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FORMULATION DEVELOPMENT AND EVALUATION OF NAPROXEN SODIUM TABLETS USP

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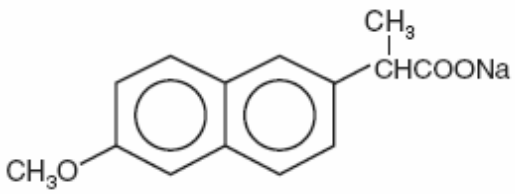
ABSTRACT

The objective of the present study is to develop a pharmaceutically stable and robust formulation of Naproxen sodium tablets USP 220mg comparable with innovator. In the present study we are reducing the excipients there by we can reduce the cost of the dosage form. The tablets of Naproxen sodium USP 220mg were successfully prepared by using wet granulation technique. Several trial formulations i.e., from F1-F10 have been taken to optimize and develop a robust formulation. The prepared tablets were evaluated for weight variation, hardness, thickness, friability, % drug content, disintegration time and in vitro drug release. Formulation F10 showed a drug release of 103.5% in 60mins which is faster than the innovator product. The stability studies, shown that the formulation F10, F11 and F12 were stable enough at 40°C / 75% RH for a period of 3 months. Therefore it can be concluded that the formulation F10 (Naproxen sodium tablets USP 220mg) is robust and stable.

Key Words: *Naproxen sodium, Maize starch, Microcrystalline cellulose, In-Vitro drug release.*

Introduction:

Tablet delivery systems can range from simple immediate release formulations to complex extended or modified release dosage forms [1]. More than 50% of drug delivery systems available in the market are oral drug delivery systems[2]. Accuracy of dose is maintained since tablet is a unit solid dosage form.



Structure 1: Chemical Structure of Naproxen Sodium

Naproxen is a non-steroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. Naproxen sodium is an odourless crystalline powder, white to creamy in color. It is soluble in methanol and water. The molecular weight of Naproxen Sodium is 252.24 and it melts at 105°C. Naproxen itself is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites

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do not induce metabolizing enzymes. Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. The elimination half-life of Naproxen is approximately 15 hours. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66-92%). A small amount (< 5%) of the drug is excreted in the feces.

Naproxen sodium tablets are indicated for the treatment of Rheumatoid arthritis, Osteoarthritis, Ankylosing spondylitis, Tendinitis, Bursitis, Acute gout[3].

Materials and Methods:

Naproxen Sodium, Maize Starch and Pregelatinized Maize Starch are obtained as gift samples from Aurobindo pharma Limited, Hyderabad. Micro crystalline cellulose, sodium starch glycolate, polyvinyl pyrrolidone K-30 (PVP), stearic acid and aquarius BP 17066 were purchased from local vendor. Other materials used were of analytical grade.

Experimental work:

Preparation Naproxen Sodium Tablets USP:

Naproxen sodium tablets containing 220 mg were prepared by wet granulation technique and formulae used in the study are shown in table 1. During formulation F1, F2 & F3 load Naproxen sodium into rapid mixer granulator (RMG) (Sainath Boilers & Pneumatics, Hyderabad) along with diluent (Maize starch, pregelatinized maize starch, sodium starch glycolate) and mixed for 5 min at slow mixer speed[4]. Dissolve the PVP K-30 in Purified hot water. Add binder into RMG while mixing at slow mixer speed. Add extra water till required consistency of mass is obtained. Granules were not found during Formulation F1 & F2. Better granules were found during Formulation F3 but DT was not matching with innovator. During formulation F4, F5, F6, F7, F8, F9 & F10 maize starch was replaced by micro crystalline cellulose. Load Naproxen sodium into RMG along with diluent (micro crystalline cellulose, pregelatinized maize starch, sodium starch glycolate) and mixed for 5 min at slow mixer speed[4]. Dissolve the PVP K-30 in purified hot water. Add binder into RMG while mixing at slow mixer speed.

Start the fluidized bed processor (Palm Glatt, Mumbai) in manual mode & set process parameters as given below. Dry the wet granules. Sift the dried granules through # 18 mesh. Load the sifted granules into Octagonal blender (Saan, Mumbai). Stearic acid (Lubricant) is added into blender by sifting it in 40 mesh and blended for 5 min at 8 rpm. Compress the blend into tablets weight of 300.0 mg. Coat the tablets to get 2.5 % buildup by using 15% aquarius BP 17066 coating solution. During formulation F4 & F5 better granules were found but disintegration time is not matching with reference sample. During Formulation F6, F7, F8 & F9 disintegration time was satisfactory but percentage drug release was lower than that of innovator sample. Granules produced during Formulation F10 have good flow property as the disintegration time and dissolution profile were matching with innovator sample. Two reproducibility batches (F11 & F12) of Formulation F10 were taken. Physical properties of the granules are similar to that of F10 and the dissolution profiles as well as the chemical properties of the tablets are same as that of F10.

Comparative data of various formulations:

A batch size of 3333 tabs was planned for each formulation and the quantity for each formulation was expressed in grams.

Table 1: Shows various Formulations of Naproxen Sodium Tablets USP

Ingredients (gms/batch)	Formulations									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Naproxen Sodium	733	733	733	733	733	733	733	733	733	733
Maize starch	206	204	214	_	112	117	109	89	69	79
Pregelatinized maize starch	36	32	20	20	20	_	_	_	_	_
Microcrystalline cellulose	_	_	_	212	100	115	110	130	150	140
Sodium starch glycolate	12	16	20	20	20	20	20	20	20	20
PVP K-30	5	7	5	7	7	7	20	20	20	20
Stearic acid	8	8	8	8	8	8	8	8	8	8

Evaluation of powder blend:

Determination of bulk density and tapped density

Bulk Density:

Apparent bulk density (B.D) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the initial volume (V_o) weight of powder (W). The bulk density was calculated using the formula.

Bulk Density (B.D) = W / V_o

Tapped Density:

The measuring cylinder containing known mass of blend was tapped for a fixed number of taps. The minimum volume (V_f) occupied in the cylinder and the weight of powder (W) was measured. The tapped density was calculated using the formula.

Tapped Density (T.D) = W / V_f

Angle of repose:

Angle of repose (*a*) was determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the heap (*r*) was measured and angle of repose was calculated.

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

Compressibility index:

The simplest way measurement of free flow property of powder is compressibility, an indication of ease with which a material can be induced to flow is given by % compressibility, which is calculated as follows:

C = [(T.D-B.D) / T.D] x 100

Where T.D and B.D are bulk density and tap density respectively.

Hausner's ratio:

Hausner's ratio is an index of ease of powder flow; it calculated as follows:

Hausner's ratio = T.D / B.D

Where T.D and B.D are bulk density and tap density respectively.

Evaluation of tablets:

All the tablets were evaluated for different parameters like hardness, thickness, friability, drug content, disintegration time and *in-vitro* drug release.

Hardness:

For each formulation hardness was tested using the Fizer hardness tester (Cadmach, India) [1, 2]

Friability:

Twenty tablets were weighed and placed in Roche friabilator (Electrolab, Mumbai) and apparatus was rotated at 25 rpm for 4 min. After

revolution tablets were dusted and weighed [1, 2]. The friability is given by the formula:

F = [1- Wo / W] x 100

Where,

Wo = weight of the tablets before the test, W = weight of the tablets after the test.

Drug content:

Two tablets were powdered and the blend equivalent to 220 mg of naproxen was weighed and dissolved in suitable quantity of distilled water. The solution was filtered, suitably diluted and drug content was analyzed spectrophotometrically at 272 nm. Each sample was analyzed in triplicate [8].

Disintegration time:

The disintegration apparatus consist of basket of six tubes with a base of metal sieve. This assembly is suspended using a hanger with a mechanism of vertical motion at affixed speed of 28-30 cycles/ minutes. The assembly moves in the vertical motion in the distilled water maintained at $37^{o}\pm0.5^{o}C$. The time required for disintegration of tablet is recorded and should meet the required time specification [9].

***In vitro* drug release**:

The *in vitro* drug release of naproxen was determined by using USP Dissolution Testing Apparatus II (Paddle type) (Electrolab, Mumbai). The dissolution test performed using 900 ml of distilled water maintained at $37^{o}\pm0.5^{o}C$. The speed of rotation of paddle was set at 50 rpm. At a predetermined time interval of 5, 10, 15, 30, 45 & 60 min, 5 ml samples were withdrawn and filtered through Whatman filter paper. Absorption of solution was checked by UV spectrophotometer at 272 nm and % drug release was calculated [10, 11].

Stability Studies:

Stability studies are an integral part of the drug development program & are one of the most important areas in the registration of pharma products [11]

Characterization of Innovator Product:

FD&C Blue #2, Hypromellose, Magnesium stearate, Micro crystalline cellulose, Povidone, Poly ethylene glycol, Pregelatinised maize starch, Maize Starch, Sodium Starch glycolate, Stearic acid.

Physicochemical Evaluation of Innovator product:

Marketed tablets are Blue Colored, Oval shaped and biconvex film coated tablet, with an average weight of 300 mg, strength of 220 mg having a thickness of 4.50 - 5.00 mm**,** hardness of 5.0 - 12.0 kg and disintegration time of 12.30 min.

***In vitro* Dissolution data of Innovator:**

Time (Min)	5	10	15	30	45	60
% Drug Release	37.9	69.6	86.9	100.8	101.6	102.8

Results and Discussion

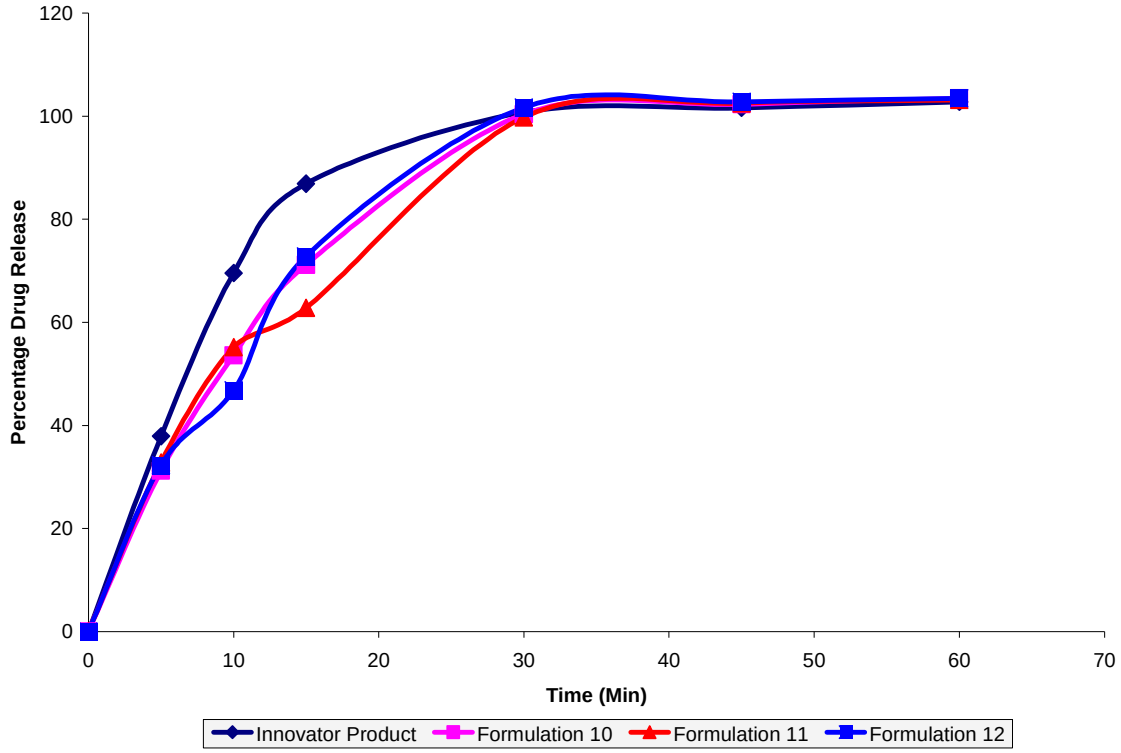
Table 2: Evaluation of Powder Blend

Parameters	Formulations									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Bulk density (gm/cm^3)	1.224 ± 0.04	1.132± 0.02	0.711± 0.003	0.651± 0.004	0.475± 0.003	0.462± 0.002	0.445± 0.002	0.438± 0.004	0.422± 0.005	0.413± 0.002
Tapped density(gm/cm^3)	1.321± 0.02	1.265± 0.04	0.654± 0.03	0.546± 0.05	0.457± 0.06	0.465± 0.02	0.453± 0.04	0.455± 0.03	0.436± 0.002	0.421± 0.003
Angle of repose	36.45	34.12	27.26	25.12	26.32	23.14	21.25	23.45	21.25	20.12
% compressibility	31.45	30.12	28.62	18.65	16.25	15.45	13.95	12.45	10.36	9.65
Hausner's ratio	1.625	1.542	1.334	1.125	1.064	1.122	1.056	1.078	1.045	1.006

Table 3: Evaluation of Naproxen sodium Tablets USP

TEST	FORMULATIONS									
	F3	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
% Weight variation (± 5%)	0.76±0.15	0.84±0.14	0.65±0.12	0.73±0.21	0.82±0.13	0.61±0.2	0.89±0.16	0.75±0.15	0.63±0.14	0.61±0.11
Hardness (Kg)	8-9	9-10	8-10	8-10	10-11	9-11	9-10	8-10	8-10	9-10
Friability -%w/w	0.41±0.03	0.16	0.14	0.15	0.4	0.21	0.18	0.20	0.19	0.18
% Drug content	99.1	99.1	99.3	99.5	99.4	99.3	99.6	99.7	99.4	99.6
Disintegration time (min)	11.15	10.53	8.58	9.01	8.34	8.51	8.47	8.54	8.53	8.57
% Drug release (after 60 min)	75.3	88.5	90.12	91.5	94.5	96.4	98.5	103.5	103.2	103.5

Fig 1: Comparative *In Vitro* Dissolution Study of Formulations F10, F11, F12 with Innovator Product.



Discussion:

The assay of Naproxen Sodium in all trials lies within the limit and complies with the specifications. The film coating process was also found to be smooth with no processing problems. There is not much variation in the release of drug from the core as well as coated tablets indicating that the coating of tablets to obtain a 2.5% weight gain is found to be sufficient to coat the tablets. Therefore formulation F11 and F12 are planned for stability study.

Stability Studies:

Naproxen sodium tablets USP 220mg were evaluated for accelerated stability studies at 40ºc/75% RH conditions. The stability study for 3 months shows that the formulation is stable enough at 40^0C/75%RH

Summary And Conclusion

Summary:

The preformulation study of Naproxen Sodium complies with specifications. Several trials (F1-F10) have been taken to optimize and develop a

robust formulation. Various processing problems were encountered during the formulation development and these were overcome with proper optimization of composition of formulation ingredients and processing conditions. The coating process of the tablets was optimized with a good release of drug from the coated tablets. The coated tablets were evaluated for the physical as well as chemical attributes and were found to be satisfactory in comparison to the market sample. *In-vitro* drug release profile of formulation F10 in purified water was found to be 103.5% in 60 min, which is faster than reference product. Two reproducibility batches F11 & F12 were taken. *In vitro* drug release profile of F11 & F12 in purified water was found to be 103.2% & 103.5% respectively in 60 mins, which is faster than reference product. Formulations F10, F11, F12 were taken and were charged for stability studies at accelerated condition.

Conclusion:

The assay of Naproxen Sodium in all trials lies within the limit and complies with the specifications. *In vitro* drug release profile of formulation F10 in purified water was found to be 103.5% in 60 min, which is faster than reference product. The stability study for 3 months shows that the formulation is stable enough at 40^0C/75%RH.

So it can be concluded that the Naproxen sodium tablets USP 220mg formulation is robust and stable.

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