TO STUDY AND TO EVALUATE THE REQUIREMENTS REQUIRED TO PROPOSE AN ALTERNATE API FOR AN APPROVED DRUG PRODUCT IN USFDA

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Submitted by

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CERTIFICATE

This is to certify that the research work entitled **"TO STUDY AND TO EVALUATE THE REQUIREMENTS REQUIRED TO PR0POSE AN ALTERNATE API SOURCE FOR AN APPROVED DRUG PRODUCT IN USFDA "** Submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **M. Aliyah Moin (Reg. No. 26106011)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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CERTIFICATE

This is to certify that the dissertation entitled "**TO STUDY AND TO EVALUATE THE REQUIREMENTS REQUIRED TO PR0POSE AN ALTERNATE API SOURCE FOR AN APPROVED DRUG PRODUCT IN USFDA"** the bonafide research work carried out by **M.Aliyah Moin (Regd. No. 26106011)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Dr.S.SHANMUGAM, M. Pharm., Ph.D.,** Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur - 603 319.

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ABBREVIATION AND MEANING

%	-	Percentage
DT	-	Dispensing tablets
µ	-	Micron
µg/ml	-	Microgram per millilitre
RA	-	Regulatory affairs
HT	-	Hypodermic tablets
cm^{-1}	-	Centimeter inverse
C_{max}	-	Peak plasma concentration
DSC	-	Differential scanning calorimetry
HPLC	-	High performance liquid chromatography
EC	-	Ethyl cellulose
edn	-	Edition
F	-	Formulation
F/C	-	Film coated
FTIR	-	Fourier transform infrared spectroscopy
g/ml	-	gram per millilitre
TT	-	Tablet triturates
HCl	-	Hydrochloric acid
SLS	-	Sodium lauryl sulphate

HPMC	-	Hydroxy propyl methylcellulose
COA	-	Certificate of analysis
ICH	-	International conference on harmonization
IP	-	Indian pharmacopoeia
kg/cm^2	-	kilogram per centimeter square
LBD	-	Loose bulk density
MHEC	-	Methyl hydroxyl ethyl cellulose
mg	-	Milligram
ml	-	Millilitre
API	-	Active pharmaceutical ingredients
NSAIDS	-	Non-steriodal anti inflammatory drugs
N	-	Normality
NaOH	-	Sodium hydroxide
NF	-	National formulary
nm	-	Nanometer
RS	-	Related substance
pH	-	Negative logarithm of hydrogen ion
PGEs	-	Prostaglandins

qs	-	Quantity sufficient
RH	-	Relative humidity
rpm	-	Revolution per minute
S.No.	-	Serial number
SD	-	Standard deviation
IR	-	Immediate release
$t_{1/2}$	-	Biological half life
TBD	-	Tapped bulk density
T_{max}	-	Time of peak concentration
USP	-	United states pharmacopoeia
UV	-	Ultraviolet
w/w	-	weight per weight
λ_{max}	-	Absorption maximum

INTRODUCTION ...

1. INTRODUCTION

1.1 Tablets: *(Lachman L, Liberman H, 2000)*

Definition:

Tablets are tamper proof solid unit dosage forms containing medicament or mixture of medicaments and excipients compressed or molded into solid cylindrical shape having either flat or convex surfaces.

1.1.1 Properties of tablets

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration.
- Tablets must be elegant in appearance, characteristic shape, colour and other markings necessary to identify the product.

- Tablets must retain all these functional attributes which include drug stability and efficacy.

1.2 Advantages and Disadvantages

1.2.1. Advantages

- Offers greatest capability of all oral dosage forms for the greatest dosage precision & least content uniformity.
- High patient compliance.
- Their cost is lowest of all dosage forms
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamper proof dosage form".
- Easiest and cheapest to packaging and shipment.
- They are having best combined properties of chemical, mechanical and microbiological properties.
- Accuracy of dose is maintained since tablet is a solid unit dosage forms.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Organoleptic properties (colour taste, appearance, and odour) are improved by coating of the tablets. Product identification is easy and marketing done with the help of grooved punches and printing with edible ink.

- As a tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.

1.2.2 Disadvantages

- Some drugs resist compression owing to their amorphous nature & low density character.
- Drugs with poor wetting, slow dissolution property, large dosages or any combination of these features may be difficult or impossible to formulate & manufacture as a tablet.
- A major disadvantage of capsules over tablets is their higher cost.
- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Slow onset of action as compared to parentrals, liquid orals and capsules.
- The amount of liquid drug (e.g., vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.
- Patients undergoing radiotherapy cannot swallow tablet.

1.3 Types and classes of tablets *(Lachman L, Liberman H, 2000)*

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.

Tablets ingested orally

1. Compressed tablets (CT)

2. Multiple compressed tablets (MCT)

   a. Layered tablets and Bi-layer tablets

   b. Compression coated tablets

3. Repeat action tablets

4. Delayed action and enteric coated tablets

5. Sugar and chocolate coated tablet

6. Film coated tablets

7. Air suspension coated tablets

8. Chewable tablets

9. Dispersible tablets

Tablets used in oral cavity

1. Buccal tablets

2. Sublingual tablets

3. Trouches, Lozenges and dental cones

Tablets used to prepare solution

1. Effervescent tablets

2. Dispensing tablets (DT)

3. Hypodermic tablets (HT)

4. Tablet triturates (TT)

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration that is, the drug delivery system should delivery system

should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.4 Oral drug delivery: *(James Swarbrick et al., 2007)*

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

For many drug substances conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with an acceptable level of safety to the patient.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow.

Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package.

1.5 Current technologies in oral drug delivery:

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced drug delivery system are manufactured or fabricated in traditional pharmaceutical formulations, such as Tablets, Capsules, Sachets, Suspensions, Emulsions, and Solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral drug delivery system may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

1 .5.1 Immediate-Release Preparations: *(Syed Azeem et al., 2011)*

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, croscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

1.5.2 Controlled-Release Preparations:

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final control release product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and control release principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and recipients that incorporate desired principles.

1.5.3 Targeted-Release Preparations: *[Leon Shargel et al., 2004].*

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints.

1.6 Manufacturing Methods of tablets: *(F. A. Rowley, et al., 2005)*

There are four general methods of tablet preparation.

- Direct compression
- Wet granulation method
- Dry granulation method
- Fluidized bed granulation

In the tablet-pressing process, it is important that all ingredients be dry, powdered, and of uniform grain size as much as possible. The main guideline in manufacture is to ensure that the appropriate amount of active ingredient is equal in each tablet so ingredients should be well-mixed. Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogenous mix of the components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation. Powders that can be mixed well do not require granulation and can be compressed into tablets through Direct Compression.

1.6.1 Direct Compression

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.

Granulation is the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation is another method used to form granules.

1.6.2 Wet granulation

Wet granulation is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard and under wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvents.

- **Procedure of Wet Granulation**
- Step 1: Weighing and Blending - the active ingredient, filler, disintegration agents, are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia and cellulose derivatives such as methyl cellulose, CMC, gelatin, and povidone. Ingredients are placed within a granulator which helps ensure correct density of the composition.

- Step 3: Screening the damp mass into pellets or granules
- Step 4: Drying the granulation
- Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity
- Step 6: Lubrication- A dry lubricant, anti adherent and glidants are added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces friction between the tablet and the walls of the die cavity. Anti adherent reduces sticking of the tablet to the die and punch.
- Step7: liquid binder, but sometimes many actives are not compatible with water. Water mixed into the powder can form bonds between powder particles that are strong enough to lock them in together. However, once the water dries, the powders may fall apart and therefore might not be strong enough to create and hold a bond.

1.6.3 Dry granulation

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification. However, the process may require repeated compaction steps to attain the proper granule end point. It requires drugs or recipients with cohesive properties.

- Some granular chemicals are suitable for direct compression (free flowing) e.g. potassium chloride.

- Tablets which have recipients with good flow characteristics and compressibility are used for direct compression of a variety of drugs.

1.6.4.Fluidized bed granulation

It is a multiple step process performed in the same vessel to pre-heat, granulate and dry the powders. It is today a commonly used method in pharmaceuticals because it allows the individual company to more fully controls the powder preparation process. It requires only one piece of machinery that mixes all the powders and granules on a bed of air.

1.7 EXCIPIENTS USED IN TABLETS: *(Ramond C Rowe., 2006)*

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub-groups. Comprising of diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners.

All of these must meet certain criteria as follows:-

- They must be physiological inert.
- They must be acceptable to regulatory agencies.
- They must be physiologically and chemically stable.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must be not interference with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.

- Cost must be relatively inexpensive.

To assure that there is no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulations studies .

1.7.1. Fillers: (Diluents)

Tablet fillers of comprise a heterogeneous group of substances. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance.

1.7.2. Binders:

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact when swallowed and then release its medicament.

- Natural polymers such as starches or gums include acacia, tragacanth and gelatin.

Synthetic polymers such as polyvinylpyrrolidine, methyl and ethyl cellulose and hydroxyl propyl cellulose. Commonly used binders are gelatin, glucose, methyl

- Cellulose, acacia, starch paste, povidone, alcohol, PVP in water, PVP in alcohol and sorbitol in water.

1.7.3. Lubricants:

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face.

In selecting a lubricant, the following should be considered:

- Lubricants markedly reduce the bonding properties of many excipients.
- Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
- Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.
- Examples of lubricants commonly used are magnesium stearic acid, talc, starch, magnesium stearate.

1.7.4. Disintegrants:

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

Examples

- Crospovidone: Crospovidone is disintegrant, crospovidone also enhances solubility.
- Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule.

1.7.5. Glidants:

Glidants are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times.

Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewabilty. In general; these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

1.7.6 Miscellaneous

1.7.6.1 Wetting Agents:

Wetting Agents in tablet formulation aid water uptake and thereby enhancing disintegration and assisting in drug dissolution. Incorporation of anionic surfactant like Sodium Lauryl Sulphate (SLS) is known to enchance the dissolution. It has been established that SLS improves permeation of drug through biological membrane since it destroys the path through which drug has to pass and thus minimizing the path length for the drug to travel. Wetting agents are mainly added

when hydrophobic drug is to be formulated into tablet. SLS, Sodium disobutyl sulfosuccinate are used as wetting agent in tablet formulation.

1.7.6.2 Dissolution Retardants:

Dissolution Retardants are incorporated into tablet formulation only when controlled release of drug is required. Waxy materials like stearic acid and their esters can be used as dissolution retardants.

1.7.6.3 Dissolution Enhancers:

They are the agents that alter the molecular forces between ingredients to enchance the dissolution of solute in the solvent. Fructose, Povidone, Surfactants are used as dissolution enhancer.

1.7.6.4 Adsorbents:

Adsorbents are the agents that can retain large quantities of liquids. Therefore liquids like Vitamin E can be incorporated into tablets by addition of adsorbents. Most commonly used adsorbents in pharmaceuticals are anhydrous calcium phosphate, starch, magnesium carbonate, bentonite, kaolin, magnesium oxide. Generally the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formulation.

1.7.6.5 Buffers:

Buffers are added to maintain a required pH since a change in pH may cause significant alteration in stability. Most commonly used buffering agent in tablet formulation includes sodium bicarbonate, calcium carbonate, and sodium citrate.

1.7.6.6 Antioxidants:

Antioxidants are added in tablet formulation to protect drug from undergoing oxidation. Antioxidants undergo oxidation in place of drug or they block the oxidation reaction or they act as synergys to other antioxidants.

1.7.6.7 Chelating Agents:

Chelating agents tend to form complexes with trace amount of heavy metals ions inactivating their catalytic activity in the oxidation of medicaments. Ethlenediamine tetra acetic acid and its salts, Dihydroxy Ethyl Glycerin, Citric Acid and Tartaric Acid are most commonly used chelators

1.7.6.8 Flavours:

Flavours are added to tablet formulation in order to make them enough in case of chewable tablet by improving the taste. Flavours are commonly used to improve the taste of chewable tablets as well as mouth dissolved tablets. Flavours are incorporated either as solids (spray dried flavours) or oils or aqueous (water soluble) flavours.

1.7.6.9 Sweeteners:

Sweeteners are added to tablet formulation to improve the taste of chewable tablets. Sweeteners used in tablet formulation- Mannitol, Lactose, Sucrose, Dextrose, Saccharin, Cyclamate, Aspartame etc.

1.8 TABLET COATING:

Coated tablets are defined as the covered with one/more layers of mixtures of various substances such as natural waxes authorized colouring materials .Coating may

also contain active ingredient. Substances used for coating are usually applied as solution/suspension under condition where vehicle evaporates.

Why Tablet Coating is required?

A number of reasons can be suggested:

- The core contains a material which has a bitter taste in the mouth or has an unpleasant odour.
- Coating will protect the drug from the surroundings with a view to improve its stability.
- Coating will increase the ease by which a tablet can be ingested by the patient.
- Coating will develop the mechanical integrity; means coated products are more resistant to mishandling (abrasion, attrition etc.)
- The core contains a substance which is incompatible in the presence of light and subject to atmospheric oxidation, i.e. a coating is added to improve stability.
- The core alone is inelegant.
- The active substance is coloured and migrates easily to stain hands and clothes.
- The coated tablets are packed on high-speed packaging machine. Coating reduces friction and increases packaging rate.
- Coating can modify the drug release profile, e.g., enteric coating, osmotic pump, pulsatile delivery.

1.8.1 Types of coating

- Sugar coating
- Film coating
- Enteric coating
- Controlled release coating
- Specialized coating
- Compressed coating
- Electrostatic coating
- Dip coating
- Vacuum film coating

1.8 .1.1 FILM COATING: *(Anand Shah et al., 2009)*

Film coating is the process whereby a tablet, capsule, or pellet is surrounded by a thin layer of polymeric material. Film coated tablets are compressed tablets with a thin layer of suitable polymer capable of forming a skin like film over the tablet. The polymeric substance most commonly used are hydroxy propyl methyl cellulose, hydroxyl methyl cellulose, the film is usually collared and has the advantage over sugar coating in that it is more durable, less bulky, and less time consuming to apply. The film coating protects the medicament from the atmospheric effects. By its composition the coating is designed to rupture & expose the core tablet at the desired location within GIT.

Table1.1 Reason for film coating

Reasons for film coating:	
Appearance	To change the colour, for branding purposes or other aesthetic reasons
Stability	To protect the active ingredient from moisture, light, and/or the acidic environment of the stomach
Taste/odour Masking	To provide an easy to swallow tablet without the bitter taste of many actives
Release characteristics	Many film coating materials have functional properties which enable the delayed (enteric) release of dosage forms

1.8.1.2 Process Description

Film coating is a deposition of a thin layer of polymer surrounding the tablet core. Conventional pan equipments may be used but now a days more sophisticated equipments are employed to have high degree of automation of coating time. The polymer is solubilised into solvent, other additives like plasticizer &pigments are added. Resulting solution is sprayed on to a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition material around each tablet core.

1.8.1.3 Process Details

Usually spray process is employed in preparation of film coated tablet. Accelacota is the type of prototype of perforated cylindrical drum providing drying air capacity. Fluidized bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column with a smaller cylindrical insert the stream of cores is rising in the centre of device together with spray mist applied in the middle of the bottom. For fluidized coating very hard tablet hardness above 10 kg/cm^2 has to be used.

1.8.1.4 Materials used in film coating:

- Opaquent extenders
- Miscellaneous coating solution components

1.8.1.5 Used film formers:

Hydroxyl propyl methyl cellulose (HPMC),Methyl hydroxyl ethyl cellulose (MHEC),Ethyl cellulose (EC),Hydroxyl propyl cellulose (HPC), sodium carboxyl methyl cellulose (CMC), Acrylate polymers, Povidone**.**

Advantages:

- It is less time consuming technology.
- Not much labour is required.
- No adverse effect on Disintegration time of tablet.
- Production cost is low because material used for coating is cheap.
- Protects drug from atmospheric changes such as light, air, moist.
- Resist cracking, Chipping.

REGULATORY AFFAIRS INTRODUCTION

1.9 REGULATORY AFFAIRS

REGULATORY AFFAIRS is the link between the company and the regulatory agencies.

It is also called as *GOVERNMENT AFFAIRS*.

Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, cosmetics and complementary medicines.

The companies responsible for the discovery, testing, manufacture and marketing of these products also want to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare.

The Regulatory Affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products .They also advice on the legal and scientific restrains and requirements, and collect, collate, and evaluate the scientific data that their research and development colleagues are generating.

They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development program of the company as a whole.

The Regulatory Affairs department will take part in the development of the product marketing concepts and is usually required to approve packaging and advertising before it is used commercially.

The Regulatory Affairs professionals help the company avoid problems caused by badly kept records, inappropriate scientific thinking or poor presentation of data. In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims and can be made for the product on labeling or in advertising.

REGULATORY AFFAIRS professionals usually have responsibility for the following areas

1) Ensuring that their companies comply with all of the regulations and laws pertaining to their business.

2) Advising their companies on the regulatory aspects and climate that would affect proposed activities i.e. describing the "regulatory climate" around issues such as the promotion of prescription drugs.

3) Working with federal, state, and local regulatory agencies and personnel on specific issues affecting their business i.e. working with such agencies as the Food and Drug Administration or European Medicines Agency.

NSAIDS INTRODUCTION

1.10 NSAID'S INTRODUCTION *(H.P. Rang,M.M. Dale.,)*

Non-steroidal anti-inflammatory drugs (NSAIDS) are among the most widely used of all therapeutic agents worldwide. They are frequently prescribed for 'rheumatic' musculoskeletal complaints and are often taken without prescription for minor aches and pains.

1.10.1Pharmacological actions *(Vane and Botting, 2001)*

NSAIDS include a wide variety of different agents of different chemical classes. Most of the drugs have three major types of effects:

- Anti-inflammatory effects
- Analgesic effects of certain sorts of pain
- Antipyretic effect: lowering of a raised temperature

In general, all of these effects are related to the primary action of the drugs-inhibition of arachidonate cyclooxygenase and thus inhibition of the production of prostaglandins and thromboxanes - though some aspects of the action of individual drugs may occur by different mechanism, in addition, some drugs have action other than those on inflammation.

There are two types of cyclooxygenase enzyme, namely COX-1 and COX-2.COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets. It has a house-keeping role in the body being involved in tissue homeostatis.COX-2 is induced in inflammatory cells when they are activated, and the primary inflammatory

cytokines-interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation.

It has become clear that the anti-inflammatory action of the NSAIDs is mainly related to their inhibition of COX-2 and that, when used as anti-inflammatory agents, their unwanted effects particularly those affecting the gastrointestinal tract-are largely a result of their inhibition of COX-1.Compounds with a selective action on COX-2 are now in clinical use, and more in development. It is expected that these COX-2 inhibitors could transform the approach to the treatment of inflammatory conditions.

Antipyretic effect

Normal body temperature is regulated by a centre in the hypothalamus that ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which leads to the set-point of body temperature being raised. NSAIDs reset the thermostat. Once there has a return to the normal set-point, the temperature regulating mechanisms then operate to reduce temperature. Normal temperature is not affected by NSAIDs.

NSAIDs are thought to be antipyretic largely through inhibition of prostaglandin production in the hypothalamus. During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of a pyrogen-IL-1.which stimulates the generation, in the hypothalamus, of E-type prostaglandins (PGEs) and these, in turn cause the elevation of the set-point for temperature.COX-2 may have a role here since it is induced by IL-1 in blood vessel endothelium in the hypothalamus. COX-3 may be implicated in fever.

There is some evidence that prostaglandins are not the only mediators of fever, hence NSAIDs may have an additional antipyretic effect by mechanisms as yet unknown.

Analgesic effect

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because they decrease production of the prostaglandins that sensitise no receptors to inflammatory mediators such as bradykinin. Therefore they are effective in arthritis, bursitis, pain of muscular and vascular orign, toothache, dysmenorrhoea, the pain of postpartum states and the pain of cancer metastases in bone-all conditions that are associated with increased prostaglandins synthesis. In combination with opioids, they decrease the pain and in some cases can reduce the requirements for opiods by as much as one third. Their ability to relieve headache may be related to the abrogation of the vasodilator effect of prostaglandins on the cerebral vasculature. There is some evidence that they have a central effect by an action mainly in the spinal cord.

Anti-inflammatory Effect

There are many chemical mediators of the inflammatory and allergic response. Each facet of the response- vasodilation, increased vascular permeability, cell accumulation, etc.-can be produced by several different mechanisms. Furthermore, different mediators may be of particular importance in different inflammatory and allergic conditions and some mediators have complex interactions with others, for example small amounts of nitric oxide (NO)stimulates cyclooxygenase activity, while large amounts inhibit it.

Drugs such as the NSAIDs reduce mainly those components of the inflammatory and immune response in which the products of COX-2 action play a significant part namely

- Vasodilation
- Oedema

1.10.2 Mechanism of Action

The main action of NSAIDs is, as stated above, inhibition of arachidonic acid-metabolising activity of COX. The cyclooxygenase enzymes are bifunctional, having two distinct activities: the main action, which gives PGG2. And a peroxidise action, which converts PGG2 to PGH2. Both COX-1 and COX-2 inhibitors inhibit only the main cyclooxygenase reaction, both COX-1 and COX-2 are associated with the membrane and each consists of a long channel with a bend at the end, the channel being wider in COX-2. The opening of the channel is largely hydrophobic. Arachidonic acid enters, is twisted round the bend and has two oxygen's inserted and a free radical extracted, resulting in the five carbon ring characteristic of prostaglandins.COX-1 inhibition, in general, is instantaneous and competitively reversible.COX-2 inhibition is time dependent, i.e. its effect increases with time.

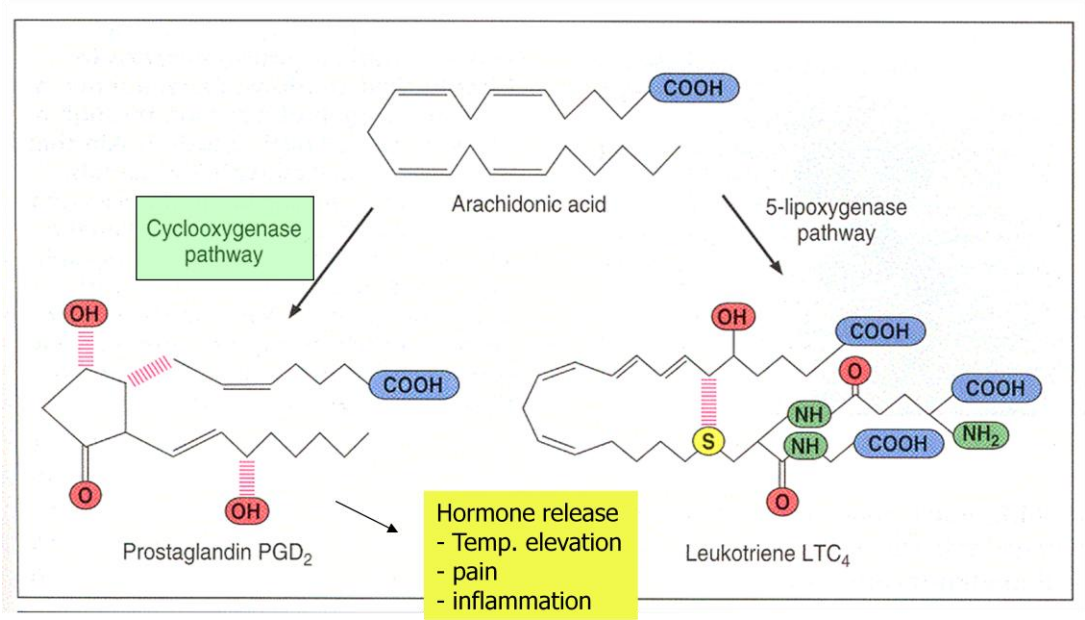


Figure.1.1 Mechanism of prostaglandins

1.10.3 CLASSIFICATION OF NSAIDs

1) COX-1 SELECTIVE INHIBITORS

- Acetylsalicylic acid at low dosage

2) NON SELECTIVE COX INHIBITORS

- Acetylsalicylic acid at high dosage
- Diclofenac
- Ibuprofen
- Ketoprofen
- Flurbiprofen

- Indomethacin

- Piroxicam

- Naproxen

3) MORE COX-2 SELECTIVE INHIBITORS

- Nimusulide

- Etodolak

-Meloxicam

- Nabumeton

4) COX-2 SELECTIVE INHIBITORS

- Celecoxib

- Etorcoxib

- Valdecoxib

1.10.4 ANTI-INFLAMMATORY EFFECTS OF NSAIDs

This effect of NSAIDs is due to the inhibition of the enzyme COX, which converts arachidonic acid to prostaglandins, TXA2 and prostacyclin.

Acetylsalicylic acid irreversibly inactivates COX-1 and COX-2 by acetylation of a specific serine residue.

Other NSAIDs reversibly inhibit COX-1 and COX-2

Additional anti-inflammatory mechanism may include:

- Interference with the potentiative action of other mediators of inflammation – bradykinin, histamine, serotonin

- Modulation of T-cell function

- Stabilization of lysosomal membranes

- Inhibition of chemotaxis

ANALGESIC EFFECT OF NSAIDS

This effect of NSAIDs is thought to be related to the peripheral inhibition of prostaglandin production, but it may also be due to the inhibition of pain stimuli at a subcortical site.

NDAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (e.g bradykinin)

ANTIPYRETIC EFFECT OF NSAIDS

This effect is believed to be related to inhibition of the interleukin-1 and interleukin-6 induced production of prostaglandins in the hypothalmus and the resetting, of the termo regulatory system, leading to vasodilation and increased heat loss.

AIM &

OBJECTIVES...

2. AIM AND OBJECTIVE

Naproxen sodium (NSAIDS) is an FDA Approved prodrug for clinical use for the treatment of rheumatic musculo skeletal pains, acute gout and other minor pains either alone or in combination with other NSAIDS drugs.

Naproxen sodium is absorbed rapidly following oral administration producing peak plasma concentration within 1-2 hour with 95% bioavailability. Elimination half life is 12-17 hours.

- It is usually administered in a dose of 220mg twice daily in order to maintain effective concentration. And the main dose related adverse effect is gastrointestinal disturbance, with increase in concentrations.
- The drug has longer half life of 12-17 hours. Hence it is suitable for immediate release preparations.
- Immediate release drug delivery systems for oral dosing are effective in achieving optimal therapy for the drugs that have longer half life.
- These preparations were able to release immediately with quicker on set of action and without dose dumping problem by incorporating super disintegrants like sodium starch glycolate.
- So the present work involves use of immediate release system for Naproxen sodium by incorporating super disintegrants will ensure the drug to release the medicament immediately for quicker on set of action which will increase the patient compliance.
- Naproxen sodium was been formulated and marketed using the API of approved vendor i. e, REDDY'S LTD by the GRANULES INDIA LTD.

- As the approved API from REDDY'S was not sufficient due to much demand for the drug Naproxen sodium in marketing field.
- An alternate vendor i. e, CHARIOTEER was proposed.
- According to regulatory point of view an alternate vendor for Active pharmaceutical ingredient can be approved if the specification standards and dissolution profile was same as compared with that of the already approved API according to the Alternate vendor guideline.
- Hence the comparison for both the specification standards and percentage drug release was done for approved vendor (REDDY'S) and alternate vendor (CHARIOTEER).

2.1 Objectives:

- To evaluate the requirements to propose an alternate Active Pharmaceutical Ingredient source for an approved drug product.
- Comparison of specification standards of both approved and alternate API source.
- Comparison of dissolution profiles for both approved and alternate API source.
- The objective of the present study is to compare both the API'S i.e approved vendor (REDDY'S) and alternate vendor (CHARIOTEER'S) and to approve the alternate vendor as equivalent to that of approved vendor.
- To formulate and evaluate Naproxen sodium immediate release Tablet of both the API'S i.e. of both approved vendor (REDDY'S) and alternate vendor (CHARIOTEER'S).

- To study the effect of different super disintegrants on drug release behaviour of the polymer.
- Based on the Pre and post formulation parameters characteristics the formulation for both the API'S was carried out and short term stability studies were performed as per ICH guidelines.

PLAN OF WORK....

3. PLAN OF WORK

The present work was carried out to evaluate the requirements to propose an alternate Active Pharmaceutical Ingredient source for an approved drug product.

The approved API source for the drug product is REDDY'S LTD and the alternate API source is Zhejiang charioteer.

Scheme of work Listed as Follows:

- Literature review
- Selection of drug
- Overview of manufacturing of drug substances (approved vendor versus vendor)
- Certificate of Analysis for finished drug product.
- Comparison of specification standards of both approved and alternate API source.
- Comparison of dissolution profiles for both approved and alternate API source.
- Tests performed for overview of standards.

❖ Performing the tests according to specification standards

- a) Solubility test

- b) Identification by IR
- c) Specific optical rotation
- d) Melting point
- e) Loss on drying
- f) Heavy metals
- g) Related substances by HPLC
- h) Partice size
- e) Bulk Density

❖ Evaluation of blend characteristics of prepared granules from both the API'S (pre compression parameters)

- a) Angle of repose
- b) Determination of Bulk density
- c) Determination of Tapped density
- d) Sieve Analysis
- e) Moisture content

❖ Evaluation of physical parameters of Naproxen sodium (post compression parameters)

- a) Disintegration
- b) Friability

- c) Thickness
- d) Hardness
- e) Weight variation

- Evaluation of dissolution profiles for Naproxen sodium tablet obtained from both the API'S.
- STABILITY STUDY
- RESULTS AND DISCUSSION
- CONCLUSION
- BIBLIOGRAPHY

LITERATURE SURVEY

4. LITERATURE REVIEW

Pakhuri Mehta.,et al., (2012) had developed and undergone validation of related substances method by HPLC for analysis of Naproxen tablet formulations. A simple, selective, rapid, and precise and isocratic reversed phase high pressure liquid chromatography was been used, mobile phase acetonitrile and Ammonium acetate buffer Ph3.8 in ratio 550:450v/v. The detection and quantification limits were 0.13 and 0.25µg/ml respectively. Statistical analysis proved the method was precise, reproducible selective, specific, and accurate for analysis of Naproxen and its impurities. The wide linearity range, short retention time, and simple mobile phase showed that the method is suitable for routine quantification of impurities in Naproxen in pharmaceutical dosage forms with high precision and accuracy.

Deepali Avinash Meher. **(2011)** had formulated and developed the fast disintegrating Naproxen tablets using simplex lattice design. The aim of present work was done to show the effect of various super disintegrants on the disintegration time and in vitro drug release rate. In this study, an attempt had been made to prepare fast disintegrating tablets. The sodium starch glycolate, cross carmellose and povidone were used in different concentrations according to simplex lattice design. The tablets were evaluated for diameter, thickness, hardness, disintegration time and in vitro dissolution studies. Disintegration time of all the formulations showed less than 88 seconds. Formulations containing cross carmellose sodium and povidone showed fastest disintegration than formulations containing sodium starch glycolate.

Neha Vishal Gandhi.,et al., (2011) Formulated and evaluated orodispersible tablets of Naproxen sodium. Naproxen sodium is an analgesic NSAID used for the treatment of pain, inflammation, rheumatoid arthritis, juvenile arthritis, gout. Present investigation was undertaken with a view to develop orodispersible tablet of Naproxen sodium which offers quick onset of action of drug and minimise the problem of gastric discomfort. In this study the tablets were prepared by direct compression method using super disintegrants e.g sodium starch glycolate, croscaramellose and povidone in different concentrations. The tablets were evaluated and results were compared, povidone was found to be the most efficacious superdisintegrants to formulate orodispersible tablets.

Rangasamy Manivannan.,et al., (2010) had formulated and evaluated Naproxen sodium tablets USP. The objective of the present study was to develop a pharmaceutically stable and robust formulation of Naproxen sodium 220 mg compared with innovator. The tablets were prepared by using wet granulation technique. Several trails formulations i.e., from F1-10 were taken to optimise and develop a robust formulation. The prepared tablets were evaluated for weight variation, hardness, thickness, disintegration, *in-vitro* drug release and stability studies.

Saravana Kumar K.,et al., (2012) had formulated and evaluated Naproxen sodium –loaded Chitosan microsphers. The chitosan based microsphers have been studied as controlled release to deliver Naproxen sodium in gastrointestinal tract. Mucoadhesive microsphers were prepared by emulsification solvent evaporation method by treating with tween-80 as surfactant, glutaraldehyde solutions as cross-linker. Upon cross inking the resulting microsphers were found to be more efficient for prolonged drug release. The release of the drug was controlled by the mechanism

of the dissolution of NS in the dissolution medium and the diffusion of NS through the mucoadhesive microsphers.

Vinay Wamorkar.,et al., (2011) had validated spectroscopic method for the estimation of Naproxen from tablet formulation. The present research work discusses the development of uv -spectroscopic method for the estimation of Naproxen. The optimum conditions for the analysis of the drug were established. The maximum wavelength was found to be 273nm. All calibrations curves show a linear relationship between the absorbance and concentration with coefficient of correlation 0.999.Standard errors in case of recovery studies was satisfactorily low and allow estimation Naproxen in concentration range in the assay of bulk drugs and tablets. The sample solution was stable upto 36 hours. It is thus concluded that the proposed method is new, simple, cost-effective, safe, accurate, precise and environment friendly.

Patil C.,et al., (2007) Formulated the oral tablets of Naproxen using guargum alone in combination with other polymers. Tablets were prepared by wet granulation using guargum, xanthian, methyl cellulose CAP as a polymer containing 100 mg of Naproxen.

Hawkey Lancet.,et al ., (1999) In this studies Hawkey revealed that the main anti-inflammatory agents are the glucocorticoids and the non steiordal anti inflammatory drugs (NSAIDs).The NSAIDS are dealt with below and, in dealing with them we describe the pharmacological actions common to all of them, their mechanism of action and unwanted effects.

F A Khan.,et al.,(2011) had validated for simultaneous determination of Naproxen and Pantoprazole sodium in capsule dosage form by RP-HPTLC. A simple sensitive and reliable spectroscopic method for the estimation of Naproxen and Patoprozole sodium in combined dosage form has been attempted. The analyte were resolved using MeOH: KH_2PO_4 buffer at a flow rate of 1.0 ml/min, on Thermo separation product quaternary gradient HPLC pump spectra containing of UV-1000 UV visible detector with data Ace software and Prontosil C18 46 (id) 250 mm. The method gave good resolution and suitable retention time. The standard and sample solution of NAP and PAN were prepared in mobile phase. The detection was carried out at 275 nm the selection of the wave length was based on λ max. This system gave good resolution and optimum retention time with appropriate tailing factor(less than2).

Padmanabh Deshpande.,et al., (2012) had validated method development for the estimation of Naproxen sodium as bulk drug in tablet dosage form by HPTLC. The present work describes as simple, precise and accurate HPTLC method. The chromatographic development was carried out on precoated silica gel 60 F_{254} aluminium plates using mixture of toluene : ethyl acetate: acetic acid (7:5:1.5:1 v/v/v) as mobile phase and densinometric evaluation of band was carried out at 230 nm Camag TLC Scanner. The method was also evaluated by the assay of commercially available tablets. The % assay was found to be 99.34 % ± 0.146.The proposed method can analysis ten or more formulations units simultaneously on a single plate and provides cost-effective quality control tool for routine analysis of Naproxen sodium as bulk drug and in tablet formulation.

Syeda kulsum.,et al. (2011) had undergone the spectrometric methods for the determination of Naproxen sodium in pure and pharmaceutical dosage forms. Two visible spectrophotometric methods have been developed for the determination of Naproxen sodium either in pure form or in their pharmaceutical formulations. The developed methods are based on reaction of Naproxen with phenol red and bromocresol green. Their absorption maximum was found to be at 422nm, and Beer's law was obeyed in concentration ranges of 60-80µg/ml and 120-160µg/ml. The colours were found to be stable for 4 hours. The proposed methods were successfully applied for determination of Naproxen in their pharmaceutical formulations.

Palavai Sripal Reddy.,et al., (2010) had undergone studies on Impurities profiling method and degradation studies for sumatriptan succinate in sumatriptan succinate and Naproxen sodium tablets. A simple, sensitive, and precise high performance liquid chromatographic method for the impurities profiling of sumatriptan succinate in sumatriptan and Naproxen tablets had been developed, validated and used for determining impurities. The impurities were well separated by the gradient program using 0.05M Phosphate buffer (pH 3.0), acetonitrile and methanol at a flow rate of 1.0m/lmin-1 with detection wavelength at 225 nm. The developed method was found to be specific, precise, accurate and robust. LOQ values for all the known impurities were below reporting thresholds.

Seren Kayiran.,et al., (2010) had undergone studies on determination of Naproxen sodium from poly (lactide-co-glycolide) corneal scaffolds. Efficient chromatographic separation was achieved on a reverse phase column with the mobile phase consisting of methanol and acetate buffer (pH5.1) at a flow rate of ml/min by using fluorescence detector at 254 nm/352nm.The developed HPLC method was successfully applied to quantitate NS in PLGA.

M Harris Shoaib.,et al., (2011) had developed and evaluated Naproxen sodium effervescent tablets. The present study focuses on developing a new, simple, cost effective formulation of Naproxen sodium using direct compression method. Nine different trial formulations were designed and evaluated. Tablets took 4 min and 36 sec to disintegrate. Dissolution was observed within 15 min. Stability studies were also found to be stable, such formulations increases patient compliance and have possibly improved bioavailability.

Harun O Rashid.,et al., (2009) had designed and formulated Naproxen sustained release tablet matrix from Methocel K 15M CR and Methocel K 100M CR. The tablets were prepared by wet granulation method along with hydrophilic matrix materials. The granules were evaluated for angle of repose, drug content. Tablets were subjected to thickness, hardness, friability and *in-vitro* release at pH 7.4 .All formulations showed first order release kinetics. The matrix tablets of Naproxen using HPMC controls the drug release effectively for 24 hrs, hence the formulation can be considered as once daily sustained release tablets of Naproxen in order to improve patient compliance.

DRUG AND EXCIPIENT PROFILE

5.1 DRUG PROFILE

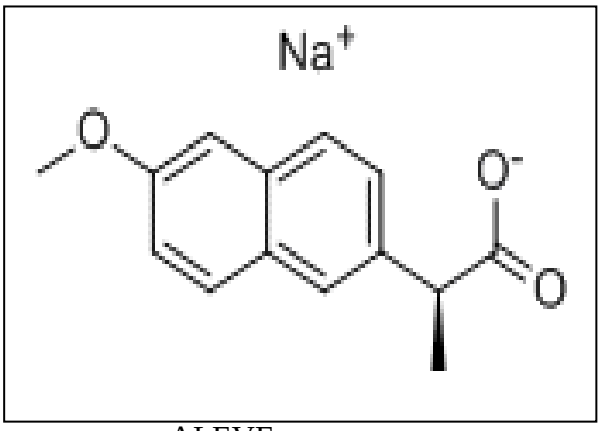
Name: Naproxen sodium

Type: Small molecule

Description: An anti-inflammatory agent with analgesic and anti pyretic Properties. Both the acid and its sodium salt are used in the treatment of rheumatoid arthritis, musculoskletal disorders, and acute gout.

State: Solid

Structure:



Synonym: ALEVE

ANAPROX

EQUIPROXE

Ec-naproSYN

BrandNames:

Naixan

Naprius

Naprux

Naprium

Niaxan

Nycoprene

Proxine

Veradol

Category : Cyclo oxygenase Inhibitors

Gout Suppressant

CAS. NO: 2204-53-1

Weight : 230.259

Chemical

Formula : $C_{14}H_{13}O_3Na$

IUPAC

Name : 2-(6-methoxynaphthalene-2-yl) propanoic acid

Solubility : Soluble in water, methanol, sparingly soluble in alcohol, very slightly in acetone, and practically insoluble in chloroform and toluene.

Melting Point : 152-157º C

Taste and odour : Tasteless, odourless

Absorption : Absorbed through GI tract

Protein Binding : 99.0%

Half life : 12-17 hours

Bioavailibility : 95.0%

Mechanism :

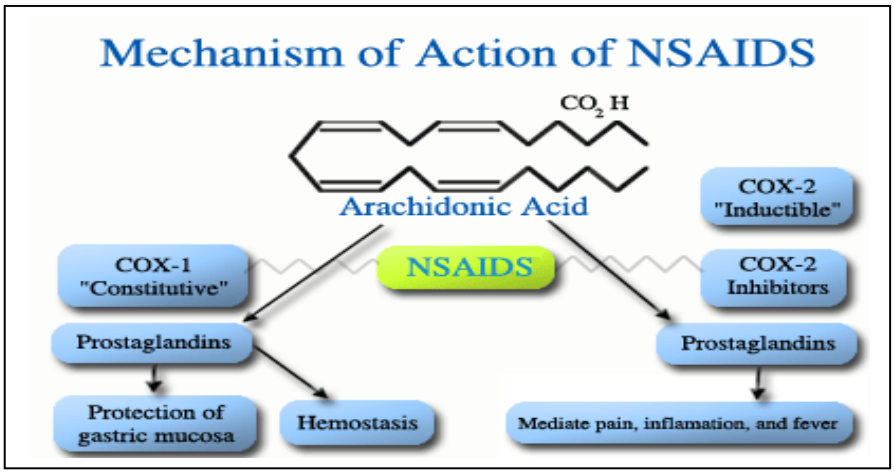


Figure 5.1 Mechanism of Action.

Indication :

It is a non steroidal anti inflammatory drug (NSAID) with analgesic and antipyretic properties, for the treatment of rheumatoid arthritis, ankylosing spondylytis and acute gout.

Pharmacokinetic Nature of Naproxen sodium

Absorption:

Naproxen itself is rapidly and completely absorbed from the GI tract.

An in-vivo bioavailability of 95% although Naproxen is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels. Food causes slight decrease in the rate of absorption.

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 500mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses(average steady state concentration) 36.5,49.2 and 56.4mg/l**,** the concentration of unbound Naproxen continues to increase proportionally to dose.

Metabolism:

Naproxen is extensively metabolized to 6-O –desmethyl naproxen, and both parent and metabolites donot induce metabolizing enzymes.

Elimination:

The clearance of naproxen is 0.13ml/min/kg. Approximately 95%of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%)or their conjugates(66% to 92%).The plasma half life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Drug Interactions:

Cyclosporine : Monitor for nephrotoxicity

Methotrexate : The NSAID, naproxen, may decrease the renal excretion of methotrexate, increased risk of methotrexate toxicity.

Warfarin : The antiplatelet effects of naproxen may increase the bleeding risk associated with warfarin.

Food Interactions:

Avoid alcohol

Take with a full glass of water

Take with food.

Side Effects

Gastro intestinal

Constipation, Heart burn, Nausea, Diarrhea, Abdominal pain.

Central Nervous System

Headache, Dizziness, Vertigo.

Dermatologic

Itching, Skin eruptions, Sweating, Purpura.

Special Senses

Tinnitus, Hearing disturbances, Visual disturbances.

Cardiovascular

Edema, Dyspnea, Palpitation

5.2 EXCIPIENT PROFILE

MICROCRYSTALLINE CELLULOSE

5.2.1 MICROCRYSTALLINE CELLULOSE *(Raymond C Rowe et al., 2009)*

1. Nonproprietary names:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

Ph Eur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

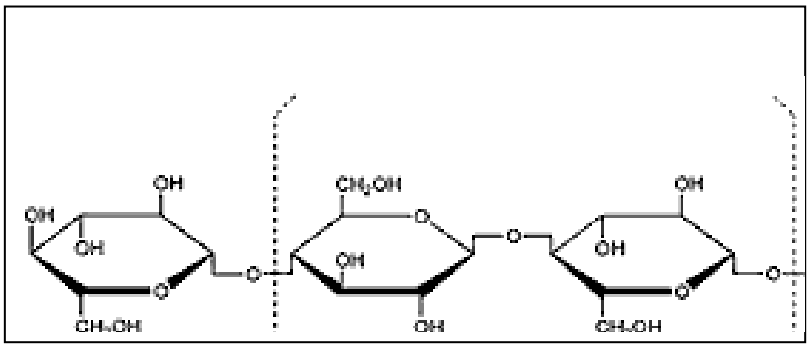
2. Synonyms:

Avicel PH, Celex, cellulose gel, Celphere, Ceolus, Crystalline cellulose, E460, Emcocel, Fibrocel, Pharmacel, Tabulose, Vivapur.

3. Chemical Name: Cellulose

4. Empirical Formula & Molecular Weight: $(C_6H_{10}O_5)_n$ **:** 36,000

5. Structural Formula:



6. Functional Category:

Adsorbent, suspending agent, tablet and Capsule diluents, tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations .Microcrystalline cellulose is also used in cosmetics and food products.

Table 5.1: Uses of Microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

8. DESCRIPTION:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

9. Typical Properties:

Angle of repose: 34.4°

Density (bulk) : 0.32 g/cm^3

Density (tapped) : 0.45 g/cm^3

Density (true) **:** 1.512-1.668 g/cm^3

Table 5.2: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size
Avicel PH-101	50
Avicel PH-102	100
Avicel PH-103	50
Avicel PH-105	20

10. Stability and Storage Conditions:

Microcrystalline cellulose is a stable, though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry, place.

11. Incompatibilities:

Incompatible with strong oxidizing agents.

SODIUM STARCH GLYCOLATE

5.2.2 Sodium Starch Glycolate (SSG)

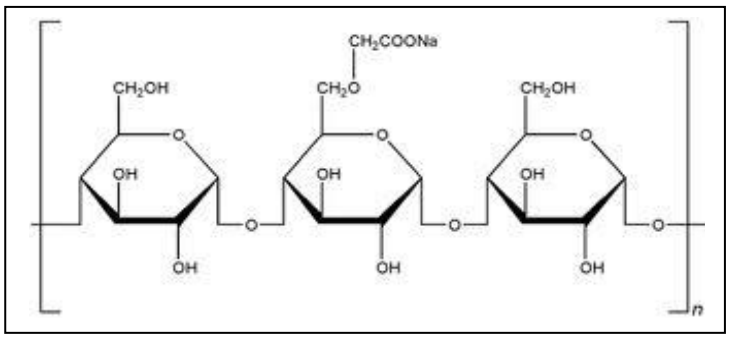
1. Synonyms:

Explotab, Primogel, Vivastar Carboxymethyl starch, sodium salt.

2. Chemical Name:

Sodium carboxymethyl starch.

3. Structure:



4. Description:

It is a white or almost white free-flowing very hygroscopic powder. The PhEur states that when examined under a microscope it is seen to consist of: granules irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded,10–35 mm in size, compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum, small crystals are visible at the surface of the granules. The granules how considerable swelling in contact with water.

5. Functional Category:

Tablet and capsule disintegrate.

6. Solubility:

Practically insoluble in water and insoluble in most organic solvents.

7. Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

8. Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain changed for up to 3 years if it is stored at moderate temperatures and humidity.

9. Applications in Pharmaceutical Formulation:

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablet prepared by either direct compression or wet granulation processes.

STEARIC ACID

5.2.3 STEARIC ACID

1. Nonproprietary Name

BP Stearic acid

JP Stearic acid

Ph Eur Acidum stearicum

USPNF Stearic acid

2. Synonym :

Crodacid, E570, Emersol, Kortacid 1895, Pristerene.

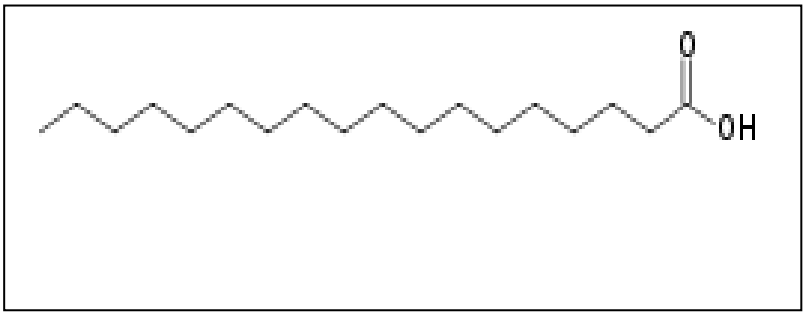
3. Chemical Name and CAS Registry Number:

Octadecanoic acid [57-11-4]

4. Empirical Formula and Molecular Weight:

$C_{18}H_{36}O_2$, 284.47

5. Structral Formula:



6. Functional Category:

Emulsifying agent, solubilising agent, tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

It is widely used in oral and topical pharmaceutical formulations. It is used in oral formulations as a tablet and capsule lubricant, it is also used as binder or in combination with shellac as a coating, and it is also used as a hardening agent in glycerine suppositories

8. Uses of Stearic acid

Table 5.3 Uses of Stearic acid

Use	Concentration (%)
Ointments and creams	1-20
Tablet lubricant	1-3

9. Description

It is a hard, white or faintly yellow- coloured, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste.

10. Typical Properties

Acid value : 200-212

Density (bulk) : 0.537g/cm^3

Density (tapped): 0.571g/cm^3

Density (true) : 0.980g/cm^3

Melting point :> 54ºC

Solubility: Freely soluble in benzene, carbon tetrachloride, chloroform and ether, soluble in ethanol, hexane and propylene glycol. Practically insoluble in water.

11. **Stability and Storage Conditions**

Stearic acid is a stable material. The bulk material should be stored in a well closed container in a cool, dry place.

12. Incompatibilities

Incompatible with most metal hydroxides and oxiding agents.

STARCH

5.2.4 STARCH

1. Nonproprietary Name :

BP Maize starch

Potato starch

Rice starch

Tapioca starch

JP : Corn starch

Wheat starch

Potato starch

Rice starch

PhEur : Maydis amylum (maize starch)

Solani amylum (potato starch)

Oryzae amylum (rice starch)

Tritici amylum

2. Synonym :

Amido, amidon , amylum

3. Chemical Name and CAS Registry Number :

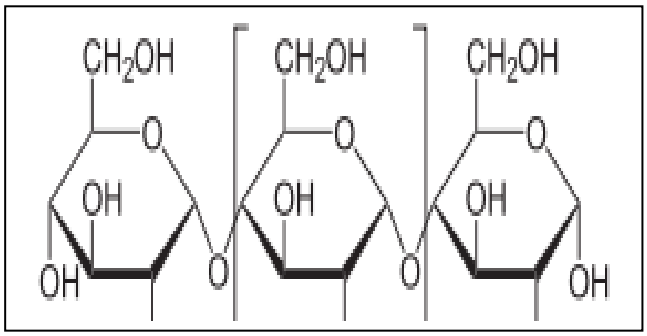
Starch, [9005-25-8]

\

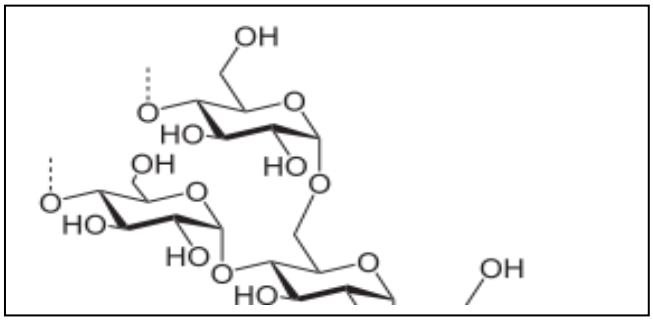
4. Empirical Formula and Molecular Weight:

$C_6H_{10}O_5$, 50,000-160,000

5. Structure:



Structure of Amylose



Amylopectine structure

6. Functional Category:

Glidant , tablet and capsule diluents , tablet and capsule disintegrant , tablet binder.

7. Applications in Pharmaceutical Formulation or Technology :

It is used as an excipient primarily in oral solid-dosage form as a binder, diluents and disintegrant

8. Description:

Starch occurs as an odourless and tasteless, fine, white coloured powder comprising very small spherical or ovoid granules.

9. Typical Properties

pH : 5.5-6.5

Density (bulk) : 0.462g/cm^3

Density (tapped): 0.658g/cm^3

Density (true) : 1.478g/cm^3

10. Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. Should be stored in an air tight container in a cool, dry place.

POVIDONE

5.2.5 POVIDONE:

1. Nonproprietary Name :

BP : Povidone

JP : Povidone

PhEur : Povidonum

USP : Povidone

2. Synonym :

E1201, Kollidon, Plasdone, PVP,1-vinyl-2-pyrrolidinone polymer.

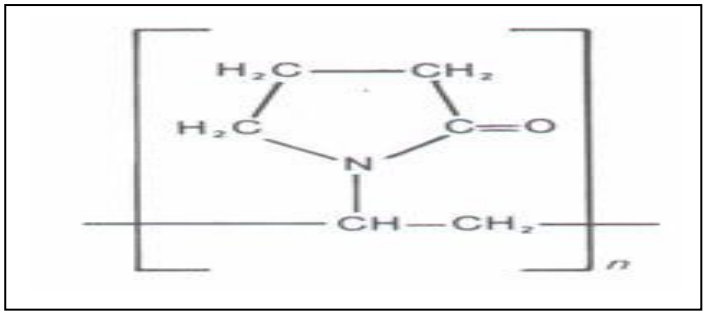
3. Chemical Name and CAS Registry Number :

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Formula :

$(C_6H_9NO)_n$, 2500-3000000

4. Structural Formula :



6. Functional Category:

Disintegrant, dissolution aid, suspending agent, tablet binder.

7. Applications in Pharmaceutical Formulation or technology :

It is used in solid-dosage forms, as a binder in wet granulation process, used as a solubilizer in oral and parenteral formulations**.**

8. Uses of Povidone :

Table 5.4: Uses of povidone

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Table binder, diluent or coating agent	0.5-5

9. Description:

It occurs as a fine, white to creamy-white coloured, odourless hygroscopic powder.

10. Incompatibility

It is compatible in solution with a wide range of inorganic salts , natural and synthetic resins , and other chemicals.

MATERIALS & EQUIPMENTS....

6.1 LIST OF EQUIPMENTS

Table 6.1: List of equipments.

NAME OF INSTUMENTS	MODEL AND MANUFACTURER
Digital Balance	Mettler Toledo PR203,China
Rapid Mix Granulator	RMG5 Anchor Mark Pvt Ltd., Ahmedabad
Fluid bed dryer	Umang Pharmatech Pvt Ltd., Mumbai
Moisture Analyzer	Advance Research Pvt Ltd., Mumbai
Tap Density Tester	Electrolab, Mumbai
Tablet compression machine	Rimek1rotary, Ahmedabad
Vernier Calliper	Mitutoyo, China
Hardness Tester	SQC & Inspection instruments, Mumbai
Disintegration Test Apparatus USP	Tab machines, Mumbai
Stability chamber	Cintex Ind. Corporation, Mumbai
Mechanical Stirrer	Neocota, Mumbai
Auto coater	Neocota, Mumbai
Dissolution Apparatus USP XXII	ElectroLab, Ahmedabad
HPLC with Autosampler	Waters, USA
pH meter	Metro HM, Switzerland
Differential scanning calorimeter	Shimadzu DSC 60, Japan
UV spectrophotometer	Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer, Japan
FTIR spectrophotometer	Brucker, Japan

6.2 MATERIALS USED

Table 6.2: List of materials.

S.No.	Drug/ Excipients	Name of supplier
1	Naproxen sodium	Granules India Ltd., Hyderabad
2	Micro crystalline cellulose	Brahmar cellulose Pvt Ltd., Cuddalore
3	Povidone K-30	Vijilak pharma, Hyderabad
4	Stearic acid	Granules India Ltd, Hyderabad
5	Corn starch	Signet chemical corporation Pvt Ltd.,
6	Sodium Starch Glycolate	SD Fine –Chem Pvt Ltd., Mumbai
7	Aquarius BP 17066	Colorcon Asia Pvt Ltd., Mumbai

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1. Performing the tests according to specification standards

7.1.1. SOLUBILITY*:* *(IP, 2007)*

Aqueous solubility is an important physicochemical property of the drug substance which determines its systemic absorption and in turns its therapeutic efficacy.

Table 7.1: Solubility specifications

Descriptive terms.	Approximate volume of solvent in milli litres per gram of solvent.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 1 to 30
Sparingly soluble	From 30to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 100 to 10,000
Practically insoluble	More than 10,000

7.1.2. pH: *(IP,2007)*

The pH is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors from which the stand point of solubility, stability and physiochemical suitability of a formulation.

Procedure:

1 g of Naproxen sodium is dissolved in 100ml of demineralised water for preparing 1% of solution. The pH value of a solution is determined potentiometrically by means of a glass electrode

7.1.3. MELTING POINT: *(IP, 2007)*

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point.

7.1.4. IDENTIFICATION TESTS*:* *(USP, 2004)*

7.1.4.1. Identification by IR:

Sample Preparation:

Dissolve 50 mg in 5 ml of water, add 1 ml of dilute sulphuric acid, and then add 5 ml of ethyl acetate shake well. Allow the two layers to separate. Evaporate the upper layer to dryness and subsequently dry at 60ºC for 15 minutes. Transfer 1-1.5 mg of the above prepared sample, use KBr as disc.

Pellet preparation of test sample:

Weight about 1 mg of sample and 100 mg of dried Potassium Bromide mix and grind in a mortar to a fine powder, spread the mixture uniformly in a die and submit in a vacuum to a pressure of about 800Mpa by using pellet making apparatus and check the pellet for uniform transparency.

Pellet preparation of standard:

Weight about 1 g of Naproxen sodium USP working standard and 100 mg of dried Potassium Bromide mix and grind in a mortar to a fine powder , spread the mixture uniformly in a die and submit in a vacuum to a pressure of about 800Mpa by using pellet making apparatus and check the pellet for uniform transparency. Record the spectra of the test sample and the reference sample over the range from about 2.6µm to 15µm (13800 cm^{-1}). Overlap the sample spectrum with reference spectra and observe the overlap spectrum of test and reference. The IR spectrum of the sample must be concordant with that of the reference spectrum.

7.4.1.2. UV:

Test solution:

Weigh about 50 mg of Naproxen powder; note it down, transfer into 100 ml volumetric flask, dissolve in methanol and make up to volume with the same solvent. Pipette out 5 ml of the above solution accurately into 100 ml volumetric flask and make up to volume with methanol.

Reference solution:

Weigh 50 mg of Naproxen working standard, note it down, transfer into 100 ml volumetric flask, dissolve in methanol and make upto volume with the same solvent. Pipette out 5 ml of the above solution accurately into 100 ml volumetric flask and make up to volume with methanol.

Record the spectrum for both the test solution and reference solution over the spectral range from 200-400 nm in 1 cm cell.

Calculate the absorptive at 272 nm for test solution and reference solution on dried basis. The difference is not more than 3 %.

Calculation:

Λ max 272 nm

$$Absorptivity\ of\ standard\ (a1) = \frac{absorbance\ \ of\ standard\ \times 100 \times 100 \times 100 \times 100}{standard\ \ weig\,ht \times 5 \times purity\ \times (100 - LOD)}$$

$$Absorptivity\ of\ sample(a2)\ \frac{absorbance\ of\ sample\ \times 100 \times 100 \times 100}{absorbance\ of\ sample \times 5 \times purity \times (100 - LOD)}$$

$$\%variation\ of\ absorptivity\ of\ sample\ to\ that\ of\ standard = \frac{(a1 - a2) \times 100}{a1}$$

The respective absorptivities at 272 nm, do not differ by more than 3%

7.1.1.3. Sodium reaction:

Dissolve 0.1 g of sample in 2 ml of water; add 2 ml of a 150 g/ml solution of potassium carbonate and heat to boiling, no precipitate is formed. Add 4 ml of potassium pyroantimonate solution and heat to boiling allow cooling with ice water and if necessary rubbing the inside of the test tube with a glass rod –a dense white precipitate is formed.

7.1.5. Specific optical rotation:

Sample preparation:

Accurately weight and transfer about 2.5 g of Naproxen sodium into a clean and dried 50 ml volumetric flask, add 15 ml of 0.1 N sodium hydroxide, shake well to dissolve the sample and make up to the mark with 0.1 N sodium hydroxide solution .

Instrument parameters:

sample temperature :25°C

cell length :1dm

$$\textbf{\textit{Sample concentration}} = \frac{\textbf{\textit{weight of the sample}} \times (\mathbf{100} - \textbf{\textit{LOD}})}{\textbf{\textit{volume of }}\mathbf{0.1}\textbf{\textit{N NaOH taken}}}$$

Procedure:

Take a clean and dried 1 dm glass cell or quartz cell. Perform blank determination by using 0.1 N sodium hydroxide as blank in a polarimeter. Then take the sample into cell and perform the specific optical rotation for sample and take five

$$[\alpha] = \lambda \frac{100 \times a}{lc}$$

α = Optical rotation at wave length 589 nm

t =Temperature

λ =Wavelength (589 nm)

a =observed rotation in degrees

l =Path length in decimeters

c =concentration of solution

7.1.6. Heavy metals: *(USP, 2004)*

Reagents:

- 6N HCl: Dilute 51.0 ml of HCl with water to 100 ml.
- 6N Ammonium Hydroxide: Dilute 400 ml of Ammonia water, stronger with water to make 1000 ml.
- 1 N Acetic acid: Add 58 ml of glacial acetic acid to sufficient water to make 1000 ml after cooling to room temperature.
- 1 N NaOH: Dissolve 40 g of sodium hydroxide in carbon dioxide free water, cool the solution to room temperature, and filter thorough hardened filter paper.

Thioacetamide Glycerin Base TS:

- Mix 0.2 ml of thioacetamide and 1 ml of glycerine base TS. Heat it on a water bath for 20 sec. Use the mixture immediately.

Lead Nitrate Stock Solution:

Dissolve 159.8 mg of lead nitrate in 100 ml of water to which has been added 1 ml of nitric acid, then dilute with water to 1000ml. Prepare and store this solution in glass container free from soluble lead salts.

Standard Lead Solution :

Each ml of the standard lead nitrate stock solution with water to 100 ml, a comparison solution prepared in the basis of 100 ml of standard lead solution 1 g of

substance being tested contains the equivalent of 1 part of lead per million parts of the substance being examined.

Standard Preparation:

Pipette out 2 ml of standard lead solution (20µg of Pb) into a 50 ml colour comparison tube and dilute with water to 25 ml, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 using short range pH indicator paper as external indicator. Dilute it with water to 40 ml and mix.

Test Preparation:

Weigh accurately 1.0 g of test sample and transfer into a separator. Add 20 ml of water and shake to dissolve the sample, add 5 ml of 1 N HCl and extract with successive 20, 20 and10 ml portions of methylene chloride. Discard the Methylene chloride extracts, take aqeous layer, make up to 25 ml with water and transfer into 50 ml colour comparison tube. Adjust the above solution with 1 N Acetic acid or 6 N Ammonium hydroxide to a pH between 3.0 and 4.0 using short range pH indicator paper as external indicator. Dilute it with water to 40 ml and mix.

Standard Preparation:

To the test preparation add 2.0 ml of lead acetate solution and adjust the above solution with 1N Acetic acid or 6N Ammonium hydroxide to a pH between 2.0 and 4.0 using short range pH indicator paper as external indicator. Dilute it with water to 40 ml and mix.

Test procedure:

Add 2.0 ml of 3.5 pH buffer solution and then 1.2 ml of thioacetamide glycine base TS to each of the tube containing the standard preparation, the test preparation and standard preparation. Dilute with water to 50 ml, mix and allow it to stand for 2 minutes.

7.1.7. Loss on Drying: *(Lachman L.,et al.,1991)*

Weigh accurately previously dried and cooled crucible and record weigh as W_1.

Transfer about 1.0 ± 0.1 g of sample into crucible, weigh accurately and record the weight of the sample and crucible as W_2.

Weigh of sample taken =W_2-W_1

Dry the sample in an oven at 105º C for 3 hrs. After completion of drying, cool the sample to room temperature in a desicator and record total weight as W_3.

Loss in weight after drying= w2-w3

Calculation:

$$\%Loss\ On\ Drying = \frac{W2-W3}{W2-W1} \times 100$$

7.1.8. Determination of percentage purity of drug: *(IP, 2010)*

Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90%–110% of the labelled amount.

- **Instrument:**

HPLC equipped with UV detector and data handling system.

Apparatus:

Analytical balance, volumetric flasks, Pipettes, 0.45µ membrane filters.

- **Chemicals and reagents:**
  - Triethylamine -GR grade
  - Glacial acetic acid-HPLC grade
  - Purified water -Milli-Q grade
  - Acetonitrile -HPLC grade
  - Naproxen sodium working standard
- **Chromatographic conditions:**
  - Column: A Stainless steel column packed with octadecyl silane bonded to porous silica (5µm)
  - Flowrate: 1.5ml/min
  - Wavelength: 260 nm
  - Column temperature: 30˚C
  - Injection volume: 20µl
  - Run time: 12 min.

- **Preparations:**

1. **Buffer preparation:** Accurately weigh and transfer about 5.0 ml of Triethylamine into 1000 ml of purified water. Adjust the pH of solution to 5.0 with 50 % glacial acetic acid. Filter the solution through 0.45µm Millex-HV PVDF filter and degassed.
2. **Mobile phase –A preparation:** Prepare a filtered and degassed mixture of buffer solution and Acetonitrile in ratio of 60:40 v/v respectively.

3. **Mobile phase –B preparation**: Prepare a filtered and degassed mixture of buffer solution and Acetonitrile in ratio of 10:90 v/v.
4. **Diluent preparation:** Mix Milli Q water and Acetonitrile in ratio of 90:10 v/v respectively.

5. Naproxen sodium Reference preparation:

A 0.1% W/V solution of Naproxen sodium RS in the mobile phase dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

6. Sample preparation:

Dissolve 50 mg of the substance under examination in 50.0 ml of the mobile phase dilute 5.0 ml of the solution to 50.0 ml of the mobile phase

- **Procedure:**

Seperately inject equal volumes (about 20µl) of the water as blank, standard preparation and sample preparation into chromatograph and record the chromatograms and measure the peak area response for analyte peak. Calculate the percentage content of Naproxen sodium taken by formula.

Percentage content of Naproxen sodium

TA / SA * SW / 250 * 2/20 * 250/TW * 100/1 * P/100 * 100

Where,

TA = Peak area response due to Naproxen sodium from sample preparation

SA= Peak area response due to Naproxen sodium from standard preparation

SW=Weight of Naproxen sodium working standard taken in mg.

TW=Weight of sample taken in mg.

P =Purity of Naproxen sodium working standard taken on, as is basis

7.1.9. Related Substances by HPLC: *(USP, 2004)*

Impurities

Impurity-A: 2-(3-hydroxy-2.2-dimethylpropoxy)-1-(6-hydroxy-2-napthyl)propan-1-one

Impurity-B: 1-(6-methoxynapthalen-2-yl) ethanone

Impurity-C: (1RS)-1-(6-methoxynapthalen-2-yl) ethanol

Impurity-D: 2-bromo-6-methoxynapthelene.

Chromatographic System:

Column : C_{18}

Wavelength : 230 nm

Flow rate : 1.5 ml/min

Column temperature : 50°C

Injection volume : 20µl

Run time : 1.5 times the retention time of impurity B.

Mobile Phase Preparation:

Mix 42 volumes of acetonitrile and 58 volumes of a 1.3g/l solution of potassium dihydrogen phosphate previously adjusted to pH 2.0 with phosphoric acid.

Solution Preparation

Test solution

Dissolve 30 mg of sample in the mobile phase and dilute to 50 ml with the mobile phase.

Reference solution (a): Dilute 1.0 ml of the test solution to 50 ml with the mobile phase, shaking then dilute 5 ml of this solution to 100 ml with mobile phase.

Sensitivity solution : Dilute 2ml of reference solution (a) to 10 ml with the mobile phase.

Reference solution (b): Dissolve each 6 mg of all the impurities in acetonitrile and dilute to 10 ml with the same solvent, get the impurities stock solution. To 1mL of the solution add 1 ml of the test solution and dilute to 50 ml with the mobile phase. Dilute 5 ml of this solution to 100 ml with the mobile phase get the reference solution-b.

Test Procedure

A) Inject 1 replicate of blank solution

B) Inject 1 replicate of sensitivity solution, and require S/N of main peak not less than 10.

C) Inject 3 replicates of reference solution (b), the resolution between the peak due to impurity C and Naproxen should not be less than 2.2. The tailing factor of impurity – A and impurity B should be between 0.8~ 1.5.

D) Inject 3 replicates of reference solution (a), record the main peak area calculate the mean peak areas and require the RSD not more than 5.0%. The tailing factor of main peak should be between 0.8~ 1.5.

E) Inject 1 replicate of test solution record each impurity peak areas, calculate the specified impurity-A and impurity-B by external standard method.

Specified Impurity:

$$\boldsymbol{Impurity - A\ or\ B}\% = \frac{\boldsymbol{AS}}{\boldsymbol{AR}} \times \frac{\boldsymbol{MR}}{\boldsymbol{MS}} \times \frac{\mathbf{1}}{\mathbf{200}}$$

Where

A_S A_R = the peak areas of impurity-A or B obtained with test solution and reference solution (b) separately.

M_S, M_R = the weight of impurity-A or B reference standard and sample separately.

$$\boldsymbol{Any\ other\ impurity}(\%) = \frac{\boldsymbol{AS}}{\boldsymbol{AR}} \times \frac{\boldsymbol{MR}}{\boldsymbol{MS}} \times \mathbf{0.1}\%$$

Where

A_S = peak area of any other impurity (maximum) expect impurity-A or B obtained with test solution.

A_R = mean area of main peak obtained with reference solution (a)

M_S = sample weight in mg

M_R = sample weight corresponding to reference solution (a) in mg

Total impurities:

$Impurity - A\% + impurity - B\% + Any\ other\ impurity +$

$total\ of\ other\ impurities\%.$

7.2. Formulation of Naproxen sodium tablets.

7.2.1. Dry mixing:

Naproxen sodium,

Microcrystalline cellulose, Corn starch and Sodium starch glycolate were loaded into the rapid mixer granulator and mixed for 10 minutes at slow mixer speed.

7.2.2. Preparation of binder:

Povidone K-30 is dissolved in purified water by stirring.

7.2.3. Wet granulation:

The binder solution was added to the above powder with the mixer at fast speed and the chopper at fast speed.

Wet mixing should be continued until the required end point was achieved.

The material was then unloaded into Fluidised Bed Dryer (FBD) bowl.

7.2.4. Drying:

The wet granules were dried until required LOD was achieved.

7.2.4. Sifting and milling:

The dried granules were then sifted through double deck vibro sifter using #16/150 or SD sifter with #16 mesh screen; knives were forward at medium speed and then resifted.

7.2.5. Blending before addition of lubricants:

Granules were then loaded into the blender for the specified time.

7.2.6. Blending after addition of lubricants:

Lubricants were then sifted through #40 mesh screen and then were added into the blender and were blended for the specified time.

A sample was analysed for physical parameters and a sample of granules were compressed into table.

Table 7.2: Process parameters used in formulation of Naproxen sodium.

S.No	Parameters	Results
1	Purified water used	0.930 l
2	Inlet temperature	76°C
3	Bed temperature	58°C
4	Atomizing air pressure	3.9m/sec
5	Fluidizing air volume	65m/sec
6	% LOD w/w at 105°C	0.67%

7.2.7. Coating:

The coating suspension was made with Aquarius BP 17066 in purified water. The suspension was used to coat the tablets in the coating pan.

Table 7.3: Coating parameters.

S.No	Parameters	Quantity
1	Aquarius BP 17066	21.0 mg
2	Purified water	119.0 ml
3	Core tablets	700

Table 7.4: Composition of Naproxen sodium tablets using both the API'S

S.No	Name of the Ingredient	REDDY'S(mg)	CHARIOTEER(mg)
1	Naproxen sodium USP	220	220
2	Microcrystalline cellulose	38.599	41.57
3	Corn starch	26.999	23.999
4	Sodium starch glycolate	2.999	5.999
5	Povidone K30	8.999	5.999
6	Water	qs	qs
7	Stearic acid	2.3999	2.3999
8	Total weight	300	300

*All the quantities are expressed as mg per tablet**.**

7.3 Evaluation of pre compression parameters for both the API'S

7.3.1. Angle of repose*:* *(USP29-NF-24)*

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher & more irregular the surface of particles the greater will be angle of repose. The interrelationship between the angle of repose and flow properties of powder are shown in the Table 3.5. Angle of repose is calculated by the following formula.

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, r=radius of the pile, h=height of the pile,

Table 7.5: Standard values of angle of repose (º).

S.No	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.3.2. Carr's Index:

Carr's Index is measured using the values of the bulk density and tapped density.

The following equation is used to find the Carr's index

$$Carr's Index = \frac{Tapped\ \ density \times Bulk\ \ density}{Tapped\ \ density} 100$$

Compressibility Index and Hausner ratio :- *(Lachman L.et al.1991)*

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$\textbf{Compressibility index} = \frac{\textbf{Tapped density} - \textbf{bulk density}}{\textbf{Tapped density}} \times \mathbf{100}$$

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped bulk density}}{\textbf{loose bulk density}}$$

Relation of flow property with Hausner's ratio and Compressibility index is shown in table

Table 7.6: Standard values of Carr's index.

Compressibility Index (%)	Flo Characteristics	Hausner's Ratio
5-10	Excellent	1.00–1.11
12–16	Good	1.12–1.18
18–21	Fair-passable	1.19–1.25
23–35	Poor	1.26–1.34
33–38	Very poor	1.35–1.45

*May be improved by glidant.

7.4 Evaluation of post compression parameters of both the API'S Formulations

7.4.1 Organoleptic properties*:* ***(****Lachman L.,et al.1991, Bankar G.S. and Rhod C.T. 1996)*

Many pharmaceutical tablets use colour as a vital of rapid identification and consumer acceptance. The colour of a product must be uniform within a single tablet is generally referred to as "mottling", from tablet to tablet, and form lot to lot non uniformity of colouring not only lacks aesthetic appeal but also could be associated by the consumer with non-uniformity of content and general poor quality of the product.

7.4.2Weight variation test *(IP, 2007, Lachman L., et al.1991)*

Weight variation test was done by weighing 20 tablets individually, by using analytical balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

7.4.3. Tablet thickness *(Lachman L., et al.1991)*

Thickness was determined for 5 preweighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. the tablet thickness should be controlled within a $\pm$5 % variation of a standard.

7.4.4. Tablet hardness *(Lachman L., et al.1991, Bankar G.S. and Rhodes C.T. 1996)*

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

7.4.5. Friability: *(Lachman L, et al.,1991; Bankar G.S. and Rhodes C.T.,1996)*

Friability is an important factor in tablet formulation to ensure that the tablet can stay intact and withhold its form from any outside force of pressure:

$$\%friability = 100 \times \frac{(W_o - W_f)}{W_o}$$

Where W_o is the original weight of the tablets, and W_f is the final weight of the tablets after the collection is put through the friabilator. Friability below 0.8% is usually considered satisfactory.

***7.46. In- vitro* disintegration test**

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured.

Table 7.7 : Specifications of Disintegration time.

Tablet Type	Time limit and Specifications
1. BP	
❖ Uncoated	<15min
❖ Coated	
• Film	<30min
• Sugar	<60min, repeat in 0.1MHCl
❖ Gastro resistant, enteric	>120min in 0.1MHCl <60min in pH 6.8(Phosphate)
❖ Effervescent	<5min in 200ml, water, 20°C
❖ Soluble	<3min
❖ Dispersible	<3min, 2 tablets in 100ml water dispersed, passed
2.USP	
❖ Uncoated	<15min
❖ Plain coated	<30 min
❖ Enteric coated	Intact for 60min in simulated gastric fluid, disintegrated in simulated intestinal fluid<monograph time
❖ Buccal	<4hour

7.4.7. In-*vitro* dissolution: **(***IP,2010)*

Dissolution means the process by which solid substance enters in the solvent to yield solution. It is controlled by the affinity between the solid substance and the solvent is a process in which a solid substance solubilises in a given solvent that is transfer from the solid surface to the liquid phase.

Medium : pH 7.4 phosphate buffer

Volume : 900 ml

Apparatus : USP-II, paddle

Speed : 50 rpm

Temperature : 37± 0.5°C

Sampling points : 60 mins.

7.5. STABILITY STUDY ***(****Manavalan R. and* Ramasamy S. 2004*)*

- **Introduction**

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

- **Objective of the study**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling

recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25^{0} C $\pm 2^{0}$ C at 60% RH ±5% for 12 Months
- **Accelerated Testing:** 40^{0} C $\pm 2^{0}$ C at 75% RH ±5% for 6 Months

In present study both the formulations of two different API'S were exposed up to 3 months stability studies at accelerated condition (40^{0} C $\pm 2^{0}$ C at 75% RH ±5%RH) to find out the effect of aging on hardness, disintegration, drug content and *In-Vitro* drug release.

- **Procedure**

Stability studies were carried out at accelerated condition (40^{0} C $\pm 2^{0}$ C at 75% RH ±5%RH) for both the formulations. The tablets were stored at 40^{0} C $\pm 2^{0}$ C at 75% RH ±5%RH for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, floating, disintegration, drug content and *In-Vitro* drug release.

7.5.1 Stability Studies: *(Bentley's.2003)*

Both the formulations were subjected to stability studies as per ICH guidelines at 30°C/ 65 % RH and 40°C / 75% RH for 3 month. Samples were taken and analyzed at time interval. Selected formulations were subjected to stability studies as per ICH guidelines sample were taken and analyzed at time interval of 15 days for 3 months.

Table 7.8: Stability Studies.

S.No	STUDY	STORAGE CONDITION	TIME PERIOD
1.	Long term	25ºC± 2ºC/60 %RH± 5ºC (or) 30C±2ºC/ 65%RH±5%RH	12 months
2.	Intermediate	30ºC±2ºC/65%RH±5%RH	6months
3.	Accelerated	40ºC ±2ºC / 75% RH ±5 % RH	6months

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

8.1. Results and Discussion for Approved vendor

8.1.1. Certificate of Analysis for the API of approved vendor:

Table 8.1: Certificate of Analysis for approved API.

S.No	Test	Result
1	Appearance	White crystalline powder.
2	Solubility	Freely soluble in water, and in methanol, sparingly in alcohol, insoluble in chloroform and toluene
.3	Specific optical rotation	-16.76
4	Assay (w/w)	99.8 %w/w
5	Heavy metals(%w/w)	Less than 0.002%
6	Loss on drying	Not more than 1%
7	Related substances impurities	Not more than 0.1 %
8	Particle size a)Small or equal to 300µm b)Small or equal to212 µm	 Not less than 90% Not less than 50%
9	Bulk density(g/ml) a)untapped b)tapped	 0.632 0.793

8.2. Performing the tests according to specification standards

8.2.1. Solubility study

Table 8.2: Solubility of Naproxen sodium for approved API formulation

Name of solvent	Solubility
Distilled water	Soluble
Methanol	Soluble
Alcohol	Sparingly soluble
Acetone	Very slightly soluble
Chloroform	Insoluble
Toluene	Insoluble

8.2.2. Melting point:

Melting point values of Naproxen sodium sample was found to be in range of 152^0C to 157^0C. The reported melting point for Naproxen sodium was 154^0C.

8.2.3Identification Tests:

8.2.3.1 Identification by FT-IR spectroscopy

The FT-IR spectrum of Naproxen sodium for the API of REDDY'S was shown in figure 8.1 and the interpretations of IR frequencies were showed in table 8.3.

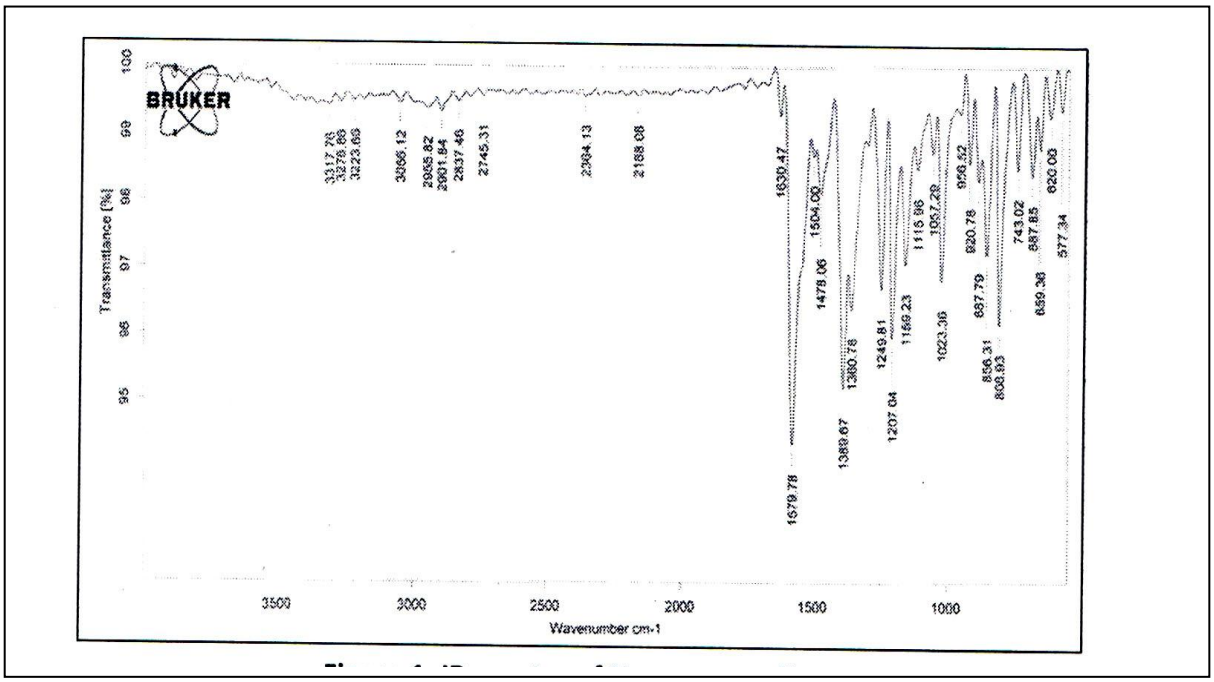


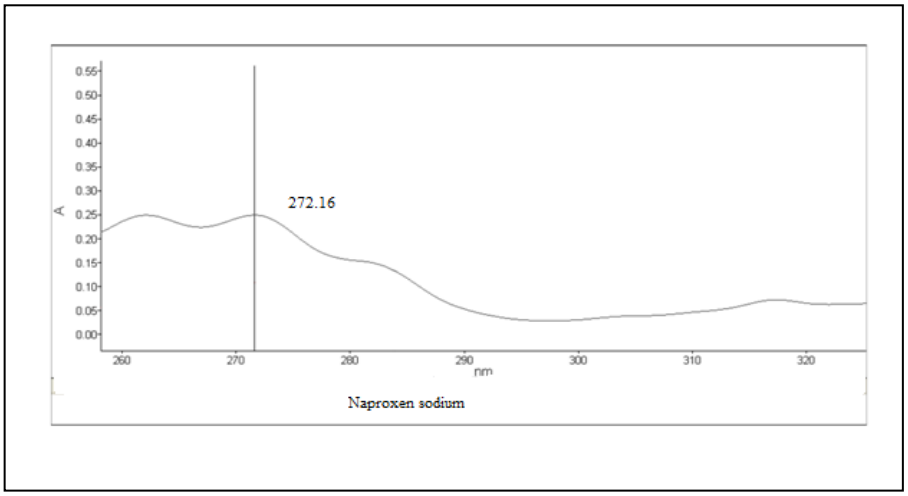
Figure 8.1: FT-IR spectrum of Naproxen sodium for approved API formulation

Table 8.3: Characteristic IR Peaks of Naproxen sodium for approved API formulation

Wave Number in cm^{-1}	Characteristics
3056.12 – 2955.82	Aromatic C-H stretching
2745.31 – 2364.13	Overtone
1630.47	C=O stretching
1579.78	Presence of C-O stretching
1478.06 -1360.78	CH_3, CH_2 bending
1207.04	C-O bending
956.52 – 620.00	CH_2 bending

8.2.3.2. UV Method:

The absorption maximum for Naproxen sodium was found to be at 272.16 nm.



. **Figure 8.2: λ max of Naproxen sodium for approved API formulation**

8.2.4. Specific optical rotation:

The reported specific optical rotation for Naproxen sodium was found to be at about -16.76.Hence the value complies with that of the standard USP values.

Table 8.4: Specific optical rotation for approved API formulation

S. No.	Specific optical rotation	Average Specific optical rotation
1	-16.76	-16.76±0.55
2	-15.8	
3	-16.76	

8.2.5. Heavy metals:

The reported amount of heavy metals for Naproxen sodium was found to be 0.001±0.00032 % w/w. Hence the value complies with that of the standard USP.

Table 8.5: Test for heavy metals for approved API formulation

S. No	Heavy metals (%w/w)	Avg. percentage of Heavy metals.
1	0.001	0.001±0.00032
2	0.0016	
3	0.0015	

8.2.6. Loss on Drying :

The percentage loss on drying after 3 hours was found to be as follows:

Table 8.6: Percentage loss on drying for approved API formulation

S. No.	Percentage LOD	Average percentage LOD
1	0.5	0.3±0.115
2	0.3	
3	0.3	

Sample passes test for loss on drying as per the limit specified in IP and USP (N.M.T 1%)

8.2.7. Related substances Impurities:

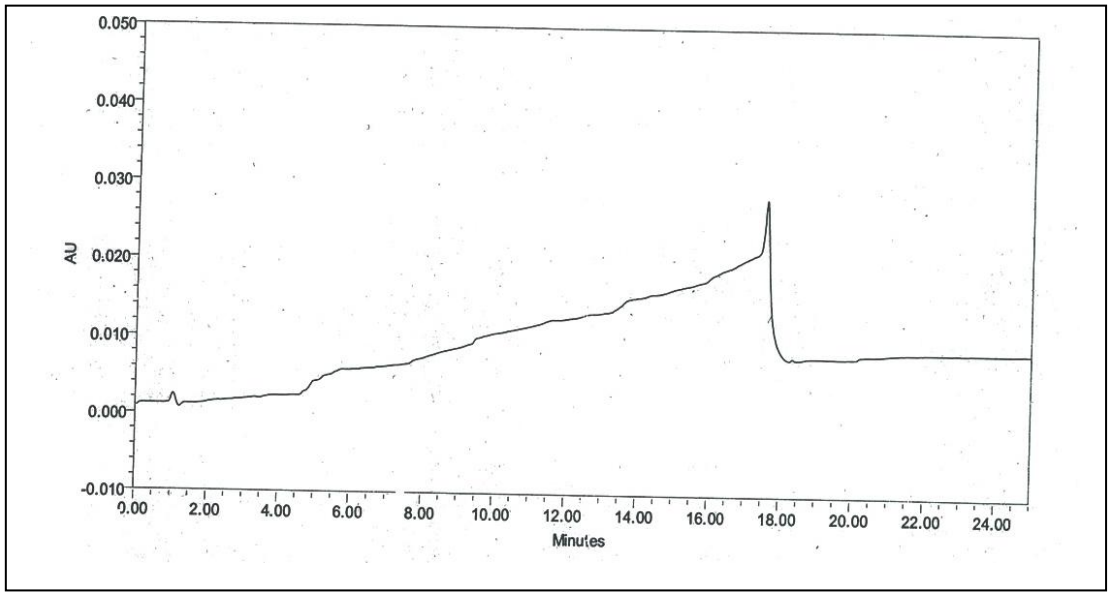


Figure 8.3: Related substances impurities Blank.

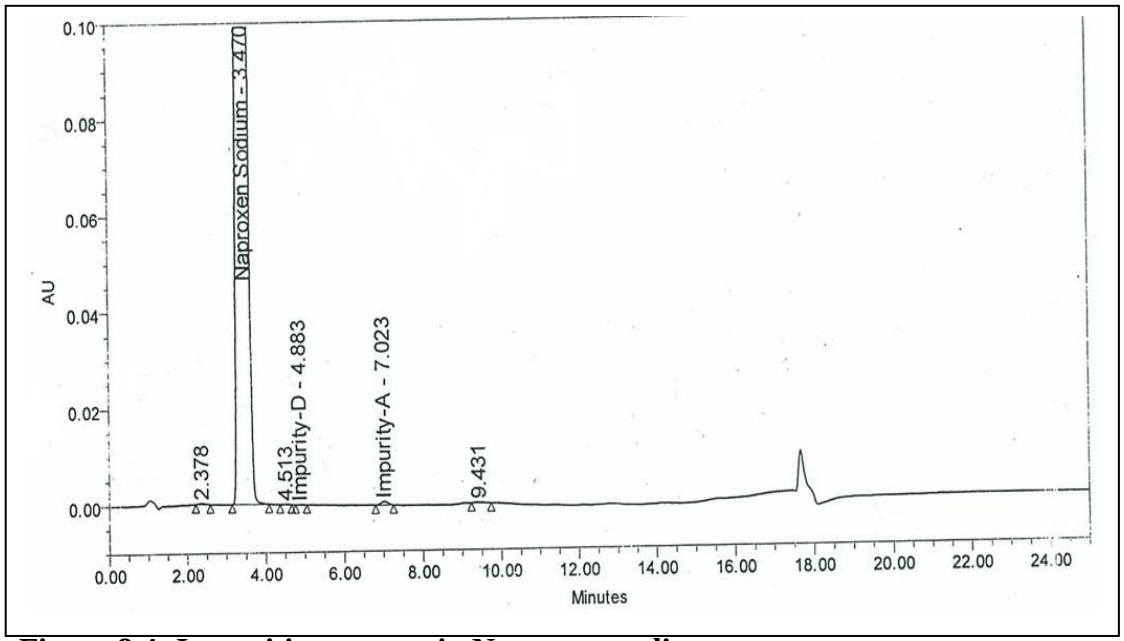


Figure 8.4: Impurities present in Naproxen sodium.

Table 8.7: Impurities present in Naproxen sodium for approved API formulation

S. No	Peak Name	RT	Area	% Area
1	**Naproxen sodium**	**2.378**	**2744**	**0.01**
		3.470	**18300022**	**99.92**
2		**4.513**	**654**	**0.00**
3	**Impurity-D**	**4.883**	**328**	**0.00**
4	**Impurity-A**	**7.023**	**8528**	**0.05**
5	**Impurity-B**	**9.050**	**-**	**-**
6		**9.431**	**1834**	**0.01**
7	**Impurity-C**	**11.760**	**-**	**-**

The related substances impurities for Naproxen sodium was found to be within the limits as per USP standards (NMT 0.1)

8.2.8. Determination of percentage purity and linearity of the drug:

8.2.8.1. Preparation of standard graph of Naproxen sodium:

The drug obeys Beer- Lambert's law in the range of 10–50µg /ml.

Table 8.8: Standard graph of Naproxen sodium in pH 7.4 phosphate buffer for approved API formulation

S. No.	Concentration (µg/ml)	Area of the peak
1	10	1281809
2	20	2563618
3	30	3845467
4	40	5127276
5	50	6409124

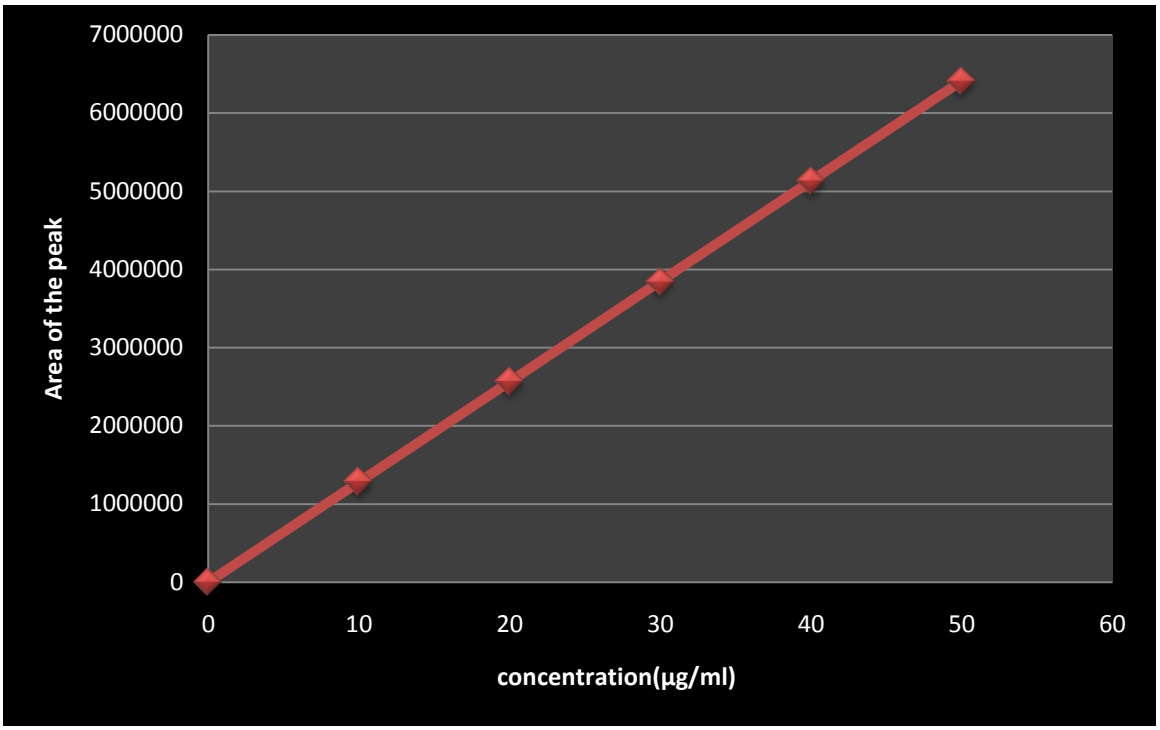


Figure 8.5: Standard graph of Naproxen sodium for approved API formulation

Table 8.9: Standard graph parameters for Naproxen sodium in pH 7.4 phosphate buffer for approved API formulation

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope	128180.9
3	Intercept	2219800

8.2.8.2. Percentage purity of drug

The percentage purity of drug was calculated by using HPLC Chromatographic method. The reported percentage purity was found to be 99.8±0.12%w/w.

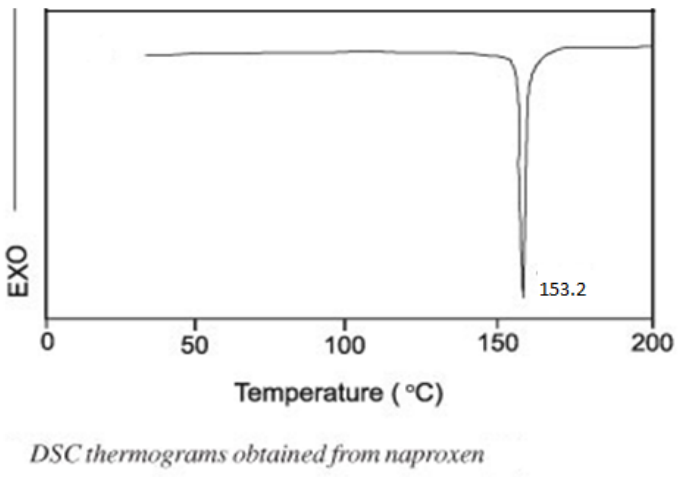
Table 8.10: Percentage purity of Naproxen sodium for approved API formulation

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.8	99.8±0.12
2	99.7	
3	99.8	

The reported % purity for Naproxen sodium in IP is 97-102% w/w.

8.3. Differential scanning calorimetry:

DSC was performed for pure drug Naproxen sodium for approved vendor.



DSC thermograms obtained from naproxen

Figure 8.6:DSC thermogram of Naproxen for approved API formulation

8.3 Evaluation of Precompression parameters for approved API

The blended powders of the formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner's ratio. The results of these evaluations were as follows: -

Table.8.11: Granulation tests for approved API formulation

S.NO	TEST	RESULT
1	Sieve analysis	
	ASTM mesh no	
	20	26.5
	40	61.5
	60	75.0
	80	83.0
	100	86.5
	200	95.5
2	Moisture content	1.95%
3	Angle of repose*	27.4°
4	Bulk density: *	
	Untapped	0.632±0.00 g/ml
	Tapped	0.793±0.00 g/ml
5	Compressibility index*	14.86 ±0.03%
6	Hausner's ratio*	1.16±0.00

All the values were expressed as mean ± SD, n=3

8.3.1. Angle of repose:

The reported angle of repose was found to be 27.4°, hence the blend was found to have good flowability.

8.3.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities were used for the measurement of Compressibility index. The loose bulk density was found to be 0.632±0.00g/ml and tapped bulk density was found to be 0.793±0.00g/ml.

8.3.3 Compressibility index (Carr's index):

The compressibility index was found to be 14.86±0.00%. The blend was found to have good flowing property as the result were found to be below 16%.

8.3.4. Hausner's ratio:

The Hausner's ratio was found to be 1.16±0.00. The result indicates the free flowing properties of the powders.

8.4 Evaluation of Post compression parameters for approved API

8.4.1. Appearance:

Surface nature of tablets was observed visually and it was concluded that they did not show any defects such as capping, chipping and lamination.

8.4.2. Organoleptic properties

Odour: Odourless

Colour: White or almost white

Nature: Crystalline powder.

8.4.3. Physico-chemical characteristics:

The physical characteristics of Naproxen sodium tablets such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 8.12.

Table 8.12: Post compression parameters for approved API formulation

S. No	Parameters	Results
1	Disintegration time *	9 minutes 45 sec
2	Hardness (kg/cm^2) **	9.6±0.79
3	Diameter (mm)*	11.17±0.01
4	Thickness (mm)*	4.76±0.07
5	Weight variation (%) ***	301±1.50
6	Friablity(%)**	0.31±0.015

All values were expressed as mean ± SD., n=3, n=6**, n=20***

8.4.4. Dimension (Thickness and Diameter):

The diameter of the tablets was found to be 11.17±0.01 mm, and thickness was found to be 4.76± 0.07 mm.

8.4.5. Tablet hardness:

The hardness of tablets was found to be 9.6± 0.79 kg/cm^2. This indicates good mechanical strength of tablet.

8.4.6. Percentage friability:

Percentage friability of all the formulations was found to be 0.31±0.015%. This indicates good handling property of the prepared matrix tablet

8.4.7. Weight variation:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 300 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The weight variation was found to be 301±1.50%. The percentage deviation from average tablet weight for the tablets was found to be within the specified limits and hence the formulation complies with the test for weight variation according to the pharmacopoeial specifications IP.

8.4.8 Drug content:

The drug content for the formulation was found to be 99.8±0.12%w/w, which was within the specified limit as per IP .The values are shown in Table 8.10

8.4.9. *In vitro* dissolution studies:

Table 8.13: Dissolution profile of the formulation.

S. No	Time in minutes*	Percentage drug released
1	5	28
2	10	49
3	15	75
4	30	88
5	45	92
6	60	97.2

*****All values were expressed as mean ±SD, n=3*.

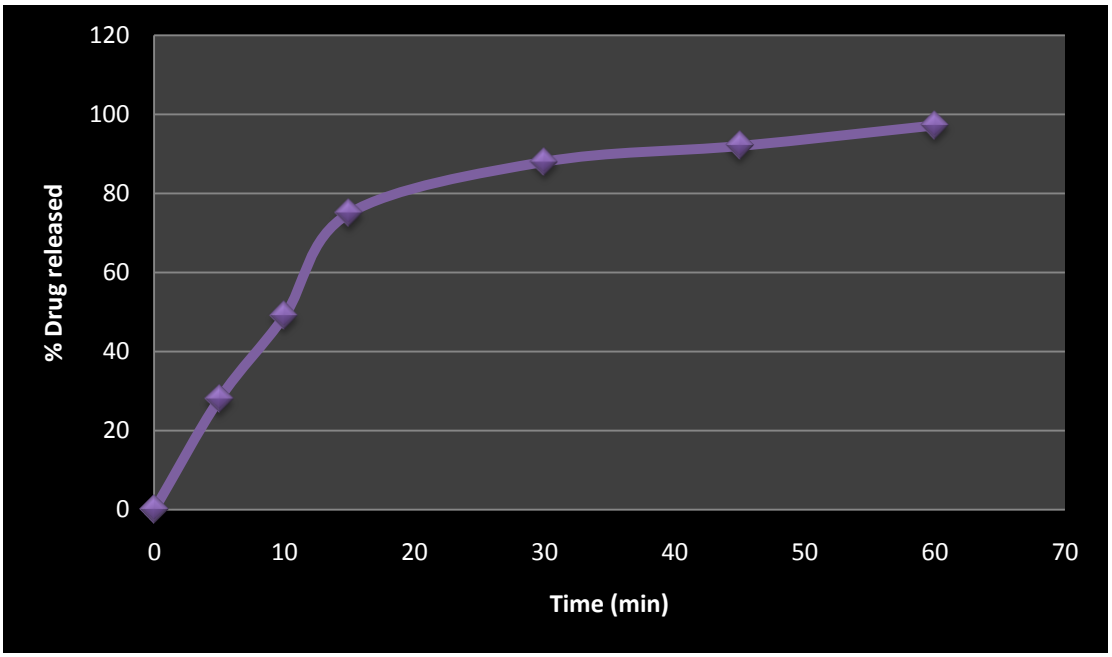


Figure 8.7: *In-vitro* drug released profile of formulation

Table 8.14: Time of in-vitro drug released of t_{25}, t_{50} t_{90} values for approved API formulation

S.No	Time in min	t_{25}	t_{50}	t_{90}
1	5	4.0322	8.0645	14.51
2	10	4.237	8.4745	15.254
3	15	4.687	9.375	16.87
4	30	7.731	15.463	27.83
5	45	11.25	22.5	40.5
6	60	14.70	29.411	52.94

8.5 Stability studies for approved API

After exposure to accelerated stability conditions the formulation was analyzed for various parameters. The results are shown in Table8.15 and Figures 8.8, 8.9, 8.10 and 8.11

Table 8.15: Stability studies for approved API formulation.

S.No	Parameters	Initial	1st month	2nd month	3rd month
1	Description	White coloured round shaped coated tablets	White coloured round shaped coated tablets	White coloured round shaped coated tablets	White coloured round shaped coated tablets
2	Disintegration* (min)	9min45 sec	9min 42 sec	9min 35 sec	9min 30sec
3	Hardness* (kg/cm^2)	9.6±0.079	9.3±0.05	9.1±0.05	8.6±0.05
4	Assay* (%w/w)	99.80±0.02	99.75±0.08	99.68±0.05	99.65±0.02
5	Dissolution* (%)	97.2±0.02	97.4±0.02	96.9±0.02	96.5±0.03

*All the values were expressed as mean± S.D, n=3.

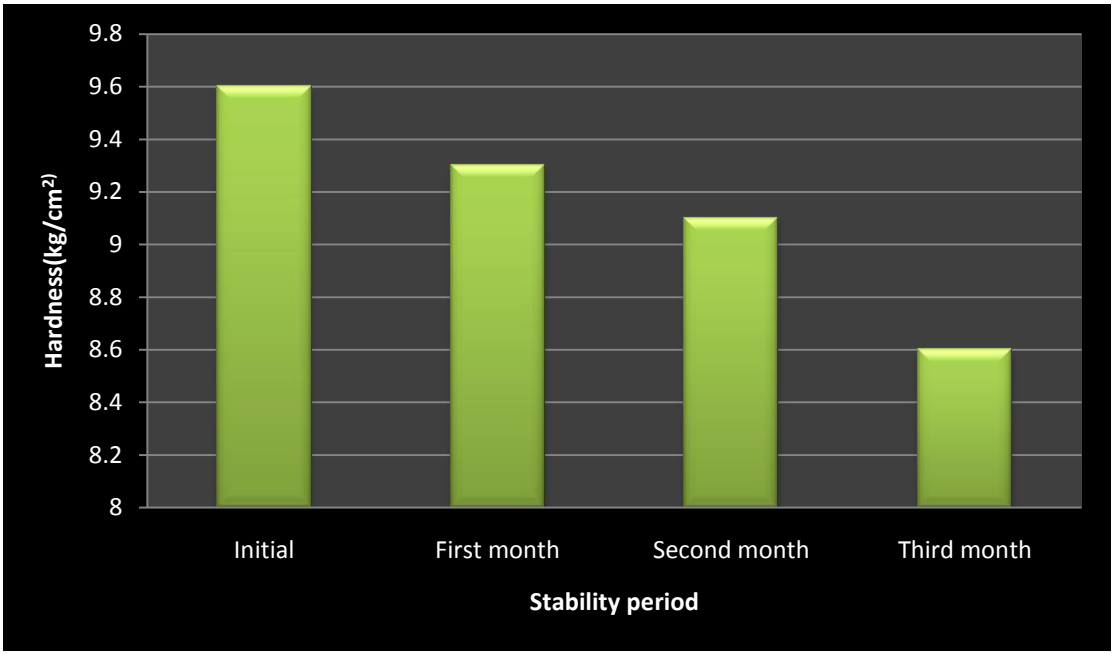


Figure 8.8: Comparison for hardness of before and after stability studies.

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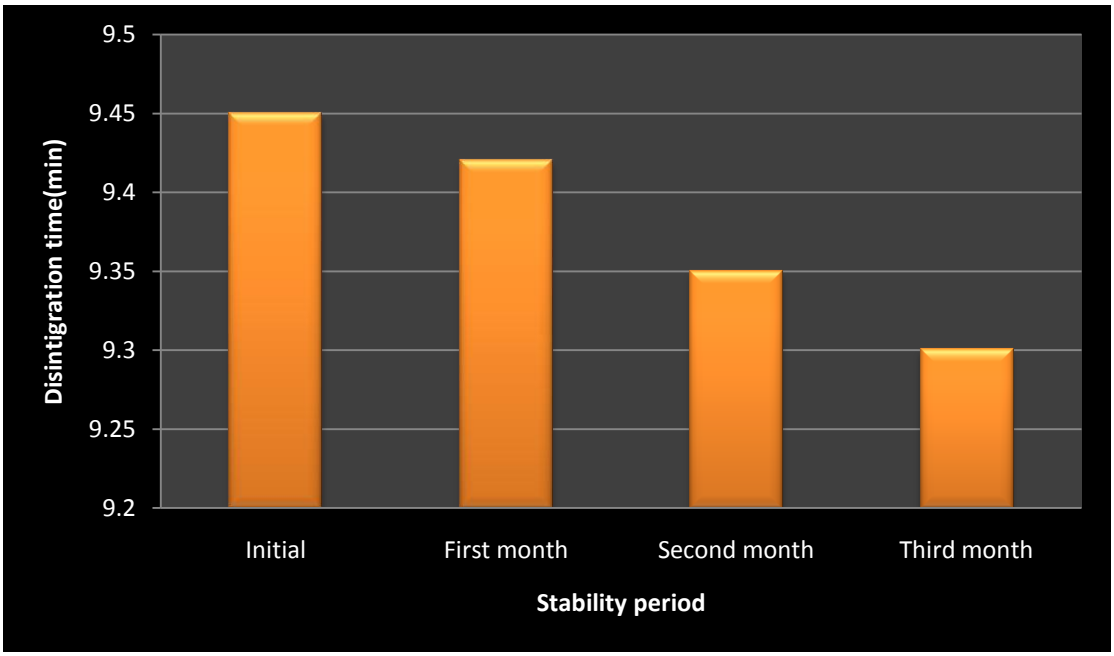


Figure 8.9: Comparison for disintegration time of before and after stability studies.

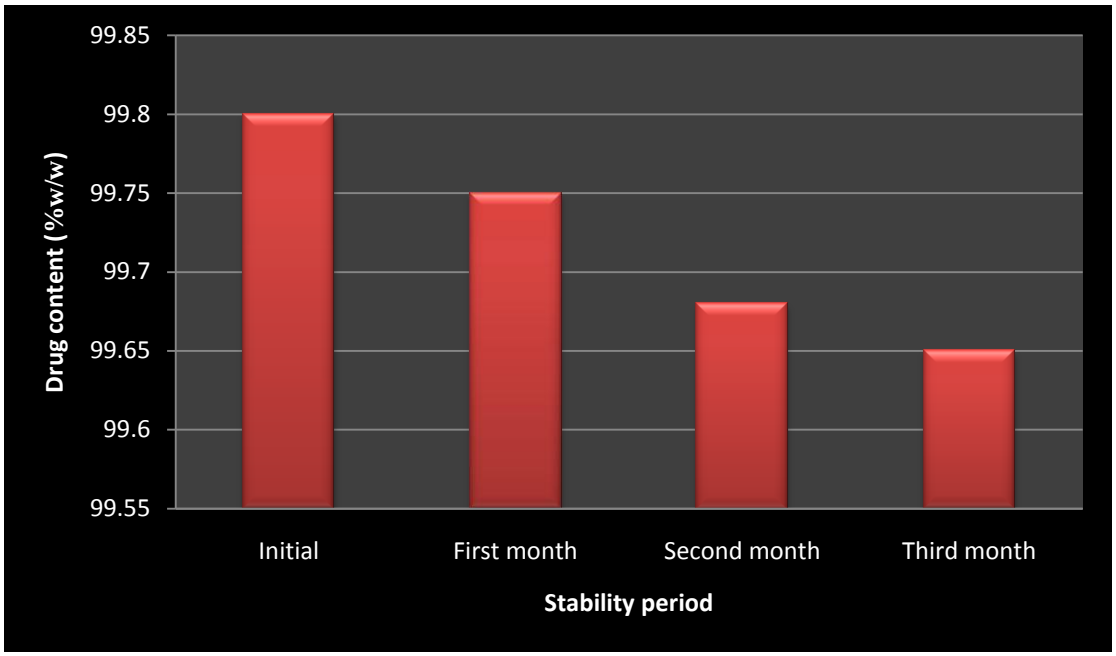


Figure 8.10: Comparison for assay of before and after stability studies.

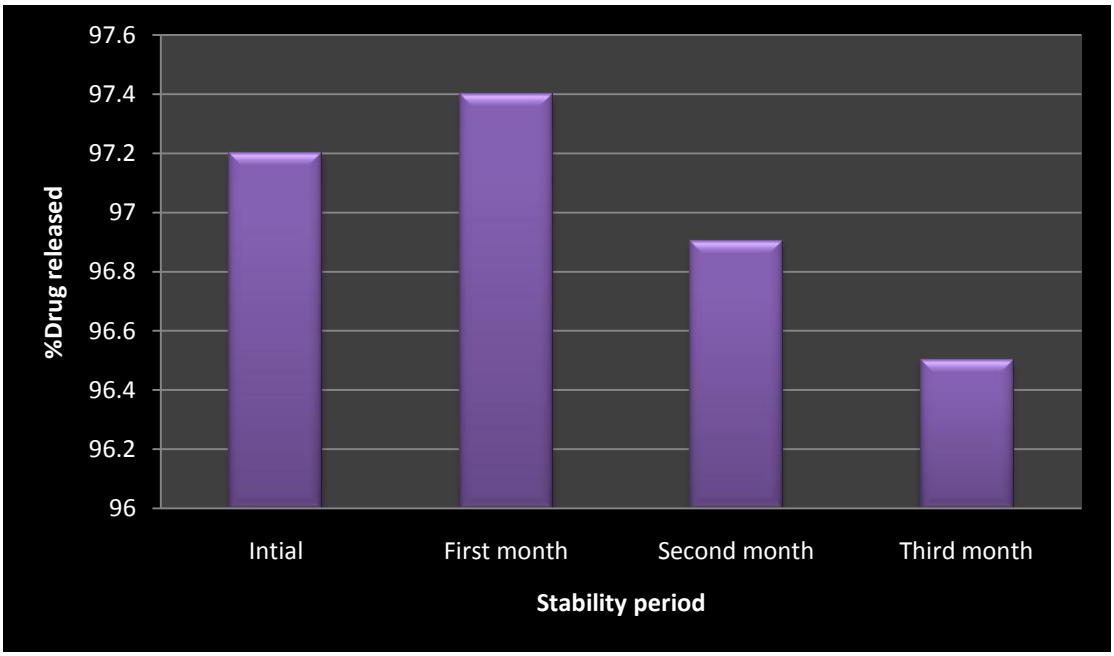


Figure 8.11: Comparison for dissolution profile of before and after stability studies.

From the above studies there was no significance difference between the evaluated data from initial and after stability studies and all the values were found in worth accepting limits. The formulation showed adequate physical stability at $40^{o}C \pm 2^{o}C$ at 75±5% relative humidity.

8.6. Results and Discussion for Alternate vendor CHARIOTEER'S

8.6.1. Certificate of Analysis for the API of alternate vendor:

Table 8.16: Certificate Of Analysis for Alternate API.

S. No	Test	Result
1	Appearance	White crystalline powder.
2	Solubility	Freely soluble in water, and in methanol, sparingly in alcohol, insoluble in chloroform and toluene
3	Specific optical rotation	-15.6
4	Assay (w/w)	99.7 %w/w
5	Heavy metals	Less than 0.002%
5	Loss on drying	Not more than 1%
6	Related substances impurities	Not more than 0.1 %
7	Particle size a)Small or equal to 300µm b)Small or equal to212 µm	 Not less than 90% Not less than 50 %
8	Bulk density(g/ml) a)untapped b)tapped	 0.631 0.80

8.7. Performing the tests according to Specification Standards

8.7.1. Solubility study:

Table 8.17: Solubility of Naproxen sodium for alternate API formulation

S. No	Name of solvent	Solubility
1	Distilled water	Soluble
2	Methanol	Soluble
3	Alcohol	Sparingly soluble
4	Acetone	Very slightly soluble
5	Chloroform	Insoluble
6	Toluene	Insoluble

8.7.2. Melting point:

Melting point values of Naproxen sodium sample was found to be in range of 152^0C-157^0C. The reported melting point for Naproxen sodium was found to be 154^0C.

8.7.3. Identification Tests:

8.7.3.1. Identification by FT-IR spectroscopy

The FT-IR spectrum of Naproxen sodium for the API of CHARIOTEER'S was shown in figure 8.12 and the interpretations of IR frequencies were showed in table 8.18.

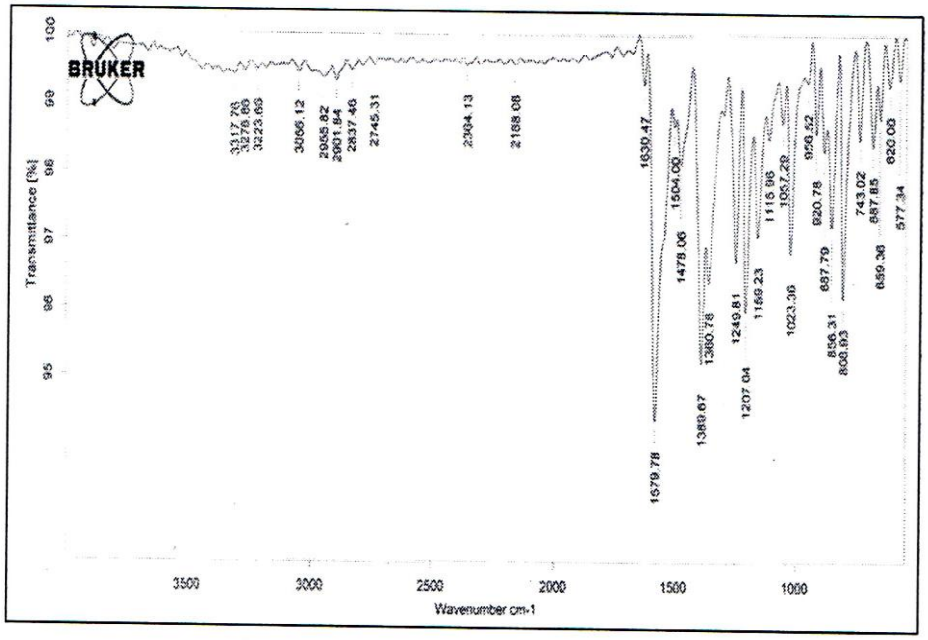


Figure 8.12: FT-IR spectrum of Naproxen sodium for alternate API formulation

Table 8.18: Characteristic IR Peaks of Naproxen sodium for alternate API formulation

Wave Number in cm $^{-1}$	**Characteristics**
3056.12 – 2955.82	Aromatic C-H stretching
2745.31 – 2364.13	Overtone
1630.47	C=O stretching
1579.78	Presence of C-O stretching
1478.06 -1360.78	CH_3, CH_2 bending
1207.04	C-O bending
956.52 – 620.00	CH_2 bending

8.7.3.2. UV Method:

The absorption maximum for Naproxen sodium was found to be at 272.2 nm.

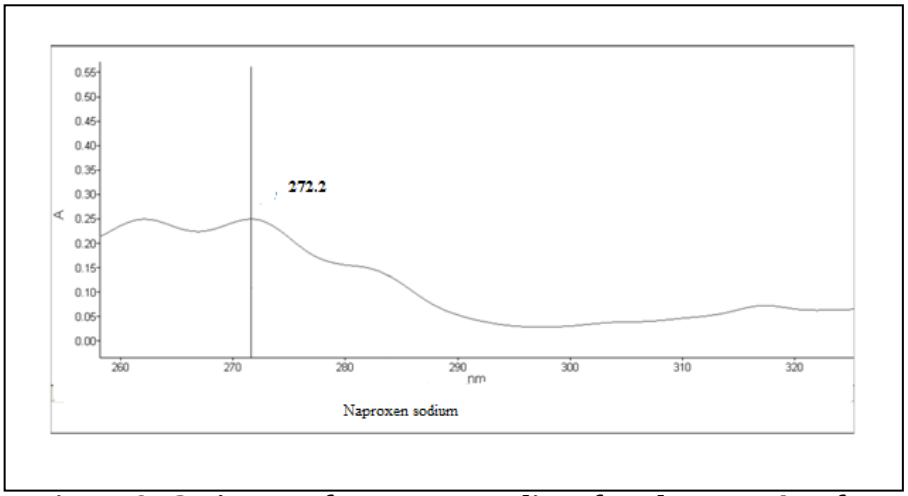


Figure 8.13.: λ max of Naproxen sodium for alternate API formulation

8.7.4. Specific optical rotation:

The reported specific optical rotation was found to be at about-15.6±0.54. Hence the value complies with that of the standard USP values.

Table 8.19: Specific optical rotation for alternate API formulation

S. No.	Specific optical rotation	Average Specific optical rotation
1	-15.4	-15.6±0.54
2	-15.8	
3	-16.7	

8.7.5. Heavy metals:

The reported amount of Heavy metals was found to be 0.001%w/w. Hence the value complies with that of the standard USP.

Table 8.20: Tests for heavy metals for alternate API formulation

S.No.	Heavy metals (%w/w)	Avg. percentage of Heavy metals.
1	0.007	0.001±0.00136
2	0.0019	
3	0.0013	

8.7.7. Loss on Drying :

The percentage loss on drying after 3 hours was found to be as follows:

Table 8.21: Percentage loss on drying for alternate API formulation

S. No.	Percentage LOD	Average percentage LOD
1	0.5	0.5±0.533
2	0.9	
3	0.5	

Sample passes test for loss on drying as per the limit specified in IP and USP (N.M.T. 1%)

8.7.8 Related substances Impurities:

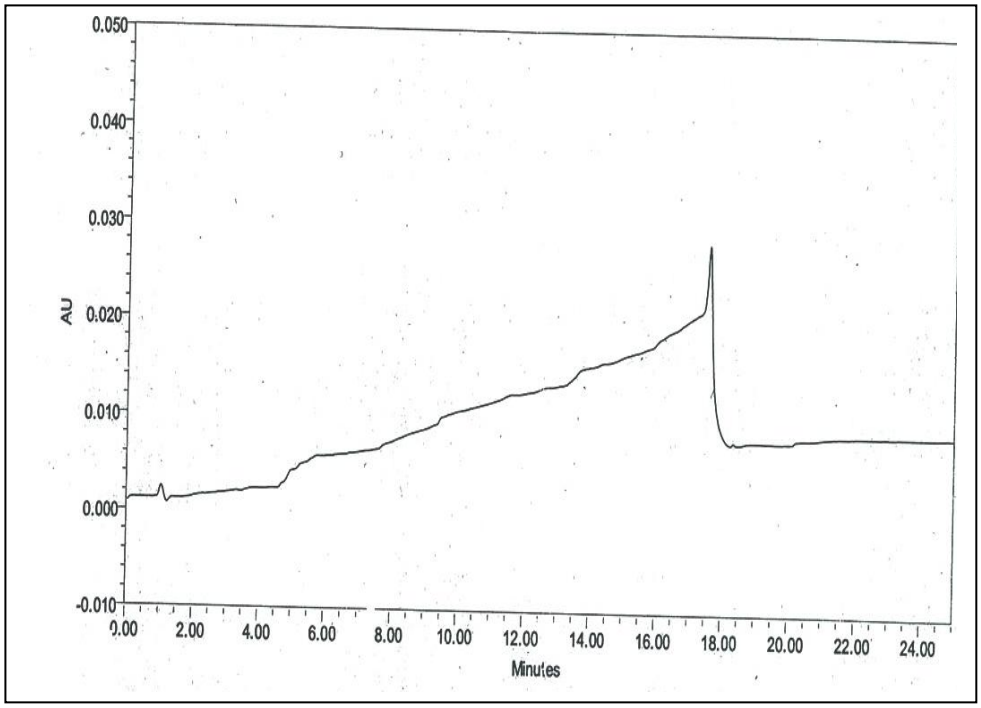


Figure 8.14: Related substances impurities blank for alternate API formulation

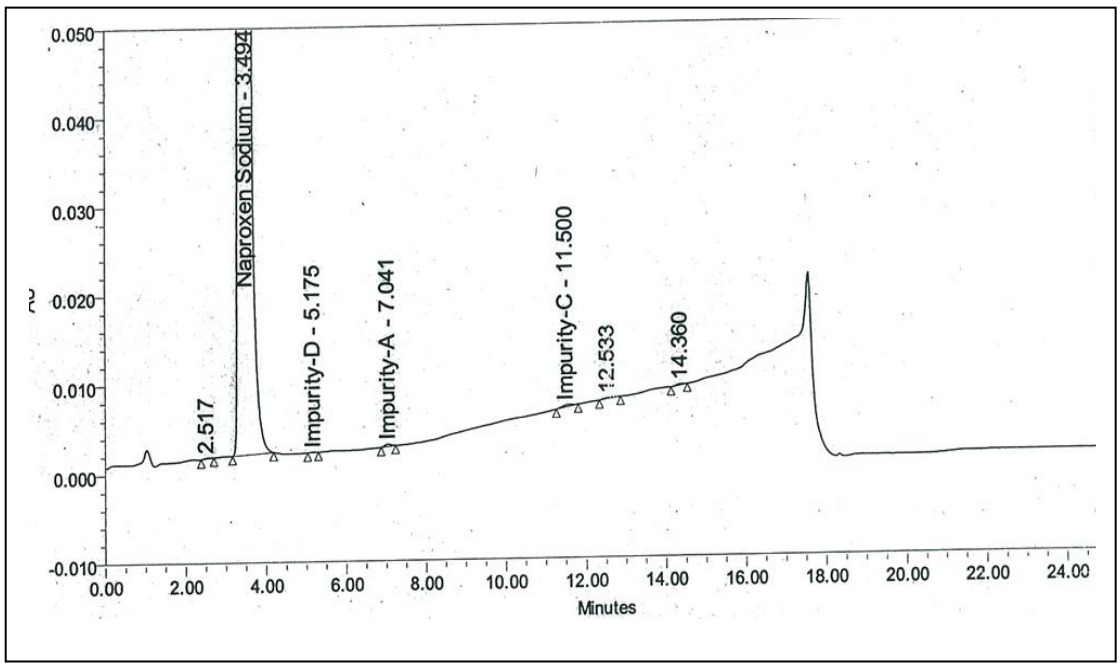


Figure 8.15: Impurities present in Naproxen sodium for alternate API formulation

Table 8.22: Impurities present in Naproxen sodium for alternate API formulation

S.No	Peak Name	RT	Area	% Area
1	Naproxen	2.517	953	0.01
		3.494	17487414	99.93
2	Impurity-D	5.175	314	0.00
3	Impurity-A	7.041	2948	0.02
4	Impurity-B	9.009		
5	Impurity-C	11.5000	3953	0.02
6		12.533	2235	0.01
7		14.360	1543	0.01

The related substances impurities were found to be not more than 0.01%.Hence it complies with USP standards.

8.7.9. Determination of percentage purity and linearity of the drug:

8.7.9.1. Preparation of standard graph of Naproxen sodium:

Table 8.23: Standard graph of Naproxen sodium in pH 7.4 phosphate buffer for alternate API formulation

S.No.	Concentration (µg/ml)	Area of the peak
1	10	1281807
2	20	2563618
3	30	3845467
4	40	5127274
5	50	6409136

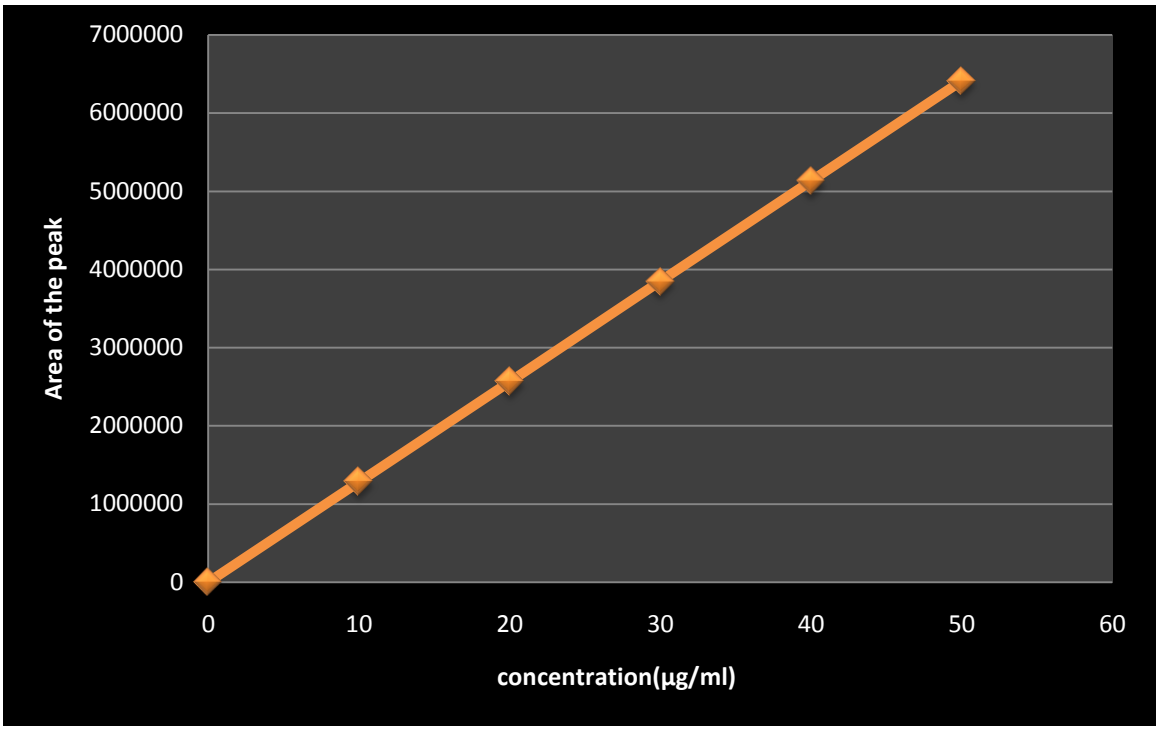


Figure 8.16: Standard graph of Naproxen sodium for alternate API formulation

Table 8.24: Standard graph parameters of Naproxen sodium in pH 7.4 phosphate buffer for alternate API formulation

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope	128180.9
3	Intercept	2219800

8.7.9.2. Percentage purity of drug

The percentage purity of drug was calculated by using HPLC Chromatographic method. The reported percentage purity was found to be 99.7±0.12%w/w.

Table 8.25: Percentage purity of Naproxen sodium for alternate API formulation

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.6	99.7±0.12
2	99.7	
3	99.7	

The reported % purity for Naproxen sodium in IP is 97-102%w/w.

8.7.9.3. Differential scanning calorimeter:

DSC was performed for the pure drug of Naproxen sodium for alternate vendor

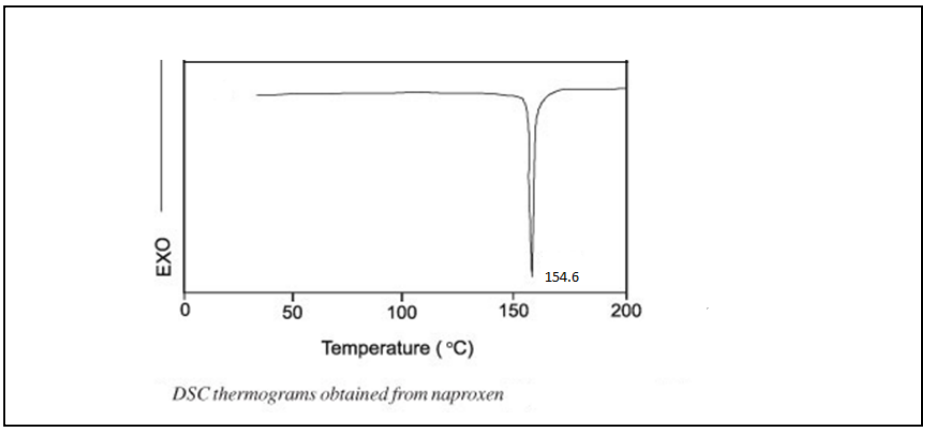


Figure 8.17: DSC thermo gram of Naproxen sodium for alternate API formulation

8.8. Evaluation of Pre compression parameters for alternate API

The blended powders of the formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hauser's ratio. The results of these evaluations were as follows: -

Table 8.26: Granulation tests for alternate API formulation

S.No	Parameters	Result
1	Sieve analysis	
	ASTM mesh no	
	20	25.5
	40	60.1
	60	78.0
	80	82.3
	100	84.6
	200	92.8
2	Moisture content*	1.86%
3	Angle of repose*	28.7°
4	Bulk density:*	
	Untapped	0.631±0.00 g/ml
	Tapped	0.80±0.00 g/ml
5	Compressibility index*	13.6±0.05%
6	Hauner's ratio*	1.19±0.02

*****All the values were expressed as mean ± SD, n=3*

8.8.1. Angle of repose:

Angle of repose was found to be at 28.7º, hence the blend was found to have good flowability.

8.8.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities were used for the measurement of Compressibility index. The Loose bulk density was found to be at 0.631±0.00 g/ml and tapped bulk density was found to be at 0.80±0.00 g/ml

8.8.3. Compressibility index (Carr's index):

The compressibility index (%) was found to be 13.6±0.05%. The blend was found to have excellent flowing property as the result were found to be below 15%.

8.8.4. Hausner's ratio:

The Hausner's ratio was found to be 1.19±0.02.The result indicates the free flowing properties of the powders.

8.9. Evaluation of Post compression parameters for alternate API

8.9.1. Appearance:

Surface nature of tablets was observed visually and it was concluded that they did not show any defects such as capping, chipping and lamination.

8.9.2. Organoleptic properties

Odour: Odourless

Colour: White or almost white

Nature: Crystalline powder

8.9.3. Physico-chemical characteristics:

The physical characteristics of Naproxen sodium tablets such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 8.27.

Table 8.27: Post compression parameters for alternate API formulation

S.No	Parameters	Result
1	Disintegration time *	9 minutes 58 sec
2	Hardness (kg/cm^2)*	9.4±0.79
3	Diameter (mm)*	11.5±0.01
4	Thickness (mm) *	4.72 ±0.01
5	Weight variation (%)***	302±0.15
6	Friability (%)*	0.34±0.01

All values were expressed as mean ± SD., n=3, n=20***

8.9.4. Dimension (Thickness and Diameter):

The diameter of the tablets was found to be 11.5±0.01 mm to and thickness was found to be 4.72 ±0.01 mm.

8.9.5. Tablet hardness:

The hardness of tablets was found to be 9.4± 0.79 kg/cm^2. This indicates good mechanical strength of tablet.

8.9.6 Percentage friability:

Percentage friability for the formulation was found to be 0.34±0.01 %. This indicates good handling property of the prepared matrix tablet.

8.9.7 Weight variation:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 300 mg, the pharmacopoeia limit for percentage deviation is ± 5%. The weight variation for the tablets was found to be 302±0.15, and hence formulation complied with the test for weight variation according to the pharmacopoeial specifications IP.

8.9.8. Drug content:

The drug content for the formulation was found to be 99.7 ± 0.12% w/w, which was within the specified limit as per IP .The values are shown in Table 8.25.

8.9.9 *In-vitro* dissolution studies:

Table 8.28: Dissolution profile of the formulation for alternate API formulation

S. No	Time in minutes*	Percentage drug released
1	5	27.6
2	10	45.0
3	15	77 .5
4	30	85 .2
5	45	92.0
6	60	99.2

*****All values were expressed as mean ±SD, n=3*

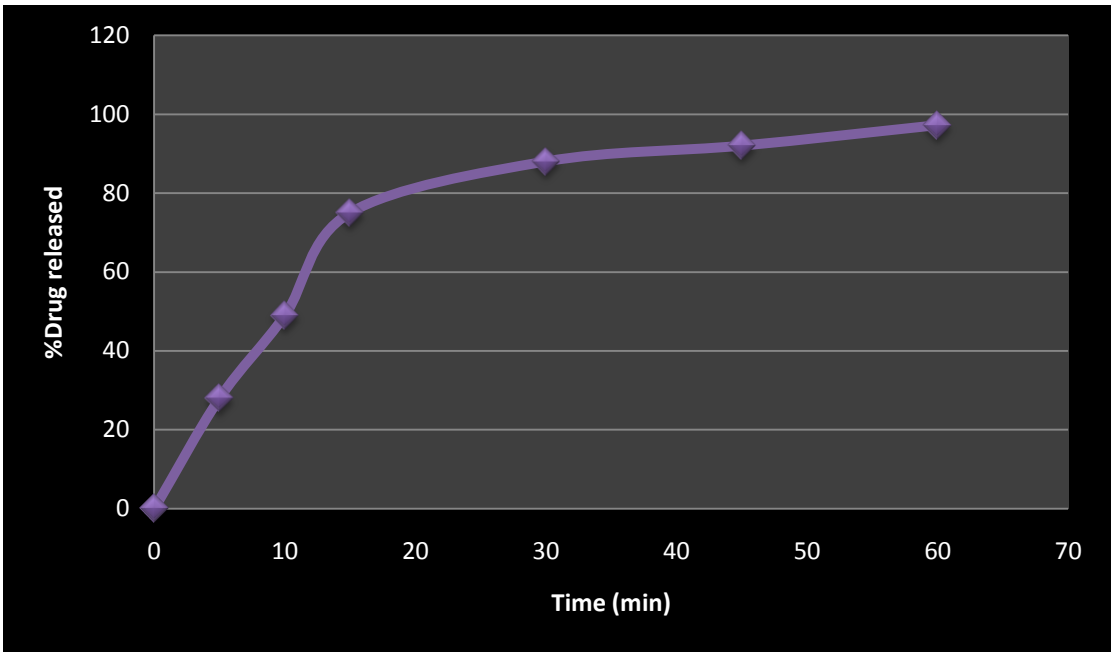


Figure 8.18: *In-vitro* drug released profile of formulation for alternate API formulation

In-vitro dissolution studies of formulation were carried out in 7.4 phosphate buffer medium and % of drug release was calculated. The formulation was kept for 60 min. It was found that the formulation meets the standard limits.

. **Table 8.29: Time of *in-vitro* drug release of t_{25},t_{50}, t_{90} values for alternate API formulation**

S. No	Time in min	t_{25}	t_{50}	t_{90}
1	5	4.166	8.33	15
2	10	4.464	8.928	16.07
3	15	4.62	9.25	16.66
4	30	7.57	15.15	27.27
5	45	11.25	22.5	40.5
6	60	14.56	29.412	52.42

8.10. Stability studies for alternate API

After exposure to accelerated stability conditions the formulation was analyzed for various parameters. The results are shown in Table 8.30 and Figures 8.19, 8.20 and 8.21.

Table 8.30: Stability studies of Alternate API Formulation.

S. No	Parameters	Initial	1st month	2nd month	3rd month
1	Description	White coloured round shaped coated tablets	White coloured round shaped coated tablets	White coloured round shaped coated tablets	White coloured round shaped coated tablets
2	Disintegration* (min)	9 min 58sec	9 min 55 sec	9 min 42 sec	9 min 39sec
3	Hardness* (kg/cm^2)	9.4±0.79	9.4±0.1	9.1±0.1	8.9±0.2
4	Assay* (%w/w)	99.7±0.12	99.6±0.1	99.54±0.1	99.1±0.17
5	Dissolution* (%)	99.2±0.1	99.0±0.05	98.8±0.15	98.6±0.1

*All the values were expressed as mean± S.D., n=3.

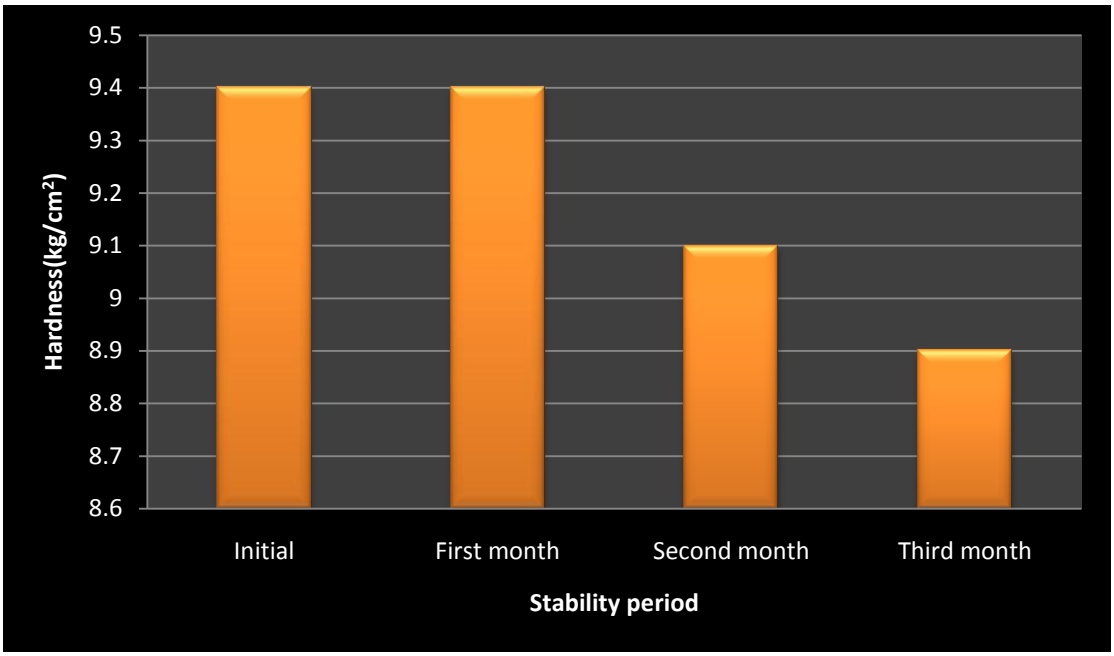


Figure 8.19: Comparison for hardness of before and after stability studies.

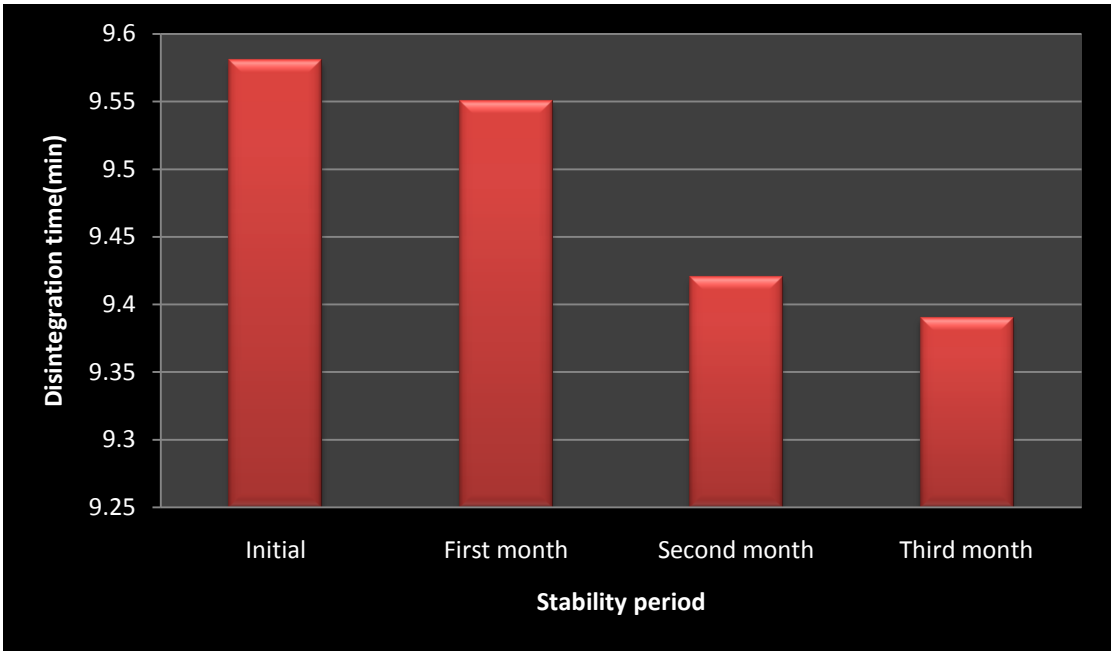


Figure.8.20: Comparison for disintegration of before and after stability studies

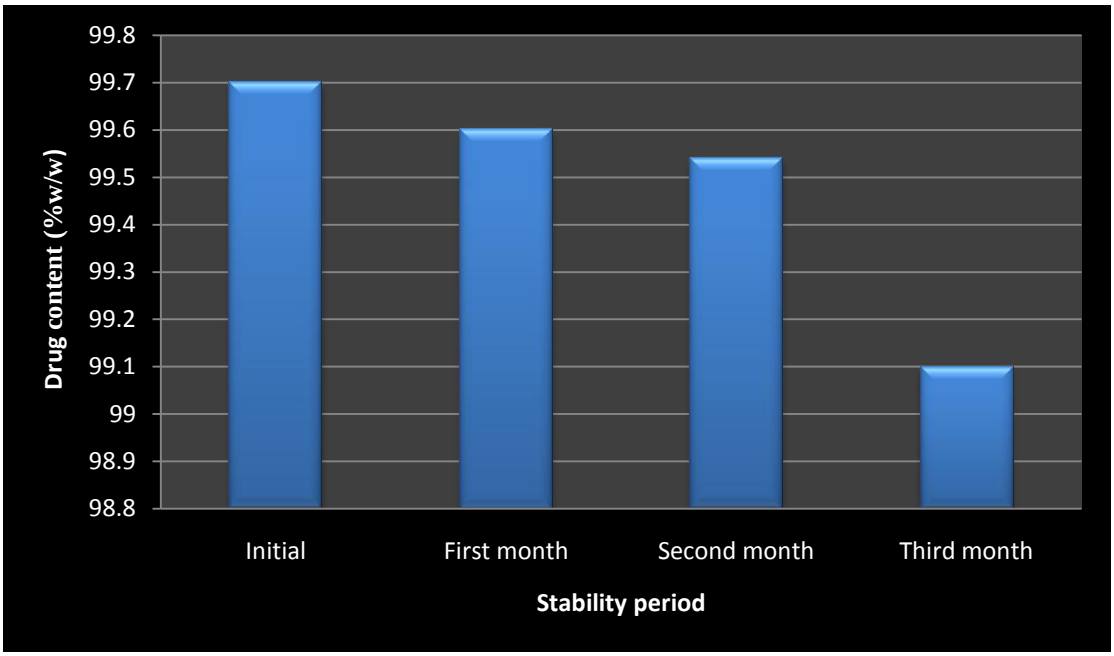


Figure: 8.21: Comparison for drug content profile of before and after stability studies

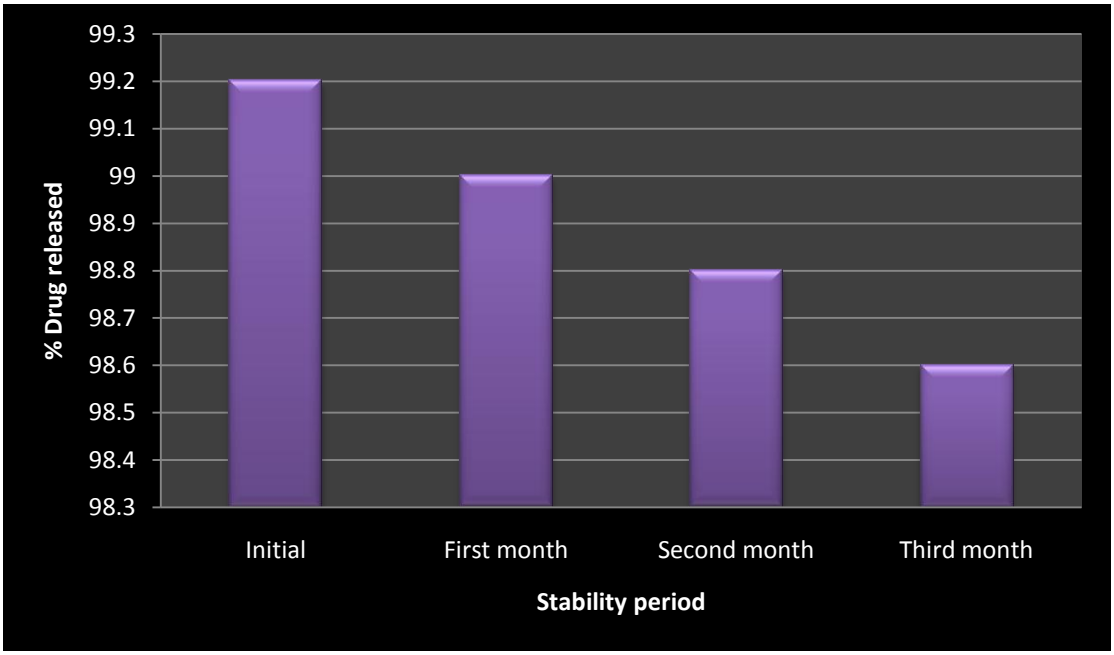


Figure.8.21: Comparison for dissolution profile of before and after stability studies

From the above studies there was no significance difference between the evaluated data from initial and after stability studies and all the values were found in worth accepting limits. The formulation was showed adequate physical stability at $40^{o}C \pm 2^{o}C$ at 75±5% relative humidity.

COMPARISION OF DISSOLUTION PROFILES OF BOTH THE API'S (APPROVED (REDDY'S) AND ALTERNATIVE (CHARIOTEER'S)

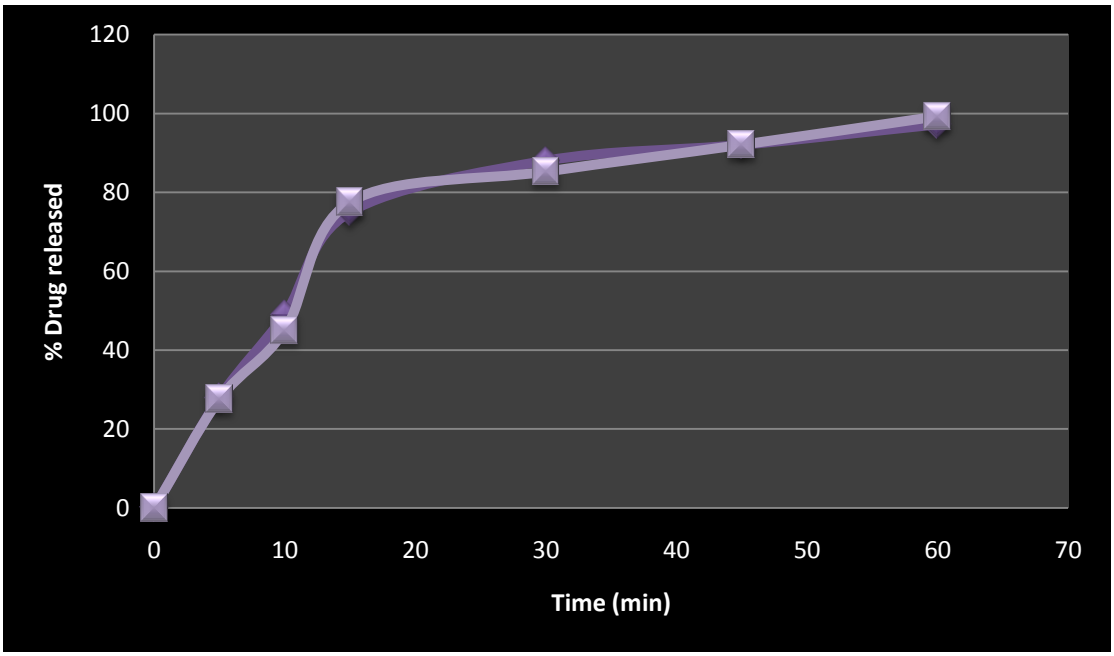


Figure.8.22: Comparison of dissolution profiles of both the API'S

The amount of percentage drug release of both the API sources was compared and was found to be similar.

8.11. Comparison of certificate of analysis for both the API'S

Table 8.31: Comparison of CERTIFICATE Of Analysis for both the API'S.

S.No	Test	REDDY'S	CHARIOTEER'S
1	Description	White crystalline powder	White crystalline powder
2	Specific optical rotation	-16.76	-15.6
3	Assay (%w/w)	99.8.	99.7
4	Untapped density (g/ml)	0.632	0.631
5	Tapped density (g/ml)	0.79	0.80
6	Loss on drying (%)	Not more than1.0%w/w	Not more than1.0%w/w
7	Related substances impurities (%)	Not more than 0.1%	Not more than 0.1%

All the above performed tests complies with the specification standards and the results obtained by both the approved API source i.e, REDDY'S and also the alternate API source i.e. CHARIOTER'S were found to be similar or almost equivalent Naproxen sodium was been formulated and marketed using the API of approved vendor i.e. REDDY'S LTD by the GRANULES INDIA LTD.

As the approved API from REDDY'S was not sufficient due to much demand for the drug Naproxen sodium in marketing field. An alternate vendor i. e, CHARIOTEER was proposed

According to regulatory point of view an alternate vendor for Active pharmaceutical ingredient can be approved if the specification standards and dissolution profile was same as compared with that of the already approved API according to the Alternate vendor guideline.

Hence the comparison for both the specification standards and percentage drug release was done for approved vendor (REDDY'S) and alternate vendor (CHARIOTEER).Hence further formulation of the drug Naproxen sodium can be carried out using the alternate API source.

8.12. FORMULATION of Naproxen sodium using Approved Alternate API (CHARIOTEER'S)

8.12 Composition of Naproxen sodium Immediate tablets using Approved Alternate Vendor.

Table 8.32: Composition of Naproxen sodium using approved alternate API

S.No	Ingredients (mg)	Formulation					
		F1	F2	F3	F4	F5	F6
1	Naproxen sodium	220	220	220	220	220	220
2	Microcrystalline cellulose	-	-	44.0	39.0	45.0	42.0
3	Corn starch	73.0	72.7	27.6	26.6	20.6	23.6
4	Sodium starch glycolate	4.6	4.9	6	6	6	6
5	Water	-	-	-	qs	qs	qs
6	Povidone	-	-	-	6	6	6
7	Stearic acid	2.4	2.4	2.4	2.4	2.4	2.4
8	Total	300	300	300	300	300	300

***All the ingredients were expressed as mg per tablet.**

8.13. Physico chemical characteristics of powder blends:

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hauser's ratio. The results of these evaluations were as follows:

Table 8.33: Physico chemical characteristics of Naproxen sodium

FORMULATION CODE	BULK DENSITY* (g/ml)	TAPPED DENSITY* (g/ml)	COMPRESSIBILITY INDEX* (%)	HAUSNER'S RATIO*	ANGLE OF REPOSE* (º)
F1	0.641±0.00	0.825±0.00	13.41±0.03	1.17±0.01	28.26±0.15
F2	0.655±0.00	0.725±0.01	12.27±0.05	1.17±0.00	26.34±0.14
F3	0.649±0.01	0.798±0.00	13.47±0.04	1.25±0.01	25.63±0.06
F4	0.631±0.01	0.587±0.01	12.30±0.03	1.17±0.02	25.31±0.24
F5	0.634±0.01	0.819±0.02	13.56±0.02	1.23±0.00	26.61±0.28
F6	0.648±0.00	0.712±0.01	12.77±0.04	1.29±0.01	27.59±0.17

*****All values are expressed as mean ±S.D., n=3.

8.12.2.1. Angle of repose:

Angle of repose ranged from 25.31±0.24 to 28.26±0.15.Hence the blend was found to have good flowability.

8.12.2.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.631± 0.01 to 0.655± 0.00 g/ml, and 0.587±0.001 to 0.825± 0.00 g/ml respectively.

8.12.2.3. Compressibility index (Carr's index):

The compressibility index (%) ranged from 12.27± 0.05 to 13.56± 0.02. The blend was found to have good flowing property as the result were found to be below 15%.

8.12.2.4. Hausner's ratio:

The Hausner's ratio ranged from 1.17± 0.00 to 1.29 ± 0.01.The result indicates the free flowing properties of the powders.

8.14. EVALUATION OF TABLETS:

8.13.1. Appearance

The tablets were observed visually and did not show any defects such as capping, chipping and lamination.

8.13.2. Physicochemical characteristics:

The physical characteristics of Naproxen sodium (F1 to F6) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F6) found to be within the limits specified in official books.

Table 8.34: Evaluation of Naproxen sodium tablets

CODE	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm^2)	Friability* (%)	Weight variation* (mg)	Drug content *(%w/w)
F1	13.20±0.166	4.6±0.152	8.2±0.115	0.44±0.015	301±0.020	99.50±0.26
F2	13.36±0.035	4.2±0.152	8.4±0.115	0.42±0.01	303±0.019	98.42±0.36
F3	13.35±0.015	4.4±0.1	8.1±0.0577	0.29±0.02	298±0.020	95.88±0.48
F4	13.31±0.02	4.7±0.1	8.6±0.230	0.54±0.025	299±0,022	99.2±0.25
F5	13.1±0.08	4.6±0.1	9.2±0.115	0.38±0.03	301±0.026	99.9±0.32
F6	13.36±0.025	4.7±0.1	9.8±0.34	0.59±0.02	303±0.022	99.2±0.26

*****All values are expressed as mean ±S.D. n=3.

8.13.2.1. Dimension (Thickness and Diameter)

Thickness and diameter specifications may be set on an individual product basis. There were no marked variations in the thickness and diameter of tablets within each formulation indicating uniform behaviour of granules throughout the compression process. The diameter of the tablets of all formulations were found to be ranged between 13.1±0.08 to 13.36±0.035 mm and thickness ranged between 4.2±0.15 to 4.7±0.1mm

8.13.2.2. Tablet Hardness:

A difference in tablet hardness reflects difference in tablet density and porosity. Which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and

formation of gel barrier. The hardness of tablets was found to be in the range of 8.1±0.057 kg/cm^2 to 9.8±0.34 kg/cm^2. This indicates good tablet strength.

8.13.2.3. Percentage Friability:

Percentage friability of all the formulations was found between 0.29±0.02 to 0.59±0.02 %. This indicated good handling property of the prepared tablet.

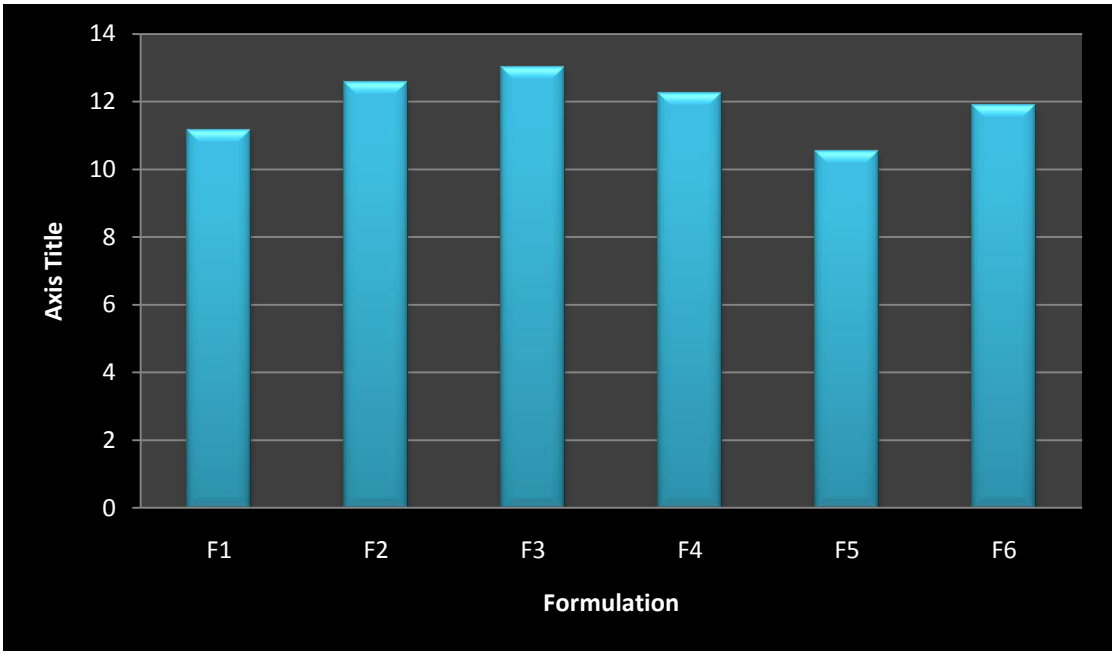
8.13.2.4. Weight Variation:

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 300 mg the pharmacopoeial limit for percentage deviation is ±5%. The weight variation for the tablets was found between 298±0.020 to 303±0.022 %.

8.13.3. In-vitro disintegration studies:

Table 8.35: Disintegration time of Naproxen sodium formulation.

CODE	Disintegration time(min)*
F1	11.15±0.104
F2	12.56±0.280
F3	13.02±0.064
F4	12.24±0.450
F5	10.5±0.30
F6	11.88±0.160



*****All values are expressed as mean ±S.D. n=3*.

Figure 8.23: Comparison of Disintegration time of formulations(F1-F6)

8.13.4. *In-Vitro* Dissolution Studies:

Table 8.36: *In-Vitro* drug released data of formulation F1

S.No	Dissolution medium	Time (min)	*Percentage drug released
1	7.4 phosphate buffer	**0**	0.00
2		**5**	27.4±0.95
3		**10**	54.3±1.24
4		**15**	66.0±0.15
5		**30**	76.8±0.45
6		**45**	82.5±0.90
7		**60**	89.2±0.79

***All values are expressed as mean ±S.D. n=3*.

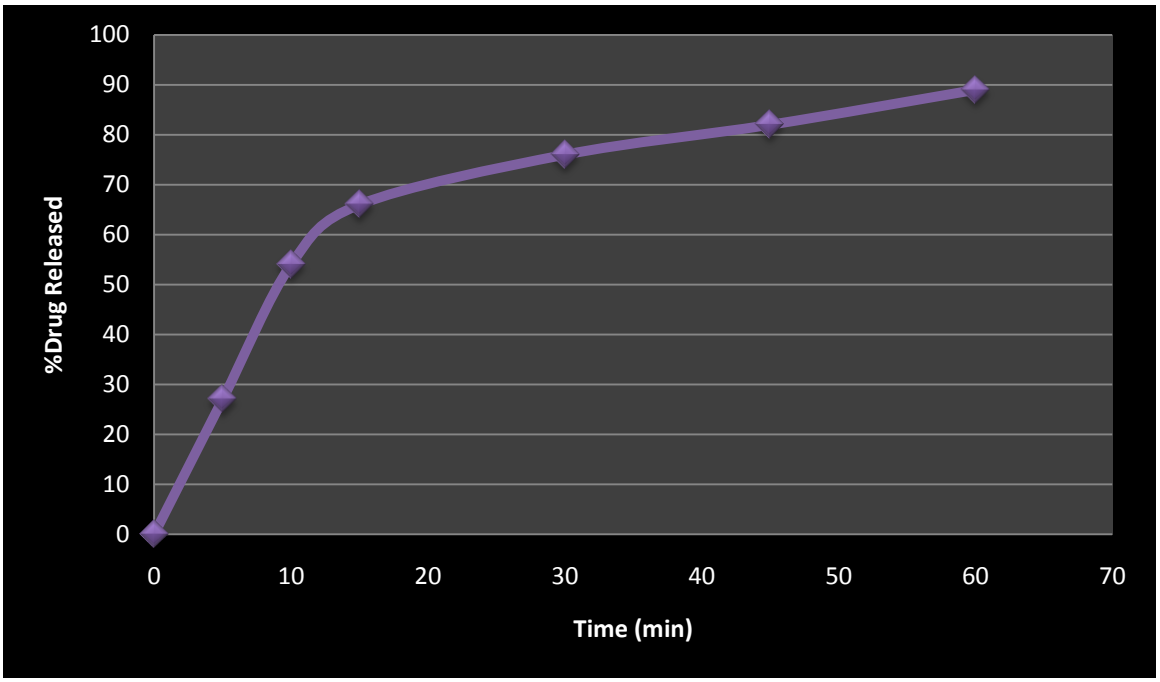


Figure 8.24: *In-Vitro* drug released profile of formulation F1.

Table 8.37: *In-Vitro* drug released data of formulation F2.

S.No	Dissolution Medium	Time (min)	*Percentage drug released
1	7.4 Phosphate buffer	**0**	0.00
2		**5**	29.8±0.61
3		**10**	54.1±0.32
4		**15**	63.3.0±1.47
5		**30**	79.0±0.50
6		**45**	87.0±1.32
7		**60**	90.2±0.1

*****All values are expressed as mean ±S.D. n=3*.

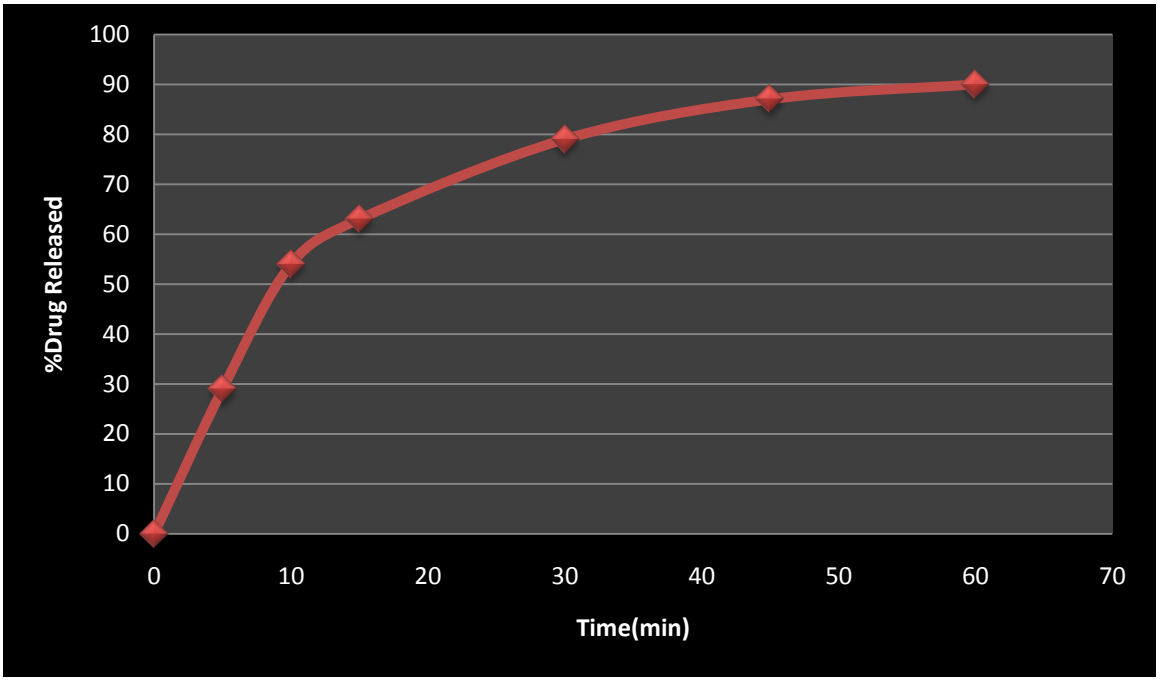


Figure 8.25: *In-Vitro* drug release profile of formulation F2

Table 8.38: *In-Vitro* drug released data of formulation F3.

S.No	Dissolution medium	Time (min)	*Percentage drug released
1	7.4 Phosphate buffer	**0**	0.00
2		**5**	24.2±0.87
3		**10**	47.1±0.15
4		**15**	68.0±0.26
5		**30**	87.5±0.87
6		**45**	91.0±0.72
7		**60**	93.5±0.5

***All values are expressed as mean ±S.D., n=3*.

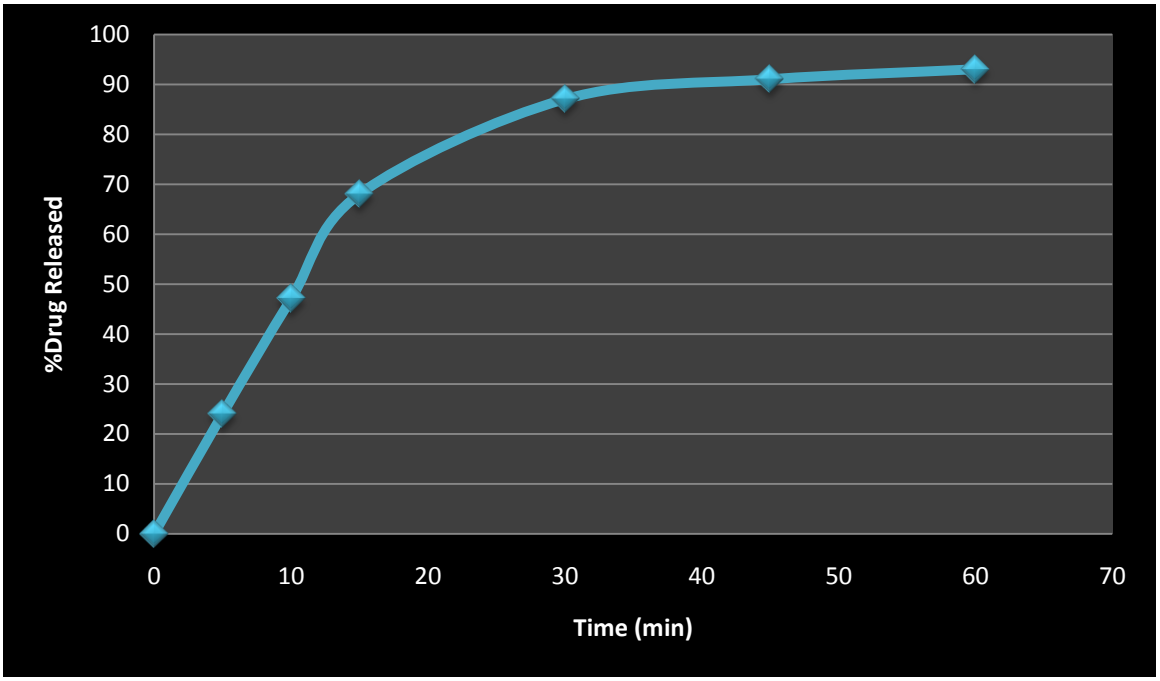


Figure 8.26: *In-Vitro* drug release profile of formulation F3

Table 8.39: *In-Vitro* drug released data of formulation F4.

S.No	Dissolution medium	Time (min)	*Percentage drug released
1	7.4 Phosphate buffer	**0**	0.00
2		**5**	31.3±0.20
3		**10**	50.8±0.64
4		**15**	74.6±0.41
5		**30**	86.6±0.55
6		**45**	90.2±0.25
7		**60**	95.4±0.70

*****All values are expressed as mean ± S.D., n=3*.

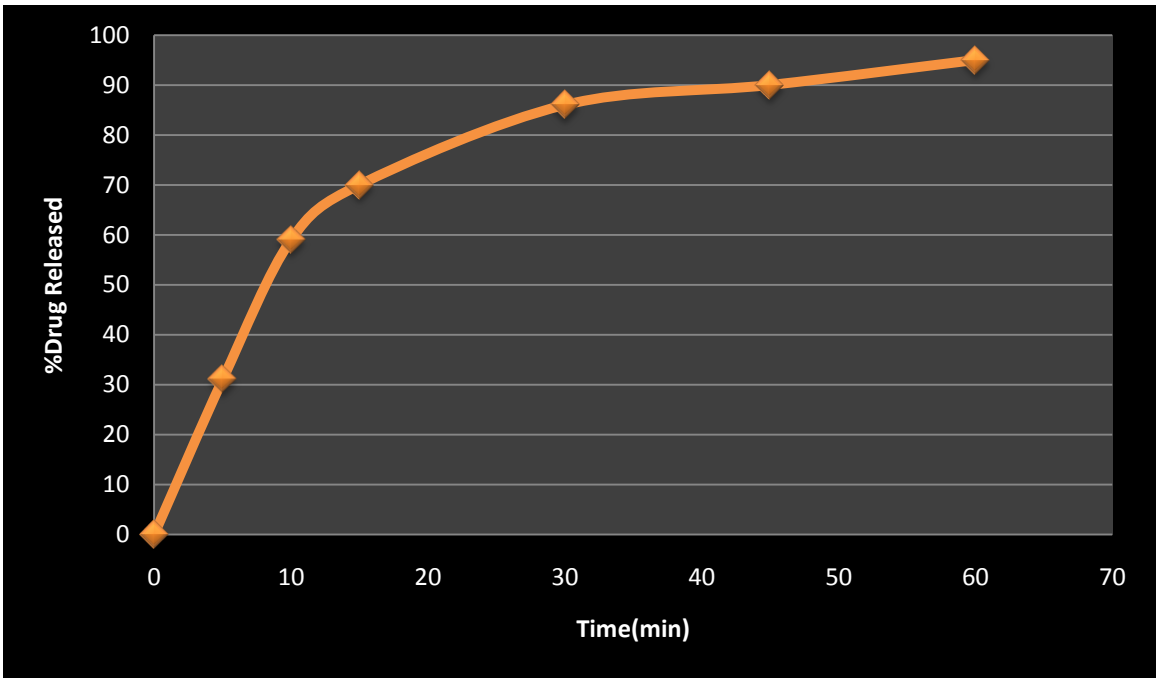


Figure 8.27: *In-Vitro* drug release profile of formulation F4.

Table 8.40: *In-Vitro* drug released data of formulation F5.

S.No	Dissolution medium	Time (min)	*Percentage drug released
1	7.4 Phosphate buffer	**0**	0.00
2		**5**	34.3±0.30
3		**10**	59.8±0.52
4		**15**	76.5±0.65
5		**30**	88.8±0.75
6		**45**	95.2±0.50
7		**60**	99.1±0.26

*****All values are expressed as mean ± S.D., n=3*.

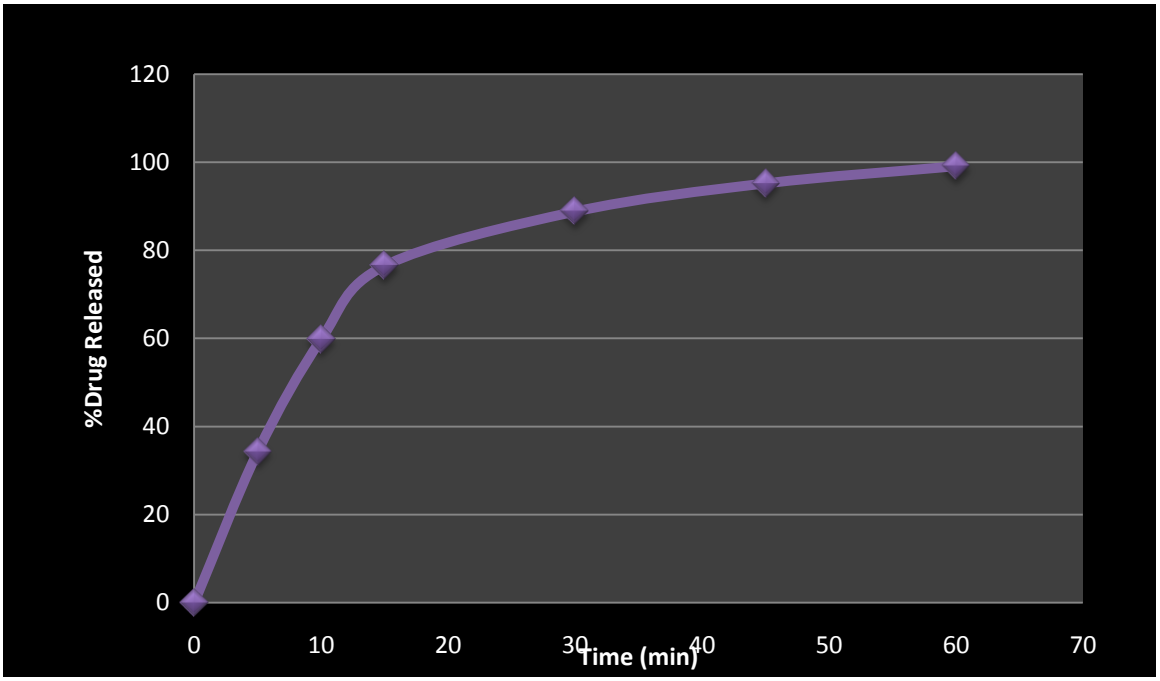


Figure 8.28: *In-Vitro* drug release profile of formulation F5.

Table 8.41: *In-Vitro* drug released data of formulation F6.

S.No	Dissolution medium	Time (min)	*Percentage drug released
1	7.4 phosphate buffer	**0**	0.00
2		**5**	27.3±0.15
3		**10**	51.8±0.91
4		**15**	68.2±1.66
5		**30**	79.1±0.41
6		**45**	80.2±0.65
		60	90.5±0.66

*****All values are expressed as mean ± S.D., n=3*.

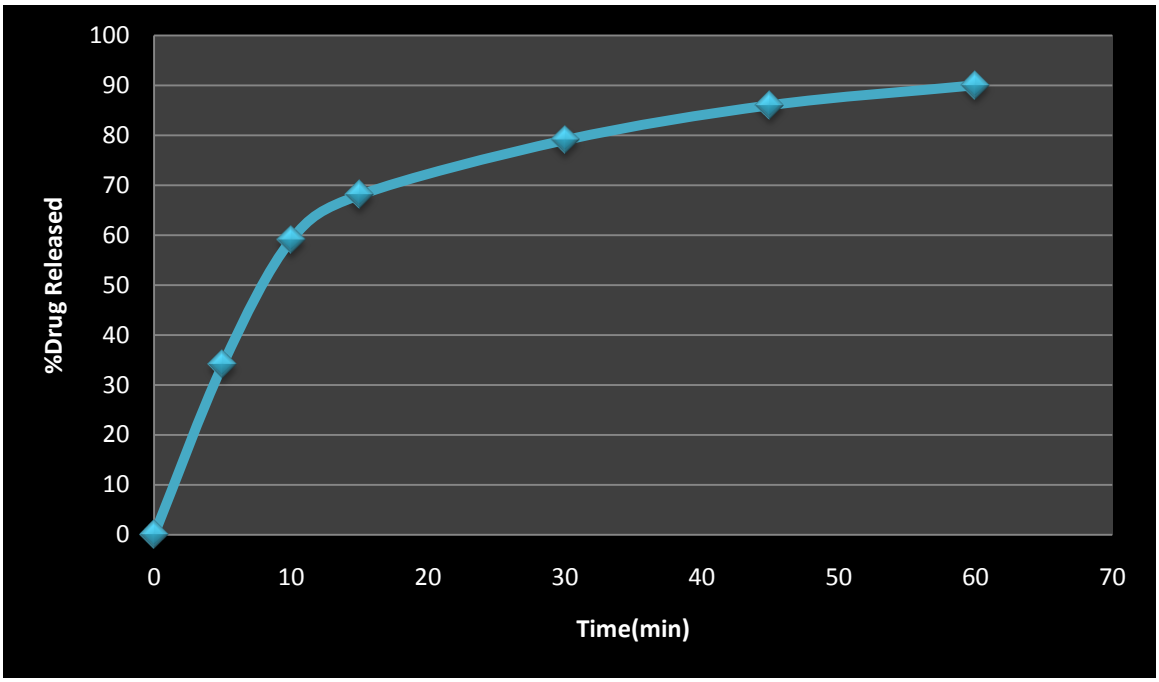


Figure 8.29: *In-Vitro* drug release profile of formulation F6.

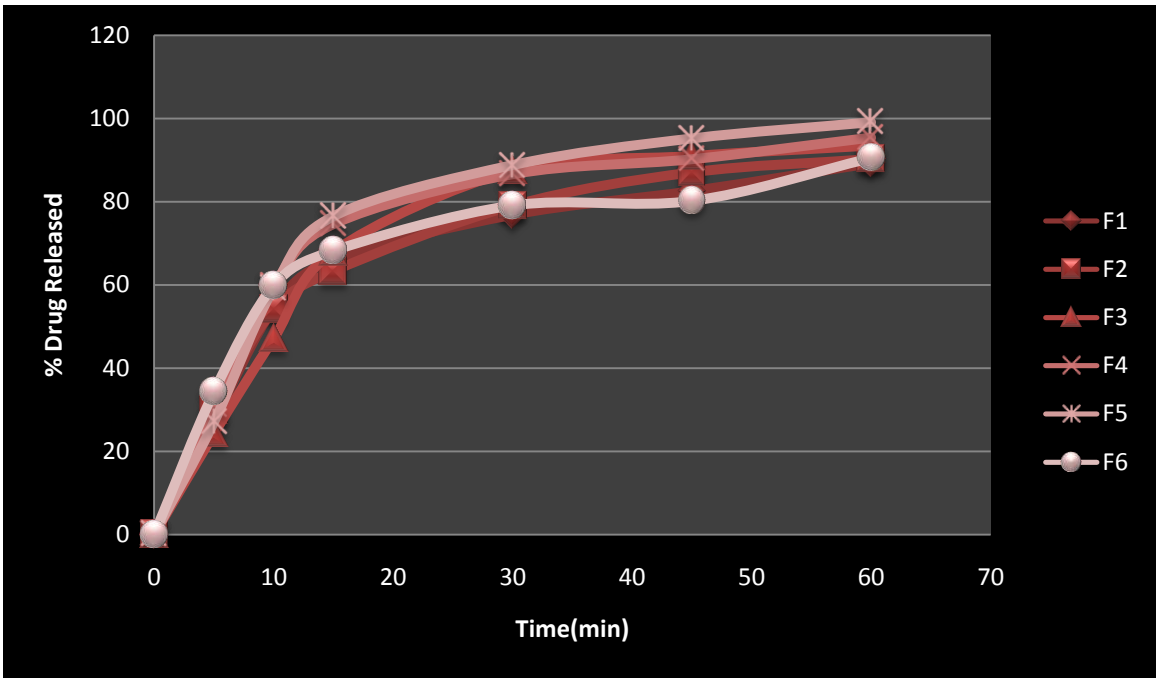


Figure 8.30: Comparison of *In-Vitro* drug released profile of formulations F1-F6.

According *to In-Vitro* drug released data of dissolution studies of formulation F1&F2 &F3 prepared by direct compression method were found to be 89.2%, 90.2% and 93.5%respectively. The drug released data of formulations containing microcrystalline cellulose as diluent were found to be 95.4%, 99.1% and 90.5% respectively. On increasing the concentration of diluents microcrystalline cellulose there was increase in the % drug release. Based on above drug released data formulation (**F5)** was showed a highest *In-Vitro* released profile among the all formulations.

Table.8.42: Percentage drug released t_{25}, t_{50} and t_{90}.

Formulations	Percentage drug released (time in min)		
	t_{25}	t_{50}	t_{90}
F1	5.48	9.20	60.53
F2	4.19	9.24	59.86
F3	5.16	10.61	57.75
F4	3.99	8.44	56.60
F5	3.644	8.36	54.49
F6	4.62	8.44	59.8

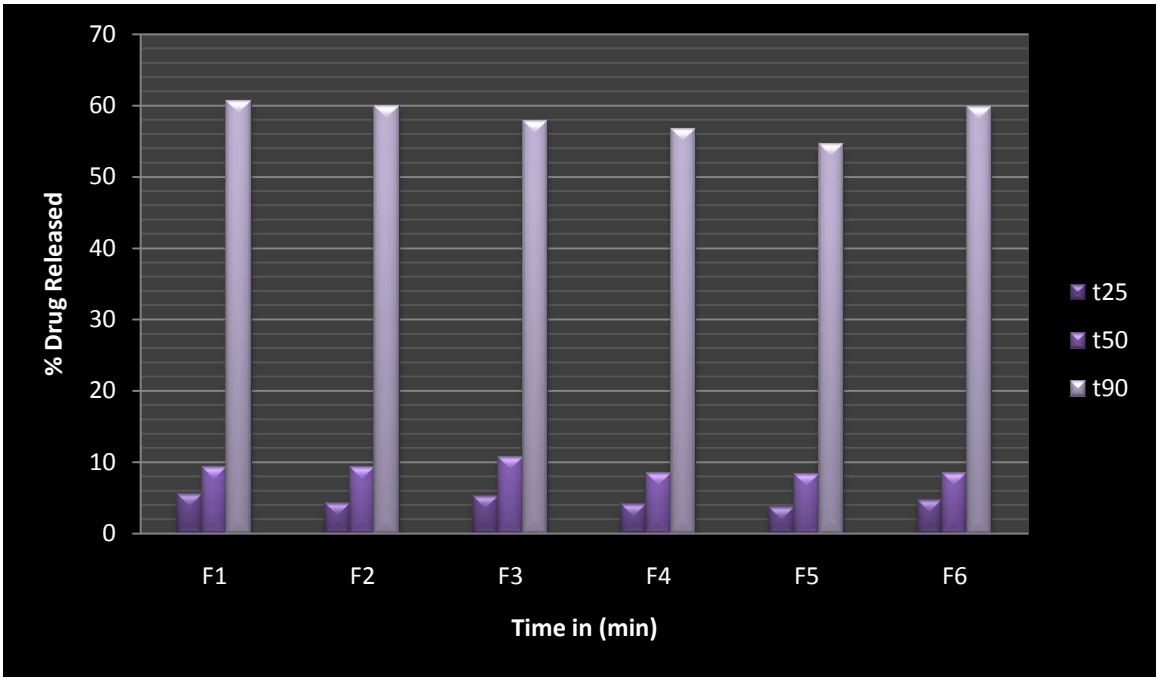


Figure 8.31: Percentage drug released of $t_{25, t50, t90}$ values.

8.15. Stability studies:

After exposure to accelerated stability conditions the formulation was analyzed for various parameters. The results are shown in table 8.43.

Table 8.43: Stability study data of optimized formulation (F5).

Parameter	**Initials**	**1st Month**	**2nd Month**	**3 rd Month**
Description	White coloured round shaped coated tablets	Complies	Complies	Complies
Disintegration* (min)	10 min 5 sec	10 min 2 sec	9 min 95 sec	9min 68 sec
Hardness* (kg/cm^2)	9.2±0.115	9.0±0.11	8.8±0.1	8.6±0.1
Assay*(%w/w)	99.9±0.32	99.6±0.1	99.4±0.1	99.2±0.1
Dissolution* (%)	99.1±0.26	98.8±0.15	98.5±0.1	98.1±0.15

*****All values are expressed as mean ± S.D., n=3*.

No major difference was found between evaluated parameters before and after stability studies and all are in acceptable limits. The tablets showed satisfactory physical stability at 40˚C±2˚C at 75 % RH±5%RH.

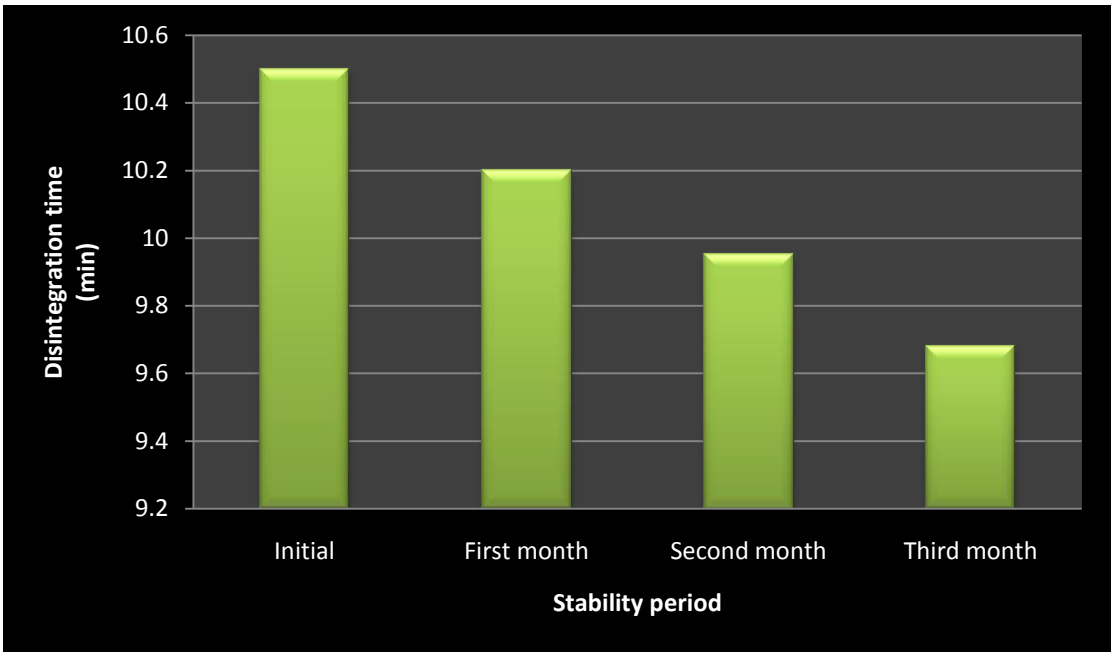


Figure 8.32: Comparison for disintegration before and after stability studies.

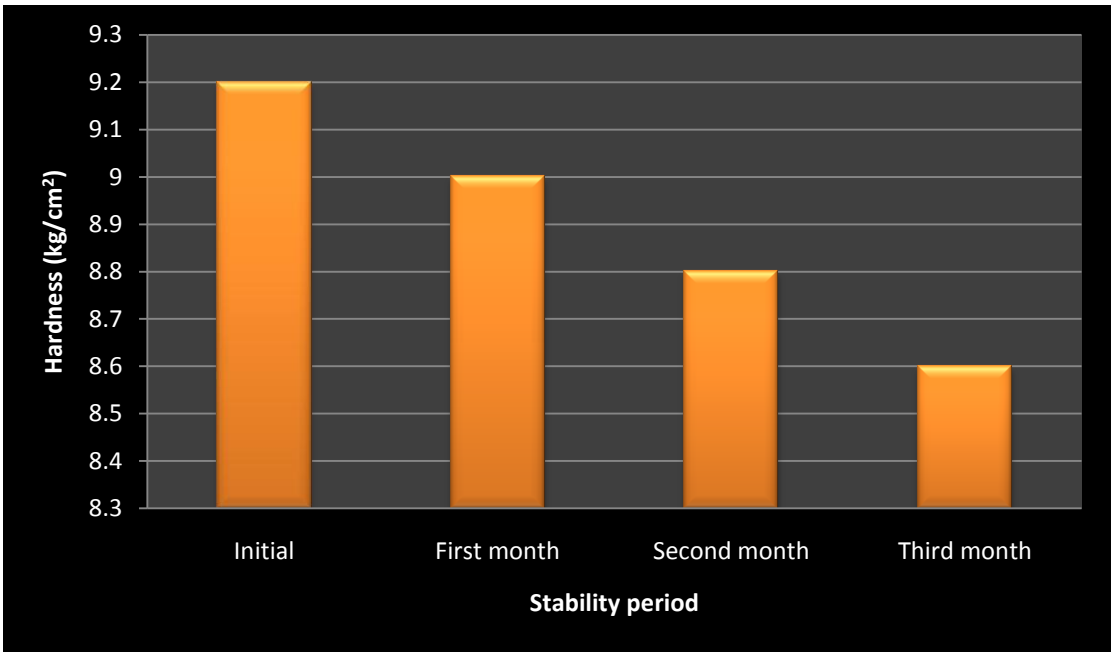


Figure 8.33: Comparison for hardness before and after stability studies.

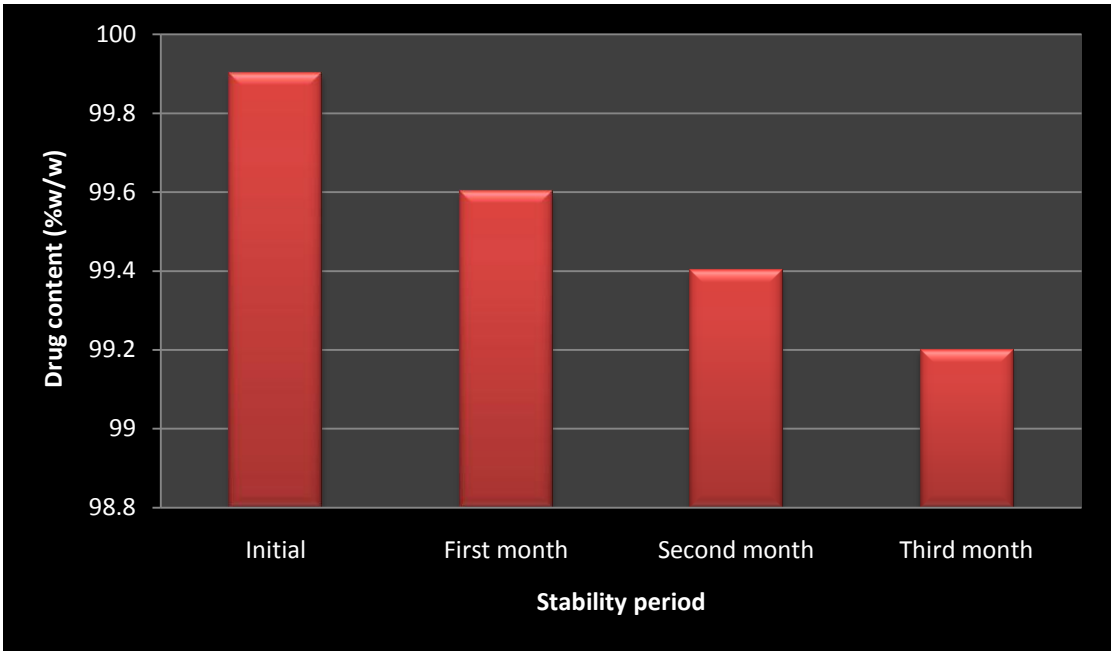


Figure 8.34: Comparison for Assay of before and after stability studies

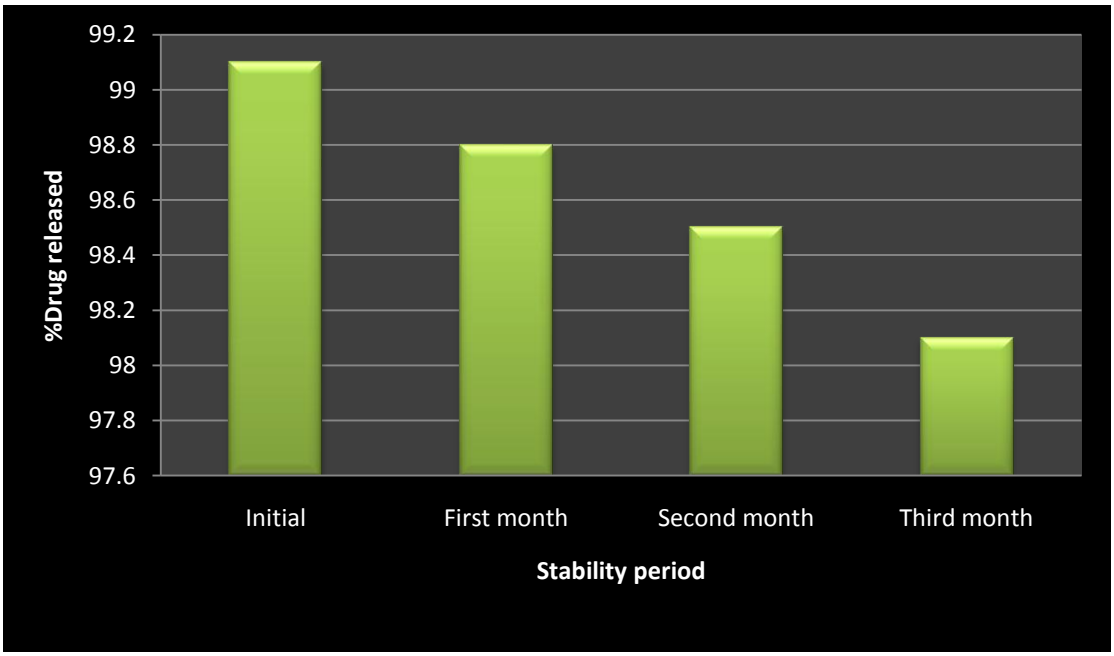


Figure 8.35: Comparison for percentage drug released of before and after stability studies

SUMMARY

&

CONCLUSION....

SUMMARY AND CONCLUSION

The specification standards and dissolution profile was compared for the drug Naproxen sodium for both approved vendor (REDDY'S) and alternate vendor (CHARIOTEER) and was found to be similar.

Hence the alternate vendor API i.e charioteer can be approved for formulation and further marketing. A Successful immediate drug delivery system was prepared with immediate release mechanism that gives immediate on set of action, by using both the approved and alternate API source.

Naproxen sodium posses Longer half life and maximum water solubility; hence it was a good candidate for Immediate release drug delivery system. The identification of drug was carried out by IR, UV and melting point.

The physicochemical parameters such as appearance, solubility study and loss on drying were performed by suitable methods for both the formulations.

The analytical profile of drug was evaluated for development of standard curve and percentage purity of drug.

Compatibility of drug was done by performing DSC study.

It was concluded that results obtained by both the API'S were found to be similar. Impurities present in the drug were found unaltered in the HPLC chromatogram and peaks in the DSC thermogram of drug disintegrant physical mixture. The powder blend was prepared by blending various ingredients in mortar and pestle for 20 min and evaluated for bulk density, tapped density, carr's index,

Hausner's ratio angle of repose.Immediate release tablet of Naproxen sodium was obtained by wet granulation method for both the API formulations.

Formulations prepared composed of povidone, sodium starch glycolate as disintegrants, and microcrystalline cellulose as diluents.

Hence by comparing the specification standards i.e certificate of analysis of both the approved API source , the certificate of analysis of alternate API source and dissolution profiles of both the API sources it can be concluded that the results of Alternate API source ie CHARIOTER is equivalent with that of the Approved API source.

According to Alternate Vendor Guideline in regulatory point of view an alternate vendor for Active pharmaceutical ingredient can be approved if the specification standards and dissolution profile was same as compared with that of the already approved API source.

Hence the formulation of Naproxen sodium can be done by using the alternate API source i.e, CHARIOTER.

Further formulation was carried out using the API of APPROVED ALTERNATE source and 6 formulations were carried out.

Out of the 6 formulations first 3 formulations were done using direct compression method and next 3 formulations were done by wet granulation method.

Formulations were prepared using same excipients and evaluation was carried out.

The performance with respect to disintegration time and % drug rele59ased F5 was selected as the best formulation as it showed its disintegration time within 10 minutes and percentage drug released at 99.9% at 60 minutes time interval.

According to stability it was found that there was no significant change in hardness, drug content and In-vitro dissolution of optimised formulation F5.

FUTURE PROSPECTS....

FUTURE PROSPECTORS

As the alternate vendor qualification was found to be successful, the selection of more alternate vendor's can be done in order to acquire surplus supply of API sources for the drugs that are in demand.

In the field of immediate release, there are many obstacles that need to be overcome in order to be able to claim true immediate release. Considering the advantages for improved delivery of drugs further clinical studies are needed to access the utility of this system for patients suffering from acute gout, musculo skeletal complaints.

This dosage forms holds promise for further systems. *In-Vitro-In-Vivo* correlation (IVIVC) will serve as a means of modelling the human organism and of gaining a better understanding of drug absorption and its dependence on *In-Vitro* release process.

Convincing results of clinical studies have yet to be obtained for a Immediate release system that displays the necessary performance behaviour and which is retained in the fasted stomach of humans for a sensible period of time after dosing. Furthermore, the system will need to release the drug with in short period of time.

Once the technology is fully accepted, these systems will probably increase with new pipeline drugs that need enhancement to their bioavailability.

Finally while the increasing the drug release profile there by immediate on set of action has been a major aim of pharmaceutical research and development in the past two decades, the increasing on set of action by Immediate release profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients.

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