Comparative study of different meloxicam generic products with the brand product

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Abstract:

This study aims to evaluate different products of meloxicam Table; Five meloxicam immediate-release generic products (15 mg Tables) were compared with the innovator, reference product, (Mobic®, Boehringer) to find the interchangeable product with the innovator product.

Different physical tests were conducted including weight uniformity, thickness, diameter, hardness, friability and disintegration test. In addition, prediction of *in-vivo* behavior was assessed by measuring the dissolution profile of meloxicam for all the products. Similarity factor (f2) was calculated to compare between the dissolution profile of the generic products with the dissolution profile of innovator product.

The results revealed that all the studied products are complied with the British Pharmacopoeia requirements. However, not all of them showed similar *in-vitro* profile to the brand product. Four out of five generic products, included in this study, showed similarity in dissolution profile to the brand one, which indicates possible bio-equivalency, with the advantages of money saving of using such generic products. One generic product showed similarity factor less than 50, which might give an indication that this generic product is not capable to be bioequivalent with the brand (innovator) product.

Overall, this study can be considered an important applicable study that gives an indication about the *in-vivo* performance of different products. In addition, the study demonstrates the applicability of a simple *in-vitro* dissolution study as a surrogate way of assessing product bioavailability instead of an expensive and complicated *in-vivo* bioequivalent study.

Key words: meloxicam, dissolution, similarity factor, bioequivalent, generic.

دراسة مقارنة لمستحضرات ميلوكسيكام المكافئة اوالجنيسة بالنسبة للمستحضر الأصلي المنشأ

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الخلاصة:

تهدف هذه الدراسة لتقييم خمس مستحضرات جنيسة لدواء الميلوكسيكام مقارنة مع المستحضر الأصلي المنشأ وذلك لإيجاد البديل المناسب والفعال من بين المستحضرات الخمسة. تم اجراء العديد من الفحوصات الفيزيائية كقياس وزن الحبوب , قطر الحبة, سمك الحبة, قياس الصلابة , الهشاشة وتفكك الحبوب. بالإضافة لذلك تم قياس درجة تحرر الدواء خارج الجسم ولجميع

المستحضرات. تم حساب معامل التشابه لتحرر الدواء للمقارنة بين مستوى التحرر الدوائي للمستحضرات الجنيسة مقارنة بالمستحضر الأصيل.

أثبتت النتائج أن جميع المستحضرات تطابق دستور الأدوية البريطاني ولكن لم تبد جميع المستحضرات تشابه لمستوى التحرر للدواء الأصلي. أظهرت أربعة من المستحضرات تشابها في مستوى التحررمقارنة بالمستحضر الأصلي مما يعني احتمالية التكافؤ الحيوي لهذه المستحضرات. أبدى مستحضر واحد معامل تشابه اقل من ٥٠ مما يعني أن هذا المستحضر لا يمكن ان يحقق تكافؤا حيويا مع الدواء الأصلي.

بالمجمل يمكن اعتبار هذه الدراسة دراسة تطبيقية تعطي تصورا عن تصرف المستحضرات داخل جسم الكائن الحي. بالإضافة لذلك أظهرت الدراسة امكانية اعتماد اختبار قياس التحرر كطريقة لقياس التوافر الحيوي بدلا من الطريقة المكلفة والمعقدة المستخدمة لقياس التكافؤ الحيوي.

الكلمات المفتاحية: دواء الميلوكسيكام, معدل التحرر ,معامل التشابه ,التوافر الحيوي, الدواء المكافئ

Introduction

Drug product selection and generic drug product substitution are major responsibilities for physicians, pharmacists and any health workers involved in drug dispensing. The evaluation of the available multisource products aid in choosing the appropriate generic which foster containment of health care costs. In U.K. the substitution of generic products account for 83% saving of the products cost (1). Nevertheless, the myth that the generic is inferior to brand product is still available in the minds of some health practitioners. In order for the product to be interchangeable it should demonstrate bioequivalency with the innovator product (brand product). During clinical development of new product, there is a need for conducting a bioequivalent study. The bioequivalent study usually conducted by measuring plasma concentration of the generic drug or its metabolite in comparison to the brand product (2). However, dissolution test can be used to predict the in-vivo behavior of the products and in some cases dissolution test can be used to determine the bioequivalency between different products (3). The introduction of the term biowaiver allowed to use dissolution study (under certain conditions) as an alternative to in-vivo bioequivalent study. For biowaiver, the product should show rapid dissolution in three phosphate buffer media (pH 1.2, pH 4.5 and pH 6.8) in order to consider the product rapidly dissolved (4,5).

The major factors that have an effect on the in-vivo performance of oral solid

dosage forms are solubility and membrane permeability. Biopharmaceutics Classification System (BCS) proposed by Amidon et al (1995) is a theoretical basis by which drugs can be classified in terms of their solubility and permeability (6). The BCS categorizes drug substances into one of four categories and these four categories are defined as follows:

- high solubility / high permeability (class I)
- low solubility / high permeability(class II)
- high solubility/low permeability (class III)
- low solubility/low permeability (class IV)

Highly soluble drugs, as the case with class I and class III, show no problem in dissolution. Class II drugs have low solubility and high permeability, so the dissolution in the gastro-intestinal lumen is a limiting step of the absorption process, consequently, the bioavailability of a poorly water-soluble drug is often limited by its dissolution rate.

Meloxicam is a potent non-steroidal anti-inflammatory drug (NSAID) with high selectivity toward cyclooxygenase-2 (COX-2) inhibitor. Meloxicam used mainly in the treatment of rheumatoid arthritis and osteoarthritis (7). It has a wide spectrum of anti-inflammatory activity combined with less gastric irritation than other NSAIDs

available prior to its introduction into the market (8).

Meloxicam (BCS class II) drug is a member of the enolic acid group of NSAIDs with a pKa values of 1.1 and 4.2 and is practically insoluble in water (9,10). Several approaches were conducted to improve the bioavailability of meloxicam including manufacturing of mouth dissolving film or including preparing of the drug as solid dispersion to improve the solubility (11) or grinding the meloxicam with PEG 6000 (12). Meloxicam is available in Iraqi market in several generic products from different pharmaceutical companies. However, no local studies conducted on such pharmaceutical products to evaluate the in-vivo performance of different products and the possibility to interchange these generics with the innovator or brand product. Recently, dissolution study were used to compare the performance of generic and brand products of several drugs like naproxen Tables (13) and metformin Tables (14). In addition, there is no information about the money saving, which can be achieved with substitution of brand with generics, that is measured by comparing the retail prices of different products .

This work aims to use simple in-vitro test to evaluate different products of meloxicam Table including five generic products in comparison with the innovator, reference product, (Mobic®, Boehringer) to find the interchangeable product with the innovator product.

Materials and Methods
Materials
Meloxicam powder was obtained from Pioneer company (Sulaymania, Iraq). All buffer constituents were from BDH. All the pharmaceutical products were purchased from retail market in Mosul, Iraq. The apparatuses used were PT-DT70 dissolution tester (Pharma Test), Erweka hardness tester, Erweka friabilator, disintegration apparatus (Pharma Test) and Shimadzo spectrophotometer.

Methods
The physical tests of Tables
The diameter, thickness, weight, hardness, friability and disintegration were measured by using digital micrometer, vernia, digital scale, Erweka hardness tester, Erweka friabilator and disintegration apparatus. All the tests were conducted according to pharmacopeial requirements.

Study of the dissolution profile
The measurement of dissolution profile was conducted according to USP 32. Type II dissolution apparatus was used, where Tables (n=6) were immersed in a vessel prefilled with 900 mL of the dissolution medium. Dissolution medium used was phosphate buffer pH 6.8 and pH 7.5. The temperature was allocated to be 37.5 ± 0.5 whereas the rotation speed was 75 rpm. Sampling conducted manually, where 5ml sample aspirated by special loop fitted with a syringe, then the samples were filtered and transferred into a test tube. Sampling was performed on different time intervals at time 5, 10, 15, 30, 45 and 60 minutes. Each aspirated 5 ml where compensated instantly with 5 ml dissolution medium. The absorbance of samples were measured at λ max 362nm by using Shimadzo UV/visible spectrophotometer with 1cm cell (14 .

The amount of dissolved Meloxicam was calculated in relative to the amount of standard Meloxicam derived from the calibration curve. Calibration curves of meloxicam powder in phosphate buffer pH 6.8 and pH 7.5 were constructed by preparing a series of different concentrations of meloxicam from stock solution of meloxicam dissolved in buffer and the absorbance was measured at λ max 362nm. Phosphate buffer pH 6.8 and pH 7.5 were prepared as follows:

37 grams of Potassium dihydrogen phosphate, 7 grams of sodium hydroxide were dissolved in 5 Liter. Stirring was continued until all material dissolved and then the pH adjusted with concentrated

sulpheric acid or concentrated sodium hydroxide using a suitable pH meter.

Similarity factor calculation

The dissolution profile of each generic products is compared with the dissolution profile of the brand one by using f2 (similarity factor)

The similarity factor (*f* 2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. *f*2 is calculated using the following equation (15), equation 1:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t}^{n} (R_t - T_t)^2 \right]^{-0.5} \right\} \cdot 100$$

…………………… eq 1   Where n is the number of time points, R_t is the dissolution value of the reference

or innovator   at time t, and T_t is the dissolution value of the test or generic at time t.

When the calculated *f*2 value for generic product showed a value between 50 and 100, the dissolution curve considered similar or bioequivalent (16).

Results and discussions

Physical characteristics

All the pharmacopieal tests were conducted on all the products including weight uniformity test, diameters, thickness, hardness and disintegration. The results which presented in Table 1 showed that all the products had acceptable weight uniformity test; there is no wide variations in weight and all the weight variations were within acceptable limits of B.P. It is worthy to mention that generic I, II and V have similar shape to the brand product. Knowing that the size and shape of the Table depend on the diameter and thickness of the Table, so the thickness and diameter of the Tables were measured. As demonstrated in Table 1 the diameter and thickness of all products were within acceptable limits .

Concerning the hardness test, results showed variations between products. Hardness for the different products ranges from about two to as high as around thirteen. The low hardness of generic V might explain the rapid disintegration of this product, however, the dissolution result is not in parallel with the rapid disintegration time. As meloxicam belongs to BCS class II, the rapid disintegration does not indicate rapid dissolution and this is clear with all the results tabulated in Table 1; there is no relationship between disintegration time and dissolution time .

The disintegration times for the different products showed variations as well. It is well known that high force of compression might prolong the disintegration time. However, the results showed no relationship could be predicted between the hardness and the disintegration time. In contrast, product with high hardness expressed very short disintegration time as in the case with generic III which express high hardness (about 13kg) with very short disintegration time (18 seconds). This is in contrast to the good correlation obtained between the hardness and the disintegration time of previous work conducted on caffeine Tables (17). On the other hand, this product (generic III) exhibited the lowest dissolution rate. This low dissolution is not in parallel with the very fast disintegration of this formula and this is explained by the low solubility of the drug as it belongs to class II BCS. It is worthy to mention that this product, generic III, is the only product that does not show a dissolution profile similarity to the brand product. Concerning the friability test, all the products showed friability less than 1% which is within the acceptable limit. In general, all the products are complied with the BP requirements.

Table 1: The comprehensive tests on all the investigated meloxicam products.

Products	Weight (mg±SD)	Thickness (mm)	Diameter (mm)	Hardness (Kg±SD)	Disintegration (minutes)	Dissolution (Q= 70%) (minutes)
Brand	180±2.4	3.05	9.12	7.1±0.32	3.88	10
Generic I	182±2.2	2.7	9.05	4.8±0.35	3.19	7.75
Generic II	181±3.6	3.43	8.61	6.2±0.9	4.66	13
Generic III	248±3.4	3.31	9.1	12.9±1.96	0.26	20.5
Generic IV	231±2.6	4.04	8.52	8.5±0.61	3.87	7.5
Generic V	180±7.6	3.48	8.39	2.6±1.6	0.16	12

Dissolution as an in-vitro bioequivalent test The bioequivalence between the multi-source (generic) products and the innovator or brand product could be measured by in-vivo bioequivalence test or in certain cases by in-vitro equivalence test. The in-vitro equivalence test included a comparative study between the dissolution profile of generic product and the innovator product, this should be conducted in three different dissolution media (Phosphate buffer pH 1.2, pH 4.5 and pH 6.8) (18)

In this work, the first dissolution profile was studied using phosphate buffer pH 6.8 as the dissolution medium. Figure 1 represents the dissolution profile of meloxicam in phosphate buffer pH 6.8, where the dissolution profile of meloxicam showed low dissolution; the dissolution does not exceed 85% within 30 minutes, which is the condition that should be achieved by the product in order to consider the product rapidly dissolved. Cumulative meloxicam release within 30 minutes in phosphate buffer pH 6.8 was 79%, 63% and 57% for generic I, generic II and brand product, respectively. In order to use dissolution test for predicting the bioavailability or what is called biowaiver of meloxicam products, the products should demonstrate similar dissolution profile in three different media including phosphate buffer pH 1.2, pH 4.5 and pH 6.8. As the dissolution of meloxicam products in phosphate buffer pH 6.8 is low, this means that there is no possibility for biowaiver. Accordingly, there is no further need to conduct the dissolution profile study in the other media (phosphate buffer pH 1.2 and pH 4.5).
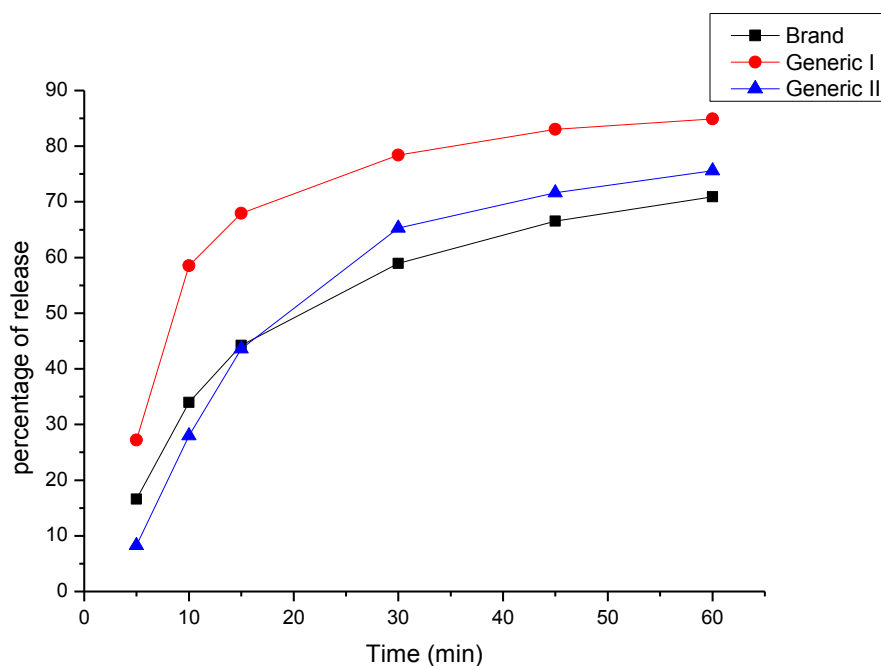
Figure 1: Release of meloxicam from different products at phosphate buffer pH 6.8.

The dissolution profiles of generic I and generic II in comparison to the brand product in phosphate buffer pH 6.8.

In order to measure the similarity factor between the generic products and brand product, the dissolution profile of each product was measured in phosphate buffer pH 7.5 for 60 minutes. The time interval was 5,10,15,30, 45 and 60 minutes.

Results, which are presented in Table 1, showed that all the generic products met the pharmacopieal specification (in achieving the dissolution of 70% of the product within 30 minutes), however not all of them showed dissolution profile similarity with the brand one.

Figure 2 shows the dissolution profiles of all the generics and brand product. The similarity factor ($f2$), which measures the dissolution profile similarity, was calculated for each generic against the brand or innovator product. Results, which are presented in Table 2, indicates that all the generic products showed similar dissolution profile with the brand product except one generic product, that is generic III. This product showed $f2$ value less than 50 (the calculated $f2$ value is 44.97). It is necessary to mention that f2 value less than 50 indicates more than 10% difference in each time point. Such results may indicate the importance of formulation factor as one of the factors that effect on the dissolution of solid dosage form such as Tables dosage form. The results of this study are in accordance with a recent study conducted to compare the dissolution profiles of nine generic products of meloxicam Tables, marketed in Argentina, by using dissolution profile comparison. Results showed that not all of the studied meloxicam products are bioequivalent and not all of them can be interchangeable with each other (19).
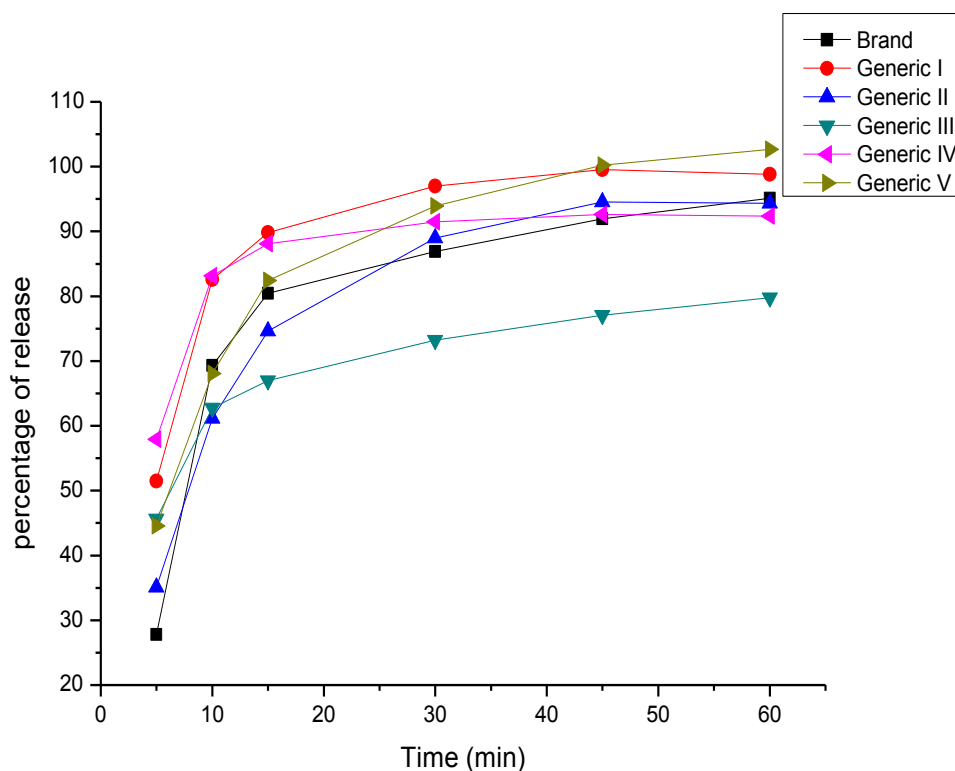
Figure 2: The dissolution profile of meloxicam from different products at phosphate buffer pH 7.5.

The dissolution profiles of all the studied generics in comparison to the brand product in phosphate buffer pH 7.5.

Table 2: The calculated similarity factor of all the generic products in comparison to the brand product.

Product	$f2$ (similarity factor)
Generic I	50.16
Generic II	63.5
Generic III	44.97
Generic IV	53.76
Generic V	62.45

Cost effectiveness of the products

The cost of all the products were calculated depending on the retail prices. Results showed that the generics of the same active ingredients are available in the market at competitive prices. The use of these generics in this study may save 64%, 50%, 86%, 70% and 90% of the cost for generic I, II, III, IV and V respectively. This is in consistent with another work conducted on antihypertensive products to reduce the blood pressure to widely established clinical guidelines in non-diabetic patient. The results showed that using of generic medication saved more than 85% of the yearly cost of using brand-name product (20). However, it is worthy to mention that one of the cheapest products in our study, generic III, showed predicted non-bioequivalency to the brand product while another cheap product (generic V) showed dissolution similarity to the brand product.

Conclusion

Using in-vitro equivalence test instead of in-vivo bioequivalence test might be a good alternative to the expensive and long bioequivalent study, which require a sophisticated instruments and numbers of

healthy volunteers. Using of dissolution study as in-vitro equivalent test will contribute in reducing the cost of introducing the generic products into the market and consequently improve patient access to reasonably priced medicine. One of the main conclusions of this study is that the single-point dissolution test serves as a quality control test but cannot provide full idea about in-vivo behavior of drugs belong to class II BCS drugs, which suffer from low solubility. The dissolution profile similarity should superimpose the single point dissolution test for class II BCS drugs.

Concerning the cost effectiveness of replacing brand product with generics, the results indicated that generics cost less than brand name product and could save money although there are differences among the prices of different generics.

This work recommended the need for a new policy for introducing the medicines in Iraqi market where only the generics of companies that follow the good manufacturing practice (GMP) is allowed. In addition, simple in-vitro dissolution profile study could aid in selecting the best choice among many products. It is worthy to mention that one of the generic products in this study is from local company (Pioneer, Sulaymania, Iraq) and it shows similarity to the brand product. This may highlight the need for more such studies to enable the dispenser to select the suitable product depending on its effectiveness irrespective of its origin as long as it shows acceptable compliance with the requirement.

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