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Formulation and evaluation of oral dissolving films of naproxen sodium from *Terminalia randii* gum

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ABSTRACT

Background: Oral films are gaining popularity and acceptance as new drug delivery systems, because of ease of administration and better patient compliance. However, most raw materials used in developing countries are imported and expensive. Therefore, there is need to develop local and naturally occurring raw materials as excipients.

Objective: This study evaluated the properties of naproxen sodium films prepared from a natural biodegradable polymer and the effect of formulation variables on the film properties.

Method: Naproxen films were produced by solvent casting method using hydroxypropyl methylcellulose and *Terminalia randii* gum as individual polymer and different combination ratios (1:1, 1:2 and 3:0). Ofada and corn starches were used as disintegrants and glycerol as plasticizer. The films were assessed for thickness, weight uniformity, surface pH, drug content, fold endurance and release properties. Compatibility of polymer, drug and excipients was assessed using Fourier Transform Infra-Red.

Results: There was thickness uniformity with surface pH ranging between 5.8 and 6.8. The fold endurance was >300 for all formulations except in absence of plasticizer and presence of *Terminalia* gum. There was significant ($p<0.05$) weight variation of the films. Disintegration time ranking was no starch < corn starch <ofada starch. Films with plasticizer had lower disintegration time. Drug released ranking was 1:1>1:2>3:0. Fourier Transform Infra-Red showed that polymer-drug-excipient were compatible.

Conclusion: *Terminalia randii* gum has potential in naproxen oral disintegrating films formulation when combined with hydroxypropyl methylcellulose in particular ratios.

Key words: Oral disintegrating film, *Terminalia randii* gum, Naproxen, Polymer

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Formulation et évaluation de films dissolvants oraux de naproxène sodique à partir de la gomme *Terminaliarandii*

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RESUME

Contexte: Les films oraux gagnent en popularité et en acceptation en tant que nouveaux systèmes d'administration de médicaments, en raison de la facilité d'administration et d'une meilleure observance des patients. Cependant, la plupart des matières premières utilisées dans les pays en développement sont importées et coûteuses. Par conséquent, il est nécessaire de développer des matières premières locales et naturelles comme excipients.

Objectif: Cette étude a évalué les propriétés des films de naproxène sodique préparés à partir d'un polymère naturel biodégradable et l'effet des variables de formulation sur les propriétés du film.

Méthode: Des films de naproxène ont été produits par une méthode de coulée au solvant utilisant de la méthylcellulosehydroxypropylet de la gomme *Terminaliarandii* comme polymère individuel et différents rapports de combinaison (1:1, 1:2 et 3:0). Des amidons d'Ofada et de maïs ont été utilisés comme désintégrants et le glycérol comme plastifiant. Les films ont été évalués pour l'épaisseur, l'uniformité du poids, le pH de surface, la teneur en médicament, l'endurance au pli et les propriétés de libération. La compatibilité du polymère, du médicament et des excipients a été évaluée à l'aide de l'infrarouge de transformée de Fourier.

Résultats: Il y avait uniformité d'épaisseur avec le pH de surface s'étendant entre 5,8 et 6,8. L'endurance de pli était >300 pour toutes les formulations sauf en l'absence de plastifiant et la présence de gomme *Terminalia*. Il y avait une variation de poids significative ($p<0,05$) des films. Le classement du temps de désintégration était zéro amidon <amidon de maïs <amidon d'ofada. Les films avec plastifiant avaient un temps de désintégration plus court. La transformée de Fourier infrarouge a montré que polymère-médicament-excipient étaient compatibles.

Conclusion: La gomme *Terminaliarandii*guma un potentiel dans la formulation de films de désintégration orale de naproxène lorsqu'elle est combinée avec l'hydroxypropylméthylcellulose dans des rapports particuliers.

Mots-clés: Film de désintégration orale, gomme *Terminaliarandii*, naproxène, polymère

INTRODUCTION

Drug administration through the oral route is the most preferred due to its ease of administration. Different dosage forms such as tablets, films, and liquids can be administered through the oral route. However, oral films are gaining popularity and acceptance as new drug delivery systems due to their ease of administration and patient compliance, rapid disintegration and enhanced bioavailability with rapid onset of action; bypass first pass metabolism and enhanced stability.[1,2] The rich supply of blood to the oral mucosa makes it relatively permeable.[1] Some studies are available on oral films are available in literature.[3-6]

Polymers which are the backbone of films can be used either alone or in combination.[7] Some natural and synthetic polymers that have been used in film formulations are: pullulan, maltodextrin, gelatin and chitosan, Hydroxypropyl methylcellulose, polyvinyl pyrrolidone, carboxymethylcellulose.[2,8-13]

Naproxen is a nonsteroidal anti-inflammatory drug of the propionic acid class used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders. It is a white crystalline powder that is practically odourless and a non-selective COX inhibitor. One of the side effects of naproxen is gastric irritation.

In this study, oral disintegrating film of naproxen was developed using a natural biodegradable polymer (terminalia gum) and hydroxypropyl methylcellulose. The effect of formulation variables on the film properties was evaluated.

METHODS

Materials

The materials used were Naproxen sodium (Letco Medical, USA), corn starch BP, of ada starch obtained from *Oryzia glaberrima* (disintegrants), glycerol (plasticizer) (Letco Medical, USA), sorbitol (sweetener) (Letco Medical, USA), hydroxypropyl methylcellulose (Letco Medical, USA), and terminalia gum obtained from *Terminalia randii(Family* Combretaceae). Terminalia plant was collected from Olabisi Onabanjo University Ago-Iwoye and authenticated by Mr O.S. Shasanya of the Forest Herbarium Ibadan located in the Forest Research Institute of Nigeria, Ibadan with a Voucher number of FHL NO 107917.

Methods

Collection and extraction of *Terminalia* gum

Terminalia gum was obtained from the incised trunk of *Terminalia randii (Family* Combretaceae). The trunk of the tree was incised and the gum exudate was allowed to dry and then hand-picked from the trees. The dried gum was washed and dried in hot air oven at 40^{0}C and then crushed with a pestle and mortar to break up the gum. The gum was hydrated in double strength chloroform water for 5 days while stirring intermittently. The mucilage obtained was strained through a clean calico cloth and the gum obtained was precipitated with 95%v/v ethanol. The precipitated gum was filtered, washed with diethyl-ether and then dried in hot air oven. The dried gum was pulverized and passed through a number 60 mesh sieve (250µm).[14]

Extraction of Ofada starch

Starch was obtained from ofada rice by soaking the grains in distilled water for 24 hours. This was blended and the slurry strained through a calico cloth. The filtrate was allowed to settle and the supernatant decanted at 12 hours interval. The slurry was re-suspended in distilled water and the starch cake collected after 72 hours. The starch was dried in hot air oven at 60^{o}C for 48 hours. The dried starch was pulverised and passed through 250 µm sieve.[15]

Preparation of oral films

Different batches of films were prepared by solvent casting method according to the formula in Table 1. The polymers (hydroxypropyl methylcellulose, *Terminalia* gum) were dispersed in water and allowed to hydrate for about 3 hours. Corn or ofada starches, sorbitol and glycerine were also

Table 1: Formulation of Oral Naproxen Films

Formulation Code	HPMC (mg)	TG (mg)	Glycerol (mg)	Corn starch (mg)	Ofada starch (mg)	Sorbitol (mg)	Naproxen (mg)	Water (mL)
F1	133.33	266.67	80	-	-	-	-	20
F2	200	200	80	-	-	-	-	20
F3	400	-	80	-	-	-	-	20
F4	-	400	80	-	-	-	-	20
F5	133.33	266.67	80	20	-	20	100	20
F6	133.33	266.67	80		20	20	100	20
F7	400	-	80	20	-	20	100	20
F8	400	-	80	-	20	20	100	20
F9	200	200	80	20	-	20	100	20
F10	200	200	80	-	20	20	100	20
F11	133.33	266.67	80	-	-	20	100	20
F12	400	-	80	-	-	20	100	20
F13	200	200	80	-	-	20	100	20
F14	400	-	-	20	-	20	100	20
F15	133.33	266.67	-	20	-	20	100	20
F16	200	200	-	20	-	20	100	20

TG: Terminalia Gum

dispersed in water. The two mixtures were mixed on a magnetic stirrer at a speed of 700 rpm for 5 minutes.

Naproxen sodium was dissolved separately and poured into the mixture and thoroughly mixed for even dispersion of the drug. The mixture was poured into a petri-dish and dried in the oven at 40^{o}C for 24 hours. The film was carefully removed and cut into 2 cm x 2 cm sizes and stored in aluminium foil for further analysis.

Evaluation of naproxen oral films

Determination of film thickness

The thickness of the naproxen oral disintegrating films was measured with a micrometre screw gauge (Anytime tools, CA, USA) at the four corners and centre. Six samples from each batch were determined. [16]

Determination of film weight

Six films of 2 cm x 2cm from each batch were weighed on an analytical balance (Mettler Toledo, USA) and the average weight of the films was determined.

Determination of drug content

The drug content was determined using UV spectrophotometer (LAMBDA XLS, PerkinElmer, USA) at 232 nm wavelength. A piece of film was dissolved in 6.8 phosphate buffer and the absorbance was taken after filtration. Determination was done in triplicate

Determination of surface pH

The film was dissolved in distilled water and the pH was determined with a pH meter (VWR, USA). Determinations were done in triplicate.

Determination of water uptake

The weight of a 2 cm x 2 cm film was determined (W_1) The film was soaked in water and allowed to swell for 1 hour and the final weight (W_2) was determined after patting gently with a filter paper. The percentage water uptake was determined from the equation:

$$\% \text{ water uptake} = \frac{W_2 - W_1}{W_1} \times 100 \quad \text{.....1}$$

Determination of fold endurance

The 2 cm x 2 cm film was repeatedly folded at the same place until the film cracked. The number of times the film was folded was denoted as the fold endurance value. [12] The experiment was performed in triplicates and average value was determined.

Determination of disintegration time

The film was placed in a petri dish containing 10 mL distilled water. It was swirled at 10 seconds interval, and the time at which the film started to disintegrate was recorded as the disintegration time. The experiment was performed in triplicates and the average value was determined.

***In Vitro* dissolution study**

In Vitro dissolution test was of 2 cm x 2 cm film from each batch carried out in 900 mL phosphate buffer (pH 6.8) at 37 ± 0.5 ^{o}C, using a dissolution apparatus (Distek Dissolution System 2100C, USA) at a speed of 50 rpm. Five (5) mL sample was withdrawn at different time interval and replaced with same amount of dissolution medium. The withdrawn sample was filtered with a 0.45 µm filter. The absorbance was determined with a UV spectrophotometer (Genesys 10S UV-VIS, Thermo Scientific, USA) at 232 nm wavelength. Determinations were done in triplicate.

Physicochemical interaction studies

Chemical interaction between drug and excipients were determined using the Fourier transform infrared (FTIR) machine (Perkin Elmer, MA, USA). Samples were placed on the diamond crystal of the FTIR machine at a spectral width of 400-4000 cm^{-1}.

Data analysis

Statistical analysis was carried out using analysis of variance with computer software GraphPad Prism® 4 (GraphPad Software Inc. San Diego, USA). At 95% confidence interval, P values less than or equal to 0.05 were considered significant.

RESULTS

Films were produced by solvent casting method. Formulation F4 prepared with TG formed brittle films which could not be characterised. Representative images of some of the films produced are presented in figures 1-3.

The thickness of the films was between 61.2-113.33 µm (Figure 4). Thickness of films increased with concentration of TG in the formulation.

The other physicochemical properties of the films are presented in Table 2. The average weight of the films was between 28.3-46.4 mg. There was significant difference ($p=0.0023$) in film weight. The ranking of weight with respect to polymer ratio (HPMC:TG) was 1:2 > 1:1 > 3:0. There was significant difference ($p<0.0001$) in drug content of the films with values between 47.2 and 87.7%. The surface pH of the films was between 5.8 and 6.8. The fold endurance of the films was greater than 300 except for formulations F15 and F16 with fold endurance of 131 and 225 respectively.

The water uptake of the formulations was between 228.17% and 675.92% (Table 3).The water uptake of films containing only Hydroxypropyl methylcellulose (HPMC) polymer was generally higher than those containing polymer combination (i.e. HPMC and TG). Films containing ofada starch had higher water uptake when compared to those containing corn starch although there was no significant difference ($p >0.05$). The disintegration time of the films was between 1.07 and 3.85 minutes (Table 3). The ranking was no starch < corn starch <ofada starch. Plasticizer free films had higher disintegration time than films containing plasticizer.

Fig. 1: Image of formulation F1 film

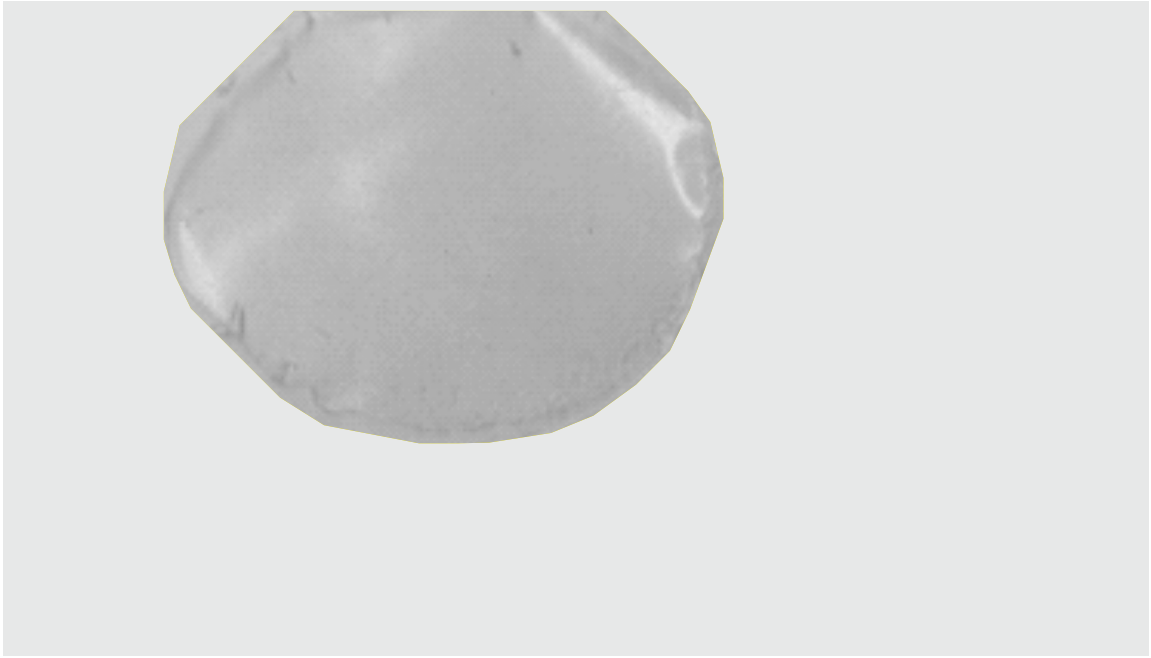


Fig. 2: Image of formulation F2 film

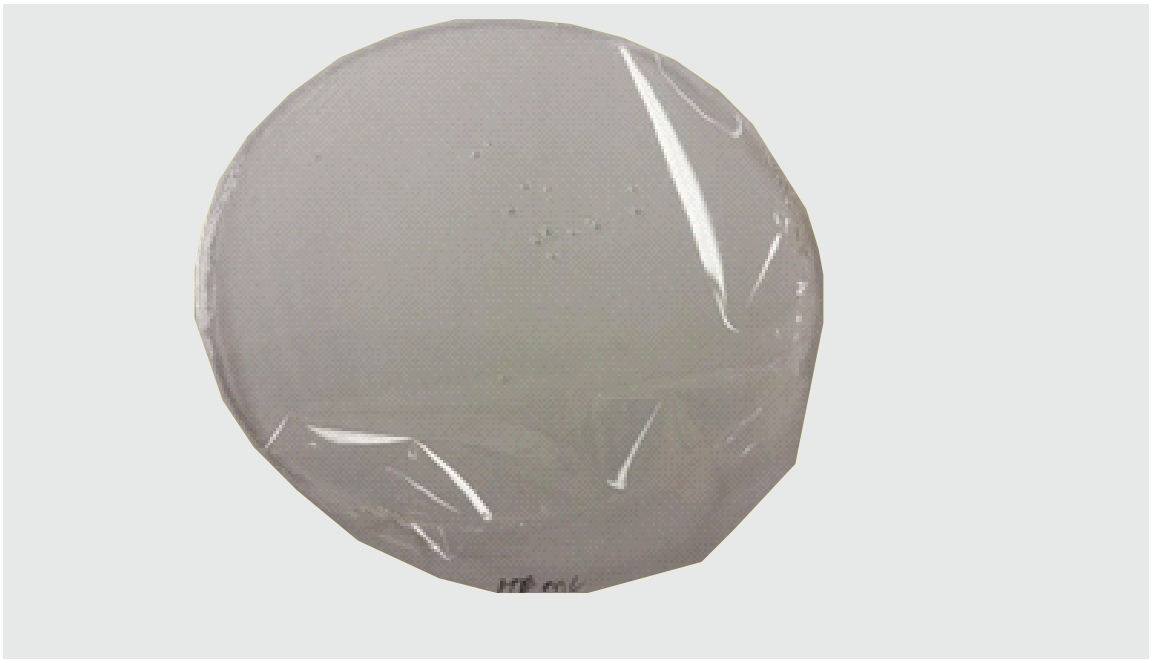


Fig. 3: Image of formulation F3 film

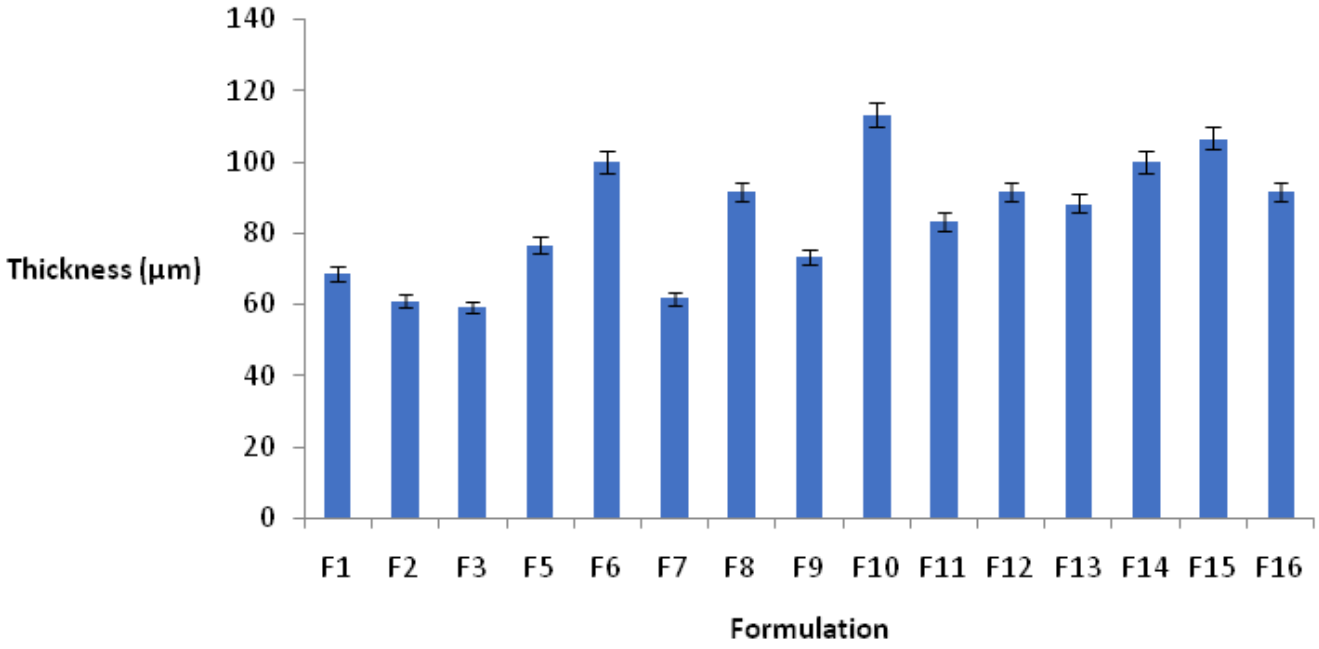


Fig. 4: Thickness of naproxen films

Table 2: Physical properties of naproxen films

Formulation Code	Weight (mg)	Drug content (%)	pH	Fold endurance
F1	39.3±10.70	-	6.7±0.26	>300±0.00
F2	29.6±3.58	-	5.8±0.17	>300±0.00
F3	28.3±6.28	-	6.1±0.01	>300±0.00
F4	-	-	-	-
F5	46.4±7.76	47.7±0.41	6.3±0.04	>300±0.00
F6	57.4±11.67	50.6±0.14	6.2±0.04	>300±0.00
F7	37.6±10.94	47.1±0.46	6.7±0.03	>300±0.00
F8	37.6±14.01	60.1±1.61	6.8±0.09	>300±0.00
F9	40.3±6.14	49.6±0.38	6.7±0.05	>300±0.00
F10	44.4±10.83	87.7±0.29	6.5±0.11	>300±0.00
F11	46.9±7.35	62.4±0.36	6.6±0.06	>300±0.00
F12	40.4±8.25	72.5±0.17	6.7±0.06	>300±0.00
F13	42.6±9.15	63.2±0.98	6.6±0.01	>300±0.00
F14	35.8±7.86	79.4±0.74	6.7±0.17	>300±0.00
F15	43.6±8.10	85.9±0.71	6.4±0.08	131±9.10
F16	36.8±8.07	73.5±0.22	6.5±0.13	225±9.00

Table 3: Percentage Water uptake and disintegration time of films

Formulation Code	Water uptake (%)	Disintegration time (Minutes)
F1	292.8±19.54	1.07±0.03
F2	531.9±5.38	1.85±0.02
F3	512.2±9.56	1.13±0.05
F4	-	-
F5	367.9±116.71	2.02±0.12
F6	305.8±15.89	2.48±0.24
F7	451.6±142.08	1.60±0.13
F8	650.1±145.66	3.85±0.21
F9	331.0±2.85	1.53±0.04
F10	333.2±20.44	2.20±0.21
F11	301.3±21.08	1.20±0.07
F12	474.9±7.50	2.75±0.06
F13	267.7±8.02	1.55±0.01
F14	675.9±46.12	2.02±0.04
F15	228.2±23.99	1.52±0.06
F16	396.9±67.95	1.85±0.11

The rate of release of naproxen was higher in formulations without disintegrant as shown in figure 5, while rate of release was slower in formulations containing plasticizer (Figure 6). The polymer ratio was observed to have effect on the amount of naproxen released from the films. Polymer ratio 1:1 (HPMC:TG) released 82% naproxen within one minute Figure 7).

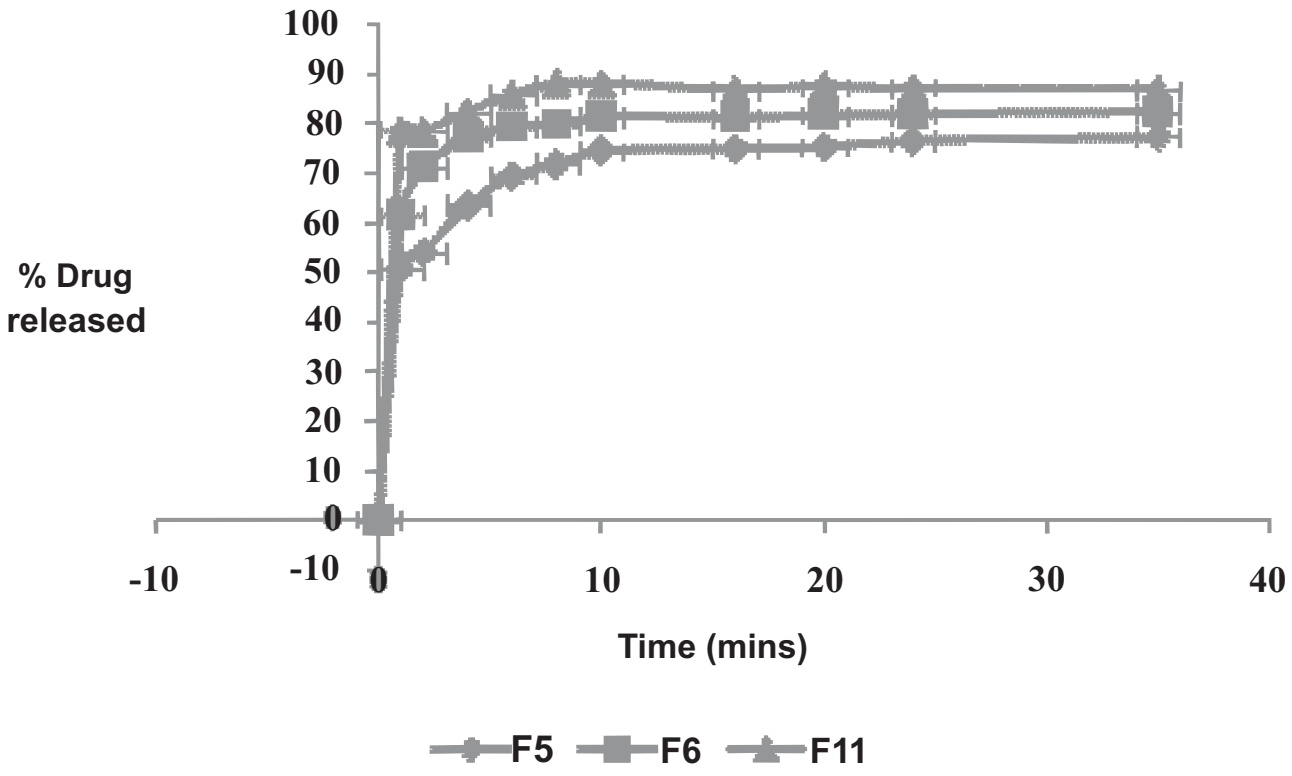


Fig. 5: Representative plot of effect of disintegrant on drug release

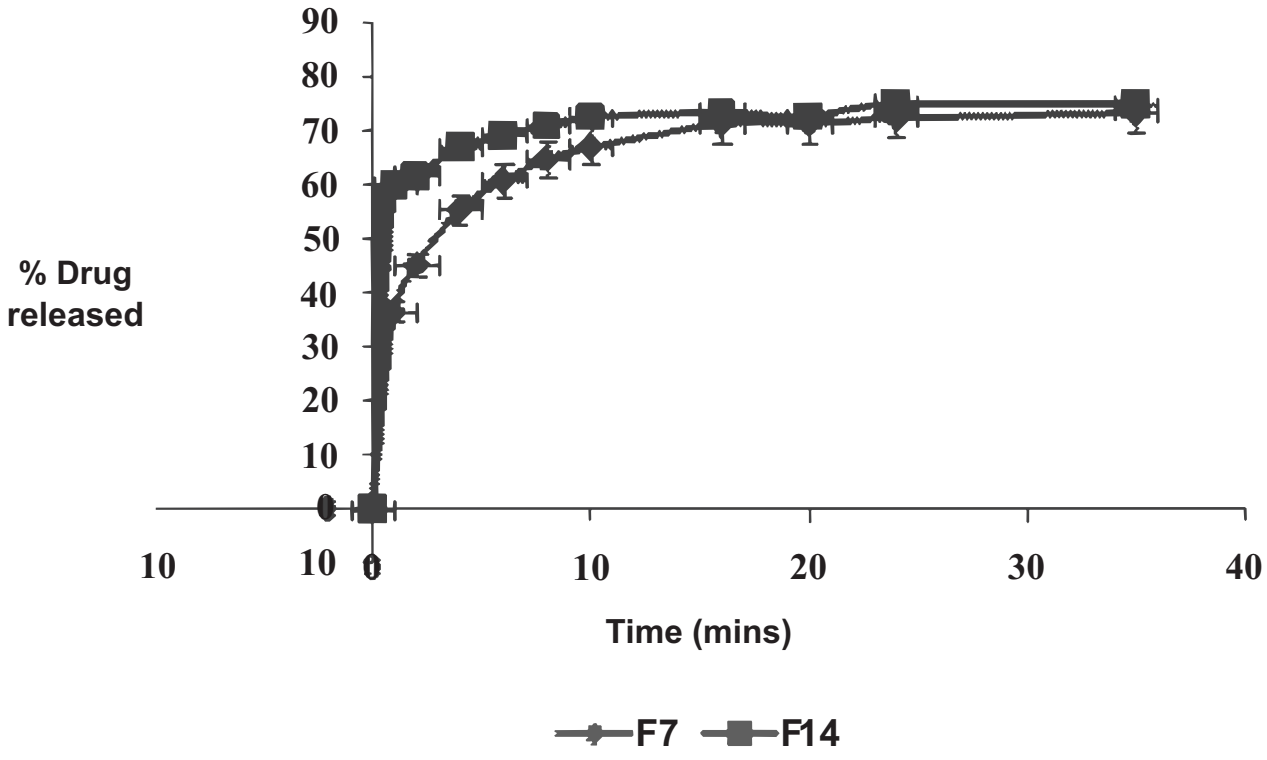


Fig. 6: Representative plot showing effect of plasticizer on drug release

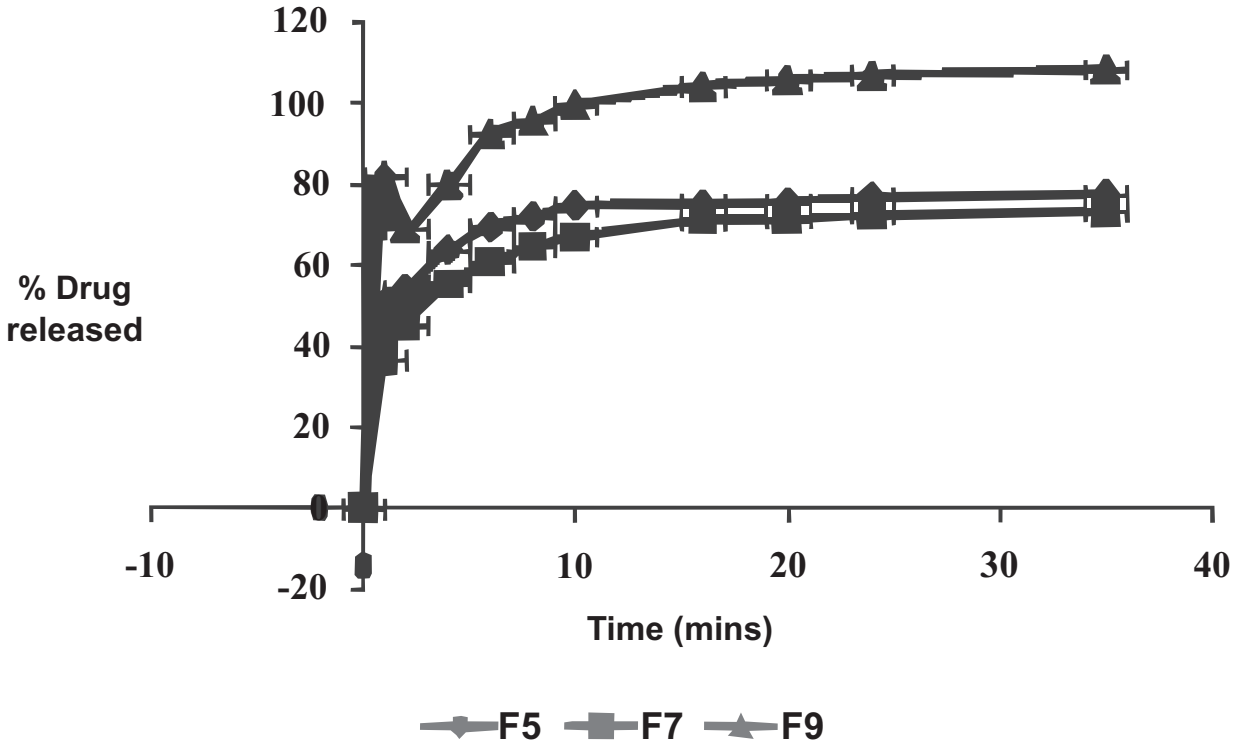


Fig. 7: Representative plots showing effect of polymer on drug release

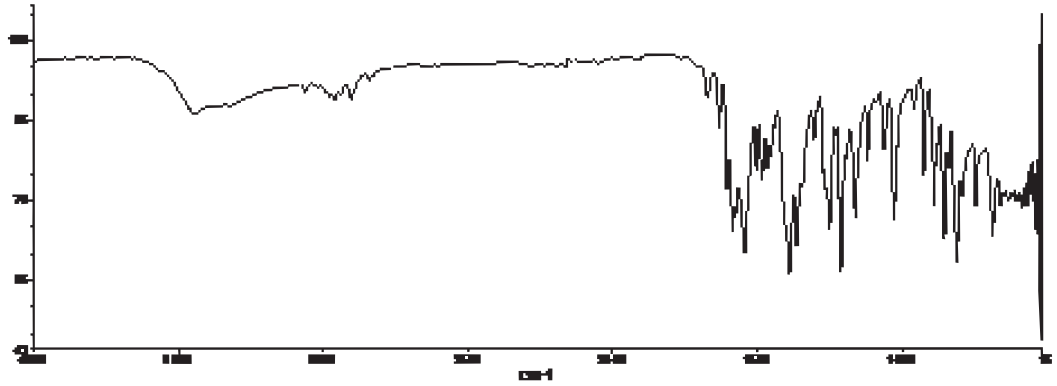
The FTIR of pure naproxen and naproxen films are presented in Figure 8. The characteristic peaks of naproxen were also observed in the FTIR of the films. The sharp peak around 2950 cm^{-1} which is C-H stretch characteristic of aromatic rings was also observed in the films. The band around 3300 cm^{-1} is the O-H stretch of carboxyl group. Peaks were observed around 1450-1510 cm^{-1} and 1650 cm^{-1} in pure naproxen. These peaks were also observed in the naproxen films. Peaks 1150 cm^{-1} – 1050 cm^{-1} in pure naproxen were observed around 1090 cm^{-1} in the films.

DISCUSSION

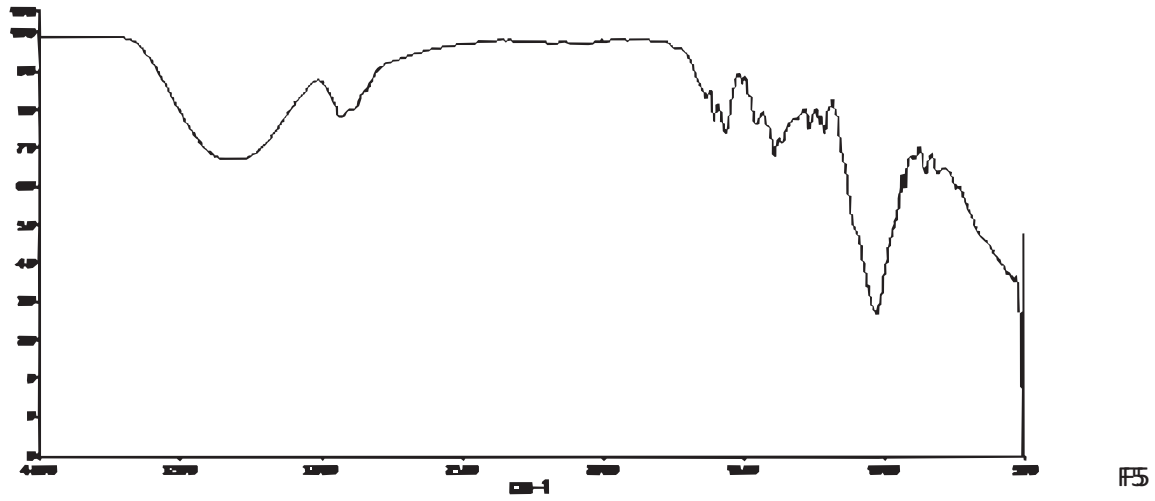
Flexible films which were easy to remove from the petri dish were formed. All the formulations formed films that were flexible and homogenous, except formulations prepared with *Terminalia* gum alone. However, when *Terminalia gum* was combined with HPMC at different ratios, the resultant films were flexible. The amount of HPMC in the combined polymers affected the flexibility of the film. Increasing the amount of TG produced films which were hard to remove from the petri dish. Liew and co-workers observed that decreasing the amount of HPMC in the formulation of donepezil film produced films that were brittle and hard to remove from the mold.[17] Also, Jaiyeoba et al., observed brittleness in films having no HPMC incorporated in the formulation.[3] Similar trend was observed in this study, reason why F4 could not be characterized. Presence of HPMC confers some level of flexibility. The addition of naproxen and disintegrant to the formulation did not compromise the films.

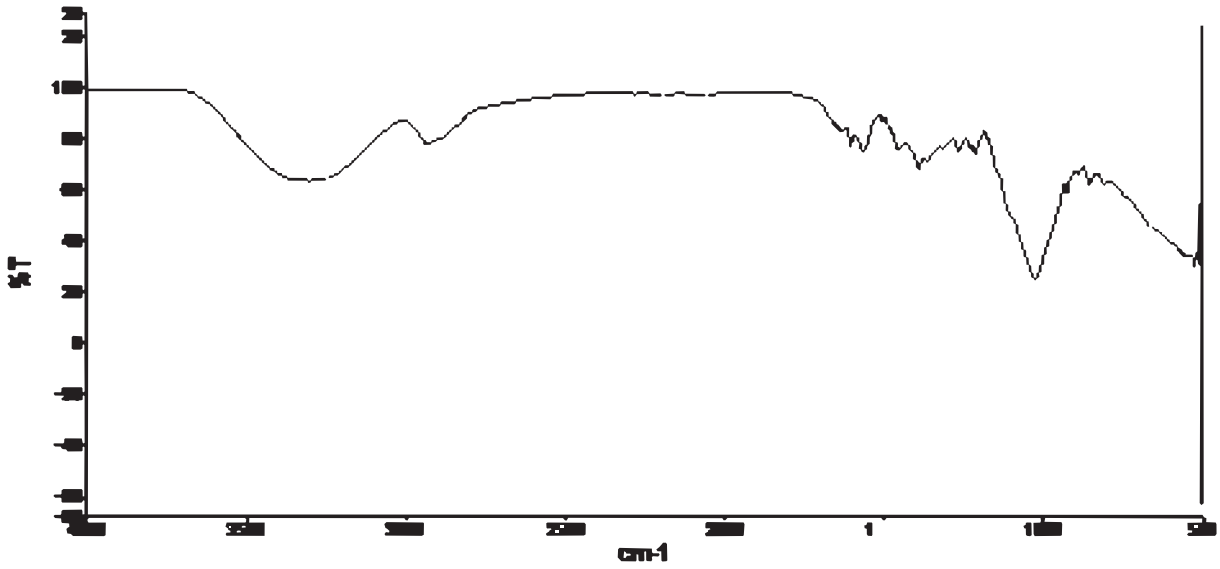
The measurement of film thickness is essential as it ascertains the uniformity of the film thickness. This is directly related to the accuracy of the dose in the film.[18,19] It has been suggested that an ideal film should be within 50 µm and 1000 µm.[18] All the films formed fell within this range. Salehi and Boddohi also observed the thickness of rizatriptan benzoate mucoadhesive films to be between 174 µm and 284 µm.[19]

Polymeric buccal films allow direct access of active ingredient into the systemic circulation, thus avoiding first pass metabolism and hence reducing the dose required or frequency of dosing.

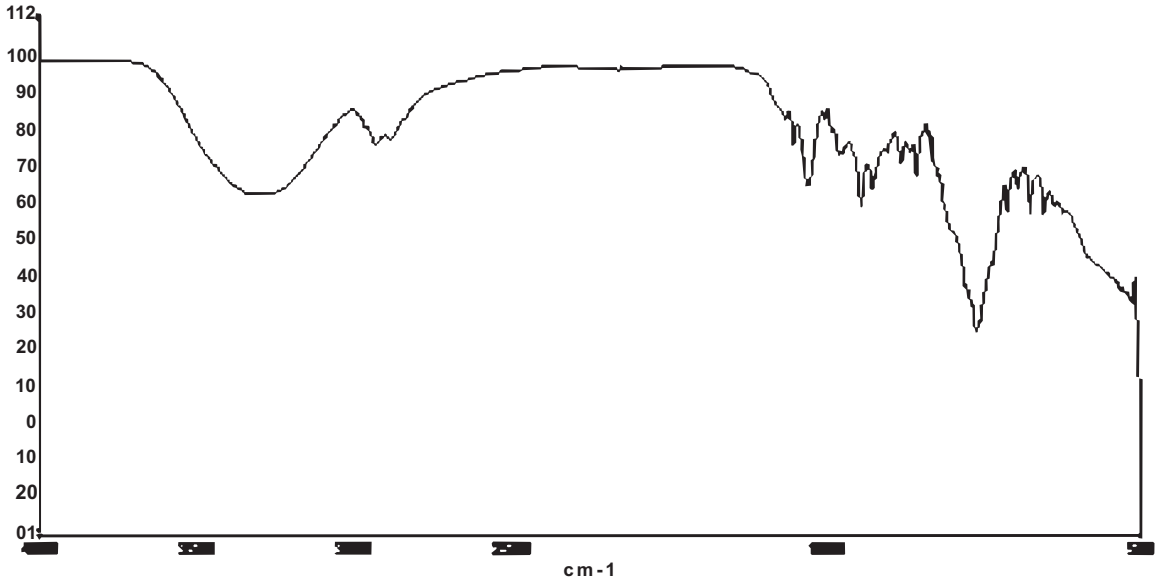


Pure naproxen

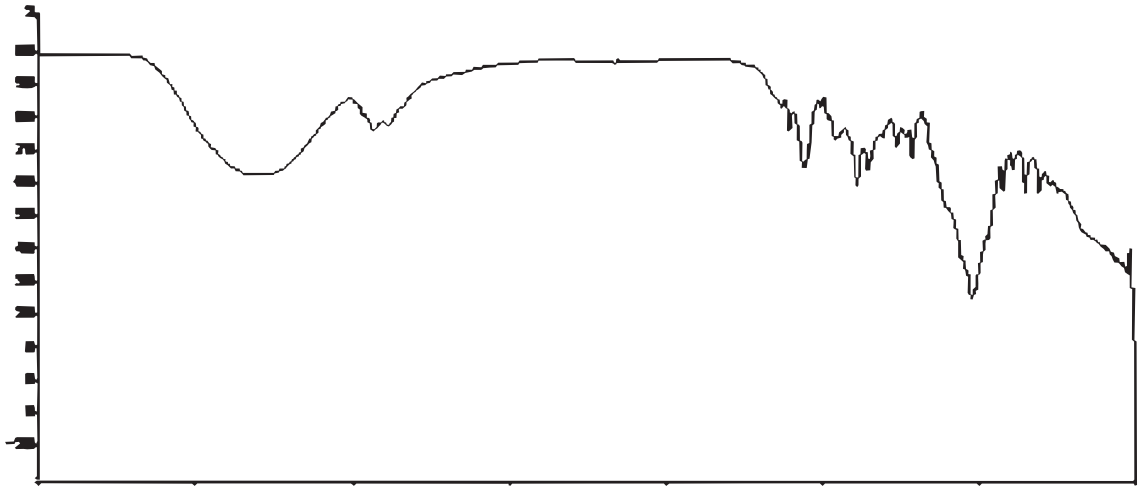




F5



F7



F9

Fig. 8: FTIR of pure naproxen and naproxen films prepared with different polymer ratio

Drug content uniformity has been one of the major challenges in film casting formulations.[20] Non uniformity of drug content was observed in the formulations. This could have been due to the prolonged drying time (24 hours) which could have led to the aggregation of drug and excipients.[21] This self-aggregation of excipients could have also caused the large variation observed in the weight of the films. Nair and co-workers suggested that non-uniformity in drug content could be attributed to large variation in weight.[18]

The surface pH of the films which were in the range 5.8-6.8 was within the pH range of the buccal cavity. This indicates that the films will not be irritating to the mucosa membrane. A film that is too acidic or basic affects the area of application and causes damage to oral mucosa membrane therefore, leading to patient discomfort.[9] The chemical nature of the polymer and excipients in the formulation can also affect the pH of the film.[18]

Polymer is the most important ingredient in film formulation as it forms the main body of the film.[17] The type and concentration of polymer has direct effect on the film properties.[5,17]

Folding endurance gives an idea about the mechanical strength as well as the flexibility of the films. It is the ability of a film to withstand breaking when folded or bended repeatedly along the same plane.[22] A good film should be flexible as it might be subjected to bending during manufacture, transportation and handling. Generally, the formulations had folding endurance greater than 300, indicating tough, flexible and non-brittle films. Folding endurance less than 300 was obtained in some formulations (F15 and F16). Other researchers have prepared flexible films with fold endurance less than 300.[17,22,24] Some researchers have reported that folding endurance value ≥ 200 is acceptable.[10]

Plasticizers play a prominent role in the formulation of film drug delivery systems. In the absence of plasticizer, a hard and brittle film is produced. Plasticizers act as internal lubricants by reducing frictional forces between polymer chains. In this study, glycerol was used as plasticizer while sorbitol was used as a sweetener. Literature has shown the use of sorbitol as plasticizer by some researchers.[25,26] Therefore, the relatively high folding endurance value (131 and 225) observed in F15 and F16 respectively without plasticizer could have been due to the plasticizing ability of sorbitol. Interestingly, F14 without plasticizer but containing only HPMC exhibited fold endurance >300. The presence of TG in F15 and F16 could have been responsible for the low values of fold endurance exhibited. This is due to the fact that TG on its own formed brittle films that were not flexible.

Hydration of films is required for polymers to get charged to be able to impart sufficient mucoadhesion. Films containing exclusively HPMC showed higher water uptake than films containing combination of HPMC and TG. This is in agreement with the report of Jaiyeoba et al.[3]The high water uptake by HPMC films could have been due to the presence of higher number of hydroxyl group which facilitated uptake of water into the film.[20] This high water uptake caused the formation of a thick gelatinous layer which could have caused resistance to erosion of the polymer, hence the high disintegration time observed in films formed with HPMC only. The resistance to erosion could also have caused the decrease in drug released observed in formulations containing exclusively HPMC.

Disintegration is an important step in release of drug from a formulation. Although, there is no official disintegration time for film formulations, all the formulations disintegrated within 4 minutes. It was also observed that films containing the starches as disintegrants had higher disintegration time. This indicates that addition of the starches did not improve the disintegration time. Incorporation of plasticizer into the films reduced the disintegration time. Other workers have shown that incorporation of plasticizer into film formulations reduced the disintegration time.[17, 27]

The effect of the formulation variables on the release properties was examined. Polymer type had significant effect on the release of the drug. As pointed out earlier, high water uptake in formulations containing exclusively HPMC, caused formation of a hydrogel layer around the drug. This could have caused increase in the diffusion path length of the drug, hence, the reduced drug released.[24]

The dissolution profile showed immediate release, indicating immediate relief to the patient. Most of the formulations released more than 60% naproxen within 1 minute. Time for 50% of drug to be released was observed to be directly related to disintegration time. F11 which disintegrated in 1.20 minutes had 50% of naproxen released in 0.5 minutes while F7 which disintegrated in 1.60 minutes had 50% of naproxen released in 2.5 minutes.

The FTIR showed that the drug (naproxen sodium) was well incorporated into the polymer and there was no

interaction between the drug and polymer.
The limitation encountered during the research, was inability to get a texture analyser for the determination of elongation and tensile strength of the films.

CONCLUSION

Terminalia randii gum has potential in the formulation of naproxen sodium oral disintegrating film when combined with hydroxypropyl methylcellulose in ratio 1:1. Polymer must be carefully chosen as this had significant effect on the release of naproxen from the films.

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