Clinical and Medical Research and Studies

www.alcrut.com

Research Article **Clinical and Medical Research and Studies** **Open Access**

Formulation And Evaluation of Naproxen Suppositories by Varying Concentration of Gelatin Base

Dr. C. Madhavi latha [1]*, Ch. Ramadevi[2], P. Harika[3], k. Rasi[3]

[1]Principal, Sree Venkateswara College of pharmacy, North rajupalem, Nellore, Aandra Pradesh, India.

[2]Associate Professor, Sree Venkateswara college of pharmacy, Nellore

[3]Assistant Professor, Sree Venkateswara college of pharmacy, Nellore

***Corresponding Author:** Dr. C. Madhavi latha, Principal, Sree Venkateswara College of pharmacy, North rajupalem, Nellore, Aandra Pradesh, India.

Received: 02 January 2024 | **Accepted:** 20 January 2024 | **Published:** 24 January 2024

Citation: C. Madhavi latha, Ch. Ramadevi, P. Harika, K. Rasi. Formulation And Evaluation of Naproxen Suppositories by Varying Concentration of Gelatin Base. J. Clinical and Medical Research and Studies. 3(1) DOI: 10.59468/2836-8525/037

Abstract

A greater risk for mild cognitive impairment (MCI), women make up almost two-thirds of Alzheimer's disease (AD) patients in the United States. The higher prevalence of AD in women has been attributed previously to longer female life expectancy or sociocultural detection biases.

Keywords: Mild cognitive impairment; neurobiologic vulnerability; Framingham study

HISTORY OF SUPPOSITORIES

The Babylonians and the Egyptians are the oldest civilizations to leave records of practical drug use dating from 2000 BCE, and both cultures used Suppositories of some form.

The Babylonians had two forms of Medical Practitioners, the Asipu (Magical Healer), and The Asu (Empirical Healer) and The Asus are the ones who used suppositories as a Dosage Form.

The Ancient Egyptians has left a great Papyrus talking about the various Dosage Forms, and Suppositories were mostly used for GIT problems.

Popularity of the Suppositories since the 1840s, the use of suppositories has increased, after Scientists have found out about the range of diseases that are best treated by suppositories.

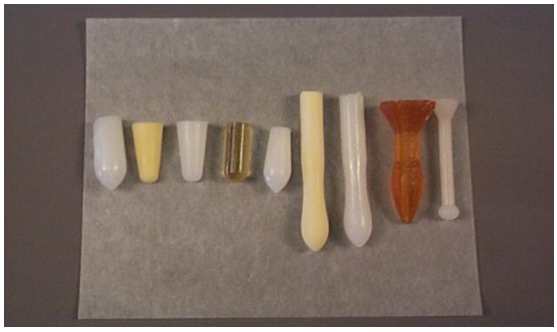
Today Suppositories are one of the Main Dosage forms that have proven its uniqueness among other dosages forms.

INTRODUCTION

Suppositories are medicated, solid bodies of various sizes and shapes suitable for introduction into body cavities. The medicament is incorporated into a base such as cocoa butter which melts at body temperature, or into one such as glycerinated gelatin or PEG which slowly dissolves in the mucous secretions. Suppositories are suited particularly for producing local action, but may also be used to produce a systemic effect or to exert a mechanical effect to facilitate emptying the lower bowel.

The ideal suppository base should be nontoxic, nonirritating, inert, compatible with medicaments, and easily formed by compression or

molding. It should also dissolve or disintegrate in the presence of mucous secretions or melt at body temperature to allow for the release of the medication. As with the ointment bases, suppository base composition plays an important role in both the rate and extent of release of medications.



Routes of Administration That Utilize Suppositories

Suppositories are medicated solid formulations that are inserted into body cavities. They are made in a variety of shapes and sizes because they are used in many different routes of administration (body cavities).

Rectal

Drugs administered via the rectum are given for a local effect or to achieve a systemic effect. Local effects may include the soothing of inflamed hemorrhoidal tissues, promoting laxation, and enemas. Using rectal administration to achieve systemic activity is preferred when the drug is destroyed in the GI tract, if oral administration is not possible because of vomiting, or the patient is unconscious or incapable of swallowing oral formulations. Rectal administration has been used to treat a variety conditions such as asthma, nausea, motion sickness, anxiety, and bacterial infections.

The most common rectal formulations are suppositories, solutions, and ointments. Suppositories are solid dosage forms that dissolve or melt when inserted into the rectum. Suppositories are manufactured in a variety of shapes. Rectal suppositories for adults are tapered at one end and usually weigh about 2 grams. Infant rectal suppositories usually weight about 1 gram or about half that of adult suppositories.

The major disadvantages of rectal suppositories:

They are not preferred by patients; they are inconvenient.

Rectal absorption of most drugs is frequently erratic and unpredictable.

Some suppositories "leak" or are expelled after insertion.

Vaginal

Vaginal administration has many advantages.

Generally there is less drug degradation via this route of administration compared to oral administration

The dose can be retrieved if necessary

There is the potential of long term drug absorption with various intrauterine devices (IUDs).

Vaginal administration does lead to variable absorption since the vagina is a physiologically and anatomically dynamic organ that causes pH and membrane permeability to change over time. There is also a tendency of some dosage forms to be expelled after insertion into the vagina.

Vaginal formulations include solutions, powders for solutions, ointments, creams, aerosol foams, suppositories, and tablets. Vaginal suppositories are employed as contraceptives, feminine hygiene antiseptics, bacterial antibiotics, or to restore the vaginal mucosa. Vaginal suppositories are inserted high in the vaginal tract with the aid of a special applicator. The suppositories are usually globular, oviform, or cone-shaped and weigh between 3 - 5 grams. Patients should be instructed to quickly dip the suppository in water before insertion. Because suppositories are generally used at bedtime and can be messy if the formulation is an oleaginous base, patients should wear a sanitary napkin to protect nightwear and bed linens.

Urethral

Urethral suppositories are not specifically described in the USP 24/NF19 either by weight or dimension. Traditionally, they are cylindrical in shape (3 - 6 mm in diameter) and vary in length according to gender. Female urethral suppositories can be 25 - 70 mm in length while male urethral suppositories can be about 50 - 125 mm in length. The one commercially available urethral suppository is actually marketed as a "pellet," and is 1.4 mm in diameter and 3 or 6 mm in length depending on strength. Urethral suppositories are unusual and may not be encountered in a compounding practice.

Inserting Rectal Suppositories

If possible, go to the toilet and empty bowels.

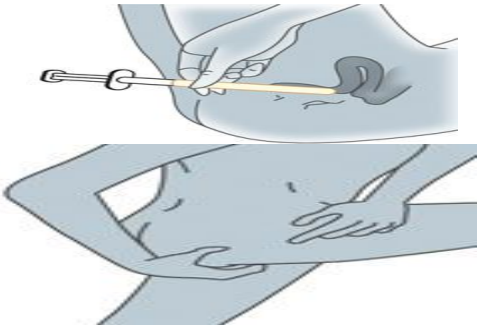
Wash hands carefully with soap and warm water.

Remove any foil or plastic wrapping from the suppository.

Lubricate the tapered end of the suppository with a small amount of K-Y® Jelly. If the jelly is not available, moisten the suppository with a small

amount of water.

Either stand with one leg on a chair, or lay on one side with one leg straight or the other leg bent toward your stomach.

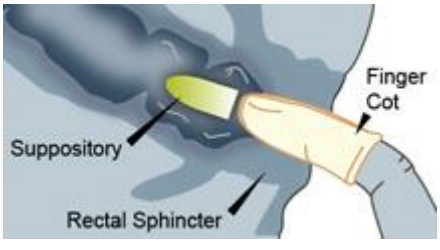


Separate buttocks to expose the rectal area.

Gently but firmly push the suppository into the rectum until it passes the sphincter (about 1/2 to 1 inch in infants, and 1 inch in adults.

Close your legs and sit (or lay) still for about 15 minutes. Avoid emptying bowels for at least one hour (unless the suppository is a laxative). Avoid excessive movement or exercise for at least one hour.

Wash hands again with soap and warm water immediately after inserting the suppository



Vaginal Inserting Suppositories

Wash your hands carefully with soap and warm water.

Remove any foil or plastic wrapping from suppository.

Place suppository in applicator.

Hold the applicator by the opposite end from where the suppository is.

Either lay on your back with your knees bent, or stand with your feet spread a few inches apart and your knees bent.

Gently insert the applicator into the vagina as far as it will go comfortably. Once you are ready, push the inside of the applicator in and place the suppository as far back in the vagina as possible.

Remove the applicator for the vagina.Wash your hands again with soap and warm water

SUPPOSITORY BASES

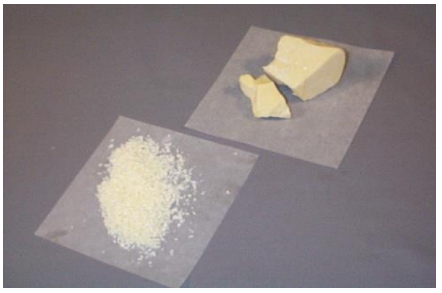
Suppository bases may be conveniently classified as according to their composition and physical properties:

Oleaginous (fatty) bases

Water soluble or miscible bases

1.Oleaginous Bases:

Oleaginous bases include Theobroma Oil and synthetic triglyceride mixtures.



Theobroma Oil or cocoa butter is used as a suppository base because, in

large measure, it fulfills the requirements of an ideal base. At ordinary room temperatures of 15° to 25°C (59° to 77°F), it is a hard, amorphous solid, but at 30° to 35°C (86° to 95°F), i.e., at body temperature, it melts to a bland, nonirritating oil. Thus in warm climates, theobroma oil suppositories should be refrigerated.

Particular attention must be given to two factors when preparing suppositories with cocoa butter base. First, this base must not be heated above 35°C (95°F) because cocoa butter is a polymorphic compound and if overheated will convert to a metastable structure that melts in the 25° to 30°C (77° to 86°F) range. Thus, the finished suppositories would melt at room temperature and not be usable.

The second factor is the change in melting point caused by adding certain drugs to cocoa butter suppositories. For example, chloral hydrate and phenol tend to lower the melting point. It may be necessary to add spermaceti or beeswax to raise the melting point of finished suppositories back to the desired range.

The newer synthetic triglycerides consist of hydrogenated vegetable oils. Their advantage over cocoa butter is that they do not exhibit polymorphism. They are, however, more expensive. Some of the bases are single entity formulations. Some of the names may denote a series of bases. In a series, the bases are varied to give a range of melting points. For example, Fattibase is a single entity base that consists of triglycerides from palm, palm kernel, and coconut oils. Wecobee is a series of bases. Wecobee FS, M, R, and S are all made from triglycerides of coconut oil. But FS has a melting point range of 39.4 to 40.5°C, M has a range of 33.3 to 36.0°C, R has a range of 33.9 to 35.0°C, and S has a range of 38.0 to 40.5°C. Other triglyceride type bases include Dehydag, Hydrokote, Suppocire, and Witepsol

2.Water Soluble/Water Miscible Bases:

Water soluble/water miscible bases are those containing glycerinated gelatin or the polyethylene glycol (PEG) polymers.

Glycerinated Gelatin is a useful suppository base, particularly for vaginal suppositories. It is suitable for use with a wide range of medicaments including alkaloids, boric acid, and zinc oxide. Glycerinated gelatin suppositories are translucent, resilient, gelatinous solids that tend to dissolve or disperse slowly in mucous secretions to provide prolonged release of active ingredients.

Suppositories made with glycerinated gelatin must be kept in well-closed containers in a cool place since they will absorb and dissolve in atmospheric moisture. In addition, those intended for extended shelf-life should have a preservative added, such as methylparaben or propylparaben, or a suitable combination of the two. To facilitate administration, glycerinated gelatin suppositories should be dipped in water just before use.

Polyethylene Glycol Polymers have received much attention as suppository bases in recent years because they possess many desirable properties. They are chemically stable, nonirritating, miscible with water and mucous secretions, and can be formulated, either by molding or compression, in a wide range of hardness and melting point. Like glycerinated gelatin, they do not melt at body temperature, but dissolve to provide a more prolonged release than theobroma oil.

Certain polyethylene glycol polymers may be used singly as suppository bases but, more commonly, formulas call for compounds of two or more molecular weights mixed in various proportions as needed to yield a finished product of satisfactory hardness and dissolution time.

Since the water miscible suppositories dissolve in body fluids and need not be formulated to melt at body temperature, they can be formulated with much higher melting points and thus may be safely stored at room temperature.

Methods of Preparation

Suppositories can be extemporaneously prepared by one of three methods.

1. Hand Rolling is the oldest and simplest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of heating the cocoa butter. A plastic-like mass is prepared by triturating grated cocoa butter and active ingredients in a mortar. The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The

cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape.

Effective hand rolling requires considerable practice and skill. The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.

2. Compression Molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mold. The method requires that the capacity of the molds first be determined by compressing a small amount of the base into the dies and weighing the finished suppositories. When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.

3. Fusion Molding involves first melting the suppository base, and then dispersing or dissolving the drug in the melted base. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them.

Suppositories are generally made from solid ingredients and drugs which are measured by weight. When they are mixed, melted, and poured into suppository mold cavities, they occupy a volume – the volume of the mold cavity. Since the components are measured by weight but compounded by volume, density calculations and mold calibrations are required to provide accurate doses.

When a drug is placed in a suppository base, it will displace an amount of base as a function of its density. If the drug has the same density as the base, it will displace an equivalent weight of the base. If the density of the drug is greater than that of the base, it will displace a proportionally smaller weight of the base. Density factors for common drugs in cocoa butter are available in standard reference texts. The density factor is used to determine how much of a base will be displaced by a drug.

The relationship is:

For example, aspirin has a density factor in cocoa butter of 1.3. If a suppository is to contain 0.3 g of aspirin, it will replace 0.3 g ÷ 1.3 or 0.23 g of cocoa butter. If the blank suppository (suppository without the drug) weighed 2 g, then 2 g - 0.23 g or 1.77 g of cocoa butter will be needed for each suppository, and the suppository will weigh 1.77 g + 0.3 g = 2.07 g. So if a pharmacist was making 12 aspirin suppositories using cocoa butter as the base, he would weigh 1.77 g × 12 or 21.24 g of cocoa butter and 0.3 g × 12 or 3.6 g of aspirin.

Aluminum metal molds come in a variety of cavity sizes and with a variety of number of cavities per mold. Common sizes vary from 1 g to 2.5 g, and common number of cavities range from 6 cavities up to 100 cavities. The two halves of the mold are held together with either nuts or some molds have 1 centered screw.

Plastic suppository shells come in long strips that can be torn into any number of cavities. The suppository mixture is poured directly into the shell up to a mark. These disposable molds do not need any lubrication regardless of the suppository mixture. When the mixture has hardened, the plastic mold is heat sealed. When a patient is ready to use a suppository, they select one shell and peel the sides of the shell off to obtain the suppository. One advantage of this type of mold is that if the suppository should melt, it will not run out of the mold. If the material can ongeals again, it will retain the suppository shape. This type of mold is available in 1 g to 5 g sizes, and many different colors.

There are also suppository molds made from flexible rubber. When the suppository mixture has congealed in these molds, the finished suppositories are "pushed" out of each cavity. If the prescription does not require all of the cavities in the strip, it can be trimmed with scissors. These flexible rubber molds are ideal if the suppositories need to be refrigerated (shells also are suitable for this purpose).

Very hard rubber molds are similar to the metal molds in that they have screws to hold the mold together. When the suppository mixture has congealed, the screws loosened, and the suppositories are removed. This photograph is a picture of an urethral mold. If you enlarge the image, you can see PEG suppositories in one side of the mold. Such thin suppositories require a great deal of investigation to get the desired consistency and strength. If the suppositories are too soft, it is very difficult to remove them from the mold. This particular casting had 70% PEG 3350 and 30% PEG 400.

Pouring and Opening Suppository Molds

Molds should be filled only when they are at room temperature. A cold or frozen mold should never be used because it can cause fractures and fissures throughout the suppository. Each cavity should be filled slowly and carefully ensuring that no air bubbles are entrapped in the cavity. To prevent layering in the suppositories, the pouring process should not be stopped until all the cavities have been filled. Molds should be allowed to set at room temperature. Refrigeration should only be used if the suppository has not congealed after 30 to 40 minutes.

Aluminum molds usually require lubrication before use. Hard rubber molds may require lubrication. One way is to use a vegetable oil spray. Other lubricants include light mineral oil when water soluble bases are being used and glycerin or propylene glycol when oleaginous bases are being used. Whatever lubricant is used, only a light coating is needed. If too much lubricant is used, the excess will pool in the tip of the suppository cavity. Any excess lubricant should be wiped off with an absorbant tissue such as a Kimwipe.

When suppository mixtures and bases cool, they contract. Some mixtures and bases have very pronounced contractions (e.g., cocoa butter, PEG) while others have much smaller ones (e.g., glycerinated gelatin). This contraction will produce a hole in the open end of the suppository. Such a hole is undesirable. If the suppository mixture is poured just immediately before it reaches its congealing temperature, the contraction will be minimized. It is also helpful to pour a small excess of the suppository mixture on top of the open end of the mold.

When filling a suppository mold, start pouring the melt at one end and pour continuously without stopping. Don't go to the next cavity until the previous cavity is filled and a slight excess has been poured to overfill the cavity. Excess base can be removed once the suppositories have congealed by trimming the top of the mold with a warm stainless steel spatula.

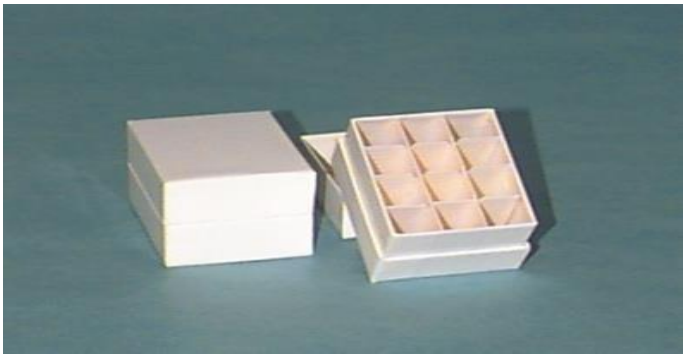
Suppositories shells are generally poured using a back light to help visualize the mark on the shell. Some molds (depending on the size or type of the suppository) cannot be poured, but the mixture is added using a syringe.

Examples of each of these pouring (or filling techniques) are given.

When the suppository mixture has congealed, the excess mass is removed from the top surface of the mold and the mold is separated into the two halves. An efficient way to separate the mold is to remove the wing nuts or loosen the centered screw and place the mold so that the posts rest on the table top. Then apply a downward pressure only on the bottom half of the mold. A knife or spatula should not be used to pry the two halves apart. This will damage the matching mold faces which have been accurately machined to give a tight seal.

Suppository shells can be opened by peeling the halves apart if this type of shell is used. There are suppository shells that do not peel apart at the bottom but must be torned along its edge. These are very difficult to open, and should not be used.

Suppositories that are not in a plastic shell mold or flexible rubber mold should be wrapped before they are dispensed. This will provide protection for the suppository and limit any oil staining that might occur from the materials contained in the suppository base.



Once the suppositories are wrapped, they are generally placed in a special box that has dividers for each suppository.

Flexible rubber molds can be packaged with the suppository still in the mold. Generally the mold is placed in a special box. Plastic shell molds must be heat-sealed. Heat sealing is generally a two step process. First the open end of the shell is "shrunk" with the aid of heat. A hair dryer (at highest hot setting) is capable of providing enough heat to shrink the plastic. There are laboratory type hot air "guns" that also can be used. The heat will cause the two sides of the opening to collapse together and begin to seal the opening. The second step is to use an electric sealer to completely seal the opening.

DRUG INTRODUCTION

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body.

Naproxen is used to treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps.

The delayed-release or extended-release tablets are slower-acting forms of naproxen that are used only for treating chronic conditions such as arthritis or ankylosing spondylitis. These forms will not work fast enough to treat acute pain.

You should not use naproxen if you have a history of allergic reaction to aspirin or other NSAID (non steroidal anti-inflammatory drug).

Naproxen can increase your risk of fatal heart attack or stroke, especially if you use it long term or take high doses, or if you have heart disease. Do not use this medicine just before or after heart bypass surgery (coronary artery bypass graft, or CABG).

Get emergency medical help if you have chest pain, weakness, shortness of breath, slurred speech, or problems with vision or balance.

Naproxen may also cause stomach or intestinal bleeding, which can be fatal. These conditions can occur without warning while you are using

this medicine, especially in older adults.

Naproxen can increase your risk of fatal heart attack or stroke, especially if you use it long term or take high doses, or if you have heart disease. Even people without heart disease or risk factors could have a stroke or heart attack while taking this medicine.

Do not use this medicine just before or after heart bypass surgery (coronary artery bypass graft, or CABG).

Naproxen may also cause stomach or intestinal bleeding, which can be fatal. These conditions can occur without warning while you are using naproxen, especially in older adults.

You should not use naproxen if you are allergic to it, or if you have ever had an asthma attack or severe allergic reaction after taking aspirin or an NSAID.

Ask a doctor or pharmacist if it is safe for you to use this medicine if you have:

heart disease, high blood pressure, high cholesterol, diabetes, or if you smoke;
a history of heart attack, stroke, or blood clot;
a history of stomach ulcers or bleeding;
asthma;
liver or kidney disease; or
Fluid retention.

Taking naproxen during the last 3 months of pregnancy may harm the unborn baby. Do not use this medicine without a doctor's advice if you are pregnant.

Naproxen can pass into breast milk and may harm a nursing baby. You should not breast-feed while using this medicine.

Naproxen is not approved for use by anyone younger than 2 years old. Do not give this medicine to a child without medical advice.

Use naproxen exactly as directed on the label, or as prescribed by your doctor. Do not take this medicine in larger amounts or for longer than recommended. Use the lowest dose that is effective in treating your condition.

Do not crush, chew, or break a naproxen tablet. Swallow it whole.

Shake the oral suspension (liquid) well just before you measure a dose. Measure liquid medicine with the dosing syringe provided, or with a special dose-measuring spoon or medicine cup. If you do not have a dose-measuring device, ask your pharmacist for one.

If you change brands, strengths, or forms of naproxen, your dosage needs may change. Ask your pharmacist if you have any questions about the type of medicine you are using.

If a child is using this medicine, tell your doctor if the child has any changes in weight. Naproxen doses are based on weight in children, and any changes may affect your child's dose.

If you use naproxen long-term, you may need frequent medical tests.

This medicine can cause unusual results with certain medical tests. Tell any doctor who treats you that you are using naproxen.

Store at room temperature away from moisture, heat, and light. Keep the bottle tightly closed when not in use.

Since naproxen is sometimes used only when needed, you may not be on a dosing schedule. If you are on a schedule, use the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not use extra medicine to make up the missed dose.

Avoid drinking alcohol. It may increase your risk of stomach bleeding.

Avoid taking aspirin while you are taking naproxen.

Ask a doctor or pharmacist before using any cold, allergy, or pain medicine. Many medicines available over the counter contain aspirin or other medicines similar to naproxen. Taking certain products together can cause you to get too much of this type of medication. Check the label to see if a medicine contains aspirin, ibuprofen, ketoprofen, or naproxen.

Ask your doctor before using an antacid, and use only the type your doctor recommends. Some antacids can make it harder for your body to absorb naproxen.

Naproxen side effects

Get emergency medical help if you have signs of an allergic reaction to naproxen: sneezing, runny or stuffy nose; wheezing or trouble breathing; hives; swelling of your face, lips, tongue, or throat.

Get emergency medical help if you have signs of a heart attack or stroke: chest pain spreading to your jaw or shoulder, sudden numbness or weakness on one side of the body, slurred speech, and feeling short of breath.

STOP USING NAPROXEN AND CALL YOUR DOCTOR AT ONCE IF YOU HAVE:

shortness of breath (even with mild exertion);
swelling or rapid weight gain;
the first sign of any skin rash, no matter how mild;
signs of stomach bleeding - bloody or tarry stools, coughing up blood or

vomit that looks like coffee grounds;
liver problems - nausea, upper stomach pain, itching, tired feeling, flu-like symptoms, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
kidney problems - little or no urinating, painful or difficult urination, swelling in your feet or ankles, feeling tired or short of breath;
low red blood cells (anemia) - pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating; or
severe skin reaction - fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.

COMMON NAPROXEN SIDE EFFECTS MAY INCLUDE:

indigestion, heartburn, stomach pain, nausea;
diarrhea, constipation;
headache, dizziness, drowsiness;
swelling in your hands or feet;
bruising, itching, rash, sweating; or
ringing in your ears.

OTHER DRUGS WILL AFFECT NAPROXEN

Ask your doctor before using naproxen if you take an antidepressant such as citalopram, escitalopram, fluoxetine (Prozac), fluvoxamine, paroxetine, sertraline (Zoloft), trazodone, or vilazodone. Taking any of these medicines with an NSAID may cause you to bruise or bleed easily.

Ask a doctor or pharmacist if it is safe for you to use this medicine if you are also using any of the following drugs:

lithium;
methotrexate;
probenecid;
a blood thinner (warfarin, Coumadin, Jantoven);
heart or blood pressure medication, including a diuretic or "water pill"; or
steroid medicine (such as prednisone).

This list is not complete. Other drugs may interact with naproxen, including prescription and over-the-counter medicines, vitamins, and herbal products. Not all possible interactions are listed in this medication guide.

ADDITIONAL INFORMATION ABOUT DRUG

People who take nonsteroidal anti-inflammatory drugs (NSAIDs) (other than aspirin) such as naproxen may have a higher risk of having a heart attack or a stroke than people who do not take these medications. These events may happen without warning and may cause death. These problems may develop at any time during treatment, but the risk may be higher for people who take NSAIDs for a long time or at higher doses. Do not take an NSAID such as naproxen if you have recently had a heart attack, unless directed to do so by your doctor. Tell your doctor if you or anyone in your family has or has ever had heart disease, a heart attack, or a stroke, if you smoke, and if you have or have ever had high cholesterol, high blood pressure, or diabetes. Get emergency medical help right away if you experience any of the following symptoms: chest pain, shortness of breath, weakness in one part or side of the body, or slurred speech.

If you will be undergoing a coronary artery bypass graft (CABG; a type of heart surgery), you should not take naproxen right before or right after the surgery.

NSAIDs such as naproxen may cause ulcers, bleeding, or holes in the esophagus (tube between the mouth and stomach), stomach, or intestine. These problems may develop at any time during treatment, may happen without warning symptoms, and may cause death. The risk may be higher for people who take NSAIDs for a long time or at higher doses, are older in age, have poor health, who smoke, or who drink large amounts of alcohol while taking naproxen. Tell your doctor if you take any of the following medications: anticoagulants (''blood thinners'') such as warfarin (Coumadin, Jantoven); aspirin; other NSAIDs such as ibuprofen (Advil, Motrin) and ketoprofen; oral steroids such as dexamethasone, methylprednisolone (Medrol), and prednisone (Rayos); salicylate pain relievers such as diflunisal, magnesium salicylate (Doan's, others), and salsalate; selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa), fluoxetine (Prozac, in Symbyax), fluvoxamine (Luvox), paroxetine (Brisdelle, Paxil, Pexeva), and sertraline (Zoloft); or serotonin norepinephrine reuptake inhibitors (SNRIs) such as desvenlafaxine (Pristiq), duloxetine (Cymbalta), and venlafaxine (Effexor XR). Also tell your doctor if you have or have ever had ulcers, bleeding in your stomach or intestines, other bleeding disorders, or liver disease. If you experience any of the following symptoms, stop taking naproxen and call your doctor: stomach pain, heartburn, vomit that is bloody or looks like coffee grounds, blood in the stool, or black and tarry stools.

Keep all appointments with your doctor and the laboratory. Your doctor will monitor your symptoms carefully and will probably order certain tests to check your body's response to naproxen. Be sure to tell your doctor how you are feeling so that your doctor can prescribe the right amount of medication to treat your condition with the lowest risk of serious side effects.

LITERATURE REVIEW

1. Laneuvill., et al. We developed an in vitro expression system for accurate kinetic analyses of the inhibition of the human prostaglandin H synthase isozymes (hPGHS-1 and -2) by non steroidal anti-inflammatory drugs (NSAIDs). Assays of instantaneous inhibition in which enzyme, 10 microM arachidonate, and an NSAID were mixed simultaneously were used to determine apparent affinities of 14 common NSAIDs for hPGHS-1 and hPGHS-2.

3. Segura Carretero ., et al. A simple, selective and sensitive heavy atom-induced room temperature phosphorimetric method (HAI-RTP) is described for the determination of Naproxen (NAP) in pharmaceutical preparations. The phosphorescence signals are a consequence of intermolecular protection when analytes are, exclusively, in presence of a heavy atom salt and sodium sulfite as an oxygen scavenger to minimize RTP quenching. This study demonstrates the effects of incorporation of known agents on the in vitro release characteristics of naproxen suppository.

4. Healy L, et al. Chiral separations of R, S-naproxen mixtures were obtained on an achiral column (ODS) with methyl-beta-cyclodextrin as a mobile phase additive using conventional and nano-LC. The optimised mobile phase composition was 20 ml methyl-beta-cyclodextrin, 20% (v/v) acetonitrile, and 50 ml .sodium acetate buffer at pH 3 using hydrochloric acid for pH adjustment. In addition to UV detection at 232 nm, amperometric detection was also investigated.

5. Anna L. Blobaum, et al. Cyclo oxygenase enzymes (COX-1 and COX-2) catalyze the conversion of arachidonic acid to prostaglandin G2. The inhibitory activity of rapid, reversible COX inhibitors (Ibuprofen, Naproxen, Mefenamic Acid, and Lumiracoxib) demonstrated a significant increase in potency and time dependence of inhibition against double tryptophan murine COX-2 mutants at the 89/90 and 89/119 positions. In contrast, the slow, time-dependent COX inhibitors (diclofenac, indomethacin, and flurbiprofen) were unaffected by those mutations

6. Kelsey C. Duggan, et al. Naproxen ((S)-6-methoxy-a-methyl-2-naphthaleneacetic acid) is a powerful non-selective non-steroidal anti-inflammatory drug that is extensively used as a prescription and over-the-counter medication. Naproxen exhibits gastrointestinal toxicity, but its cardiovascular toxicity may be reduced compared with other drugs in its class.

7. Matthew J. Walters, et al. Despite the fact that naproxen has been marketed for many years, the molecular basis of its interaction with cyclo oxygenase (COX) enzymes is unknown. We performed a detailed study of naproxen-COX-2 interactions using site-directed mutagenesis, structure-activity analysis, and x-ray crystallography. The results indicate that each of the pendant groups of the naphthyl scaffold is essential for COX inhibition, and only minimal substitutions are tolerated.

8. Wen-Chi L. Chang, et al. Recent efforts to improve the vascular and gastrointestinal safety of nonsteroidal anti-inflammatory drugs (NSAIDs) have included the addition of a nitric oxide-donating moiety. The ability of the common NSAID naproxen and nitric oxide (NO)-naproxen to inhibit azoxymethane-induced aberrant crypt foci in the rat colon has been demonstrated. However, the chemo preventive activity of these agents against spontaneous colorectal tumors has not been reported.

9. Clinton J. Grubbs, et al. A variety of studies were performed with naproxen (a standard NSAID with a good cardiovascular profile), sulindac, and their nitric oxide (NO)-derivatives. In Fisher 344 rats, OH-BBN (2x/week for 8 weeks by gavage) induced invasive urinary bladder cancers. When treatment was initiated one week following the final dose of OH-BBN, both naproxen (400 ppm) and sulindac (400 ppm) were highly effective preventive agents at these human equivalent doses.

10. S. Labbozzetta,. et al. A simple and rapid open-vessel focused microwave-assisted extraction (FMAE) method followed by LC analysis was developed for the determination of naproxen in suppositories. Parameters which might affect the FMAE method, such as nature and volume of the extraction solvent, temperature and extraction time were optimized. The extraction solvent consisted of methanol/sodium hydrogen carbonate (pH 8.7; 0.1 M) (50:50, v/v). Extractions were performed by reaching the target temperature of 70 °C in a 7 min linear ramp and then maintaining the target temperature for 3 min.

11. H Berry, et al. A double-blind cross-over study of 35 out-patients with rheumatoid arthritis showed that Naproxen and Indomethacin suppositories were both effective forms of treatment in rheumatoid arthritis, both being significantly superior to placebo in terms of relief of morning stiffness.

12. S. Hargoli., et al. The aim of this work was to develop the best formulations for naproxen suppositories. The effects of different bases and surfactants on the physicochemical characteristics of the suppositories were determined by several tests such as weight variation, melting point, assay, hardness, and release rate. All formulations met the standard criteria for tested physicochemical parameters; weight variation (97-112%), content uniformity (97-105%), melting point (4.66-8.7 min) and hardness tests (>5400 g).

13. Wilasrusmee S1, et al. To assess the effectiveness of rectal naproxen for reducing perineal pain after vaginal complications.A double-blind randomized controlled trial of 142 post partum women randomly allocated to receive either naproxen (71 patients) or placebo (71 patients) suppositories. The first dose was given immediately after complete perineal suturing, while the second dose was given 6 hours post partum. The validated Thai short-form McGill pain questionnaire was used to evaluate perineal pain at 0, 6, and 24 hours post partum. Pain scores were analyzed using the unpaired t test.

14. Hassan MA, Tous SS et al. Naproxen (NPX), 6-methoxy-a-methyl-2-naphthal ene acetic acid, belongs to an important group of medicines called nonsteroidal antiinflammatory drugs with antiinflammatory, analgesic and antipyretic properties and is widely used in the treatment of rheumatic and other inflammatory diseases and for the relief of mild to moderate pain. Oral administration is the route choice for drug administration. However, oral drug delivery becomes impossible in certain cases such as nausea, vomiting or convulsion.

15. Samy EM1, et al. Naproxen (NPX), 6-methoxy-a-methyl-2-naphthal ene acetic acid, belongs to an important group of medicines called nonsteroidal antiinflammatory drugs with antiinflammatory, analgesic and antipyretic properties and is widely used in the treatment of rheumatic and other inflammatory diseases. physicochemical and pharmaceutical factors such as solubility, particle size, partition coefficient, pKa, concentration of active

substances, composition of the base, melting temperature range, viscosity, spreading in situ of suppository bases affect the rate and extent of drug absorption from suppositories .

16. Samy EM1., et al. The aim of this work was to develop the best formulations for naproxen suppositories. The effects of different bases and surfactants on the physicochemical characteristics of the suppositories were determined by several tests such as weight variation, melting point, assay, hardness, and release rate.The aim of this work was to develop the best formulations for naproxen suppositories.

17. D Swinson, et al. Using implicit solvent model and replica exchange molecular dynamics, we examine the propensity of a nonsteroidal anti-inflammatory drug, naproxen, to interfere with Aß fibril growth. We also compare the antiaggregation propensity of naproxen with that of ibuprofen. Naproxen's antiaggregation effect is influenced by two factors.

18. Joel Musee, et al. While a great deal has been discovered concerning the potential physiological and pathological role of prostanoids, much is left to be determined. The widespread distribution of both COX-1 and COX-2 coupled with the capacity of most vascular beds, smooth muscle, as well as leukocytes to respond to prostanoids make drawing generalities difficult. The problems with the majority of currently used NSAID's concern.

19. Joel Musee, et al. This study demonstrates the effects of incorporation of known agents on the in vitro release characteristics of naproxen suppository. The aim of this work was to develop the best formulations for naproxen suppositories. The effects of different bases and surfactants on the physicochemical characteristics of the suppositories were determined by several tests such as weight variation, melting point, assay, hardness, and release rate.

20. Dewachter I, et al. Recent efforts to improve the vascular and gastrointestinal safety of nonsteroidal anti-inflammatory drugs (NSAIDs) have included the addition of a nitric oxide-donating moiety. The ability of the common NSAID naproxen and nitric oxide (NO)-naproxen to inhibit azoxymethane-induced aberrant crypt foci in the rat colon has been demonstrated.. Low-dose naproxen and low-dose NO-naproxen decreased the multiplicity of gross small intestinal adenomas by 70.3% (mean ± SEM – 9.9 ± 1.45, P = 0.04) and 64.0% (12.0 ± 1.9), respectively, as compared to that of control mice (33.3 ± 14.0). No additional benefit was obtained by administering a higher dose of either agent.

21. Harry S. Cooper,. et al. Epidemiological evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the risk for Alzheimer's disease (AD). Certain NSAIDs can activate the peroxisome proliferator-activated receptor-gamma (PPARgamma), which is a nuclear transcriptional regulator. Here we show that PPARgamma depletion potentiates beta-secretase [beta-site amyloid precursor protein cleaving enzyme (BACE1)] mRNA levels by increasing BACE1 gene promoter activity. Transcription.

22. Daniel Boring, et al. A variety of studies were performed with naproxen (a standard NSAID with a good cardiovascular profile), sulindac, and their nitric oxide (NO)-derivatives. In Fisher 344 rats, OH-BBN (2x/week for 8 weeks by gavage) induced invasive urinary bladder cancers. Finally, the effects of naproxen and NO-naproxen on modulation of gene expression in the livers of treated rats were determined. Limited, but similar, gene expression changes induced by both agents were observed.

AIM AND OBJECTIVE OF PRESENT WORK

Naproxen is an NSAID used to treat rheumatoid arthritis, osteoarthritis, anky losing spondylitis, poly articular juvenile idiopathic arthritis, tendinitis, bursitis, acute gout, primary dysmenorrhea, and mild to moderate pain .

Naproxen has poor and pH dependent water solubility in order to enhance its dissolution different water soluble bases shall be used. Suppositories shall be evaluated for various parameters like, weight variation, content uniformity, and in-vitro dissolution studies.

Naproxen thus a significant increase in the drug dissolution rate in the rectum (pH 7.4).different concentrations of glycerin in glycero-gelatin suppositories was used .for rectal administration the glycerin place important role because it has humectants category.

PLAN OF WORK

Preparation of suppositories:

By using different concentrations of glycero-gelatin bases naproxen suppositories was prepared. Naproxen displacement value was calculated.

Evaluation of suppositories:

The following tests was performed for the evaluation of suppositories

Assay
Weight variation
Hardness
Thickness
Dissolution profile

DRUG PROFILE

Name : Naproxen

Type : Small Molecule

Chemical Formula : $C_{14}H_{14}$

Solubility : Lipid Soluble

Half-life : The observed terminal . elimination half-life is approximately 15 hours.

IUPAC Name:

(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid

Protein Binding:

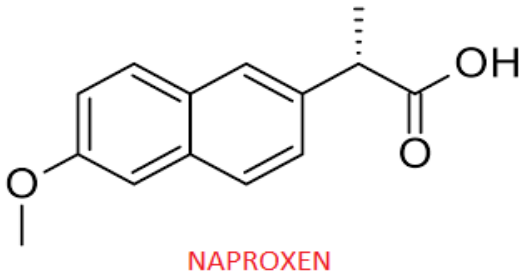
Naproxen is greater than 99% albumin-bound.

Description :

An anti-inflammatory agent with analgesic and antipyretic properties. Both the Acid and its sodium salt are used in the treatment of rheumatoid arthritis and other Rheumatic or musculoskeletal disorders, dysmenorrheal, and acute gout.

Structure:

Naproxen is a propanoic acid derivative related to the aryl acetic acid group of non-steroidal anti-inflammatory drugs. The chemical names for Naproxen and Naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen and Naproxen sodium have the following structures, respectively.



NAPROXEN

Naproxen has a molecular weight of **230.26** and a molecular formula of **C14H14O3.**

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (Cmax); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption Naproxen itself is rapidly and completely absorbed from the GI tract with an in vivo bioavailability of 95%. Based on the pharmacokinetic profile, the absorption phase of NAPRELAN® Tablets occurs in the first 4-6 hours after administration. This coincides with disintegration of the tablet in the stomach, the transit of the sustained release microparticles through the small intestine and into the proximal large intestine. An in vivo imaging study has been performed in healthy volunteers that confirms rapid disintegration of the tablet matrix and dispersion of the microparticles. The absorption rate from the sustained release particulate component of NAPRELAN® Tablets is slower than that for conventional naproxen sodium tablets. It is this prolongation of drug absorption processes that maintains plasma levels and allows for once daily dosing. Food Effects No significant food effects were observed when twenty-four subjects were given a single dose of NAPRELAN® Tablets 500 mg either after an overnight fast or 30 minutes after a meal. In common with conventional naproxen and naproxen sodium formulations, food causes a slight decrease in the rate of naproxen absorption following NAPRELAN® Tablets administration. Distribution Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day, there is a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However the concentration of unbound naproxen continues to increase proportionally to dose. NAPRELAN® Tablets exhibit similar dose proportional characteristics. Metabolism Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes. Elimination The elimination half-life of NAPRELAN® Tablets and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2-3 doses of NAPRELAN® Tablets. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66-92%). A small amount (

FOOD INTERACTIONS

Avoid alcohol.

Take with a full glass of water.

Take with food.

DRUG INTERACTIONS

S.NO	NAME OF THE DRUG	INTERACTION
1	16-Bromoepiandrosterone	The risk or severity of adverse effects can be increased when Naproxen is combined with 16-Bromoepiandrosterone.
2	19-norandrostenedione	The risk or severity of adverse effects can be increased when Naproxen is combined with 19-norandrostenedione.
3	4-Androstenedione	The risk or severity of adverse effects can be increased when Naproxen is combined with 4-Androstenedione.
4	5-androstenedione	The risk or severity of adverse effects can be increased when Naproxen is combined with 5-androstenedione.
5	Abciximab	Naproxen may increase the anticoagulant activities of Abciximab.
6	Acebutolol	Naproxen may decrease the antihypertensive activities of Acebutolol.
7	Aceclofenac	The risk or severity of adverse effects can be increased when Naproxen is combined with Aceclofenac.
8	Acenocoumarol	Naproxen may increase the anticoagulant activities of Acenocoumarol.
9	Acetovanillone	The risk or severity of adverse effects can be increased when Naproxen is combined with Acetovanillone.

S.NO	NAME OF THE INGREDIENTS	CATEGORY
1	Naproxen	Drug
2	Glycerine	Humectant
3	Gelatine	Suppository Base
4	Liquid paraffin	Lubricant
5	Disodium hydrogen phosphate	Preparation of P^H7.4
6	Potassium Di Hydrigen Phosphate	Preparation of P^H7.4
7	Purified water	Vehicle

MATERIALS AND METHODS

List of ingredients:

Naproxen was a gift from Dr.Reddys laboratories IDA-bollaram, Hyderabad, Glycerin, Gelatin, Liquid paraffin were purchased from delta scientific company, Vijayawada. For the preparation of ph 7.4 buffer disodium hydrogen phosphate, potassium Di hydrogen phosphate was purchased from Delta scientific company, Vijayawada.

LIST OF INGREDIANTS

LIST OF EQUIPMENTS USED:

S. No.	Equipment	Manufacturer	Model no
1	Electronic Balance	CAL-ON	AUX220

2	Heating Mantiles	Remi	YH-17
3	Laboratory Stirrer	Remi	RQT-124A
4	pH Meter	Thermo	Orion 2 Star
5	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
6	Suppositories Moulds	Adelphi	6-SP
7	Hardness tester	Tanco labs	T3
8	REFRIGIRATOR	LG	180 L

METHOD OF PREPARATION OF SUPPOSITORIES:

Different Concentration Of glycero- gelatin suppositories was prepared by fusion molding method. In this different concentration of glycerine is used for the preparation of glycero gelatin base.

S.NO	FORMULATION CODE	BASE COMPOSITION	
1	F1	Glycerin-70%	Gelatin-20%
2	F2	Glycerin-80%	Gelatin-20%
3	F3	Glycerin-90%	Gelatin-20%

The method involves first melting the glycerol-gelatin suppository base, and then dispersing or dissolving the naproxen drug in the melted base. The mixture is removed from the heat and poured into a pre cooled suppository mould. After the moulds are placed in a rifrigirator.When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them.

EVALUATION OF SUPPOSITORIES

Physicochemical Analysis of Suppositories:

1. Weight variation:

The weight of five separate suppositories was checked and means weight value was calculated.

2. Melting point:

Melting point was measured by the collodion tube method for three suppositories.

3. Hardness test:

Hardness was measured by the resistance to crushing using hardness tester

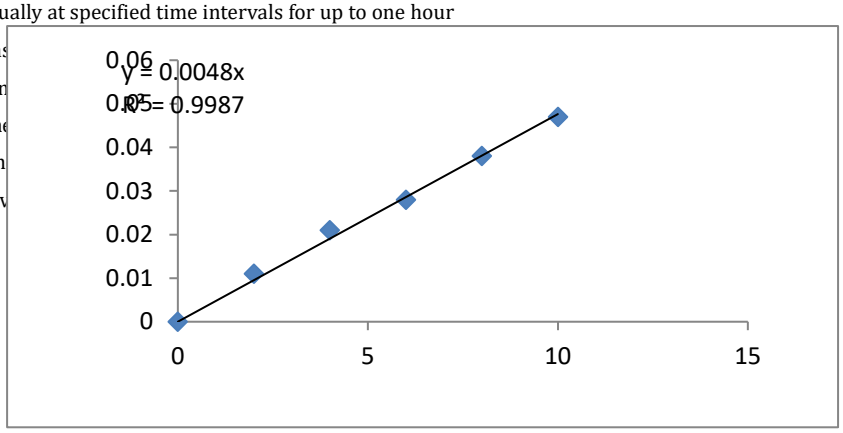
4. Content uniformity:

The uniformity of drug content for each base was determined by dissolving glycerol-gelatin base suppositories in phosphate buffer at pH 7.4 in 37°, after 30 min stirring, the absorbance was measured by spectrophotometry at a wavelength of 332.2 nm after dilution. The procedure was repeated to determine the uniformity of drug content of remaining concentrations of glycero-gelatin suppositories using repeated extraction with phosphate buffer (pH 7.4). To ensure complete extraction of the drug from the bases, blank suppositories without the drug were prepared and subjected to the same analytical procedure to serve as the blank for spectrophotometric determination.

5. Dissolution profile:

A number of *in vitro* dissolution techniques for determination of the dissolution rate of drug substances from suppositories such as dialysis method and through a flow cell method were described in the literature.In this study, the *in vitro* dissolution rate of Naproxen from the suppositories was examined using the basket method. The temperature was maintained at 37° and the stirring rate was kept constant at 50 rpm. 900 ml phosphate buffer (pH 7.4.), was used as a dissolution medium, and samples of 10 ml test

solution were collected manually at specified time intervals for up to one hour for different concentrations withdrawn volume of the san dissolution medium containe analyzed for Naproxen con study, the amount of dissolv spectrophotometer.



RESULTS

The following tests should be performed for evaluation of suppositories

Calibration curve for naproxen:

A calibration curve was plotted over a concentration range of 0 – 10 µg.ml, using the stock solution of concentration 1000 µg/ml. Accurately measured standard stock solution of naproxen (0.2, 0.4, 0.6, 0.8 and1.0 ml) were transferred to a separate series of 10.0 ml of volumetric flasks and diluted to the mark with pH 7.4 phosphate buffer. The absorbance of each solution was measured at 332 nm. Calibration curve was constructed by plotting absorbance versus concentrations at 332 nm.

Table.1: Standard calibration curve for naproxen

S.No	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.011
3	4	0.021
4	6	0.028
5	8	0.038
6	10	0.047

Fig.1: Standard calibration curve for naproxen

EVALUATION TESTS

Weight variation:

Table.2: Results of weight variation for formulation-I

FORMULATION I	
S.NO	**WEIGHT OF SUPPOSITORIES(GM)**
1	2.48
2	2.49
3	2.49
4	2.50
5	2.49
Mean	2.49
S.D	0.00632

Table.3: Results of weight variation for formulation-II

FORMULATION II	
S.NO	**WEIGHT OF SUPPOSITORIES(GM)**
1	2.40
2	2.42
3	2.44
4	2.39
5	2.38
Mean	2.406
S.D	0.0215

Table.4: Results of weight variation for formulation-III

FORMULATION-III	
S.NO	**Weight Of Suppositories(gm)**
1	2.41
2	2.38
3	2.39

4	2.40
5	2.41
Mean	2.39
S.D	0.011

Melting point:

It should melt at rectal temperature 36ºc or dissolve or disperse in body fluid. For eutectic mixtures and in tropical climate the melting range of the base should be higher.

Table.5: Results of Melting point for formulations

MELTING POINT(ºC)			
S.NO	**Formulation I**	**Formulation II**	**Formulation III**
1	**37**	**37**	**36**
2	36	38	37
3	38	39	39
4	36	35	38
5	38	36	37
Mean	37	37	37.4
S.D	0.894	1.414	1.019
CV	2.416	3.821	2.724

Hardness test:

Hardness test results showed that hardness of all formulations was more than 5400 gm (proper hardness).

Table.6: Results of Hardness test for formulations

HARDNESS (gm)			
S.NO	**Formulation I**	**Formulation II**	**Formulation III**
1	5500	5630	5590

2	5420	5600	5690
3	5460	5430	5360
4	5680	5670	5290
5	5720	5620	5630
Mean	5556	5590	5512
S.D	120.92	83.18	157.53
C.V	2.176	1.488	2.857

Content Uniformity:

UNIFORMITY CONTENT (Mg)			
S.NO	**Formulation I**	**Formulation II**	**Formulation III**
1	248	248	249
2	246	249	248
3	245	247	247
4	249	246	249
5	249	249	248

Mean	247.4	247.8	248.2
S.D	1.624	1.166	0.748
C.V	0.656	0.470	0.301

Table.7: In vitro drug release studies for prepared formulations

In Vitro Drug Release Studies:

S.No	Time (Min)	Absorbance			
		Standard	**F1**	**F2**	**F3**
1	10	0.278	0.062	0.073	0.090
2	20	0.640	0.238	0.234	0.249
3	30	0.664	0.344	0.303	0.293
4	40	0.718	0.418	0.365	0.347
5	50	0.724	0.471	0.379	0.367
6	60	0.950	0.504	0.381	0.370

Table.8: In vitro drug release studies from standard drug of naprosyn-250mg

S.No	Time (min)	Absorbance	%Drug released	Log % Drug released	% Drug remaining	Log % Drug remaining
1	0	0	0	0	100	2
2	10	0.278	11.23	1.050	88.77	1.948
3	20	0.640	23.34	1.368	76.66	1.884
4	30	0.664	36.67	1.564	63.33	1.801
5	40	0.718	76.87	1.885	23.13	1.364
6	50	0.724	88.32	1.946	11.68	1.067
7	60	0.950	98.34	1.992	1.662	0.220

Table.9: In vitro drug release studies from formulation-I

S.No	Time (min)	Absorbance	%Drug released	Log % Drug released	% Drug remaining	Log % Drug remaining
1	0	0	0	0	100	2

2	10	0.062	10.2	1.008	89.8	1.953
3	20	0.238	28.38	1.453	71.62	1.855
4	30	0.344	32.69	1.514	67.31	1.828
5	40	0.418	78.06	1.892	21.94	1.341
6	50	0.471	88.39	1.956	11.61	1.064
7	60	0.504	97.58	1.989	2.42	0.381

Table.10: In vitro drug release studies from formulation-II

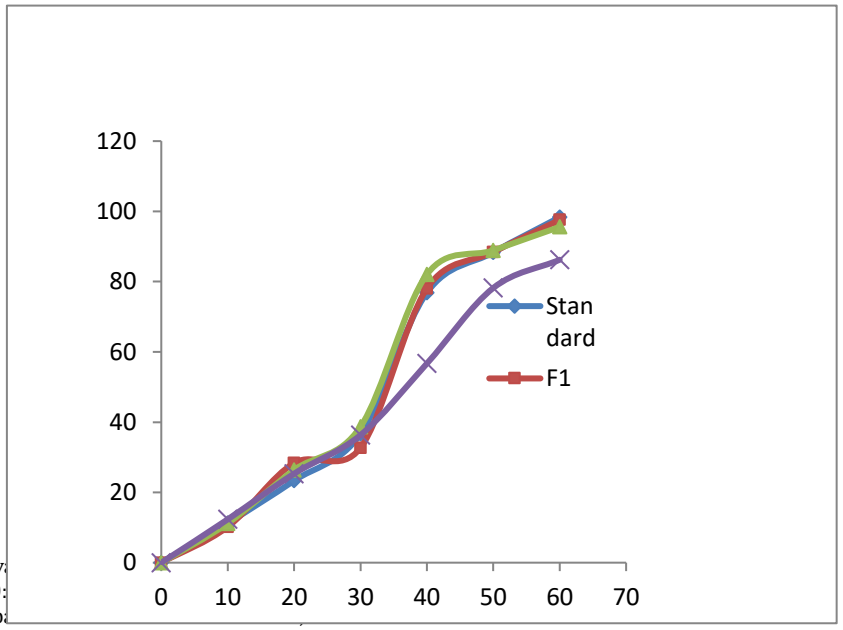
S.No	**Time (min)**	**Absorbance**	**%Drug released**	**Log % Drug released**	**% Drug remaining**	**Log % Drug remaining**
1	0	0	0	0	100	2
2	10	0.073	11.2	1.049	88.8	1.948
3	20	0.234	26.38	1.421	73.62	1.866
4	30	0.303	38.69	1.587	61.31	1.787

5	40	0.365	82.06	1.914	17.94	1.253
6	50	0.379	88.90	1.948	11.1	1.045
7	60	0.381	95.58	1.980	4.42	0.645

Table.11: In vitro drug release studies from formulation-III

S.No	**Time (min)**	**Absorbance**	**%Drug released**	**Log % Drug released**	**% Drug remaining**	**Log % Drug remaining**
1	0	0	0	0	100	2
2	10	0.090	12.32	1.090	87.68	1.942
3	20	0.249	25.32	1.403	74.68	1.873
4	30	0.293	36.32	1.560	63.68	1.804
5	40	0.347	56.69	1.753	43.31	1.636
6	50	0.367	78.20	1.893	21.8	1.338
7	60	0.370	86.23	1.935	13.77	1.138

Fig.2: In Vitro Dissolution studies for standard and formulations F-I, F-II, F-III



Conclusion and summary:

In this research work 3 formulations of developed by fusion molding method with v and gelatin (70:30)in First formulation,(80: (90:10) in third formulation. The liquidp Disodium hydrogen phthalate buffer and purified water were used as vehicles,the developed formulations were evaluated according to guide lines the parameters like weight variation,melting point , Hardness test ,content variation uniformity,dissolution studies and disintegration studies were performed ,mean ,standard deviationvalues found within the limits ,Regarding the drug invitro release first formulation shows satisfactory results comparable to two other formulations

REFERENCE

Crama A, Breitkreutzb J, Desset-Brèthesc S, Nunnd T, Tuleuf C, Challenges of developing palatable oral pediatric formulations, Int J Pharm, 365, 2009, 1-3.

Florence AT, Neglected diseases, neglected technologies, Int J Pharm, 350, 2008,1-2.

M.J. Rathbone, J. Hadgraft, Absorption of drugs from the human oral cavity, Int. J.Pharm. 74 (1991) 9–24.

Y. Rojanasakul, L.-Y. Wang, M. Bhat, D.D. Glover, C.J. Malanga, J.K.H. Ma, Thetransport barrier of epithelia: a comparative study on membrane permeability and charge selectivity in the rabbit, Pharm. Res. 9 (1992) 1029–

1034.

A.V. Gore, A.C. Liang, Y.W. Chien, Comparative biomembrane permeation of tacrine using yucatan minipigs and domestic pigs as the animal model, J. Pharm. Sci. 87 (1998) 441–447.

A.H. Shojaei, Buccalmucosa as a route for systemic drug delivery: a review, J. Pharm.Pharm. Sci. 1 (1998) 15–30.

W.R. Galey, H.K. Lonsdale, S. Nacht, The in vitro permeability of skin and buccalmucosa to selected drugs and tritiated water, J. Invest. Dermat. 67 (1976) 713–717.

Michael J. Rathbone, Jonathan Hadgraft , Absorption of drugs from the human oral cavity, International Journal of Pharmaceutics Vol 74, Issue 1, 2 August 1991, Pg:9-24.

H. Zhang, J. Zhang, J.B. Streisand, Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications, Clin. Pharmacokinet. 41 (9) (2002) 661–680.

Doheny K, You really expect me to swallow those horse pills? Am Druggist. 1993; 208:34-35.

Roila F, Hesketh PJ, Herrstedt J. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 2006;17:20–28. [16314401]

Jenns K. Importance of nausea. Cancer Nurs 1994;17:488–493. [7820827]

Hariharan M, Bogue A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms. Drug Delivery Technol 2009;9:24–29.

Borsadia SD, O'Halloran D, Osborne JL. Quick-dissolving films, a novel approach to drug delivery. Drug Delivery Technol2003;3:63–66.

Liang AC, Chen, Li-Lan H. Fast-dissolving intraoral drug delivery systems, Expert Opinion., 2001; 11(6):981-986.

Oral Thin Films," in Orally Disintegrating Tablet and Film Technologies, 5th ed., Technology Catalysts International, Falls Church, VA, 2008.

Gavaskar, B., Vijayakumar, S. and Sharan, G., "Overview on fast dissolving films." Int. J. pharm. Pharma. Sci. 2010, 2(3), 29-33.

Peppas, N.A. and P.A. Buri, 1985. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Controlled Release, 2: 257-275.

Tabak, L.A., M.J. Levine, I.D. Mandel and S.A. Ellison, 1982. Role of salivary mucins in the protection of the oral cavity. J. Oral Pathology and Med., 11: 1-17.

Dixit RP, Puthli SP. Oral strip technology: Overview and future potential, Journal of Controlled Release, v;139: 97.

Corniello C, Quick dissolving strips: from concept to commercialization, Drug Del. Technol, 6(2), 2006, 68-71.

Frankhauser C, Slominski G, Meyer S, Disintegrable oral films, U.S. Patent 2007/0202057, Aug. 30, 2007.

Kulkarni N, Kumar LD, Sorg A, Fast dissolving orally consumable films containing an antitussive and a mucosa coating agent, U.S. Patent 2003/206942, Nov. 6, 2003.

Ali S, Quadir A, High molecular weight povidone polymer-based films for fast dissolving drug delivery applications, Drug Del. Technol, 7 (6), 2007, 36-43.

Sakellariou P, Rowe RC, Interactions in cellulose derivative films for oral drug delivery, Prog. Polym. Sci, 20, 1995, 889-942.

Banker GS, Film coating theory and practice, J. Pharm. Sci, 55, 1966, 81-89.

McIndoe LME, Rowe RC, Sheskey PJ, Owen SC, Handbook of Pharmaceutical Excipients, Pharmaceutical press, London, 2006,128-130.

Rowe FC, Forse SF, The effect of polymer molecular weight on the incidence of film cracking and splitting on film coated tablets, J. Pharm. Pharmacol,32(8), 1980, 583-584.

Rowe RC, Forse SF, The effect of plasticizer type and concentration on the incidence of bridging of intagliations on film-coated tablets, J.Pharm.Pharmacol, 33(3), 1981, 174-175.

Singh P, Guillory JK, Sokoloski TD, Bhatia VN, Effect of Polyethylene glycol 4000 on the intestinal absorption of four barbiturates, J. Pharm. Sei, 55, 1966, 63-68.

Prakash I, DuBois GE, Clos JF, Wilkens KL, Fosdick LE, Development of rebiana, a natural, non-caloric sweetener, Food Chem. Toxicol, 46(7), 2008, S75- 82.

Sharma R, Parikh RK, Gohel MC, Soniwala MM, Development of taste masked film of Valdecoxib for oral use, Ind. J. Pharm. Sci, 69 (2), 2007,320-322.

Sau-hung S, Robert S, Lori D, Fast dissolving orally consumable films, U.S. Patent 6596298, July 22, 2003.

Mishra R, Amin A, Quick API Delivery, Pharmaceutical Technology Europe, 2007, 1-5.

Coppens KA, Hall MJ, Mitchell SA, Read MD, Hypromellose, Ethyl cellulose and Polyethylene oxide used in hot melt extrusion, Pharmaceutical Technology, 2005, 1-6.

Frey, Film Strips and Pharmaceuticals, Pharma Mfg & Packag Sourcer, 2006, 92–93.

Mahesh A, Shastri N, Sadanandam M, Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use, Curr Drug

Deliv,7, 2010, 21-7.

Chen, M., Tirol, G., Schmitt, R., Chien, C. and Dualeh, A., "Film forming polymers in fast dissolve oral films" AAPS Annual meetings posters and papers, T3200, 2006.

Anand V, Kataria M, Kukkar V, Saharan V, Choudhury PK, The latest trends in the taste assessment of pharmaceuticals. Drug Discovery Today, 12, 2007, 257-265.

Patel MV, Prajapati BG, Patel MM, Effect of hydrophilic polymers on buccoadhesive Eudragit patches of Propranolol hydrochloride using factorial design, AAPS PharmSciTech,8, 2007, Article 45.

Semalty M, Semalty A, Kumar G, Formulation and characterization of mucoadhesive buccal films of glipizide, Indian J Pharm Sci, 70, 2008, 43–8.

Felton L., P. O'Donnell and J. McGinity, Mechanical properties of polymeric films prepared from aqueous dispersions, in: Aqueous polymeric coatings for pharmaceutical dosage forms, 3rd edition, J. McGinity, L. Felton (Eds), Vol. 176, Drugs and the Pharmaceutical Sci., pp: 108.

Fulzele, S.V., P.M. Sattuwar and A.K. Dorle, 2002. Polymerized rosin: novel film forming polymer for drug delivery, International J. Pharmaceutics, 249(1-2): 175 -184.

Linda S, Crawford SM, Taylor PA. The comparative effectiveness of ondansetron and granisetron in once daily dosage in the prevention of nausea and vomiting caused by cisplatin: a double blind clinical trial. The Pharm J 2000; 265 (7104): 59-62.

Sweetman SC, editor. Martindale: The Complete Drug Rd Reference, 33 ed. London: Pharmaceutical Press; 2002. p. 1227-8.

Kulkarni Parthasarathi Keshavarao, Dixit Mudit, Gunashekara K, Shahnawaz Anis, Singh Mangla N, Kulkarni Ajay, Formulation and evaluation of Mouth Dissolving Film containing Rofecoxib, IRJP, 2 (3), 2011, 273-278.

Rakesh Patel, Naik Shardul, Jigar Patel, Ashok Baria, Formulation Development and Evaluation of Mouth Melting Film of Ondansetron, Arch Pharm Sci & Res,1(2), 2009, 212 – 217.

Shivani Singh, Satyam Gangwar, Garima Garg, Vipin Garg, Sharma PK, Formulation and evaluation of rapidly disintegrating film of Levocetrizine Hydrochloride, Der Pharmacia Lettre, 2(2), 2010, 434-439.

Hiroyoshi Shimoda, Kazumi Taniguchi, Misao Nishimura, Katsuhiko Matsuura, Tadao Tsukioka, Hirotaka Yamashita, Naoki Inagaki, Kazuyuki Hirano, Mayumi Yamamoto, Yasutomi Kinosada, Yoshinori Itoh, Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy, European Journal of Pharmaceutics and Biopharmaceutics, 73(3), 2009, 361-365.

Francesco Cilurzo , Irma Cupone, Paola Minghetti, Francesca Selmin, Luisa Montanari, Fast dissolving films made of maltodextrins, European Journal of Pharmaceutical and Biopharmaceutics, 70(3), 2008, 895-900.

Aditya Dinge, Mangal Nagarse, Formulation and Evaluation of Fast Dissolving Films for Delivery of Triclosan to the Oral Cavity, AAPS PharmSciTech, 9(2), 2008, 349–356.

Yoshifumi Murata, Takashi Isobe, Kyoko Kofuji, Norihisa Nishida, Ryosei Kamaguchi, Preparation of Fast Dissolving Films for Oral Dosage from Natural Polysaccharides, 3(8), 2010, 4291-4299.

Mashru RC, Sutariya VB, Sankalia MG, Parikh PP, Development and evaluation of fast-dissolving film of salbutamol sulphate, 31(1), 2005, 25-34.

Swamy.p.v, amit kumar T, shirsand S.B, patil, Design and evaluation of buccal patches of granisetron hydrochloride, Indian j.pharm. Educ. Research(2010), 44(1)

Mital S. Panchal, Mr. Hiren Patel, Mrs. Aarti Bagada, Dr. K.R.Vadalia, Formulation and Evaluation of Mouth Dissolving Film of Ropinirole Hydrochloride by Using Pullulan Polymers, Vol, 1,3 (2012), 60-72.

Dahiya S, Asati S, MallurwarV. Formulation and evaluation of Granisetron hydrochloride Orodispersible tablets. Bull. Pharm. Res. 2011;1(2):41-6.

Raymond C Rowe, Paul J Sheskey and Siân C Owen *Handbook of Pharmaceutical Excipients* Fifth Edition.

http://www.drugbank.ca/drugs/DB00889.

http://dailymed.nlm.nih.gov/dailymed

www.ncpri.ro/pullulan/en/index.htm

New monograph for Hypromellose Acetate Succinate (In-Process Revision). Pharmaceutical Forum 2003; 29(1): 142–146.

Refe for dissolution test: http://www.listerine.com/product-pocket-paks.jsp

Reference For mechanism of granisetron

1. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d0e05816-ccf8-4008-b5de-4d3fbc3de3c1