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Development and evaluation of sustained release matrix tablets of naproxen

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ABSTRACT

The present investigation is concerned with development and evaluation of Sustained release matrix tablets containing Naproxen using the hydrophilic polymer hydroxy propyl methyl cellulos (HPMC K100M & HPMC K15M).Preformulationstudy was done initially which include characterization of polymers, drug identification, FTIR compatibility and result directed for the further course of formulation. The tablets were prepared by direct compression method and evaluation done. Tablets were compressed by tablet compression machine (Karnavati Rimek Mini press1)and evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, kinetic release data. The in vitro release studies indicated that the sustained release matrix tablet dosage forms containing higher concentration of HPMC K100M& HPMC K15M showed slower release. Concentration of alone HPMC K100M& HPMC K15M when used results obtained are not follow proper release rate but when used in combination follow better release as required. The invitro release data was treated with mathematical equations, and it was concluded that naproxen released from the tablet followed Peppas model. Hence sustained release drug delivery system of Naproxen is a promising approach as it can lead to decrease in the frequency of administration and ultimately lead to better patient compliance.

Keywords:- Sustained release drug delivery system, Naproxen, invitro drug release,Direct compression method.

INTRODUCTION

Conventional drug delivery system:-
The oral route of drug administration is the most important method of administering drugs for systemic effects. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose**[1],[2],[3].** Sustained release dosage form design embodies this approach to the control of drug action, that is through a process of either drug modification or dosage form, the absorption process and subsequently drug action can be controlled**[4], [5].**

OBJECTIVES:-

- To develop sustained-release matrix tablets of Naproxen, one of the most potent, non steroidal anti-inflammatory agents used in the treatment of arthritic pain.
- To investigate the possibility of interaction between the polymers and copolymers and also between polymers and drugs by Fourier Transform Infrared Spectroscopy.

- To optimize formulation as per specification.
- To characterize formulation as per specification.
- To evaluate the prepared sustained release matrix tablets of Naproxen for various evaluation parameters.

MATERIALS AND METHODS

Materials:-
Naproxen was obtained as a gift sample from Microlab,Banglore, HPMC K100M, HPMC K15M were purchased from Colorcon Asia, Goa. Ltd. All other chemicals were of analytical grade.

Method:- [6], [7],[8].
UV Spectroscopy:-
Preparation of 0.1N HCl:-
A quantity of 8.5 ml of HCl was diluted with fresh distilled water to produce 1000 ml.

Standard Curve of Naproxen:-
Preparation of Stock Solution: Stock solution of Naproxen (100µg) was prepared in 0.1N HCl. The UV spectrum was recorded at 230 nm. The solution of 1to5 µg/ml prepared from appropriate dilution with 0.1N HCl. The absorbance of each solution was recorded using UV spectrophotometer at wavelength absorption maximum.

Construction of Calibration curve of Naproxen in 0.1 N HCl:-
100mg of Naproxen accurately weighed and dissolved in pH buffer 1.2 and made a volume up to 100ml, made concentration of 1000 µg /ml. 10ml of solution was pipette out and dilute with 10ml pH 1.2 buffer solution make concentration of 100 µg /ml. From stock solution aliquot ranging from 0.1 to 0.5ml pipette out and diluted with pH 1.2 buffers to get concentration range 1 to 5 µg /ml. The absorbance measured at 230 nm against blank solution. Standard graph plotted by keeping concentration on x-axis and obtained absorbance on y-axis.

Drug-Excipients Compatibility Studies:-
Infrared Absorption Spectroscopy:-Infrared spectra recorded on infrared spectrophotometer in KBr press IR spectrum of pure drug (Naproxen) and its physical mixture was carried out by using FT-IR.

FORMULATION DEVELOPMENT: [9], [10],[11].
Preparation of Naproxen sustained release matrix Tablet:-
Matrix tablets containing Naproxen were prepared by direct compression technique using HPMC K100M and HPMC K15 Polymers and Naproxen were mixed homogeneously using glass mortar and pestle. Mixture were compressed into tablet by tablet compression machine (Karnavati Mini press-I) by using 12 mm punch to obtain tablets of desired specifications.

Table No.1:-Composition of Naproxen sustained release matrix tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7
Naproxen	250	250	250	250	250	250	250
HPMCK100M	30	50	75	-	-	-	15
HPMCK15M	-	-	-	30	50	75	15
Lactose	160	140	115	160	140	115	160
Magnesium stearate	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10
Total weight	455	455	455	455	455	455	455

EVALUATION PARAMETERS:- [12], [13], [14],[15].
Pre-Compression Evaluation Parameters:-
Bulk density and Tap density:-Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using a formula:-

$$\text{Bulk Density(g/ml)} = \frac{\text{weight of sample in gm}}{\text{volume occupied by sample in ml}}$$

The final volume was recorded and the tap density was calculated by the following equation:-

$$\text{Tapped Density(g/ml)} = \frac{\text{weight of powdered blend}}{\text{Tapped volume of the packing}}$$

Compressibility Index and Hausner Ratio:-

$$\text{Compressibility Index} = \frac{\text{Bulk Density-Tapped Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table No.2:-Relationships between % Compressibility and Flow ability

%Compressibility	Flowability	Hausner Ratio
5 – 15	Excellent	1.00 – 1.11
12 – 16	Good	1.12 – 1.18
18 – 21	Fair to Passable	1.19 – 1.25
23 – 35	Poor	1.26 – 1.34
33 – 38	Very Poor	1.35 – 1.45
> 40	Very Poor	1.46 – 1.59

Angle of repose:-

Angle of repose is defined as the maximum angle between the surface of a pile of the powder and the horizontal plane. Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel is secured with its tip with height h (2 cm), above a plane of paper kept on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. Angle of repose was determined by substituting the values of the base radius's and height of the pile 'h' in the given equation given below

Where,
$\tan \theta = h/r$
θ = Angle of repose,
h = Height of pile,
r = Radius of base.

Table No.3:-Relationships between Angle of repose and Flow property

Sr. No.	Angle of repose	Flow property
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Pre-Compression Evaluation Parameters:-

Appearance:-The tablets were identified visually by checking the difference in color.

Thickness:-Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using verniar caliper on 3 randomly selected samples.

Hardness:-Hardness of the all tablet formulations was determined by Monsanto hardness tester and precision dial type hardness tester .It is expressed in kg/cm^2.

Friability:- Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastics chamber that revolves at 25 rpm for 4 mins dropping the tablets

through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined:-

Percentage Friability $= \frac{W - W_0}{W}$ X 100
Where,
W0= initially weight
W= weight after friability
Percentages Friability of tablets less than 1% are considered acceptable

Weight variation test:-
Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation.

Table No.4:-Weight variation tolerances for uncoated tablets

Sr. No.	Average mass	Percentage deviation
1.	130mg or less	±10
2.	More than 130 mg and less than 324 mg	±7.5
3.	324 mg or more	±5

In-vitro dissolution studies:-
Dissolution test was carried out using USP II (electro lab) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium 900 ml and was maintained at 37±0.5°C for first two hrs and 3-12hrs performed with phosphate buffer pH7.4 (900ml) at 37±0.5°C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, whenever necessary and were analyzed for the Naproxen at 331 nm by using a double beam UV spectrophotometer.

Release Kinetics of Drug [16],[17],[18]:-
1. Zero Order Kinetics:
Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$$f_t = Kt$$
Where, f_t = the fraction of drug dissolved in time's
K = Rate Constant
t = Time

This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

2. First Order Kinetic:-
This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in theoretical basis.

$$\text{Log } Q_t = \log Q_0 + Kt/2.303$$
Where Q_t = Amount of drug released in time't'.
Q_0 = Initial amount of drug in the solution.
K = Rate Constant.

3. Higuchi Model:-
This model is applicable to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrices.

$$f_t = Kt^{1/2}$$
Where, f_t = Amount of drug released in time't'

4. Koresmayer Peppas Model:-
This model is relating exponentially the drug release to the elapsed time (t):
$ft = at^n$
Where, a = constant incorporating structural and geometric characteristics of the drug dosage form.
n = Release exponent

This model is widely used; when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

RESULTS AND DISCUSSION

Preformulation Study of Naproxen:-

Description:-
Colour -white to off-white,
State-crystalline,
Odour –odourless.
Melting point:-Melting point of Naproxen was found to be 152-154^{0}c
Solublity: It is freely soluble in ethanol, methanol and very slightly soluble in water.

Calibration Curve of Naproxen in Buffer of pH 1.2

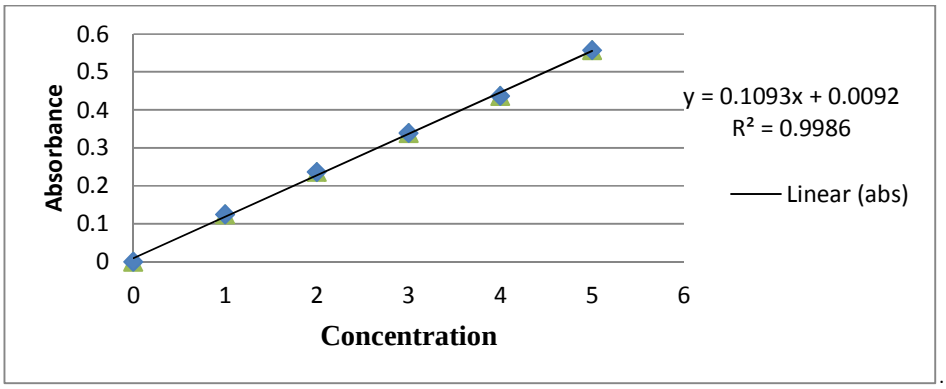

Figure No:-1 Calibration curve of Naproxen

Excipents Compatablity Studies-
FTIR Study:-

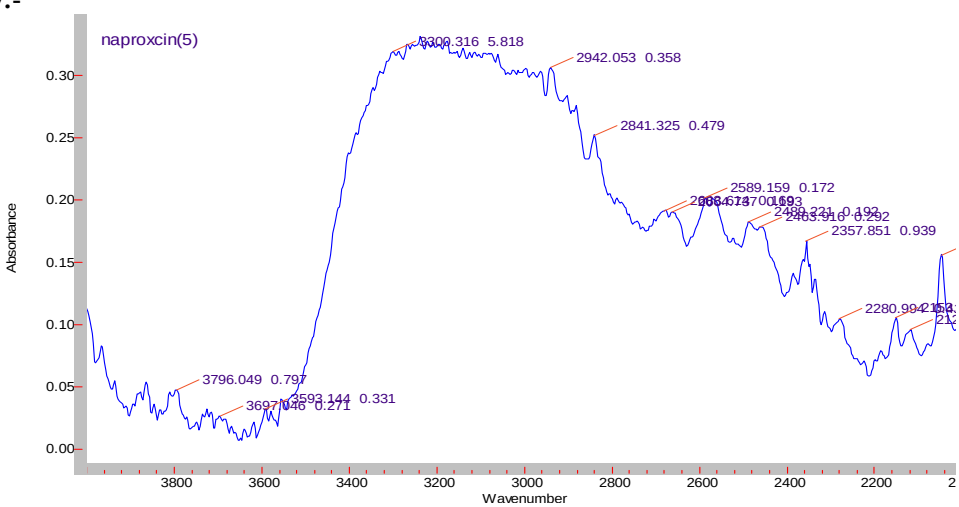

Figure No:-2 FTIR Spectra of Naproxen

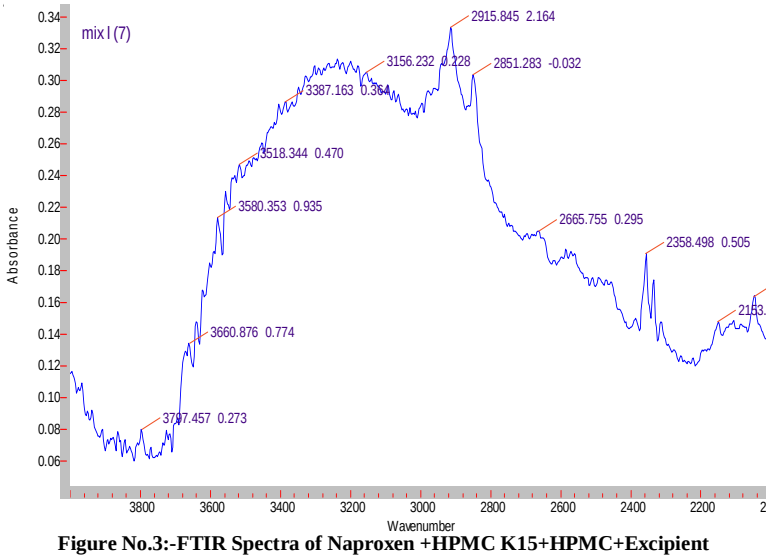

Figure No.3:-FTIR Spectra of Naproxen +HPMC K15+HPMC+Excipient

Pre-Compression Evaluations Parameters:-

Table No.5:-Flow properties of granules prepared by different techniques

Batch Code	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (CI)	Hausner's ratio (HR)
F1	27.68$^{\theta}$	0.46	0.54	14.81±0.42	1.17±0.74
F2	28.53$^{\theta}$	0.44	0.51	13.72±0.46	1.15±0.25
F3	29 .86$^{\theta}$	0.47	0.56	16.07±0.35	1.19±0.28
F4	29.13$^{\theta}$	0.45	0.53	15.09±0.65	1.20±0.40
F5	28.54$^{\theta}$	0.52	0.67	22.38±0.69	1.28±0.51
F6	27.57$^{\theta}$	0.58	0.68	14.70±0.71	1.18±0.60
F7	28 .23$^{\theta}$	0.48	0.58	17.24±0.68	1.2±0.65

Post-Compression Evaluations Parameters:-

Table No.6:-Evaluation of physical parameters

Batch Code	Average Wt. in (mg) ±SD	Hardness (kg/cm2) ±SD	Thickness (mm) ±SD	Friability (%)	Drug Content Uniformity (%)±SD
F1	452±2.64	4.9±0.20	2.3±0.11	0.14	98.25±1.15
F2	456±2.51	4.7±0.20	2.1±0.12	0.12	99.28±1.73
F3	455±1.00	5.2±0.10	2.4±0.17	0.10	99.68±1.00
F4	458±2.00	5.6±0.15	2.6±0.20	0.21	100.01±1.00
F5	457±2.51	5.3±0.11	2.4±0.18	0.24	99.98±1.73
F6	454±4.72	5.2±0.05	2.1±0.10	0.12	100.10±2.64
F7	453±4.16	5.8±0.17	2.4±0.13	0.17	99.72±1.15

In-Vitro Drug Release Studies:-

Table No.7:-In-Vitro Drug Release Data

Time(hr)	F1	F2	F3	F4	F5	F6	F7
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	1.2	1.1	0.8	0.98	0.69	0.6	1.4
2	1.8	1.64	1.23	1.56	1.13	1.08	1.98
3	3.2	2.98	2.70	2.60	2.44	2.31	4
4	6.8	4.93	4.11	5.90	4.12	3.97	7.6
5	13.7	10.44	8.67	12.55	9.77	8.62	15.6
6	20.9	18.54	17.33	18.55	16.40	15.33	22.1
7	26.78	24.22	21.30	24.66	21.33	19.58	36.3
8	30.22	27.30	25.41	26.44	24.30	21.22	51.3
9	41.33	36.31	32.44	35.41	33.26	30.16	65.2
10	46.73	43.32	39.51	40.39	36.69	33.58	74.6
11	53.32	50.34	46.42	49.44	44.31	39.61	82.7
12	60.44	58.41	52.36	58.33	54.42	50.36	90.1

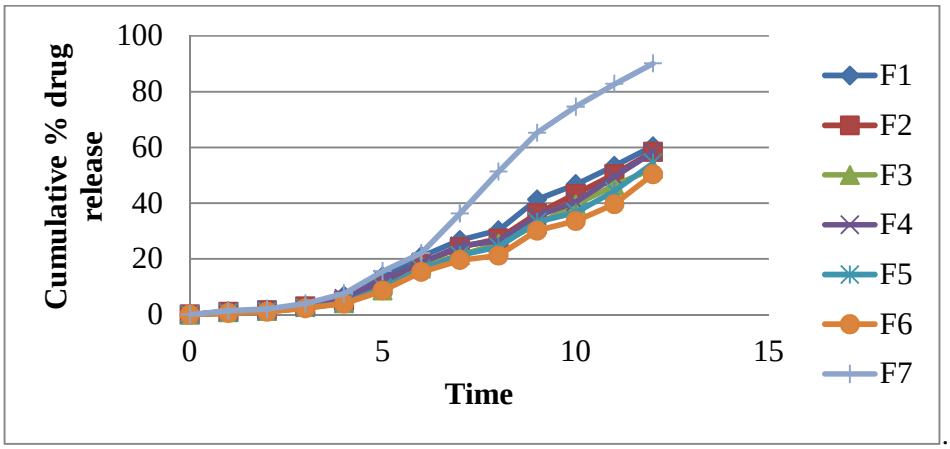

Figure No.4:-Comparative In-vitro Release Profile According to zero order kinetics for formulations F1-F7

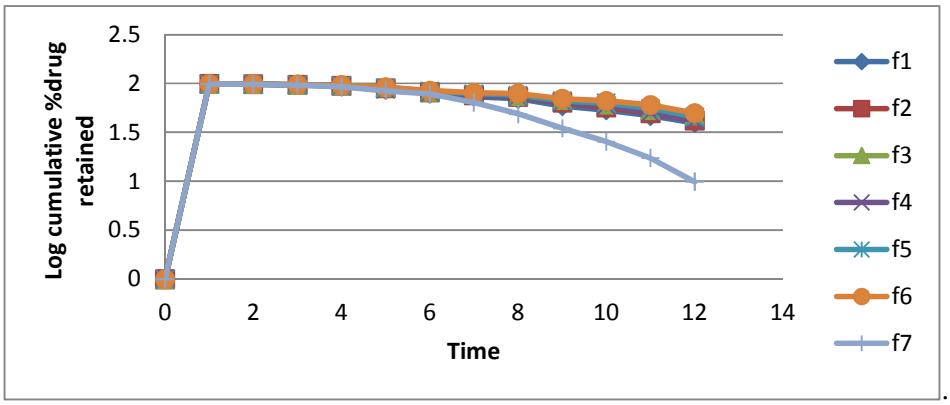

Figure No.5:-Comparative In-vitro Release Profile According to first order kinetics for formulations F1-F7

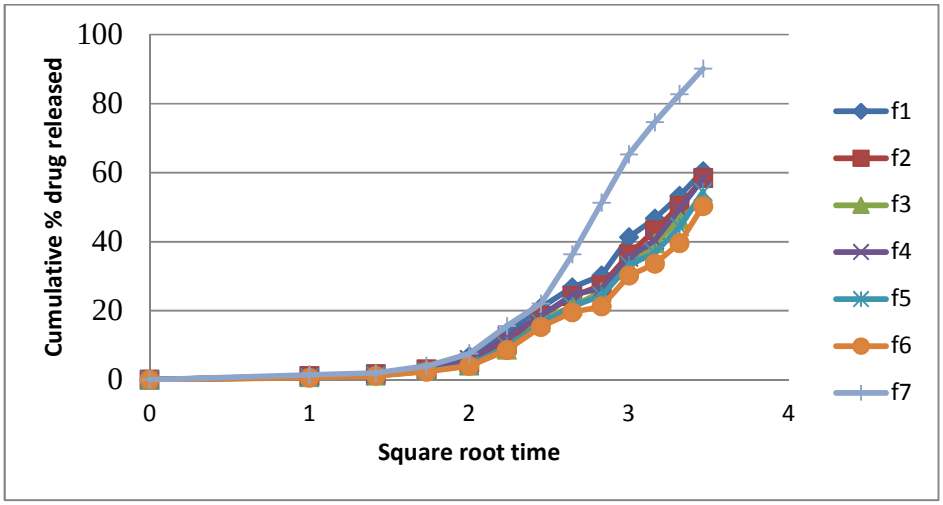

Figure No.6:-Comparative In-vitro Release Profile According to Higuchi Matrix kinetics for formulations F1-F7

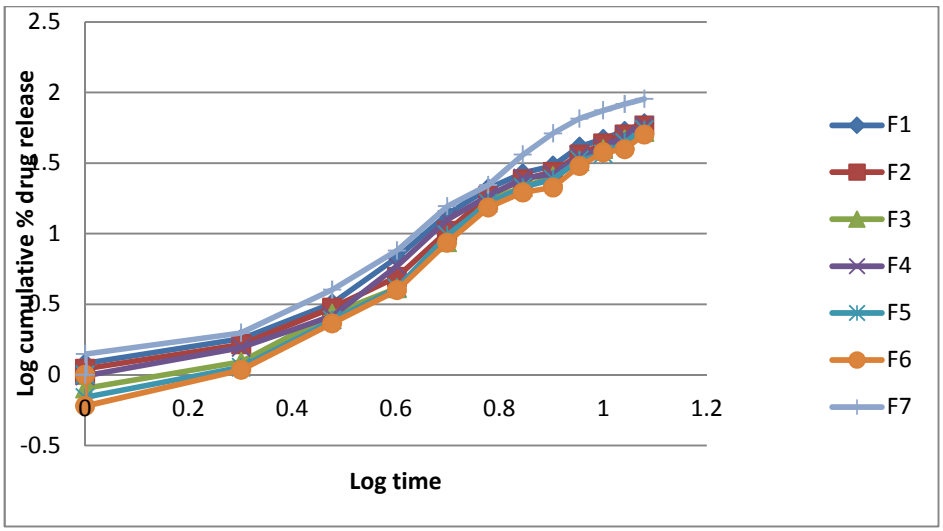

Figure No.7:-Comparative In-vitro Release Profile According to Korsmeyer Peppas kinetics for formulations F1-F7

KINETIC DATA:-

Table No.8:-Drug Release Kinetic Model

Formulation Code	Zero-order	First-order	Higuchi Model	Peppas Model	Best Fit Model
F1	0.957	0.057	0.788	0.971	Peppas
F2	0.943	0.066	0.764	0.963	Peppas
F3	0.948	0.068	0.770	0.957	Peppas
F4	0.947	0.069	0.772	0.966	Peppas
F5	0.937	0.082	0.757	0.957	Peppas
F6	0.934	0.095	0.753	0.957	Peppas
F7	0.934	0.006	0.753	0.967	Peppas

SUMMARY:-

The present study was undertaken with an aim to formulate and evaluate the Naproxen sustained release matrix tablets by using different proportion of polymers (Hydroxy propyl methyl cellulose k15 & k100 &). Preformulation study was done initially which include characterization of polymers, drug identification, FTIR compatibility and

result directed for the further course of formulation. Based on preformulation studies of different batches of Naproxen were prepared by using selected excipients. Tablet blends were evaluated for bulk density, tapped density, carr's index, hausner's ratio and angle of repose before being compressed as tablets. The tablet blends indicate good flowability which is desirable for content uniformity and less weight variation in final tablets. Various formulations of sustain release matrix tablets of Naproxen were formulated using different proportion of polymers by direct compression method. The tablets were evaluated for physical characterization, in-vitro release study. Observation of all formulations for physical characterization had shown that, all of them comply with the specification of official pharmacopoeias and standard references.Result of in-vitro release profile indicate that among all the formulations, F7 was found to be better formulations as it showed 90.10% drug release within 12 hours. The in-vitro release data was plotted for various kinetic models and indicating peppas for formulations no 7 with R^2value 0.967 respectively.

CONCLUSION

The result of the present study demonstrated that the hydroxy propyl methyl cellulose were used as a drug release retardant and drug release was dependent on polymers proportion. The drug release was extended over a period of 12 hours and the to be good without capping and chipping.

- The present investigation described the influence of concentration of polymer (HPMC K100M & HPMC K15) on Naproxen release.
- The in-vitro dissolution profiles of all the prepared Naproxen sustained release matrix tablet formulations were found to extend the drug release over a period of 10 to 12 hours and the drug release rate decreased with increase in polymer concentration.

IR spectroscopic studies indicate no drug-excipients interaction in the prepared formulations.

- Comparing the all formulations, sustained release formulation of F7 was considered as optimized formulation which exhibited 90.10 % of drug release in 12 hours.
- From the result it was observed that drug and polymer ratio influence the in vitro drug release of Naproxen sustained release matrix tablets. Hence, the sustained release matrix system of Naproxen is expected to provide clinician with a new choice of safe and more bioavailable formulation in the management of inflammation.

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