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ORIGINAL ARTICLE

Formulation Development and Assessment of Naproxen Sodium Tablet (Anti Rheumatic Agent)

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ABSTRACT

Background: Naproxen sodium has been extensively used as an anti-pyretic, anti-inflammatory and analgesic agent. Naproxen sodium tablet contains non-active ingredients like maize starch, microcrystalline cellulose, cross povidone, cross carmellose, lactose mono hydrate and magnesium stearate.

Objective: The objective of the study is to devise a method which caters to diverse aspects such as manufacturing and analysis associated with Naproxen Sodium.

Methods: All these non-active ingredients were blend with active using wet granulation technique. Different disintegrating agents were used for the enhancement of dissolution and disintegration property of newly formulated pharmaceutical product. In-process and finished product quality control tests were conduct which include weight variation test, uniformity test, hardness test, disintegration and dissolution test. UV spectrophotometer and HPLC analysis was also performed.

Conclusion: The results were found satisfactory plus the new formulation of naproxen sodium tablet passed the all criteria for analysis as specified in the BP/USP. The percent assay of granules was performed by both techniques that are HPLC and UV spectroscopy. The percent pharmaceutical assay, the individual weights, average weights, thickness, disintegration time of core and coated tablets, hardness and friability of core tablets plus dissolution test of coated tablets met the limits specified in the BP and USP.

INTRODUCTION

The drug category of nonsteroidal anti-inflammatory drugs (NSAIDs) is extensively prescribed for the reduction of tenderness and inflammation. NSAIDs are associated with risks of nephrotoxicity, inflammation of the gastrointestinal tract, ulcer specifically peptic in addition to worsened cardiovascular outcomes [1]. Naproxen and naproxen sodium are non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit prostaglandin synthesis [2]. Naproxen, is a nonspecific COX inhibitor [3]. Naproxen sodium is beneficial in the treatment of degenerative joint diseases along with knee and jip joint deformities. The drug is effective in acute gout and is said to reduced swelling in such patients [4]. Naproxen is also effective in primary Dysmenorrhea [5].

Tablets are manufactured by applying appropriate force to a powder and compressing the powder mixture into a coherent compact [6-8]. Wet granulation method is the most stable method and various pharmaceutical companies are using this form of technique for manufacturing of tablets. Up till now it is the

most comprehensive means of tablet processing with all of the required functionality of a firmness mix i.e. good flow, good compatibility, uniform distribution of drug and controllable drug release [9, 10]. For higher level dose drugs, poor flow and compression of the active signifies that wet granulation might be the only practicable way of producing tablets, and for lower dose drugs the granulation procedure is seen as being capable of producing the drug molecules to lock into granules and thereby minimizing the chances for segregation and reduced content uniformity [11, 12].

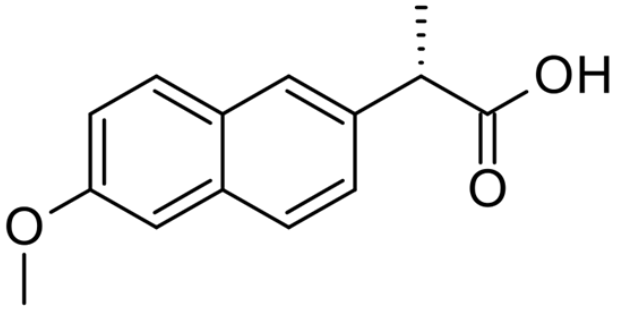

Figure 1. structure of Naproxen.

METHODLOGY

Manufacturing of naproxen sodium tablet by wet granulation technique

The naproxen sodium, microcrystalline cellulose pH 102, cross povidone, cross carmellose, primogel maize starch and lactose monohydrate were passed through 16 mesh sieves in mixer and were mixed for 15 minutes. previously prepared Maize starch paste with water was added to the mixture and again mixed for 15 minutes. After mixing it with the maize starch paste, the wet mass was spread on a drying tray and dried at 70 degrees centigrade to 80 degrees centigrade until the level of moisture remained not more than 30%. After drying the mixture was blended for 5 to 10 minutes.

Coating of the tablets was carried out using PEG 6000, Iron Oxide Yellow, HPMC, Talcum. Tablets were evaluated for all Pharmacopoeial parameters listed in USP/BP. As shown in Table **1**.

Analysis of naproxen sodium

Quality control testing during the manufacturing of the tablets becomes essential for the assurance that tablet parameters do not vary from one production batch to another. The specification of tablets includes the following [13].

Weight variation test

The weight variation test is used prior to a batch release on the other hand, rarely for the drug stability testing [14]. The desired weight of every tablet and the mean weight of 20 tablets in the sample are determined. This test is performed to ensure that all tablets in a batch are, within reasonable limits, of the same potency. A perfect manufacturing procedure would yield a batch of tablets having identical weight and medicament content.

Thickness test

Tablet thickness from production to production run is measured. Tablet thickness is very important for the appearance of tablets, but correspondingly to ensure that each production lot will be in working order by means of particular packing stuff [16]. If the tablets are denser than quantified, they may no longer be confined in the given size bottle or blister pack [17].

Test of hardness

The tablet splintering under conditions of storage, carriage and management before usage depends on its hardness [16]. Tablet should be hard enough to endure or tolerate manufacturing, packaging plus conveyance. Conversely, should not be too hard to amend disintegration as well as dissolution [18].

Friability test

Friability is the property of the tablets to remain intact, when tablets are subjected to a rotator motion, e.g. during the tablet coating processing of, tablet packaging or transport, as this may cause small particles to abrade from the surface of the tablet. The Roche friabilator is the most frequently used to measure friability and is rotated at 25rpm for 4mins. After processing reweigh the tablets. Weight loss indicate as the percent friability and the loss of weight should not more than 1% [19].

Disintegration test

Disintegration test is another quality control test useful for accessing potential importance of formulation and variable in biopharmaceutical properties of tablets. The drug release process from a tablet include a step at which tablet disintegrates into fragments [20].

ASSAY: (Analysis of Naproxen Sodium Granules)

Procedures are provided for determining of assay and test for compliance with the Pharmacopoeial standards of characteristics, potency, excellence in quality, and excellence in purity [22]. Assay of formulation of naproxen sodium tablet was carried out using HPLC and UV spectrophotometer.

Analysis of Naproxen Sodium Granules

Naproxen Sodium Granules was carried out using HPLC instrument. Acetonitrile (HPLC grade), Glacial acetic acid (AR grade) and distilled water were used as reagents. Solvent mixture was prepared in the ratio of (90:10) and mobile phase in the ratio of (50:49:1) Remaining chromatographic condition are stated in Table **2**.

Standard preparation

50mg of Naproxen sodium working standard was weighed accurately and transferred into a 50ml volumetric flask. About 25ml solvent mixture was added and sonicated for 10 minutes. After specified time, the volume was made up with solvent mixture and mixed well. Then 5ml of the above dilution was pipette out into a 50ml volumetric flask and the volume was made up with the mobile phase and shake well. The solution was filtered through 0.45µm filter paper.

Sample preparation

The average weight of the granules was weighed accurately and transferred into a 100ml volumetric flask. Then about 50ml of solvent mixture was added and the solution was sonicated for 30 minutes. After specified time, the volume was made up with solvent mixture and mixed well. The solution was filtered through whattman filter paper. 2ml of the above dilution was taken into a 50ml volumetric flask, the volume was made up with the mobile phase and mixed well. The solution was filtered through 0.45µm filter paper. Equal volumes of standard and sample preparations (20µl) were injected separately into HPLC system, and the peak area was recorded.

Assay of Granules by UV method

25.0mg of Standard Naproxen Sodium USP was weighed and dissolved in 50ml volumetric flask and the desired volume was made up. 10ml of the prepared solution was taken in another 50ml volumetric flask and the volume was made-up to 50ml and mixed well. 2 granules samples each of 350.0mg were also weighed. Methanol was used as a diluent for standard and sample solution. The absorbance was measured at the wavelength of 332 nm.

Dissolution test

For critical in vitro drug release, drug dissolution testing is usually used by various pharmaceutical companies to evaluate batch-to-batch uniformity of solid oral dosage forms such as tablets, for drug development and also to predict in vivo drug release profiles [21].

Chemical analysis of coated tablet's Dissolution by UV method is carried out by using Monobasic Sodium phosphate, Anhydrous Dibasic Sodium phosphate, distilled water and by preparing a dissolution medium (0.1M, pH 7.4 phosphate buffer). Dissolution medium comprised of 15.72g of monobasic sodium phosphate and 69.0g of anhydrous dibasic sodium phosphate dissolved in water to make 6000ml. The pH was adjusted to 7.4 ± 0.1 (see dissolution conditions in Table **3** and percentages of dissolution condition in Table **4**).

Standard preparation

32.0mg of Standard Naproxen Sodium USP was weighed and dissolved in 50ml volumetric flask and the volume was made up. 5ml was taken from the stock solution in another 50ml volumetric flask and the volume was made-up to 50ml.

Sample preparation

900ml 0.1M phosphate buffer pH 7.4 ± 0.1 was placed in each of six dissolution vessels. When temperature of the system stables at 37ºC ± 0.5ºC, 1 tablet was added in each of the six dissolution vessels, taking care to exclude air bubbles from the surface of the tablet. After specified time, sample was withdrawn from a about a midway between the surface of the medium and top of the rotating blade not less than 1cm from vessel wall. It was filtered through whattman filter paper. 5ml of the filtrate was pipette out into a 50ml volumetric flask and the volume was made up with dissolution medium and mixed well.

The absorbances of the standard and sample preparations were measured on a spectrophotometer at 332nm using dissolution medium as a blank.

RESULTS

The results of naproxen sodium tablet were evaluated by the formulation and development parameter as described in BP and USP. In this study tablets were evaluated against physical tests. In weight variation test the average weight of tablet was found to be 701.615 mg/tab. 13.5kg was measured as the average hardness. The average thickness was evaluated to be 6.75mm, the average disintegration time was 10 minutes and friability in percent was 0.0028%. Assay of formulation of naproxen sodium tablet was carried out using HPLC and UV spectrophotometer. The average results of pharmaceutical assay by UV spectrophotometer were calculated as 103.85% and by HPLC were calculated as 104.29%. The dissolution was performed as described in USP and BP and the average dissolved percent was 95.93% that comply with the limits Results given in Table **1-5**.

The chromatogram obtained are shown in Figure **2** and Figure **3**.

The dissolution was performed as described in specifications in the USP and BP and the average dissolved percent was calculated as 95.93% that comply with the limits.

All parameters and their result are elaborated in Table **6**.

Table 1: Active and non-active parts of naproxen sodium tablet composition and coating materials in formulation development.

S. No	Ingredients	Ingredients For Coating
1	Naproxen Sodium	HPMC 6cps
2	Maize Starch	Titanium Dioxide
3	MCC Ph 102	Talcum
4	Cross Povidone	PEG 6000
5	Cross Carmellose Sodium	IPA
6	Primogel	
7	Lactose Monohydrate	
8	Magnesium Stearate	

Table 2: Chromatographic conditions of pharmaceutical assay of naproxen sodium tablets.

Column	C 18 (250 x 4.6 mm)
Wave length	254nm.
Flow rate	1ml / min.
Temperature	Ambient
Injection volume	20µl

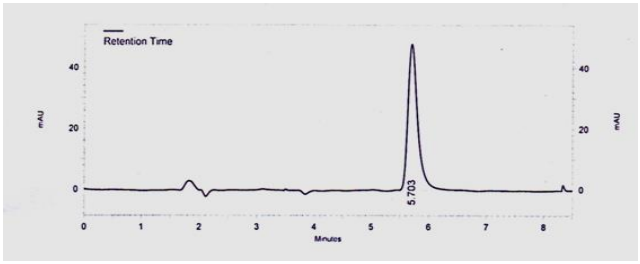

Figure 2: Chromatogram of naproxen sodium standard.

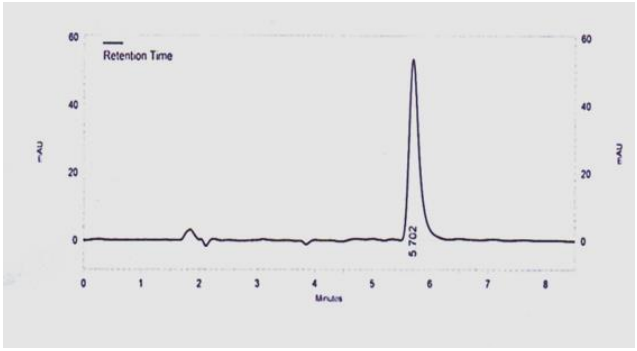

Figure 3: Chromatogram of naproxen sodium samples (granules).

Table 3: Dissolution conditions of naproxen sodium tablets.

Medium	0.1 M phosphate buffer pH 7.4 ± 0.1
Volume	900ml
Speed	50 rpm
Temperature	37° ± 0.5°C
Time	45 minutes

Table 4: Percentages of different tablets in dissolution test.

S. No.	Percentages of tablet %
Tablet sample 1	93.9
Tablet sample 2	99.7
Tablet sample 3	91.6
Tablet sample 4	94.3
Tablet sample 5	96.7
Tablet sample 6	99.4

Table 5: Percentage assay of granules in pharmaceutical assay by UV spectrophotometer and HPLC.

S. No.	Result % by UV	Result % by HPLC
Granule sample 1	104.75	104.75
Granule sample 2	102.95	103.83

Table 6: Evaluation of new formulation and comparison with different formulation available in market.

Parameters	New Formulation	Formulation 1	Formulation 2
Thickness (mm) (n=20)	6.75 mm	5.5mm	6.0mm
Hardness (kg) (n=20)	13.5 kg	10.0 kg	12.88 kg
Weight (mg) (n=20)	701.6mg	750.5mg	650.8mg
Friability (%) (n=10)	0.257 %	0.406%	0.510%
Disintegration (minutes) (n=6)	10 minutes	11 minutes	13 minutes
% Assay by HPLC (n=2)	104.29 %	99.5%	98.8%
%Assay by UV spectrophotometer (n=2)	103.85%	100.3%	99.5%
Dissolution% (n=6)	95.93%	90.8%	92.5%

DISCUSSION

Tablets were evaluated against various physical tests including Assay and its test procedures were provided for determining compliance with the Pharmacopoeial standards of identity, strength, quality, and purity [22]. For weight variation test the average weight of tablet was calculated by weighing 20 tablets individually (Toledo B204-S, Switzerland) and the average weight were found to be 701.615 mg/tab (+5% = 736.695, -5% = 666.534). Hardness test normally consists of breaking or crushing the tablet by application of a compressive load. 20 tablets were used and their hardness were determined individually by using Hardness Tester (Fujiwara, Tokyo). The average hardness was 13.5kg and it complies with the limit which was NLT 4 kg of individual hardness. Thickness and diameter variation were carried out on 20 tablets by using vernier caliper. The average thickness was 6.75mm. Friability test was performed to measure the resistance to abrasion. 20 tablets were placed in the Friability chamber. Friabilator (H. Jurgens Germany) was then rotated for 100 revolutions. The tablets were removed from the chamber, dusted and reweighed. Percentage of friability were recorded as 0.0028% and comply with the limit as prescribed in the BP and USP, that is not more than 1%. Disintegration test was carried out by using the USP disintegration apparatus (Erweka ZT-2, Germany) using 900ml water (purified) at 37 + 2 ^{o}C. The average disintegration time was 10 minutes which comply with the limit as prescribed in the BP and USP that is not more than 15 minutes of identity, strength, quality, and purity [22]. Assay of formulation of naproxen sodium tablet was carried out using HPLC (Shimadzu, Japan) and UV spectrophotometer (Shimadzu, Japan) the average results of pharmaceutical assay by UV spectrophotometer and HPLC were calculated as 103.85% and 104.29%.

CONCLUSION

The research study aims to meet each and every step of manufacturing and analysis of its granules plus physical parameters and chemical analysis of core and coated tablets. The results were found satisfactory plus the new formulation of naproxen sodium tablet passed the all criteria for analysis as specified in the BP/USP. The percent assay of granules was performed by both techniques that is HPLC (Shimadzu, Japan) and UV spectroscopy (Shimadzu, Japan). The percent pharmaceutical assay, the individual weights, average weights, thickness, disintegration time of both core and coated tablets, hardness and friability of core tablets plus dissolution test of coated tablets met the limits specified in the BP and USP.

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