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Dissolution profile evaluation of selected brands of amoxicillin-clavulanate potassium 625 mg tablets retailed in Hawassa town, Sidama Regional State, Ethiopia

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Abstract

Poor quality amoxicillin-clavulanate potassium tablets have been recently discovered in generic drugs related to Augmentin-like medicines containing amoxicillin and clavulanic acid, as well as its derivatives containing falsified active ingredients. One of the most important dosage form characteristics are a detailed active pharmaceutical ingredients dissolution release profile evaluation obtained through dissolution testing. The dissolution test is used in the development of both brand-name and generic drugs. Prior to beginning bioequivalence studies, it is critical to compare the dissolution profiles of various pharmaceutical products. As a result, dissolution is a critical quality control parameter for drugs because it has a direct impact on absorption of pharmaceutical products. Dissolution profile evaluation of seven brands of amoxicillin-clavulanate potassium tablets is retailed in Hawassa town, Sidama Regional State, Ethiopia. The seven brands of amoxicillin-clavulanate potassium tablets were collected from Hawassa town, Sidama Regional State, Ethiopia. The dissolution study was conducted as per USP40-NF35. Then, the dissolution profile test results were compared by one-way ANOVA Dunnett's test, model independent, and model dependent method. All of the included brand tablets complied with a single-point dissolution study specification. All brand tablets had similar dissolution profiles ($p > 0.05$), difference factor (f1) < 15%, and dissolution efficiency (≤ 10**%**). However, the f2 (similarity factor) value justifies that all brand tablets were not within USFDA specification (≥50%). The evaluated brands followed the Korsemeyer-Peppas followed by the Weibull curve models. All brand tablets passed the single point USP dissolution specification and the USFDA therapeutic interchangeability guideline. The similarity factor (f2), on the other hand, confirmed that none of the tested brand tablets were interchangeable with the innovator product. Therefore, researchers, national medicine regulatory bodies, and the manufacturer should conduct a properly designed dissolution test as proof of an in vitro bioequivalence study supported by in vivo bioavailability data.

Keywords Amoxicillin-clavulanate potassium tablet, Quality, Dissolution profile, Hawassa town, Ethiopia

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Plain language summary

Dissolution profile evaluation of seven brands of amoxicillin-clavulanate potassium tablets retailed in Hawassa town, Sidama Regional State, Ethiopia.

Why was the study done? Ever since a medicine must dissolve before it can be absorbed. Because the rate at which a drug dissolves from a dosage form generally influences the rate and amount of absorption. The Food and Drug Administration (FDA) should recommend that amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of Augmentin with no significant difference in absorption after oral administration. When given orally, drugs with slow dissolution rates have intermittent and inadequate absorption, resulting in limited bioavailability. Aside from that, when a significant portion of the medicine fails to dissolve, only a tiny amount of active pharmaceutical ingredients (API) is available for absorption into the systemic circulation, resulting in the failure to produce the targeted therapeutic effect. The unabsorbed portion of the drug, on the other hand, causes the drug's associated side effects.

What did the researchers do? The researchers attempted to evaluate and compare the dissolution profiles of the different brands of amoxicillin-clavulanic acid collected from Hawassa town pharmaceutical market to determine the percentage drug release, the mechanism of drug release from the dosage form, and the bioequivalence status of the various brands included in the study. The researcher also attempts to examine dissolution challenges and provide scientific solutions to avoid them in the pharmaceutical environment in the future.

What did the researchers find? The study endeavored to assess the seven brands of amoxicillin-clavulanate potassium tablets collected from the Hawassa town pharmaceutical market. All of the included brand tablets complied with a single-point dissolution study specification. All brand tablets had similar dissolution profiles ($p > 0.05$), difference factor (f1) < 15%, and dissolution efficiency (≤ 10**%**). However, the f2 (similarity factor) value justify that all brand tablets were not within USFDA specification (≥50%). The evaluated brands followed the Korsemeyer-Peppas followed by Weibull curve approaches. Furthermore, dissolution efficiency was considered to ascertain the interchangeability of all products with innovator product. All tested brands were pharmaceutically equivalent to the innovator product (AC001), with a dissolution efficiency value within ± 10%. The mean dissolution time (MDT) determined from accumulative curves of dissolved as a function of time revealed that brand code AC004 (1.3) had the smallest MDT while brand code AC007 (8.8) had the longest MDT from the tested amoxicillin brands, and brand code AC003 (1.02), and AC005 (1.03) had the smallest MDT while brands code AC001 (99.8) had the longest MDT from the tested clavulanate potassium brands.

What do the findings mean? The study has identified some important quality control parameters for dissolution profile establishment during manufacturing of the pharmaceuticals for clinical purposes and market authorization. From a bioequivalence point of view, fit factors, mean dissolution time, and dissolution efficiency are not identical for the same dosage form that is produced in different brand forms from different manufacturing companies. Dissolution profile evaluation served as the foundational quality criteria for comprehending the product quality attributes because it was related to the medications' bioavailability. It aims to offer general suggestions for dissolution testing, strategies for establishing dissolution specifications related to the biopharmaceutical's properties of the drug substance, statistical techniques for comparing dissolution profiles, and a procedure to assist in determining when dissolution testing is sufficient to grant a waiver for an in vivo bioequivalence study.

Introduction

The semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor clavulanate potassium are used in an oral antibacterial combination known as amoxicillin/clavulanate potassium (the potassium salt of clavulanic acid) (Huong and Hoang 2009). Furthermore, with the addition of clavulanic acid, the spectrum is increased to include beta-lactamase-producing strains as well as broadening the coverage to include other bacterial species (Evans et al., 2023). As a result, amoxicillin/clavulanate potassium has both broad-spectrum antibiotic and β-lactamase inhibitor characteristics. Augmentin as the first brand for containing a combination of amoxicillin and clavulanate.

This drug listed as an essential medicine by the World Health Organization and has synergistic activity against a wide range of commonly encountered susceptible pathogens while also having a lower resistance potential than antibiotics in other groups. They were chosen as access group antibiotics (WHO, 2019b). They are critical antibiotics that must be widely available, affordable, and of high quality. As per Biological classification systems;

amoxicillin/clavulanic acid considered as class-III antibiotics with highly soluble, and less permeable. Permeability is rate limiting step in drug absorption. Therefore, *in vivo-in vitro* correlation (IVIVC) could not be expected (Al-Tabakha et al. 2017a, b). If an active component is considered highly soluble, it is acceptable to assume that it will not cause any bioavailability issues if the dose system is quickly dissolved in the physiological pH range expected after product administration (Davis 2005). In quality scenario" dissolution is an important a quality control tool which describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing (EMA 2010).

Recently, amoxicillin potassium clavulanic acid consumption has risen in parallel with the global spread of new and re-emerging life-threatening diseases (Bewley-Taylor and Nougier 2018). Patient may face with side effects of unabsorbed part of the drugs across the systematic circulation due to lack of strict follow-up at the manufacturing site during formulation process. This fact drew the attention of organizations, healthcare experts, and researchers who wanted to learn more about the quality of the product in the context of in vitro bioequivalence dissolution study. Because it probes both the extent and rate of in vivo drug product release, dissolution is a critical quality control parameter for drugs because it has a direct impact on absorption. It is also a key modeling input for pharmacokinetics because it examines both the extent and rate of in vivo drug product release (CDER 2020).

Prior to beginning the bioequivalence investigations, the characterization of the dissolution of pharmaceutical products is essential for comparing the dissolution profiles (Muselík et al. 2021). Several approaches have been suggested by Scale-UP, and Post Approval changes (SUPAC) for evaluation of the dissolution profiles in order to decide the interchangeability and the drug releases kinetics of drug substances from those; statistical comparison, model independent (curve fitting) and model dependent approaches were predominant (EMA 2010, FDA 1997, Muselík et al., 2021).

The reports from the World Health Organization pertain to the discovery of counterfeit Augmentin (amoxicillin trihydrate-potassium clavulanate) in Uganda and Kenya (WHO, 2019a). In the pharmaceutical markets of these countries, there have been instances of substandard generic drugs resembling Augmentin, which contain amoxicillin and clavulanic acid along with counterfeit active ingredients. This under dosing may induce drug resistance. Antibiotic resistance is a serious hazard to human health, and development, compromising the ability to treat a wide range of illnesses. Amoxicillin-clavulanic acid potassium salt is an essential component of modern medicine, and the cornerstone of the bacterial infection treatment. One of the most commonly recommended drugs in hospitals, and across areas, in particular, in Hawassa town, Ethiopia. Antibiotic medication resistance, which has been a major impediment in the pharmaceutical industry, may be induced by the high consumption rate. Worku et al.(2022) observed that a very astonishing amoxicillin-clavulanic acid resistance for isolated salmonella species in Hawassa town (Worku et al., 2022). When a medicine is of poor quality, it might lead to difficulties when given to patients. As a result of low quality, patients may encounter drug adverse effects. Low-quality medicines are not only detrimental to one's health, but also a waste of money for both the government and individual customers (WHO, 2017). Considering the aforementioned issue, the study was endeavored to assess, and evaluate the dissolution profile of different brands of amoxicillin-clavulanate potassium 625 mg tablets retailed in Hawassa town, Sidama Regional State, Ethiopia.

Materials and methods

Study area and period

The samples were collected from Hawassa town, Sidama Regional State, Ethiopia. The experimental portion of the study was conducted at Jimma University Drug Quality Control Laboratory from March to June 2021. The town is located 273 km south of the capital, Addis Ababa via Bishoftu, and 1125 km north of Nairobi, Kenya (Paulose T 2022). According to Hawassa town health office report, public hospitals ($n=2$), private primary hospitals ($n=4$), public health centers ($n=10$), health posts ($n=15$), private clinics ($n=51$), private pharmacy ($n=21$), and drug stores ($n=121$) were found to deliver health service for a total population of 133,097 (CSA 2023). The map of study area was displayed in Fig. 1.

Equipments

HPLC (Agilent 1260 Series, Darmstadt, Germany), Analytical Balance (Mettler Toledo, Greifensee, Switzerland), dissolution test apparatus (type II, Tian Jin Optical Instruments, Tianjin, China), Water Purification System (Thermo Scientific, Model-7143, Waltham, MA, USA), sonicator, PH meter, filter paper with mesh size of 0.45 µm were used.

Chemicals and reagents

HPLC grade water was prepared at Jimma University Laboratory of Drug Quality (JuLaDQ) using ultra-pure water purification system, monobasic sodium phosphoric acid (chromo solve HPLC grade ≥ 99.9% = UN.1648, Lot

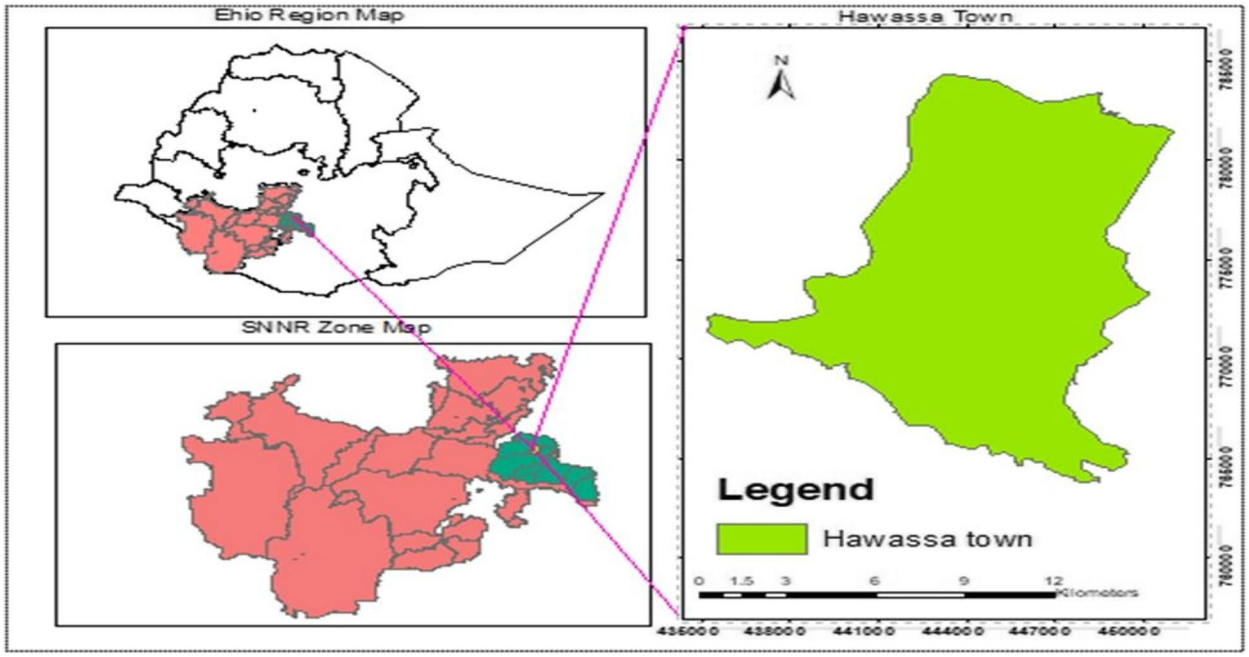

Fig. 1 Map of the study area

52BD06354), methanol (potency = 99.8%), HPLC grade (Mf. date Feb 2016, Exp. date Jan 2021, and lot/batch no. H170751602), phosphoric acid (potency = 85%, Batch/Lot no. 60,091), amoxicillin trihydrate (purity = 100%), and potassium clavulanate (purity = 89%) working standards obtained (gift) from EFDA (Addis Ababa, Ethiopia) were used.

Sampling techniques and sample collection

Sampling strategy was conducted as per the guideline proposed by World Health Organization for field surveys of the quality of medicines. Random sampling technique was used in the selection of the sites. In general, the sampling technique followed relevant guideline that used for surveying the selected medicines from the market (WHO 2015).

All available brands of amoxicillin-clavulanate potassium tablets were collected from the private pharmacy and drug store retail outlets by mystery shopper approach. They blinded from the purpose of study and only instructed to collect samples estimated one hundred tablets ($n = 100$) per each brand of amoxicillin-potassium clavulanate tablets were purchased from the selected drug retail outlets, in their original package, as applied by the manufacturers. During sample collection, all relevant information's encompassing; name of drug substance, country of origin, manufacturing company, expiry date, manufacturing date, and batch/lot number were recorded in their original packaging as provided by manufacturer. After purchasing, they running out of the sight of the outlets and important information about all the collected samples were recorded. The collected samples were transported to Jimma University Drug Quality Control Laboratory and stored under storage condition specified on the label of the product until analysis (Table 1).

Dissolution profile comparison study

The selected seven brands of an amoxicillin-clavulanate potassium tablets subjected to dissolution profile evaluation test. The test was conducted as per US Pharmacopeia (USP40-NF35, 2017), and the model independent parameters were compared based on Food Drug and Authority guidance for industry for dissolution testing

Table 1 General information on amoxicillin-clavulanate potassium tablet samples

Brands code	Batch N°	Mfg. date	Exp.date
AC001[a]	RH4J	10/2019	OCT 2022
AC002	P3GO30	07-2019	07-2022
AC003	EL50180443	10-2019	10-2022
AC004	17,181,057 A	11-2019	10-2022
AC005	BoBBV0009	06-2019	05-2022
AC006	0299	08-19	08-2022
AC007	19,150,217	07-2019	08-2022

[a] AC001 innovator drug

of immediate release solid oral dosage forms (FDA 1997). In addition, the model dependent parameters were performed as per a critical overview of Food Drug Authority and European Medicine Authority statistical methods to compare in vitro drug dissolution profiles of pharmaceutical products (Muselík et al., 2021) .

Performance verification test

According to the US Pharmacopeia, a system suitability test was performed routinely before sample analysis could begin. It is done to ensure a chromatographic system's competence for a specific analysis by verifying its tailing factor, resolution, and relative standard deviation (USP40-NF35, 2017). The performance verification process was initiated to ensure the reliability of dissolution analytical methods, providing assurance for the analytical techniques.

Dissolution procedure

Dissolution test was performed by using USP dissolution apparatus type 2 and dissolution media water. For dissolution, one tablet placed in each vessel (6 vessels) for each brand, containing 900 ml of dissolution medium and adjust temperature of 37 °C ± 0.5 °C, time duration of 30 min and a frequency of 75 rotations per minute (RPM) (USP40-NF35, 2017). A set volume of 900 ml of dissolution medium, distilled water, was accurately measured using a 1000-ml measuring cylinder and pour into each of the six-glass vessel and maintained at a temperature of 37 °C ± 0.5 °C. Standard thermometers were place in each vessel to cross check the temperature. The parameters of dissolution apparatus set and add one tablet of each brand into each of six dissolution vessels.

The dissolution apparatus was immediately start, 10 mL of the sample solution withdrawn at the end of 5, 15, 30, 45, and 60 min from each dissolution vessel, and replaced with 10 mL of dissolution medium after each sample withdrawal. After the necessary dilution, each solution was filtered by using membrane filter (0.45 µm) and filtered sample injected volume of 20 µL at flow rate 2 mL/min transfer into HPLC vial and triplicate injections were used per sample. The sample solutions were analyzed and calculated using Eq. 1 for amoxicillin trihydrate and clavulanate by using HPLC (USP40-NF35, 2017).

$$\%\text{Drug release} = \text{PtxWSxPotency of Working}\ \frac{\text{Standards}}{\text{PS}} \times \text{Wt} \tag{1}$$

Where Pt = area under the curve (AUC) of test solution; WS = concentration of standard; PS = area under the curve (AUC) of the standard used; and Wt = concentration of test solution.

Acceptance value for dissolution test is as follows: not less than 85% (Q) of the labeled amount of amoxicillin trihydrate ($C_{16}H_{19}N_3O_5S$) and not less than 80% (Q) of the labeled amount of potassium clavulanate ($C_8H_9NO_5$) are dissolved in 30 min.

Data analysis

Analytical data obtained from the experimental part of the study was analyzed using Microsoft Excel, SPSS version-20, and KinetDS-3.0 software program. The data were analyzed at a 95% confidence interval ($p < 0.05$). The dissolution profiles of those tablets were also compared statistically using One-way analysis of variance using Dunnett's test, model-independent, and model-dependent approaches.

Model independent approaches

To compare the dissolution profiles of amoxicillin-potassium clavulanate tablets under study, model-independent methods were considered by applying fit factors (F 1 and F 2), dissolution efficiency (DE), and mean dissolution time (MDT).

Fit factors

The difference factor (f1) and similarity factor (f2) of all formulations (AC001 to AC007) were determined to choose the optimum formulation from the tested brands using Eqs. 2 and 3. Two dissolution profiles were considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 (FDA 1997).

$$f1 = \left\{ \left[\sum_{t=1}^{n} |Rt = Tt| \right] / \sum_{t=1}^{n} [Rt] \right\} \times 100 \tag{2}$$

$$f2 = 50 \log \left\{ \left[\frac{100}{\sqrt{1 + \sum_{t=1}^{n} \{Rt - Tt\}2/n}} \right] \right\} \tag{3}$$

Where n is the number of time points, Rt is the dissolution value of comparator product at time t, and Tt is the dissolution value for the test product.

Dissolution efficiency

Dissolution efficiency is the area under the dissolution curve within a time range (t1–t2). DE was calculated by using the following Eq. 4.

$$DE = \frac{\int_{t1}^{t2} y.dt}{y100(t2 - t1) \times 100} \tag{4}$$

Table 2 Mathematical models for comparison of dissolution profiles Amoxicillin-potassium clavulanate 625 mg tablets

Models	Equation
Zero-order kinetic model	$Qt = Q0 + K0t$
First-order kinetic model	$logQt = logQ0 - k1t/2.303$
Second-order kinetic model	$\frac{1}{Q} = k.t + \frac{1}{Qo}$
Higuchi kinetic model	$Qt = Kh \times t^{1}/_{2}$
Weibull kinetic model	$log[-ln(1-m)] = \beta log(t - Ti) - log\alpha$
Hixson-Crowell kinetic model	$\sqrt[3]{Qo} - \sqrt[3]{Qt} = Khc.t$
Korsemeyer-Peppas kinetic model	$Mt/M \propto = Ktn$

Qt is the amount of drug released in time *t*, Qo is the initial amount of drug, and $Mt/M \propto$ is the amount of drug released at time *t*/the amount of drug released at infinite time *t*

m is accumulated fraction of the drug, β is shape parameter, and α is scale parameter

Ti is location parameter; n is releasing exponent; and ko, k_1, kh, khc, and k are releasing rate constant

where *y* is the percentage dissolved at time *t*. The integral of the numerator which is the area under the curve was calculated using the following equation.

$$AUC = \sum_{i=1}^{n} (t1 - ti - 1)(yi - 1 - yi)/2$$

where t_i is the *i*th time point, and y_i is the % of dissolved product at time *t*.

Mean dissolution time

Mean dissolution time was also considered using in the study to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer (Sanam et al., 2012).

$$MDT = \sum [ti.\Delta Qi]/Q\infty$$

Not: ti is an intermediate time of the intervals of sampling time, Qi is the amount of API dissolved in every interval of *t*, and *Q* is the maximum of API dissolved.

Model dependent approaches

Several mathematical models have been proposed to study dissolution profiles in order to decide the kinetics of drug release (Muselík et al., 2021). The models were evaluated by selecting a certain parameter based on % cumulative drug releases vs. time taken. To understand amoxicillin-potassium clavulanate tablets release kinetics, various mathematical models' dependent approaches were employed, as discussed under Table 2. The samples were analyzed in a dissolution study to assess the dissolution profile at various time intervals.

Table 3 Performance parameters test results

System suitability parameters	Value	USP 40-NF35 limit	Compliance
Tailing factor	0.83	NMT 1.5	√
Resolution	5.9	NLT 3	√
Relative standard deviation	1.31	NMT2%	√

√; compliant

The results of the dissolution test must be expressed in mathematical terms; this is realized by fitting various models to the cumulative dissolution curves. These samples were then entered into KinetDS software to ascertain the release kinetics of the drug substances. The goodness of fit was determined based on the value of the correlation coefficient ($r2$).

Results

Seven brands of amoxicillin-potassium clavulanate tablets having label strength of 625 mg and manufactured from different countries were purchased from drug store and private pharmacy found in Hawassa town, Sidama Regional State of Ethiopia. All the products tested were within their expiry date. The tablets were analyzed for the dissolution profiles comparison in accordance to USP limit .

Performance verification

The method performance parameters were determined by six replicate injections of about 20 µl of amoxicillin and potassium clavulanate working standard solution into the HPLC. Then, the system suitability was checked by analyzing tailing factor (symmetricity of the peak), resolution and precision (USP40-NF35, 2017).

The system is found suitable in respect of all of these system suitability tests as per requirements of USP40-NF35. The results of the experiment were listed in Table 3.

Dissolution test results

Figures 2 and 3 showed that at 30 min, all brands release more than 85% of their total amoxicillin-active pharmaceutical ingredients, and 80% of their total clavulanate potassium active pharmaceutical ingredients. This indicates that the products may release a significant amount of the drug for absorption into the systemic circulation. The graph depicted the time-dependent dissolution profiles of amoxicillin and potassium clavulanate, which provide information about batch-to-batch consistency and bioavailability of the brands, respectively.

As depicted in Figs. 2 and 3, different amoxicillin tablets and clavulanate potassium tablets exhibited different drug release patterns at different time

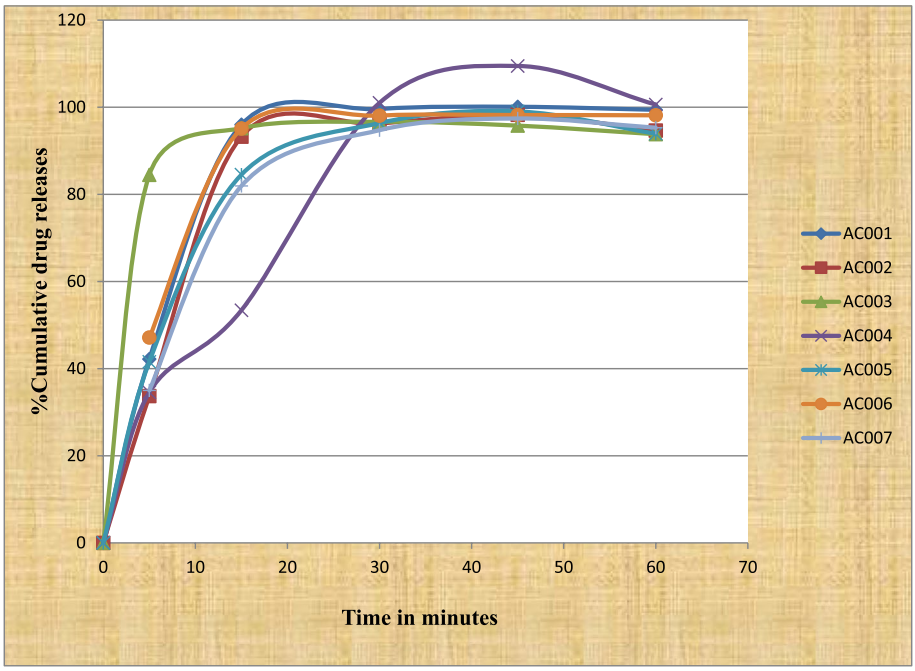

Fig. 2 Time dependent dissolution profile of amoxicillin tested brands ($n=5$)

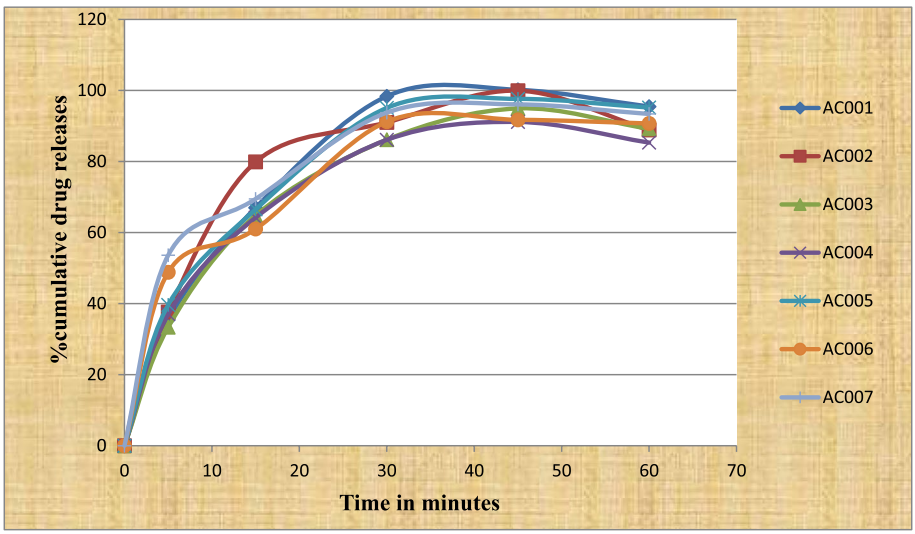

Fig. 3 Time dependent dissolution profile of potassium clavulanate tablets ($n=5$)

points and it can be observed that AC003 (84.49%) and AC007 (53.61%) of tested brands of amoxicillin and potassium clavulanate release their API content in a short period of time.

Dissolution profile comparison

The dissolution profiles of the tested amoxicillin potassium clavulanate products differed, as shown in Figs. 2 and 3. One-way ANOVA was used with Dunnett's test between innovator and tested brands at a 95% CI to determine the source of variation. According to the statistical one-way ANOVA Dunnett's test results, there was no significant difference between the innovator and the tested brands of Amoxicillin potassium clavulanic acid ($P>0.05$) (Tables 4 and 5). This signifies that the presence of amoxicillin clavulanate potassium products that are statistically equivalent with respect to their dissolution profile releases.

Table 4 Dunnett's multiple comparisons test for dissolution profile of Amoxicillin brands tested with comparator

(I) brands	(J) innovator	Mean difference (I-J)	Std. error	Sig.	95% confidence interval	
					Lower bound	Upper bound
AC002	AC001*	−4.23800	15.73779	0.982	−47.2223	38.7463
AC003	AC001*	5.72400	15.73779		−37.2603	48.7083
AC004	AC001*	−7.65200	15.73779		−50.6363	35.3323
AC005	AC001*	−4.37600	15.73779		−47.3603	38.6083
AC006	AC001*	−0.12200	15.73779		−43.1063	42.8623
AC007	AC001*	−6.58000	15.73779		−49.5643	36.4043

*which indicates, comparator product

Table 5 Dunnett's multiple comparisons test for dissolution profile of clavulanate potassium tablet brands tested with innovators

(I) tested brands	(J) innovator	Mean difference (I-J)	Std. error	Sig.	95% confidence interval	
					Lower bound	Upper bound
AC002	AC001*	0.18200	15.00620	0.997	−40.8041	41.1681
AC003	AC001*	−5.60000	15.00620		−46.5861	35.3861
AC004	AC001*	−6.52800	15.00620		−47.5141	34.4581
AC005	AC001*	−0.48200	15.00620		−41.4681	40.5041
AC006	AC001*	−2.59800	15.00620		−43.5841	38.3881
AC007	AC001*	1.96800	15.00620		−39.0181	42.9541

Comparisons of dissolution profile by model independent parameters

The presence of statistically equivalent products does not guarantee that the generic brands can be interchanged with the innovator product. As a result, model-dependent methods were used to confirm the pharmaceutical interchangeability. As the f2 (similarity factor) value justify that tested brands of amoxicillin (AC003, AC004, and AC007), and clavulanate (AC003, and AC004) values were outside of acceptable range of USFDA that are less than 50% (Evans et al., 2023). The calculated result of f1 (difference factor) confirmed that all tested brands were interchangeable with the innovator products (f1 < 15%). Furthermore, dissolution efficiency was considered to ascertain the interchangeability of all products with innovator product. All tested brands were pharmaceutically equivalent to the innovator product (AC001), with a dissolution efficiency value within ± 10%.

The mean dissolution time (MDT) determined from accumulative curves of dissolved as a function of time revealed that brand code AC004 (1.3 min) had the smallest MDT while brand code AC007 (8.8) had the longest MDT from the tested amoxicillin brands, and brand code AC003 (1.02) and AC005 (1.03) had the smallest MDT while brands code AC001 (99.8) had the longest MDT from the tested clavulanate potassium brands (Table 6).

Table 6 The model dependent results for the seven brands of tablets contained amoxicillin-clavulanate potassium 625 mg tablets (500 mg/125 mg)

Brands code	Amoxicillin					Clavulanic acid potassium salts				
	f1	f2	DE%	Difference DE	MDT	F1	F2	DE%	Difference DE	MDT
AC001[a]	-	-	87.6	0	7.1	-	-	79.9	0	9.8
AC002	4.86	51.05	84.1	3.5	6.7	0.23	98.4	80.3	−0.4	6.4
AC003	6.55	44.58	90.23	-2.63	2.3	7.06	45.05	74.1	5.8	1.02
AC004	8.75	38.3	77.9	9.7	1.3	8.2	41.75	72.9	7	8.7
AC005	5.03	85.102	83.4	4.2	6.7	0.61	91.63	78.9	1	1.03
AC006	0.13	99.4	87.1	0.5	6.8	3.27	61.48	75.9	4	9.8
AC007	7.52	41.56	81.4	6.2	8.8	2.48	67.3	80.3	−0.4	8.4

[a] AC001 innovator product, *DE* dissolution efficiency, *MDT* mean dissolution time, *Difference of DE* innovator- tested brands

Dissolution kinetics

To determine the release kinetics of drug substances from the dosage form, mathematical models have been extensively used for the parametric representation of dissolution data (Muselík et al., 2021). After fitting these models to the individual unit dissolution data, the parameters were chosen based on their suitability. In the study, the best parameter used in the selection of the best models available for comparison was the model with the highest Correlation Coefficient (r2). Considering this criterion, the Korsemeyer Peppas-model was the best model for dissolution data comparison followed by Weibull model (Table 7).

Discussion

Dissolution of a drug is a widely used quality control parameter, and it is one of the analytical techniques for evaluating a pharmaceutical product's drug release characteristics and consistency. Its significance lies in the fact that in order for a drug to be effective, it must first be released from the product and dissolves in the gastrointestinal fluids before it can be absorbed into the bloodstream. According to the study, all of the brands tested released the required amount of drug substances in 30 min, as specified by USP, which states that amoxicillin and potassium clavulanate tablets should release > 85% (Q) and > 80% (Q) of the labeled amount respectively (USP40-NF35, 2017). The dissolution profiles of the tested amoxicillin potassium clavulanate products differed, as shown in Figs. 2 and 3. This difference might be attributed to difference in excipients used and difference in manufacturing process used by various manufacturing industries. To determine source of variation in inter, and intra batches, one-way ANOVA Dunnett's test were employed at a 95% CI. The statistical test results revealed, there was no significant difference between the innovator and the tested brands of amoxicillin potassium clavulanic acid ($P > 0.05$). This indicated the presence of amoxicillin potassium clavulanate products that are statistically equivalent with respect to their dissolution profile releases.

Despite the fact that statistical equivalence does not guarantee biopharmaceutical equivalence, the dissolution profiles of all of the brands were similar ($p > 0.05$). As a result, model-dependent methods were employed to validate pharmaceutical interchangeability. As the f2 (similarity factor) value justify that tested brands of amoxicillin (AC003, AC004, and AC007), and clavulanate (AC003, and AC004) values were outside of acceptable range of USFDA that are less than 50% (FDA 1997). The calculated result of f1 (difference factor) confirmed that all tested brands were interchangeable with the innovator products (f1 < 15%). The similarity factor f2 is more sensitive than the difference factor f1 in detecting dissimilarities between dissolution curves, and the fit factor values depend on the number of sampling time points chosen. This report different from study performed in in United Arab Emirates (UAE) on ten different brands of amoxicillin/clavulanic acid salt tablets, and reported that all of the brands can be used interchangeably with the innovator drug (Nessa et al., 2020).

Furthermore, dissolution efficiency was considered to ascertain the interchangeability of all products with innovator product. According to Simionato et al., the innovator and test products are equivalent if the difference in dissolution efficiency is within the appropriate limit (± 10%) (Simionato et al., 2018). Based on this criterion, all tested brands were pharmaceutically equivalent to the innovator product (AC001); with a dissolution efficiency value is < 10%.

The mean dissolution time (MDT) determined from accumulative curves of dissolved as a function of time revealed that brand code AC004 had the smallest mean dissolution time while brand code AC007 had the longest mean dissolution time from the tested amoxicillin brands. Brand code AC003, and AC005, had the smallest mean dissolution time while brands code AC001, had the longest mean dissolution time from the tested potassium clavulanate brands. Brands code; AC004, AC003, and AC005 had the minimum mean dissolution time, and so it may require a short time to dissolve, and might have a fast onset of action while brands code; AC007, and AC001, had the highest mean dissolution time (Sanam et al., 2012). Hence, the medication could be defined by a gradual discharge of the drug from the medication form and a prolonged initiation of its effects. Typically, the average dissolution time represents the release of the drug substance from the medication form and the effectiveness of the polymer in slowing it down. A greater average dissolution time indicates a reduced rate of drug release from the medication form. Consequently, the polymer exhibits a delayed onset of action and a stronger capability to retain the drug, while a lower drug-retaining ability leads to a quicker onset of action.

A meaningful and validated dissolution profile may be important in the context of a production lot scale-up and post-approval change, identifying important manufacturing variables, defining and evaluating a possible in vitro-in vivo association/correlation, and assessing the possibility of bio-equivalency study waivers. Because the USP point estimate approach is insufficient for comparing dissolution profiles (which may govern in-vivo input rate and pharmacokinetics), a mathematical "model-dependent" approach is a better tool for determining drug substance release from the formulation. The model with the highest correlation coefficient ($r2$) value was

Table 7 The correlation coefficients of different release kinetic models for the seven brands of Amoxicillin clavulanate potassium 625 mg tablets (500 mg/125 mg)

Brands code	Amoxicillin						Clavulanic acid potassium salts					
	Model dependent parameters						Model dependent parameters					
	Zero-order	First-order	Higuchi	Weibull	Hixson-Crowell	Korsemeyer-Peppas	Zero-order	First-order	Higuchi	Weibull	Hixson-Crowell	Korsemeyer-Peppas
AC001	0.4747	0.4603	0.6092	0.7142	0.4647	0.9833	0.6997	0.6612	0.7254	0.6325	0.6766	0.9146
AC002	0.4522	0.4438	0.3255	0.7773	0.4464	0.9787	0.5791	0.5429	0.3856	0.7306	0.5554	0.9837
AC003	0.3082	0.3209	-0.6667	0.5745	0.3125	0.9144	0.7375	0.6764	0.7419	0.9381	0.6986	0.9258
AC004	0.7708	0.7568	0.8478	0.8459	0.7638	0.9303	0.7031	0.6642	0.5525	0.9208	0.6788	0.9175
AC005	0.5579	0.5262	0.1940	0.8494	0.5366	0.9894	0.7403	0.7006	0.6568	0.9275	0.7156	0.9342
AC006	0.4734	0.4609	− 0.3226	0.8326	0.4648	0.9834	0.7633	0.7595	0.2220	0.8877	0.7615	0.9169
AC007	0.5995	0.5470	0.5168	0.9122	0.5638	0.9953	0.7524	0.7398	− 0.2598	0.9012	0.7448	0.9339

considered to be the best fit to the release data (Wójcik-Pastuszka et al., 2019). According to the current study, the Korsemeyer Peppas model (with a higher *r*2-value) provided the best adjustment for all brands, while the Weibull model provided the best fitting model for brand codes AC003, AC004, and AC007 with the highest determination coefficients.

Limitation of the study

There were a number of restrictions on this quality control study, which should be recognized. The sample size of the brands included in the study was small, and the findings were difficult for drawing general conclusion. By far, the limitation of this study, which was intended to summaries the quality status of the pharmaceuticals sold on the market, is that it did not assess the all-quality control parameter or utilize straightforward statistics, making it difficult to comprehend the results.

Conclusions and recommendation

The current study found all of the brands met USP pharmacopoeia specifications for drug substance release from dosage forms. The fit factor results indicated that all tested brands met the f1 (difference factor (f1 < 15%) acceptance criteria. However, as evidenced by the f2 (similarity factor) value, the tested brands' amoxicillin (AC003, AC004, and AC007) and clavulanate (AC003 and AC004) values were less than 50%, which is result in interchangeability issues. All tested brands were pharmaceutically equivalent to the innovator product. According to the current study, the Korsemeyer-Peppas model (with a higher *r*2-value) provided the best adjustment for all brands, while the Weibull model provided the best fitting model for brand codes AC003, AC004, and AC007 with the highest determination coefficients.

Based on the fit factors f2 (similarity), brands code AC003, AC004, and AC007 may be not be considered bioequivalent and interchangeable with the innovator drug. Therefore, researcher, the national medicine regulatory body especially EFDA, and the manufacturer should conduct a properly designed dissolution test as proof of in vitro bioequivalence study supported by an in vivo bioavailability data.

Authors' contributions

EE, RT, and TM authors designed the study and verified the methodologies. EE has performed the sample collection. EE, HT, and MD performed the laboratory analysis. RT and TM supervised the research work. EE and YT have been performed statistical software and have played a role in the analysis and interpretation of the laboratory output. YT prepared the first draft of the version of the manuscript. All authors prepared, read, revised, and approved the final version of the manuscript.

Declarations

Availability of data and materials

All the study quality control information was available within the article. If readers need additional supporting documents, it can be made available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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