dx.doi.org/10.14227/DT290322PGC2

Comparative Analysis of Commercially Available Acetaminophen Tablets in Saudi Arabia

Aiman Y. Alwadi[1*], Ghosoun M. Arafeh[1], Mohammad S. Almehlesi[2], Hamzah M. Maswadeh[2], Ibrahim M. Salman[1], and Omar Z. Ameer[1]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, Alfaisal University, Riyadh, Saudi Arabia.
[2]Department of Pharmaceutics, College of Pharmacy, Qassim University, Buraidah, Saudi Arabia.

e-mail: aalwadi@alfaisal.edu

ABSTRACT

Acetaminophen is a widely used oral analgesic and antipyretic medication; however, quality control parameters may differ across various brands. The aim of the present study was to evaluate and compare critical quality attributes, including in-vitro dissolution characteristics, of five acetaminophen tablet brands (labeled A–E) from the Saudi market and determine their pharmaceutical equivalence. All brands were tested for conformity with the United States Pharmacopoeia (USP) standards, through evaluation of weight variation, hardness, friability, disintegration, and dissolution. Dissolution profiles were compared using model-dependent and independent approaches relative to the innovator brand A (Panadol). All tested brands passed the weight variation and friability tests with deviations of less than 5% from the average weight and less than 1% weight loss, respectively, with the exception of brand C showing relatively higher friability (1.13%). All brands displayed variable disintegration times; however, all were compliant with USP specifications. All studied tablets released less than 80% of the drug within 30 minutes; however, brands B and C had lower drug release rates, area under the curve (AUC), and dissolution efficiency (DE) compared with the innovator. Brand E, on the other hand, had a higher drug release rate, AUC, DE, and mean dissolution time (MDT), and thus was pharmaceutically inequivalent to the innovator. All tested brands exhibited a non swellable matrix diffusion-controlled dissolution as assessed by the Korsmeyer-Peppas model of drug-release kinetics. In conclusion, all acetaminophen brands were able to pass USP specifications to justify interchangeability. Minor variations in in-vitro dissolution characteristics could reflect inherent manufacturing compounding differences.

KEYWORDS: Acetaminophen, quality control, comparative analysis, dissolution, disintegration.

INTRODUCTION

Saudi Arabia has the largest pharmaceutical market in the Middle East and African region, with a net worth of $8.2 billion US dollars in 2018 (*1*). This market has been witnessing a fierce competition among various pharmaceutical companies, including innovator and generic brands (*1*). Innovator companies spend a huge portion of their resources during clinical trials for the development of a novel drug product (*2*). This is rewarded through achieving a drug patent for a certain period of time, protecting their products from competition in the market (*2*). However, when the patent of an innovator drug product expires, other pharmaceutical companies

*Corresponding author

will have the opportunity to produce their own generic drug brands, hence creating a swirl in market competition (*2*). For a generic drug application to receive an approval, applicants must validate their generic drug and declare it as pharmaceutically equivalent to an approved, safe, and effective reference product. Specifically, the generic drug must contain identical amounts of the same active ingredient in the same dosage form and route of administration, and must meet all specified compendial standards of strength, quality, purity, and identity (*3*). Additionally, these specifications require in-vivo bioequivalence assessments, with products demonstrating comparable bioavailability profiles (i.e., active ingredients must be absorbed from a drug product and made available at the site of action at a similar rate and extent) (*2*, *3*).

The World Health Organization (WHO) encourages the evaluation of healthcare expenditure and the improvement of medicine access through timely evaluation of drug dosage forms to ensure that all medications are pharmaceutically qualified and therapeutically equivalent before they reach the patient (*4*–*6*). Even though many generic drug brands are widely available in the market, effective quality control and monitoring approaches may be inadequate or even absent in many developing countries. Concurrently, the emergence of a wide variety of generic products have fed into the widespread distribution of substandard and counterfeit drug products in the pharmaceutical market (*7*). Substandard drug products, as defined by the WHO, are genuine drugs produced by certain authorized manufacturers that do not meet the quality specifications affixed for them by the national or international standards (*8*). Around 10% of medical products are found to be either falsified or of a substandard quality, and this could be related to poor storage conditions, difficulties in medicine access by healthcare providers or patients, technical hindrance and limitations in manufacturing, or fragile local authority governance over pharmaceutical products regulations (*4*).

Establishing firm measures of quality control of medications of different manufacturing origins is essential and imperative for medications to exhibit the therapeutic effects they are intended to treat (*9*). A plethora of quantitative assessments of drug products exists, particularly for dosage forms that are self-administered in tablet or capsule formulations (*10*). Typically, assessments that function to accurately define the physicochemical properties of various dosage forms and their stability profiles and determine bioavailability are performed during early drug design stages and during subsequent monitoring of production quality (*10*). For tablet dosage forms, any chemical breakdown or interaction between tablet components may alter their physicochemical properties, thereby potentially affecting the bioavailability from a tablet system (*10*). Tablets must be fabricated to withstand chipping, abrasion, and breakage; and each unit in a given batch should contain the active pharmaceutical ingredient (API) within a narrow range of the labeled strength. Thus, the main physical properties of tablet formulations are their mechanical strength and consistent weight and/or drug content. These can be assessed using the friability, hardness, and uniformity of dosage units tests (*11*–*15*). API can only be absorbed once released from the tablet into the solution. Accordingly, disintegration, which refers to the breakdown of tablets into smaller particles, is the first step driving the release of drug from immediate- release (IR) tablet dosage forms (*16*, *17*). The prediction of in-vivo bioavailability of most oral drug formulations depends greatly on in-vitro dissolution studies. These studies play an imperative role as a quality control tool for monitoring batch-to-batch consistency of drug release from a particular dosage

form and as an in-vitro surrogate for in-vivo performance (*18–20*). The United States Food and Drug Administration (FDA) and WHO have approved Biopharmaceutics Classification System (BCS) class 1 and 3 drugs for IR oral dosage forms, which recognizes in-vitro dissolution tests to be equivalent (i.e., for obtaining a biowaiver) to the in-vivo tests in comparing generic with innovator brand products to determine interchangeability (*21*, *22*). Pharmaceutically, dissolution testing is therefore essential during the drug development stages and data derived from this testing method can estimate correlation between drug release and absorption, and serve as a valuable tool for marketing approval (*18*, *23*).

Acetaminophen (USA) or paracetamol (Europe) is chemically known as *N*-acetyl-para-aminophenol or N-(4-hydroxyphenyl) ethanamide and N-(4-hydroxyphenyl) acetamide (Fig. 1). It is an over-the-counter (OTC) drug used for its antipyretic and mildly analgesic effects (*24*, *25*). The drug plays an active role in the inhibition of prostaglandin synthesis in the central nervous system and is highly selective for cyclooxygenase enzymes (*26*, *27*).

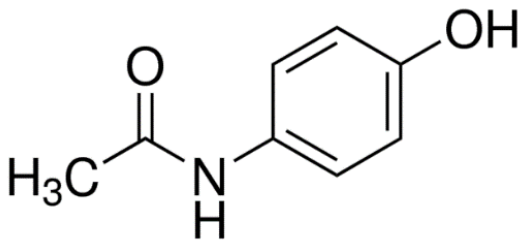

Figure 1. Chemical structure of acetaminophen.

In Saudi Arabia, acetaminophen is marketed as IR tablet, capsule, and suppository forms in doses ranging from 100 to 650 mg per unit. It is also available in syrup, solution, suspension, and granule dosage forms in a wide range of strengths. Acetaminophen, having high solubility and low permeability, is a BCS class 3 compound according to the current BCS criteria (*28*). The extent of absorption of this class of compounds is rarely affected by differences in composition; however, differences in the rate of absorption between brands and formulations were documented in some studies (*28*). Essentially, the presence of sodium bicarbonate in some of these drug products was reported to increase the rate of absorption, probably due to effects on gastric emptying. Taking into account acetaminophen's therapeutic uses, wide therapeutic index, and uncomplicated pharmacokinetic properties, in-vitro dissolution data collected in accordance with the relevant guidelines can be safely used for declaring bioequivalence (BE) of two acetaminophen formulations (*28*). Because of its desirable therapeutic effects and safety profile, acetaminophen is considered one of the most popular OTC drugs and is available in several generic brands, particularly in a tablet formulation, from different pharmaceutical companies (*29*). The existence of substantial differences between the innovator and generic brands is anticipated and may, in some cases, impact the end user experience and contribute to significant variability in the predicted therapeutic response (*30*). Accordingly, the current study aimed to investigate in-vitro quality control parameters of five commercially available acetaminophen tablet brands (500 mg) to assess their conformity with the United States Pharmacopeia (USP) standards. Further, the study aimed to investigate drug-release kinetics for selected brands and determine their pharmaceutical equivalence with the innovator brand (Panadol).

MATERIALS AND METHODS

Chemicals and Reagents

Acetaminophen reference standard (RS) was donated by Deef Pharmaceutical Industries (Qassim, Saudi Arabia) and originally manufactured by Albemarle (USA). Reagents used throughout the study were of analytical grade, including 38% hydrochloric acid (HCl; Scharlab, Spain), disodium hydrogen phosphate (Sigma-Aldrich, USA), and potassium dihydrogen phosphate (Sigma-Aldrich, USA). Friability, hardness, uniformity of dosage units, disintegration, and dissolution tests were done according to *USP* chapters <1216>, <1217>, <905>, <701>, and <711>, respectively (*31*–*34*).

Tablet Samples

Five brands of acetaminophen tablets (500 mg) were purchased from different retail pharmacies in Riyadh, Saudi Arabia including Panadol (lot: AY8W, exp: 11/2024, GSK, Ireland), Fevadol (lot: 132459, exp: 07/2025, SPIMACO, Saudi Arabia), Adol (lot: 210017, exp: 04/2025, Alpha Pharma Industry, Saudi Arabia), Omol (lot: 0220024 exp: 12/2023, National Pharmaceutical Industries, Oman), and Panadrex (lot: LT424, exp: 09/2025, Kuwait Saudi Pharmaceutical Industries, Kuwait). Acetaminophen brands were labelled from A to E, with A being the innovator and the others being the generic products.

Standard Curve Preparation

A stock solution (100 µg/mL) of acetaminophen was prepared by dissolving 100 mg of RS in 10 mL of 0.1 N HCl. The solution was then brought up to volume using 0.1 N HCl. Aliquots of the stock solution were further diluted in 0.1 N HCl to concentrations within Beer-Lambert's range (4–12 µg/mL) and scanned at a wavelength of 243 nm using UV/Visible spectrophotometer (Jenway 6705, UK). The resultant plot of absorbance versus concentration (r^2 = 0.9993) was used for later analyses.

Mechanical Calibration and Performance Verification of Dissolution Apparatus and UV/Visible Spectrophotometer

Tests for mechanical calibration and performance verification of dissolution apparatus (Erweka DT 128 light, Germany) were done on routine basis (i.e., every 6 months) as per USP specifications as follows. For mechanical calibration, both equipment environment and dissolution test assembly are regularly checked. Bench tops that limit vibration and has not more than 1° surface inclination are used to support dissolution apparatus. All vessels and individual parts of the paddle system are uniquely identified and checked for conformance with *USP* <711> in terms of dimensions, inclination alignment, rotation speed, temperature control, and presence of gross defects. For performance verification testing, a dissolution test is carried out using USP Prednisone Tablets RS; 500 mL of deaerated purified water is used as the dissolution medium, and the test is set at 50 rpm and 37 ± 0.5 °C for 30 minutes. After 30 minutes of testing and with rotation continuing, sampling and filtration using 0.45-µm membrane filters are done. Release of prednisone is determined following UV absorbance measurements at 242 nm and comparison with reference standard preparations.

Validation and monitoring of UV-Visible spectrophotometer is performed on a monthly basis

following the standard operation procedure. Testing is done to verify the wavelength accuracy, stray light limit, resolution power, absorbance accuracy, and stability, in addition to baseline flatness, noise, and reproducibility of the instrument.

Friability Test

For the friability test, 20 tablets were randomly selected, weighed, and placed into a friabilator chamber (Roche Friabilator, Germany) set at 25 rpm for 4 minutes. The tablets were subsequently weighed again and the differences in weight were calculated as percentage friability. The same procedure was repeated for all acetaminophen tablet brands. Requirements are met if the percentage friability is not more than 1.0% (*31*).

Hardness Test

A sample of 20 tablets from each brand was randomly selected and placed one by one in a tablet hardness tester (Erweka TBH 125, Germany) as per the *USP* specifications (*35*). The degree of force in kiloponds (kp) required to break a tablet across the diameter was measured.

Uniformity of Dosage Unit Test

To test for weight variation, 20 tablets from each brand were randomly selected and weighed individually using an electronic balance (KERN PFB 300-3, Germany). The average weights and percentage deviations from the mean values for each brand were calculated. Requirements are met if the weights of not more than two tablets deviate from the average weight of the same brand by more than 5%, and no single tablet can differ in weight by more than 10% (*32*).

Disintegration Test

Complying with *USP* <701> standards , six tablets from each brand were individually placed inside each of the six tubes of the basket of disintegration test apparatus (ED 2L, Electrolab, Mumbai, India) (*33*). The media temperature was maintained at 37 ± 2 °C, and the test started immediately after the basket assembly was attached. The disintegration time is the time required for no particles to remain in the system's basket. If all six tablets disintegrate, the brand passes the test. If one or two tablets do not fully disintegrate, then 12 additional tablets are tested. Only two tablets out of the total of 18 tested tablets are allowed to fail complete disintegration (*33*).

Dissolution Test

The dissolution test was carried out according to the USP paddle method (apparatus II) and was done in six replicates (vessels) for each brand. The temperature of the medium was maintained at 37 ± 0.5 °C, and the stirring speed was set to 50 rpm. In all the experiments, 5 mL samples were withdrawn from each vessel at 10, 20, 30, 50, 80, and 120 minutes and replaced with equal volumes of fresh dissolution medium. Samples were filtered using 0.45-µm membrane filters (Merck, USA), diluted to concentrations within Beer-Lambert's range, and their absorbance was measured using a UV/Vis spectrophotometer (*34*). Absorbance values were then correlated with the previously constructed standard curve (r^2 = 0.9993) to calculate the concentration of drug released at each time interval.

Drug-Release Kinetics

In this study, the in-vitro drug release data were fitted to the zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Weibull mathematical models to determine the best model that describes the mechanism and kinetics of drug release from the tested brands. The zero-order model describes systems in which the drug release rate is independent of the concentration of dissolved species, whereas the first-order model, on the other hand, describes the drug release from systems where dissolution rate is dependent on the concentration of the dissolving species (*36*).

The Higuchi model 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 (*36*). Drug release from systems where there is a change in the surface area and diameter of particles or tablets is described by the Hixson-Crowell model (*36*).

Korsmeyer and Peppas put forth a simple equation relating drug release from a polymeric system with its specific type of dissolution (*37*). The Weibull function is a mathematical model lacking physicochemical fundament and can be used to study the dissolution rate (*38*).

A model is considered the best descriptor of drug-release kinetics when it displays the highest correlation (R^2) values (*39*). The pertinence of the release models employed was also tested using the Akaike Information Criteria (AIC), which is a measure of the best fit based on maximum probability (*40*). When comparing data sets of different brands, the model associated with the smallest AIC value is considered the best fit.

In addition, a comparison of dissolution profiles was carried out employing model-independent approaches including difference (f_1) and similarity (f_2) factors, area under the curve (AUC), dissolution efficiency (DE), and mean dissolution time (MDT).

Statistical Analysis

All comparisons were run using GraphPad Prism software, version 6.01. Two-way analysis of variance (ANOVA) followed by Dunnett post-hoc analysis was used to compare dissolution profiles of tested acetaminophen 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 acetaminophen brands against the innovator product. The best fitting drug-release model was selected based on comparisons of fit parameters, coefficient of determination (R^2), and AIC provided by DDSolver (*41*).

RESULTS AND DISCUSSION

Ongoing in-vitro assessment of pharmaceutical dosage forms is key to ensuring optimal quality control and is a prerequisite for bioequivalence studies. Five different tablet brands of acetaminophen were tested for their weight variation, hardness, friability, disintegration, and dissolution. All drug samples were within their shelf-life at the time of investigation. Characteristics of studied brands are shown in Table 1.

Table 1. Characteristics of 500-mg Acetaminophen Tablet Formulations

Brand Code	Price ($)[b]	Appearance	Diameter (mm), mean ± SD	Thickness (mm) mean ± SD
A[a]	1.47	White, elliptical	17.67 ± 0.029	5.098 ± 0.059
B	1.41	White, elliptical	17.77 ± 0.040	5.822 ± 0.051
C	2.37	White, circular	12.89 ± 0.061	5.221 ± 0.081
D	2.11	White, circular	12.60 ± 0.018	4.092 ± 0.039
E	2.50	White, elliptical	19.14 ± 0.039	7.118 ± 0.066

[a] Innovator acetaminophen brand; [b] Latest price per packet in USD.

The main objectives of the uniformity of dosage units test are to ensure good manufacturing practices, appropriate tablet size, and the content uniformity of the formulation (*42*). To that end, friability and weight variation tests were carried out first. The tablet weight variations in all the tested brands were low (≤ 3.5% deviation from the average). These results complied with the *USP* specification (*32*). The highest weight variation was observed for brand C, approaching 3.5%. With respect to hardness, the mean values were in the range of 14.10–23.20 kp (Table 2). Although no specific goals were explicitly stated in the *USP* regarding tablet breaking force, the obtained results for all tested brands were relatively comparable, except for brand B, demonstrating relatively higher kp values. The *USP* states that the tablets friability should be less than 1% (*31*). This specification was met by all tested brands except brand C (Table 2), which showed higher friability values compared with all other brands. The reason behind the latter finding cannot be delineated in this study but could be related to specific batch issues, including differences in excipients composition and/or improper transport or storage of the product. Very low moisture levels can result in more friable tablets , so the high temperatures and dry climate characteristics of the area coupled with inappropriate transport/storage conditions could have contributed to the friability data of brand C (*10*, *14*).

Disintegration may be directly related to the dissolution and subsequent bioavailability of a drug, and a drug incorporated in a tablet formulation is released more rapidly as the tablet disintegrates (*16*). As shown in Table 2, all tested brands compiled with the *USP* specification for disintegration, (*33*). It is noteworthy that although brand B showed the highest hardness as stated above, the disintegration of this brand was the fastest. This could be related to the presence of a high concentration of disintegrant excipients that offset the high kp for this brand.

The dissolution of a drug from an oral solid dosage form is a necessary criterion for its bioavailability, and as such the drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed (*19*, *20*). Acetaminophen tablets should release not less than 80% of the drug at 30 minutes, which is *USP* requirement that was met by all tested brands (Fig. 2) (*34*). When comparing the dissolution profiles of tested brands with that of the innovator (brand A) using a plot of the cumulative drug release versus time, the drug release rate for brands B (83 ± 7% vs 88 ± 10%) and C (82 ± 11% vs 88 ± 10%) was significantly lower, whereas that of brand E was markedly higher (97 ± 7% vs 88 ± 10%), all $p < 0.05$. These differences could be attributed to existing differences in shape and size of each pharmaceutical formulation as well as the amount and type of excipients used (*43*, *44*).

Table 2. Weight Variation, Hardness, Friability, and Disintegration Results for 500-mg Acetaminophen Tablet Formulations

Brand Code	Weight (g) mean ± SD	Hardness (kp) mean ± SD	Friability (% loss)	Disintegration Time (sec)[b]
A[a]	0.598 ± 0.010	16.64 ± 1.394	0.001	300
B	0.610 ± 0.008	23.20 ± 2.950	0.160	5
C	0.643 ± 0.012	14.10 ± 0.931	1.133	160
D	0.560 ± 0.003	15.55 ± 0.883	0.625	139
E	0.650 ± 0.013	15.80 ± 2.778	0.076	86

[a] *Innovator acetaminophen brand.*

[b] *Maximum time registered for complete disintegration.*

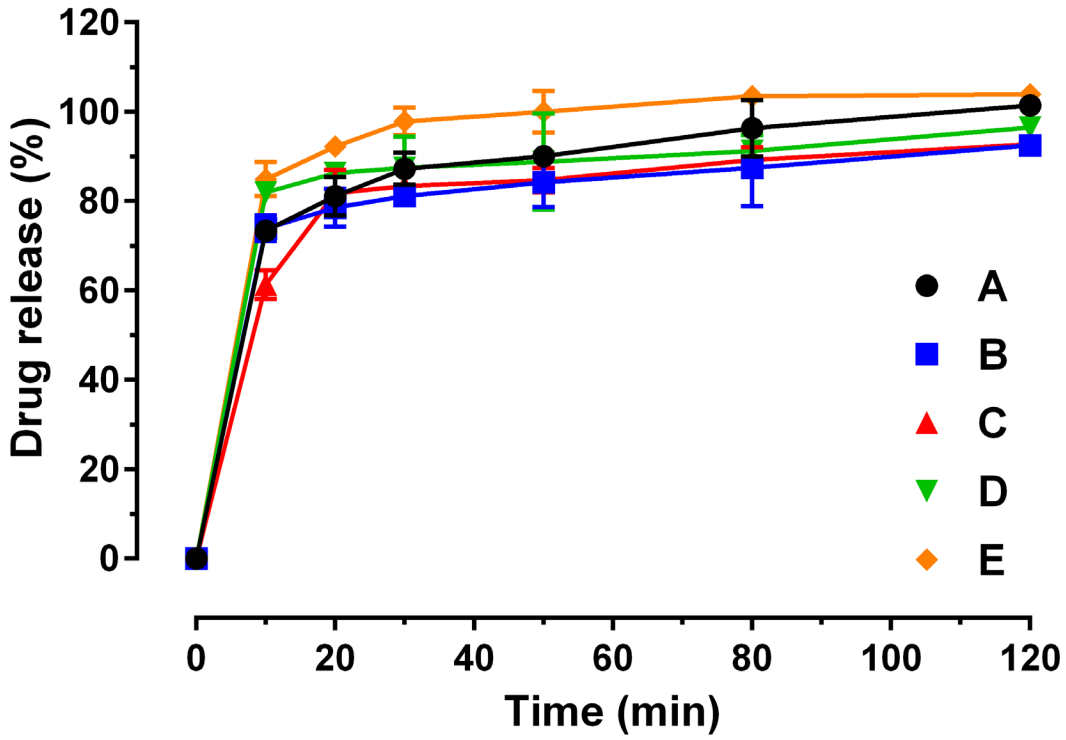

Figure 2. Dissolution profiles of commercially available acetaminophen 500-mg tablet brands (A–E). Data points are mean percentage of labeled amount (n = 6) dissolved at each sampling time with corresponding error bars (standard deviation).

To study the mechanism of drug release, the dissolution profiles of the five tested products were evaluated by fitting the experimental data to zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models (Table 3). The data for all five products demonstrated poor fit patterns with the zero-order model (i.e., low R^2 values, 0.279 – 0.680). In contrast, when the dissolution data were plotted according to the first-order, Korsmeyer-Peppas, and Weibull models, stronger fit patterns (i.e., high R^2 values, 0.868–0.999) were obtained. The Korsmeyer-Peppas model provided the highest R^2 and lowest AIC values, suggesting that drug-release kinetics for all tested brands are best described by this model (Table 3). The release exponent (n)

of the Korsmeyer-Peppas model was < 0.5 across all studied acetaminophen formulations, indicating a non-swellable matrix diffusion-controlled mechanism of drug release (*37*).

With respect to model-independent dissolution profiles comparison (Table 4), the values for AUC and DE of brands B and C were statistically smaller ($p < 0.05$) compared with the innovator, indicating less overall dissolution than that of the innovator. The values for AUC and DE of brand E were significantly higher ($p < 0.05$) compared with the innovator, indicating a higher dissolution efficiency for this particular brand. This conclusion was further supported by the fact that brand E exhibited significantly faster dissolution, as evidenced by the markedly lower MDT value for this brand (Table 4).

Table 3. Modeling of Release Kinetics of 500-mg Acetaminophen Tablet Formulations

Model		Brand A[a]	Brand B	Brand C	Brand D	Brand E
Zero-order	K_0	0.538	0.456	0.493	0.448	0.510
	R^2	0.441	0.374	0.417	0.320	0.341
	AIC	62.08	61.75	61.56	63.13	64.28
First-order	K_1	0.105	0.095	0.081	0.143	0.178
	R^2	0.959	0.868	0.930	0.936	0.993
	AIC	41.70	48.85	44.71	44.54	30.43
Higuchi	K_h	11.87	11.03	11.06	11.69	12.86
	R^2	0.510	0.384	0.498	0.279	0.341
	AIC	59.16	59.63	58.50	61.54	62.27
Hixson-Crowell	K_{hc}	0.013	0.012	0.012	0.013	0.013
	R^2	0.664	0.542	0.680	0.463	0.495
	AIC	56.51	57.55	55.35	59.47	60.41
Korsmeyer-Peppas	K_{kp}	55.61	60.25	51.10	71.63	69.65
	R^2	**0.999**	**0.999**	**0.981**	**0.998**	**0.998**
	AIC	**15.54**	**9.22**	**37.58**	**17.88**	**16.75**
Weibull	α	2.113	1.308	0.887	0.940	2.149
	β	0.443	0.235	0.160	0.202	0.600
	R^2	0.996	0.998	0.998	0.998	0.996
	AIC	27.67	19.39	22.27	23.04	30.51

[a] *Innovator acetaminophen brand.*

R^2: regression constant; AIC: Akaike Information Criteria. ***Bold*** *indicates the best fit model.*

It is imperative to appreciate that the fit factors (f_2 and f_1) are of value when comparing dissolution profiles as per the FDA recommendation (*45*). These fit factors were calculated for each brand using brand A (innovator) as a reference (Table 4). The f_2 value is believed to be more sensitive in predicting dissimilarities between dissolution curves than f_1, but these values are dependent on the number of sampling time points selected. According to the FDA, f_1 values less than 15 and f_2 values greater than 50 should ensure equivalence between the dissolution curves and are suggestive of an average difference of no more than 10% at each sample time point. With this stipulation in mind, the dissolution curves corresponding to brands B, C, and D (not E) were similar and thus considered pharmaceutically comparable to that of the reference formulation, thereby assuring their interchangeability (Table 4).

Table 4. Pair-Wise Comparison of Dissolution Profiles for 500-mg Acetaminophen Tablet Formulations.

Brand Code	AUC (min %)	MDT (min)	DE (%)	f_2	f_1
A[a]	10504.0	16.4	87.5	N/A	N/A
B	9758.0*	14.5	81.3*	67	4
C	9775.5*	14.5	81.4*	53	12
D	10337.5	12.8	86.1	61	10
E	11438.5*	9.9*	95.3*	48.25	17

Data were analyzed by one-way ANOVA followed by Dunnett post-hoc analysis.
[a] Innovator acetaminophen brand.
** Statistically significant difference ($p < 0.05$) vs innovator (A).*
AUC: area under the curve; MDT: mean dissolution time; DE: dissolution efficiency; f_1: difference factor; f_2: similarity factor.

CONCLUSION

In summary, five acetaminophen brands were able to pass all *USP* specifications for physical properties, with the exception of brand C failing only the friability test. The dissolution profiles obtained with the analyzed products were found to be quite different across tested products, indicating that the results from dissolution tests are formulation-dependent. The Korsmeyer-Peppas model was the best fit, with maximum determination coefficients and smallest AIC values. In general, brands B and C exhibited poor drug release kinetics while brand E surpassed those of the innovator. When fit factors are considered, only brand E is deemed as pharmaceutically inequivalent with the innovator.

Relative variations were observed amongst the in-vitro dissolution profiles of acetaminophen tablets of different commercial preparations. As acetaminophen is a BCS class 3 drug, these products are grossly interchangeable; however, evaluations and assessments of the different excipients, particularly brands B, C, and E, are required to determine their effects on the overall characteristics of these drug products. These data will help inform policies and regulations adopted by the Saudi Arabia's Pharmaceutical Agencies with respect to ensuring appropriate production quality, providing ideal transport and storage conditions, and ultimately guaranteeing optimal product effectiveness to the end user.

ACKNOWLEDGMENTS

The authors thank Ms. Sawsan Sumeir (Office of Research, Alfaisal University) for administrative assistance.

FUNDING

This study was funded by Alfaisal University internal research grant (IRG 21313). The funder had no other role in the study.

CONFLICTS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

REFERENCES

1. Alrasheedy, A. A.; Hassali, M. A.; Wong, Z. Y.; Aljadhey, H. AL-Tamimi S.K. SF. Pharmaceutical Policy in Saudi Arabia. In *Pharmaceutical Policy in Countries with Developing Healthcare Systems*; Babar, Z. U. D., Ed.; Adis: Cham, 2017; pp 329–347. DOI: 10.1007/978-3-319-51673-8_16.
2. Lionberger, R. A. FDA critical path initiatives: opportunities for generic drug development. *AAPS J.* **2008**, *10* (1), 103–109. DOI: 10.1208/s12248-008-9010-2.
3. Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). U.S. Department of Health and Human Services, Food and Drug Administration, 2017.
4. Substandard and falsified medical products. World Health Organization. January 31, 2018. https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products (accessed August 1, 2022).
5. Global Surveillance and Monitoring System for Substandard and Falsified Medical Products. World Health Organization: Geneva, 2017.
6. Uddin, M. S.; Mamun, A. A.; Hossain, M. S.; Asaduzzaman, M.; Sarwar, M. S.; Rashid, M.; Herrera-Calderon, O. In vitro quality evaluation of leading brands of ciprofloxacin tablets available in Bangladesh. *BMC Res. Notes* **2017**, *10* (1), 185. DOI: 10.1186/s13104-017-2507-y.
7. Odeniyi, M. A.; Adegoke, O. A.; Adereti, R. B.; Odeku, O. A.; Itiola, O. A. Comparative analysis of eight brands of sulfadoxine-pyrimethamine tablets. *Trop. J. Pharm. Res.* **2003**, *2* (1). DOI: 10.4314/tjpr.v2i1.14581.
8. Definitions of Substandard and Falsified; Medical Products. World Health Organization: Geneva. 2017.
9. Al Ameri, M. N.; Nayuni, N.; Anil Kumar, K. G.; Perrett, D.; Tucker, A.; Johnston, A. The differences between the branded and generic medicines using solid dosage forms: In-vitro dissolution testing. *Results Pharma Sci.* **2012**, *2*, 1–8. DOI: 10.1016/j.rinphs.2011.12.001.
10. Lachman, L.; Lieberman, H. A.; Kanig, J. L.; Eds. Tablets. In *The Theory and Practice of Industrial Pharmacy,* 3rd ed. Lea and Febiger: Philadelphia, 1986, p. 296.
11. Smith, A. N. Compressed tablets; resistance to wear and tear. *Pharm J*. **1949**, *109* (4480), 194.
12. Burlinson, H.; Pickering, C. The disintegration of compressed tablets; the effect of age and certain associated factors. *J. Pharm. Pharmacol.* **1950**, *2* (10), 630–638.
13. Webster, A. R.; Van Abbe, N. J. A test for the mechanical strength of compressed tablets. *J. Pharm. Pharmacol.* **1955**, *7* (11), 882–891.
14. Ahmad, I.; Shaikh, R. H. Effect of temperature and humidity on hardness and friability of packaged paracetamol tablet formulations. *Pak. J. Pharm. Sci.* **1994**, *7* (2), 69–78.
15. Green, G.; Berg, C.; Polli, J. E.; Barends, D. M.; Brown, W. E. Pharmacopeial standards for the subdivision characteristics of scored tablets. *Pharm. Forum* **2009**, 35 (6), 1598–1612.
16. Du, J.; Hoag, S. W. Characterization of excipient and tableting factors that influence folic acid dissolution, friability, and breaking strength of oil- and water-soluble multivitamin with minerals tablets. *Drug Dev Ind Pharm*. **2003**, *29* (10). DOI: 10.1081/DDC-120025871.
17. Mukesh, P. Ratnaparkhi, Shilpa P. Chaudhari, Suresh B. Dhiwar RRG. Marketed Formulations: Quality Evaluation of Conventional Release Paracetamol Tablet. *Res J Pharm Tech.* **2012**, *5* (3), 390–392.
18. Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res.* **1998**, *15* (1), 11–22. DOI: 10.1023/A:1011984216775.
19. Olaniyi, A. Principles of Pharmacokinetics. *Essential Medicinal Chemistry*, 3rd ed.; Hope Publications: Ibadan, Nigeria, 2005; pp 59–79.
20. Babalola, C. P. Bioavailability and bioequivalence (BA/ BE) assessment. In Olaniyi, A. A.; Babalola, C. P.; Oladeinde, E. O.; Adegoke, A. O.; Eds. *Towards better quality assurance of drugs in the 3rd millennium: biopharmaceutical methods in drug quality assurance. Proceedings of fourth national workshop, 20th-24th of August, 2001*. Univeresity of Ibadan: Ibadan, Nigeria, 2001, p. 79.
21. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*; WHO Technical Report Series, No. 937, Annex 7; World Health Organization: Geneva, 2006; pp 347–438.
22. *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Silver Spring, MD, 2017.
23. Shah, V. P. Dissolution: A quality control test vs. A bioequivalence test. *Dissolut. Technol.* **2001**, *8* (4), 6–7. DOI:

10.14227/DT080401P6.
24. Dinç, E.; Ertekin, Z. C.; Ünal, N. Three-way analysis of pH-UV absorbance dataset for the determination of paracetamol and its pKa value in presence of excipients. *Spectrochim Acta A Mol Biomol Spectrosc*. **2020**, 230, 118049. DOI: 10.1016/j.saa.2020.118049.
25. Majid, M.; Mishra, R.; Mishra, B. K. Effects of various carriers on the solubility of paracetamol. *Res J Pharm Tech.* **2009**, *2* (2), 419–420.
26. Moriarty, C.; Carroll, W. Paracetamol: pharmacology, prescribing and controversies. *Arch. Dis. Child. Educ. Pract. Ed.* **2016**, *101* (6), 331–334. DOI: 10.1136/archdischild-2014-307287.
27. Graham, G. G.; Davies, M. J.; Day, R. O.; Mohamudally, A.; Scott, K. F. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* **2013**, *21* (3), 201–232. DOI: 10.1007/s10787-013-0172-x.
28. Yu, L. X.; Amidon, G. L.; Polli, J. E.; Zhao, H.; Mehta, M. U.; Conner, D. P.; Shah, V. P.; Lesko, L. J.; Chen, M. L.; Lee, V. H.; Hussain, A. S. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm. Res.* **2002**, *19* (7), 921–925. DOI: 10.1023/A:1016473601633
29. Bertolini, A.; Ferrari, A.; Ottani, A.; Guerzoni, S.; Tacchi, R.; Leone, S. Paracetamol: new vistas of an old drug. *CNS Drug Rev.* **2006**, *12* (3-4), 250–275. DOI: 10.1111/j.1527-3458.2006.00250.x.
30. Davit, B. M.; Nwakama, P. E.; Buehler, G. J.; Conner, D. P.; Haidar, S. H.; Patel, D. T.; Yang, Y.; Yu, L. X.; Woodcock, J. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Ann. Pharmacother.* **2009**, *43* (10), 1583–1597. DOI: 10.1345/aph.1M141.
31. <1216> Frability. In *USP-NF*. The USP Convention, Inc.: Rockville, MD, 2022.
32. <905> Uniformity of dosage units. In *USP-NF*. The USP Convention, Inc.: Rockville, MD, 2022.
33. <701> Disintegration. In *USP-NF*. The USP Convention, Inc.: Rockville, MD, 2022.
34. <711> Dissolution. In *USP-NF*. The USP Convention, Inc.: Rockville, MD, 2022.
35. <1217> Tablet breaking force. In *USP-NF*. The USP Convention, Inc.: Rockville, MD, 2022.
36. Singhvi, G.; Singh, M. Review: In-vitro drug release characterization models. *Int J Pharm Stud Res*. **2011**, 2 (1):77–84.
37. Chime, S. A.; Onunkwo, G. C.; Onyishil, I. I. Kinetics and mechanisms of drug release from swellable and non swellable matrices: A review. *Res J Pharm Biol Chem Sci.* **2013**, *4* (2): 97-104.
38. Dash, S.; Murthy, P. N.; Nath, L.; Chowdhury, P. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm.* **2010**, *67* (3), 217–223.
39. Venkata Srikanth, M.; Sreenivasa Rao, N.; Ambedkar Sunil, S.; Janaki Ram, B.; Kolapalli, V. R. M. Statistical design and evaluation of a propranolol HCl gastric floating tablet. *Acta Pharm. Sin. B* **2012**, *2* (1), 60–69. DOI: 10.1016/j.apsb.2011.12.008.
40. Simionato, L. D.; Petrone, L.; Baldut, M.; Bonafede, S. L.; Segall, A. I. Comparison between the dissolution profiles of nine meloxicam tablet brands commercially available in Buenos Aires, Argentina. *Saudi Pharm J.* **2018**, *26* (4), 578–584. DOI: 10.1016/j.jsps.2018.01.015.
41. Zhang, Y.; Huo, M.; Zhou, J.; Zou, A.; Li, W.; Yao, C.; Xie, S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *AAPS J.* **2010**, *12* (3), 263–271. DOI: 10.1208/s12248-010-9185-1.
42. Yoshida, I.; Sakai, Y. The applications of the content uniformity test and the weight variation test on process validation tests of multiple ingredient preparations. *Chem. Pharm. Bull. (Tokyo)* **1999**, *47* (5), 678–683. DOI: 10.1248/cpb.47.678.
43. Molavi, F.; Hamishehkar, H.; Nokhodchi, A. Impact of tablet shape on drug dissolution rate through immediate released tablets. *Adv. Pharm. Bull.* **2020**, *10* (4), 656–661. DOI: 10.34172/apb.2020.079.
44. van der Merwe, J.; Steenekamp, J.; Steyn, D.; Hamman, J. The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and bioavailability. *Pharmaceutics* **2020**, *12* (5), E393. DOI: 10.3390/pharmaceutics12050393.
45. *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.