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FORMULATION AND EVALUTION OF FAST DISSOLVING TABLETS OF NAPROXEN SODIUM BY DIRECT COMPRESSION METHOD

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ABSTRACT

Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. The aim of this work is to prepare and evaluate fast dissolving tablets of Naproxen sodium using super disintegrates like croscarmellose sodium, crospovidone, sodium starch glycolate to improve patient compliance. Naproxen is used to relieve pain from various conditions such as headaches, muscle aches, tendonitis, dental pain and menstrual cramps. It also reduces pain, swelling and joint stiffness caused by arthritis, bursitis and gout attacks. Naproxen sodium should not be prescribed to a person who is suffering from Asthma, Blood disorders, Nasal polyps, heart disease (such as previous heart attack), high blood pressure, liver disease, stroke, throat/stomach/intestinal problems (such as bleeding, heartburn, ulcers).Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation studies were primarily done to investigate the physicochemical properties of drug and also to establish its compatibility. The results confirmed that the physical mixture and solid dispersion formulation blends showed improved flow property when compared with pure drug. Immediate release tablets of Naproxen Sodium FDT'S were prepared by direct compression method using 10 station compression machines equipped with flat faced 9 mm punches. The Naproxen Sodium FDT'S were subjected to many in-process evaluation parameters such as physical appearance, weight variation, hardness, friability, % drug content and disintegration time. All the values are within the limits as per USP. The disintegration time of formulations were found to be within 2±0.10 sec to 4±0.20 sec. The prepared tablets were evaluated for *in vitro* drug release studies.

INTRODUCTION

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children and patients mentally retarded, uncooperative and nauseated or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in Administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous system. Drugs with poorwetting ,slow dissolution properties, intermediate to large dosage, and optimum absorption in the gastrointestinal tract or any combination of these features may be difficult or impossible to

formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability. Bitter tasting drugs, drugs with an objectionable odor,or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulation and to achieve better patient compliance. One such approach is"fastdissolvingtablets"(FDT).

AIM AND OBJECTIVE:

Naproxen sodium is a Non-steroidal anti-inflammatory drug commonly used for the reduction of pain, fever, inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps. It works by inhibiting both cox-1 and cox-2 enzymes. The aim of this work is to prepare and evaluate fast dissolving tablets of Naproxen sodium using super disintegrates like croscarmellose sodium, crospovidone, sodium starch glycolate to improve patient compliance.

Specific objectives of the research are as follows;

- Formulation of fast dissolving tablets of Naproxen sodium using super disintegrants.
- Evaluation of prepared FDT's for dissolution, disintegration, hardness, etc.
- Selection of best formulation.
- Characterization of best formulation by FTIR.
- Short term stability studies of optimized formulation.
- Comparison of the best formulation with that of the product.

Naproxen is used to relieve pain from various conditions such as headaches, muscle aches, tendonitis, dental pain and menstrual cramps. It also reduces pain, swelling and joint stiffness caused by arthritis, bursitis and gout attacks. Naproxen sodium should not be prescribed to a person who is suffering from Asthma, Blood disorders, Nasal polyps, heart disease (such as previous heart attack), high blood pressure, liver disease, stroke, throat/stomach/intestinal problems (such as bleeding, heartburn, ulcers).

PREFORMULATION STUDIES:

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. A complete evaluation of physicochemical properties may provide a rationale for designing formulation or support the need for molecular modification or merely confirm that there are no significant barriers to the compound development.

The goals of the Preformulation studies are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine kinetic release rate profile.
- To establish its compatibility with different excipients.

Precompressional parameters like angle of repose, bulk density, tapped density, carries compressibility index and Hausner's ratio were determined for all the powder blends of Naproxen sodium fast dissolving tablet formulations.

FORMULATION OF FAST DISSOLVING TABLETS:

Six batches of tablets containing Naproxen sodium were formulated using various super disintegrates like crospovidone (CRP), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) in concentrations ranging from 5%. Alone and in combination in the concentration of 5%. The tablets were prepared by direct compression method. All the ingredients were properly mixed for 30min in a polyethylene bag to obtain a uniform blend. The blend was further lubricated with magnesium stearate for 5min.The blend was compressed into tablets with an average weight of 250mg using 9mm flat punch in a rotary tablet press (Rimek).

RESULTS AND DISCUSSION:

PREFORMULATION STUDIES:

Preformulation studies were primarily done to investigate the physicochemical properties of drug and also to establish its compatibility.

Calibration Curve of Naproxen Sodium: Standard calibration curve of Naproxen Sodium was obtained by plotting absorbance vs concentration using UV spectroscopy. The λ_{max} ofNaproxen Sodium in Methanol was determined to be 331nm. The standard

calibration curve shows r^2 value of 0.998. The curve is found to be linear in the Beer's range between 50-250µg/ml.

Evaluation of Flow Properties:

All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. From the flow properties evaluation of pure drug it was concluded that Naproxen Sodium has very poor flow property (Table2).The flow characteristics of blend are measured by angle of repose. The data obtained from angle of repose for the formulations were found to be in the range of 25.3^0 to 34^0(Table 3). All the formulations prepared showed angle of repose less than 34^0, which reveals good flow property. The bulk density and tapped density for the blend was performed. The data obtained from bulk density and tapped density for formulation blend varied from 0.36gm/ml to 0.38 gm/ml and 0.50gm/ml to 0.52gm/ml respectively. The results of Carr's consolidation index or compressibility index for the formulation blend ranged from 16.31% to 20.02% (Table 4). The results of Carr's index reveal that formulation blend shows fair flow property.Hausner's ratio of the formulation blend ranged from 0.91 to 1.19. All the formulations prepared showed Hausner's ratio less than 1.19, which indicates good flow property.From the above results, it was confirmed that the physical mixture of dug and excipients showed improved flow property when compared with pure drug.

EVALUATION

Evaluation of tablets:

Six batches of Naproxen Sodium FDT'S of total weight 250mg were prepared by direct compression using 10 station rotary tablet machine (Rimex) equipped with 9mm flat faced punches. These tablets were subjected to many in-process evaluation parameters such as physical appearance, weight variation, and hardness, friability, and % drug content and disintegration time and *in-vitro* dissolution studies.All the tablets were round and flat in shape with no visible cracks having smooth appearance.The weight of all tablets was within the range of 248mg to 250mg for formulations. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than 7.5%, i.e., in the pharmacopoeia limits, which provide good uniformity in all formulations.The hardness of all the tablets prepared was found to be within the range of 3.0kg/cm2 to 3.4kg/cm2. In all the formulations the hardness test indicates good mechanical strength. In the friability test, the percentage weight loss of all formulations varied from 0.54% to 0.75%, which is within the acceptable limits. This indicates that all the tablets withstand the mechanical shocks during handling. In the friability the percentage weight loss of all formulations varied from 0.54% to 0.73% which is within the acceptable limits. This indicates that all the tablets with stand the mechanical shocks during handling.The % Drug content of all batches of tablets was determined and it was within the range of 99.20% to 99.8%, indicating good uniformity among different formulation of tablets. The disintegration time of formulations containing was found to be between 0±0.10sec. This indicates that the formulations have fast disintegrating capacity. F1 disintegrates faster than others.

***In vitro* Dissolution studies:**

In vitro drug release studies for the prepared Naproxen Sodium tablets were conducted for a period of 30 minutes using USP type II dissolution apparatus. Dissolution of all the formulations was carried out using pH 7.4phosphate buffers at 50 rpm speed. At every interval, 5ml of sample was withdrawn, appropriate dilutions were done and the sample was analyzed at 331nm by UV Visible Spectrophotometer. Formulation containing 5% cross crosspovidone (F1), crosscamellose sodium (F2), Sodium starch glycolate (F3). 99% magnesium stearate and Naproxen sodium respectively. Formulation containing 2.5% of crosspovidone and 2.5% of crosscamellose sodium (F4) of Naproxen sodium. Formulation containing 2.5% of crosscamellose sodium and 2.5% of Sodium starchglycolate (F5). Formulation containing 2.5% of crosspovidone and 2.5% of Sodium starchglycolate (F6).

The *in vitro* drug release from **Naproxen Sodium** containing different super disintegrants were found in following ascending order: **Crosspovidone > Croscarmellose sodium > Sodium starch glycolate.**

From the results,it was confirmed that F1 formulation(containing (5%crosspovidon as superdisintegrant) has disintegrated rapidly(within 2±0.10sec.) and released the drug at a faster rate(i.e., 99.8±0.007% in 15min). Hence,it was selected as an optimized formulation. The optimized formulation F1 was compared with marketed formulation Naproxen 100MG with respect to disintegration time 10±0.15sec for F1 and 58±0.52sec for marketed product) and *in-vitro* drug release and the results were shown in Table 4& FIG 2. From results it was observed that the drug release was more rapid from F1 formulation was comparable with that of marketed formulation.

Release Kinetics:

The kinetics and release mechanism was estimated by the regression plots for Zero order and First order. The in vitro release data obtained for ***Naproxen Sodium*** tablets were fitted into various kinetic models. The results were shown in the Fig 6 and Table 4. When r2 values of regression plots for First order and Zero order were considered, r2 values for the First order was found to be more than Zero order. Hence it was confirmed that the drug release from Naproxen Sodium tablets followed first order release kinetics. Therefore the release rate in formulations dependent on concentration or amount of drug incorporated.

Short term stability studies:

Short term stability studies were conducted for the optimized formulation F1 of Naproxen Sodium tablets at 4^0C, at room temperature and 45^0C for 3 months. There was no significant change in the %drug content and in disintegration time (table 8).

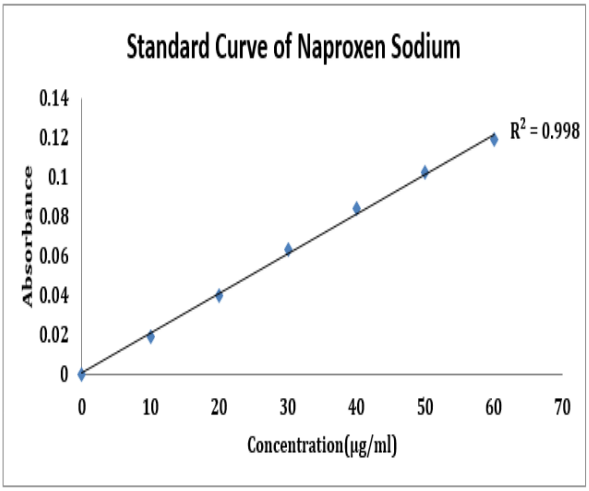


Fig1 Calibration curve of Naproxen Sodium

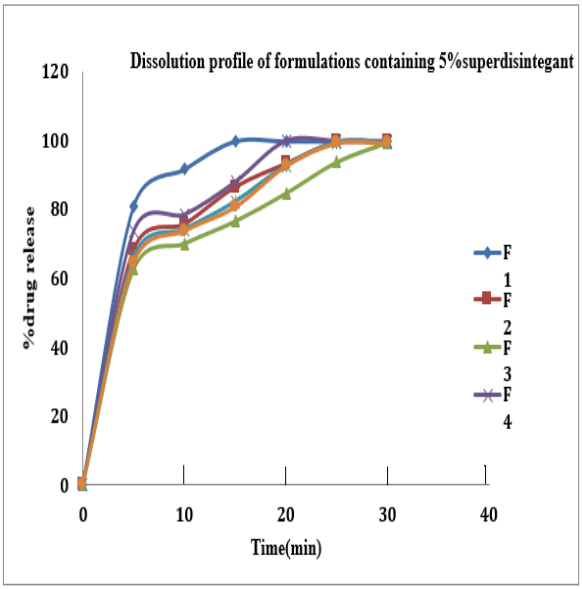


Fig 2 Comparison of dissolution profiles of formulations with 5% concentration of Croscarmellose sodium, Crospovidone, sodium starch glycolate

Table 1 List of materials

S. No.	MATERIALS	SUPPLIER
1.	Naproxen sodium	Granules India Limited, Hyd
2.	Sodium starch glycolate	Sd fine chemicals limited, Mumbai
3.	Crospovidone	Sd fine chemicals limited, Mumbai
4.	Croscarmellose sodium	Sd fine chemicals limited, Mumbai
5.	Microcrystalline cellulose	Sd fine chemicals limited, Mumbai
6.	Magnesium stearate	Sd fine chemicals limited, Mumbai
7.	Talc	Sd fine chemicals limited, Mumbai

Table 2 Calibration of Naproxen Sodium

Concentration	Absorbance
10	0.019
20	0.04
30	0.063
40	0.084
50	0.102
60	0.119

Table 3 Flow properties of Pure Drug

Parameters	Results
Angle of repose	34
Bulk density	0.38gm/ml
Tapped density	0.52gm/ml
Carr's index	27.7%
Hausner's ratio	1.19

Table 4 Pre compressional evaluation parameters of Naproxen Sodium Tablets

Formulation Code	Angle of Repose(0)*	Bulk density (gm/cc)*	Tapped density (gm/cc)*	Carr's index (%)*	Hausner's Ratio*
F1	26.7±0.13	0.38±0.045	0.52±0.036	0.52±0.036	16.31±0.018
F2	28.2±0.11	0.42±0.072	0.69±0.028	0.69±0.028	17.0±0.010
F3	25.3±0.12	0.31±0.036	0.62±0.031	0.62±0.031	15.60±0.024
F4	29.4±0.14	0.34±0.053	0.60±0.019	0.60±0.019	16.10±0.027
F5	26.8±0.11	0.41±0.081	0.70±0.026	0.70±0.026	15.96±0.016
F6	28.9±0.16	0.36±0.058	0.714±0.029	0.714±0.029	14.19±0.022

*All values represent mean±SD,n=3

Table 5 Post compressional evaluation parameters of FDT'S of Naproxen Sodium

Formulation Code	Thickness (mm)*	Weight Variation (mg)*	Hardness (kg/cm2)*	Friability (%)	Disintegration Time(sec)*	Drug content (%)*
F1	2.9±0.15	250±1.92	3.4±0.25	0.54	0.10±2	99.8±0.97
F2	2.8±0.27	230±1.80	4.1±0.17	0.62	0.18±6	99.7±0.93
F3	3.1±0.19	230±2.44	3.6±0.19	0.64	0.12±5	99.6±1.17
F4	3.0±0.11	250±2.00	3.8±0.11	0.68	0.18±5	99..5±1.14
F5	2.9±0.19	220±2.19	3.5±0.21	0.69	0.16±4	99,21±1.12
F6	3.0±0.18	250.7±1.65	3.4±0.18	0.73	0.20±6	99.5±1.14

*All values represent mean±SD,n=3

Table 6 Dissolution profile of Naproxen Sodium FDT'S

Time (min)	%drug release from Naproxen Sodiumtablets mean ±SD*					
	F1	F2	F3	F4	F5	F6
5	80.9±0.008	73.5±0.006	68.3±0.009	66.19±0.006	64.6±0.005	62.6±0.002
10	91.6±0.004	78.3±0.008	75.7±0.003	74.2±0.003	73.80±0.007	70.1±0.004
15	99.80±0.001	87.8±0.009	86.5±0.008	82.3±0.009	80.7±0.009	76.6±0.006
20	------	99.2±0.003	93.3±0.002	92.8±0.004	92.6±0.005	84.7 ±0.008
25	-----	----	99.6±0.001	99.5±0.002	99.2±0.003	93.8±0.010
30	------	------	-----	-------	----	*99.5*±0.002

*All values represent mean±SD,n=3

Dissolution profiles of F1, F2 and F3

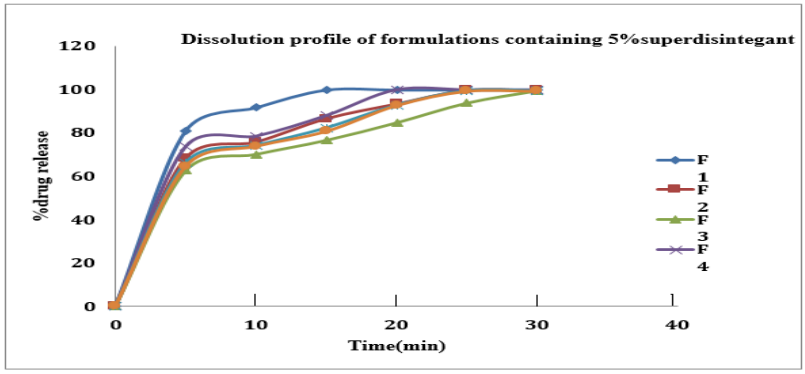


Fig 2 Comparison of dissolution profiles of formulations with 5% concentration of Croscarmellose sodium, Crospovidone, sodium starch glycolate

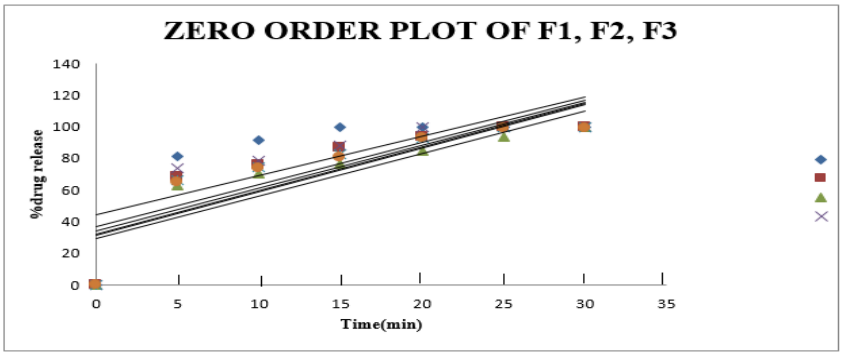


Fig 3 Zero order plots of Naproxen Sodium formulations with 5%superdisintegrant

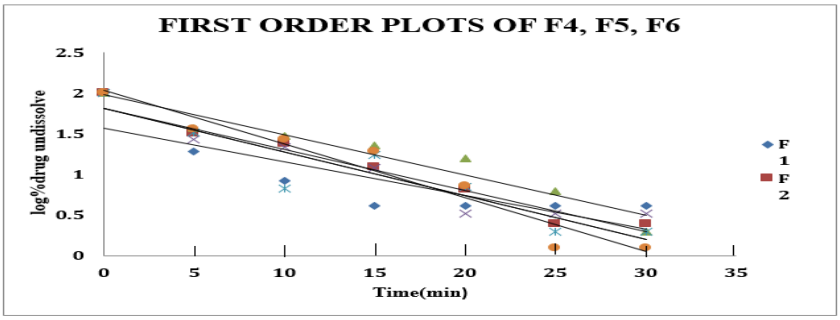


Fig 4 First order plots of Naproxen Sodium formulations with 5%superdisintegrants

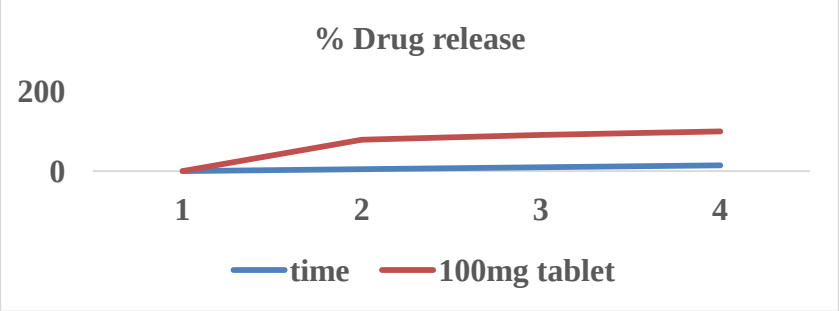
Table 7 Regression values of Naproxen Sodium formulations (F1-F6)

Formulations	r^2 value	
	First order	Zero order
F1	0.722	0.527
F2	0.941	0.698
F3	0.931	0.653
F4	0.906	0.757
F5	0.856	0.724
F6	0.941	0.735

Comparison of optimized formulation (F5) with marketed product (F1):

Table 8 In-vitro dissolution profile of marketed drug and F1

Time	%Drug released	
	100mg tablet of Anaprox or Naprosyn	F1
0	0	0
5	79.2	80.9
10	91.0	91.6
15	99.9	99.80
20	--	--
25	--	--
30	--	--



Summary & Conclusion: Naproxen sodium using super disintegrants. The aim of this work is to prepare and evaluate fast dissolving tablets of Naproxen sodium using super disintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate to improve patient compliance.Naproxen Sodium is an anti NSAID {Non-steroidal anti-inflammatory drug} drug with poor water solubility and low bioavailability. The main aim of the present study was to enhance the solubility and dissolution rate of Naproxen Sodium. Crospovidone, Croscarmellose sodium and Sodium starch glycolate were selected as superdisintegrant. Talc was selected as diluent and taste masking agent, microcrystalline cellulose was selected as direct compressible diluent and magnesium stearate was selected as lubricant in the formulation of tablets. The solubility of Naproxen Sodium was determined in water and different pH buffers (phosphate buffer of pH 6.5, pH 6.8 and pH 7.4) and better solubility was seen in methanol. Naproxen Sodium FDT'S were prepared using Crospovidone, Croscarmellose sodium and Sodium starch glycolate were selected as superdisintegrant in the concentration ranges of 4%,5% each. All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The results confirmed that the physical mi5xture and solid dispersion formulation blends showed improved flow property when compared with pure drug. Immediate release tablets of Naproxen Sodium FDT'S were prepared by direct compression method using 10 station compression machines equipped with flat faced 9mm punches. The Naproxen Sodium FDT'S were subjected to many in-process evaluation parameters such as physical appearance, weight variation, hardness, friability, % drug content and disintegration time. All the values are within the limits as per USP. The disintegration time of formulations were found to be within 2±0.10 sec to 4±0.20 sec. The prepared tablets were evaluated for *in vitro* drug release studies. The *in vitro* drug release from Naproxen Sodium FDT'S containing different superdisintegrants was found in following ascending order: **Crospovidone > Croscarmellose sodium > Sodium starch glycolate**

When r2 values of regression plots for First order and Zero order were considered, R2 values for the First order was found to be more than Zero order. Hence it was confirmed that the drug release from Naproxen Sodium FDT'S followed first order release kinetics. The *in vitro* drug release from Naproxen Sodium FDT'S it was confirmed that F1 formulation (containing 5% crospovidan as super disintegrants) has disintegrated rapidly (within

2±0.10sec) and released the drug at a faster rate(i.e., 99.8±0.007% in 15min). The optimized formulation F1 was compared with marketed formulation NORVASC 10MG with respect to disintegration time and *invitro*drug release (4±0.15sec for F5 and 58±0.52sec for marketed product). Short term stability studies were conducted for the optimized formulation F1 of Naproxen Sodium FDT'S with 5% crospovidon as superdisintegrant at 40C, at room temperature and 45^0C for 3 months. There was no significant change in the %drug content and in disintegration time.

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