Original Article

FORMULATION AND EVALUATION OF NAPROXEN MONOLITHIC SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT

In present investigation the sustained release matrix tablet of naproxen was formulated to study effect various grades of HPMC and insoluble filler. The model is based on a novel dosage form designed to deliver a drug into the gastrointestinal tract in a controlled manner. Matrix tablets were prepared by wet granulation method. As a pre-requisite and part of pre-formulation studies, drug along with selected excipients and as optimized formulation was subjected to FT-IR studies. It was found that no interaction among excipients occurred, as no extra peaks obtained. Tablets were evaluated for various IP-QC tests like hardness, friability, content uniformity, physical appearance and in-vitro release by USP paddle apparatus. Model equations of zero and first order,*Higuchi, Hixson-Crowell* and *Peppas,*intended to elucidate the drug release mechanism, were fitted to the release data. Mathematical modeling of *in-vitro* dissolution data indicated the best-fit release kinetics was achieved with firstorder release kinetics with r^2 vales of 0.915, which evidenced that the formulations are useful for a controlled release of naproxen. Simultaneously, from *Hixson-Crowell* equation shape dependency was also studied with r^2 values of 0.973. By *Peppas* equation the value of r^2 for optimized formulation was found to be 0.563and for n value of 0.603. This indicates the release from formulated tablet follows *Non-Fickian* release mechanism.

Keywords: Naproxen, HPMC, insoluble filler, FT-IR, mathematical models, Non-Fickian

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INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as

the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with acceptable level of safety to the patient.[1]

Naproxen, (S)-2-(6-methoxynaphth-2-yl) propionic acid (**Figure 1**), is one of the most potent nonsteroidal anti-inflammatory agents; it also presents analgesic and antipyretic properties. The anti-inflammatory effects of naproxen, and most of its other pharmacological effects, are generally thought to be related to its inhibition of cyclooxygenase and consequent decrease in prostaglandin concentrations.[2] Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form. For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimal variations. Sustained-release products have become important for the oral administration of many drugs because they give more consistent blood levels.[3] One of the most commonly used methods of modulating tablet drug release is to include it in a matrix system. The classification of matrix systems is based on matrix structure, release kinetics, controlled release properties (diffusion, erosion, swelling), and the chemical nature and properties of employed materials.[4] Matrix systems are usually classified in 3 main groups: hydrophilic, inert, and lipidic.
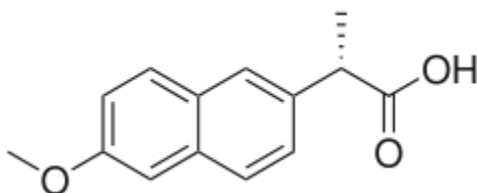

Figure 1: Chemical structure of Naproxen

METHOD AND MATERIALS

Naproxen was generously supplied as gift sample by Ajanta Pharmaceutical Ltd (Mumbai, India). Hydroxy propyl methyl cellulose (HPMC) of two grades (K4M and K1000M) was purchased from local vendor. All ingredients used like di-basic calcium phosphate, magnesium stearate, talc, ethyl cellulose were purchased from local vendor.

Solubility studies

Aqueous solubility is a useful pre-formulation parameter mainly for poorly water-soluble drugs such as naproxen. Bioavailability problems are often present when the aqueous solubility of a drug is less than 10 mg/mL over the pH range 1-8.[5]From literature analysis it was observedthat the dissolution rate represents the limiting factor in the bioavailability of naproxen in solid dosage forms.[6] Naproxen solubility at 37°C in 7.2 buffer phosphate solution was determined by preparing saturated naproxen solutions that were maintained at 37.0°C ± 0.5°C in a water bath and continually shaken until saturated.[7] Withdrawn samples were filtered through a millipore filter (pore size 0.45 mm), and assayed by ultra-violet visible spectrophotometer at 278 nm.

Formulation of sustained release matrix tablet

Eleven formulations corresponding to the different types of matrix tablets (varying proportions of matrix forming agents) were studied. Tablet formulations containing 365 mg of naproxen, binder agents, fillers, and lubricants were prepared by wet granulation followed by compressing the blended powders, using a single-punch compression machine *Cmach* (Ahmadabad, India), and 10-mm diameter flat beveled punches. Tablets compositions are given in **Table 1**.

The total dose of naproxen for once-daily SR formulation was calculated by *Robinson Eriksen*equation using available pharmacokinetic data.[8]

The zero-order drug release rate constant (k_0) was calculated using following equation

$$k_0 = D_I \times k_e$$

where D_I is the initial dose (i.e., conventional dose = 250 mg) and $k_e$is first-order rate constant for overall elimination.

$$k_e = 0.693 / t_{1/2}$$

where $t_{1/2}$ = Biological half-life of naproxen = 12 h

Therefore $k_e = 0.693 /12 = 0.05775$ mg/h.

Availability rate $R = k_e x\ \mathbf{DI}$

$$= 0.05775x\ 250= 14.43\ \text{mg/h.}$$

$\mathbf{D_M}$ $=$ $\mathbf{K_0(T-t_{1/2})}$

$$= 14.43(24-12)= 173.25$$

Loading dose $= \mathbf{D_L= DI – R}x\ \mathbf{t_{max}}$

Therefore $\mathbf{D_L} = 250-(14.43 \times 4)= 192.28$ mg.

Maintenance dose $\mathbf{D_M}$=R x $\mathbf{H}$

Where, H = Number of hours for which sustained action is desired after initial release.

$$\mathbf{D_M} =173.25$$

Total dose required $\mathbf{D_T = D_L + D_M}$

$$= 192.28+173.25 = 365.53\text{mg}$$

Total dose calculated was 365.53mg.But for formulation convenience total dose was rounded to 365mg/tablet.

Table 1: Composition of naproxen sustained release matrix formulations

Ingredients (in mg)	FORMULATION										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10*	F11*
Naproxen	365	365	365	365	365	365	365	365	365	365	365
Ethyl cellulose	80	-	-	-	-	-	-	-	-	-	-
HPMCK100M	-	30	50	100	-	100	50	-	50	100	-
HPMCK4M	50	20	20	20	50	-	-	100	50	-	100
Di-calcium phosphate	20	100	80	30	100	50	100	50	50	-	-
PVP K30	30	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10

* Average weight of formulation was 515 mg/tab.

Weight Variation and Hardness Determination

To study tablet weight variation, 20 tablets of each formulation were weighed using electronic balance (Schimadzu, Japan). For each formulation the hardness of 10 tablets was also evaluated using Pfizer hardness tester.

In-vitro dissolution studies

In vitro dissolution tests were used to simulate the gastrointestinal tract physiological conditions. For dissolution and drug release studies, the US Pharmacopoeia Paddle method II was used. Thedissolution medium consisted of 900 mL 0.1 m, $_pH$ 7.2, phosphate buffer solution[9], maintained at 37.5°C ± 0.5°C and stirred at 100 rpm. Samples (5 mL) were withdrawn at predetermined time intervals for 24 hours and immediately replaced with equal volumes of dissolution medium. Samples were filtered to remove suspended, insoluble tablet components

and assayed by UV-Visible spectrophotometer at 278 nm. To mimic the gastric fluid environmental conditions, 0.5%v/v*TWEENS 80* was added to all dissolution medium.

Release kinetics data analysis

To analyze the mechanism of drug release from thematrix tablets, the release data were fitted to thefollowing equations:

Zero-order equation: $Q = k_0t$

Where Q is the amount of drug released at time t, and $k_0$is the release rate;

First-order equation: $\ln (100-Q) = \ln100-k_1t$

Where Q is the percent of drug release at time t, and $k_1$is the release rate constant;

Higuchi's equation: $Q = k_2t_{1/2}$

Where Q is the percent of drug release at time t, and $k_2$is the diffusion rate constant. [10]

Drug Content (Assay)

The drug content of the matrix tablets was determined according to *in-house* standards. It meets requirements if amount of active ingredient in 10 tested tablets falls in the range of 90% to 110% of the standard amount.Ten tablets were weighed and taken into a mortar followed by crushing to fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of naproxen was transferred to a 100 mL volumetric flask containing 70 mL of 0.5%v/v of tween80 7.2 phosphate buffer. It was shaken by mechanical means for 1hr. Then it was filtered and diluted to 100 mL. From this resulting solution 1 mL was diluted to 50 mL with same phosphate buffer solution and absorbance measuredat 278 nm against blank.

Drug excipient compatibility studies

Drug molecule being a chemical entity is prone for various types of chemical/ decomposition/ degradation reactions. For development of effective and safe formulation drug should be compatible with various excipients used in formulation. Hence to study compatibility of developed formulation, various excipients and drug compositions were made and studied by FT-

IR (8400 Series, Shimadzu, Japan) spectroscopy. Samples were analyzed between wave numbers 4000 and 400 cm^{-1}. The peaks were analyzed for interpretation compatibility of ingredients.

RESULTS AND DISCUSSION

In vitro drug release depends on several factors, such as the manufacturing process, the type of excipient, and the amount of drug. In this work the effect of matrix forming polymers on naproxen release was studied. Drug solubility is an important parameter of the pre-formulation studies. Naproxen is a weak acid with greater solubility in alkaline than in acidic media; therefore, its release profiles are $_p$H dependent and its solubility is higher when $_p$H is increased. The naproxen equilibrium solubility in $_p$H 7.2 phosphate buffer solution determined at 37°C was 6.0 mg/mL. Thus, sink conditions existed for naproxen release at this $_p$h.

Tablets with acceptable physical properties were obtained in all formulations studied. The tablet batches complied with the weight variation and hardness requirements stated in the European Pharmacopoeia.[11] All parameter evaluated were as presented in **Table No 2**. Test for weight variation was complied since all formulations were found to be in range of 600 mg (± SD). Hardness or crushing strength of formulation is a parameter which provides resistance of shocks that tablet might face during various stages of manufacturing as well as storage. From **Table No 2**, mean hardness of tablet was found to be 10 kg/cm^2(± SD).Friability test was found to be passing for all tablets with mean value of 0.5% (± SD). To assure effectiveness of formulation, it must contain accurate and effective amount of active pharmaceutical ingredient. Assay of all formulations was found to be complying with mean value of 100 %(± SD).

Effect of matrix forming polymers on *in-vitro* dissolution was studied using two polymers with different grades of HPMC. The use of HPMC K 4 M (formulations I, V, and VIII) and HPMC K 100 M (formulations II, IIII, VI, and VII) matrices in different concentrations was evaluated. Also based on available literature effect of di-calcium phosphate, insoluble filler, in combination with matrix forming agent, formulations X and XI, with tablet formulated without filler was studied.

As it can be seen from **Figure 2 a**, matrix forming agent and its concentration has profound effect on sustaining release from formulation. Formulation F1 containing ethyl cellulose and moderate amount of low viscosity matrix forming agent (HPMC K4M) was able to sustain release only for ~10h. As combinations of low and high viscosity (HPMC K 100M) forming agents were formulated, release was sustained with respect to composition (formulation F2, F3, and F4). Trials were also performed to study effect of these matrix forming agents without combinations. In this study release was sustained only for 12-16 hours, as these matrix forming agents failed to control rate and extent of release. Hence, trial containing equal amount of both polymers in moderate concentration was done, and found to be sustaining and controlling release for 24. It could be rationalized from this optimized formulation that, initially due to low viscosity of HPMC K4M, it starts to form matrix rapidly but could not retain its integrity longer than 10-14 hours. On other side, HPMC K 100M forms matrix at relatively slower rate but could last for 24 hours.

Table 2: Physical evaluation of naproxen matrix tablets

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Content Uniformity (mg/tab)
F1	601.3±0.6	10 ± 0.15	0.46 ± 0.01	98.67±0.45
F2	599.5±0.7	9.2 ± 0.12	0.43 ± 0.05	99.41±0.38
F3	603.4±0.5	10 ± 0.15	0.37 ± 0.04	98.68±0.89
F4	597.5±0.9	9.8 ± 0.14	0.49 ± 0.02	99.59±0.20
F5	599.6±0.7	11± 0.25	0.52 ± 0.06	100.21±0.45
F6	602.1±0.3	12± 0.30	0.55 ± 0.02	98.63±0.52
F7	601.1±0.1	10± 0.15	0.52 ± 0.01	99.17±0.24
F8	600.3±0.2	11± 0.25	0.44 ± 0.06	99.74±0.57
F9	604.2±0.6	12 ± 0.30	0.38 ± 0.04	97.28±0.80
F10	598.8±0.5	10± 0.15	0.26 ± 0.05	99.43±0.74
F11	602±0.5	12± 0.30	0.58 ± 0.05	98.37±0.23

*All values represent mean ± SD, n=3

The effect of insoluble filler/diluents was also studied in present work. In last two formulations F 10 and F 11, efforts were made to formulate tablets with highest possible matrix forming agent's concentration and without insoluble filler di-basic calcium phosphate. These formulations should showed good physical characters, but *in-vitro* dissolution was not able to sustain longer than ~ 15 h. This indicates that if we use insoluble diluents with matrix forming agents, it helps to maintain not only integrity of formulation but also provide positive deviation on release from formulation (**Figure 2 b**). From data obtained it was decided formulation 7 as optimized.

The model-dependent or curve fitting approach has been successfully used to compare *in vitro* dissolution profiles of solid dosage forms. To explore the release pattern, results of the i*n vitro*

dissolution data were fitted to the various models, which characterizes the transport mechanism. Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e., Fickian diffusion, case II transport, or anomalous transport). In the case of the Fickian release mechanism,the rate of drug release is much less than that of polymer relaxation (erosion). So the drug release is chieflydependent on the diffusion through the matrix. In the present study, the limits considered were n= 0.45(indicates a classical Fickian diffusion-controlled drug release) and n= 0.89 (indicates a case II relaxationalrelease transport; non-Fickian, zero-order release). In the non-Fickian (anomalous) case, the rate of drugrelease is due to the combined effect of drug diffusion and polymer relaxation. Case II release generally refersto the polymer relaxation. Values of n between 0.45 and 0.89 can be regarded as an indicator of bothphenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport.

The data obtained were also put in *Korsmeyer-Peppas*model in order to find out n value, which describes the drug release mechanism.From the release exponent in the *Korsmeyer-Peppas* model (n = 0.603), it can be suggested that themechanism that led to the release of naproxen was an anomalous diffusion with constant release rate adequate fora sustained release dosage form (**Table 3**). However, the release data analysis applying these mathematical models canbe purely empirical, and no definitive conclusion can be drawn concerning the dominating mass transportmechanism.

**Figure 2: Effect of polymer concentration on *in-vitro* dissolution of naproxen sustained released tablet formulations**
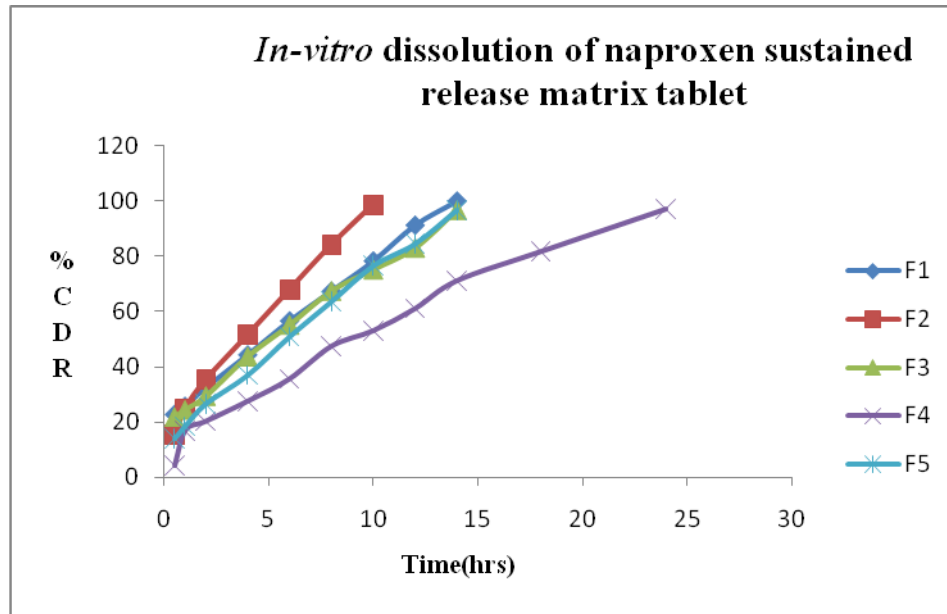
(a)
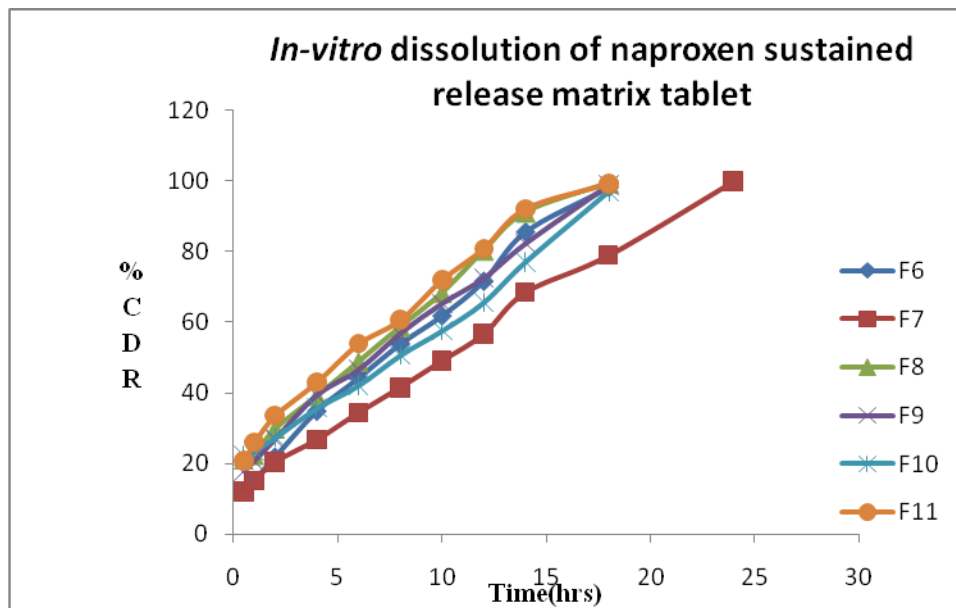
(b)

Table 2: *In-vitro* release kinetic analysis of naproxen sustained release formulation

Formulation code	Zero order (r^2)	First order (r^2)	*Higuchi* (r^2)	*Korsemeyer-Peppas*		*Hixson-Crowell* (r^2)
				(r^2)	n	
1	0.824	0.910	0.946	0.423	0.573	0.907
2	0.738	0.810	0.916	0.483	0.599	0.801
3	0.976	0.939	0.954	0.423	0.524	0.953
4	0.794	0.946	0.946	0.481	0.566	0.947
5	0.884	0.970	0.960	0.519	0.617	0.928
6	0.898	0.924	0.959	0.449	0.630	0.946
7	0.895	0.915	0.949	0.563	0.603	0.937
8	0.882	0.949	0.956	0.420	0.520	0.954
9	0.927	0.876	0.922	0.549	0.540	0.938
10	0.847	0.973	0.975	0.408	0.492	0.964
11	0.920	0.906	0.935	0.394	0.518	0.952

Effectiveness of any formulation depends on selection of compatible excipients in final formulation. To study compatibility of excipients used in formulation, FT-IR studies were performed. From these studies (**Figure 3**), it was concluded that all excipients were compatible and stable with final formulation, since no unintentional peaks generated.

Figure 3: FT-IR of naproxen, and tablet formulation
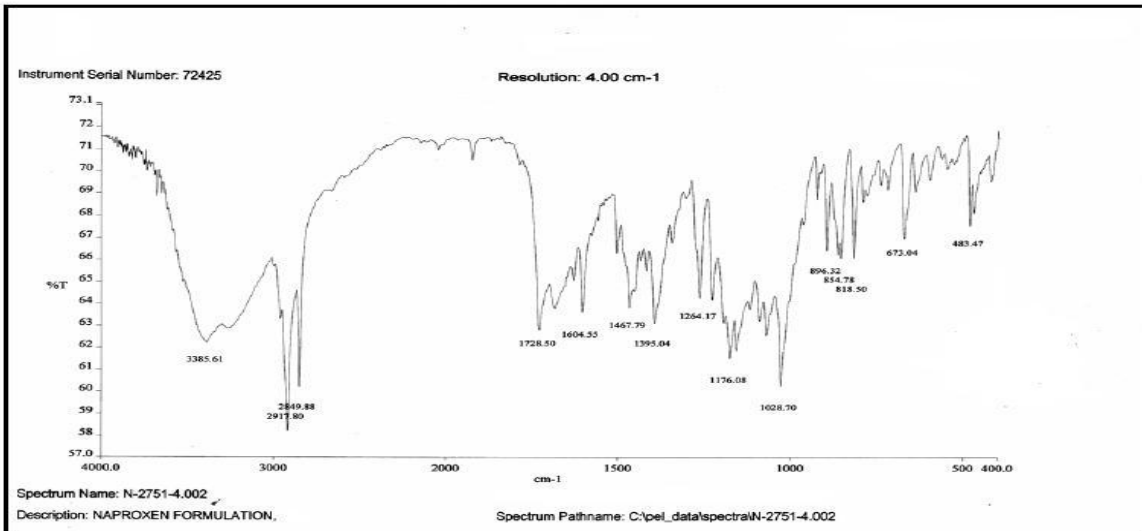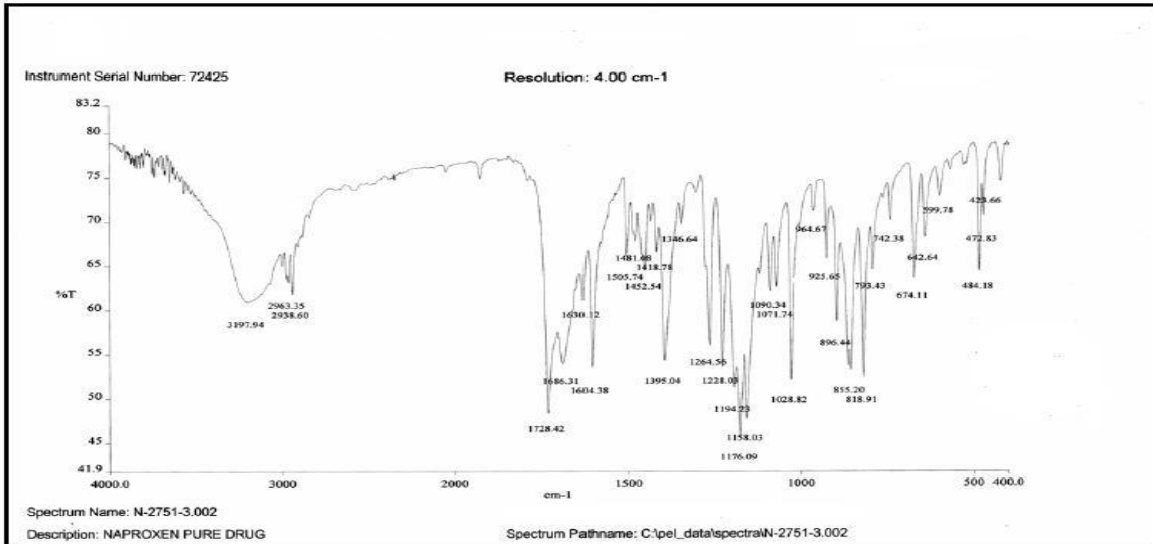
CONCLUSION

Sustained release matrix tablet of naproxen was formulated and evaluated to study effect of various grades of matrix forming agent and filler. It was observed from FT-IR data that functional groups of naproxen remained unchanged after blending with excipients, indicating compatibility of formulation. Tablets were found to be of good physical appearance with average hardness of 10 kg/cm^2(±SD), friability 0.52 % (±SD). Two grades of HPMC K 4M, K 100M were used as matrix forming agents. It was found that, combination in equal (1:1) proportion of both polymers can sustain the release for 24 h, rather than any one polymer in higher proportion. The drug was released at first order release with Higuchi release mechanism. Hixson-Crowell equation showed good dependency with higher r^2 values. From Peppas equation it was understood that, release follows the Non-Fickian release mechanism as n value was 0.603. Filler used are supposed to do not possess any interference on various formulation parameters. But in the present investigation it was found that, addition of insoluble filler helps in extending release from matrix tablet. This investigation is particularly important as, selection of soluble filler or lack of filler was profound effect on nature of formulation.

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