In–Vitro Bioavailability and Pharmaceutical Evaluation of Five Brands of Mefenamic Acid Tablets Marketed in Oman

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ABSTRACT

Background: Mefenamic acid, an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug used to treat pain of different etiology. Many different brands and dosage forms of Mefenamic acid are available in the Omani market that places health practitioners in a dilemma of drug substitution in case of non availability of a particular brand.

Aim/Objective: The aim of the present study was to evaluate the pharmaceutical and chemical equivalence of five brands of Mefenamic acid tablets marketed and commonly prescribed in Oman.

Materials and methods: Five brands of Mefenamic acid tablets (500 mg) were purchased from the retail pharmacy outlets and their pharmaceutical quality were assessed by using in-vitro tests as per the British Pharmacopoeia (BP) and unofficial standards as recommended by the manufacturers. The assessment of tablets included the evaluation of uniformity of weight and thickness, friability, crushing strength, disintegration, dissolution rate and content uniformity by UV spectrophotometric method.

Results: All brands except one, passed official and unofficial in-vitro quality control tests prescribed for the tablets. One brand did not comply with the standard assay of content of active ingredient.

Conclusion: Thus based on the above results, it can be concluded that four out of five brands of Mefenamic acid tablets are pharmaceutically equivalent and thus can be substituted for each other.

INTRODUCTION:

Mefenamic acid is a Non steroidal anti-inflammatory drug (NSAID) and is widely used to treat pain and inflammation. It is routinely prescribed for the prophylaxis of premenstrual migraine headache [1]. Chemically it is 2-(2,3-dimethylphenyl) amino benzoic acid (Fig. 1) and occurs as white to light yellow microcrystalline powder, practically insoluble in water, slightly soluble in alcohol and in methylene chloride [2].

However, it dissolves readily in dilute solutions of alkali hydroxides. Mefenamic acid (MA) acts by competitively inhibiting COX1 and COX 2, thereby reducing the production of Prostaglandin, which is implicated in inflammation and pain pathology. There are many multinational brands and dosage forms of MA available in the Omani market.

Keywords: Disintegration; Dissolution; Mefenamic acid tablets; Pharmaceutical equivalence.

The various brands available in the market are considered pharmaceutically equivalent if they contain the same amount of active ingredient in the identical dosage form and meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity), but may differ in characteristics such as shape, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling requirements etc [3]. The pharmaceutical equivalent drug products can help the practitioners and pharmacists in substitution of one brand for the other in case of non availability; however this substitution is quite controversial and is often met with suspicion among patients and physicians [4]. It is the joint responsibility of the manufacturers and the drug law enforcing agencies to ensure that various marketed pharmaceutical products containing the same active ingredient in the identical dosage forms are uniform, safe and effective. The safety and efficacy of drug products can be guaranteed when their quality is reliable and is reproducible from batch to batch. To ensure the requisite quality, drug manufacturers are required to test their products during and after
MA is one of the commonly used NSAID in clinical practice for the treatment of musculoskeletal pain and inflammation, therefore, it is necessary to monitor and ascertain the quality of the various brands available in the market. The quality i.e. safety and efficacy of solid dosage form such as tablets can readily and satisfactorily be assessed by carrying out dissolution studies and in vitro Pharmaceutical tests. The present study was carried out to investigate and assess the pharmaceutical quality of five different brands of MA 500 mg tablets marketed in Oman using in vitro methods as per the British Pharmacopoeia (BP) and unofficial standards as recommended by the manufacturers to ascertain that all brands are pharmaceutically equivalent. The assessment of tablets included the evaluation of uniformity of weight and thickness, friability, crushing strength, disintegration, dissolution rate and chemical assay by UV spectrophotometric method to determine the content of active pharmaceutical ingredient (API).

Ten tablets from each brand were randomly selected and their hardness was determined (n=10).

**Friability**

For friability testing, ten randomly selected tablets from each brand were initially weighed and placed in a friabilator chamber (Bellstone, Hi-Tech International, India). The friabilator was operated at 25 rpm for 4 minutes (up to 100 revolutions). Thereafter, tablets were removed, dusted and reweighed. The percent (%) friability was calculated by using following formula [7]. The test was repeated three times for each brand of MA tablets.

\[
\text{% Friability} = \frac{\text{Weight before test} - \text{Weight after test}}{\text{Weight before test}} \times 100
\]

**Thickness**

Thickness of the tablets was measured in millimetres with the help of a micrometer screw gauge. Random samples of 10 tablets were selected from each brand and their thickness was measured.

**Weight uniformity**

The weights of twenty tablets were determined individually using an electronic digital balance to evaluate weight variation among tablets. The average tablet weight and standard deviation were calculated and compared with the permissible limits.

**Disintegration**

A digital tablet disintegration test apparatus (Bellstone Hi-Tech International, India) was used for disintegration test. A 900 mL beaker was filled with distilled water and was maintained at 37 ± 0.5°C. Six tablets of each brand were selected and placed in each of the cylindrical tubes of the basket and connected to the disintegration apparatus. To avoid the floating of tablets while tube move upwards and downwards in water, discs were used. The time taken to break each tablet into small particles and pass out through the mesh at the bottom of the tube was recorded. Mean disintegration time was calculated for each of the brands.

**Dissolution or in-vitro bioavailability test**

USP tablet dissolution test apparatus (Bellstone, Hi-Tech International, India), rotating basket type, was used to study the in-vitro drug release pattern of MA tablets using distilled water as dissolution medium (900 mL). Aliquots (5mL) were
withdrawn at 0, 10, 20, 30, 40 and 50 minute time intervals for the analysis of drug concentration. The samples were diluted appropriately with 0.1M NaOH solution and filtered before measuring absorbance at 286 nm using UV visible spectrophotometer (UV Analyst CT 8200, Taiwan). The content of MA in each sample was determined based on the calibration curve obtained with serial dilutions of the pure drug at 5, 10, 15, 20, 25, and 50µg/mL (Table 1).

Table 1: Standard Absorbance values of Mefenamic acid for plotting standard curve by UV spectrophotometer

<table>
<thead>
<tr>
<th>Stock number</th>
<th>Stock concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>0.2411</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.4832</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>0.7301</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>0.9603</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1.2351</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>2.3820</td>
</tr>
</tbody>
</table>

Content Uniformity

For content uniformity a series of working solutions with different MA concentrations were prepared in 0.1 M NaOH solution. A stock standard solution (500µg/ml) was prepared by dissolving 50 mg of pure MA powder in 100 mL of 0.1 M NaOH. Working standards for constructing a calibration curve were prepared by pipetting 10, 5, 4, 3, 2 and 1 ml aliquots of the stock standard solution into separate 100 mL volumetric flasks and diluting to volume with 0.1 M NaOH. The absorbance of each solution was measured at 286 nm and a calibration curve was constructed. Using the standard curve, the amount of MA in each brand was determined.

Data analysis

Data for hardness, friability, thickness, weight uniformity test, disintegration, % drug release by dissolution and content uniformity of the tablets were analyzed by determining the mean ± standard deviation. ANOVA single factor was used for determining significance. P values <0.05 were considered as significant.

RESULTS AND DISCUSSION:

Mefenamic acid is a commonly prescribed analgesic for musculoskeletal pain and inflammation. Currently many generic and multinational brands of this drug are available in the Pharma market in the gulf region. It has been observed that multi sourcing of a drug product might lead to variability in clinical responses and eventually dissatisfaction among prescribers and consumers. Small differences in the manufacturing process, different formulation factors such as type and amount of excipients, packaging or storage factors and substandard as well as counterfeit products could alter the disintegration, dissolution and other parameters that consequently lead to variation in therapeutic response [8].

Spurious and substandard drugs do not comply with the pharmacopoeial standards and thus would not produce the desired therapeutic effect [9]. Drug quality is a matter of concern in many developing countries as there are confirmed reports of high incidence of drug preparations, which are not of acceptable quality [10]. Counterfeit drug products are not only available in developing countries but also in Europe and United states [11]. These drugs cause not only wastage of money but also create health hazards.

Preliminary physicochemical evaluation of pharmaceutical products is of great importance in ensuring the quality of drug products. Quality control tests such as dissolution provides valuable information about the in-vitro bioavailability and bioequivalence of oral solid dosage forms. This study was undertaken to evaluate the physicochemical properties of five brands of MA tablets using in-vitro quality control tests (Hardness, Friability, Thickness, Weight variation, Disintegration time, Dissolution rate and Content uniformity) with an aim to assess whether these five brands are pharmaceutically equivalent or not.

The results of various quality control tests performed on five brands of MA tablets are presented in Table no 2 and Table no 3. A liner regression of the standard absorbance data of working solutions (Table 2) in statistical software, SPSS gave the following equation which was used to determine the MA content of analyzed tablets.

\[ y=0.0476x+0.0133 \quad (R^2 = 0.9995) \]

Hardness of MA tablets was found to be in the range of 3.4 to 6.53 Kg/cm² indicating all brands have good mechanical strength except Brand E. The hardness values of four brands met the pharmacopoeial requirement and based on the results it could be expected that tablets would exhibit resistance to capping or breakage while handling during
transportation and storage. However, a significant difference was observed in the mean crushing strength of the tablets by ANOVA test.

Table 2: Results of official and unofficial quality control tests on five brands of Mefenamic acid tablets

<table>
<thead>
<tr>
<th>Brand</th>
<th>Hardness (Kg/cm²) Mean±SD, (n=10)</th>
<th>Friability (%) Mean±SD, (n=10)</th>
<th>Thickness (mm) Mean±SD, (n=10)</th>
<th>Weight uniformity (mg) Mean±SD, (n=20)</th>
<th>Disintegration time (Min) Mean±SD, (n=6)</th>
<th>p-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.53±0.54</td>
<td>0.26</td>
<td>7 ±0.0</td>
<td>761±7.88</td>
<td>07:11 ±0.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B</td>
<td>6.35±0.59</td>
<td>0.29</td>
<td>6 ±0.0</td>
<td>785.35±8.63</td>
<td>10:41±0.16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C</td>
<td>6.18±0.36</td>
<td>0.29</td>
<td>6.15±0.071</td>
<td>816.8±12.23</td>
<td>14:45 ±0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D</td>
<td>4.68±0.35</td>
<td>0.07</td>
<td>6.09±0.099</td>
<td>742.5±5.97</td>
<td>14:09 ±0.11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E</td>
<td>3.4±0.17</td>
<td>0.63</td>
<td>6.03±0.067</td>
<td>717.15±9.32</td>
<td>03:02±0.47</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*SD: standard deviation, n: numbers of tablets, all experiments were done in triplicate

Table 3: Content uniformity assay of Mefenamic acid in five brands by Ultra Violet spectroscopic method

<table>
<thead>
<tr>
<th>Brand</th>
<th>% Mefenamic acid content Mean±SD</th>
<th>Remarks as per the BP permissible limit (95-105%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>102.6 ±7.07</td>
<td>Passed</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>105 ±6.39</td>
<td>Passed</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>104.4 ±6.84</td>
<td>Passed</td>
<td>0.041b</td>
</tr>
<tr>
<td>D</td>
<td>103.5 ±2.32</td>
<td>Passed</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>89.14 ±5.96</td>
<td>Failed</td>
<td></td>
</tr>
</tbody>
</table>

*SD: standard deviation, P<0.05 by ANOVA single factor

Weight loss due to friability in all marketed preparations was found to be less than 1% indicating that all tested brands are mechanically stable and will not undergo any wear or tear during transportation. Brand E showed the maximum % weight loss (0.63%) compared to other tested ones (0.07-0.29%). However, all the brands met the Pharmacopoeial standard.

Tablet thickness of all five brands of MA tablets was within the permissible limits (average±5%) and thus met manufacturer’s requirements. Result confirmed that they are uniform in size and shape.

Weight uniformity test for tablets is required to ensure that the drug content in each tablet is distributed in a narrow range around the label strength because slight variation in weight of tablet reflects variation in the content of active ingredient. According to the BP, drug products whose strength is >250 mg, permissible limit of ±5% of the average is required to pass the test for weight uniformity. All of the tested products possessed acceptable uniformity of weight as per the pharmacopoeial limit i.e. mean±5%. The p-value for weight uniformity was found to be statistically significant (<0.05) by ANOVA single factor test.

Disintegration evaluates availability of a drug for dissolution and absorption from the gastro-intestinal tract. The results presented in table 2 reveals rapid disintegration of all the products. Fast disintegration is required for analgesics in order to get prompt relief.

All the products meet the disintegration limit set by the British Pharmacopoeia. According to the BP 2009, the time limit for disintegration of film coated tablets is <30 min. Statistical analysis showed a significant difference in mean disintegration time of five brands. The compendial requirement for content uniformity is met if % content of tablets with average weight above 250 mg falls within 95-105% [2]. Mean average content of analyzed MA tablets by UV method was found to be in the range of 89.48 -105% (Table 3). The amount of active ingredient in brand E is less than 95% of the labeled amount as required by BP, so it failed the content uniformity test. The p-value obtained by Anova single factor was found to be significant as it was less than 0.05.

Pharmaceutical availability or in-vitro availability by dissolution testing provides useful and reliable information regarding in-vivo bioavailability of drug.
product [12]. It is considered as reliable, sensitive and rationale for predicting drug bioavailability. Figure 2 shows the % drug release of MA tablets by dissolution test and was found to be satisfactory for all brands. Brand A showed the highest drug release after 10 minutes whereas Brand D had the slower release rate initially but after 30 minutes it showed the better dissolution profile than other brands. However, no correlation could be drawn between disintegration time and dissolution profile of MA tablets.

Figure 2: Dissolution profile of different brands of MA tablets

CONCLUSION:
The results indicated that the overall quality of all tested brands was satisfactory as they met the requirements of the official and unofficial quality control tests except brand E. Brand E failed to pass the content uniformity tests as its mean drug content was found to be outside the compendial tolerance limit i.e., (95-105%), though all the tested tablets of Brand E were uniform in size, shape, color, thickness and weight. The hardness of brand E was found to be 3.4±0.17 Kg/cm² which was least among all the tested brands and was also less than the ideal hardness recommended by the manufacturers. However, the loss on the friability was well within the prescribed limits. They also showed good absorption and drug release profile on disintegration and dissolution studies. Mefenamic acid content of brand E was found to be less than the labeled amount. It was found to contain 445.7 mg (89.14±5.96 %), which fall outside the British Pharmacopoeia permissible limit of 95-105% (475-525mg) of labeled amount. This unexpected result might be due to manufacturing problem or due to incorrect storage conditions such as high temperature and humidity that could lead to decomposition of active pharmaceutical ingredient in tablets. In a similar study on the physicochemical equivalence conducted by Eichie et al on 19 brands of ibuprofen tablets in Nigerian market, only 12 brands passed the uniformity of content test and only 4 brands could pass the dissolution test [13].

Thus based on the results of this pilot study, it can be concluded that one brand of Mefenamic acid is not pharmaceutically or chemically equivalent with other four brands and therefore, cannot be substituted in case of non availability of other brands. This warrants manufacturer and drug regulatory authorities to step up the quality control and cGMP procedures. However, the results of this study could not be generalized as all brands of Mefenamic acid tablets were purchased from one pharmacy and were having the same manufacturing batch number. Also it is very unlikely that brand E is counterfeit or substandard as in Oman the drug regulatory authority closely monitors and control the quality of drugs available in the market.

Further detailed study on large and different batches of tablets collected from different regions should be carried out to support the findings of this pilot study to ensure safety, quality and efficacy of this commonly used analgesic drug.

ACKNOWLEDGEMENT:
The authors would like to thank Dean, Associate Dean and Head, Dept of Pharmacy, Oman Medical College for providing necessary research facilities.

REFERENCES:


