Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, BahauddinZakariya University Multan, Pakistan
ISSN: 2410-6275 **Jun, 2019** **DOI:** 10.22200/pjpr.2019264-70

Research Article

Comparative in Vitro Equivalence Evaluation of Naproxen Available in Karachi, Pakistan

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Received: Aug, 16, 2020
Revised: Oct, 06, 2020
Accepted: Jan, 12, 2021
Online:

Abstract

Naproxen, a non-steroidal anti-inflammatory drug which affect the activity of cyclooxygenase enzyme. It worked by inhibiting the synthesis of prostaglandins by decreasing the activity of the enzyme, cyclooxygenase, resulted in decrease formation of prostaglandin precursors. It had been indicated in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and acute mucoskeletal disorders. The main objective of this study was to identify the best bioequivalent brands available in Karachi, by observing their results in order to make the treatment cost-effective. Three different brands of Naproxen (500mg) were taken in the study that were observed under six quality control parameters i.e. weight variation test, hardness test, thickness test, friability test, disintegration test, and dissolution test as per specified by British and US Pharmacopeia BP/USP. All the test requirements were compiled by all three brands of naproxen. Disintegration time for all three brands was within 15 minutes that follows BP/USP standards. All the brands showed more than 80% drug release within 30 minutes. The study showed that almost all the brands of Naproxen available in Karachi had met the specification for quality control analysis.

Keywords: Macrolide Antibiotic, Hydrophilic, ocular films, In-Vitro and Ex-Vivo

Introduction

Naproxen is a naphthylpropionic acid derivative, presently marketed as a single enantiomer as the only non steroidal anti-inflammatory drug. It is indicated in the conditions of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and acute mucoskeletal disorders (Katzung, 2012). It works by inhibiting the synthesis of prostaglandins by decreasing the activity of the enzyme, cyclo-oxygenase, which eventually results in decreased formation of prostaglandin precursors. The onset of action occurs within 1 hour and takes the duration up to 7 hours as an analgesic. It is almost 100% absorbed orally. The time to peak serum concentration occurs within 1 to 2 hours that persists up to 12 hours. It is highly protein bounded i.e. (>90%) (Steinmeyer, 2000). The free fraction of naproxen is significantly higher in women as compared to men but, the half life is same in both sexes, that in condition of normal renal function, the half life of naproxen is about 12 to 15 hours (Woodhouse and Wynne, 1987, Upton *et al.*, 1984).

The anti-inflammatory activity of NSAIDS is chiefly mediated by inhibition of prostaglandin biosynthesis. There are other possible mechanism of action for NSAIDS that includes, inhibition of chemotaxes, down regulation of IL-1 production, decrease production of superoxide and free radicals and interference with calcium mediated intracellular events (Abukhalaf *et al.*, 2004). NSAIDS works by decreasing the sensitivity of vessels to bradykinin and histamine affect the production of lymphokine from T-lymphocytes and converse the vasodilation of inflammation. NSAIDS are generally analgesic, anti-inflammatory and anti-pyretic to various extent and nearly all NSAIDS inhibit platelet aggregation except COX-2 selective agents and non-acetylated salicylates (Kean and Buchanan, 2005, Abukhalaf *et al.*, 2012). In conditions like; Rheumatoid arthritis, Osteoarthritis and alkylosing spondylitis, usually 500 mg to 1 g BID is given, where as in acute gout, initially 750 mg is

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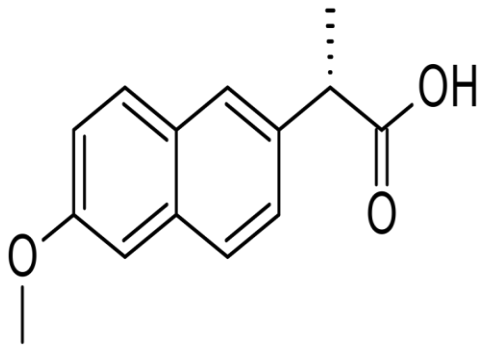
administered followed by 250mg every 8 hours until the attack has subsided. The lowest effective dose of naproxen is given in the elderly patients whereas; in children over 5 years of age 5mg/kg BID is given (Todd and Clissold, 1990, Morgan *et al.*, 1993, Péez-Gutthann *et al.*, 1999).

Several researches have been performed earlier with respect to Naproxen (Scharf *et al.*, 1982, MOORE and CHAPPUIS, 1988, Junco *et al.*, 2002, Bellavance and Meloche, 1990). There are several other brands of naproxen available in Karachi but, these three brands (Proxen, Dolonap, and Flexin) were selected because of its commonly usage and easily accessibility in the market.



NAPROXEN

Materials and methods

A comparative study was performed by taking three different brands of uncoated tablets of Naproxen 500 mg (Proxen, Dolonap, and Flexin). The active used in this study was gifted from Platinum Pharmaceuticals (Pvt) Ltd, tablets were purchased from the local market and the solvents and reagents were purchased from Sigma Eldritch. Physicochemical parameter has been tested of the following tablets in order to compare the multinational brand with those of local brands containing the same active. Brand Flexin has been used as a reference brand and Proxen and Dolonap has been used as a sample brand.

Weight Variation Test: It is an in-process test parameter that assures the content uniformity in the dosage form unit during compression (Reddy et al., 2012). It was performed by taking 20 tablets of the three respective brands of Naproxen 500mg (Proxen, Dolonap and Flexin) available in the market. They were conducted on Electronic balance FX-400 and observed that the weight of all the 20 individual tablets lies within the range of USP/BP limits that is NMT 2 of the 20 tablet should cross ± 10% deviation (Reddy *et al.*, 2012).

Thickness and Diameter Test: To determine the thickness and diameter, 20 tablets of each brand were analyzed using Vernier calipers which assess the level of compaction in tablets throughout the process of punching (Reddy *et al.*, 2012, OR *et al.*, 2009).

Hardness Test: To determine the breaking point and structural integrity of the three different brands of 500mg Naproxen. 20 tablets of each brand were analyzed on MH-1 of Galvano Scientific hardness tester (Mehmood *et al.*, 2016).

Friability Test: The phenomena is to determine the percentage of weight loss by the tablet due to mechanical action or aberration to know the lamination, capping and crushing strength of the table (Mehmood *et al.*, 2016) t. 10 tablets of each brand were observed on fribilator at 25 rpm or 100 rotations in 4 minutes. It should be within the USP limits i.e. NMT 1% (Mehmood *et al.*, 2016). Friability of the tablets are calculated by:

$$\% \text{ Friability} = \frac{W1 - W2}{W1} \times 100$$

Disintegration Test: To verify the taken tablets of 3 brands of 500mg Naproxen (Proxen, Dolonap, and Flexin) disintegrate

within the specified time set by USP/BP, 6 tablets of each brand were observed on Curo model no Ds-0702 (Mehmood *et al.*, 2016, Sveinsson *et al.*, 1993).The tablet were placed in the six tubes of the basket covered with the disc at temperature 35°C - 39°C. Water has been used as an immersed aqueous fluid , at the specified time, the basket was taken up fromthe medium and observed for the tablets if they disintegrate completely. The disintegrating time should NMT 15 minutes according to USP/BP when placed in an aqueous medium (Mehmood *et al.*, 2016, Sveinsson *et al.*, 1993).

Dissolution Test: To verify the release of drug i.e. active ingredient from the tablet when dissolute in medium of specified volume. Single tablet of each brand of 500mg Naproxen (Proxen, Dolonap, Flexin) were tested on GDT-7L of Galvano Scientific (Qamar *et al.*, 2017). It concludes that the amount of active ingredient released from the tablet should be within the specified limits i.e. as per USP, each tablet should completely be dissolved after 20 minutes at 50 rpm and at 37°C. Water was used as a medium to dissolute the tablets and the dissolute tablet solution was determined on spectrophotometer at 273nm. It should not be <80% after 20 minutes (Qamar *et al.*, 2017).

Result

The results of all the testing parameters has been summarized in the form of tables and discussed later. The specifications of the three brands of Naproxen 500mg taken in this study is given in table 1.

Table 1: Specification of the Naproxen brands

No	Brand Name	Serial no	Batch number
1	Proxen	Drug-01	P06077
2	Dolonap	Drug 02	211
3	Flexin	Drug-03	112126XV

1. **Weight variation Test:** 20 tablets of the respective brand of naproxen 500mg (Proxen, Dolonap, Flexin) were weighed. The upper and lower limit (mean ±3S), standard deviation and mean weight were then calculated (see table 2). Thus, by observing the values we found that the standard deviation of all three brands were within the official limits.

Table 2: Statistical Weight Variation Test:

S.no	Name of Drug	Average weight (mg)	Standard Deviation (%)	Upper Limit (UCL) (X+3S)	Lower Limit (LCL) (X-3S)
1	Proxen	535.4	0.0047	0.5497	-0.0095
2	Dolonap	754.5	0.0181	0.8088	-0.0362
3	Flexin	718.9	0.0081	0.7434	-0.0164

2. **Thickness & Diameter Test:** The thickness and diameter of all three brands of naproxen 500mg (Proxen, Dolonap & Flexin) has been calculated and summarized as the mean, standard deviation and upper and lower limit in the table 3 and table 4 respectively. According to the USP/BP, the results of all three brands (Proxen, Dolonap & Flexin) for the test of thickness and diameter are within the limit.
3. **Hardness Test:** The sample tablets of all three brands of naproxen 500mg were tested and the observed values i.e. mean, standard deviation and upper control limit & lower control have been found to be within the control limits, summarized in the table 5.

Table 2: Statistical Thickness Test

S.no	Name of Drug	Average thickness (mm)	Standard Deviation (%)	Upper Limit (UCL) (X+3S)	Lower Limit (LCL) (X-3S)

1	Proxen	0.244	0.0029	0.2535	-0.0058
2	Dolonap	0.235	0.0027	0.2433	-0.0055
3	Flexin	0.234	0.0029	0.2428	-0.0058

Table 3: Statistical Diameter Test

S.no	Name of Drug	Average diameter (mm)	Standard Deviation (%)	Upper Limit (UCL) (X+3S)	Lower Limit (LCL) (X-3S)
1	Proxen	0.6248	0.0013	0.6287	-0.0026
2	Dolonap	0.7145	0.0012	0.7182	-0.0024
3	Flexin	0.5029	0.0011	0.5062	-0.0022

Table 4: Statistical Hardness Test

S.no	Name of Drug	Average Hardness (Kg)	Standard Deviation (%)	Upper Limit (UCL) (X+3S)	Lower Limit (LCL) (X-3S)
1	Proxen	3.779	0.1075	4.101	-0.2151
2	Dolonap	3.769	0.0727	3.987	-0.1454
3	Flexin	4.001	0.1086	4.327	-0.2173

4. Friability Test: Friability test has been performed and according to the USP, the percentage weight loss by the tablet should not be more than 1% and the observed values of the all three brands of aproxen 500mg have been found to be within the control limits and summarized in the table 6.

Table 6: Friability Test

S.no	Name of Drug	Batch Number	Friability (%)	Limits	Comments
1	Proxen	P06077	0.11	NMT 1%	Within Limts
2	Dolonap	211	0.09	NMT 1%	Within Limts
3	Flexin	112126XV	0.14	NMT 1%	Within Limts

5. Disintegration Test: It has been observed that among the three different brands of naproxen 500mg i.e. Proxen, Dolonap and Flexin. Proxen disintegrated within 1 minute and 30 seconds, Flexin took a little more time to disintegrate as compared to Proxen i.e. 2 minutes and 10 seconds, whereas Dolonap was found to be the most time taking tablet to disintegrate among all three brands of naproxen 500mg i.e. 6 minutes. Inspite of that, the disintegration time of all three brands of naproxen 500mg have been found to be within the control limits set by USP i.e. NMT 15 minutes. (see table 7)

Table 7: Disintegration Test

S.no	Name of Drug	Batch Number	Disintegration Time (mins)	Limits	Comments
1	Proxen	P06077	1 min 30 sec	NMT 15mins	Within Limts
2	Dolonap	211	6 mins	NMT 15 mins	Within Limts
3	Flexin	112126XV	2 mins 30 sec	NMT 15 mins	Within Limts

6. Dissolution Test: As per the USP, the tablets should be completely dissolved after 20 minutes at 50 rpm at 37°C. The absorbance and percentage of all three brands of naproxen 500mg at 30 minutes have been evaluated and found to be within the specified limits i.e. NLT 80% and have been summarized in the table 8.

Table 8: Dissolution at 30 minutes

S.no	Name of Drug	Batch N0	Dissolution at 30 mins	BP/USP Limit	Deviation from BP/USP
1	Proxen	P06077	100.23%	NLT 80%	Within Limts
2	Dolonap	211	101.56%	NLT 80%	Within Limts
3	Flexin	112126XV	99.20%	NLT 80%	Within Limts

Discussion:

Weight Variation: To evaluate the uniformity of dosage form, weight variation and content uniformity test were performed. It has been specified in USP that the uncoated tablets having the weight of >324mg should have the standard deviation of ± 5%. It is appropriate to conduct the test of uniformity of dosage form when 25% of each tablet contains 25mg or more drug substance. The previously conducted studies showed that the specified limits were within the USP/BP range that complies with the current study. Weight variation was performed in the current research because the amount of active ingredient in all the three brands of Naproxen (Proxen, Dolonap & Flexin) was 500 mg. It has been observed that the result of reference brand and the other two brands are within the specified limits set by USP/BP. (see table 2).

Thickness & Diameter Test: The thickness and diameter of all three brands of naproxen 500mg (Proxen, Dolonap & Flexin) has been calculated and summarized as the mean, standard deviation and upper and lower limit in the table 3 and table 4 respectively. The previously conducted studies showed that the specified limits were within the USP/BP range that complies with the current study. Tablet thickness can be varied without affecting its weight. This happens due to pressure applied to the tablets, compression and difference in granulation length of punches if wear or tear can also be the cause of thickness variation. The result of thickness and diameter test showed that the reference brand and the other two brands of naproxen were within the specified limits of USP/BP and were bioequivalent.

Hardness Test: To determine the structural integrity of tablet, they were exposed to certain amount of pressure to bear mechanical shocks of handling during production, packaging and transport. According to the USP/BP, the official range of hardness is not less than 4 kg pressure required to break a tablet. The sample tablets of all three brands of naproxen 500mg were tested and the observed values i.e. mean, standard deviation, upper control limit & lower control have been found to be within the control limits, summarized in the table 5. This test also showed that the reference brand was bioequivalent with the other two brands of Naproxen taken in the study. Also, the previously conducted studies showed that the specified limits of Hardness test were within the USP/BP range that complies with the current study.

Friability Test: Friability test has been performed to estimate the percentage of weight loss by the tablet due to mechanical action, in order to understand and evaluate how well the tablet hold up to processes like coating, packing, shipping etc. The previously conducted studies showed that the specified limits of Friability test were within the USP/BP range that complies with the current study. According to the USP, the percentage weight loss by the tablet should not be more than 1% and the observed values of the all three brands of Naproxen 500mg have been found to be within the control limits and summarized in the table 6.

Disintegration Test: It has been observed that among the three different brands of naproxen 500mg i.e. Proxen, Dolonap and Flexin, Proxen disintegrated within 1 minute and 30 seconds, Flexin took a little more time to disintegrate as compared to Proxen i.e. 2 minutes and 10 seconds, whereas Dolonap was found to be the most time taking tablet to disintegrate among all three brands of naproxen 500mg i.e. 6 minutes. Inspite of that, the disintegration time of all three brands of naproxen 500mg have been found to be within the control limits set by USP i.e. NMT 15 minutes (see table 7). The previously conducted studies also showed that the specified limits were within the

USP/BP range that complies with the current study.

Dissolution Test: As per the USP, the tablets should be completely dissolved after 20 minutes at 50 rpm at 37°C. The absorbance and percentage of all three brands of naproxen 500mg at 30 minutes have been evaluated and found to be within the specified limits i.e. NLT 80% and have been summarized in the table 8. Also, the previously conducted studies showed that the resulted absorbance and percentage of Naproxen at 30 mins were within the USP/BP range that complies with the current study.

Conclusion

After observing the results of all the parameters performed on the three brands of Naproxen 500mg. It has been concluded by this study that, the reference brand (i.e Flexin) taken in this study is bioequivalent with the other two brands of Naproxen (Proxen & Dolonap) respectively. Thus, the other two brands of Naproxen (Proxen & Dolonap) can be used to make the treatment cost effective.

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