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Formulation of Naproxen Sustained Release Tablets

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Abstract: *The main purpose of review of Sustained release dosage form is to achieve the slow release of drug over and extended or long period of time and give the complete knowledge of sustained release dosage forms. Sustained release dosage forms is to provide pharmaceutical ,pharmacokinetic and pharmacodynamics properties of drug that increase the therapeutic efficacy of dosage forms.Sustained release dosage forms is used to improve the patient's compliance. It minimizes the side effects by minimizing the dose frequency .It also increases the safety margin of potent drug and reduction in fluctuation takes place. Basically this dosage form is used to optimize the delivery of medication. By optimizing the delivery of medications we control on the therapeutic effect of dosage forms...*

Keywords: Sustained release, Dose frequency, Drug properties , Biological half life

I. INTRODUCTION

In the description of oral dosage forms . It involves all the modified release properties these are following ; delayed release, repeated action release, prolonged release, sustained release,extended release and controlled release.
Sustained release tablets is defined as the type of dosage form in which two part takes place first part of drug is initial dose which is released immediately which achieves therapeutic effect and remaining part is released slowly to achieve therapeutic effect which is for long period of time but not constant or same. Sustained release means the slow release of the drug for a long period of timeThe design of sustained release tablets to provide a quick effect of a drug plasma level that stage same within therapeutic index of a drug for the specific period of time or gaining a plasma concentration of drug that shows sustained release that remains or stays within therapeutic range.
Sustain release tablets are taken once or twice in a day.During the treatment of diseases or disorder conventional dosage forms are required to take 3 to 4 times in a day to achieve the same therapeutic effect.
The main purpose of the administrating a single dose of sustained release dosage form which is an longer period of time to maintain the same concentration of drug in blood serum which is improve the patients complaints and provide a therapeutic effect of drug.

OBJECTIVES OF SUSTAINED RELEASE TABLETS :
• To achieve the slow or extended release of drug.
• To improves the patients compliance.
• It provides the pharmacodynamics, pharmacokinetic properties.
• To minimize the dose frequency.
• To minimizes the side effects.
• It increases the safety margin.
• To optimize the delivery of medication.

ADVANTAGES OF SUSTAINED RELEASE TABLETS :
1] Patient Compliance :
In the long term treatment of chronic diseases or disorders lack of compliance occurs. Effects of treatment of drug which is a depends on the patient's ability to comply with the regimen. Patience compliance are improved by following factors such as his understandings, awareness related disease process, patience faith in treatment which is important to improve the patience health or strict treatment plan. Complications of therapeutic regimen or plan, cost of treatment,

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local and systemic side effects of the dosage forms. By the administration of sustained release tablets which shows the improvement in problem of lack of patient Compliance.

2] Reduced fluctuation :
A sustained release tablets can minimizes the frequency of drug dosing & maintain a concentration in blood circulation & target cells.

3] Reduced total Dose :
In this there is no need to increase the frequency of dose because when we administered the sustain release dosage form which shows the effect over an extended period of time.So it minimizes the dose frequency as well as side effects, which is great for economy.

4] Improved efficiency in treatment :
Optimal therapy of disease requires effective delivery of medication to the tissue, organ and targeted site.Some doses are requires in large amount for specific therapeutic effect at particular site.When we give the doses in large amount there is chances to show some toxicological, undesirable and immunological diseases at non targeted site.For these improvement administered the sustained release dosage form which provides the better management in acute and chronic disease conditions.

5] Economy :
The initial cost of sustained release products is greater than the conventional dosage form because of the special nature of these compounds but overall average cost of treatment or therapy over a extended period of time may be less.

DISADVANTAGES OF SUSTAINED RELEASE TABLETS:
1] Dosage form design :
The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

2] Patient variation :
Sustained release dosage forms are designed for the normal peoples that is on the basis of average drug biologic half-life. Some disease conditions which alter drug disposition, patient variation and so this are not accommodated.

3] Economic factors :
In the manufacturing of sustained release tablet some products, processes and equipments are costly so some economic factors are assessed.

4] Poor In-Vivo and In-Vitro correlations :
In sustained release dosage form, the drug release rate is reduced to achieve drug release over a gastro intestinal tract.Here so called "Absorption Window"becomes important may give rise to undesirable drug absorption in-vivo excellent in-vitro release characteristics.

5] Dose dumping :
In sustained release formulation dose dumping of a drug introducing potential toxic quantities of the drug into the systemic circulation. Some drugs have a narrow therapeutic index which can lead to those dumping in case of potent drug. e.g. Phenobarbital.

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FACTORS AFFECTING SUSTAINED RELEASED DOSAGE FORMS :
PHARMACOKINETIC AND PHARMACODYNAMICS FACTORS
• Biological half life.
• Absorption.
• Distribution.
• Metabolism.
• Margin of safety/Therapeutic index.

DRUG PROPERTIES RELEVANT TO SUSTAINED RELEASE FORMULATIONS
• Dose size.
• Ionisation , pka and aqueos solubility.
• Partition coefficient.
• Drug stability.
• Protein binding.

PHARMACOKINETIC AND PHARMACODYNAMICS FACTORS BIOLOGICAL HALF LIFE :
Those drugs which are having biological half-life of 2-8 hours which are suitable for sustain release dosage forms, since they minimizes the dosing frequency.This drugs having very short biological half-life which is requires a excessive large amount of drug in each dosage form to maintain the sustained effects.

ABSORPTION :
Absorption rate of sustained release formulation depends on rate of releasing of the drug from dosage form and the drugs which is absorbed by the active transport and absorption is limited to intestine.

DISTRIBUTION :
The distribution of drug in body is most important factors in overall elimination process.This is not only lower's the concentration of drug in blood but it also can we read limiting in it's equilibrium with blood.The apparent volume of distribution is depending on the time of drug

METABOLISM :
Drugs which are metabolized before absorption either in the lumen or tissue of the intestine, which can show lower bioavailability from slower releasing dosage form.Drugs which are having variation in bioavailability due to the first pass metabolism or intestinal metabolism which are not suitable for sustain release dosage forms.

MARGIN OF SAFETY / THERAPEUTIC INDEX :
Safety margin of a drug can be considered as therapeutic index.It can be show as; Therapeutic index = (TD)50 / (ED)50 .If the therapeutic index is more than 10 then a drug is considered to be safe i.e larger the ratio then drug is more safe.Safety margin is directly proportional to the ratio of therapeutic index.Some drugs having narrow therapeutic index which is more accurate maintain the plasma concentration within the narrow therapeutic range.

2]DRUG PROPERTIES RELEVANT TO SUSTAINED RELEASE FORMULATIONS DOSE SIZE :
The maximum dose size for a conventional dosage form is range between 500-1000mg.This dose size is also apply for sustained release dosage forms.Dose size is important parameter for the safety involved in large amounts administration with narrow therapeutic range.

IONISATION, PKA AND AQUEOUS SOLUBILITY :
Most of the drugs having weak acids or weak bases for a drug to be it get absorbed.It must be dissolves surrounding the site of action in aqueous phase and then partition into the absorbing membrane takes place.

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PARTITION COEFFICIENT :

Partition coefficient is majorly affected the bioavailability of drug.Biological membrane is lipophilic in nature.Transport of the drug majorly depends on the partition coefficient.Those drugs which is having low partition coefficient are not suitable for sustained release formulation.

Eg :- barbichuric acid and vice versa.

DRUG STABILITY :

When drugs are administered they come into contact with acid-base hydrolyzes and enzymatic degradation.Then the drug is unstable in stomach and drug release system which provides the medication over and extended period of time.Whereas the drug eat unstable in intestine show the less bioavailability.

PROTEIN BINDING :

It is well known in which many drugs are bind with the plasma proteins which affect on the duration of drug action.Most part of the blood proteins are re-circulated and not eliminated.

Drug protein binding can serves a prolonged release profile especially when if a high degree of drug binding occurs.

PARAMETERS FOR DRUG WHICH IS FORMULATED IN SUSTAIN RELEASE DOSAGE FORM :

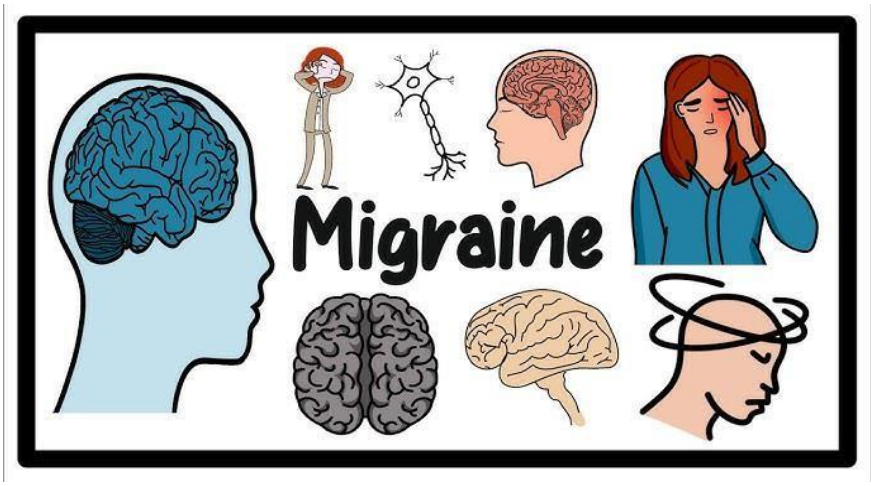
1) Physio-chemical parameters for drug selection :

• Molecular weight/size<1000 Daltons.
• Solubility>0.1 mg/ml for pH 1 to pH 7.8.
• Apparent partition coefficient is high.
• absorption mechanism diffusion.
• General absorbability from on GI segments.

Pharmacokinetic parameters for drug selection :

• Elimination half life of dosage form is between 2-8 hours.
• Total clearance should not be dose dependent.
• Elimination rate constant required for design.
• Apparent volume of distribution (Vd),If the apparent volume of distribution (Vd) and minimum effective concentration (MEC) is larger then required dose size should be increased.

MIGRAINE :-



The term migraine is originated from Greek word "hemicrania" meaning one side of the head.Migraine is a severe condition which is having a wide variety of symptoms.Painful headache is a main feature of the migraine in many

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patients. It involves pulsating headache, usually occurs to one side (unilateral) which comes in attacks lasting 4-48 hours.Other symptoms like feeling sick, vomiting, irritability, dizziness,nasal congestion and sensitivity to light sound and smells.Migraine is one of the common causes of throbbing headaches.
According to IHS, migraine mainly contains 16% of primary headaches. Migraine affects the 10-20% of the general population. In India 15 - 20% of people suffer from migraine.Migraine
majorly affects 18% of women and 6% of men in the United States So, migraine affects women more than men. For both men and women, the prevalence of migraine is increases in adult life and decreases after midlife.In girls and womens, the rate of migraine is greater between age 10 and 30 years.Migraine is and undertreated.

DEFINITION OF MIGRAINE :
"Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting."

DIAGNOSIS OF MIGRAINE :
Headache attacks are occurs for 4-72 hours (which is untreated).

• Headache has atleast two of the following;
• Unilateral location.
• Pulsating quality.
• severe pain intensity.
• It is caused by avoidance of daily routine physical activity like walking or climbing stairs.
• During a headache at least one of the following;
• Nausea and vomiting.
• Photophobia and phonophobia.

DRUG USED IN MIGRAINE :
1] ABSORPTIVE MEDICATIONS :
1) ANALGESICS WITH CAFFEINE :
Ex :- Acetaminophen, Aspirin and Caffeine.

2) TRIPTANS :
Ex :- Suma, Riza, Nara, Algo, Zolmi 5-HT antagonists.

3) NON-STEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDS) :
Ex :- Ibuprofen, Naproxen sodium.

4) ANTIEMETICS :-
Ex :- Domeperidone.

5) ANALGESICS WITH CAFFEINE AND BARBITURATES.
2] PREVENTIVE MEDICATIONS :

1) NSAIDS :
Ex :- Ketoprofen, Naproxen sodium.

2) BETA BLOCKERS :
Ex :- Propanol , Timolol maleate and Metoprolol.

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3) CALCIUM CHANNEL BLOCKERS :
Ex :- Diltiazem and Nifedipene.

4) ANTIDEPRESSANTS :
Ex :- Fluoxetine, Paroxetin and Setraline.

5) ANTICONVULSANTS :
Ex :- Valproic acid or Divalproex sodium.

DRUG PROFILE :

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID).
Naproxen is a pain medication that relieves inflammation and joint stiffness. Other NSAIDs in the same medication class include acetylsalicylic acid, diclofenac, ibuprofen, and meloxicam.Naproxen works by blocking the enzyme that produces prostaglandins. Prostaglandins play an essential role in inflammation. The body produces them at the site of injured tissue, and they cause redness, heat, swelling, and pain.Naproxen is available as naproxen or naproxen sodium. The major difference between naproxen and naproxen sodium is that naproxen sodium is more rapidly absorbed.The body reaches peak levels of naproxen in 2–4 hours and naproxen sodium in 1–2 hours, meaning that it absorbs naproxen sodium faster than regular naproxen. Naproxens are act as a anti inflammatory agent. Naproxen is used to treat the various types of inflammation which is due to pain fever.Naproxen release pain which is occurs due to inflammation such as migraines, osteoarthritis, kidney stones, rheumatoid arthritis, gout, menstrual cramps. Naproxen sodium is available in both immediate release as well as sustained release. Sustained release formulations may take more time to show effect than the immediate release so, when immediate pain occurs it is less useful.Sustained release dosage forms are required in chronic conditions and long lasting pain which is useful in this conditions.There are mainly two types of neproxen which is;
• Regular naproxen
• Naproxen sodium
Regular naproxen comes under an oral immediate-release tablet, an oral delayed-release tablet, and an oral suspension. Naproxen sodium comes as an oral immediate-release tablet and an oral extended-release tablet.

PHARMACOKINETICS OF NAPROXEN :
• Absorption
• Distribution
• Metabolism

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1] Absorption :

Naproxen is non steroidal anti inflammatory drug.When naproxen drug given orally the absorption rate is high and complete.When neproxen drug enters in GIT rapidly dissolves the particles of drug or dosage form.The sodium salts produce higher plasma level of neproxen.

The absorption of neproxen sodium in GIT is complete.When oral and intravenous dosage are administered oral dosage are shows more effect compared by intravenous dosage.

2] Distribution :

After absorption naproxen iis distributed or circulates in blood and binds to the plasma albumin.Neproxen has small amount of distribution, about 10% of body.Neproxen has very long half life 10 to 11 hours in humans.

Plasma level of neproxen in blood is directly proportional to therapeutic range of dose.

3] Metabolism :

Naproxen is acidic in nature .It is highly bound to the albumin so the simple metabolism takes place.After the administration of naphroxen it is completely absorbed.Half life of nephroxen is very long so we administer twice in a day.

The kinetics of naproxen binding to serum albumin can maintain the plasma level.Both naproxen and product of it's metabolite transformations are excreted in the urine (95%).

PHARMACODYNAMICS OF NAPROXEN :

The main action of naproxen is inhibite the action of prostaglandins.Naproxens acts on the all actions of prostaglandins and related thromboxane and prostacyclin.All Non steroidal anti- inflammatory l drugs acts similarly but there is chances of difference in tolerance and inhibition which affect the efficiency of dosage forms.It has also shows antipyretic and analgesic effect.In recent research shows the compound causing capability of greater inhibition in one part than other part.

USES OF NAPROXEN :

• Naproxen is majorly used in the treatment of migraine.
• Naproxen is acts as a anti- inflammatory agent which is used to minimizes the excessive inflammation of rheumatoid arthritis, osteoarthritis and kidney stones.
• Naproxen is analgesics which gives therapeutic effects.
• Naproxen shows the more therapeutic effect of anti-inflammatory drugs as compare to other drugs like Aspirin, Ibuprofen.
• Naproxen is also used to reduce the pain and symptoms of dysmenorrhea.
• Naproxen is acts as a painkiller in menstrual cramps.
• It is also used to reduce the dental pain.

MATERIAL AND INSTRUMENTS :

Following ingredients are used in formulation of naproxen sustained release tablet; 1] Active pharmaceutical ingredients; Naproxen Sodium

2] Excipients :

• Hydroxy propyl methylcellulose.
• Ethyl cellulose.
• Microcrystalline cellulose.
• Magnesium stearate.
• Providone.
• Sodium bicarbonate.

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1] ACTIVE PHARMACEUTICAL INGREDIENTS :
Active Pharmaceutical Ingredients are the active ingredients contained in a medicine.
It is that part of the medicine that produces the intended therapeutic effects. For example, in a painkiller, the active ingredient relieves pain.
Naproxen Sodium (C14H13NaO3) :
This is the active pharmaceutical ingredients responsible for the therapeutic effect.

2] EXCIPIENTS :
These are the inactive ingredients that helps in the formulation and release of the medication. Some common excipients are used in naproxen sustained release tablet include :-
Hydroxy propyl methylcellulose (HPMC) :- it is a polymer that forms gel like matrix, controlling the release of drug.
Ethyl cellulose :- It is another type of polymer that provides sustained release properties.
Microcrystalline cellulose :- It act as a filler and binder in tablet formulation.
Magnesium stearate :- A lubricant that aids in tablet compression.
Providone :- It helps in improving the dissolution of the drug.
Sodium bicarbonate :- It can be used as a pH modifier in the formulation.

INSTRUMENTS :
1. Coating pan
2. Fluid bed granulators
3. Tablet compression machine
4. Blending machine
5. Dissolution tester
6. Tablet hardness tester
7. Stability chambers
8. Electronic weighing balance
9. Friability test apparatus

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10. pH meter
11. Eight station rotary tableting machine

METHOD OF PREPARATION :

Following methods are used in the preparation of naproxen sodium.

1] Formulation
2] Weighing and mixing.
3] Granulation.
4] Compression.
5] Coating.
6] Quality control.

1] FORMULATION :

Determine the desired release profile and select the appropriate excipients and release mechanisms.

2] WEIGHING AND MIXING :

Weigh the required amount of naproxen sodium and excipients according to the formulation. Thoroughly mix them together to ensure uniform distribution.

3] GRANULATION :

Granulate the mixture to form uniform granules.

This can be done using wet granulation or dry granulation techniques.

4] COMPRESSION :

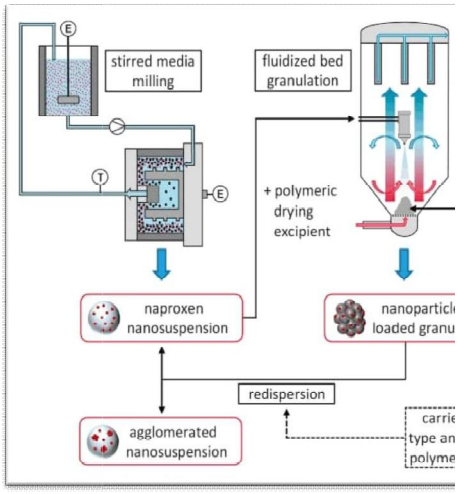
Compress the granules into tablet form using a tablet press. The tablets should be designed to provide sustained release of the medication.

5] COATING :

Apply a coating to the tablets if desired to further control the release of the drug. The coating can be designed to dissolve slowly or be pH-dependent.

6] QUALITY CONTROL :

Perform quality control tests to ensure the tablets meet the required specifications for release rate, drug content, and other parameters.



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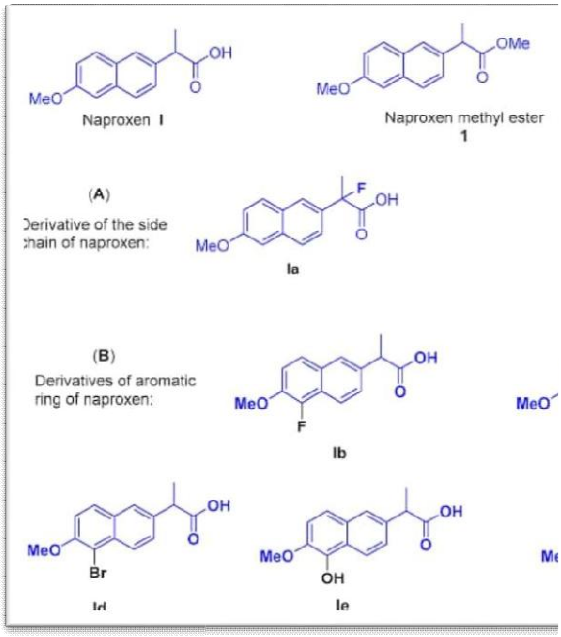

CONCLUSION:

From the about discussion it is concluded that Sustained Release Tablet is one of the most effective dosage forms. It is helpful in increasing patients compliance and also improves efficiency in the treatment of migraine.It minimizes the side effects by minimizing the dose frequency .So, the developed tablet can show the maximum therapeutic effect as compared to other like Ibuprofen, Aspirin on the treatment of migraine.

RESULTS

1. Pre-formulation Studies

Melting Point: 154°C (Matches standard value)

Solubility: Sparingly soluble in water, freely soluble in alcohol and acetone

Drug-Excipient Compatibility: FTIR spectra showed no significant interaction between naproxen and selected excipients.

Formulation Techniques:

Wet Granulation Technique: This method has been used to prepare sustained-release matrix tablets of naproxen using different concentrations of HPMC-K4M, HPMC-K100, and DCP polymers.

Matrix Tablets: Naproxen sustained-release matrix tablets have been formulated using various grades of HPMC and insoluble fillers to study their effect on drug release

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Final Product

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