International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 14, Issue 2, 2022

Original Article

FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF NAPROXEN SODIUM

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Received: 04 Nov 2021, Revised and Accepted: 10 Jan 2022

ABSTRACT

Objective: The aim of this investigation was to prepare ODFs containing Naproxen Sodium, an NSAID, using solvent casting method and to evaluate them to put together a dosage form which can be taken without water, is easy to administer, has a rapid onset of action and can surmount first pass metabolism. Six distinct formulations of naproxen sodium ODF (F1-F6) were created in this investigation by varying the quantity of croscarmellose sodium, a super disintegrant.

Methods: Naproxen Sodium ODF's were prepared by solvent casting method. Evaluation of prepared ODF's was done by considering various parameters such as film thickness, folding endurance, disintegration time, surface pH, weight variation, *in vitro* dissolution test, content uniformity and FTIR.

Results: F6 has shown to be the best fast release formulation in terms of disintegration time (less than 1 minute) and dissolution (103.5 % after 30 min). Formulation F6's other film characteristics, such as weight variation, thickness, pH, and folding endurance, were all within the USP limit.

Conclusion: By virtue of quick disintegration self-administration without water or chewing, oral fast dissolving film (OFDF) is one such new technique to enhance consumer acceptance. The film is an excellent intraoral fast-dissolving medication delivery method by which a wide range of medicines, including neuroleptics, cardiovascular drugs, analgesics, anti-asthmatic, antihistamines and drugs for erectile dysfunction, can be manufactured. From the standpoint of the patient, oromucosal medication delivery is appealing since it allows for easy administration without the need to swallow, as well as better patient safety. As a novel delivery mechanism, the notion of a quick-dissolving dosage form has gained popularity. By lowering dose frequency, this method will deliver optimum therapeutic efficacy, improved bioavailability, and maximum stability. This will also surmount first-pass metabolism of drugs. This method allows for faster medication absorption from the pre-gastric region, perhaps resulting in a faster onset of action.

Keywords: ODF, Patient compliance, Naproxen sodium, Super disintegrant, Surmount first pass

DOI: https://dx.doi.org/10.22159/ijcpr.2022v14i2.1953 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Drug delivery methods alter the profile of a drug's release, absorption, distribution, and elimination in order to improve product efficacy, safety, and patient comfort and compliance. Because of its versatility, the convenience of use, and painlessness, as well as patient compliance, the oral route of administration is regarded the most frequent route for systemic medication effects [1, 2]. In terms of flexibility, fast dissolving films are the most advanced solid dosage form. Orally dissolving films (ODFs) are a type of oral drug delivery system that was developed based on transdermal patch technology [3]. Orodispersible film (ODF) has recently received increased interest because of its particular advantages for target populations such as toddlers and the elderly who have trouble swallowing [4].

These films might include soluble, insoluble, or taste-masked pharmacological compounds. Aqueous polymer matrices with a wide molecular weight range are commonly used in the film's formation, aiding in the achievement of specific physical properties. Selecting appropriate polymer types to fulfill specific API loading demands and rate of dissolution might result in tailor-made properties [5]. Polymer that dissolves in water, medicine, plasticizer, surfactant, sweetener, colors, flavors and saliva stimulating agents are some of the common ingredients in ODF's. The polymer is a key component of the oral film; it serves as the backbone that retains and regulates the drug's release. The use of super disintegrants is the most common method for producing fast dissolving films [6]. pH modifiers have been suggested as a viable method for enhancing the dissolution and bioavailability of medicines with pH-dependent solubility. A pH modulator might change the drug particles' microenvironmental pH to one that facilitates drug breakdown [7].

A very thin oral strip is put on the patient's tongue or any other oral mucosal tissue as part of the delivery system. The strip is instantaneously moistened by saliva, and the film quickly hydrates, disintegrates and dissolves to release the medicine for oromucosalabsorption [8]. As a result, the oral mucosa is an appealing location for drug administration [9].

These dosage forms are useful in patients who have an active lifestyle, such as pediatrics [10], geriatrics, bedridden, emetic patients, diarrhea, acute allergy reactions, or coughing. Oral disintegrating dosage forms provide an extra benefit in the treatment of individuals with mental illnesses. FDOFs are also beneficial when a local anesthetic, such as for toothaches, mouth ulcers, cold sores, or teething, is required. For the systemic distribution of active pharmaceutical ingredients (APIs) for over-the-counter (OTC) medicines, ODF's are given intraorally.

Advantages

ODFs have numerous advantages, including the convenience of use for pediatricians [10] and the fact that they do not require water for ingestion-a useful feature for patients who travel. They have a pleasant tongue feel, which helps to modify people's perceptions of the drug as bitter, especially in children. As saliva travels down into the stomach, certain medicines may be absorbed from the mouth, throat, and esophagus, increasing drug bioavailability. These vanquish the hepatic first-pass metabolism [11], resulting in increased bioavailability and a decrease in dosage. The risk of suffocating or choking while using traditional solid formulations is eliminated, resulting in increased safety. When a quick start of action is necessary, ODFs come in handy. Because the medication is in a solid-state until it is ingested, ODFs maintain their stability for longer periods of time. As a result, ODFs combine the benefits of solid dosage forms in terms of stability and

liquid dosage forms in terms of bioavailability to produce a desired and optimized drug delivery system.

Disadvantages

They have certain disadvantages, such as being difficult to handle due to their fragility [11]. Drugs that are unstable at the pH of the buccal cavity cannot be given. This method cannot be used to deliver drugs that irritate the mucosa. Only drugs with a low dosage need can be given. OFDF's are delicate and must be protected from water, thus they require specific packaging which is usually expensive. Dose homogeneity is a difficult technological problem to solve.

Analgesic and antipyretic effects are seen in naproxen. Its sodium derivative is an odourless crystalline powder that is rapidly and completely absorbed from the gastrointestinal system, with 95% *in vivo* bioavailability and is extensively converted to 6-o-desmethyl naproxen [12].

The goal of this study is to develop a naproxen sodium oral fast dissolving film with improved bioavailability and NSAID properties. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that is derived from naphthylpropionic acid. It has been proven to be helpful in both experimental and clinical rheumatoid arthritis pain.

MATERIALS AND METHODS

Materials

Naproxen sodium was received from Hetero Pharmaceuticals Ltd. Other excipients such as HPMC, sodium saccharin, propylene glycol, croscarmillose sodium, methanol were bought from SD Fine Chemicals Ltd., Mumbai, India.

Formulation development of fast dissolving films

Preliminary trials for component screening

The selection of polymer type and concentration is crucial in the development of a successful rapid dissolving film; many polymers were tested for their film forming properties. In this research, HPMC was employed as a film former. Blank films were prepared and evaluated for thickness, surface appearance, stickiness and film clarity.

Preparation of fast-dissolving oral films containing API

The polymeric solution (Solution A) was made by dissolving the required amount of HPMC in distilled water (70%). With constant stirring maintained by a magnetic stirrer, a certain amount of drug (Naproxen sodium) which was dissolved in 4 ml of methanol, polyethylene glycol, and other excipients were dissolved in the remaining water (30%)(Solution B) [13]. With constant stirring, solution B was progressively added to polymeric solution A. For defoaming, the final solution was set aside for 30 min. After defoaming, the solution was put into a petri plate and dried in a hot air oven at 50 °C for 25-30 min. The film was gently peeled off the petri plate and cut into sections of the proper shape and size. The disintegration time, folding endurance, drug release, etc., of several optimal combinations of film containing HPMC and CCS were investigated as shown in tables 1 and 2.

Table 1: Composition of different formulations

Formulation code	Drug (mg)-naproxen sodium	HPMC (mg)	Sodium saccharin (mg)	Propylene glycol (ml)	Cross–carmellose sodium (mg)	Methanol (ml)	Water (ml)
F1	100	300	10	0.1	5	3	10
F2	100	300	10	0.1	10	3	10
F3	100	300	10	0.1	15	3	10
F4	100	300	10	0.1	20	3	10
F5	100	300	10	0.1	25	3	10
F6	100	300	10	0.1	30	3	10

Evaluation of prepared naproxen sodium loaded ODF

Drug excipient interaction study using FTIR [14, 15]

The experimental formulations were undergone compatibility studies by using FTIR. IR investigations may be performed to identify functional groups as well as establish incompatibilities between the pharmaceutical drug and excipients. Infrared spectroscopy was utilised to examine the pure drug, the optimised formulation, and all of the excipients used in the production of ODFs' (Bruker model alpha).

Weight variation [16]

Each film formulation yielded three 2 × 2 cm2 films, which were cut at random. On an electronic scale, each film was weighed separately, and the mean weight for each batch was determined.

Thickness [17]

The thickness of each oral film was measured using a screw gauge in five distinct locations. Each oral film formulation's average thickness and standard deviation were calculated.

Stickiness [18]

Films were taken and pressed against the finger tips and the results were recorded.

Folding endurance [19]

Folding a film with a consistent cross sectional area and thickness until it breaks was used to determine it. The folding endurance value is the number of times the film could be folded without breaking. This test guarantees the film's tensile strength.

Disintegration time [19]

The disintegration time was determined by putting the film strip (2 x 2 cm2) in a 6 cm diameter Petri dish containing 6 ml of pH 6.8 phosphate buffer. The time it took for the film to completely disintegrate was recorded. All measurements were made three times and the average values were recorded.

***In vitro* dissolution test [19]**

The graph depicts the drug release findings derived from *in vitro* dissolution tests. *In vitro* drug release experiments were conducted utilising an Electrolab Dissolution Apparatus (paddle technique) at 37±1 °C taking 900 ml of phosphate buffer as the dissolving medium. The paddle rotation speed was set at 100 rpm. 5 ml dissolving medium was removed from the dissolution device at intervals of 5, 10, 15, 20, 25 and 30 min and replaced with new media. A UV spectrophotometer set at 273 nm was used to measure the absorbance of the withdrawn liquids and the % drug release was calculated.

Drug content [20]

Random sampling of all batches was used to determine drug content. In the phosphate buffer, the ODF (2 x 2 cm^2) was dissolved (50 ml). The solution was filtered before being analyzed in the UV spectrophotometer. The drug content was calculated as the average of three measurements.

Surface pH [19, 20]

The film was assessed on a Petri plate for this test. It was then wet with 0.5 ml phosphate buffer and maintained for 30 seconds. After bringing the electrode of the pH metre in touch with the surface of

the formulation and allowing 1 minute for equilibration, the pH was recorded. For each formulation, the average of three determinations was taken.

RESULTS AND DISCUSSION

Physical properties

Weight variation, thickness, film clarity, surface appearance, stickiness and folding endurance were measured according to the USP/IP guidelines and tabulated in table 2. All the weights of films were found to be fall within the range. Thickness is one of the property of films which ascertains the uniformity of film. An ideal film should have a thickness range between 0.05 mm-0.1 mm. All the films prepared were found to fell within the limit. Film clarity gives an idea about any impurity present in the film. The prepared films are clear from impurities. Folding endurance explains about the mechanical strength and flexibility of the films. A good film with folding endurance greater than 300, indicates it is tough, flexible and non-brittle films. But the prepared films were flexible with folding endurance of less than 300. The surface pH of the prepared films was maintained between the ranges of 6-7, which were appropriate in accordance with the observed standards.

Table 2: Physical properties of fast dissolving films

Formulation	Wt. variation (mg)	Thickness (mm)	Film clarity	Surface appearance	Stickiness	Folding endurance
F1	95	0.1	Clear	Smooth	Non-Sticky	150+8
F2	98	0.1	Clear	Smooth	Non-Sticky	150+8
F3	102	0.1	Clear	Smooth	Non-Sticky	150+8
F4	105	0.1	Clear	Smooth	Non-Sticky	150+8
F5	107.3	0.1	Clear	Smooth	Non-Sticky	150+8
F6	112	0.1	Clear	Smooth	Non-Sticky	150+8

Table 3: Disintegration time of prepared naproxen sodium fast dissolving films

Formulation	Disintegration time (sec)
F1	53
F2	50
F3	52
F4	48
F5	45
F6	40

Disintegration time

The average disintegration time taken by a 2 x 2 cm^2naproxen sodium fast dissolving films was less than 60 seconds as shown in table 3. It is observed that addition of plasticizers (propylene glycol) has decreased the disintegration time.

In vitro dissolution studies

The drug release results obtained from the *in vitro* dissolution studies is represented in the graph fig.1. The study showed drug release of 99.5% from the F6 optimized formulation within the time period of 30 min as it consists of 3% of CCS. On the other hand, F4 and F5 formulations also showed a fair drug release of 96% and 98.9% in 30 min respectively. The dissolution profile showed immediate release of drug from the biological fluids of the body indicating immediate relief to the patient.

Drug content

Drug content studies is performed to determine the amount of active drug present in 2x2 cm^2 film. The test results are mentioned in table 4.

UV Absorbance studies

The absorbance of naproxen sodium at various concentrations of (1-10µg/ml) was determined by using a UV Spectrophotometer (Lab India). A standard calibration curve was drawn based on the obtained data as shown in fig. 2.

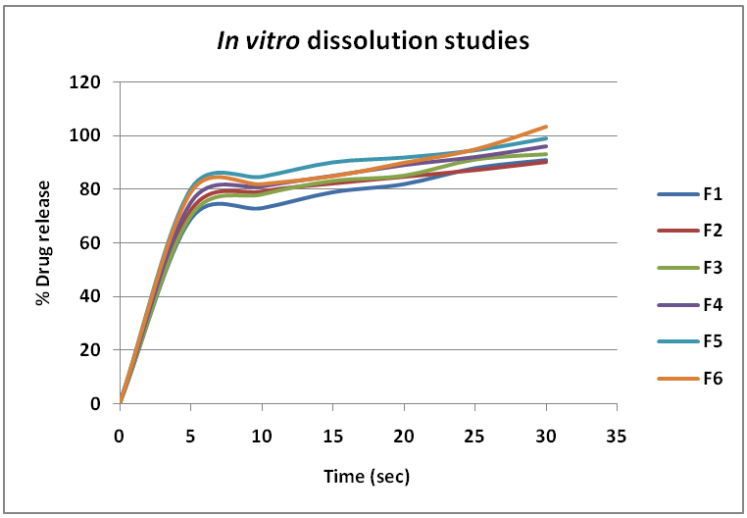

Fig. 1: *In vitro* dissolution studies of naproxen sodium ODF

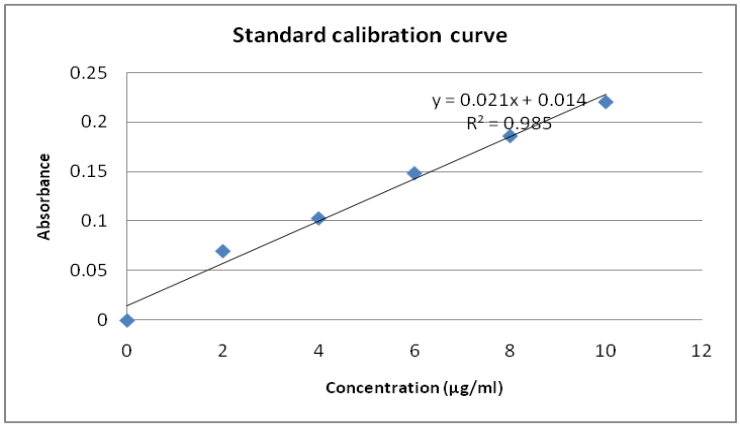

Fig. 2: Standard calibration curve of naproxen sodium

Table 4: Drug content % in the prepared films

Formulation	Drug Content (%)
F1	93
F2	95.5
F3	96.3
F4	97.1
F5	98.7
F6	99.2

FTIR studies

The FT-IR spectra of pure medication Naproxen, polymers, and their physical combinations were collected between 400 and 4000 cm^{-1} to assess compatibility. FTIR spectrum of HPMC shown in the fig. 3. The characteristic peaks were observed at 3566.66, 2903.12, 1456.76 and 1058.92 cm^{-1}, revealing the presence of OH group stretching, C-H group, vibration of OH and C-O group stretching respectively. FTIR spectrum of croscarmellose sodium shown in the fig. 4, the characteristic peaks were observed at 3674.57, 2958.47 and 1748.11 cm^{-1}, revealing the presence of OH stretching, C-H group, C-O group stretching respectively. FTIR spectrum of sodium saccharin shown in fig. 6, the characteristic peaks were observed such as C=O absorption at 1647.40 cm^{-1}, C-C benzene ring stretching at 1558.40 cm^{-1},-SO_2-N stretching at 1251.48 and 1145.93 cm^{-1}, carbonyl bending were appeared at 971.14 and 746.09 cm^{-1}. The FTIR spectrum of propylene glycol (fig. 5) shows C-H stretching at 1376.21, OH stretching at 3700-3100 cm^{-1}, broad band between 1100 and 900 cm^{-1}comes from the stretching vibrations of C-O in C-O-H bonds. The FTIR spectrum of Naproxen Sodium (fig. 7) showed characteristic peaks at 1263.67 cm-1 due to C-O stretching, 1604.44 cm^{-1} due to COO-stretching, C-C aromatic stretching at 1632.71 $cm^{-1}$and C-H aliphatic stretch at 2898.45 cm^{-1}. In the improved formulation, all of the naproxen's distinctive peaks (C-O, C-H, C=O, C-C) were detected in their original range, suggesting that there was no interaction between the naproxen and other excipients. The FTIR showed that the drug was well incorporated into the polymer and there was no incompatibility between the drug and polymer.

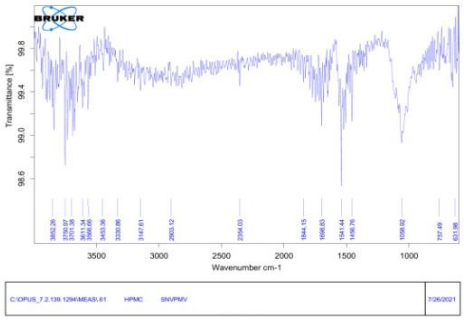

Fig. 3: FTIR of HPMC

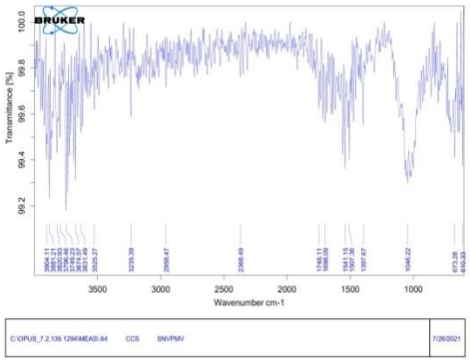

Fig. 4: FTIR of croscarmellose sodium

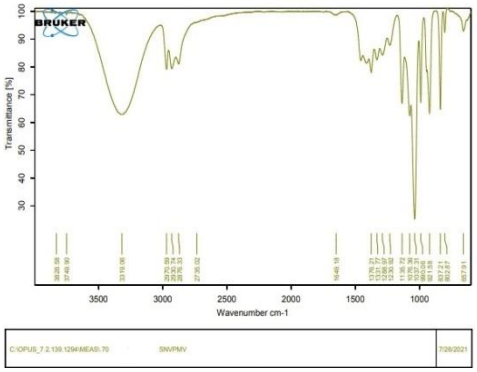

Fig. 5: FTIR of propylene glycol

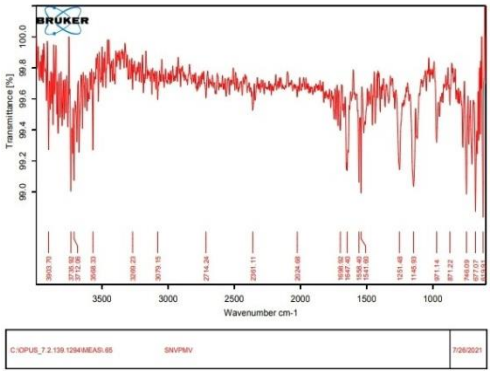

Fig. 6: FTIR of saccharin sodium

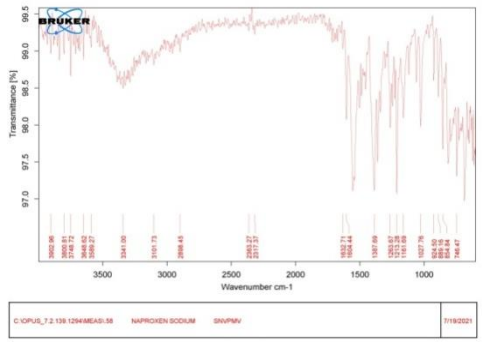

Fig. 7: FTIR of naproxen sodium

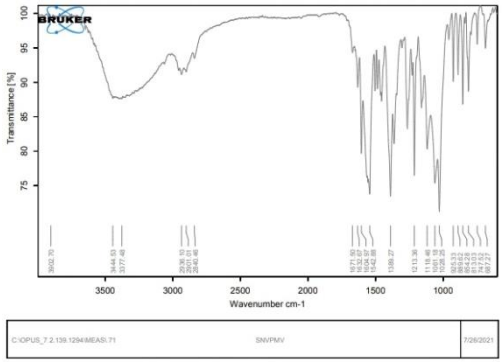

Fig. 8: FTIR of naproxen sodium ODF

CONCLUSION

Using a super disintegrant at various concentrations, this work revealed the effective production and assessment of naproxen sodium ODFs. Formulation F6 was the best of the formulations, with 3 % w/w CCS as a super disintegrant. The FTIR and Electro lab dissolution apparatus were used to conduct a compatibility investigation and an *in vitro* dissolution research. In terms of disintegration time and dissolution, F6 has shown to be the finest quick release formulation with disintegration time less than 1 minute and dissolution-103.5 percent after 30 min. Other film properties of Formulation F6, including weight variation, thickness, pH, and folding endurance, were also within the USP limit. As a result, the improved formulation F6 was shown to be more resilient and stable, as well as having a better immediate release characteristic and better bioavailability.

ACKNOWLEDGEMENT

We are thankful to Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, India for providing necessary facilities for the research work.

DATA AVAILABILITY

Not declared

FUNDING

Not declared

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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