVA followed by Dunnett post-hoc analysis. No statistical significance was found between brands *vs.* innovator (A), ($p>0.05$). [a]Innovator diclofenac potassium brand. [b]Latest price per packet in USD.

(LOT: YG0145, EXP: 08/2023, Jamjoom Pharmaceuticals, Saudi Arabia) and Joflam (generic) (LOT: 2211, EXP: 10/2023, Jordan River Pharmaceutical Industries, Jordan). These diclofenac products were labelled from A to D, with A being the innovator and the others were arbitrarily allocated generic tablets (Table 1). All experiments in this study were carried out at least six months prior to the product expiration dates labeled on the medication packages.

Standard curve preparation

The RS of diclofenac potassium was used to make a stock solution of 100 µg/mL in 0.05 M phosphate buffer (PB). A calibration curve with a concentration range of 2-18 µg/mL (Beer-Lambert's range) was prepared by diluting aliquots of the stock solution in PB. Concentration of diclofenac potassium was measured in triplicate by UV/Visible spectrophotometer (Jenway 6705, UK) at a wavelength of 276 nm. Calibration curve (r^2=0.9946) was designed to be used for further analysis as previously demonstrated (Alwadi et al., 2022).

Friability test

Friability procedure was carried out following USP <1216> (<1216> Frability. In USP-NF. The USP Convention, 2022) guideline using a randomly selected sample of 20 tablets. These tablets were weighed and placed into a friabilator chamber (Roche Friabilator, Germany) rotating at 25 rpm. Following the 4-min run at 100 revolutions, the tablets were weighed again and the differences in weight were calculated as percentage friability (Alwadi et al., 2022). The same procedure was repetitive for all diclofenac potassium tablet brands. Requirements are met if the percentage friability was not more than 1.0 (<1216> Friability) (United States Pharmacopeial Convention, 2020).

Hardness test

Hardness assessment was executed in accordance with USP guidelines of <1217> (United States Pharmacopeia, 2022) using 20 tablet samples. Briefly, arbitrarily selected tablets from each brand were tested individually between the 2 plungers of hardness tester (Erweka TBH 125, Germany) and their individual breaking forces were documented in kilopond (kp) units (Alwadi et al., 2022).

Uniformity of dosage unit test

Tablet weight variation test was conducted in compliance with USP <905> Uniformity of dosage units guidelines using randomly selected sample of 20 tablet samples (United States Pharmacopeial Convention, 2012). These tablets were weighed individually using an analytical scale (KERN PFB 300-3, Germany). Consequently, the average weights and percentage deviations from the mean values for each brand were calculated (Alwadi et al., 2022). Compliance is established if the weights of not more than 2 tablets deviate from the average weight of the same brand by more than 5% and no tablet differs in weight by more than double that percentage, as previously mentioned (Alwadi et al., 2022; United States Pharmacopeial Convention, 2012).

Disintegration test

Six tablets of Cataflam innovator and each of the generics were individually placed inside the six tubes of the basket of disintegration machine ED 2L (Electrolab, Mumbai, India), as designated in USP <701> specifications (United States Pharmacopeial Convention, 2019). The volume of 800 mL of simulated gastric fluid (SGF) media (0.1 N HCl diluted solution without enzymes and pH 1.2) was poured into a beaker encompassing the disintegration basket and temperature was maintained at 37 ± 2°C (Alwadi et al., 2022). Tests were started instantly after the basket assembly was fix attached. The disintegration time is the time during which no particles remain in the system's basket. If all six tablets disintegrate, the brand passes the test. If one or two tablets do not entirely disintegrate, then 12 additional tablets are re-tested. Only two tablets out of the total of 18 tested tablets are permitted to fail completing the disintegration course (Alwadi et al., 2022; United States Pharmacopeial Convention, 2019).

Dissolution test

Tablet dissolution test was performed according to the USP paddle method (Apparatus II) and carried out in six replicates (vessels) containing phosphate buffer of pH 6.8 as the dissolution medium (Alwadi et al., 2022). The temperature of the medium was maintained at 37 ± 0.5°C and the stirring speed was set to 75 rpm. Liquid samples of 5 mL were withdrawn from each vessel at time intervals of 5, 10, 15, 30, 45 and 60 min and replaced with equal volumes of fresh SGF. Samples were then filtered using 0.45-µm membrane filters (Merck, USA), diluted as indicated, and their absorbance was measured using a UV/Vis spectrophotometer (Jenway 6705, UK) (United States Pharmacopeial Convention, 2018). Subsequently, absorbance values were then correlated with the previously plotted standard curve (r^2= 0.9946) in order to calculate the amount of drug released at each time interval.

Drug-release kinetics

In this study, the *in vitro* diclofenac potassium release profiles were plotted against the zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Weibull mathematical models).

Zero-order model

It describes systems in which the drug release rate is independent of the concentration of dissolved species (Singhvi and Singh, 2011). In its simplest form, zero order release can be represented as equation [1].

$$Q = Q_0 + K_0 t \quad [1]$$

where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution, and K_0 is the zero-order release constant.

First-order model

It describes the drug release from systems where dissolution rate is dependent on the concentration of the dissolving species (Gouda et al., 2017). Drug release that follows first order kinetics can be represented by the equation [2].

$$\log Q = \log Q_0 - K_1 t / 2.303 \quad [2]$$

where K_1 is the first-order release constant expressed in time^{-1} or per hour, Q_0 is the initial drug concentration, and Q is the percent of drug remaining at time t.

Higuchi model

It describes drug release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release from matrix is related to the rate of drug diffusion (Singhvi and Singh, 2011). This model is represented by the following equation [3].

$$Qt = K_h (t) 0.5 \quad [3]$$

where Qt is the amount of drug released in time t, and K_h is the release constant for the Higuchi model.

Hixson-Crowell model

It describes drug release from systems where there is a change in the surface area and diameter of particles or tablets as follows in following equation [4] (Singhvi and Singh, 2011).

$$Q_0^{1/3} - Q_t^{1/3} = K_{hc} t \quad [4]$$

where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{hc} is the release constant for Hixson-Crowell rate equation.

Korsmeyer and Peppas model

They put forth a simple relationship, which described the drug release from a polymeric system follow which type of dissolution as represented by the following equation [5].

$$\log (Mt/M\infty) = \log K_{kp} + n \log t \quad [5]$$

where $Mt/M\infty$ is a fraction of drug released at time t, Mt is the amount of drug released over time t, $M\infty$ is the amount of drug at the equilibrium state, n is the diffusional exponent or drug release exponent, and Kkp is the Korsmeyer release constant (Gouda et al., 2017).

Weibull function model

It is a mathematical model lacking physicochemical fundament and can be used to study the dissolution rate. The following equation [6] represents the model.

$$M = M_0 \left[1 - e^{-\frac{(t-T)^\beta}{\alpha}}\right] \quad [6]$$

where M is the amount of drug dissolved as a function of time t, M_0 is the total amount of drug being released, T accounts for the lag time measured as a result of the dissolution process, and parameter α denotes a scale parameter that describes the time dependence, while β describes the shape of the dissolution curve progression (Dash et al., 2010).

To identify any linear relationship between drug release profiles and different drug release kinetic models; the r^2 measure showing the highest value would be taken in consideration, as it would be highly correlated with the best descriptor of that drug-release kinetics model (Alwadi et al., 2022).

Table 2. Weight variation, hardness, friability and disintegration results of diclofenac potassium innovator and generic tablet dosage form.

Brand code	Weight (g)	Hardness (kp)	Friability loss (%)	Disintegration time[b] (sec)
A[a]	0.316 ± 0.011	6.79 ± 0.920	0.728	420.33 ± 50.10
B	0.266 ± 0.005*	8.46 ± 1.010*	0.075	497.33 ± 61.37
C	0.204 ± 0.003*	13.10 ± 0.980*	0.294	1104.8 ± 83.87*
D	0.258 ± 0.005*	8.20 ± 0.730*	0.116	595.67 ± 149.6*

Data represent mean ± standard deviation, (n = 20). Data were analyzed by one-way ANOVA followed by Dunnett post-hoc analysis for weight, hardness, and disintegration time. * Statistically significant difference ($p<0.05$) vs innovator (A). For friability loss (%), no statistical analysis was done because the values are representative of friability loss equation. [a] Innovator diclofenac potassium brand. [b] Maximum time registered for complete disintegration.

Besides r^2 values, dissolution profiles were compared based on the area under the curve (AUC), dissolution efficiency (DE), mean dissolution time (MDT), dissimilarity factor (*f*1), the similarity factor (*f*2) (Maswadeh et al., 2010) and Akaike Information Criteria (AIC) in which the smallest AIC value represents the best fit (Alwadi et al., 2022).

Statistical analysis

All analyses in this study were done using GraphPad Prism software, version 6.01. Two-way analysis of variance (ANOVA) followed by Dunnett post-hoc correction for multiple comparisons was used to compare dissolution profiles of diclofenac potassium tested brands in terms of drug-release patterns. DDSolver version 1.0 (Microsoft Excel add-in) was used for dissolution data modeling as well as pair-wise dissolution profiles comparison of generic diclofenac potassium products against the innovator brand (Cataflam). The best fitting drug-release model was selected based on comparisons of fit parameters, coefficient of determination (r^2) and AIC provided by DDSolver sofware (Zhang et al., 2010). Results of AUC, DE and MDT related to the different diclofenac potassium manufacturers were compared by one-way ANOVA followed by Dunnett post-hoc analysis (Alwadi et al., 2022).

RESULTS

Dissolution and release behavior studies are essential to ensure the bioequivalence of generic medicines with their counterpart brand. All medicinal regulatory bodies around the world apply strict rules for approval of generic products, with the main comparative parameter being dissolution. In this study, three generic diclofenac potassium products were compared with the innovator brand in relation to differences in dissolution behaviors. The study further identified the mechanisms and kinetics of release behaviors of all the tested samples.

Table 1 shows the organoleptic properties, diameters, thicknesses, and the prices in the Saudi market of all the tested tablets. All the tested tablets had the same round shape, with the innovator brand having a relatively larger diameter (≈ 0.8 mm larger), yet not significant when compared with all other generic products. Similarly, all generic products were ≈ 0.9 – 1.6 mm thinner than the innovator brand. No statistical differences ($p>0.05$) were existed between the generics and the innovator brand A in tablets' diameter and thickness measures.

Table 2 depicts the physical properties of tested tablets including average weights, hardness, friability and disintegration times. In line with the dimensions of the tested samples, the innovator tablets weighed significantly ≈ 0.05-0.1 g higher compared with the generic tablets. All tested samples showed low variation from their average weights, with the standard deviation ranging between 0.003-0.011 g. The deviations from the average weights for all tested tablets were within the USP acceptable range of less than 5% (Prasanthi et al., 2015).

For the hardness values of tested tablets, recorded values were above 4 kp, values which aligned with the hardness limit accepted by pharmaceutical industries (Rudnic and Schwartz, 1990). Brand C showed almost double the crushing force of the innovator and this measure was also numerically higher than other two generic brands B and D, which in turn, were also significantly harder than A. Despite those differences all the tested brands showed friability loss values within the USP acceptable limit of less than 1% (United States Pharmacopeial Convention, 2020).

Measurement of disintegration times revealed that the innovator tablets and brand B followed by brand D, yet the later were significant to innovator A, had a range of disintegration time (≈ 7-10 min), which was below the USP acceptable limit of 15 min (United States Pharmacopeial Convention, 2019). In a remarkable contrast, brand C showed a disintegration time of 18.5 min, which largely exceeded the acceptable limit. Thus, both brands C and D tablets were significantly longer to disintegrate when compared to brand A.

Fig. 2 shows the cumulative dissolution release profiles (% of drug release versus time) for the tested

samples where the release time was studied up to 60 min.

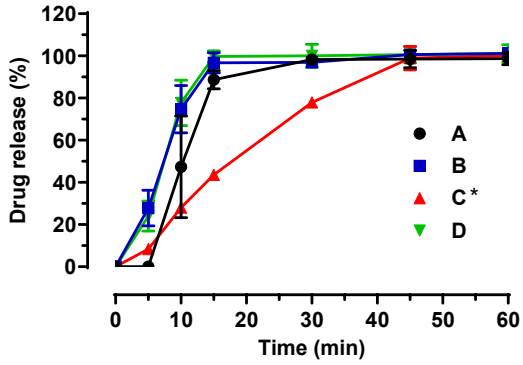

Figure 2. Dissolution profiles of commercially available diclofenac potassium 50 mg tablet brands (A–D). Data points are mean percentage of labeled amount dissolved at each sampling time with corresponding error bars.

Data represent mean ± standard deviation (n=6). * Statistically significant difference (p<0.05) vs innovator (A).

The innovator tablets displayed no release following 10 min of running the testing, at which time brands B and D had released around 25%. Brand C, in contrast, released 8.5% of the drug by 10 min, and this value was markedly lower when compared at the same time interval with brands B and D. By 15 min, and in line with the expected release profile of water-soluble drugs, the innovator brand and brands B and D showed more than 85% release, with brands B and D achieving almost complete release profiles of 97% and 99% respectively. In contrast, brand C released only 43% after 15 min and 78% after 30 min. This was almost half the release percentage of other tested brands. Obviously, the dissolution profile over 60 min for brand C tablet was overall significantly different ($p<0.05$) than that of the innovator A, supporting the findings in Table 2.

Table 3 shows all essential dissolution parameters including AUC, MDT, DE, $f2$ and $f1$, which were calculated from the dissolution release profiles of all the tested brands.

Here, dissolution parameters of all the generic brands were statistically compared with the innovator. Statistical analysis of the AUCs revealed significant differences in AUCs of all the generic brands in comparison with the innovator brand. More specifically, AUCs for brands B and D were significantly larger than that of the innovator whereas brand C had smaller AUC relative to the innovator brand. Likewise, the AUC dependent variable (DE) was higher for brands B and D compared with the innovator brand while brand C had smaller DE values compared with that of the innovator. The MDT values were in line with the release profiles of the tested brands. Brand C, which showed slower release profile (less than 50% after 15 min), again showed significantly longer MDT compared with the innovator brand. The similarity ($f2$) and difference ($f1$) factors were calculated using all release data generated from the overall dissolution curve, whereby $f1$ values of <15 and $f2$ values of >50 indicated no dissimilarities within all the time intervals. Indeed, $f2$ values for all the tested brands were found to be less than 50, hence indicating dissimilarities in the release profiles of all tested samples relative to the innovator.

The mechanism of drug release was determined by fitting the (x-y) release profile against zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models. Table 4 shows the correlation of the x-y release profiles of the tested brands with the abovementioned kinetic models, with r^2 and AIC representing the degree of correlation of each release profile with the specific kinetic model.

Values of r^2 that were close to 1 and AIC that were close to zero (lowest value) indicated the highest correlation of release profile with the kinetic model. With the exception of brand C fit parameters, r^2 was far from 1 (low values) and AIC values were far from zero (above 50) for zero order, Korsmeyer-Peppas and Higuchi, indicating that none of these models fit the release profile of the tested brands.

Table 3. Pair-wise comparison of innovator and generic diclofenac potassium tablets dissolution profiles.

Brand code	Area under the curve AUC (min %)	Dissolution efficiency DE (%)	Mean dissolution time MDT (min)	Similarity factor f_2	Difference factor f_1
A[a]	4815.3 ± 136.6	80.3 ± 2.276	10.01 ± 1.509	NA	NA
B	5201.6 ± 238.8*	86.7 ± 3.981*	8.62 ± 2.113	41.01	16.04
C	4021.6 ± 105.2*	67.0 ± 1.754*	19.88 ± 1.212*	34.55	22.08
D	5273.3± 101.7*	87.9 ± 1.087*	7.88 ± 0.538	40.78	16.60

Data represent mean ± standard deviation, (n = 6). Data were analyzed by one-way ANOVA followed by Dunnett post-hoc analysis. *Statistically significant difference (p<0.05) vs innovator (A). For $f2$ and $f1$ values were calculated using mean dissolution profiles of each brand to evaluate their range spectrum.
[a]Innovator diclofenac potassium brand.

Table 4. Modeling of innovator and generic diclofenac potassium tablets drug release kinetics.

Model		Brand A[a]	Brand B	Brand C	Brand D
Zero-order	K_0	1.653	1.376	1.796	1.384
	r^2	0.647	0.563	0.922	0.532
	AIC	62.81	62.72	50.90	63.66
First-order	K_1	0.075	0.120	0.045	0.123
	r^2	0.878	0.950	0.957	0.928
	AIC	53.36	45.55	44.68	48.58
Higuchi	K_h	14.889	16.139	12.985	16.314
	r^2	0.791	0.752	0.921	0.721
	AIC	57.12	56.76	49.02	58.03
Hixson-Crowell	K_{hc}	0.021	0.025	0.012	0.025
	r^2	0.899	0.912	0.983	0.890
	AIC	52.02	49.52	38.29	51.52
Korsmeyer-Peppas	K_{kp}	16.843	34.186	6.394	34.567
	r^2	0.793	0.860	0.961	0.827
	AIC	59.06	54.72	46.15	56.68
Weibull	α	0.863	168.924	103.409	1571.71
	β	0.385	2.301	1.514	3.137
	r^2	**0.999**	**0.998**	**0.997**	**0.999**
	AIC	8.54	23.33	29.11	12.81

All data calculated using DDSolver modeling, hence there are no replicates. [a]Innovator diclofenac potassium brand; K_0: zero-order release constant; r^2: regression constant; AIC: Akaike Information Criteria; K_1: first-order release constant; K_h: Higuchi release constant; K_{hc}: Hixson-Crowell release constant; K_{kp}: Korsmeyer-Peppas release constant; α: Weibull time dependence scale parameter; β: Weibull dissolution curve progression shape scale parameter. Bold print indicates the best fit.

In contrast, first order and Hixson-Crowell were somehow fitting the release profiles of the tested brands, with r^2 ranging between 0.878-0.957 and 0.890-0.983 for the first order and Hixson-Crowell, respectively. Calculated AIC values for those two models were still higher than 40 (far from zero) for all the tested brands. In stark contrast, Weibull model was the best fit for the release profiles of all tablet brands, with r^2 ranging between 0.997-0.999 and AIC below 30 for all brands. Furthermore, Weibull exponents of shape β for the innovator was <1, exhibiting parabolic cumulative drug release curve. In contrast, all the tested generics displayed β>1, which is consistent with a sigmoidal relationship for drug release kinetics (Jahromi et al., 2020).

DISCUSSION

It is customary viable to regularly scrutinize branded medicines based on multiple key factors including the therapeutic application, market size, and sociodemographic factors. This holds particularly true when it comes to those therapies that are frequently sourced such as over the counter (OTC) medications, have serious adverse effects when misused or used chronically, or do not undergo further testing after regulatory approval. Henceforth, for a medication as popular as diclofenac, which is frequently consumed by the general public to manage pain and inflammation, data generated from this study are both timely and pressing. Indeed, this *in vitro* investigation of diclofenac potassium 50 mg oral tablets marketed under the brand names of Rapidus, Fast-Flam, and Joflam revealed some notable variations and similarities when compared with the innovator brand, Cataflam. Thus, tablets from different brands were assessed for all physicochemical factors that can affect their release behaviors. As described in Table 1, the innovator brand showed relatively larger dimensions relative to the tested generic tablets. Increased tablet size is known to affect the disintegration and dissolution time due to increased contact with the disintegration/dissolution media (Molavi et al., 2020). Practically, this factor resulted in a slight, albeit insignificant, difference in disintegration times (Table 2) between brands A and B, where the disintegration

time of the innovator was slightly less (420 s) when compared with brands B (497 s), yet significant to that of D (595 s) and C (1105 s). The effect of the larger tablet size for the innovator extended to the dissolution data (Table 3). However, in contrast with Noyes Whitney equation, according to which the dissolution rate is proportional to tablet size (Gao et al., 2021), the larger size of the innovator branded tablet did not result in a higher dissolution rate relative to the other brands (Fig. 2), with exception of brand C, which was significantly lower than the innovator A.

In relation to the physical properties of the tested tablets (Table 2), all the tested physical properties (weight, hardness, friability) were within the acceptable USP limits, yet the weight and hardness of all brands did vary relative to the branded diclofenac potassium tablets. What is remarkable here, is that the hardness of brand C was much higher than that of the innovator, which likely affected the results of the dissolution time and profile. High hardness properties of a tablet indicate less porosity within its core, which can in turn reduce penetration of the dissolution/disintegration media into the tablet and thus contribute to much slower disintegration and dissolution (Rudnic and Schwartz, 1990). Predictably, the disintegration time of brand C was quite long relative to the other brands, lasting for almost 18 min and thus failing the recommended USP standard of 15 min. A disintegration time that exceeds the USP standard can markedly influence the dissolution properties of the drug and can consequently impact the onset of action of the consumed medication.

Expectedly, the mean dissolution time (MDT) of brand C was significantly higher than all other tested samples (Table 3). These results are in accordance with the noticeably higher disintegration times recorded for brand C. AUC and DE, on the other hand, were significantly different for all the tested brands when compared with that of the innovator. More specifically, greater AUCs and DEs were noted for brands B and D relative to the innovator, and these were comparatively smaller for brand C. Furthermore, analysis of $f2$ and $f1$ values revealed dissimilarities in the release profile at all tested time intervals. We believe that these differences must have impacted the cumulative dissolution release behaviors of the tested samples (Fig. 2). The differences in the dissolution behavior of brand C can be interpreted based on its physical properties and can thus be owed to the higher hardness of its tablets and their prolonged disintegration time. The noted release profiles of brands B and D do not seem explainable by the recorded physical properties of those brands, as their properties were to a great extent reminiscent of that of the innovator brand. Alternatively, these differences are potentially attributable to the various chemical ingredients added to brands B and D (e.g., binders, disintegrants, film coating materials and even the lubricants) to mimic the release behavior of the innovator brand. Such ingredients seem to have resulted in higher release parameters when compared with those of the innovator.

Study of drug release kinetics (Table 4) showed that the best model to fit the release behavior of the brands and innovator was Weibull model. This suggests that novel DDs mathematical representation of diclofenac potassium contributed a predictable drug release profile for all tested tablets. These results are of great significance when further pursuing *in vitro* and *in vivo* pharmacokinetic-pharmacodynamic correlation studies (Jahromi et al., 2020).

CONCLUSION

Variations in *in vitro* tablet quality parameters of oral diclofenac potassium do exist, and this can be related to inherent differences in the manufacturing process across different pharmaceutical companies. The formula of brand C, unlike that of brands B and D, seems to undermine the purpose of a diclofenac IR formulation, given its longer DT, lower DE and slower dissolution release profile relative to that of the innovator. This makes brand C less appealing as it is likely to have a slower onset of action compared to the overall within the specification's innovator and brands B and D. Lastly, these differences in dissolution behavior, however, do not seem eventually to drastically impact drug release kinetics of diclofenac potassium branded tablets. Collectively, these data should be taken in consideration by national and perhaps international pharma and health regulatory bodies when reviewing tablet manufacturing quality of important medications like diclofenac potassium.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

ACKNOWLEDGMENTS

Administrative and financial assistance during the progression of this work were thankfully supported by Ms. Sawsan Sumeir from the Office of Research & Innovation and internal research grant #21313 from Alfaisal University.

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