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Research

Formulation and Evaluation of Naproxen Sodium 220 Mg Modified Release Tablet Using Novel Technology

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Abstract

Development of an experimental design (DOE) aimed at enhancing the modified release formulation of Naproxen Sodium 220 mg through innovative technology. This experimental approach focuses on improving the assay of Naproxen Sodium release tablets by incorporating DisintegrantsValidation of this method will encompass the processes of raw material dispensing, sifting, dry mixing, binder preparation, wet mixing, drying, milling, lubrication, compression. This study illustrates that the solid dispersion technique can significantly enhance the dissolution rate of Naproxen. The results are consistent with numerous other investigations into solid dispersion methods, indicating that this strategy serves as a viable option for pharmaceutical companies seeking to prolong the life cycle of products that exhibit poor solubility. A comparative analysis of the dissolution profiles was performed across various media, both with and without surfactants.

The findings clearly demonstrate that an increase in the concentration of Disintegrants does not lead to interactions with the drug when combined with other excipients, thereby facilitating sustained drug delivery over prolonged periods. The improved formulation, developed through factorial design, can be administered as a single daily dose. The experimental design lays the groundwork for further optimization. In this investigation, Trial #3 emerged as the formulation that most effectively satisfies all criteria for an optimal formulation

Keywords: Naproxen Sodium, Formulation, Evaluation, Modified Release Tablet, Novel Technology

INTRODUCTION

Formulation and evaluation of Naproxen Sodium 220 mg Modified release tablet using novel technology. The present scope is to: Design of experiment (DOE) for Improved Modified release formulation of Naproxen Sodium 220 mg using novel technology Design of Experimental approach for enhancing assay using Disintegrants in Naproxen Sodium release tablets The proposed method shall be used for the quantification of

active Naproxen Sodium The proposed method shall be validated for Dispensing of raw material, Sifting, Dry mixing, Binder preparation, wet mixing, Drying, milling, lubrication and Compression Controls of critical process parameters and Critical process attributes. Control on the in process parameters: Blend uniformity, Loss of drying. Water by KF, Bulk density , tapped density, Particle size, description, assay, dissolution, weight of 10 tablets, Disintegration time, hardness, weight variation and Uniformity of the dosage form.

The recent advancement pertains to a novel formulation of naproxen that provides immediate pain relief equivalent to the administration of 440 mg (or two 220 mg tablets) of naproxen sodium, in addition to offering prolonged pain relief for a duration of 24 hours. This innovation is characterized by a single solid dosage form that effectively integrates an immediate release component of naproxen sodium with an extended release layer of the same compound. Specifically, the invention is realized in the form of a bilayer tablet that delivers an immediate release of 300-320 mg of naproxen sodium, succeeded by a gradual release of 450-480 mg of naproxen sodium. This formulation is intended to ensure 24 hours of pain relief when consumed as a single bilayer tablet. The bilayer design allows for an immediate release (IR) of naproxen sodium from one layer, while the other layer provides a sustained release of the remaining naproxen sodium, thereby maintaining extended pain relief for up to 24 hours. Naproxen, traded below the brand designation Aleve between others, is a nonsteroidal anti-inflammatory drug (NSAID) used to necessity pain, menstrual cramps, inflammatory diseases such as rheumatoid arthritis, gout and fever. It is taken orally. It is available in immediate and delayed release preparations. Surprise of effects is within an hour and lasts for up to10 hours.

Common side properties include dizziness, headache, bruising, allergic reactions, heartburn, and abdominal pain. Plain one-sided effects include an enlarged risk of heart disease, stroke, gastrointestinal bleeding, and stomach ulcers. The heart disease danger may be minor than with other NSAIDs. It is not endorsed in people with kidney problems. Use is not optional in the third trimester of pregnancy.

MATERIALS AND METHODS

Equipment	Equipment Number	Make and Model
Vibrator sifter	PRO-0024	Russell Finex
Roll compactor	PRO-0003	Alexanderwerk
Multimill	PRO-0028	Shiv Shakti Multi Mill Machine
Blender	PRO-0018	Pharma fab
Compression Machine	PRO-0009	Killan
Metal Detector	PRO-0014	METTLER TOLEDO
DE duster	PRO-0032	Prim pharma
Stirrer	PRO-0029	JKM Engineers
Coating Machine	PRO-0020	Neocota
Balance	PRO-0016	Mettler Toledo
Hardness tester	PRO-0023	Erweka Tester
Friability Tester.	PRO-0027	Pharmaceuticalsky
DT apparatus	PRO-0029	Effem Technologies
Moisture Analyser	PRO-0030	METTLER TOLEDO

Principle of the Manufacturing Equipment

Sifter, RMG, Fluid Bed Dryer, Multi mill, Octagonal blender, Compression Machine, Coating, Metal detector, Metal detector, Check weigher, Analytical balance, Moisture analyzer, Bulk density apparatus, Vernier caliper

METHODOLOGY

Naproxen is a nonselective COX inhibitor. As an NSAID, naproxen looks to apply its anti-inflammatory action by plummeting the production of inflammatory mediators called prostaglandins. It is metabolized by the liver to inactive metabolites.

Mechanism of Action

Naproxen 250+ Tablet is a non-steroidal anti-inflammatory medicine (NSAID). It mechanism by blocking the discharge of certain chemical messengers that reason fever, pain and inflammation (redness and swelling).

Drug Profile

Naproxen is categorized as a no steroidal anti-inflammatory drug (NSAID). It is a propionic acid derivative associated with the aryl acetic acid class of NSAIDs. This medication is effective in managing acute pain as well as discomfort associated with rheumatic conditions. It serves as a first-line treatment option for various clinical scenarios that necessitate analgesia, owing to its overall tolerability and efficacy. Naproxen is available in both delayed-release and immediate-release formulations, and it can be combined with sumatriptan for the treatment of migraines, as well as with esomeprazole to reduce the risk of gastric ulcer development..

Solubility

Naproxen USP is a crystalline compound that appears as an odourless substance, ranging in colour from white to off-white. It exhibits lipid solubility and is nearly insoluble in water at low pH levels, while demonstrating high solubility in water at elevated pH levels. The octane/water partition coefficient for naproxen at a pH of 7.4 is between 1.6 and 1.8. In contrast, naproxen sodium USP is characterized as a crystalline solid with a white to creamy white appearance, and it is readily soluble in water at neutral ph.

Naproxen tablets USP are offered in light orange hues, with formulations containing 250 mg, 375 mg, and 500 mg of naproxen USP, intended for oral use. The inactive components include microcrystalline cellulose, croscarmellose sodium, iron oxide red, iron oxide yellow, povidone, and magnesium stearate

Naproxen sodium tablets USP are offered in two formulations: blue tablets containing 275 mg of naproxen sodium USP and blue tablets containing 550 mg of naproxen sodium USP, both intended for oral use. The inactive components include croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate, microcrystalline cellulose, and talc. The coating suspension for both the 275 mg and 550 mg naproxen sodium tablets consists of hypromellose, titanium dioxide, polyethylene glycol, FD&C blue #2, and iron oxide red.

Chemical Formula: C14H14O3
STORAGE : Store below 30°C
Indication: Naproxen is specified for the organization of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, tendinitis, bursitis, acute gout, primary dysmenorrhea, and for the relief of mild to moderate pain. Additional, it is first-line therapy for osteoarthritis, acute gouty arthritis, dysmenorrhea, and musculoskeletal inflammation and pain.
The melting point: 498.2 - 503.6 °F.

Critical Process Parameters in Manufacturing

Quality target product profile for test product was decided based on Reference product information, Literature and requirement of dosage form.

Critical Process Parameter

Sr.No	Steps	Parameter
1	Sifting	Milling speed ,Screen Size, Mesh size
2	Extra Granular Material	Mesh size
3	Lubrication	Blend Speed ,Blend time
4	Roll compaction	Milling ,Screen ,Retention

Critical product control Parameter

Test	Standard
Description	Dissolution by UV
Identification	The transitions minima spectra obtained from the sample shall be corresponded to transitions minima spectra obtained from the Naproxen reference standard
Weight variation (mg)	8.924 g-9.746 g
Thickness (mm)	6.30 mm-7.28
Hardness (N)	NLT 160 N
Friability (%m/m)	NMT 1.0
Disintegration time (minute)	NMT 15 minutes
Dissolution by UV	NLT 80% (Q) of label claimed –Gemfibrozil($C_{15}H_{22}O_3$) is dissolved in the 45 minutes
Uniformity of dosage	85-115 with RSD not more than 6.0%)
Water content % m/m	NMT 4.0% m/m

Test	Standard
Assay (%) Blend	NLY 95.0 to NMT 105
Related Substance	
Impurity A	NMT 0.1%
Other Impurities	NMT 0.2%
Total impurities	NMT 0.5%

RESULTS AND DISCUSSIONS

Process Parameters and critical quality attributes

Unit Parameter	Process Parameter	Quality Attributes
Dry Mixing	Order of addition	Particle size distribution, Bulk/tapped density ,flow properties
	RMG amperage	
	Impeller Speed and time	
	Mixing	
Wet Granulations	Binder addition time	Granules size, Granule shape, flow properties
	Impeller Speed	
	Chopper Speed and Run time	
	Binder fluid temperature	
	Post granulation fix time	
Milling	Speed of mill	Blend Uniformity flow, Particle size and distribution , Granules size and distribution, granules strength and uniformity solid form
	Screen size	
	Feeding rate	
Drying	Inlet temperature, inlet air flow, volume	Granule size and distribution , granules strength and uniformity, particle size, bulk/tapped density, moisture content, residual solvents
	Bowl temperature	
	Exhaust temperature	
	Shaking interval	
	Product temperature	
Blending	Blender type	Blend uniformity and flow properties
	Blender RPM	
	Blending time	
Compression	Compression speed	Target weight, weight uniformity, content uniformity thickness, friability and DT
	Compression force	
	Force speed frame type and speed	
Coating	Spray rate and RPM	Weight gain

Selection of Excipient

Microcrystalline cellulose, Lactose Ph. Eur, Sodium starch glycolate, Silica Colloidal anhydrous Hydroxypropyl cellulose (HPC), During process development, the manufacturing steps and critical process parameters. The method of manufacture is Sifting, blending sifting blending, compaction, milling, sifting, pre lubrication compression, coating and packing

Material	Function	Manufacturer	% per dosage form
Dry **mixing**			
Naproxen USP	Active	Century Pharmaceuticals Limited	330
Microcrystalline Cellulose	Dilute	Dupot	56.115
Lactose	Binder	Adama Agricultural	38.040
Sodium Starch Glycolate	Super Disintegrate	SDFE Pharma	28.50
Silica Colloidal anhydrous	Glidant	Deguss	3.50
Hydroxypropyl cellulose (HPC)	Binder		4.8
Purified water	Diluent	In-house	--

Material	Function	Manufacturer	% per dosage form
Sodium stearyl fumarate	Lubricant		3.7950
Coating			
Opadry blue	Coating solution	Colorcon	17.89
Purified water	Solution	In-house	--
The quantity of the active is based on 100 % assay and can be adjusted with the microcrystalline cellulose to get constant weight. Purified water should not available –it should in the limit as water content			

Manufacturing Flow

Following steps are followed during manufacturing in controlled temperature and humidity

Process Parameters and critical quality attributes

Unit Parameter	Process Parameter	Quality Attributes
Dry Mixing	Order of addition	Particle size distribution , Bulk/tapped density ,flow properties
	RMG amperage	
	Impeller Speed and time	
	Mixing	
Wet Granulations	Binder addition time	Granules size, Granule shape, flow properties
	Impeller Speed	
	Chopper Speed and Run time	
	Binder fluid temperature	
	Post granulation fix time	
Milling	Speed of mill	Blend Uniformity flow, Particle size and distribution , Granules size and distribution, granules strength and uniformity solid form
	Screen size	
	Feeding rate	
Drying	Inlet temperature, inlet air flow, volume	Granule size and distribution , granules strength and uniformity, particle size, bulk/tapped density, moisture content, residual solvents
	Bowl temperature	
	Exhaust temperature	
	Shaking interval	
	Product temperature	
Blending	Blender type	Blend uniformity and flow properties
	Blender RPM	
	Blending time	
Compression	Compression speed	Target weight, weight uniformity, content uniformity, Hardness thickness, friability and DT
	Compression force	
	Force speed frame type and speed	

Process Parameters and critical quality attributes

Unit Parameter	Process Parameter	Quality Attributes
Dry Mixing	Order of addition	Particle size distribution , Bulk/tapped density ,flow properties
	RMG amperage	
	Impeller Speed and time	
	Mixing	
Wet Granulations	Binder addition time	Granules size, Granule shape, flow properties
	Impeller Speed	
	Chopper Speed and Run time	
	Binder fluid temperature	
	Post granulation fix time	
Milling	Speed of mill	

Unit Parameter	Process Parameter	Quality Attributes
	Screen size	Blend Uniformity flow, Particle size and distribution , Granules size and distribution, granules strength and uniformity solid form
	Feeding rate	
Drying	Inlet temperature, inlet air flow, volume	Granule size and distribution , granules strength and uniformity, particle size, bulk/tapped density, moisture content, residual solvents
	Bowl temperature	
	Exhaust temperature	
	Shaking interval	
	Product temperature	
Blending	Blender type	Blend uniformity and flow properties
	Blender RPM	
	Blending time	
Compression	Compression speed	Target weight, weight uniformity, content uniformity, hardness, thickness, friability and DT
	Compression force	
	Force speed frame type and speed	
Coating	Product temperature	Visual attributes, weight of core tablet, appearance, and % weight gain, Film thickness, residual solvent.
	Total pre heating time	
	Individual gun spray rate	
	Air pressure	
	Inlet air flow, temperature , dew pint	
	Exhaust temperature , air flow	
	Product temperature	
	Total coating time	

Dispensing and Quantity of Material

1. **Dispensing:** Raw material to be used in the manufacturing shall be procured from the approved vendor
2. All raw material shall be dispensed in the control condition to avoid cross contamination

Batch size 150000 tablets: Material to dispense

Material	Function	Manufacturer	% per dosage form
		Dry **mixing**	
Naproxen USP	Active	Century Pharmaceuticals Limited	330
Microcrystalline Cellulose	Dilute	Dupot	56.115
Lactose	Binder	Adama Agricultural Solutions	38.040
Sodium Starch Glycolate	Super Disintegrate	SDFE Pharma	28.50
Silica Colloidal anhydrous	Glidant	Deguss	3.50
Hydroxypropyl cellulose (HPC)	Binder		4.8
Purified water	Diluent	In-house	--
Sodium stearyl fumarate	Lubricant		3.7950
		Coating	
Opadry blue	Coating solution	Colorcon	17.89
Purified water	Solution	In-house	--
The quantity of the active is based on 100 % assay and can be adjusted with the microcrystalline cellulose to get constant weight. Purified water should not available –it should in the limit as water content.			

Equipment used during Manufacturing

Equipment	ID of Equipment	Make	Date of Qualification
Sifter	PDE 781	Shree Bhagwati Machtech India Pvt. Ltd	23-03-2023
Rapid Mixture granulator -RMG	PDE 581	SANN	20-01-2023
Fluid bed Equipment	PDE 231	Glatt	03-05-2023
Octagonal blender	PDE 627	SANN	07-02-2023
Compression Machine	PD127	Fette	05-06-2023
Metal detector Sifter with de duster	PDE 128	SMMS	19-04-2023
Hardness tester	PDE 063	Rockwell	15-02-2023
Friability	PDE 069	Panomex	29-03-2023
Disintegration Apparatus	PDE 051	Agilent 100 automated disintegration	08-04-2023
Coating Machine	PDE 629	Gancoata	29-01-2023

Manufacturing Process flow –parameter-Equipment

Sr.no	Steps	Parameter	Equipment used
1. 1	Raw material to be used in the manufacturing shall be procured from the approved vendor		
2	**Sifting: Sift all the material**		
	Naproxen USP	# 20	Sifter Verification of sieve integrity before and after use
	Microcrystalline Cellulose	# 20	
	Lactose	# 20	
	Sodium Starch Glycolate	*# 20*	
	Silica Colloidal anhydrous	*# 20*	
	Hydroxypropyl cellulose (HPC)	*# 20*	
3	**Preparation of the binder** Ext Hydroxypropyl cellulose (HPC) and purified water mixing and stirring	25 minute	Till clear solution
4	**Dry mixing** In RMG mix material	15 minutes	RMG
	Naproxen USP	30 RPM	Impeller speed
	Microcrystalline Cellulose Lactose Sodium Starch Glycolate	OFF	Chopper Speed
5	**Wet Granulation**		
		2-3 minute	Addition of binder solution
		30 RPM	Impeller speed
		OFF	Chopper Speed
6	**Drying**	*NMT 80°C*	*Inlet temperature*
		NMT 60 °C	*Exhaust temperature*
		NMT 40 °C	*Proud bed temperature*
		3-5 % w/w	*LOD % w/w*
7	**Sifting** and milling of the granules	*30#*	Sieve size
		2.5,2.00 mm	Co-mill
		2500-3500 RPM	Co mill speed
8	**Sifting**	40#	Sieve size
9	**Pre Lubrication**	15 minute	Blending time
		05	RPM-Speed
10	**Lubrication** Add Silica Colloidal anhydrous to lubricant	15 minute 05	Blending time RPM-Speed
11	**Compression**		
	Unload the blend and compressed on 45 station of compression machine	Turret speed Punch and die	Compression machine

Sr.no	Steps	Parameter	Equipment used
		In process parameter	
12	**Coating** Mask the core tablet	Spray rate Weight gain Atomization pressure	Coating Machine

Before Compaction-Premixing results: sample is withdrawal for the blend uniformity, Bulk density, tapped density and water content

Sampling point	NAP230115	NAP230116	NAP230117
1	100.1	100.4	96.2
2	98.3	96.4	99.7
3	97.7	100.7	98.4
4	98.0	98.9	98.1
5	100.4	100.6	98.4
6	96.6	98.1	97.8
7	96.5	99.3	99.6
8	97.6	98.1	98.5
9	99.3	98.8	99.6
10	99.2	98.7	98.2
Mean	98.4	97.0	97.0
SD	1.82	1.61	1.04
% RSD	1.76	1.64	1.05
Bulk Density (g/ml)	0.354	0.370	0.365
Tapped Density (g/ml)	0.519	0.524	0.543
Water by KF (% m/m)	1.2	1.2	1.3

Lubrication results

sample is withdrawal for the blend uniformity ,Bulk density ,tapped density and water content

Sampling point	NAP230115	NAP230116	NAP230117
1	98.7	96.5	98.7
2	96.7	97.6	100.4
3	98.4	99.3	100.1
4	99.3	99.8	98.3
5	100.4	96.6	96.5
6	96.6	98.5	97.6
7	98.4	99.6	99.3
8	97.0	98.2	100.4
9	98.1	97.0	97.6
10	98.8	98.5	99.3
Mean	98.6	97.1	98.4
Minimum	96.7	96.5	96.5
Maximum	100.4	99.3	100.4
% RSD	0.94	1.15	1.21
Description	White to off white granules	White to off white granules	White to off white granules
Assay (%)	99.7	98.8	99.6
Water content % m/m	1.3	1.4	1.6
Bulk Density (g/ml)	0.478	0.560	0.601
Tapped Density (g/ml)	0.630	0.739	0.745
Particle size Analysis (Retention)			
20# Mesh	19.36	18.25	17.45
30# Mesh	36.12	35.12	38.12
40# Mesh	53.32	49.86	51.23

Sampling point	NAP230115	NAP230116	NAP230117
60# Mesh	74.62	63.74	71.8
100# Mesh	76.61	67.38	77.2
120# Mesh	85.56	81.32	84.4

Rational for the selection of the critical parameter

1. *Sieving:* Mesh size aperture present in liner inch. Sieving is essential to devoid of foreign particles present if any,
2. Pre lubrication, blend uniformity is important to make ensure that the active ingredients are homogeneously mixed.
3. Final blend: assay water, Assay, Bulk density and particle size shall be carried out. To ensure the potency of the blend meets the defined criteria.

This research demonstrates that the dissolution rate of Naproxen can be significantly improved through the solid dispersion technique. The findings align with several other studies investigating solid dispersion methods, suggesting that this approach is a practical solution for pharmaceutical companies aiming to extend the life cycle of existing products that suffer from poor solubility.

A comparative study of the dissolution profiles was conducted in various media, both with and without surfactants. All physical and chemical parameters were found to be satisfactory and consistent with the quality target product profile. Consequently, the quantities of active pharmaceutical ingredient (API) have been optimized for the formulation, and the batch studies meet the specified criteria. A bioequivalence study can be performed on the optimized formula.

CONCLUSION

The current research anticipates the application of Quality by Design (QbD) in the manufacturing of Naproxen tablets utilizing polymers. The results clearly indicate that as the concentration of Disintegrants increases, the combination of Disintegrants with other excipients does not interact with the drug, and vice versa, which contributes to the sustained delivery of the drug over extended periods. The enhanced formulation derived from factorial design can be administered as a single daily dose. The experimental design provides a framework for further optimization. In this study, Trial #3 was identified as the formulation that best meets all criteria for an optimal formulation.

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