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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF NAPROXEN SODIUM BY DIRECT COMPRESSION METHOD.

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ABSTRACT

Present study deals with formulation and evaluation of naproxen sodium orodispersible tablets by direct compression method using superdisintegrants. Orodispersible tablets or fast dissolving tablets are the solid unit dosage forms that dissolve or disintegrate rapidly in the mouth without chewing or water [**1**]. ODTS provide improved patient compliance particularly for pediatric and geriatric patients with difficulty in swallowing. Naproxen sodium is a NSAID that is used to treat pain and inflammation in various conditions. As it is an analgesic drug rapid action is a desired feature. Gastric discomfort is one of the major side effects associated with the drug, which can be minimized by formulating it as ODT's. Naproxen Odts were prepared by direct compression method, the most easiest and cost effective way to prepare tablets with common ingredients and, by limited number of processing steps using super disintegrants cross carmellose sodium in different concentrations (5,10,15,20,25). The powder blend was subjected to pre compression evaluation parameters like bulk density, tapped density, and angle of repose. All Formulations are evaluated for weight variation, hardness, wetting time, water absorption time, disintegration time and in vitro dissolution studies. The drug excipient compatibility was verified by FTIR. The pre compression evaluation results revealed that all formulations were of good flowability. The hardness and friability results indicated good mechanical strength with acceptable disintegration time. The optimized formulation F5 showed good in vitro drug release profile with maximum drug being released at all time intervals making it ideal for development as ODT's. The compiled results of pre compression and post compression evaluation parameters along with FTIR was presented.

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INTRODUCTION

Oral route of administration is considered as most preferred route because of various advantages like ease of administration, pain avoidance, and patient compliance **[2].** Tablets are the most popular dosage forms among the all the existing dosage forms. However, many elderly patients, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid intake/diets have difficulties swallowing these dosage forms. People who are traveling or have little access to water are similarly affected **[3].**

To overcome this problems, oral dispersible tablets also known as fast dissolving tablets are developed. Over the decade the demand for these odts has been increased due to its significant impact on the patient compliance for geriatric, paediatric populations **[1].** Orally disintegrating tablets are also called as orodispersible tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, quick disintegrating tablets rapid dissolving tablets, porous tablets, and rapimelts **[4].**

FDA defined ODT as solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue**.** Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing **[5].** They dissolve rapidly in the mouth usually within seconds without the need of water and prevent problems of swallowing to provide quick onset of action. With this dosage form, there is no risk of obstruction, which can be beneficial to travelling patients or have little access to water. First pass hepatic metabolism and gastric degradation can be avoided by pregastric absorption of drugs through ODT's, which reduces the dose and increase the bioavailability. Thus, ODT's enhances safety and efficacy of drug molecule by being a convenient and more patient compliant dosage form **[6].**

Naproxen sodium, [(+)-(S)–2-(6-methoxynaphthalen-2- yl) propanoic acid], is a nonsteroidal anti-inflammatory drug (NSAID) **[7],** that is used for various painful indications such as the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout **[8]** with lower indications of gastro-intestinal adverse effects**.**

Naproxen is BCS (class -II) drug that is , practically insoluble in water at low pH and freely soluble in water at high pH soluble in lipids. It is soluble in ethanol (95%) and in methanol [9]. It is used for the treatment of pain, inflammation, fever and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, migraine and menstrual cramps. As it is an analgesic drug rapid action is a desired feature. When formulated as ODT's due to the presence of super disintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Gastric discomfort that is one of the major side effects of the naproxen can be minimized by formulating it as ODT's because they provide pregastric absorption.

Naproxen sodium is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the dissolution rate which can be improved by ODT's dosage form **[7]**. Naproxen has half-life of 12-24hrs and it is well absorbed on oral administration after achieving plasma concentration (C_{max}) within 1-2 hrs of administration **[10]**. It is a weakly acidic drug, and remain in partially non ionized form at oral cavity's pH, which favours its pregastric absorption.

Hence all the above mentioned characteristics of the naproxen makes it an ideal candidate for formulating as ODT with regards to patient compliance by reducing its side effect and increasing the rapidity**[6]** and thus, naproxen was choosen as model drug for the present study.

The main approach of the study was to develop orodispersible formulations of naproxen sodium offering an acceptable disintegration time less than 3 minutes and at the same time have good dissolution rate, possess sufficient mechanical strength, reduced gastric discomfort, and improved bioavailability.

MATERIALS AND METHODS

Naproxen sodium was a gift sample from Hetero Drugs Pvt.Ltd (Hyderabad). Cross carmellose sodium, magnesium stearate, talc, MCC, sodium saccharin and lactose were obtained from SD Fine Chemicals. All the other ingredients used were of analytical grade.

Estimation of Naproxen Sodium

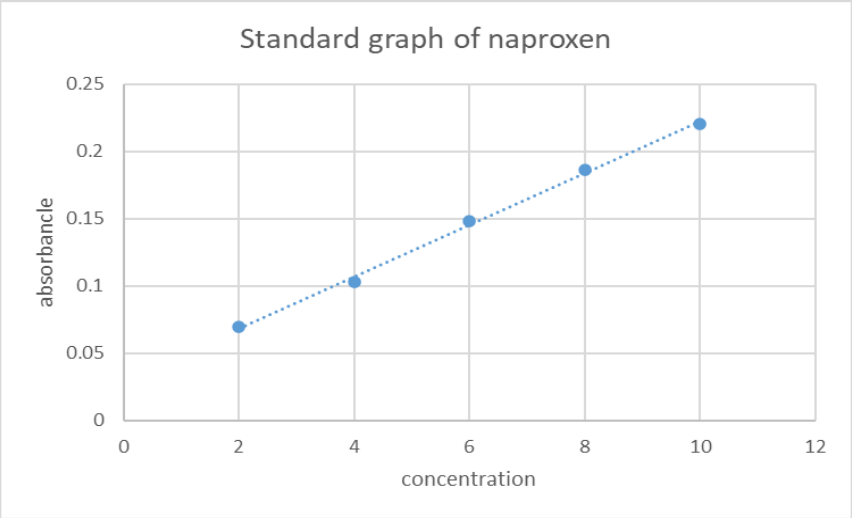
Naproxen sodium was estimated by Spectrophotometric method at 273 nm in phosphate buffer of pH 6.8.

Construction of calibration curve

Accurately weighed amount of Naproxen sodium was dissolved in methanol (3-4 ml) to prepare 1 mg/ml solution. 1 ml of this solution is dissolved in 100 ml of buffer and this is used as secondary stock solution. From this solution dilutions were made with pH 6.8 phosphate buffer to prepare a series of standard solutions containing 2,4,6,8, and 10 µg/ml of Naproxen sodium. The solutions were analysed in the region 200-400 nm using UV spectrophotometer (LAB INDIA UV) and the absorbance was measured at 273 nm using phosphate buffer (pH 6.8) as blank. The calibration curve of Naproxen sodium was plotted as shown in the Graph 1.

Table 1: Calibration table.

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.07
3	4	0.103
4	6	0.148
5	8	0.186
6	10	0.22



Graph 1: Calibration curve of the drug (µg/ml).

Formulation of orodispersible tablets

Naproxen ODT's were prepared by direct compression method using superdisintegrant cross carmellose sodium at concentrations of 5%,10%,15%,20% and 25%. Naproxen sodium, cross carmellose sodium, lactose, MCC, sodium saccharin, were passed through 60 mesh sieve. Talc and magnesium stearate were sieved separately through 40 mesh sieve. A weighed quantity of each ingredients were taken in a mortar and pestle and the resulting powder blend was uniformly mixed and compressed into 500mg tablets using 8 mm round flat punches on single station rotary tablet machine. The composition of each formulation of naproxen sodium orodispersible tablets is given in table 2.

Table2. Formulation table of naproxen sodium orodispersible tablets.

Ingredients (mg)	F1	F2	F3	F4	F5
Naproxen Sodium	100	100	100	100	100
Microcrystalline cellulose	184	186	184	182	179
Cross carmellose sodium	5	10	15	20	25
Lactose	184	186	184	181	179
Sodium saccharin	10	10	10	10	10
Talc	2	2	2	2	2
Magnesium stearate	5	5	5	5	5
TOTAL	500	500	500	500	500

EVALUATION OF TABLETS

Precompression evaluation of powder blend

The powder mix was evaluated for various flow properties such as angle of repose, bulk density, tapped density, carr's compressibility index.

Angle of repose

The angle of repose was determined by fixed funnel method. Accurately weighed powder blend was taken in a funnel which is adjusted at a height such that the tip of funnel touches the apex of the heap of powder. The blend is allowed to flow freely through

the funnel and the diameter and height of the powder heap is measured and the angle of repose was calculated using the following formula:

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

where θ is the angle of repose, h is the height and r is the radius of the powder heap.

Bulk density

Bulk density was measured by taking the powder blend into a graduated cylinder and noting down the initial volume of the cylinder as bulk volume (V_b) and mass(m) of the powder the taken. The bulk density is calculated using formula:

Bulk density = Mass of powder(m)/ bulk volume of the powder (V_b)

Tapped density

Tapped density is measured by taking a weighed mass of powder in a 25ml graduated cylinder and noting down the initial volume of the cylinder. The cylinder is then mechanically tapped 50 times. The volume of powder occupied after tappings (V_t) is noted and the tapped density is calculated as follows

Tapped density = mass of the powder(m)/tapped volume of the powder (V_t)

Carr's Compressibility index

Carr's compressibility index determines the flow property characteristics of the powders and can be calculated by the following.

$$\text{Carr's index (\%)} = e_t - e_b / e_t \times 100$$

Where e_t is the tapped density and e_b is the bulk density of the powder.

Post compression evaluation of tablets

Weight Variation.

The weight variation test is carried out by randomly taking the weight of 20 tablets individually. The average weight was calculated and comparing the individual weights with the average weight. The percentage weight variation was calculated using the below formula and then compared with pharmacopeial specifications.

Hardness

Hardness of a tablet is the force required to break it. The hardness of the prepared tablets was measured using Monsanto hardness tester in terms of kg/cm$^{2.}$.The tablet is placed in between the jaws of the tester and rotated at constant force until the tablet is broken. At this point, the reading on the tester are noted. The hardness limits for tablets should be within range of 4-6 kg/cm$^{2.}$.

Thickness

Thickness of the prepared tablets was measured using vernier calipers. Thickness of tablets is expressed in mm.5 tablets from each formulation were used and their average values were taken. The limits for thickness deviation for each tablet is 5% **[11].**

Friability

Friability is the measure of tablet ability to withstand shock and abrasion.

Friability of the tablets was determined using Roche Friabilator. Test was carried out by placing 10 preweighed tablets in the apparatus that is operated for 100 revolutions for 4min (25rpm/ min) and then subjecting them for wear and tear. The tablets are then dusted and reweighed and the percentage weight loss (friability) was calculated using the formula.

$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight} \times 100}{\text{initial weight}}$$

Friability below 1% is considered as acceptable [**12**].

Drug content

One tablet from each formulation was crushed in a mortar and pestle. 5 mg of naproxen tablet crushed powder was taken and dissolved in 20ml of ethanol. The solution was then filtered and 0.1 ml of filterate was taken and diluted to 10 ml in a standard flask. The absorbance of the resulting solution was measured spectrophotometrically at 273nm in UV visible spectrophotometer (UV LAB INDIA). The drug content was measured using the standard calibration curve and the average percentage drug content was calculated using the formula.

$$\text{Drug content} = \frac{\text{concentration} \times \text{dilution factor}}{1000}$$ **[13].**

Wetting time and absorption time

One tablet from each formulation whose weight is already taken is placed on the piece of a tissue paper that is folded twice and place in a petridish containing 6ml of water. And the time taken for complete wetting of the tablet is noted down as the wetting time. The wetted tablet is then weighed and the water absorption ratio R is determined using the following equation

$$R = W_a - W_b / W_b \times 100 \quad [14]$$

Where W_b and W_a are the weights of tablets before and after water absorption, respectively.

In vitro disintegration

The disintegration is a process of breakdown or converting the tablet into pieces or smaller particles. In vitro disintegration test was carried out using USP disintegration apparatus. Six tablets from each formulation were placed individually in each tube of disintegration apparatus containing 900ml water at 37±0.5°C. Time taken for complete disintegration of the entire tablet is recorded and their average is taken. Time taken for the disintegration of orodispersible tablets is in seconds.

In vitro dissolution studies

In vitro dissolution of the odts is carried out USP type 2 dissolution apparatus (paddle type) operated at 100rpm containing 900ml of phosphate buffer (pH 6.8) and maintained at 37±0.5°C as dissolution medium. One tablet from each formulation is placed in the beaker with the medium and a samples of 5ml were withdrawn from each beaker at regular intervals of 5 min for 30min (samples of 5ml were taken after 5,10,15,20,25, and 30min). and the same volume is replaced with fresh medium. The drug content was determined by suitably diluting the sample with buffer and measuring the absorbance of the sample spectrophotometrically at 273nm.the concentration was calculated from the standard calibration graph of the naproxen drug. Finally, the amount of the drug release is calculated from which the percentage drug release can be calculated using the formulas below

$$\text{Amount of drug release} = \frac{\text{concentration} \times \text{dilution factor} \times 900}{1000}$$

$$\%\ \text{drug release} = \frac{\text{amount of drug release} \times 100}{\text{Label claim}} \quad [15]$$

FTIR drug excipient interaction Studies

IR studies identifies the functional groups and can also be used to determine the incompatibilities between the drug and excipients. FTIR studies for the pure drug and various excipients as well as the optimized formulation blend were carried out using FTIR (BRUKER ALPHA MODEL,) to detect any possible drug-excipient interactions which can be identified in by the change in the position or disappearance of any characteristic peak of the compound.

RESULTS AND DISCUSSION

Pre compression evaluation

All the precompression parameters of powder blend such as bulk density, tapped density. Angle of repose and carr's index is presented below table 3.

Angle of repose

Angle of repose indicates the flowability of the powder blend. Good flowing powders have low angle of repose values while the poor ones have higher values. All the formulation blends showed good to acceptable flow properties with the angle of repose values ranging from $23.45^0 - 30^0$. The results are tabulated below in table 3.

The **bulk density** of the precompression blend was found to be within a range of 0.49- 0.534

The **tapped density** of all the formulation blends was within the range 0.61-0.70

Carr's index

Carr's index values were found within a range 13.05-28.34 revealing that all the formulations were of good to acceptable flowability.

Table 3 – Precompression parameters of powder blend.

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose (degrees)	Carr's Index (%)
F1	0.537	0.705	30.05	23.29
F2	0.533	0.613	28.23	13.05
F3	0.542	0.624	27.14	13.14
F4	0.498	0.695	33.32	28.34
F5	0.514	0.675	23.45	23.85

Post compression parameters

The results of the post compression parameters such as hardness, weight variation friability, thickness, drug content uniformity are given in below table 3.

The other parameters like disintegration time. Dissolution time wetting time and absorption ratio are given in the table 4 below.

Weight variation

Weight of all the tablets were found to be uniform and within the prescribed USP limits. The average weight of each tablet was found to be in the range of 488 to 493 mg.

Hardness

Hardness of all tablet formulations was found to be within the acceptable range. The hardness values were found to vary from 3.53-4.21kg/cm^2. The hardness results of the tablets prepared were as in the below table 4.

Friability

The percentage friability of all the formulations was observed between 0.4-0.8% indicating that the tablets are of good mechanical characteristics. The results are given in the table 4.

Table 4 – Post compression parameters of Naproxen Orodispersible tablets.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	2.43	3.53	0.809
F2	2.32	4.03	0.408
F3	2.40	4.13	0.604
F4	2.23	4.18	0.641
F5	2.26	4.21	0.623

Wetting time and Water absorption ratio

The wetting time and the water absorption ratio are considered as important parameter for understanding the ability of the disintegrant to swell and absorb in presence of small amount of water. The wetting time of all the formulation was found to be within 22 sec- 36sec.The decrease in the wetting and dispersion time in all the formulations is because of the increasing concentration of the super disintegrant that absorbs water and swells resulting in rupture of tablets.[21] The results are given in the below table 5.

In vitro disintegration time

Disintegration time is very important for the orodispersible tablets which need to be less than the one minute. It was evident from the results that the disintegration time was inversely proportional to the concentration of the super disintegrant ccs as it decreased from 59 sec for F1 with 5% of ccs to 39 sec for F5 containing 25% of it. The disintegration time of the optimized formulation was found to be within the limits that is 39 sec. The results are given in the below table 5.

Table 5 - Post compression parameters of Naproxen Orodispersible tablets.

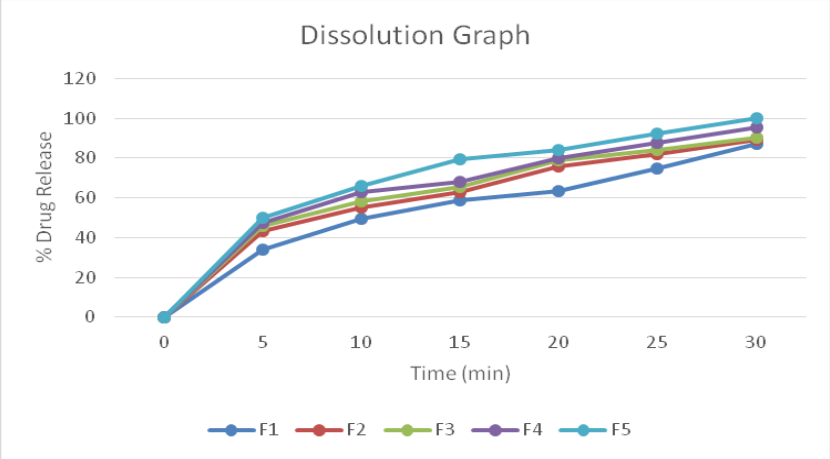
Formulation code	Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio	Drug content (%)
F1	59	32	58.60	92.89
F2	54	30	63.23	93.45
F3	48	27	69.60	96.83
F4	43	24	58.13	98.22
F5	39	22	72.27	99.95

In vitro dissolution studies

The drug release results obtained from the invitro dissolution studies is represented in the graph. In vitro drug release studies were carried out using ELECTROLAB dissolution apparatus USP type-2 paddle method at temperature 37±1°C, taking 900 ml of phosphate buffer (pH 6.8) as dissolution medium. The speed of the paddle rotation was set at 100 rpm. For every 5min 5 ml of the sample from each formulation was taken and analyzed spectrophotometrically at 273nm for 30 min. Optimized formulation F5 showed best percentage drug release of 99.9% in 30 min. The dissolution results are presented in the graph and table 6.

Table 6 - Dissolution profiles of the formulations.

Time (min)	% Drug Release				
Formulation code	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	33.8	43.1	45.7	47.5	49.9
10	49.7	54.9	58.3	62.7	65.8
15	58.9	62.7	65.7	68.2	79.2
20	63.2	75.8	78.9	79.8	83.9
25	74.8	82.1	84.2	87.6	92.3
30	87.3	89.2	90.1	95.2	99.9



Graph 2 : Comparative graph showing dissolution profiles.

FTIR drug excipient interaction studies

IR studies identifies the functional groups and can also be used to determine the incompatibilities between the drug and excipients. The pure drug, the optimized formulation and all the excipients used in the preparation of ODTs were analyzed in FTIR (Bruker model alpha).

The drug sample showed characteristic functional group peaks at 1213.28 cm−1 that are corresponded to C–O stretching (acid), 1604.44 cm−1 due to COO– stretching, 1641.31 cm−1 due to C–C aromatic stretching a, and at 2898.45 cm−1 due to C–H aliphatic stretch.IR characteristics mentioned for sample drug were found to be in compliance with that reported for pure naproxen sodium.[16]

Lactose showed characteristic functional group peaks at 3460.12 -3696.13 cm^{-1} due to stretching vibrations of C-O-H bonds of lactose alcohol. Two sharp bands were found at 3045-2958.84cm^{-1} due to C-H stretching vibrations. [17]

Talc showed characteristic vibrations of hydroxyl groups linked to Si (Si-OH) and Mg (Mg-OH) at 3441 and 3671.54cm^{-1}. Then bands with intense peaks at 1040cm^{-1} are contributed by the siloxane group (Si-O-Si) stretching vibrations while bands found at 669.16$cm^{-1}$are due to Si-O Mg bond.[18]

Magnesium stearate shows characteristic twin peaks at 1540.22 and 1463.55 cm^{-1} that are attributed by asymmetric carboxylate (COO^-)stretching vibration and symmetric vibrations of carboxylate group respectively. The peaks at 2916.03 and 2840.34 cm^{-1} are due to the C-H stretching vibrations.[19]

The FTIR spectrum of mcc shows characteristic band of O-H stretching vibrations of hydroxyl group at 3566.42cm^{-1}.C=O bands of aldehyde were found at 1771.27cm^{-1}. Peaks at 1507.62$cm^{-1}$are associated with CH_2 bending vibrations. C-O stretching vibrations at 1362.80 were associated with the CH_2 – OH group. C-O-C bands were found at 1051.22cm^{-1}.[20]

Sodium saccharin showed characteristic peaks at 1647.40cm^{-1} due to c=o bonds.C-C bond stretching vibrations were found at 1558.40cm^{-1}. Peaks found at 1251.48 cm^{-1}, and 1145.93cm^{-1} were attributed to SO_2-N- stretching vibrations. Carbonyl C=O bending vibrations were found at 971.14and 746.09cm^{-1}.

All the characteristic peaks of the naproxen C-O, C-H, C=O, C-C were found in their original range in the optimized formulation indicating that there was no interaction between the naproxen and other excipients.

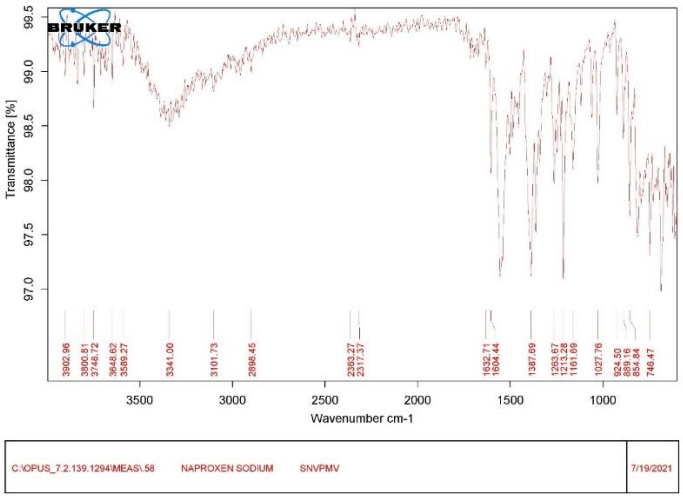


Figure 1: FTIR of Naproxen Sodium.

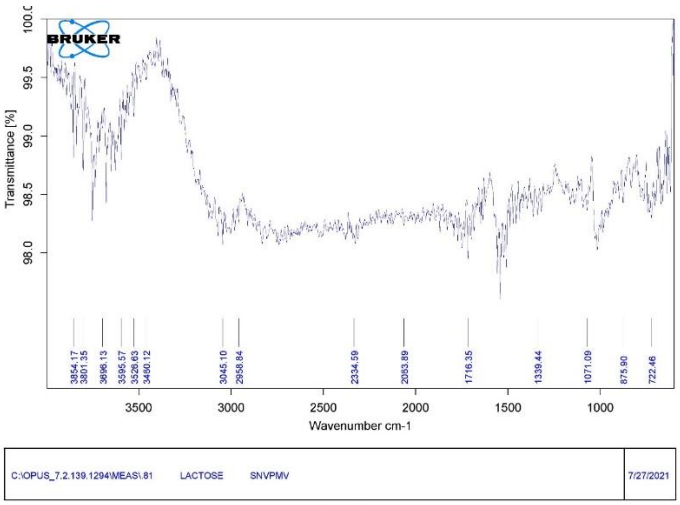


Figure 2: FTIR of lactose.

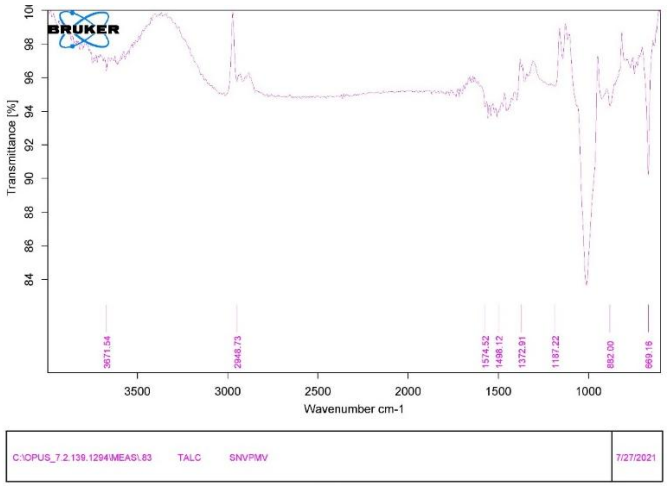


Figure 3: FTIR of talc.

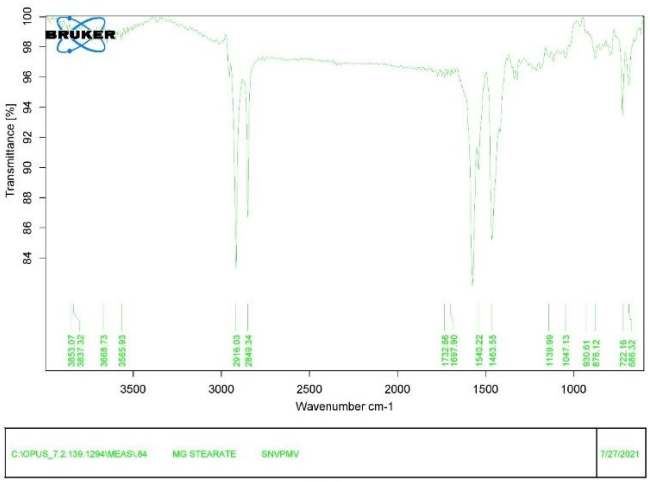


Figure 4: FTIR of Magnesium stearate.

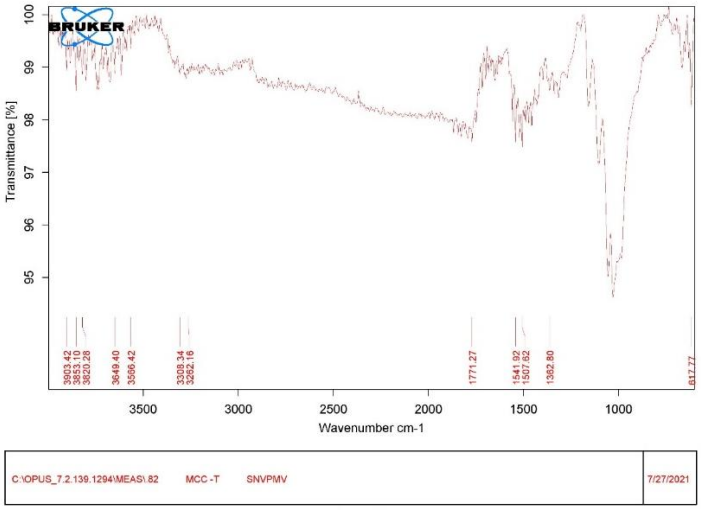


Figure 5: FTIR of MCC.

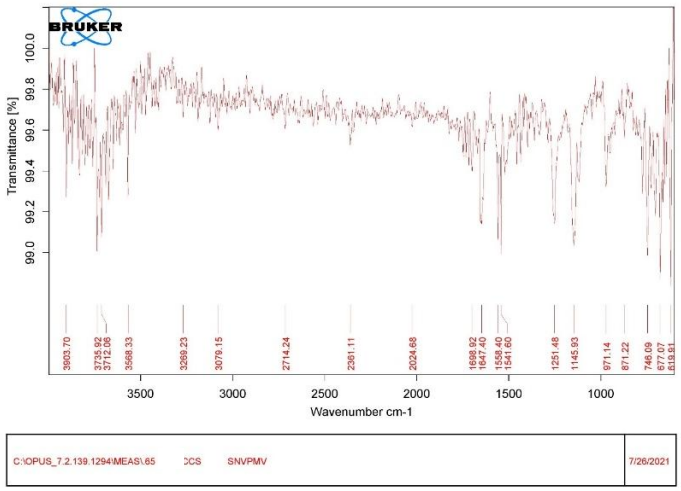


Figure 6: FTIR of Sodium saccharin.

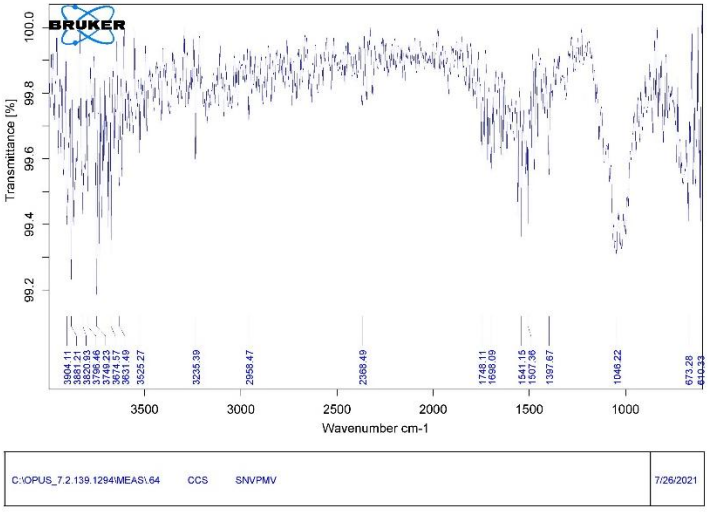


Figure 7: FTIR of Cross carmellose sodium.

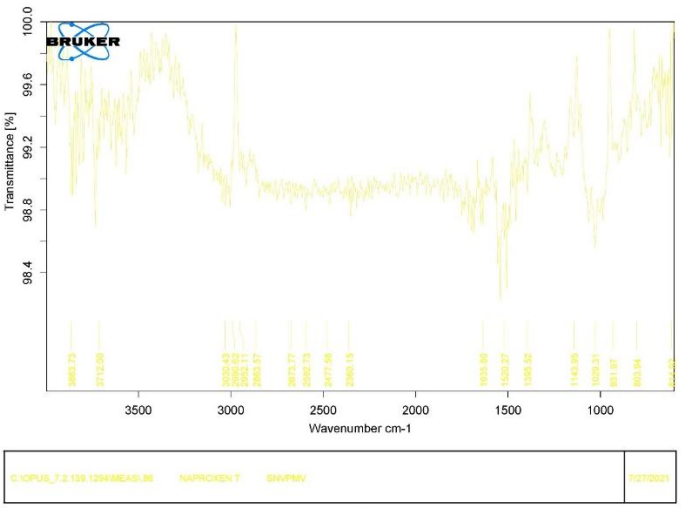


Figure 8: FTIR of Optimised formulation.

CONCLUSION

The oral dispersible tablets of naproxen sodium were successfully prepared by the direct compression method. The tablets prepared were evaluated for FTIR studies, various precompression parameters, post compression like weight variation, hardness, friability, thickness, drug content, wetting time, disintegration and in vitro dissolution and the results were found to be within limits. After observing all the results of evaluated parameters, Formulation F5 with 25% of CCS was found to be optimised formulation with the results that almost satisfies all the acceptance criteria required as ODTS. From the above study we can conclude that the formulation F5 can be developed as Naproxen sodium ODTs for better patient compliance than the conventional dosage forms available commercially in the market. ODTS are very much suitable for children having no primary teeth and for geriatric patients who have lost their teeth permanently. Thus,With the continued development of new pharmaceutical excipients, in near future it is expected that this delivery system will get much importance as that of conventional delivery.

ABBREVIATIONS

ODT	- Oro Dispersible Tablets
CCS	- Cross Carmellose Sodium
MCC	- Micro crystalline cellulose
UV	- Ultra Violet
FTIR	- Fourier Transform Infrared Spectroscopy
USP	- United states Pharmacopoeia
NSAIDs	- Non- Steroidal Anti- Inflammatory Drugs

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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