Research Article

Comparative *In Vitro* Quality Evaluation of Different Brands of Naproxen Tablets Available in Bangladesh

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ABSTRACT

This study was designed to evaluate and compare several *in vitro* quality parameters of six commercially available brands of naproxen 500 mg in Bangladesh, including the innovator brand Naprosyn®. General quality parameters such as physical appearance, diameter, thickness, hardness, uniformity of weight, friability and disintegration time were determined according to established protocols. Drug content was assayed using a validated UV spectrophotometric method and *in vitro* dissolution profiles were measured and compared with innovator brand using model independent approach of difference factor (f_1) and similarity factor (f_2). All the brands complied with the official USP specifications for content uniformity, friability and disintegration time. Assay of drug content revealed that all but one brand of naproxen failed to contain 90-110% of labelled claim, which is the USP requirement for naproxen sodium tablets. While the complied brands contained active ingredient ranging between 93% up to 109%, the substandard brand possessed only 80.3% naproxen sodium. In the *in vitro* dissolution testing that same brand failed to meet the USP requirements again, having only 66.87% release in 45 minutes while all the other brands complied by having a percent release of more than 80% within that same time frame. These findings reflected upon the difference factor (f_1) and similarity factor (f_2) of the brands because four of the five generic brands were statistically evaluated to have satisfactory f_1 and f_2 values with respect to the sixth innovator brand. The brand that failed to comply in both the disintegration and dissolution test was also calculated to have poor f_1 and f_2 values. Our study indicates that five out of the six brands complied with quality parameters and can be used interchangeably. Further study should be conducted to determine the presence of more substandard brands of naproxen in Bangladesh market.

Keywords: Naproxen tablets, United States Pharmacopeia (USP), *In Vitro* quality evaluation, Dissolution test.

INTRODUCTION

One of the major challenges to pharmaceutical product quality, as recognized by the Food and Drug Administration (FDA), is the limited information on current quality of marketed pharmaceutical products due to a lack of formal means for post market surveillance.[1] Substandard drugs can prove to be lethal; as was seen with the treatment of malaria using substandard drugs having low amount of active ingredient or low availability of those ingredients due to poor formulation, leading to accelerated resistance to previously effective drugs.[2] Thus post market monitoring of generic drugs can serve two purposes, for one it is a confidential tool in evaluating quality, therapeutic efficacy and overall safety of commercially available brands.[3] The other more practical purpose is ascertaining the chemical and biopharmaceutical equivalency of multiple generic brands in the market to ensure that they are therapeutically equivalent and can be safely interchanged.[4] In this study, our aim was to compare the different *in vitro* quality parameters of locally available generic and innovator brands of naproxen 500 mg immediate release tablets in Bangladesh.

Naproxen ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid), first introduced as Naprosyn® in 1976, is a powerful non-selective non-steroidal anti-inflammatory drug (NSAID), that is extensively used as a prescription and over-the-counter (OTC) medicine throughout the world.[5] It is a propionic acid derivative possessing analgesic, anti-inflammatory and antipyretic properties[6] and is effective in the management of acute[7] and chronic pain.[8] Naproxen is a non-selective NSAID, which means it inhibits both COX-1 and COX-2 enzymes with nearly comparable IC_{50} values and in the process exhibits significant side effects in the gastrointestinal tract.[9] It is treated as a prescription drug in many parts of the world but in countries like Canada, UK and USA it is available as an over-the-counter (OTC) medication.[6] In Bangladesh, more than 50 generic brands of naproxen tablets are available. Being an OTC drug, this large choice of available brands means that there is a higher chance of substandard products running amok in the market and thus quality and safety parameters should be monitored continuously.[10]

We extensively reviewed literature related to the comparative analysis of naproxen brands available in Bangladesh and could not find history of any recent post marketing studies conducted. Therefore this present study aimed to evaluate and compare *in vitro* quality parameters of six different locally available brands of naproxen 500 mg tablets, including the innovator brand Naprosyn® (Roche, distributed by Radiant Pharmaceuticals Ltd.) applying both

non-compendial and official methods as described in USP Pharmacopeia 38-National Formulary 33.[10]

MATERIALS AND METHODS

Drug

Standard of naproxen sodium was a kind gift from Radiant Pharmaceuticals Ltd, Bangladesh.

Dosage form

Six brands of naproxen tablets (500 mg), including the innovator brand Naprosyn®, were purchased from Lazz Pharma, a local drug store in Dhaka city. The samples were properly inspected for their manufacturing license numbers (DAR), batch numbers, production date and shelf life. They were randomly given code from A-F (Naprosyn® was brand B) and stored in proper conditions.

Solvents and Reagents

Analytical-reagent grade potassium dihydroxide phosphate was purchased from Daejung Chemical & Metals Co. Ltd (South Korea). Sodium hydroxide was obtained from Qualikems Fine Chem Pvt. Ltd (India). Double distilled water was used during various procedures of the study.

Determination of Uniformity of Weight

20 tablets from each of the six brands were individually weighed using an electronic analytical balance (AUX-220, Shimadzu, Japan). The average weights for each brand were calculated and the maximum and minimum deviations from mean were determined.

Determination of Diameter and Thickness

Diameter and thickness of 20 tablets from each of the six brands were individually measured using digital slide calipers (Electrotech, Bangladesh). Average diameter and thickness for each brand were then calculated and the maximum and minimum deviations from mean were determined.

Hardness Test

Tablet crushing strength was measured using an automatic tablet hardness tester (8M, Dr Schleuniger, Switzerland). Ten tablets were selected randomly from each brand and the minimal pressure required for crushing each tablet was recorded.

Friability Test

Twenty tablets from each brand were collectively weighed and subjected to abrasive force by using an Electrolab friabilator (EF-2, India) at 25 rev/min for total 4 minutes. The tablets were then collectively weighed again and compared with their initial weight to calculate percent friability.

Disintegration Test

Six tablets from each of the six brands were tested for their disintegration time in distilled water at 37°C using Electrolab tablet disintegration tester (ED-2L, India). The disintegration time was recorded as time required for completely passing the tablet through the sieve in such a way that not a single particle remained on the basket of the machine.

Assay of Drug Content

A simple and selective UV spectrophotometric method was used for determining the potency of the tablets. Standard solution was prepared by measuring 10 mg of standard naproxen sodium and dissolving the powder in 0.1 M of phosphate buffer media (pH 7.4). For preparing the sample solution, twenty tablets from each brand were weighed and grinded to fine powder using mortar and pestle. Powder containing 10 mg of drug was then dissolved in the phosphate buffer media. Both standard and sample solutions were then subjected to sonication followed by filtration using filter paper. The solution was further diluted 40 times so that the diluted solution contained 2.5 µg/ml drug. The stock solution was then diluted into 10 individual concentration ranging between 0.25 µg/ml -2.5 µg/ml and absorbance values of the solutions were measured at maximum wavelength (λ_{max}) of 231 nm using a UV Spectrophotometer (UV1280, Shimadzu, Japan). A ten-point calibration curve of standard naproxen sodium was then drawn using MS Excel which is shown in Figure 1. The maximum absorbance value of 231 nm was obtained by scanning samples from 200 nm to 400 nm.

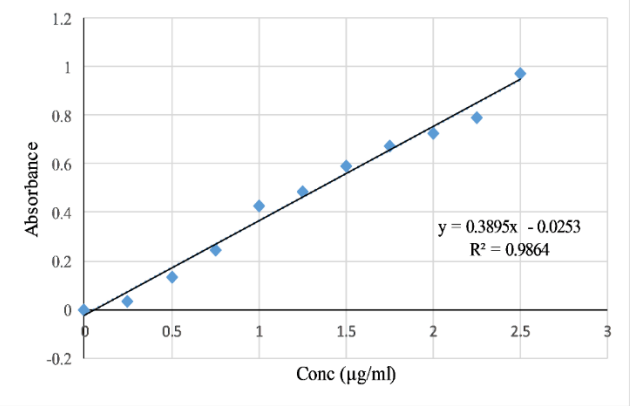

Figure 1: Ten-point calibration curve of standard naproxen sodium (R^2 indicates correlation coefficient)

Dissolution Test

For determining their dissolution profiles, six tablets of each brand were tested using a USP apparatus II (paddle, 50 rpm) type tablet dissolution tester (EDT-08LX, Electrolab, India). 900 ml of 0.1 M phosphate buffer maintained at 37 ± 0.5°C was used as the dissolution medium. 10 ml of dissolution sample was withdrawn at 0, 5, 15, 30, 45 and 60 minutes and simultaneously replaced with equal volume of buffer solution to maintain sink condition. Samples were then filtered and assayed using UV Spectrophotometer (UV1280, Shimadzu, Japan) at 231 nm wavelength. The concentration of the sample at each time intervals were then calculated from the ten-point calibration curve of standard naproxen sodium.

Data Analysis

The diameter, thickness, hardness and uniformity of weight were analyzed with simple statistics while dissolution profiles were characterized using difference factor (f_1) and similarity factor (f_2).

RESULTS AND DISCUSSION

Physical Appearance

Visual inspection of the tablets showed that all the brands had very negligible variation in their physical appearance. All tablets of each brand presided from the same batch and had an expiration date greater than two years from the time of this study.

Diameter and Thickness Testing

Regular monitoring of the diameter and thickness of marketed tablets can help to detect potential problems related to their content uniformity at an early stage of production.[11] From the data presented in Table-1 it can be seen that the diameter and thickness of each brand had minimal deviation from their average values, which is indicated by their low standard deviation.

Test for Uniformity of Weight

Tests for content uniformity are essential to ensure that manufacturers are complying with Good Manufacturing Practices (GMP) and patients are taking a precise pharmaceutical dose every time they consume a tablet.[12] According to USP specifications for content uniformity, tablets weighing more than 324 mg should have no more than ±5% deviation in their weight.[13] No more than 2 tablets out of 20 can cross this limit and not a single tablet may cross double of this specified limit.[13] If we analyze the data in Table-1 it is clear that weight of all the brands were clearly above 324 mg. Relative standard deviation for all brands were well under ±5% and not a single tablet of any of the brands had a deviation greater than the specified limit of ±5%.

Hardness Testing

Tablet hardness measurement is a non-compendial test but still considered significant because hardness can affect other quality parameters of the tablet such as disintegration time and friability.[14] If a tablet requires a minimum 40N force to break then it is considered to have adequate hardness.[15] From the data presented in Table-1 it can be seen that tablet hardness of all the brands were within 68-107.55N range and can be considered satisfactory.

Table-1: Summary of the *in vitro* quality control tests undertaken on different brands of naproxen tablets. (*Mean ± SD, ** Mean ± RSD)

Brand Code	Diameter (mm)*	Thickness (mm)*	Uniformity of Weight (mg)**	Hardness (N)*	Friability (%)	DT (min)	Drug Content (%)
A	12.49±0.03	4.167±0.03	546.4±1.13	88±1.25	0.055	1.51	92.60
B	12.995±0.01	4.148±0.02	541±1.32	99.37±0.57	0.093	2.07	101.97
C	7.612±0.01	5.217±0.04	646.4±1.33	107.55±0.73	0.17	29.88	80.36
D	12.08±0.02	6.65±0.05	761±0.57	106.07±0.87	0.026	5.94	108.66
E	12.58±0.03	5.8±0.03	617.45±0.4	68±0.43	0.081	3.44	105.23
F	8.54±0.05	7.14±0.01	883.05±0.91	77.57±0.61	0.25	3.77	95.59

Friability Testing

The tendency of a tablet to lose its component particles due to abrasion, friction or mechanical shock is termed as friability.[16] A high friability value is an indication of excessive loss of drug content during downstream processing such as coating procedures, storage and handling.[17] Friability is a compendial test and according to USP a tablet's friability should not exceed 1%.[13] All of the brands complied with this USP specification as their friability values were well under 1%.

Disintegration Testing

Tablet disintegration is considered as the first stage of the bioavailability cascade because a faster disintegration time can result in quicker absorption of the API and a faster onset of action of the desired therapeutic effect.[18] USP recommends that all uncoated and film coated tablets should disintegrate within 30 minutes.[13] Although all the brands were film coated and disintegrated within the specified time limit, it should be noted that Brand C had a disintegration time of 29.88 minutes, which is only marginally below the limit of acceptance (Table-1).

Assay of Drug Content

For naproxen sodium tablets USP specifies that content of active ingredient should be within the limit of 90-110%.[13] From the data presented in Table-3 it is clear that all brands except brand C (80.36%) complied with this specification limit. Brand C almost failed to pass the disintegration test as mentioned before and now the low content of active ingredient means that it has another defect in its overall quality compared to the other brands.

Dissolution Testing

Dissolution of a tablet depends on its disintegrating into smaller particle and eventual absorption and the rate of this dissolution is an important criterion for quality control of a

manufactured tablet.[19] The results of dissolution studies of the brands are graphically presented in Figure-2. According to USP specification for naproxen sodium tablets, each brand must be dissolved more than 80% of its labelled claim within 45 minutes of the test.[13] We analyzed both inter-brand and intra-brand variation in dissolution profiles and found that apart from brand C all other brands had dissolved more than 80% of their labelled claim within just 15 minutes of the test. Brand C however had only 66.87% release after 45 minutes and only reached 80% dissolution level after 60 minutes (81.42%). This low level of dissolution for brand C was expected as it had already shown poor disintegration time and failed in the active ingredient assay as well. All other brands had similar drug release profile and complied with USP specifications.

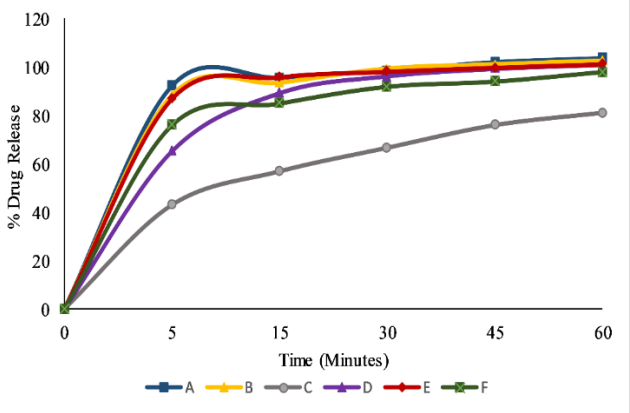

Figure 2: Dissolution profile of different brands (A-F) of naproxen tablets

Comparison of Dissolution Data

To compare the dissolution profiles of the brand their difference factor (f_1) and similarity factor (f_2) were analyzed. The f_1 and f_2 factors are a simple method of measuring similarity between pairs of dissolution profiles. Difference factor (f_1) is a measure of relative error between two dissolution curves and is calculated as percentage difference between two curves at each point.[20] Similarity factor (f_2) on the other hand is a measurement of similarity in the (%) of dissolution between two curves and is calculated as a logarithmic reciprocal square root of the sum of squared error.[20] The following equations were employed to calculate f_1 and f_2 -

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100$$

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

Here, n is the number of time points, R_t is the dissolution value of reference product at time t and T_t is the dissolution value for the test product at time t. Similarity factor (f_2) is used by both FDA[21] and the Committee for Medicinal Products for Human Use (CHMP) of European Agency for the Evaluation of Medicinal Products (EMEA) as a means to compare dissolution profiles.[22] According to FDA standards two dissolution profiles can be considered bioequivalent and similar if f_1 is between 0-15 and f_2 is between 50-100.

Table 2 shows the comparison of difference factor (f_1) and similarity factor (f_2) of different brands in respect to brand B, which was our reference brand Naprosyn®. For brands A, D, E and F the f_2 values were between 50-100 and the f_1 values were between 0-15 which indicates that they are similar in terms of their dissolution profile and can be used interchangeably. However, in case of brand C, difference factor was a lot more than 15 (33.03) and similarity factor was far lesser than 50 (25.95) which clearly means that brand C had poorer dissolution profile compared to that of the innovator brand of naproxen sodium.

Table 2: Difference factor (f_1) and similarity factor (f_2) of different brands in respect to innovator brand Naprosyn® (Brand B)

Pair Comparison	Difference factor (f_1)	Similarity factor (f_2)
A vs B	1.81	83.15
C vs B	33.03	25.95
D vs B	6.89	50.59
E vs B	1.52	88.01
F vs B	8.1	55.95

CONCLUSION

Six brands of naproxen sodium, including the innovator brand Naprosyn® were subjected to a number of *in vitro* analysis tests according to standard procedures of the monograph of USP 38-NF 33. The results showed that all six brands were compliant with USP specifications for identification, content uniformity and disintegration time. Five brands, including the innovator brand, complied with the assay of drug content and dissolution profile as specified in USP. Those five brands can also be used interchangeably because out of them, four were generic brands and were equivalent to the fifth innovator brand (Naprosyn®) in terms of their dissolution profile and patients can safely switch between those brands with consultation of the prescriber. However, one brand failed both assay of drug content test and dissolution test and had a poor dissolution profile, which was very much dissimilar to the innovator brand, and we recommend that it should not be considered as an alternative to the other brands. *In vivo* testing of the brands will probably help to further ascertain our findings regarding the quality of marketed brands of naproxen in Bangladesh.

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