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The differences between the branded and generic medicines using solid dosage forms: *In-vitro* dissolution testing

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ABSTRACT

Introduction: Dissolution is the amount of substance that goes into solution per unit time under standardised conditions of liquid/solid interface, solvent composition and temperature. Dissolution is one of the most important tools to predict the *in-vivo* bioavailability and in some cases to determine bioequivalence and assure interchangeability.

Aim: To compare the differences in dissolution behaviour of solid dosage forms between innovators (reference products) and their generic counterparts (tested products).

Methods: Four replicates for each batch of 37 tested medicines was carried out using A PT-DT70 dissolution tester from Pharma Test. A total of 13 branded medicines and 24 generic counterparts were obtained locally and internationally to detect any differences in their dissolution behaviour. They were tested according to the British Pharmacopeia, European Pharmacopeia and the US Pharmacopeia with the rate of dissolution determined by ultra-violet Spectrophotometery.

Results: Most tested medicines complied with the pharmacopoeial specifications and achieved 85% dissolution in 60 min. However, some generic medicines showed significant differences in dissolution rate at 60 and 120 min. Many generic medicines showed a slower dissolution rate than their branded counterparts such as the generic forms of omeprazole 20 mg. Some showed an incomplete dissolution such as the generic form of nifedipine 10 mg. Other generics showed faster dissolution rate than their branded counterpart such as the generic forms of meloxicam 15 mg. Moreover, some generics from different batches of the same manufacturer showed significant differences in their dissolution rate such as the generic forms of meloxicam 7.5 mg. Nevertheless, some generic medicines violated the EMA and the FDA guidelines for industry when they failed to achieve 85% dissolution at 60 min, such as the generic form of diclofenac sodium 50 mg.

Conclusion: Most medicines in this study complied with the pharmacopeial limits. However, some generics dissolved differently than their branded counterparts. This can clearly question the interchangeability between the branded and its generic counterpart or even among generics.

1. Introduction

Encouraging generic drugs and substitution from multiple sources into the healthcare system is aimed at maximising population health subject to a budget constraint. This, as a result can improve the overall healthcare delivery systems [1]. For example, in the US, generic drugs represent 47% of all prescriptions dispensed in 1999, 61% in 2006 and 69% in 2008 [2]. Approving generic drugs in the US has resulted in an average savings of 77% of the product cost within 1 year [3]. Similarly, the UK's generic substitutions have been widely successful; they account for 83% [4]. This increase has occurred because any drug products that are considered bioequivalent must be identical in quality (active ingredient, strength, purity, content uniformity, disintegration and dissolution rates) [5]. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of substandard generics and fake drug products. As a consequence, healthcare providers and patients are usually concerned when selecting one drug from among several bioequivalent ones during the treatment regime [5,6].

In order to maintain a quality control procedure in research and development, dissolution testing has been employed over the past 50 years to detect the influence of critical manufacturing

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variables and in comparative studies *in-vitro–in-vivo* correlation (IVIVC) [7]. It can be used to pin point formulations that may present potential bioequivalence problems. Therefore, it is considered one of the most important tools to predict the *in-vivo* bioavailability and in some cases replacing clinical studies to determine bioequivalence. Dissolution testing *in-vitro* is also considered critical because drug release from the solid dosage form after oral administration is a prerequisite for drug absorption and bioavailability [8]. It is a very important test and considered the rate limiting step in the sequence of steps leading to absorption of the drug into systemic circulation [9]. Absorption is the process of transporting the drug substances from the gastrointestinal lumen into the systemic circulation [10]. It is the first step before the distribution, metabolism and elimination (ADME) properties of drugs in the human body. An important feature of drug quality assurance includes the ability to confirm that the correct manufacturing procedures have been followed for a given batch, that the product performs effectively throughout its shelf life and that batch-to-batch reproducibility of the product meets regulatory requirements [11].

Dissolution is defined as the amount of substance that goes into solution per unit time under standardised conditions of liquid/solid interface, solvent composition and temperature [12]. Although dissolution cannot be used as a predictor of therapeutic efficiency; it can be used as a qualitative and a quantitative tool, which can provide important information about biological availability of a drug as well as batch-to-batch consistency [13]. In the cases when the *in-vitro* results fail to predict the *in-vivo* performance of a drug product, larger clinical studies are needed to assess the product bioavailability, thus additional cost will be added to the drug development expenses [11]. Therefore, dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and validation of dissolution methods and is an important part of good manufacturing practice [12]. With modern technology and advancement in research of drug delivery and more emphasis on *in-vivo* predictability of therapeutic effect by means of *in-vitro* test, dissolution tests have been gaining more and more popularity [14]. Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The ultimate aim of performing dissolution tests is to predict the extent release and absorption of the administered drug *in-vivo*, i.e. *in-vitro–in-vivo* correlation. However, extended release performance obtained *in-vitro* does not necessarily mean that the formulation will perform similarly *in-vivo* [14].

The pharmacological activity of a drug can be evaluated by assessing its dissolution behaviour. Therefore, *in-vitro–in-vivo* correlation (IVIVC), which is a direct relationship between bioavailability of a drug and its *in-vitro* dissolution rate is demonstrated. Drug absorption from solid dosage form following oral administration depends on the stages disintegration, disaggregation, drug release from the pharmaceutical form, its dissolution under physiological conditions and the permeability through the biological membranes [15]. These considerations indicate that an *in-vitro* dissolution test is a very important stage to predict the drug *in-vivo* performance. The bioavailability, which describes the rate and extent of the active drug that is absorbed, may be altered by any factor that changes the disintegration and dissolution drug process [15]. For a new compound, dissolution testing is performed mainly to evaluate the stability of formulations, rate of drug release, monitor product consistency and establish *in-vitro–in-vivo* correlations [16]. This type of correlation would match changes in the *in-vitro* dissolution rate to meaningful *in-vivo* product performance quality. To utilise the dissolution test as a surrogate for bioequivalence, IVIVC must be predictive of *in-vivo* performance of the drug [9].

The FDA guidance for industry indicates that for highly soluble drugs a single point dissolution test specification of 85% in 60 min or less is sufficient as a routine quality control test for batch-to-batch uniformity [17]. Similarly the EMA guidance which states that "*In cases where more than 85% of the active substances are dissolved within 15 min, the similarity of dissolution profiles may be accepted as demonstrated*" [18]. This test is mainly designed to obtain correlation with *in-vivo* performance of the formulation. If a good correlation is obtained with an *in-vitro* test, the test may serve as a routine quality control or may be useful in screening new drug formulations [8]. Historically, dissolution testing has been a key tool to measure product performance during the development stage and to characterise the drug release mechanism. Commercially, dissolution testing is used to confirm product consistency and to evaluate the quality of the product during its shelf life and to assess post approval changes and the need of bioequivalence studies [16].

2. Objective

The aim of this study was to compare the differences in dissolution rate of solid dosage forms between innovators (reference products) and their generic counterparts (test products).

3. Methods

The development of a dissolution procedure involves selecting the dissolution tester, media, apparatus type (Paddle or basket) and hydrodynamic (agitation rate) appropriate for the product. The Low-Head Tablet Dissolution Test Apparatus (model PT-DT70) equipped with six dissolution vessels [19] from Pharma Test Company was used to conduct this study. The dissolution tests were carried out using 37 medicines (tablets and capsules) containing the same drug substances but different types and/or amount of excipients. A total of 13 innovator (branded) medicines and 24 generic counterparts were obtained locally and internationally to detect any differences in their dissolution behaviour (Table 1). All the tested tablets and capsules stored according to conditions described on their labels and were weighed individually before performing the dissolution test using Sartorius AZ64 Research Analytical Weighing Balance. The average weight of the obtained tablets and capsules were calculated using Microsoft Office Excel 2007 (Table 3). The temperature was maintained at 37 ± 0.5 °C during the dissolution test for 2 h (120 min) [20].

The dissolution test was performed by manually pipeting out 5 ml samples of dissolution medium at 5, 15, 30, 60, 90 and 120 min and transferring to tubes. The medium, apparatus type and agitation rate for each drug were prepared according to the British Pharmacopeia (2011) [21], European Pharmacopeia (2007) [22] and the US Pharmacopeia (USP-30) [23]. The test was carried out on four replicates for each batch using the paddle method (apparatus type 2). Deionised water at purity of 18.2 MΩ cm was used for the preparation of dissolution media and was obtained from ultra water system (Model Purelab®). Samples were filtered appropriately through a 20 μm filter before measuring the absorbance using ultra-violet/visible spectrophotometery (model 6715 UV/Vis. Sectrophotometer, Jenway) (Table 2).

In order to demonstrate whether the method was suitable for its intended purposes, it was validated through precision (repeatability and reproducibility) parameters based on relative standard deviation. Validation of dissolution methods was necessary for the formulation research and development. The precision of an analytical procedure was determined by repeated analysis ($n=4$) expressed the closeness between a series of measurements

Table 1
Characteristics of the branded medicines (reference products) used in the dissolution study.

Formulation	Brand name®	Strength (mg)	Type (tablet/ capsule)	Indication	Batch no.	Manufacturer
Nifedipine	Adalat®	10	Capsule	Antihypertensive agent	ITA07KZ	Bayer Schering Pharma (Germany)
Amoxicillin	Amoxil®	500	Capsule	Antibiotic to treat bacterial infections	449630	GlaxoSmithKline (UK)
Amoxicillin and Clavulanate Potassium	Augmentin®	375	Tablet	Antibiotic to treat bacterial infections	500791	GlaxoSmithKline (UK)
Amoxicillin and Clavulanate Potassium	Augmentin®	1000	Tablet	Antibiotic to treat bacterial infections	471504	GlaxoSmithKline (UK)
Loratadine	Claritine®	10	Tablet	H_1 histamine antagonist used to treat allergies	ORXFA14005	Shering-Plough Labo N.V. (Belgium)
Ciprofloxacin	Ciproxin®	250	Tablet	Antibiotic to treat bacterial infections	ITA0924	Bayer Schering Pharma (UK)
Omeprazole	Losec®	20	Capsules	Proton Pump Inhibitor to treat peptic ulcer disease	MK7422	AstraZeneca (UK)
Meloxicam	Mobic®	7.5	Tablet	Nonsteroidal anti-inflammatory to treat arthritis	044155	Boehringer Ingelheim (UK)
Meloxicam	Mobic®	15	Tablet	Nonsteroidal anti-inflammatory to treat arthritis	905341	Boehringer Ingelheim (Germany))
Mefenamic Acid	Ponstan®	500	Tablet	analgesic and anti-inflammatory	15249	Chemidex Pharma Ltd (UK)
Diclofenac Sodium	Voltaren®	50	Tablet	analgesic and anti-inflammatory	TO418	Novartis (Italy)
Capecitabine	Xeloda®	500	Tablet	Chemotherapeutic agent to treat metastatic breast and colorectal cancers	X0115B01	Roche (Mexico)
Simvastatin	Zocor®	20	Tablet	Anticholesteremic agent	305435	MSD (UK)

Table 2
In-vitro dissolution procedures for different medicines.

Drug	Dissolution medium	Volume (ml)	Agitation rate (revolutions per minute)	UV Analysis (wavelength, nm)
Adalat 10 mg	0.1 M hydrochloric acid	900	50	340
Amoxil 500 mg	Water	900	75	272
Augmentin 1000 mg	Water	900	75	272
Augmentin 375 mg	Water	900	75	272
Claritine 10 mg	0.1 M hydrochloric acid	900	50	280
Ciproxin 250 mg	0.1 N hydrochloric acid	900	50	276
Losec 20 mg	Phosphate Buffer, pH 7.4	900	75	302
Mobic 7.5 mg	Phosphate Buffer, pH 7.5	1000	50	362
Mobic 15 mg	Phosphate buffer, pH 7.5	1000	50	362
Ponstan 500 mg	0.05 M Tris buffer	900	100	285
Voltaren 50 mg	0.1 N hydrochloric acid	900	50	276
Xeloda 500 mg	Water	900	50	304
Zocor 20 mg	0.01 M sodium dihydrogen orthophosphate containing 0.5% w/v of sodium dodecyl sulphate, pH 7.0	900	50	238

obtained from multiple sampling of the same homogeneous sample under the same conditions. Repeatability expresses the precision under the same operating conditions over a short interval of time. Reproducibility expresses the precision between laboratories, in this study standardised procedures from pharmacopoeias was included [24].

4. Results

Dissolution testing involves dissolving the solid dosage form of a drug compound under controlled conditions, followed by collection and analysis of the sample to determine the percentage of drug dissolved at certain time point. The volume of the dissolution medium was kept constant and corrected mathematically using Microsoft Office Excel 2007 and Minitab 16 (Minitab Inc, Pennsylvania, PA, USA). The results of this study were expressed as % (95% Confidence Intervals (CI)). Variations were evaluated using the one-way analysis of variance (ANOVA) and $P \leq 0.05$ was considered statistically significant. Dissolution profile compares the percentage of a drug substances dissolved relating to time and represents an alternative to assessment of solid forms before clinical tests [15]. Tables 3 and 4 show the percentages of the dissolution of all drugs at 60 and 120 min, respectively.

5. The dissolution rate of generic medicines compared to their branded counterpart at 60 min, Table 3

When comparing the dissolution rates between the branded medicines and their generic counterparts at 60 min, 21% (5/24) of the generic medicines had shown statistically significant differences than their branded counterpart. On one hand, some generics showed different and incomplete dissolution rates than their branded counterparts such as the generic form of capecitabine 500 mg ($P=0.001$). Another example is meloxicam 15 mg where its generic A showed a slower dissolution rate than its branded counterpart ($P=0.001$), Fig. 1. In addition, the generic form (Generic A1) of meloxicam 7.5 mg had shown slower dissolution rate than its branded counterpart ($P=0.032$). Another example is that the dissolution rate of the generic form (Generic A) of omeprazole 20 mg had shown a slightly slower dissolution rate than its branded counterpart ($P=0.054$). Moreover, some

Table 3
Shows the percentages of the dissolution rate of the generic medicines (test products) compared to their branded counterparts which was taken as the reference at 100% of the expected dissolution rate at 60 min.

Drug name	Average weight (g)	% of drug dissolved at 60 min	95% Confidence interval	*P* value
Adalat®	0.59875	100		0.001
Generic A	0.61532	87	(82–92)	
Amoxil®	0.691810	100		0.263
Generic A	0.68846	99	(91–107)	
Generic A1	0.698708	104	(96–113)	
Generic B	0.698363	104	(96–113)	
Augmentin® 375 mg	0.67019	100		0.132
Generic A	0.66545	83	(64–108)	
Augmentin® 1000 mg	1.48098	100		0.145
Generic A	1.44494	95	(88–102)	
Claritine®	0.10000	100		0.449
Generic A	0.09970	101	(98–104)	
Generic B	0.11713	99	(96–102)	
Ciproxin®	0.38277	100		0.613
Generic A	0.39973	101	(93–109)	
Generic B	0.40445	103	(95–111)	
Losec®	0.29163	100		0.054
Generic A	0.29875	94	(87–101)	
Generic B	0.28517	101	(94–109)	
Mobic® 7.5 mg	0.18218	100		0.032
Generic A	0.11150	101	(90–113)	
Generic A1	0.11150	89	(79–100)	
Mobic® 15 mg	0.18217	100		0.001
Generic A	0.182165	91	(83–100)	
Generic A1	0.22036	100	(91–110)	
Generic B	0.22170	114	(104–126)	
Ponstan®	0.69577	100		0.063
Generic A	0.74245	92	(82–104)	
Generic B	0.82695	97	(86–109)	
Voltaren®	0.21431	100		0.200
Generic A	0.20725	103	(60–176)	
Generic B	0.22830	72	(42–122)	
Xeloda® 500 mg	0.63751	100		0.003
Generic A	0.98755	86	(80–93)	
Zocor®	0.20649	100		0.738
Generic A	0.20322	98	(66–146)	
Generic B	0.20330	90	(60–133)	

Brand: The innovator product. Generic A: counterpart of the branded medicine, Generic A1: same manufacturer with different batch number of the generic A and Generic B: second generic counterpart of the same branded medicine.

Table 4
Shows the percentages of the dissolution rate of the generic medicines (test products) compared to their branded counterparts which was taken as the reference at 100% of the expected dissolution rate at 120 min.

Drug name	% of drug dissolved at 120 min	95% Confidence interval	*P* value
Adalat®	100		0.003
Generic A	86	(80–93)	
Amoxil®	100		0.005
Generic A	105	(98–113)	
Generic A1	104	(97–112)	
Generic B	113	(105–121)	
Augmentin® 375 mg	100		0.127
Generic A	87	(71–106)	
Augmentin® 1000 mg	100		0.019
Generic A	94	(90–99)	
Claritine®	100		0.132
Generic A	103	(99–107)	
Generic B	101	(97–105)	
Ciproxin®	100		0.905
Generic A	100	(95–105)	
Generic B	101	(96–106)	
Losec®	100		0.001
Generic A	113	(105–123)	
Generic B	124	(115–135)	
Mobic® 7.5 mg	100		0.204
Generic A	101	(91–113)	
Generic A1	94	(84–105)	
Mobic® 15 mg	100		0.043
Generic A	98	(89–107)	
Generic A1	104	(95–114)	
Generic B	109	(99–119)	
Ponstan®	100		0.047
Generic A	92	(84–101)	
Generic B	90	(82–98)	
Voltaren®	100		0.312
Generic A	101	(44–231)	
Generic B	64	(28–147)	
Xeloda® 500 mg	100		0.008
Generic A	90	(84–96)	
Zocor®	100		0.733
Generic A	106	(77–145)	
Generic B	96	(70–132)	

Brand: The innovator product. Generic A: counterpart of the branded medicine, Generic A1: same manufacturer with different batch number of generic A and Generic B: second generic counterpart of the same branded medicine.

generics showed an incomplete dissolution such as the generic form of nifedipine 10 mg, Fig. 3.

On the other hand, a number of generics showed that they can dissolve faster than their branded counterparts. For example, the generic form (Generic B) of meloxicam 15 mg showed faster dissolution rate than its branded counterpart ($P=0.001$), Fig. 1. Moreover, other generics showed batch to batch variation during the dissolution test. This is clearly shown, for example, in generic A and generic A1 of meloxicam 15 mg and meloxicam 7.5 mg, Table 3. Nevertheless, some generic medicines failed to follow the EMA and the FDA role of 85% dissolution in 60 min. For instance, 76% of generic B in diclofenac sodium 50 mg had only dissolved at 60 min compared to 100% dissolution of its branded counterpart, Fig. 2.

6. The dissolution rate of generic medicines compared to their branded counterpart at 120 min, Table 4

When comparing the branded medicines with their generic counterparts at 120 min, more than half (54%, 13/24) of the tested generic medicines were found significantly different ($p \leq 0.05$) than their branded counterpart. Some generic medicines showed slower and incomplete dissolution rates than their branded counterpart. For example, the generic form of nifedipine 10 mg (Fig. 3) and capecitabine 500 mg showed much slower dissolution rate than their branded counterpart ($P=0.003$, 0.008, respectively). The generic form of amoxicillin and clavulanate potassium 1000 mg had also shown a slower dissolution rate than its branded counterpart ($P=0.019$). In addition, the generic form (Generic A) of meloxicam 15 mg has shown a slower dissolution rate than its branded counterpart ($P=0.043$). In mefenamic acid 500 mg, the generic A and B also showed a significantly lower dissolution rate than their branded counterpart ($P=0.047$).

Other generics showed that they can dissolve faster than their branded counterpart. For example, all tested generic forms (Generic A, A1 and B) of amoxicillin 500 mg dissolved faster than their branded counterpart ($P=0.005$), Fig. 4. The generic forms (Generic A and B) of omeprazole 20 mg also dissolved faster than their branded counterpart ($P=0.001$). Likely, the generic forms (Generic A1 and B) of meloxicam 15 mg had shown faster dissolution rates than their branded counterpart ($P=0.043$), Fig. 1. Nevertheless, some generics showed batch to batch variation in their dissolution rate; for example, the generic forms (generic A and A1) of meloxicam 15 mg ($P=0.043$).

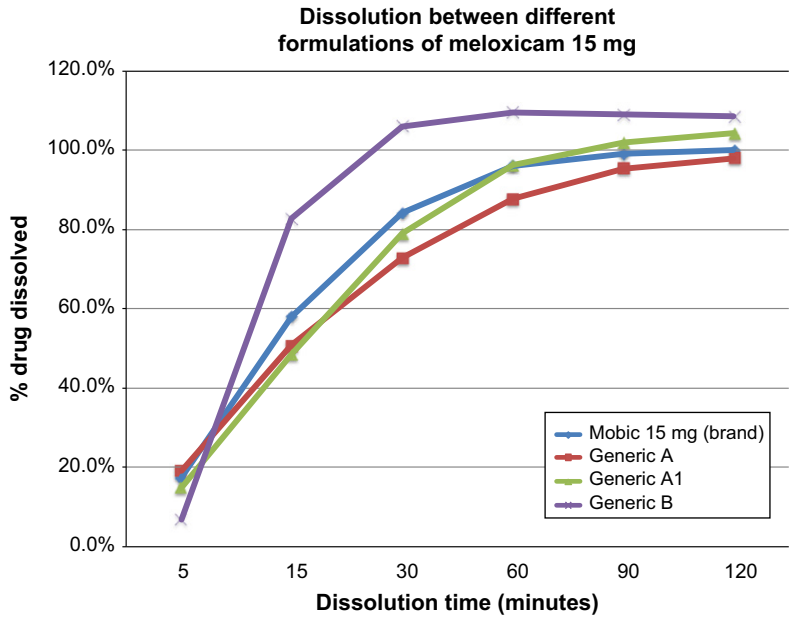

Fig. 1. The differences in dissolution rate between the branded Mobic® 15 mg and its generic counterparts (Generic A: counterpart of the branded medicine, Generic A1: same manufacturer with different batch number of generic A and Generic B: second generic counterpart of the same branded medicine).

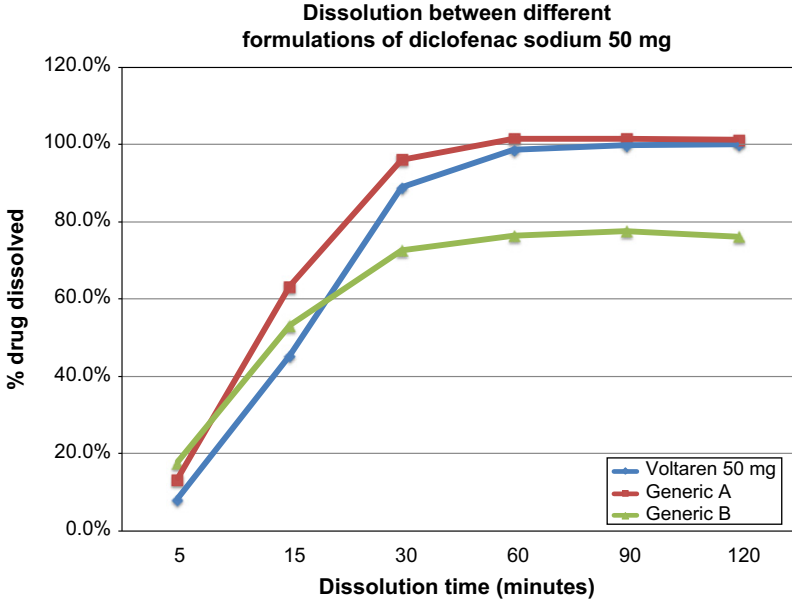

Fig. 2. The differences in dissolution rate between the branded Voltaren® 50 mg and its generic counterparts (Generic A: counterpart of the branded medicine and Generic B: second generic counterpart of the same branded medicine).

7. Discussion

The results of this study are found compatible with others in Refs. [5,25,26].

The dissolution rate profile revealed that many of the branded and generic medicines tested in this study complied with the British Pharmacopeia (2011) [21], European Pharmacopeia (2007) [22] and the US Pharmacopeia (2010) [23]. Most drugs in this study achieved 85% dissolution at 60 min or less. This is compatible with the EMA and the FDA guidance for industry indicating that for highly soluble drugs a single point dissolution test specification of 85% in 60 min or less is sufficient as a routine quality control test for batch-to-batch uniformity [17]. This can reflect that the *in-vivo* bioavailability of these drugs would be similar to *in-vitro* since dissolution testing is commonly used to predict *in-vivo* behaviour of the oral dosage formulation.

Many generic medicines in this study showed significant differences from their branded counterparts during the dissolution tests. Some generics showed incomplete dissolution and others showed that they dissolve slower or faster than their branded counterparts. Nevertheless, significant differences in dissolution rate were also shown in batch to batch comparison. Some generics from the same manufacturer with different batches of the same drug showed significant differences. This illustrates that substitution among generics themselves can be risky. Unfortunately, some other generic medicines in this dissolution test failed to achieve the 85% dissolution at 60 min. These differences in dissolution rate between the branded and their

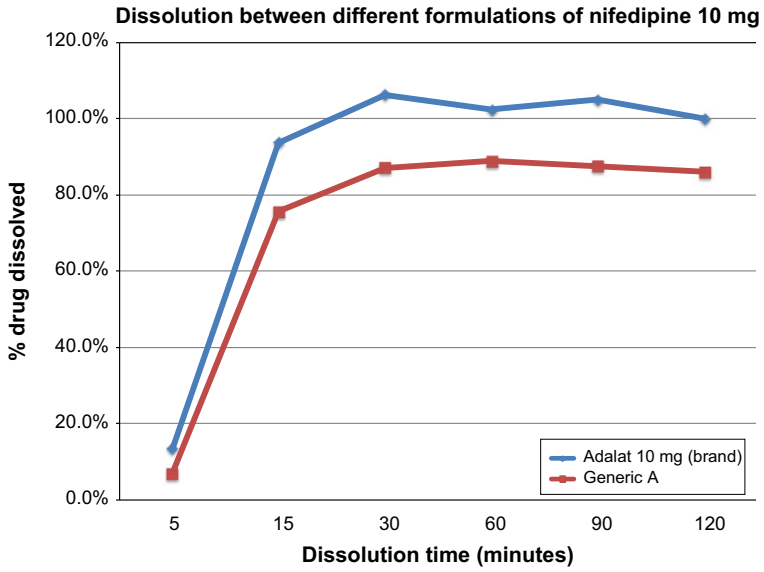

Fig. 3. The differences in dissolution rate between the branded Adalat® 10 mg and its generic counterparts (Generic A: counterpart of the branded medicine).

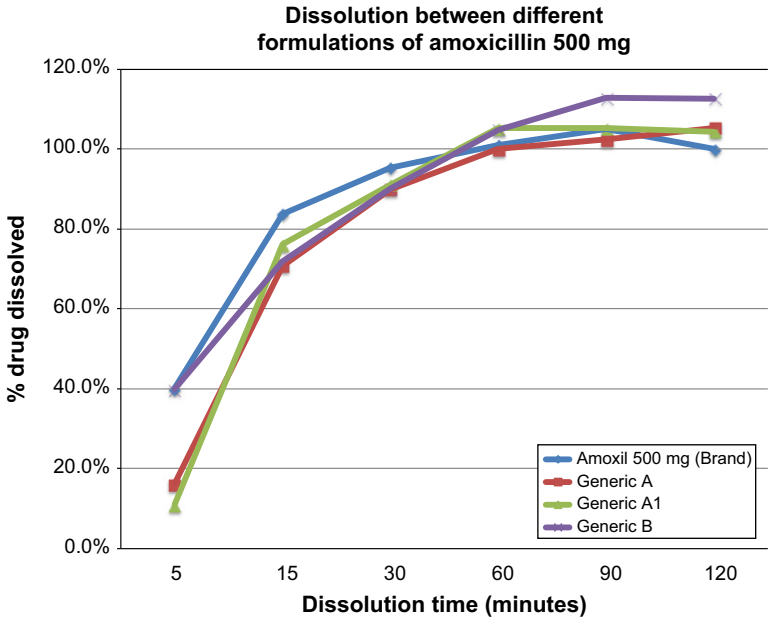

Fig. 4. The differences in dissolution rate between the branded Amoxil® 500 mg and its generic counterparts (Generic A: counterpart of the branded medicine, Generic A1: same manufacturer with different batch number of generic A and Generic B: second generic counterpart of the same branded medicine).

generic counterparts could impact the drugs' effectiveness and side-effects profiles [27].

There are many potential factors that can explain the differences between the branded and their generic counterparts. Those include the manufacturer, apparatus type, surface area of a drug, surfactants, storage, dosage form and the level and type of excipients. Manufacturer of the drug can play a major part in its dissolution profile. In the literature, it is reported that there are variable clinical responses to the same dosage form of a drug product supplied by different manufacturers. For example, a study compared 19 different generic formulations of simvastatin tablets and capsules obtained from international manufacturers to the US innovator product regarding pharmaceutical quality. It revealed that manufacturing standards for the international generics were not equivalent in quality aspects with the US innovator drug, a significant variability was also found among foreign-made tablets themselves [28]. Similarly, another study compared the dissolution behaviour of six diclofenac sodium prolonged release tablets of different brands obtained from the national market. It reported that the release characteristics vary considerably among different manufacturers and that even identical formulations showed rather dissimilar release profiles. Therefore the interchangeability of these drugs is questioned [25].

The apparatus type (paddle vs. basket) can also affect the dissolution test and it depends largely on the physiochemical properties of the dosage form [29]. Another possible reason for the difference in dissolution rate is the difference in particle or surface area of the drug particles [30]. Solid dosage form may or may not disintegrate when interacting with gastrointestinal fluid after oral administration following their design. Since disintegration determines to a large extent the area of contact between the solid and liquid, it usually plays a vital role in the dissolution

process. However, it should be noted that there is no automatic correlation between disintegration and dissolution, especially with poorly soluble drugs [29].

The use of surfactant such as sodium lauryl sulphate, which is essential for poorly soluble drugs such as simvastatin can also affect the dissolution rate [31]. In cases where a higher concentration of surfactant is used can lead to faster dissolution and any correlation with *in-vivo* performance can be lost, therefore a low surfactant is a modifier of choice [31]. The storage of a drug can also affect their dissolution profile. For example, a study evaluated the differences between the branded and their generic counterpart of diclofinac sodium on the dissolution rate after storing under 40 °C, 75% relative humidity. It revealed that the dissolution rate of the generic form of diclofinac sodium was reduced significantly during storage time compared to its branded counterpart [32]. Another Egyptian study detected wide variations in *in-vitro* performance of omeprazol capsules. It revealed that the branded medicine was found more resistant to changes caused by the packaging material than its generic counterparts [33].

Differences in dissolution rates between the branded and their generic counterpart drugs can also be related to the composition of excipients. This can mainly influence the side-effects profiles of the generic drugs. Results in this study, like others in the literature, suggests that when performing generic substitution, switching among generics and/or switching from one form to another for the same medicine, patient monitoring should be essential especially for the side effects [34]. Excipients are substances other than the pharmacologically active ingredients, which include binders, fillers, disintegrates, lubricants, sweeteners, preservative, flavours, colours, printing inks, etc. [35,36].

Although excipients are considered the inactive ingredients that do not have therapeutic effect, some studies have revealed that excipients can cause various side effects [36]. In many cases the performance of a drug can greatly depend on the quality of excipients used in manufacturing and on the quality of the process [25]. In the literature, for example, it was reported that the excipients in one of the generic form of simvastatin caused the rapid release of the drug during the first 5 min of the dissolution test [37]. Moreover, a study showed that different formulations of digoxin (cardiac glycosides, narrow therapeutic index drug) yielded tremendous differences in the dissolution profiles. The study indicates that either batch-to-batch or amongst brands bio-in-equivalence originates from differences in dissolution rates [38]. It is well known that digoxin is a narrow therapeutic index medicine, which means that small changes in dissolution rates can make problems because of too many side effects or too little effectiveness [38].

8. Conclusion

This study indicates that dissolution test is well established, reproducible, reliable and valuable tool for characterising a drug product at different stages in its lifecycle. The results clearly raise a question about the interchangeability between branded medicines and their generic counterparts and among generics themselves. This strongly suggests the need to assess patients after performing generic substitution. In addition, the role and regulation surrounding drug substitution should be strengthening to maintain the quality of care. Likewise, Danish Medicines Agency has terminated the generic substitution for oral medicines containing ciclosporine or tacrolimus [39]. Healthcare providers should take into account that definitely generics save money, but recognise that in some cases it may be advisable to monitor patients upon generic substitution of some classes of drugs, such as narrow therapeutic index or transplant drugs.

9. Main limitations of the study

Dissolution test is used to forecast the *in-vivo* behaviour of a drug. However, definite conclusions about the bioavailability and bioequivalence of these products should be conducted *in-vivo* studies. It is critical that the *in-vitro* test should mimic the *in-vivo* conditions as closely as possible. Given the nature of the human GI tract and various factors that affect its activity, the generalisation of dissolution conditions and results of this study is not recommended. *In-vivo–in-vitro* comparison studies are required to confirm findings in this study.

Competing interests

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Authors' contribution

Mubarak N. Al Ameri: Designed and conducted the study, supplied the medicines, analysed the results and wrote the paper. *Nanda Nayuni*: Contributed in conducting the study. *David Perrett*: Analysed the results. *Anil Kumar*: Contributed in providing medicines from the international market. *Arthur Tucker*: Revised the paper. *Atholl Johnston*: Designed the study, analysed results and revised the paper.

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