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FORMULATION AND EVALUATION OF NAPROXEN SUSTAINED RELEASE MATRIX TABLET

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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 cellulose (HPMC K100M & HPMC K4M).Preformulation study 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. Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both polymers and insoluble filler could be successfully employed for formulating sustained release matrix tablets of naproxen. All the formulations containing drug, polymer and DCP as filler sustained the drug release for 24 h. The drug release rate was slower with the tablet containing combination of HPMC K100M and EC polymers compared to with that of combination of two hydrophilic polymers (HPMC-K100M and HPMC-K4M). Wet granulation method was used and found to extend the drug release for 24 h. 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, Di calcium phosphate (DCP)*

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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 pharmacodynamic profiles with acceptable level of safety to the patient [1].

The oral route of drug administration is the most important method of drugs for systemic effects. It can be said that at least 90% of all drugs used to produce systemic effect by oral route of drug that are administered orally, solid oral dosage forms represents the preferred loss of product because from one usual in that dose of the drug has been accurately placed.

The new therapeutic entity in world is of little value without an appropriate delivery system. Tablet drug delivery system ranges from relatively simple immediate-release (IR) formulation to complex extended release or modified release dosage forms. The most important role of drug delivery systems is to get the drug "delivered" at the site of action in sufficient amount and with the appropriate rate. However, it must also meet a number of other essential criteria including physical and chemical stability to be produced in a manner that assures the proper amount of drug in each and every dosage unit and in each batch produced, and, as per as possible, patient acceptability (for example reasonable size and shape, taste, color, etc. To encourage patients to take the drug and thus comply with the prescribed dosage regimen) to oral dosage forms tablets and capsules are commonly employed. Tablets has a number of advantages such as they are a unit dose from having dose precision, cost is lowest of all oral dosage forms, most compact, easiest and cheapest package required, product identification is simple and ease of swallowing etc.

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic action However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentration falls below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Drugs with short half-life requires frequent administration, which leads to poor patient compliance, The fluctuating drug levels may lead to precipitation of adverse effects, especially for drugs with small therapeutic index. In recent years a wide variety of newer oral drug delivery systems like sustained/controlled release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects [2].

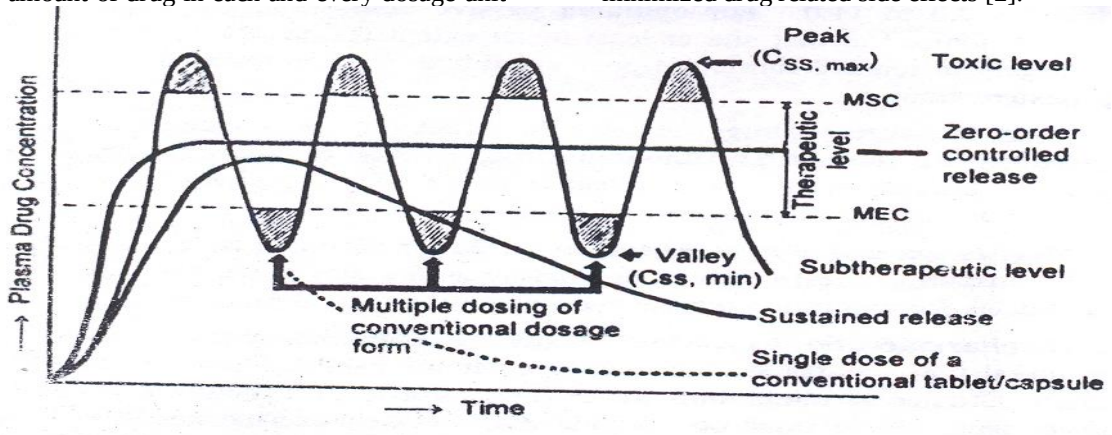

Fig.1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MCS=Maximum Safe Concentration, MEC=Minimum Effective Concentration)

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chossen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

Table No. 1: Technologies used for CRDDS [3].

S.NO	DESIGN OR TYPE OF THE SYSTEM	RELEASE MECHANISM
1	**Dissolution Controlled CR System** -Encapsulation (includingMicroencapsulation) -Barrier coating -Embedment into a matrix of fatty materials -Repeated action of coatings -Coated plastic materials or hydrophilic materials Ex: Matrix Dissolution Control	The dissolution of drug from system.
2	**Diffusion Controlled CR system** Reservoir Devices (Fatty polymer coated systems) Matrix Devices (Fatty polymer dispersed system)	The diffusion of the drug solution through a water-insoluble, permeable polymeric film.
3	**Dissolution and Diffusion Controlled CR systems** Non disintegrating polymeric matrix. Hydrophilic matrices.	Diffusion of a drug solution through a porous matrix.
4	**Ion-Exchange Resin CR System**	Ion-Exchange between the resin-drug complex and ions in the GI tract.
5	**pH-Independent formulations**	Influenced by change in pH and ionic permeability of the membrane coating.
6	**Osmotically Controlled CR systems**	Water entering by Osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice.
7	**Altered-Density systems**	Diffusion from high-density pellets or from floating.

Table No. 2: Types of polymers used in matrix system[4]

Type of polymer	Examples
Insoluble, inert	Poly ethylene; poly vinyl chloride; methyl acryl ate – methacrylate copolymers; Ethyl cellulose.
Insoluble, erodible (fatty compounds)	Carnauba wax; stearyl alcohol, stearic acid; poly ethylene glycol;castor wax; tri glycerides; poly athylene glycol mono stearate.
Hydrophilic polymers	Methyl cellulose; Hydroxy ethyl cellulose; Hydroxyproply methyl cellulose;Sodiumcarboxy Methyl cellulose; Sodium alginate; Guar gum; Chitosan; Hydroxy propyl cellulose; Carbopol; Poly ethylene oxide; Poly vinyl alcohol; Galacto mannose; Alginicacid;Pectin

MECHANISM OF DRUG RELEASE FROM MATRIX SYSTEMS [3-5]

In sustained release dosage forms the drug released for a prolonged period of time along the entire length of GIT (especially up to the terminal region of small intestine) with normal transit of the dosage form. The drug release mechanisms for matrix devices are generally.

1. Dissolution controlled release
2. Diffusion controlled release.
3. Combination of both dissolution and diffusion.
4. Osmotic pressure controlled system.

1. Dissolution Controlled Release

Controlled release oral products employing dissolution as the rate-limiting step are in principle simplest to prepare. Even if the drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier, which has a slow rate of dissolution.

We assume the dissolution process where the rate of diffusion from the surface to the bulk of the solution through an unstirred film is the rate-limiting step. In this case the Noyes - Whitney Equation would describe the dissolution process. At steady state.

$$Dc/dt = K_D A (Cs-C)$$

Dc/dt = the dissolution rate

K_D = the dissolution rate constant

Cs = the saturation solubility of the drug (or) maximum drug solubility

C = the concentration of the drug in the bulk of solution

D = diffusion oefficient

V = volume of the dissolution medium and

h = thickness of the unstirred liquid film.

From the above expression it can be seen that the rate of dissolution i.e., availability is approximately proportional to the solubility of the drug in the dissolution media (Cs) provide constant surface area and diffusion path length are maintained. This equation predicts constant dissolution rate as long as and present to maintain (Cs) constant and provided surface area change. To account for the particle size decrease and change in surface area accompanying the dissolution, Hixson and Crowell's cubic root law of dissolution used

$$W_0^{1/3} - W^{1/3} = Kt$$

Where

W_0 = Original mass of drug

W = mass of the drug remaining to dissolve at time t

K = dissolution rate constant.

The common forms of dissolution controlled formulation categories are:

A) Encapsulation dissolution control

B) Matrix dissolution control (or) Reservoir Devices

A) Encapsulation Dissolution Control

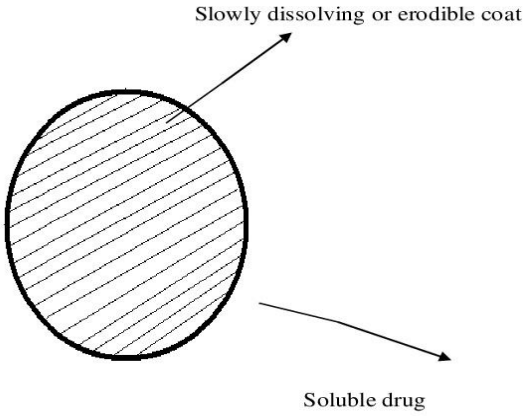

Fig.2: Encapsulation Dissolution Control release system

In this method the drug particles are coated or encapsulated by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes, etc. The resulting pellets may be filled as such in hard gelatin capsules (Spansules) or compressed into tablets. The dissolution rate of coat depends upon the solubility and thickness of the coating, which may range from 1 to 200 microns.

B) Matrix Dissolution Control

Matrix systems are also called as monoliths. Since the drug is homogenously dispersed throughout a rate-controlling medium. Here the rate of drug availability is controlled by the rate of penetration of dissolution fluid in to the matrix by altering porosity of tablet, decreasing wettability or by itself getting dissolved at a slower rate.

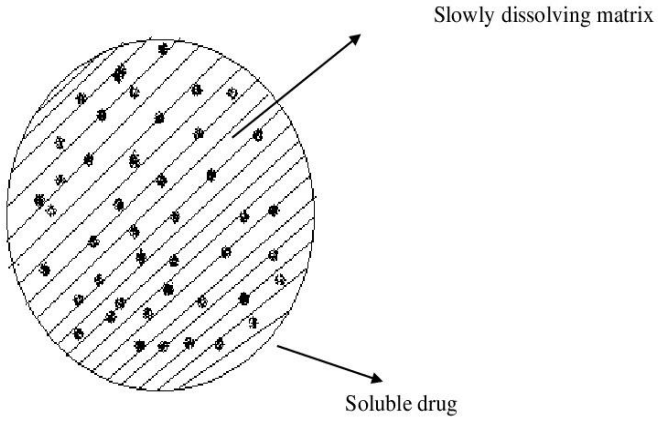

Fig.3: Matrix Dissolution Controlled release system

2. Diffusion Controlled Release

In these types of systems, the rate-controlling step is not the dissolution rate but the diffusion of dissolved drug through a polymeric barrier. Diffusion controlled release products are basically of two types.

A. Encapsulated diffusion control (or) Reservoir devices

B. Matrix diffusion control

A) Encapsulated Diffusion Control

In this system water insoluble polymeric material encases a core of drug. The polymer can be applied by coating or micro encapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release in to the surrounding fluid by diffusion.

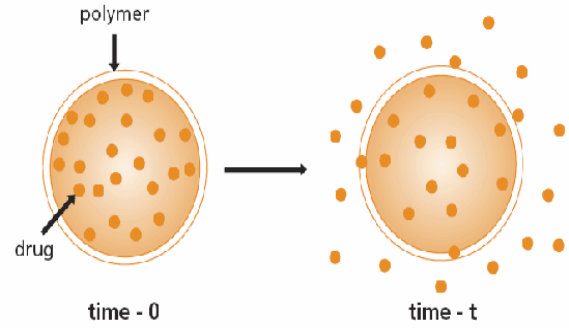

Fig. No 4: Drug release by diffusion across the insoluble membrane of reservoir devices

The release rate is given by equation

$Dm/dt = ADK \Delta C/I$

Where

A is the area

D is the diffusion coefficient

K is the partition coefficient of the drug between the membrane and drug core.

I is the diffusion path length

ΔC is the concentration difference across the membrane.

An important parameter in the above equation is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration of the drug in the core. If the partition coefficient is high, the core will be depleted of the drug in a short time course of the drug. To obtain a constant drug release rate all the terms in the right hand side of the above equation must be held constant.

B) Matrix Diffusion Control

In this method the drug is disposed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophilic substances.

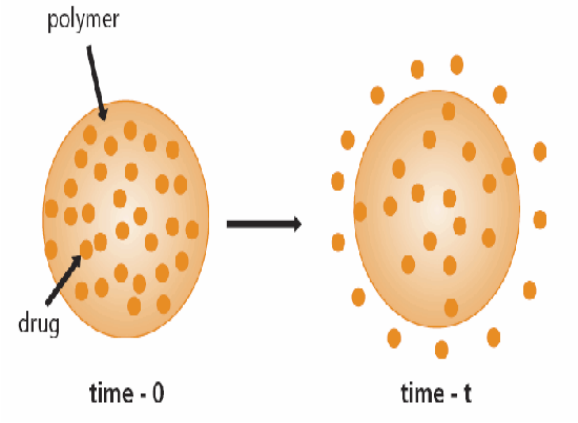

Fig No 5: Diffusion Controlled Devices a) Rigid matrix b) Swellable matrix

Materials used for rigid matrix are PVC and fatty stearic acid and beeswax. Swellable matrix systems are popular for sustaining the release of highly water-soluble drugs. The polymers used generally HPMC, sodium CMC or polycrylamide etc. The drug and the gum are granulated together with a solvent such as alcohol and composed into tablets.

The release of drug from such initially dehydrated hydrogels involves simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via swelling controlled diffusion mechanism.

Higuchi has derived the equation describing drug release from this system.

$$Q = \sqrt{(DE/T)(2A - ECs)Cst}$$

Where

Q is the weight in g rams of drug released per unit area at time‘t’.

D is the diffusion coefficient of drug in release medium.

ε is the porosity of matrix.

Cs is the solubility of drug is release medium

T is the tortuosity of matrix.

A is the concentration of drug in the tablet expressed in gm/m.

The assumptions made above equation are:

1. A pseudo steady state is maintained during release.
2. Cs i.e., excess solute is present.
3. C = 0 in solution at all times (perfect sink)
4. Drug particles are much smaller than matrix.
5. The diffusion coefficient remains constant.

For the purpose of data treatment the above equation is usually reduced to

$$Q = Kt^{1/2}$$

Where K is constant so that the plot of amount of drug released verses the square root of time should be linear if the system is diffusion controlled.

Depending on the properties of the matrix and polymer system, deviation from constant release can occur. For example in the case of insoluble matrix, the drug may have to diffuse through tortuous pathway to reach the bulk solution. To account for this a tortuosity correction factor is added to the release equation. With polymer encapsulated systems swelling or erosion of the membrane will lead to change in the drug release rates.

The most popular drug delivery system has been matrix system containing uniformly dissolved or dispersed drug such as tablets and granules, because of its fabrication. However the release behaviour is inherently first order in nature with continuously diminishing release rate for all three standard geometries: slab, cylinder, and sphere. This is the result of increase in diffusional resistance and a decrease in effective area at the diffusion front as drug release proceeds. Use of zero order delivery systems optimizes the therapy by maintaining drug concentration for prolonged periods.

Methods for alerting the kinetics of drug release from the inherent first order behaviour to zero order have involved the use of geometry factors, erosion, and dissolutions, swelling mechanisms, non-uniform drug loading and matrix membrane combinations.Swelling phenomena are generally encountered in both hydrophilic and hydrophobic polymer matrices during release of the entrapped water-soluble drugs in aqueous environment.

The release of water-soluble drugs from initially dehydrated hydrogels generally involves the simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. This involves a moving diffusional from separating an undissolved core from the partially extracted region and swelling polymer front. As a consequence of swelling chain relaxation takes place, there by releasing the drug. In case of glassy polymers relaxation is time dependent. This is the source deviation from Fick's law.

In case where the sorption process is completely governed by the rate of polymer relaxation the so-called case II transport, characterized by linear dependence in both the amount of diffused and the penetrating swelling front position results. In most systems the intermediate situation, which is often termed non-Fickian (or) anomalous diffusion will prevail wherever the rates of diffusion and polymer relaxation are comparable.

By Korsemeyer and Peppas equation one can express the fraction release M_T/M_α as a power fraction of time't' for the short time period.

$$M_t / M_\alpha = K^1 t^n$$

Where 'K' is the constant characteristic of the system.

'n' is an exponent characteristic of the system

n = 0.5, the drug follows well known Fickian diffusion mechanism

n>0.5 Fickian or anomalous diffusion mechanism

n = 1 describes a case II transport mechanisms.

Usually non–Fickian release is observed till the polymer chain rearrange to an equilibrium state. Once the hydrogel matrix is significantly hydrated, the drug release becomes Fickian.

The relative important of relaxation and diffusion can in principal be estimated with the Deborah number, De that the ration of the characteristic relaxation time λ to a characteristic diffusion time 'θ' ($\theta = L^2/D$) Where L is length.

$D_c = \lambda / \theta$

When $D_e << 1$ relaxation is much faster than diffusion and Fickian diffusion is observed. This occurs well above the glass transition temperature (T_g) where gels are rubbery and the diffusion coefficient 'D' is generally a strong junction of concentration. When $D_e \sim 1$ relaxation and diffusion interact leading to complex transport behaviour that is termed non-Fickian.

3. Combination of both dissolution and diffusion:

In such system, the drug core is encased in a partially soluble membrane. Pores are thus created to dissolution of part of the membrane.

Which:

1. It permits entry of aqueous medium into core and drug dissolution.
2. Diffusion of dissolved drug out of system.

An example of obtaining such a coating is using a mixture of ethyl cellulose with PVP or methyl cellulose; the latter dissolves in water and creates pores in the insoluble ethyl cellulose membrane.

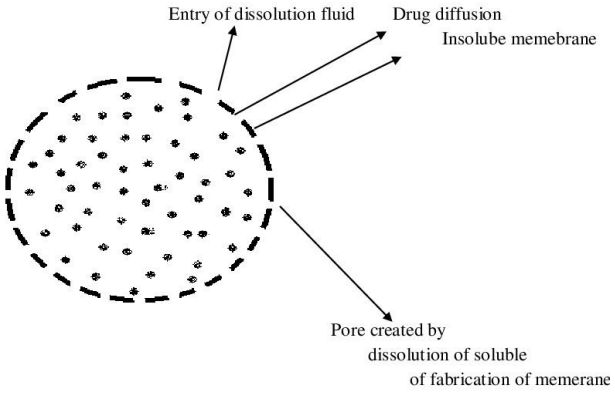

Fig. No 6: Combination of both dissolution and diffusion controlled

4. Osmotic pressure controlled system:

Definition:Movement of solvent from lower to higher concentration.

The passage of solvent into a solution through semipermeable membrane. The solution-diffusion mechanism for most system, an oral osmotic pump, popularly called as oros, works on the principle of osmotic pressure to release the drug at a constant zero order rate. A core comprising of drug and somatically active substance such as potassium chloride or mannitol is surrounded by a rigid semipermeable memebrane coating such as cellulose ester or cellulose ether having an orifice of 0.4 mm diameter produced by laser beam for drug exit. When exposed to GI fluid water flows though the semipermabile membrane into tablet due to osmotic pressure difference which dissolves the drug, pumps it out through the orifice by the osmotic force. Such devices can be used to target specific area of the GIT.

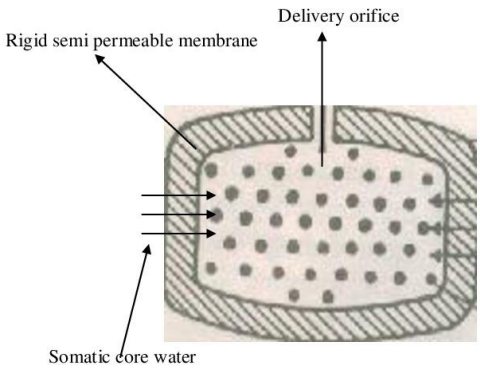

Fig. No 7: Oral Somatic pump

Table No.3: Composition of Naproxen sustained release matrix formulations

Ingredients (in mg)	FORMULATION CODE										
	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	-	-	-	-	-	-	-	-	-	-
HPMC-K100M	-	30	50	100	-	50	50	-	100	100	-
HPMC-K4M	50	20	20	20	50	-	50	100	-	-	100
Di-Calcium Phosphate	20	100	80	30	100	100	50	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
Total weight (mg)	565	565	565	565	565	565	565	565	565	515	515

Evaluation of precompression blend [5-9]

Angle of repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heapof the granules. The granules were allowed to flow through the funnel freely onto the surface.

The diameter of the powder cone measured and angle of repose was calculated using the following equation.

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values less than 25, 25-30, 30-40, and more than 40 indicates excellent, good, passable, and poor flow properties respectively

Determination ofbulk density and tapped density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0

Tapped density = W/V_f

Where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

Compressibility index (Carr's index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

CI = (TD-BD) x 100/TD

Where, TD is the tapped density and BD is the bulk density

Table No 4: Carr's index values

S.No.	Carr's index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

***Hausner's* ratio**

It is the ratio of tapped density and bulk density. *Hausner* found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Hausner's ratio = TD/BD

Table No 5: *Hausner's* ratio values

S.No.	*Hausner's* ratio values	Properties
1	1.00	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.45-1.59	Very poor
7	>1.60	Very, very poor

Evaluation of post compression blend [5-9]

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch ten tablets were measured for the hardness and average of ten values were noted along with standard deviation.

Friability test

From each batch, twenty tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% Friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

Weight variation test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using

electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = (W_A–W_I) x 100/ W_A

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

Assay

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the twenty tested tablets lies within the range of 90% to 100% of the standard amount.Twenty tablets were weighed and taken into a mortar and crushed into fine powder.

An accurately weighed portion of the powder equivalent to about 100 mg of naproxen was transferred to a 100 mL volumetric flask of pH 7.2 phosphate buffer (containing 0.5% v/v of *TWEENS* 80).It was shaken by mechanical means for 1h. Then it was filtered through a Wattman filter paper (No.1) and diluted to 100 mL with same phosphate buffer solution. From this resultant solution 0.6 mL was taken, diluted to 10 mL with same medium and absorbance was measured against blank at 278 nm

***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. The dissolution medium consisted of 900 mL 0.1 m, P^H7.2, phosphate buffer solution, maintained at 37.5ºC ± 0.5ºC 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 278nm. To mimic the gastric fluid environmental conditions, 0.5%v/v *TWEENS 80* was added to all dissolution medium.

Kinetic analysis of dissolution data [8,10-13]

To analyze the*in-vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent.

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = K_0 t \qquad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \qquad (2)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \qquad (3)$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad (4)$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the *in-vitro* drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Zero - order release kinetics [8]

It defines a linear relationship between the fractions of drug released versus time

$$Q = kt$$

Where, Q is the fraction of drug released at time t

k is the zero order release rate constant

A plot of the fraction of drug released against time will be linear if the release obeys zero - order release kinetics.

First - order release kinetics [8]

Wagner assuming that the exposed surface area of a formulation decreased exponentially with time during dissolution process suggested that drug release from most slow release formulation could be described adequately by apparent first- order kinetics. The

equation used o describe first- order release kinetics is

$$\ln (1-Q) = -k_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.
Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi (Diffusion) model [12]
It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$Q = k_2 t^{1/2}$ Where, k_2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Korsmeyer - Peppas model [10,11]
A plot of the fraction of logarithm of % drug released against logarithm of time will be linear if the release obeys Korsmeyer - Peppas equation.

$\text{Log } Q = \log k_3 + n \log t$

Where, k_3 is the release rate constant
n is diffusional exponent.

$C = K_0 t$

Where, K_0 is zero-order rate constant expressed in units of concentration / time and t is the time.

$\text{Log } C = \log C_0 - K_1 t/2.303$

Where C_0 is the initial concentration of drug and K_1 is first order constant.

$Q = K_{11} t^{1/2}$

Where, K_H is the constant reflecting the design variables of the system.

Mechanism of drug release [10,11]
Korsmeyer *et. al.*,(1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer - Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices.Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Table No. 6: Diffusion exponent and solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Swelling index studies [15]
The swelling index of all formulated tablets was determined in pH 7.2 phosphate buffer solutionat room temperature. The swollen weight of the tablet was determined at the end of specified (Dissolution test) time interval. The wetted samples were then dried in an oven at 60ºC . The increase of the weight on the tablet reflects the weight of the liquid uptake The swelling index was calculated by following equation as

$$Q = 100(W_w - W_i) / W_i$$

Where Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.
The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using following equation.

$$E = 100(W_i - W_f) / W_i$$

Where W_f is the final mass of the same dried and partially eroded sample.

Note: After removing frompH7.2 phosphate buffer solution, tablets were placed on blotting paper such that maximum wet can be removed from matrix.

Stability studies [20]
Adequate stability data of drug and its dosage form is essential to ensure the strength safety, identity, quality purity and *in-vitro* release rate that they claim to have at time of use. Sustained release product should release predetermined amount of drug at specified time intervals, which should not change on storage. Any considerable deviation from.sustainedrelease would render release product useless.

Stability is defined as "the capacity of drug product to remain within specification established to ensure its identity, strength, quality and purity".The purpose

of stability study is not only to characterize the degradation of drug product but also to establish expiration dating period or shelf-life applicable to all future batches of drug product.

Stability studies are of three types:

1. Long Term Stability Studies
2. Intermediate Stability Studies
3. Accelerated Stability Studies

Accelerated stability studies are useful in following ways:

1. The result provide estimate of kinetic parameters for the rate of reaction.
2. The results can be used to characterize the relationship between degradation and storage condition.
3. The results provide critical information on design and analysis of long-term stability studies under ambient conditions at the planning stage.

Developed tablet formulations were wrapped in aluminium foils individually and placed in stability chamber. Conditions were set at 40ºC, 75% RH, room temperature (25ºC, 60% RH) and 2-8 ºC as per ICH guidelines. Stability studies were carried out for three months. Samples were withdrawn at an interval of 1, 2 and 3 months analyzed for *in-vitro* dissolution.

EXPERIMENTAL RESULTS:

The oral route is the one, most frequently used for drug administration. Oral dosage forms are usually indicated for systemic effects resulting from drug absorption through various epithelia and mucosa of the gastro intestinal tract. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. In present study, attempts were made to prepare such drug delivery systems using various combinations of hydrophilic-hydrophobic polymers and effect of insoluble filler by using optimization techniques. Drug molecule was selected from various probable candidates as is one of the most potent nonsteroidal anti-inflammatory agents; naproxen, (S)-2-(6-methoxynaphth-2-yl) propionic acid 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. Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form

Drug authentication studies

Purity is the critical parameter that affects pharmacokinetic and pharmacodynamic performance of the drug substance. Therefore, the drug substance used for the study must be checked for its purity.

Determination of melting point [19]

Melting point of naproxen was determined and compared with that of reference value. Melting point was found to be comparable with that of reference value.

Table No 7: Melting point analysis of Naproxen

Sl. No.	Sample	Sample Melting (ºC)	Reference Melting (ºC)
1.	Sample 1	150-153	151
2.	Sample 2	150-152	
3.	Sample 3	150-152	

Solubility studies [16]

Naproxen was found to be freely soluble in pH 7.2 phosphatebuffer as well as in solvents like methanol, ethanol and acetone. Other solvents were also studied and results were presented in **Table No.12**

Table No 8: Solubility analysis of Naproxen [16]

Sl. No.	Solvent	Solubility
1.	Purified Water	Insoluble
2.	pH 7.4 phosphate buffer	Freely soluble
3.	Methanol	Soluble
4.	Ethanol	Sparingly soluble
5.	Chloroform	Soluble

From above mentioned values it was confirmed that drug is following solubility pattern as per literature.

Fourier Transform Infrared Spectroscopy [17,18]

The infra-red spectrum analysis of naproxen and combination of various excipients was done using KBr pellets.In FTIR, sharp distinct peak of naproxen was observed at 1215cm^{-1}. No shift of either drug or excipient peaks were occurred indicating compatibility of all excipient with drug. The IR spectra of pure naproxen drug showed the characteristic absorption bands are as follows: COO^- at 1585 cm^{-1}, aromatic CH_3-CH stretching at 2957 cm^{-1}, aliphatic CH_3O stretching at 2904 cm^{-1}, C-H stretching of aromatic ring at 3058cm^{-1}, carboxyl keto group showed absorption band at 1631 cm^{-1}.This data

was verified and confirmed from IP and available literature information. Hence drug was found to be pure. To study possible drug and excipient interactions blends were also analyzed.

No drug-polymer interaction was observed in the FTIR spectra of the powder mixture of optimized formulation. Since the absorption peaks of the drug still could be detected in the mixture**.** In the entire FTIR spectrum these peaks are observed indicating the stable nature of naproxen with various excipients.

The FT-IR spectrum of pure drug and FT-IR spectra of the formulations showed that there is a negligible difference in the position of characteristics of absorption bands of the functional groups of the drug and the drug has remained in its normal form even when the formulations were prepared from it without undergoing any chemical interaction with the different polymers and other excipients used during the study. Thus, it is clear from FT-IR study that there is no interaction of the drug with the polymer and other excipients

SUMMARY:

Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both polymers and insoluble filler could be successfully employed for formulating sustained release matrix tablets of naproxen. All the formulations containing drug, polymer and DCP as filler sustained the drug release for 24 h. Among the hydrophilic matrix formers, the rate of drug release was in the following order.
F-7 > F-8 > F-11 > F-5 > F-4 > F-3 > F-2 > F-6 > F-9 > F10

The drug release rate was slower with the tablet containing combination of HPMC K100M and EC polymers compared to with that of combination of two hydrophilic polymers (HPMC-K100M and HPMC-K4M). Wet granulation method was used and found to extend the drug release for 24 h.

For determination of drug-excipient compatibility, FTIR studies were conducted and in all FTIR spectrums the characteristic drug peak was observed. From this no drug- excipient interaction was observed.
To explore the release pattern, results of the *in-vitro* dissolution data were fitted to the various models like Zero, First, Higuchi, Korsemeyer-Peppas and HixsonCrowell equation which characterizes the transport mechanism. Based on various mathematical models the magnitude of the release exponent 'n' indicates the release mechanism

The optimized formulation follows zero-order kinetics, since values of zero order release are higher (R^2 values 0.998) than that of first order release data (R^2 values 0.934-0.985). To study release mechanism Higuchi release mechanism was employed and it was found to having R^2 values of 0.931 to 0.990. Further R^2 values of Hixson-Crowell cube root equation indicates that release of formulation is relatively shape dependent. Lastly, a Korsemeyer-Peppas equation was used to study mechanism of release. For these, R^2 values were found to be in the range of 0.920 to 0.996 and n-value were found to be 0.599.

Hence release for optimized formulation F-7 was found to be Non-Fickian Release Mechanism. The drug release was controlled by more than one process. By observing *in-vitro* dissolution profile of various polymer concentrations it shows that upon increasing the concentration the rate and extent of drug release was decreased, due to its total porosity in the matrices.

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