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Capecitabine: An *In-vitro* Comparison between the Branded Xeloda® 500 Mg and its Intended Copy Capeda 500 Mg

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Abstract

Introduction: Dissolution is an example of *in-vitro* test which can be used to identify formulations that may present potential bioequivalence problems. It 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. 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.

Aim: To compare the differences in the dissolution behaviour between two anticancer formulations, Xeloda® 500 mg (reference product) and Capeda 500 mg (test product).

Methods: Four replicates for each batch of the tested medicines were carried out using a PT-DT70 dissolution tester (Pharma Test) to detect any differences in their dissolution behaviour. Samples at nine time intervals were tested according to the US Pharmacopeia with the rate of dissolution determined by ultra-violet spectrophotometery.

Results: All the tested medicines complied with the pharmacopoeial specifications, the EMA and the FDA guidance for industry when achieved 85% dissolution in 60 minutes. However, Capeda 500 mg (test product) showed slower, different and incomplete dissolution rate compared to Xeloda® 500 mg (reference product) at both 60 and 120 minutes. Other visual differences in the weight, size, clarity of solution, presence of un-dissolved residue and particles during the dissolution test were also detected.

Conclusion: Results in this study clearly raise a question about the interchangeability between Xeloda® 500 mg and its Intended copy Capeda 500 mg. Awareness of these scientific concerns should be considered when a clinical choice between these two drugs is required. Differences between the innovator and copy medicines with regard to pharmacokinetics, clinical efficacy and safety may exist. Thereby, patients' monitoring after performing drug substitution of these two medicines is strongly recommended.

Keywords: Dissolution test; Differences between the branded and generic medicines; Absorption and dissolution methods; Capecitabine; Xeloda® ; Capeda

Introduction

Generic drug usually means a drug that has the same qualitative and quantitative composition of the active ingredient and the same pharmaceutical form as the reference branded drug, and whose bioavailability with the reference drug has been demonstrated by an appropriate bioequivalence study [1]. Generic substitution is defined as switching between a branded product and a generic version of the same drug (such as switching from Taxotere® to docetaxel) [2]. Promoting generic substitution from multiple sources into the healthcare system is aimed at maximising population health subject to improve the overall healthcare delivery systems [3]. This strategy of drug substitution is proven to be effective since it is often easier to intervene on the expenditure of medicines because of their identified cost [4-6]. 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, health care providers and patients are usually concerned when selecting one drug from among several bioequivalent ones during the treatment regime [7, 8].

Dissolution is an example of *in-vitro* test which can be used to identify formulations that may present potential bioequivalence problems. It 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 [9]. 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 [10]. Dissolution is considered as the rate limiting step for a drug to be absorbed from solid dosage form following oral administration. It is the process of transporting the drug substances from the gastrointestinal lumen into the systemic circulation [11]. Absorption is the first step before the distribution, metabolism and elimination (ADME) of drugs in the human body. It usually depends on the stages of disintegration, disaggregation, drug release from the pharmaceutical form, its dissolution under physiological conditions and permeability through the biological membranes, (Figure 1) [12, 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 [14]. 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 [9]. The importance of dissolution testing, for example, has recently directed the UK MHRA (Medicines and Healthcare products Regulatory Agency) to suspend the license of the generic Teva (levothyroxine 100

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mcg) tablets over dissolution fears. Levothyroxine is typically used to treat hypothyroidism. The dissolution testing of Teva product showed that it differed from other products in the amount of levothyroxine that is released over time. Therefore, some patients have experienced a loss of control of thyroid stimulating hormone (TSH) levels. Therefore, the interchange ability between Teva and its branded counterpart was questioned by the MHRA and its license was suspended [15].

It is very common that any report in literature on formulation and development of any solid dosage form starts with dissolution testing. Drug dissolution can play an important role in both the development process of a new formulation and as a mean of production control. Therefore, the FDA guidance for industry indicates that for highly soluble drugs a single point dissolution test specification of 85% in 60 minutes or less is sufficient as a routine quality control test for batch-to-batch uniformity [16]. Similarly the EMA guidance which stated that *"In cases where more than 85% of the active substances are dissolved within 15 minutes, the similarity of dissolution profiles may be accepted as demonstrated"* [1].

Capecitabine is an oral pro-drug of 5-fluorouracil (5-FU) which is indicated as anticancer for the treatment of metastatic breast, oesophagogastric and colorectal cancers [17,18]. Unlike the intravenous chemotherapeutic agent 5-FU, Capecitabine is tumor-specific as it generates 5-FU preferentially in tumor tissue [19-21]. 5-fluorouracil/leucovorin (5-FU/LV) was the historical mainstay of treatment of many cancers. This tumor-selective activation of Capecitabine potentially provides tumor-targeted therapy with improved efficacy and reduced toxicity. In addition, Capecitabine's oral administration regimen provides convenient, patient-orientated treatment in a home-based setting and avoids catheter-related complications [22-24]. Compared with 5-FU, Capecitabine has demonstrated superior response rate, equivalent time to progression and overall survival [25], favorable safety profile [26] and cost savings by fewer hospitalisations for the management of treatment-related adverse events [22]. Xeloda is the branded copy of capecitabine and Capeda is an intended copy of Xeloda which was marketed in Lebanon in 2010, three years before the loss of Xeloda's patent in the EMA region for 2013 [27,28] (Figure 2).

Breast cancer is the most common malignant disease in women which is considered a public health issue on a global scale. It is considered the second most common cancer in the world and the most common cancer among women [29]. In Europe, in 2004, there was an estimate of 2.9 million new cases of breast cancer and 1.7 million deaths each year [30]. In the US, 28% of the estimated cancer cases with US women in 2010 were breast cancer [31]. Gastric cancer is the second most common cause of cancer-related death in the world – killing around 800,000 people each year, yet it is only the fourth most commonly diagnosed cancer – around one million people are diagnosed each year. The incidence of gastric cancer varies hugely geographically, with a much bigger prevalence in Eastern countries than in the West, and between men and women with men more prone to stomach cancer than women [32]. Similarly the colorectal cancer which remains the third most common cancer among male and females in the US and the most common cause of death [33]. In Europe, the incidence of colorectal cancer is one in 20 [34].

Objective

The aim of this study was to compare the differences in dissolution rate of solid dosage forms between Xeloda® 500 mg as the innovators (reference products) to its intended copy Capeda 500 mg (test products).

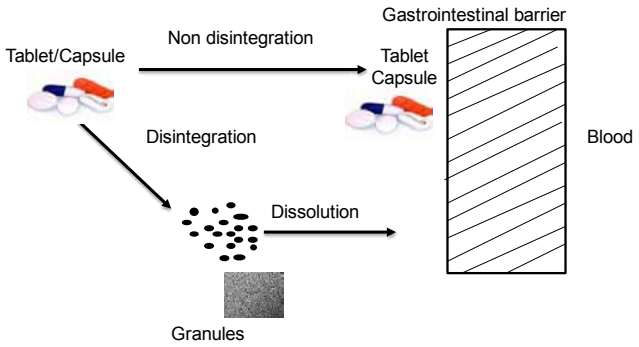

Figure 1: Schematic diagram of the dissolution process [13].

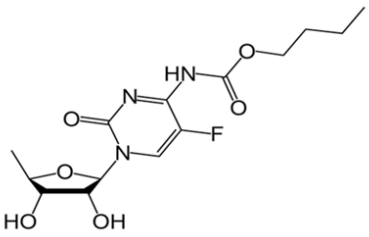

Figure 2: The structural formula of capecitabine [28].

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 [35] from Pharma Test Company was used to conduct this study. The dissolution tests were carried out on May 2011 using four tablets of each medicine contained the same amount of drug substances but different types and/or amount of excipients, (Table 1). All the tested tablets were stored according to the 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 was calculated using Microsoft Office Excel 2007 [36]. The temperature was maintained at 37 ± 0.5ºC throughout the dissolution test for 120 minutes.

The dissolution test was performed by manually pipetting out 5 ml samples of dissolution medium at nine time intervals (5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes) and transferring them to the tubes. The medium, apparatus type and agitation rate for each drug were prepared according to the US Pharmacopeia (USP-30) [37]. The test was carried out in 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 micron filter before measuring the absorbance using ultra-violet/visible spectrophotometery (model 6715 UV/Vis. Spectrophotometer, 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 [38]. The precision of an analytical procedure was determined by repeated analysis, (n=3) expressed the closeness between a series

of measurements 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 [39].

Results

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 result of this study was 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 [12].

The dissolution rate of Xeloda® 500 mg (branded medicine) compared to Capeda (intended copy medicine) at 60 minutes, (Table 3 and Table 4).

When comparing the dissolution rate between Xeloda® 500 mg to its generic counterpart Capeda 500 mg at 60 minutes, the generic medicine showed a statistically significant difference in the dissolution behaviour (P=0.003). Capeda 500 mg showed much slower and different dissolution behaviour than its branded counterpart. When 100% of the reference Xeloda® 500 mg dissolved at 60 minutes, only 86% (95% CI 80-93) of its intended copy Capeda 500 mg dissolved (Table 5).

The dissolution rate of copy medicines compared to their branded counterpart at 120 minutes are shown in (Table 6 and Table 7).

When comparing the dissolution rate between Xeloda® 500 mg to its intended copy Capeda 500 mg at 120 minutes, the intended copy also showed a statistically significant difference in the dissolution behaviour (P=0.008), (Figure 3). Capeda 500 mg showed different and incomplete dissolution compared to its branded counterpart medicine. When 100% of the branded Xeloda® 500 mg dissolved in 120 minutes, only 90% (95% CI 84-96) of its generic counterpart's Capeda 500 mg dissolved (Table 8).

Visual differences detected between the branded Xeloda® 500 mg and its intended copy Capeda 500 mg during the dissolution test

There were some visual differences detected between the branded Xeloda 500 mg and its intended copy Capeda 500 mg during the dissolution test. For example, there were differences in the weight between both tested drugs. This was weighted by Sartorius AZ64 Research Analytical Weighing Balance. The average weight of Xeloda® 500 was 0.64 g compared to 0.99 g of Capeda 500 mg. Differences in the tablet size were also detected between both tested drugs. The tablet size of Xeloda® 500 mg was 14.47 mm (length)×7.00 mm (width)×4.12 mm (depth) compared to 18.22 mm (length)×7.87 mm (width)×4.71 mm

Formulation	Strength (mg)	Type (Tablet/Capsule)	Expiry date	Batch No.	Manufacturer
Xeloda®	500	Tablet	10/2012	X0115B01	Roche (Mexico)
Capeda	500	Tablet	12/2012	LT6026	BPI (Lebanon)

Table 1: Characteristics of the medicines tested in the dissolution study.

Formulations	Type (brand/copy)	Dissolution medium	Volume (ml)	Agitation rate (revolutions per minute)	UV Analysis (wavelength, nm)
Xeloda®	**Brand**	**Deionised** water	900	50	304
Capeda	**Copy**	**Deionised** water	900	50	304

Table 2: *In-vitro* dissolution procedures for the tested medicines.

Time (minutes)	Run 1 (%)	Run 2 (%)	Run 3 (%)	Run 4 (%)	Mean %	Standard deviation (%)	Coefficient of variation (%)
5	15.9%	17.2%	30.6%	25.3%	22%	6.9%	31.2%
10	41.6%	44.2%	66.1%	52.8%	51%	11.0%	21.5%
15	63.2%	68.2%	84.1%	68.7%	71%	9.1%	12.8%
20	78.7%	80.5%	92.4%	82.2%	83%	6.1%	7.4%
30	94.7%	93.4%	98.5%	93.7%	95%	2.4%	2.5%
45	100.7%	100.4%	100.0%	98.7%	100%	0.9%	0.9%
60	100.7%	99.9%	100.7%	98.7%	100%	0.9%	0.9%

Table 3: The percentage of Xeloda® 500 mg dissolved at 60 minutes.

Time (minutes)	Run 1 (%)	Run 2 (%)	Run 3 (%)	Run 4 (%)	Mean (%)	Standard deviation (%)	Coefficient of variation (%)
5	73.9%	51.6%	60.9%	63.9%	63%	9.2%	14.6%
10	85.5%	72.5%	77.3%	77.2%	78%	5.4%	6.9%
15	87.8%	76.9%	85.8%	82.0%	83%	4.8%	5.8%
20	87.5%	78.3%	87.2%	83.2%	84%	4.3%	5.1%
30	87.2%	78.0%	88.4%	83.8%	84%	4.7%	5.6%
45	87.7%	79.2%	91.0%	85.0%	86%	5.0%	5.8%
60	87.2%	79.6%	91.9%	86.7%	86%	5.0%	5.8%

Table 4: The percentage of Capeda 500 mg dissolved at 60 minutes.

Drug Name	Average weight (g)	% of drug dissolved at 60 minutes	95% Confidence Interval	P Value
Xeloda® 500 mg	0.63751	100		0.003
Capeda 500 mg	0.98755	86	(80- 93)	

Table 5: The percentages of the dissolution rate of the copy medicines (Capeda) compared to their branded counterpart (Xeloda) at 60 minutes.

Time (minutes)	Run 1 (%)	Run 2 (%)	Run 3 (%)	Run 4 (%)	Mean %	Standard deviation (%)	Coefficient of variation (%)
5	16.3%	17.6%	31.3%	25.9%	23%	7.1%	31.2%
10	42.6%	45.3%	67.6%	54.1%	52%	11.3%	21.5%
15	64.7%	69.7%	86.1%	70.2%	73%	9.3%	12.8%
20	80.5%	82.4%	94.5%	84.1%	85%	6.3%	7.4%
30	96.9%	95.6%	100.8%	95.9%	97%	2.4%	2.5%
45	103.0%	102.7%	102.3%	101.0%	102%	0.9%	0.9%
60	103.0%	102.2%	103.0%	101.0%	102%	1.0%	0.9%
90	102.0%	101.6%	100.7%	100.1%	101%	0.8%	0.8%
120	100.0%	100.5%	100.5%	99.0%	100%	0.7%	0.7%

Table 6: The percentage of Xeloda® 500 mg dissolved at 120 minutes.

Time (minutes)	Run 1 (%)	Run 2 (%)	Run 3 (%)	Run 4 (%)	Mean (%)	Standard deviation (%)	Coefficient of variation (%)
5	75.6%	52.8%	62.3%	65.4%	64%	9.4%	14.6%
10	87.5%	74.2%	79.1%	78.9%	80%	5.5%	6.9%
15	89.8%	78.6%	87.8%	83.9%	85%	4.9%	5.8%
20	89.5%	80.1%	89.2%	85.2%	86%	4.4%	5.1%
30	89.2%	79.8%	90.5%	85.8%	86%	4.8%	5.6%
45	89.8%	81.0%	93.1%	86.9%	88%	5.1%	5.8%
60	89.2%	81.5%	94.0%	88.8%	88%	5.2%	5.8%
90	88.5%	83.5%	95.5%	90.5%	89%	5.0%	5.6%
120	89.3%	83.8%	94.9%	92.2%	90%	4.8%	5.3%

Table 7: The percentage of Capeda 500 mg dissolved at 120 minutes.

Drug Name	% of drug dissolved at 120 minutes	95% Confidence Interval	P Value
Xeloda® 500 mg	100		0.008
Capeda 500 mg	90	(84- 96)	

Table 8: The percentages of the dissolution rate of the intended copy (Capeda) compared to their branded counterpart (Xeloda) at 120 minutes.

(depth) of its intended copy Capeda 500 mg, (Figure 4). The sizes of tablets were measured using Electronic Digital Calliper [40]. Moreover, Capeda 500 mg showed poorer clarity of solution and presence of un-dissolved residue and particles during the dissolution test compared to its branded counterpart Xeloda® 500 mg (Figure 5).

Discussion

According to the result of this study, the dissolution rate profile of the branded Xeloda® 500 mg and its intended copy Capeda 500 mg complied with the pharmacopeial limits [37]. All of the tested medicines achieved 85% dissolution at 60 minutes or less. This is found to be compatible with the EMA and the FDA guidance for industry [1,16]. Two-points dissolution specification were selected in this study to ensure 85% dissolution in order to characterise the quality of all the tested products [16]. This can reflect that the *in-vivo* bioavailability of these products would be similar to that *in-vitro*, since dissolution testing is commonly used to predict *in-vivo* behaviour of the oral dosage formulation. However, Capeda 500 mg showed significant differences in the dissolution behaviour compared to its branded counterpart Xeloda® 500 mg at 60 and 120 minutes. For example, Capeda 500 mg showed slower, different and incomplete dissolution rate compared to its branded counterpart at both 60 and 120 minutes. Other differences in the weight, size, clarity of solution, presence of un-dissolved residue and particles during the dissolution test were also detected.

The relationship between the drug weight and its performance is not yet clear. However, depending on the cause of these differences, it might elevate the side effects and/or drug interactions [41]. The tablets size of Capeda 500 mg was much bigger than its branded counterpart. For example, the tablet size of Capeda 500 mg has reached 18.22 mm compared to 14.47 of Xeloda® 500 mg. According to the literature, the easiest size of tablets to swallow is 7-8 mm and the easiest size to handle is one larger than 8 mm [41]. For example, in a survey a total of 26% of patients declared that the main reason causing the difficulty in swallowing was the size of the tablet followed by the surface, form and the taste of the tablet [42]. Another study in the literature has confirmed that medicine adherence was greatly influenced by the decline of swallowing ability especially for elderly and patients with oesophageal diseases [43]. This indicates the potential impact of the tablet size on patients' compliance and adherence as well as the clinical outcomes.

The intended copy in this study showed poorer clarity of solution and presence of un-dissolved residue and particles compared to its branded counterparts. This, however, might impact patient safety by increasing the drug's side effects and drug interactions. According to the literature, particles, degradation products and residual solvents all pose potential threats to patient safety [44]. A study in the literature, for example, was conducted to compare the pharmaceutical quality of 34 generic formulations of ceftriaxone (antibiotic agent) to their branded counterpart Rocephin®. It was found that all the 34 tested generic medicines failed to meet Roche specifications for Rocephin®. A total of 18 generics tested in this study contained more than five times the number of particles found in their branded counterparts and violated the quality standards specified in the European and the US Pharmacopoeias. The most common failures amongst generic medicines were clarity of solution. It concluded that none of the generics tested in this study can be considered pharmaceutically equivalent to Rocephin® [44].

Findings in this article are compatible with others in the existing literature [7,8,45,46]. For example, a study evaluated the quality of 31 commercially available generic formulations of docetaxel obtained from 14 countries revealed that the most tested generic formulations contained a lower amount of docetaxel and/or high level of impurities and did not comply with the original branded specifications compared to the innovator product Taxotere® [47]. Another study compared

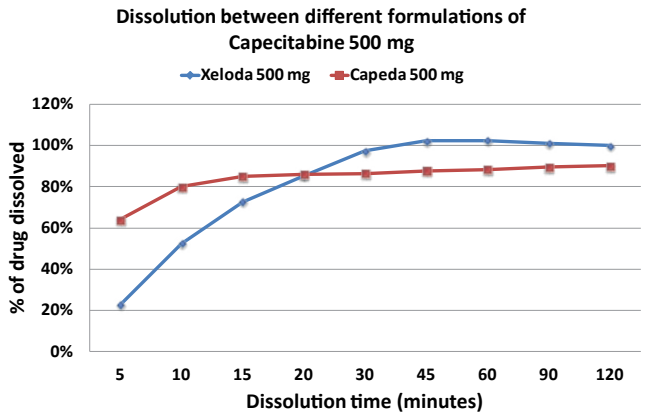

Figure 3: The differences in dissolution rate between the branded Xeloda® 500 mg and its copy counterpart Capeda 500 mg.

Figure 4: The differences in size between the branded Xeloda® 500 mg (B, left), 14.47 mm (length)×7.00 mm (width)×4.12 mm (depth) and its intended copy Capeda 500 mg (G, right), 18.22 mm (length)×7.87 mm (width)×4.71 mm (depth).

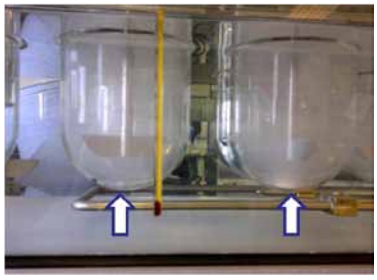

Figure 5: The differences between the branded Xeloda® 500 mg (left) and its intended copy Capeda 500 mg (right) after 60 minutes dissolution.

the dissolution behaviour of six diclofenac sodium prolonged release tablets of different brands obtained from the national market. It revealed that the release characteristics varied considerably among different manufacturers and that even identical formulations showed rather dissimilar release profiles. Therefore, the interchangeability of these drugs was questioned [45].

A similar study had compared 13 generic alendronate preparations from Latin-America with the innovator product. It revealed that nine generics showed faster dissolution and three generics showed slower dissolution than their branded counterparts. It was suggested that slower disintegration may reduce efficacy and faster disintegration could increase the risk of oesophagitis (prolong contact of the oesophageal mucosa with the drug) [48]. Moreover, a dissolution test was performed on different brands of alendronic acid showed that the highest release was found for the branded drug and the dissolution rate of the generic formulations was significantly lower than their branded counterpart in the early stage of dissolution [49].

Differences in dissolution rates between the branded and its generic counterpart drugs can be related to the composition of excipients. This can mainly influence the side-effect profiles of the generic drugs. Excipients are substances other than the pharmacologically active drug and include binders, fillers, disintegrators, lubricants, sweeteners, preservatives, flavours, colours and printing inks [50,51]. Although excipients are considered the inactive ingredients that do not have a therapeutic effect, some studies have revealed that excipients can cause various side effects [51]. 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 [45]. It is mentioned in the literature, for example, that the excipients in one of the generic forms of simvastatin caused the rapid release of the drug during the first five minutes of the dissolution test [52].

Drug binding and extractable impurities affect drug dissolution profiles [53]. A study comparing meloxicam 15 mg to its generic counterpart revealed that the dissolution profile for the generic product was statistically different from that of the branded product regarding the drug release percent of the pharmaceutical form [12]. Another study showed that different formulations of digoxin yielded tremendous differences in the dissolution profiles. The study indicated that either batch-to-batch or amongst brands bio-in-equivalence originated from differences in dissolution rates [54]. Similar dissolution study was performed on three commercial solid dosage forms of levothyroxine which is a narrow therapeutic index drug used as a hormone replacement for patients with thyroid problems. It revealed that the three products had drastically different dissolution profiles with respect to both shape and percentage of levothyroxine dissolved. This can impact the oral absorption and bioavailability of the active ingredient which may result in bioequivalence problems between various available products [55].

Another dissolution study was performed to evaluate and compare 25 internationally available piroxicam (non-steroidal anti-inflammatory drug) products using the US Pharmacopeial specifications. It revealed that 72% of the tested products failed to meet the USP requirement, several by a wide margin. Also, when the dissolution test for the capsules was applied to five different formulations of piroxicam tablets, 80% of the tablets failed to meet the USP requirement [56].

Conclusion

The results of this study clearly raise a question about the interchangeability between the branded Xeloda® 500 mg and its intended copy Capeda 500 mg in treating cancer patients. Awareness of these scientific concerns should be considered when a clinical choice between these two products is required. This is strongly suggesting the need to monitor patients after performing substitution of these two medicines. The results of this study show that differences may exist between the innovator and copy drugs with regard to pharmacokinetics, clinical efficacy and safety. Therefore, healthcare providers should take into account that definitely generics and copies save money; but are they good for us?

Main limitations of the study

The 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 *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 are not recommended. *In-vivo* comparison studies are required to demonstrate findings in this study.

Competing Interests

This study was funded by the William Harvey Research Institute at Queen Mary University of London. The authors have no financial or proprietary interest in the subject matter or material discussed.

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