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To study and to evaluate the requirements required to propose an alternate API source from an approved drug product in USFDA

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ABSTRACT

The aim of the present investigation is to study and evaluate to propose an alternate API source from an approved drug product and to further undergo formulation using the approved API. According to alternate vendor guideline from Regulatory Affairs, an alternate API can be approved if the specification standards and dissolution profile of both the alternate and approved API source are same. Naproxen sodium API specification standards were performed with reference to USP standards for both, approved and alternate API'S. Naproxen sodium USP 220 mg was formulated using both the API'S and the dissolution profile was compared and found to be similar. Since all the standards and dissolution profile was found to be similar the alternate API can be considered equivalent to approved API. Using the approved alternate API source further formulation of USP 220 mg, six formulations were carried out and further evaluated for assay, disintegration, hardness and dissolution.

Key words: Naproxen sodium approved API, Alternate API, USFDA.

1. INTRODUCTION

Naproxen sodium is a non steroidal anti inflammatory drug (NSAID) with analgesic and antipyretic properties. Naproxen sodium is an odourless crystalline powder white to creamy in colour, soluble in water and methanol. Naproxen is rapidly and completely absorbed from GIT tract with an *in-vitro* bioavailability of 95%. The elimination half life of Naproxen sodium was found to be approximately 17 hrs. Naproxen sodium tablets are indicated for the treatment of Rheumatoid arthritis, osteo arthritis, ankylosing spondilytis and acute gout [1-5].

The Active Pharmaceutical Ingredient of Naproxen sodium for formulation was taken from two vendors, one vendor is USFDA approved and the other API vendor is taken from china based company. The alternate vendor (i.e) china based company is compared with the USFDA already approved API and thus both the approved and alternate API'S are proved to be equivalent.

Specification standards of both the API'S were performed and formulation using both the API'S was carried out. Dissolution profiles of both were compared. Once the alternate API is approved, the formulation was carried out using the alternate API and six formulations were performed and then evaluated [4].

2. MATERIALS AND METHODS

2.1. Materials

Naproxen sodium (API) was taken from two vendors, one vendor which is USFDA approved and other unapproved vendor was taken from china based company. Corn starch, micro crystalline cellulose, sodium starch glycolate, povidone K-30 and aquaris BP 1706 were gifted from Granules India Limited, Hyderabad.

2.2. Methodology

2.2.1. Preparation of Naproxen sodium tablets USP 220 mg

Naproxen sodium tablets 220 mg were prepared by wet granulation technique using both the approved and alternate API'S and formulae used in the study are shown in table -1. After comparing the specification standards and dissolution profile of both the API'S (i. e) after the alternate API was proved to be approved, formulation of Naproxen sodium using approved alternate API was done. Six formulations were performed.

During the formulation F1and F2, Naproxen sodium was loaded into rapid mixer grinder (RMG) along with (diluents corn starch) and mixed for 5 minutes at slow mixer speed, add magnesium stearate to it and directly compress it. Granules were not formed properly. So, in formulation F3 another diluent i.e micro crystalline cellulose was added and compressed

directly. Granules were not formed properly even after adding microcrystalline cellulose.

Table -1: Composition of Naproxen sodium tablets using both the API'S

Name of the Ingredient	Approved API	Alternate API
Naproxen sodium USP	220	220
Microcrystalline cellulose	38.599	41.57
Corn starch	26.999	23.999
Sodium starch glycolate	2.999	5.999
Povidone K30	8.999	5.999
Water	Qs	Qs
Stearic acid	2.3999	2.3999
Total weight	300	300

The next three formulations (i.e) F4, F5 and F6 were done using wet granulation technique and binder povidone K-30 was added by dissolving povidone in purified hot water. Both the diluents (i.e) microcrystalline cellulose and corn starch were used in these formulations. Out of the six formulations F5 was found to be the best formulation as it showed a decrease in the disintegration time and the % drug released at 60 minutes was found to be good out of the six formulations [1].

2.2.2. EVALUATION OF BLENDS

2.2.2.1. Performing the tests according to specification standards [6,7]

2.2.2.1.1. Specific optical rotation

Sample preparation

Accurately weight and transfer about 2.5 g of Naproxen sodium into a clean and dried 50 ml volumetric flask, add 15 ml of 0.1 N sodium hydroxide, shake well to dissolve the sample and make up to the mark with 0.1 N sodium hydroxide solution .

Procedure

Take a clean and dried 1 dm glass cell or quartz cell. Perform blank determination by using 0.1 N sodium hydroxide as blank in a polarimeter. Then take the sample into cell and perform the specific optical rotation for sample and take five

$$[\alpha] = \lambda \frac{100 \times a}{lc}$$

α = Optical rotation at wave length 589 nm

t =Temperature

λ =Wavelength (589 nm)

a =observed rotation in degrees

l =Path length in decimeters

c =concentration of solution

2.2.2.1.2. Loss on Drying

Weigh accurately previously dried and cooled crucible and record weigh as W_1.

Transfer about 1.0 ± 0.1 g of sample into crucible, weigh accurately and record the weight of the sample and crucible as W_2.

Weigh of sample taken = W_2.W_1

Dry the sample in an oven at 105º C for 3 hrs. After completion of drying, cool the sample to room temperature in a desicator and record total weight as W_3.

Loss in weight after drying= w2-w3

Calculation:

$$\%Loss\ On\ Drying = \frac{W2 - W3}{W2 - W1} \times 100$$

Heavy metals:

Prepare test solution reference solution and blank solution (1, 2 and 3). Add 2ml of pH 3.5 in solutions 1, 2 and 3 separately, precipitation occurs.

Dilute 40 ml with anhydrous ethanol. Add 1.2 ml of thioacetamide reagent, mix and filter. Examine the solution after 2 minutes. Compare the solutions.

2.2.2.2. Evaluation of pre compression parameters of both the API'S Formulations [6]

2.2.2.2.1. Angle of repose

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher & more irregular the surface of particles the greater will be angle of repose. Angle of repose is calculated by the following formula.

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, r=radius of the pile, h=height of the pile.

2.2.2.2.2. Compressibility Index and Hausner's ratio

In recent years the compressibility index and the closely related Hausner's ratio have

become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped bulk density}}{\text{loose bulk density}}$$

2.2.2.3. Evaluation of post compression parameters of both the API'S Formulations [6, 7]

2.2.2.3.1. *In- vitro* disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured.

2.2.2.3.2. Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

2.2.2.3.3. *In-vitro* Dissolution

The *In-vitro* dissolution was carried out using USP Dissolution testing apparatus type 2 (paddle method, Electro lab) The tablets were placed in pH 7.4 phosphate buffer, the apparatus was run at 37ºC ± 0.5ºC and rotating speed of 50 rpm in 900 ml dissolution medium for 60 min. 5 ml aliquots were withdrawn at intervals of 5, 10 ,15, 30, 45 and 60 min and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Absorbance was measured at 262 nm using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer.

2.2.2.3.4. Stability studies

To assess the drug and formulation stability, stability studies were done according to International Conference on Harmonization and World Health Organization guidelines. The tablets were stored at 40ºC/75% relative humidity in closed high-density polyethylene bottles for 3 months. Tablets were analyzed at specific time intervals for hardness, drug content, disintegration and *in vitro* drug release studies.

3. RESULTS AND DISCUSSION

3.1. Performing the tests according to specification standards

The reported specific optical rotation of approved API was found to be at about -16.76, and for alternate API was found to be at about-15.6±0.54. Hence the value complies with that of the standard USP values. The reported amount of heavy metals for approved API was found to be 0.001±0.00032 % w/w, and for alternate API was found to be 0.001%w/w. Hence the value complies with that of the standard USP. The percentage loss on drying after 3 hours for approved API was found to be 0.3±0.115, and for alternate API after 3 hours was found to be 0.5±0.533.

The percentage purity of drug for approved API was reported to be 99.8±0.12%, and for alternate API was found to be 99.7 % w/w. All the above results have been mentioned in Table no. 2.

Table - 2: Performing tests according to specification standards

Test	Specification standards	Approved API	Alternate API
Appearance	White crystalline powder.	White crystalline powder.	White crystalline powder.
Solubility	Freely soluble in water, and in methanol.	Freely soluble in water, and in methanol.	Freely soluble in water, and in methanol.
Specific optical rotation	-15.3 to -17.0	-16.76	-15.6
Assay (% w/w)	NLT 98.0 to 102	99.8	97.8
Heavy metals(%w/w)	Less than 0.002%	Less than 0.002%	Less than 0.002%
Loss on drying (% w/w)	NMT 1%	NMT 1%	NMT 1%

3.2. Evaluation of Pre compression parameters

The reported angle of repose for approved API was found to be 27.4°, and for alternate API was found to be 28.7º, hence the blend was found to have good flowability.

The loose bulk density for approved API was found to be 0.632±0.00g/ml and tapped bulk density was found to be 0.793±0.00g/ml. The Loose bulk density for alternate API was found to be at 0.631±0.00 g/ml and tapped bulk density was found to be 0.80±0.00 g/ml.

The compressibility index for approved API was found to be 14.86%, and for alternate API was found to be 13.6%. The blend was found to

have excellent flowing property as the result were found to be below 15%.

The Hausner's ratio for approved API was found to be 1.16, and for alternate API was found to be 1.19. The result indicates the free flowing properties of the powders. All the above results have been mentioned in Table no.3.

Table - 3: Evaluation of Pre and post compression parameters

Parameters	Approved API	Alternate API
Angle of repose (°)	27.4	28.7
Bulk density		
Untapped (g/ml)	0.632±0.00	0.631±0.00
Tapped (g/ml)	0.793±0.00	0.80±0.00
Compressibility index (%)	14.86±0.03	13.6±0.05
Hauner's ratio	1.16±0.00	1.19±0.02
Disintegration time	9 min 45 sec	9 min 58 sec
Hardness (kg/cm²)	9.6 ± 0.79	9.4 ± 0.79
Weight variation (%)	301± 1.50	302± 0.15
Friability (%)	0.31±0.015	0.34±0.01

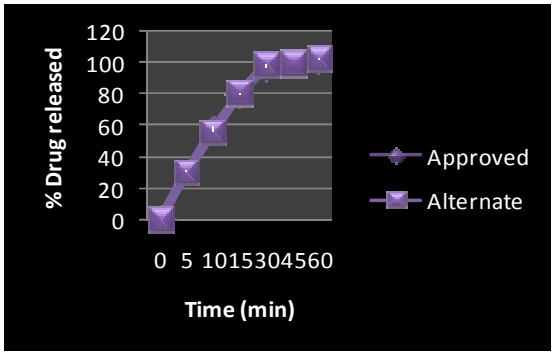
3.3. Evaluation of Post compression parameters

The hardness of tablets for approved API was found to be 9.6± 0.79 kg/cm², and the hardness of tablets for alternate API was found to be 9.4± 0.79 kg/cm². This indicates good mechanical strength of tablet. .

Percentage friability of all the formulations of approved API was found to be 0.31±0.015%, and percentage friability for the formulation of alternate API was found to be 0.34 %. This indicates good handling property of the prepared matrix tablet. Percentage drug released of approved API was found to be 97.2 and for the formulation of alternate API was found to be 99.2.

All the above results have been mentioned in Table No:3 and the comparison graph for percentage drug released for both the API'S was mentioned in Figure No: 1

Figure - 1: Comparison graph of dissolution profiles of both the approved and alternate API formulations



3.4. Formulation of naproxen sodium using approved alternate vendor

3.4.1. Evaluation of pre and post compression parameters

Angle of repose ranged from 25.31±0.28 to 28.26±0.15. The LBD and TBD ranged from 0.631± 0.01 to 0.655± 0.00 g/ml, and 0.587 ±0.001 to 0.825± 0.00 g/ml. The compressibility index (%) ranged from 12.30 ± 0.03 to13.56± 0.0. The Hausner's ratio ranged from 1.17± 0.01 to 1.29 ± 0.01, 13.56± 0.0.

Hardness of tablets was found to be in the range of 9.8kg/cm2 to8.1 kg/cm². Percentage friability of all the formulations was found between 0.46±0.46 to 0.35±0.06%. Percentage drug released of all the formulations was found between 89.2±0.90% to 99.1±0.26%. All the above results have been mentioned in Table No: 4, 5, 6 and comparison graph for percentage drug released has been mentioned in Figure No: 2

Figure - 2: Comparison graph of In-vitro drug release profile of formulations F1 to F6 of approved alternate API.

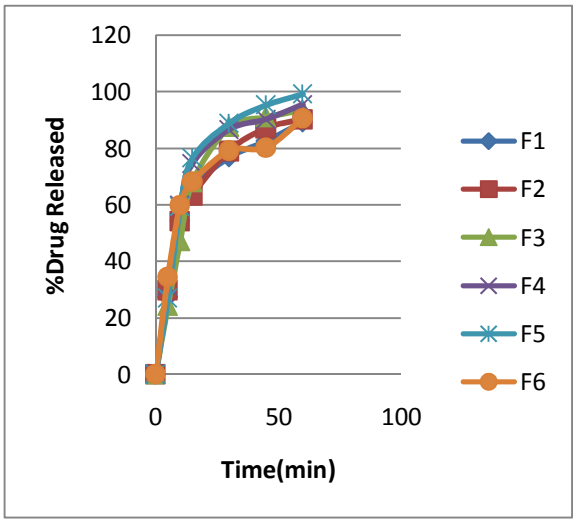


Table - 4: Composition of Naproxen sodium tablets using Approved Alternate Vendor

Ingredients (mg)	Formulation					
	F1	F2	F3	F4	F5	F6
Naproxen sodium	220	220	220	220	220	220
Microcrystalline cellulose	-	-	44.0	39.0	45.0	42.0
Corn starch	73.0	72.7	27.6	26.6	20.6	23.6
Sodium starch glycolate	4.6	4.	6		6	6
Water	-	-	-	qs	qs	qs
Povidone	-	-	-	6	6	6
Stearic acid	2.4	2.4	2.4	2.4	2.4	2.4
Total	300	300	300	300	300	300

Table - 5: Physical characteristics of lubricated blend

Formulation code	Bulk Density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (º)
F1	0.641±0.00	0.825±0.00	13.41±0.03	1.17±0.01	28.26±0.15
F2	0.655±0.00	0.725±0.01	12.27±0.05	1.17±0.00	26.34±0.14
F3	0.649±0.01	0.798±0.00	13.47±0.04	1.25±0.01	25.63±0.06
F4	0.631±0.01	0.587±0.01	12.30±0.03	1.17±0.02	25.31±0.24
F5	0.634±0.01	0.819±0.02	13.56±0.02	1.23±0.00	26.61±0.28
F6	0.648±0.00	0.712±0.01	12.77±0.04	1.29±0.01	27.59±0.17

Table - 6: Physicochemical characterization of Naproxen sodium

CODE	Diameter (mm)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Drug content (% w/w)
F1	13.20±0.166	4.6±0.152	8.2±0.115	0.44±0.015	301±0.020	99.50±0.26
F2	13.36±0.035	4.2±0.152	8.4±0.115	0.42±0.01	303±0.019	98.42±0.36
F3	13.35±0.015	4.4±0.1	8.1±0.0577	0.29±0.02	298±0.020	95.88±0.48
F4	13.31±0.02	4.7±0.1	8.6±0.230	0.54±0.025	299±0,022	99.2±0.25
F5	13.1±0.08	4.6±0.1	9.2±0.115	0.38±0.03	301±0.026	99.9±0.32
F6	13.36±0.025	4.7±0.1	9.8±0.34	0.59±0.02	303±0.022	99.2±0.26

Table -7: Stability study data of optimized formulation (F5)

Parameter	Initials	1 Month	2 Month	3 Month
Description	White coloured round shaped coated tablets	Complies	Complies	Complies
Disintegration time(min)	10 min 5 sec	10 min 2 sec	9 min 95 sec	9 min 68 sec
Hardness(kg/cm^2)	9.2	9.0	8.8	8.6
Assay(%w/w)	99.9	99.6	99.4	99.2
Dissolution (%w/w)	99.1	98.8	98.5	98.1

3.4.2. Stability studies

No statistically significant differences were observed in Hardness, percentage drug content, disintegration and percentage drug release in optimized formulation at the end of 3 months of stability studies. So, it can be concluded that the formulation is stable for short term storage conditions. Results were given in the table 7.

4. CONCLUSION

The specification standards and dissolution profile was compared for the drug Naproxen sodium for both approved vendor (Reddy's) and alternate vendor (Charioteer) and was found to be similar. Acording to Alternate Vendor Guideline in regulatory point of view an alternate vendor for Active Pharmaceutical Ingredient (API) can be approved if the specification standards and dissolution profile was same as compared with that of the already approved API source.

Hence the alternate vendor API i.e Charioteer can be approved for formulation and further marketing. Further formulation was carried out using the API of approved alternate source and 6 formulations were carried out and evaluated.

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