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FORMULATION AND EVALUATION OF FLOATING BILAYERED TABLETS OF NAPROXEN AND SUMATRIPTAN

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ABSTRACT

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Usual treatment for migraine includes "double therapy" consisting of an NSAID (Naproxen) and 5HT- agonist (Sumatriptan). The aim of the present investigation was to develop a bilayer floating tablets of Naproxen and Sumatriptan for effective treatment of Migraine. Naproxen is newly developed NSAID having analgesic and anti-inflammatory activity,Sumatriptan is the most effective vasoconstrictor among the Triptans for treatment of migraine. Bilayer floating tablets were formulated using direct compression method, it consist of two layers i.e IR layer containing Naproxen and floating SR layer containing Sumatriptan. The IR layer comprises ofpolysplasdone XL as super disintegrant and the SR layer contains Methocel as release retarding polymers. Sodium bicarbonate was used as gas generating agent in the floating layer. In order to optimize, the best formulation among the six formulations from IR and SR was selected on the basis of their dissolution profiles. IR layer tablets IR5 containing 15mg of polypasdone was found to be optimum and released 98.24% of Naproxen in 300mins. The optimized floating SR layer tablet of Sumatriptan SR3 containing Methocel containing 50mg showed 99.3% of drug release at the end of 12 hours. The optimized IR 6 and SR 3 fomulation was combined and made into bilayer floating tablet. The optimized bilayer tablet of Naproxen and Sumatriptan was evaluated for various evaluation parameters i.e Hardness 2.5kg/cm^2, Friability 0.56%, floating lag time 2mins 20sec and floating time of 24 hours. All the results of evaluations was found to be within limits and the final optimized bilayer formulation released 98.24% of

Naproxen in 30mins and 98.67% of Sumatriptan in 12 hours. The optmised formulation was fitted in the Kinetic models and it follows korsmeyerpeppas kinetics and the release mechanism was Case II Non- fickian refers to a combination of both diffusion controlled and erosion controlled-drug delivery.

KEYWORDS: Naproxen, Sumatriptan, SR floating layer,Floating bilayer tablets, polyplasdone, methocel, floating lag time and floating time.

3 MATERIALS AND METHODS

The following materials are used in the present study

1. Ingredients
2. Equipments

1. INGREDIENTS

The Materials used in the present work are as follows

Table 3.a List of ingredients

Source	category	Source
Naproxen Sodium	NSAID	Ranbaxy laboratories
Sumatriptan	Vaso constrictor	Ranbaxy laboratories
Methocel	Tablet binder, coating agent	Merck Specialities Pvt Ltd, Mumbai, India
Polyplasdone XL	super disintegrent	Merck Specialities Pvt Ltd, Mumbai, India
Explotab	super disintegrent	Merck Specialities Pvt Ltd, Mumbai, India
Sodium bicarbonate	Effervescent agent	Merck Specialities Pvt Ltd, Mumbai, India
Magnesium stearate	Lubricant	Merck Specialities Pvt Ltd, Mumbai, India
Micro crystalline cellulose	Diluent	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Lubricant and glidant	Merck Specialities Pvt Ltd, Mumbai, India
0.1N Hcl	buffer	-

EQUIPMENTS

Table 3.b List of equipments

S.NO	EQUIPMENTS	MANUFACTURER	MODEL	PURPOSE
1	Digital balance	Wensar weighing scales Ltd.	PGB-600	Weighing
2	Bulk Density Apparatus	Thermo lab	ETD- 1020	Density
3	Tablet hardness tester	Lab Hosp Corporation		Hardness
4	Friability test apparatus	Lab Hosp		Friability
5	Vernier caliper	Aerospace		Thickness
6	FTIR	Agilent technologies	Cary 630 FTIR	Drug excipient

	spectrophotometer			compatibility
7	pH Meter	Systronics	Digital - 335	Ph
8	Compression machine	Rimeka	RSB4 - 1	Punching
9	Tablet dissolution apparatus	LAB INDIA	DS 8000/S	% Drug release
10	UV/Visible Spectrophotometer	Elico, PG instruments	T60 UV	Analytical estimation
11	DSC	HITACHI		Drug excipient compatibility

3.1 DRUG PROFILE

A. DRUG PROFILE OF IMMEDIATE RELEASE LAYER[42]

NAPROXEN

Description: An anti-inflammatory agent with analgesic and antipyretic properties. Both the acid and its sodium salt are used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea, and acute gout. [PubChem]

Structure

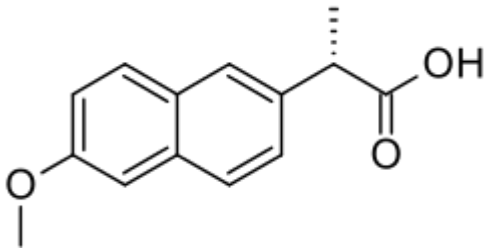


fig 3.1 a structure of Naproxen

Chemical Name : (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid

Molecular Formula : $C_{14}H_{14}O_3$

Molecular Weight : 230.2592 gram/mole

Appearance : Solid

Solubility : Water solubility - 250 g / L

Melting Point : 153 °C

PKa : 4.15

Category : nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid class

Pharmacokinetic Data

Absorption: Naproxen itself is rapidly and completely absorbed from the GI tract with an in vivo bioavailability of 95%. Although naproxen itself is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose.

Protein Binding: At therapeutic levels naproxen is greater than 99% albumin-bound.

Metabolism: Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

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

Excretion: Renal

Mechanism of Action: The mechanism of action of naproxen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity.

Uses: For the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout. Also for the relief of mild to moderate pain and the treatment of primary dysmenorrhea.

Side Effects: Gastrointestinal problems such as heartburn, constipation, diarrhea, ulcers and stomach bleeding. It was found that high-dose naproxen induced near-complete suppression of platelet thromboxane throughout the dosing interval and appeared not to increase cardiovascular disease (CVD) risk, whereas other high-dose NSAID regimens had only transient effects on platelet COX-1 and were associated "with a small but definite vascular hazard". Conversely, naproxen was associated with higher rates of upper gastrointestinal bleeding complications in comparison to other NSAIDs.

Marketed Products

S No	Brand Name	Manufacturers	Dosage form	Strength
1	Aleve	Bayer	Tablet	220mg

B. DRUG PROFILE OF SUSTAINED RELEASE LAYER- SUMATRIPTAN[43]

SUMATRIPTAN

Proprietary Name : Imitrex, Imigran, Treximet

Chemical structure :

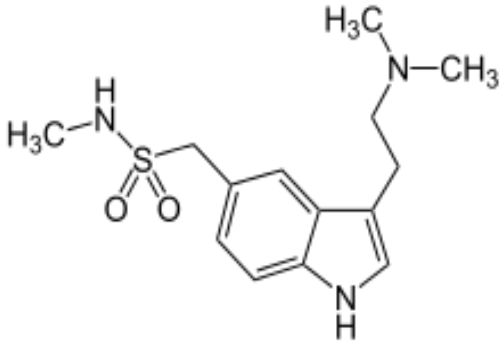


Fig 3.1.b: Structure of Sumatriptan

Chemical Name : 1-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-*N*-methyl-methanesulfonamide

Molecular Formula : $C_{14}H_{21}N_3O_2S$

Molecular weight : 295.4

Category : Vasoconstrictor agent, Serotonin Antagonist, Serotonin 5-HT1 receptor agonist, Serotonin receptor agonist.

Appearance : a white to off-white powder.

Solubility : Soluble in water and saline

Melting point : 169-171 °C.

pKa : 9.74

Absorption : Approximately 15%

Half life : 2.5 hours.

Protein binding : 14-21%

Metabolism : MAO

Elimination : 60% urine, Feces 40%.

Mechanism of action : The 5-HT_{1B} and 5-HT_{1D} receptors function as autoreceptors, which inhibit the firing of serotonin neurons and a reduction in the synthesis and release of serotonin upon activation. After sumatriptan binds to these receptors, adenylate cyclase

activity is inhibited via regulatory G proteins, incrases intracellular calcium, and affects other intracellular events. This results in vasoconstriction and inhibtion of sensory nociceptive (trigeminal) nerve firing and vasoactive neuropeptide release.

Side effect: convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

3.2 EXCIPIENT PROFILE[44]

A. POLYPLASDONE XL

Nonproprietary Names

BP: Crospovidone, PhEur: Crospovidone, USP-NF: Crospovidone.

Synonyms

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL.

Chemical Name and CAS Registry Number

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

Structural formula

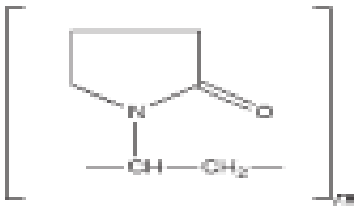


Fig3.2.a: Structure of Polyplasdone XL

Functional Category: Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly

soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

B. EXPLOTAB

Nonproprietary Names: BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate, USP-NF: Sodium Starch Glycolate.

Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar.

Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

Structural Formula

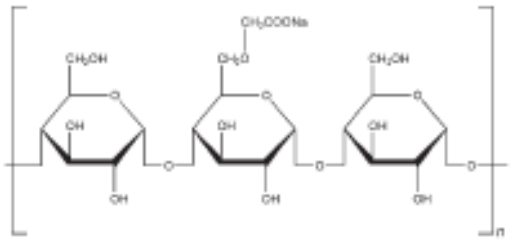


Fig 3.2.b: Structure of Explotab

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 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 component 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 show considerable swelling in contact with water.

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 unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

C. METHOCEL

General Descriptions

Nonproprietry Names: BP: Hypromellose, USP : Hypromellose.

Synonyms: HPMC2208**,** Benecal MHPC, Pharmacoat.

Description: It is odorless & tasteless, white or creamy white colored Fibrous or granular powder.

Structural Formula

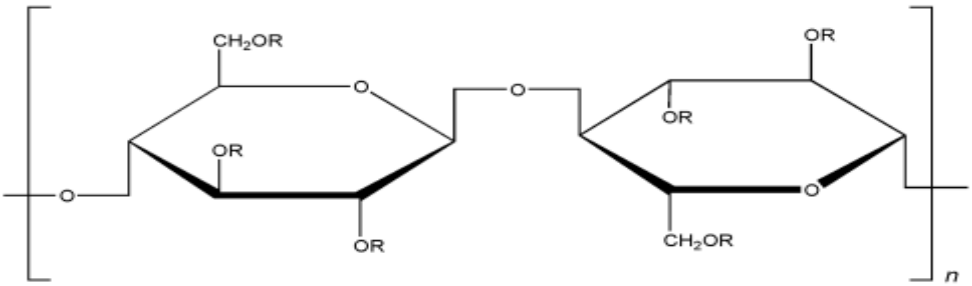


Fig3.2.c: Structure of Methocel

Functional categories **:** Tablet binder, Coating agent, Film former stabilizing agent, Suspending agent, Viscosity increasing agent.

Solubility **:** It is soluble in cold water but insoluble in Chloroform, ethanol (95%) & ether but Soluble in mixture of ethanol & dichloromethane mixture of methanol & dichloromethane, mixture of alcohol.

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous Hypromellose.

P^H : 5.5 – 8.0 for a 1 % w/w aqueous solution.

Melting point: Brown at 190- 200^{0}C; chars at 225-230^{0}C.

Specific gravity: 1.26

Loss on drying **:** < 5.0 %

Density (bulk) **:** 0.341 gm / cm^3

Density (tapped) : 0.557 gm / cm^3

Stability and storage Conditions: Hypromellose powder is a stable material although it is hydroscopic after drying. Solutions are stable at pH 3.Upon heating and cooling hypromellose undergoes a reversible gel transformation. Viscosity of solutions is reduced by increasing the temperature. Depending upon the grade and concentration of material, the gel point is 50-90°C. It is stable material although it is hygroscopic after drying. It should be stored in a well -closed container in a cool dry place.

Incompatibilities: Incompatible with some oxidizing Agents.

Application: It is widely used oral & topical pharmaceutical formulations primarily used in film-coating, binder in tablets in concentrations of 2 – 5 %.

D. SODIUM BICARBONATE[45]

Non-proprietary names: BP/EP: sodium bicarbonate

Synonym: Baking soda, e-500, and monosodium carbonate.

Chemical name: carbonic acid, monosodium salt, monosodium carbonate.

Empirical formula: NaHCO3

Molecular weight: 84.01

Category: alkalizing agent, therapeutic agent.

Description: it is an odorless, white crystalline powder with slight alkaline taste.

Acidity/ alkalinity: pH 8.3 for freshly prepared 0.1m aqueous solution at 250c.

Density: 2.159 g/cm3

Solubility: Soluble in water, practically insoluble in ethanol.

Stability and storage: Sodium bicarbonate is stable in dry air but slowly decomposes in Moist air and should therefore be stored in well-closed container in a cool dry place.

Safety: Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

Applications

1. Employed as a source of carbon dioxide in effervescent tablets and granules.
2. Also used to buffer the drug molecules that are weak acids.
3. Used in solutions as buffering agent.

E. MICROCRYSTALLINE CELLULOSE

Synonyms : Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460;Emcocel; Ethispheres;

Chemical Name: Cellulose

Empirical Formula: $(C_6H_{10}O_5)n$ where n ≈ 220.

Molecular Weight: ≈36 000

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

USES OF MICROCRYSTALLINE CELLULOSE

Table 3.2.a: Uses of MCC

Use	Concentration (%)
Adsorbent	20–90
Anti adherent	5–20
Capsule binder/diluents	20–90

Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Description: Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and application.

Melting point: 260–270°C.

Moisture content: Typically less than 5% w/w. microcrystalline cellulose is hygroscopic.

Particle size distribution: Typical mean particle size is 20–200 μm.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids.

Safety: It is widely used in oral pharmaceutical formulations is generally regarded as a relatively nontoxic and nonirritant material. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

F. MAGNESIUM STEARATE

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Molecular weight: 591.34.

Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$

Functional category: Tablet and capsule lubricant

Applications in pharmaceutical formulation technology: It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 % and 5.0 % w/w.

Description: Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Crystalline forms: High purity magnesium stearate has been isolated as a trihydrate, dihydrate and an anhydrate.

Flowability: Poorly flowing, cohesive powder.

Melting range: 117-150^{o} C (commercial samples) 126-130^{o} C (high purity magnesium stearate).

Solubility: Practically insoluble in ethanol, ethanol (95 %), ether and water; slightly soluble in warm benzene and warm ethanol (95 %).

Stability and Storage Conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with strong acids, alkalis and iron salts strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloid salts.

Method of manufacture: Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium Chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

Safety : Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

G. TALC

Synonyms : Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Functional category: Anticaking agent; Tablet and Capsule diluent; Tablet and Capsule lubricant.

Applications in pharmaceutical formulations: Used in oral solid dosage formulations as a lubricant and glidant (1-10%), Dissolution retardant in the development of controlled release products. Used as dusting powder (90.0-99.0), Lubricant properties in cosmetics and food properties, Talc is widely used in oral solid dosage formulations as lubricant and diluents.

Description: Talc is a very fine, white to greyish-white coloured, odorless, impalatable crystalline powder. It adheres to the skin readily. Insoluble in water, dilute acids, alkalis and organic solvents.

Moisture content: Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Stability and storage conditions: Talc is a stable material and may be sterilized by heating at 160^0C for not less than 1 hr. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Talc is incompatible with quaternary ammonium compounds.

Method of manufacture: Talc is a naturally occurring hydropolysilicate mineral found in many parts of the world including: Australia; China; Italy and the US. Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as: asbestos (tremolite), carbon, dolomite, iron oxide and various other magnesium and carbonate minerals. Following this process the talc is finely powdered, treated with dilute Hydrochloric acid, washed with water and then dried. It is the processing variables of agglomerated talc that strongly influence its physical characteristics.

Safety: Talc is mainly used in tablet and capsule formulations. Following oral ingestion talc is not absorbed systemically and may thus be regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas, hence it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants**.**

3.3. PREFORMULATION STUDIES

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. Characterization of the drug is a very important step at the Preformulation phase of product development followed by studying the properties of the excipients and their compatibility.

3.3.1 MICROMERITIC PROPERTIES

a. ANGLE OF REPOSE

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula

$\theta = \tan^{-1}$ (h/r) = $\tan^{-1}$ (height of pile/0.5base)

Where, θ = Angle of repose; h = Height of the pile; r = Average radius of the powder cone.

b. BULK DENSITY

Bulk Density of a compound varies substantially with the method of crystallization, milling or formulation. Usually, bulk density is of great importance when one considers the size of a high-dose drug product or homogeneity of a low-dose formulation. The homogeneity of a low-dose formulation in which there are large differences in drug and excipient could lead to segregation).

Apparent Bulk density (gm/ml) of the drug was determined by pouring (preseived 40-mesh) gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Bulk density = Weight of powder / Bulk volume

Limits: It has been stated that the bulk density values having less than 1.2 g/cm3 indicates good packing and values greater than 1.5 g/cm3 indicates poor packing.

c. TAPPED DENSITY

Tapped densities the drug was determined by pouring gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density = Weight of powder / Tapped volume

d. COMPRESSIBILITY INDEX (CARR'S INDEX)

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powders tend to possess free flowing properties. A useful

empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

e. HAUSNER'S RATIO: Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's Ratio = Tapped density /Bulk density

Table no.3.3.a: Acceptance Criteria Of Flow Properties

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

3.3.2. DRUG-EXCIPIENTS COMPATIBILITY STUDIES BY FTIR

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra-Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

FTIR STUDIES

FTIR studies were performed on drug and the optimized formulation using FTIR (Agilent technologies, India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

DIFFERENTIAL SCANNING STUDIES

Differential scanning calorimetry or DSC is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature

increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned**.**

3.4 FORMULATION DEVELOPMENT

3.4.1 FORMULATION OF NAPROXEN IMMEDIATE RELEASE LAYER: BY DIRECT COMPRESSION METHOD

PROCEDURE

Direct compression: Accurately weighed amounts of drug, super disintegrants, binder and diluents were mixed geometrically in a mortar. This mixture was passed through No.40 sieve. The powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 9 mm round, flat-faced punches.

Table: 3.4.1a Formulation of immediate release layer Naproxen

Ingredients	IR1	IR2	IR3	IR4	IR5	IR6
Naproxen Sodium (mg)	100	100	100	100	100	100
Explotab(mg)	5	10	15	-	-	-
PolyplasdoneXL(mg)	-	-	-	5	10	15
Mg. Stearate(mg)	2	2	2	2	2	2
Talc(mg)	2	2	2	2	2	2
MCC PH 102(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight mg	200	200	200	200	200	200

Optimisation of Sodium bicarbonate

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table 3.4.1b: optmisation of sodium bicarbonate concentration

Ingredients	EF1	EF2	EF3
Sumatriptan(mg)	50	50	50
METHOCEL(mg)	50	50	50
$NaHCO_3$(mg)	5	10	15
Colour (Sunset yellow) (mg)	2	2	2
Mg.Stearate(mg)	2	2	2
Talc(mg)	2	2	2
MCC pH 102 (mg)	Q.S	Q.S	Q.S
Total weight(mg)	200	200	200

FORMULATION OF SUSTAINED RELEASE LAYER

BY DIRECT COMPRESSION METHOD: Accurately weighed amounts of drug, sustained release polymer, binder and diluents were mixed geometrically in a mortar. This mixture was passed through No.40 sieve. The powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 9 mm round, flat-faced punches.

Table 3.4.1c: Formulation composition for sustained release layer

Formulation No.	**SR1**	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**
Sumatriptan (mg)	50	50	50	50	50	50
Methocel(mg)	12.5	25	50	-	-	-
$NaHCO_3$(mg)	15	15	15	15	15	15
Mg. Stearate (mg)	4	4	4	4	4	4
Talc (mg)	4	4	4	4	4	4
MCC PH 1029mg	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight(mg)	200	200	200	200	200	200

3.4.2. FORMULATION OF OPTIMISED BILAYER TABLETS OF NAPROXEN AND SUMATRIPTAN

PROCEDURE: The Gastroretentive Bilayered Floating Tablets were prepared by direct compression method and wet granulation method. The immediate release layer granules were prepared by direct compression technique and the controlled release layer is prepared by wet granulation technique. The controlled release layer mixture was compressed in 8mm flat faced punches on a Rimek tablet press. Before final compression immediate release layer poured on sustained release layered.

Table 3.4.2 a: formulation of optimized bilayer tablet

S.NO.	**INGREDIENTS**	**IR5**	**SR3**	**OPTIMISED FORMULA**
1.	Naproxen (mg)	100	--	100
2.	Sumatriptan (mg)	--	50	50
3.	Polyplasdone eXL (mg)	10	--	12.5
4.	methocel (%)	-	50	50
5.	microcrystalline cellulose (mg)	Q.S.	Q.S.	Q.S.
6.	magnesium stearate (mg)	2	4	6
7.	talc (mg)	2	2	4
8.	Sodium bicarbonate (mg)	-	15	15
9	Colouring (mg)agent(saffron)	-	4	4
10	Total weight (mg)	200	200	400

3.5. ANALYTICAL METHOD

3.5.1 ANALYTICAL METHOD FOR ESTIMATION OF NAPROXEN IR

a) Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve

10mg of Naproxen pure drug was dissolved in 10ml of methanol (primary stock solution). From primary stock, 1ml of solution was taken and make up with 10ml of 0.1N HCl (100µg/ml) from this secondary stock solution 0.5, 1, 1.5, 2 and 2.5 ml was taken and diluted up to 10 ml with 0.1N HCl to obtain 5, 10 ,15 ,20 and 25µg/ml concentration. The absorbance of the above dilutions was measured at 227 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. Similar procedure was followed for sumatriptan at 271 nm.

STANDARD GRAPH OF NAPROXEN

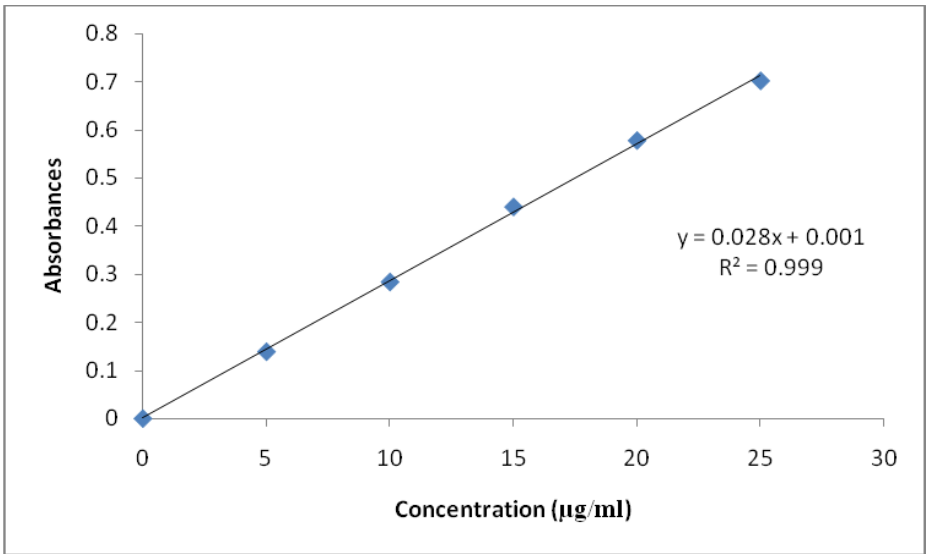


Figure 3.5 a: Standard graph

Table 3.5 a: Standard graph data

Conc [µg/mL]	Abs
0	0
5	0.139
10	0.284
15	0.44
20	0.578
25	0.702

STANDARD GRAPH OF SUMATRIPTAN

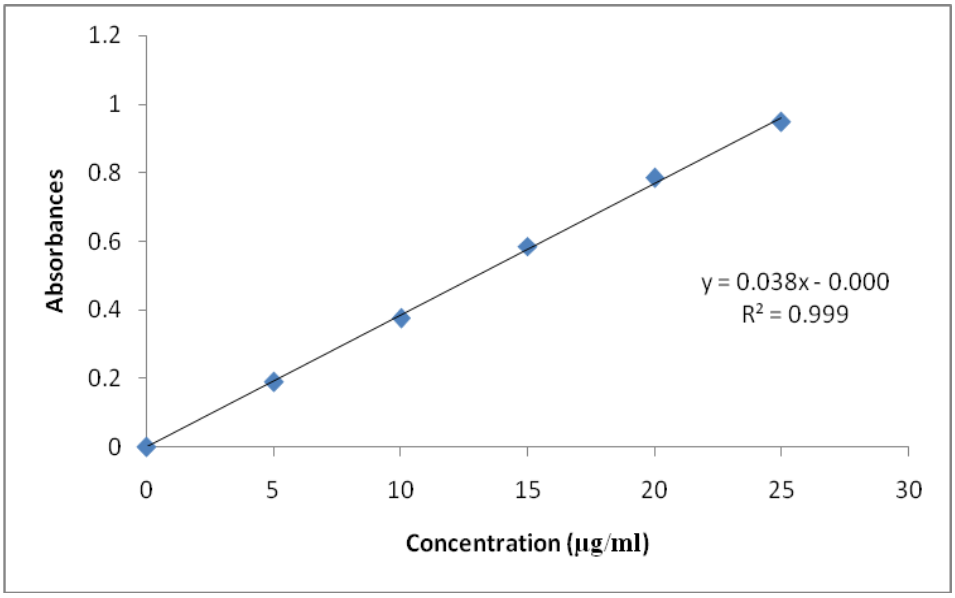


Figure 3.5 b: Standard graph

Table 3.5 b: Standard graph data

Conc [µg/mL]	Abs
0	0
5	0.189
10	0.376
15	0.585
20	0.784
25	0.947

3.6 EVALUATION OF GASTRORETENTIVE BILAYER FLOATING TABLETS OF NAPROXEN AND SUMATRIPTAN[38, 39, 40]

The prepared formulations were evaluated for the following parameters:

1. THICKNESS

The thickness of the tablets was measured by Vernier calipers. It is expressed in **mm**.

FIG. 3.6.a.- Vernier Calipers

2. HARDNESS TEST

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm2.

Fig-3.6.b.: Monsanto Hardness tester

3. FRIABILITY TEST

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W) final. The % friability was then calculated by

%F = initial weight-final weight/initial weight x 100

Where,

% F= Friability in percent

% friability of tablets <1% were considered acceptable.

Fig-3.6.c.: Roche Friabilator

4. WEIGHT VARIATION TEST

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of tablet by U.S. Pharmacopoeia.

Table no.3.6.a: I.P limits for weight variation

Standard limit value in weight variation test Average Weight of a tablet	Percentage Deviation
130mg or less	±10
>130mg and <324mg	±7.5
324mg or more	±5.0

5. IN VITRO BUOYANCY STUDIES

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT).The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1 N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time

6. DRUG CONTENT UNIFORMITY

FOR IMMEDIATE RELEASE NAPROXEN TABLETS

Tablet containing drug is dissolved in 100 ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1 ml of filtrate was taken

in 50 ml of volumetric flask and diluted up to mark with 0.1N HCl and analyzed spectrophotometrically at 282nm for sustained release layer of Naproxen.

FOR SUSTAINDE RELEASE SUMATRIPTAN TABLETS

Ten tablets were weighed and powdered and 250mg equivalent weight of Sumatriptan was accuarately weighed and transfered in 100ml volumetric flask. It was dissolved and made up the volume with 0.1N HCl pH- 1.2. Subsequently the solution was filtered and suitable dilution were made and analyzed at 275nm using UV-Visible spectroscopy.

7. DISINTEGRATION TEST

By using disintegration apparatus, tablets were tested for disintegration time at 37± 0.5^0C taking distilled water as medium.

Fig.3.6.d.-Disintegration Apparatus

9. IN VITRO DISSOLUTION STUDIES

In-vitro release studies were carried out USP II paddle type dissolution test apparatus. 900 ml of 0.1 N HCl (PH 1.2) was filled in dissolution vessel and the temperature of the medium were set at 37° C ± 0.1°C.The speed was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time intervals and analysed by using UV- Spectroscopy.

Dissolution study for immediate layer

900ml of 0.1N HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hour and

then the medium 0.1 N HCl was taken and process was continued at 50 rpm. At definite time intervals of 5 ml of the medium was withdrawn, filtered and again 5ml fresh medium was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 227 nm using UV-spectrophotometer.

Dissolution study for sustained floating layer

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of medium was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with medium and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer.

Dissolution study for Bilayer Tablets

The dissolution study of bilayer tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus 900ml of 0.1N HCl was used as dissolution medium agitated at 50 RPM, at temperature of $37^{o}\pm 0.5^{o}$C. 5 ml samples were withdrawn at 5, 10, 15, and 20 min to estimate the release of Naproxen, and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hrs for estimating Sumatriptan release. The samples were analyzed for Naproxen and Sumatriptan by UV Spectrophotometry at their respective λ max values. The samples collected for first twenty minutes were analyzed for Naproxen content at 227 nm in UV spectrophotometer by keeping the solution containing Sumatriptan formulation as blank to minimize the interference. The samples collected for 0.5 – 12 hrs were analyzed for the release of Sumatriptan at 227nm in UV spectrophotometer by keeping the solution containing Naproxen formulation as blank to minimize the interference.

KINETIC MODELS

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t/ M_\infty = K t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

4 RESULTS AND DISCUSSION

DRUG EXCIPIENT COMPATIBILITY STUDIES BY FTIR:

FTIR OF NAPROXEN

Table 4.0.a : KBr disc value of Naproxen

S.No	KBr disc value (cm^{-1})	indication
1	793	benzene
2	1157	OH group
3	2893	Secondary OH

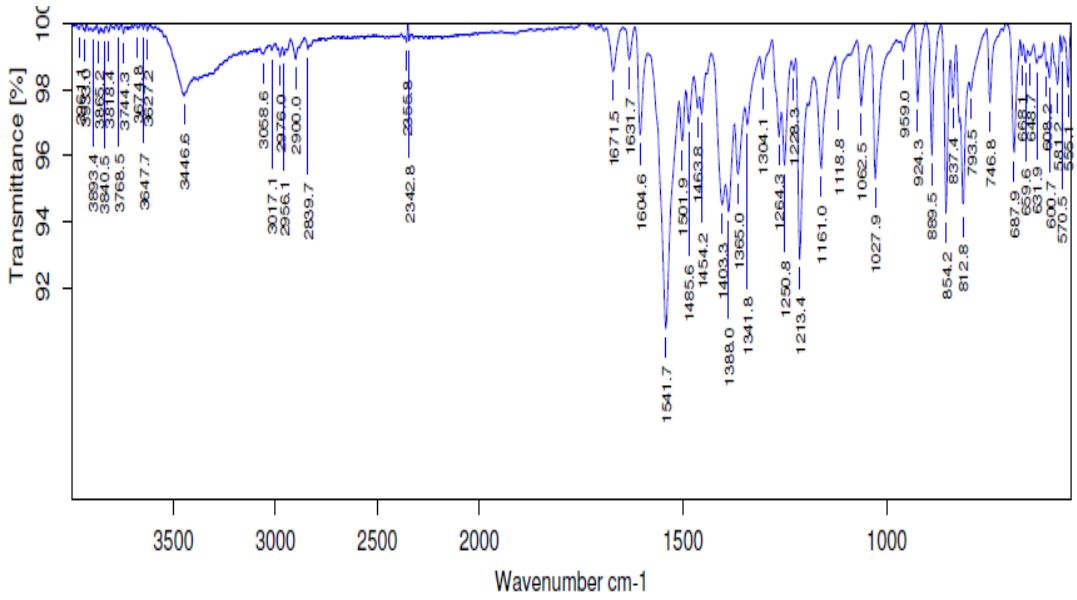


Fig 4.0. a : FTIR spectrum of Naproxen

FTIR OF SUMATRIPTAN

Table 4.0. b: KBr disc value of Sumatriptan

KBr disc value (cm^{-1})	Indication
1266	Amine
777	Benzene
2682	Nitrile
3359	Methyl

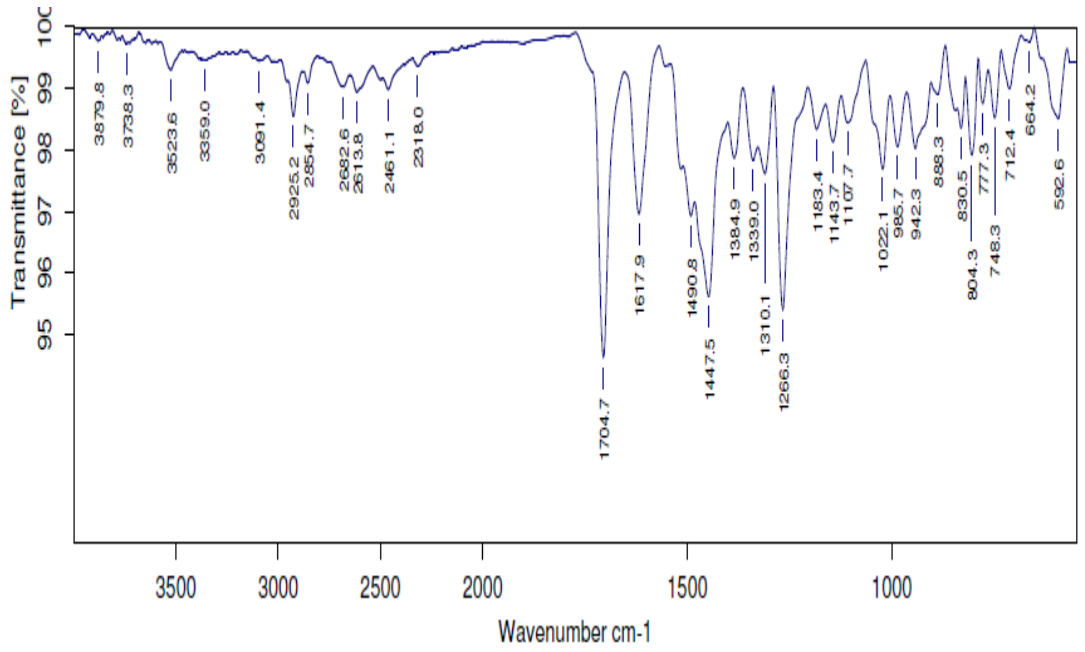


Fig 4.0.b : FTIR spectrum of Sumatriptan

FTIR OF POLYPLASDONE

Table 4.0.c: KBr disc value of Polyplasdone

KBr disc value(cm^{-1})	Indication
745	Ketone
1657	Ehthnyl
745	alkyne

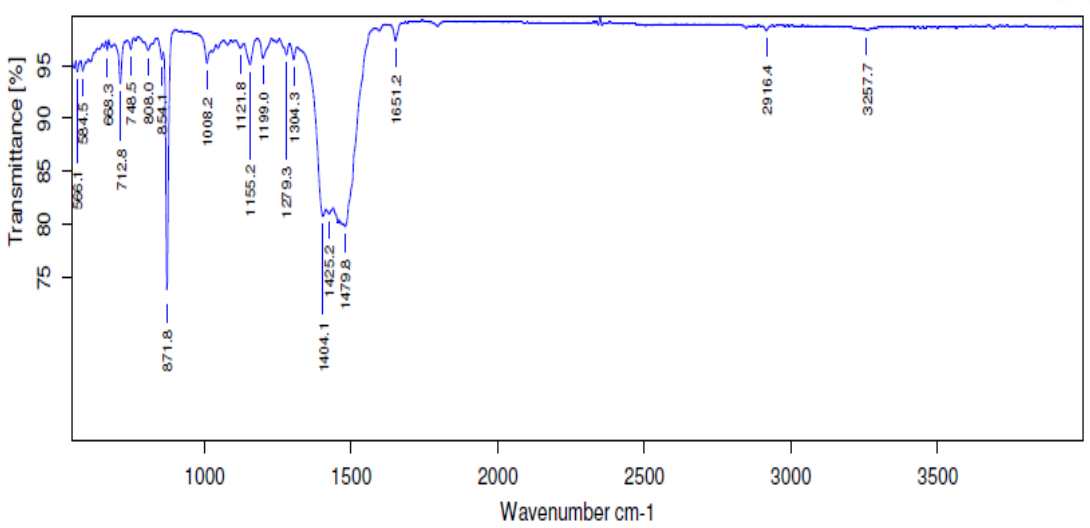


Fig 4.0.c: FTIR spectrum of Polyplasdone XL

FTIR OF METHOCEL

Table 4.0.d: KBr disc value of Methocel

KBr disc value (cm^{-1})	Indication
925	Alkyne
1367	Methyl
1681	C=0
3031	=C-H
3765	OH

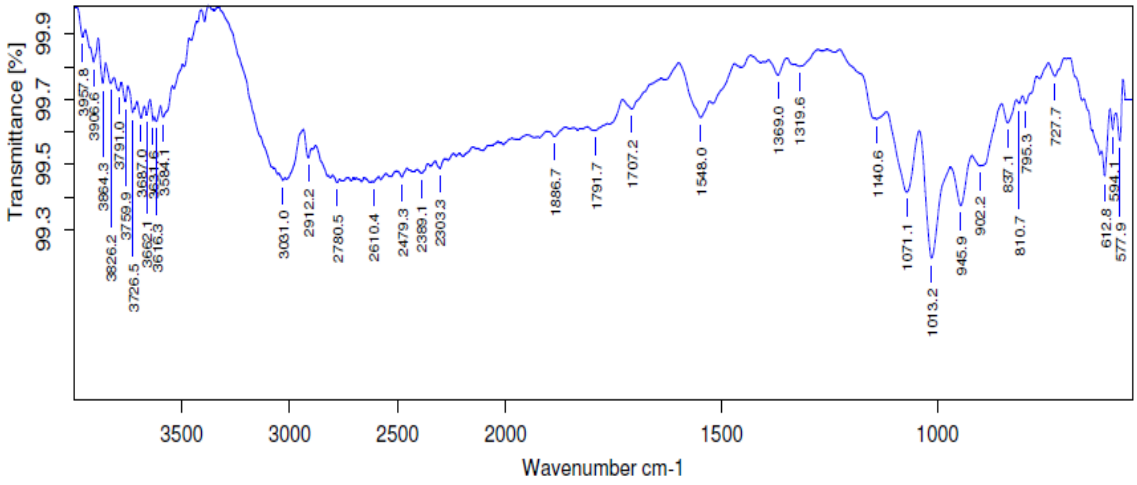


Fig 4.0.d: FTIR spectrum of Methocel

FTIR OF FORMULATION

Table 4.0.e KBr disc value of formulation

KBr disc value (cm^{-1})	Indication
764	Benzene
747	RCH=CHR
1265	C-N amine
1366	Methyl
1644	Ketone
2845	Nitrile
3441	OH

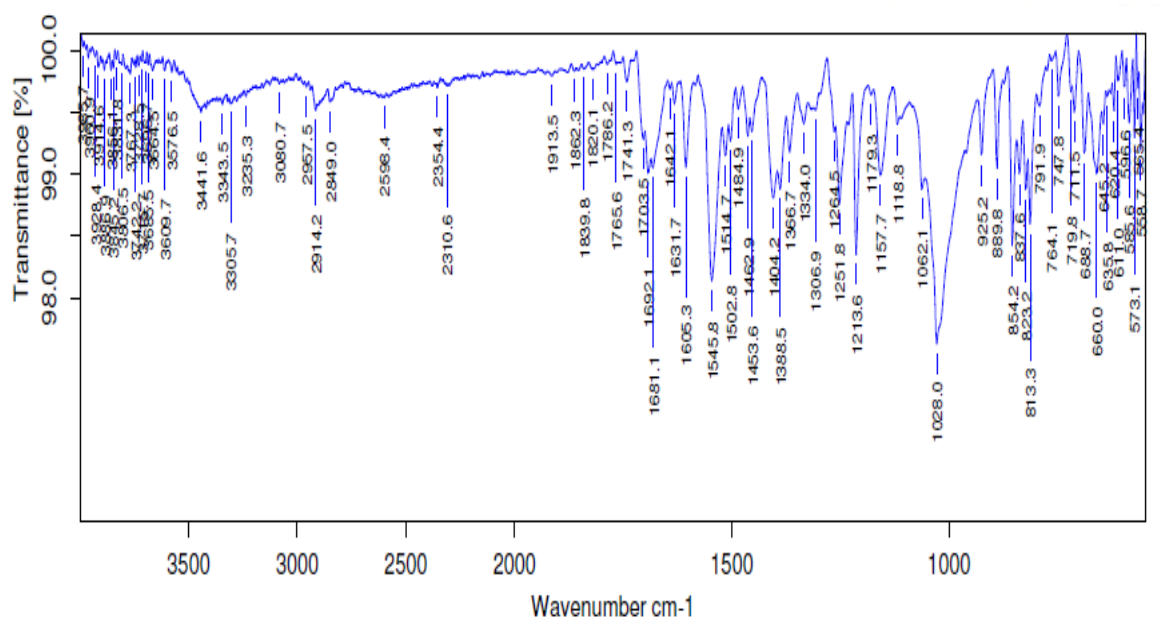


Fig 4.0.e : FTIR spectrum of Formulation

DISCUSSION

FTIR ANALYSIS OF NAPROXEN

FTIR analysis of Naproxen was obtained using KBr pellet technique and the peaks mentioned in standards are compared with those obtained. The peaks were found to be at 793 cm^{-1} indicates presence of benzene ring, 1157 cm^{-1} presence of OH group, 2893cm^{-1} indicates the presence of secondary OH group.

FTIR ANALYSIS OF SUMATRIPTAN

The FTIR of Sumatriptan was obtained in the range of 400-4000cm^{-1} using KBFR pellet technique and the peaks obtained are as follows presence of amine group at 1266cm^{-1}, at 777 cm^{-1} benzene ring, at 2682cm^{-1} showed presence of nitrile group, at 3359cm^{-1} C-H stretching of methyl group.

FTIR OF POLYPLASDONE XL

The FTIR of polyplasdone XL was carried out using KBr pellet technique and peaks obtained were compared with that of the standard. The FTIR studies showed C=O stretching vibration at 1657 cm^{-1} from ketone group, 3257 cm^{-1} showed the presence of alkyne group and CRH=RCH stretching at 745cm^{-1}.

FTIR OF METHOCEL

The FTIR studies of methocel showed the presence of following functional groups.

C-H stretching at 1367 cm^{-1}, 3765 cm^{-1} peak indicating the presence of OH group, at 1681 cm^{-1} presence of C=O group, C-H stretching of alkyl group at 3031 cm^{-1}.

INFERENCE:

The FTIR of pure drugs, excipients and formulation was carried out.. it was found that there is no significant change in the peaks obtained when compared with the formulation. Thus indicating that there is no drug excipient interaction.

DRUG EXCIPIENT COMPATIBILITY STUDIES BY DSC

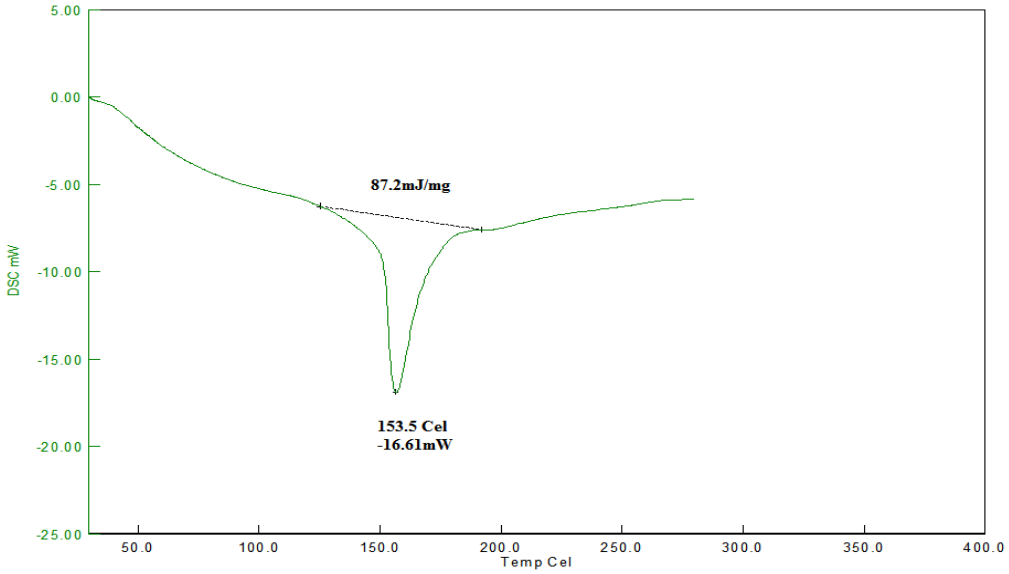


Fig 4.0.f: DSC of Naproxen

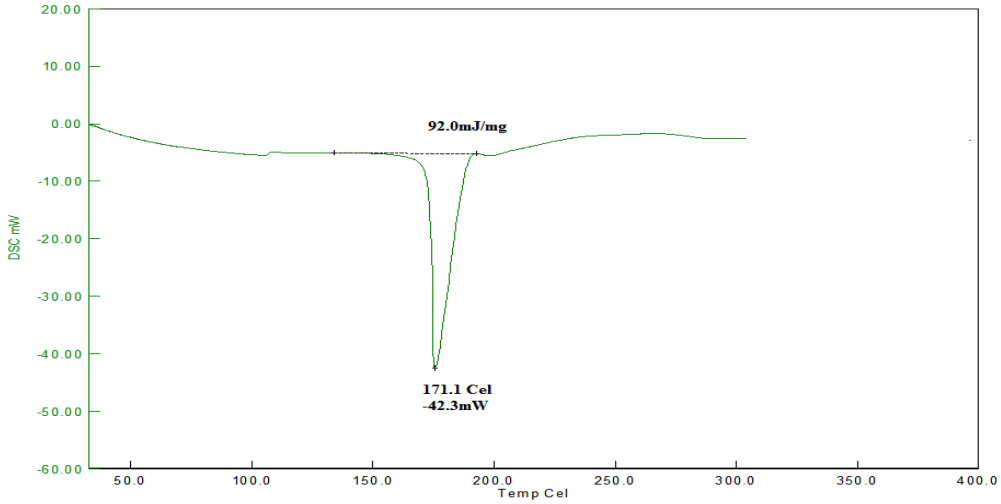


Fig 4.0.g: DSC of Sumatriptan

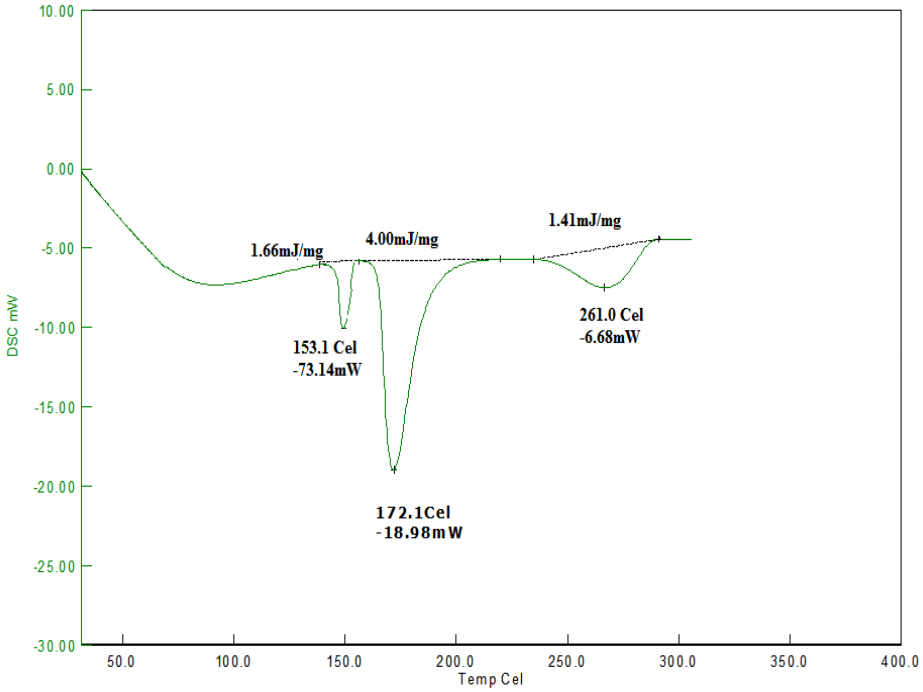


fig 4.0.h: Dsc Of Drug And Excipient

INFERENCE

The compatibility study found that the main thermic peak of pure drug 1 (naproxen) found at 153^{0}C and pure drug 2 (sumaptriptan) was found at 171^{0}C when it was mixed with excipients and made tablet the main endothermic peak of formulation was found to be the same.

It was observed that there is no significant change between the formulation and pure drug. So it indicates that is no the drug is thermodynamically stable.

4.1 PREFORMULATION STUDIES

A. PREFORMULATION STUDIES FOR IMMEDIATE RELEASE LAYER OF NAPROXEN

Table 4.1a: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
IR1	26.01	0.49	0.57	14.03	1.16
IR2	24.8	0.56	0.65	13.84	1.16
IR3	22.74	0.56	0.68	17.64	1.21
IR4	25.33	0.54	0.64	15.62	1.18
IR5	26.24	0.55	0.67	17.91	1.21
IR6	26.12	0.56	0.66	15.15	1.17

DISCUSSION: Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.56 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties. The 2983ptimized batch IR5 has good flow properties.

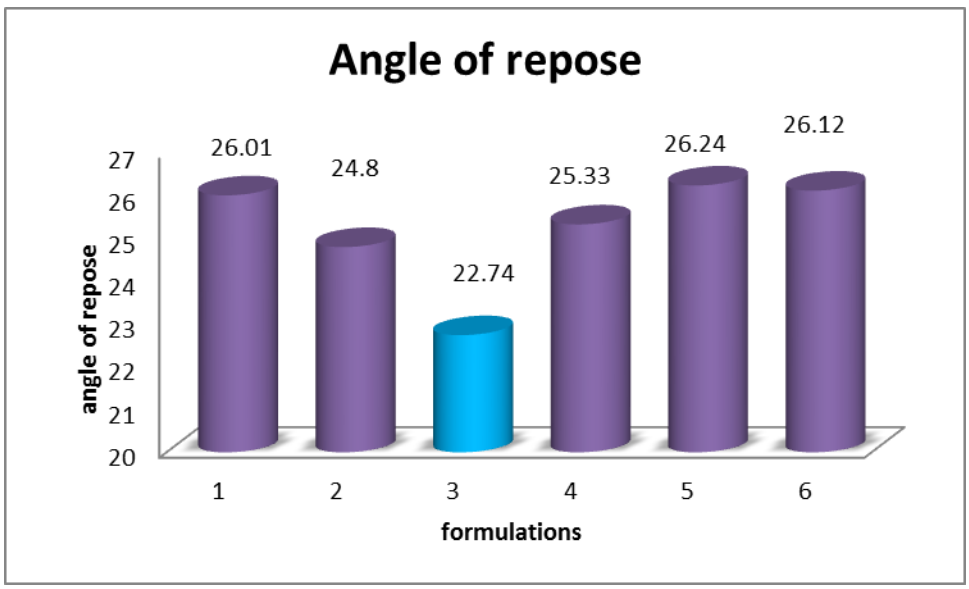


Fig 4.1a : Angle of repose of Naproxen IR tablets

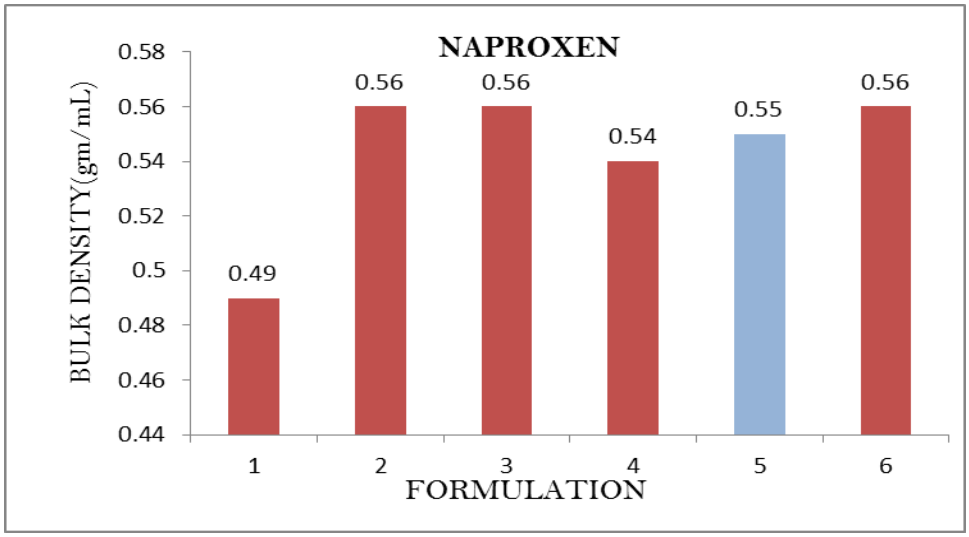


Fig 4.1b: Bulk density of Naproxen IR tablets

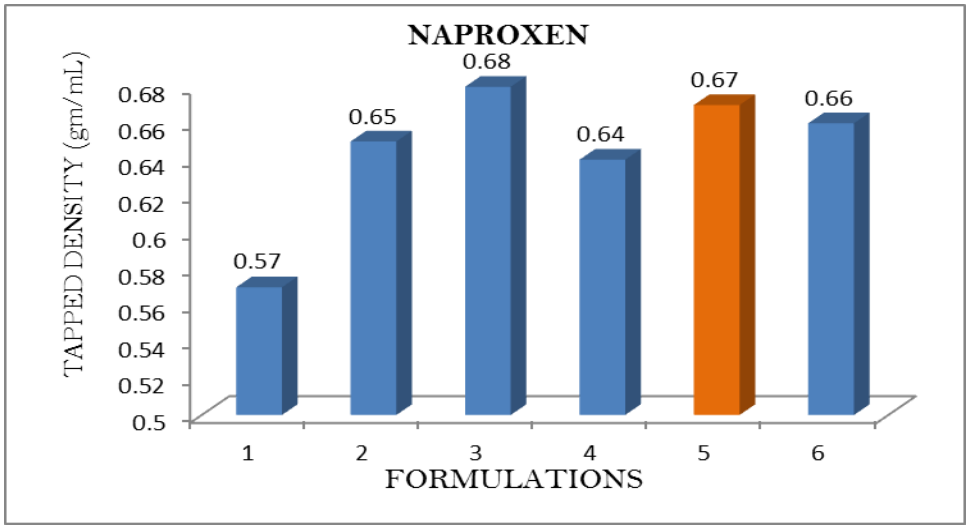


Fig 4.1 c: Tapped density of Naproxen IR tablets

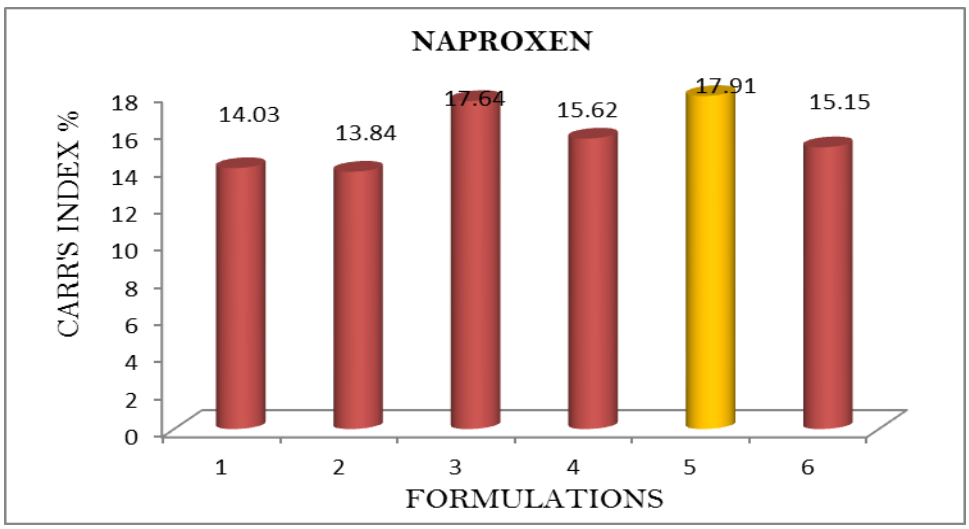


Fig 4.1c : Carrs index of Naproxen IR tablets

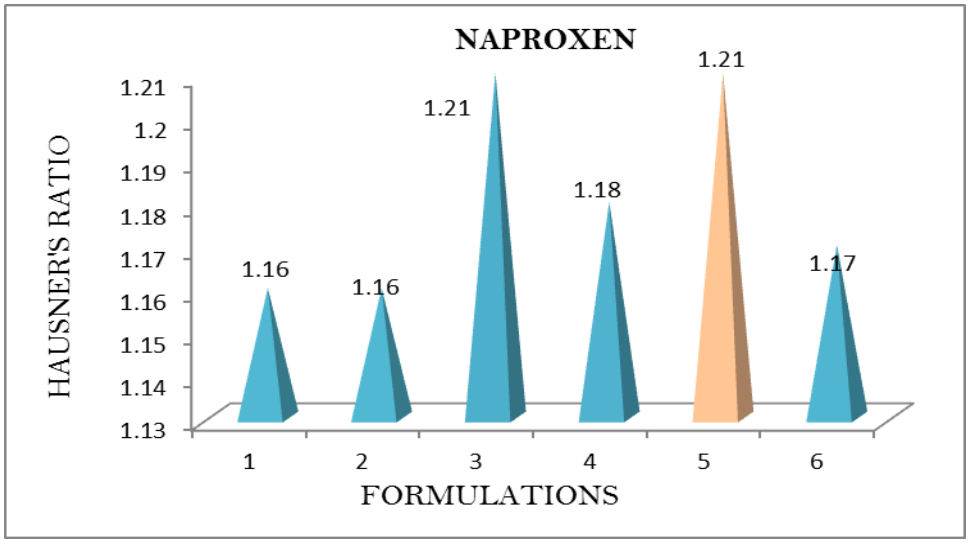


Fig 4.1 d : Hausners ratio of Naproxen IR tablets

B. PREFORMULATION STUDIES FOR SUSTAINED RELEASE LAYER OF SUMATRIPTAN

Table 4.1 b: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
SR1	25.12	0.59	0.66	11.86	1.11
SR2	26.8	0.48	0.54	12.5	1.12
SR3	23.74	0.56	0.66	17.85	1.17
SR4	26.33	0.44	0.55	18.18	1.18
SR5	25.21	0.48	0.57	16.66	1.16
SR6	27.18	0.51	0.59	15.68	1.15

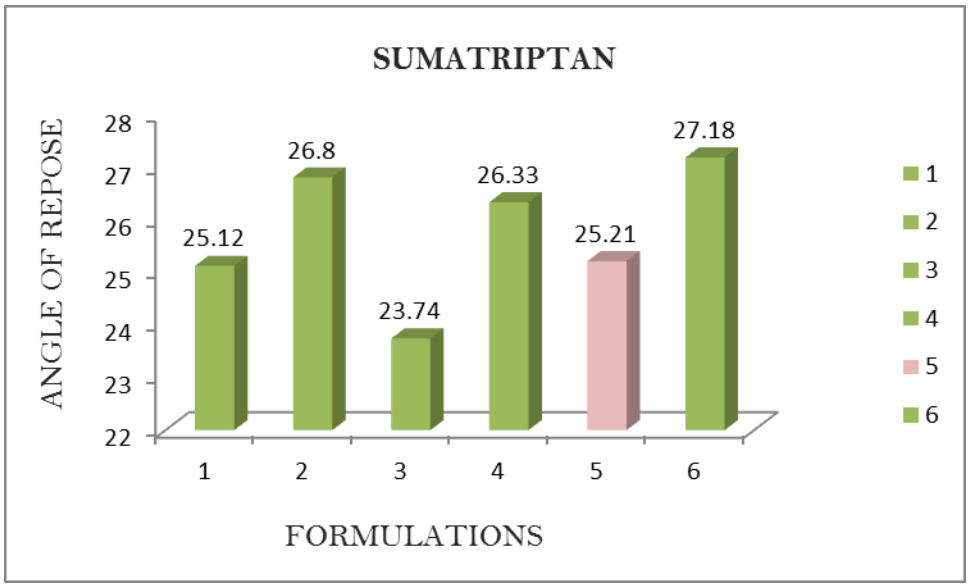


Fig 4.1 e: Angle of repose of Sumatriptan SR tablets

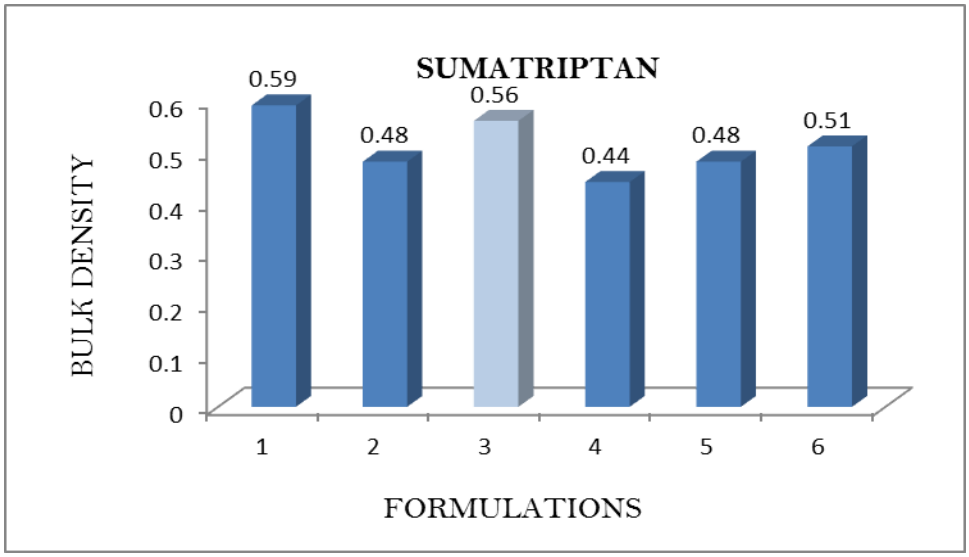


Fig 4.1 f: Bulk density of Sumatriptan SR tablets

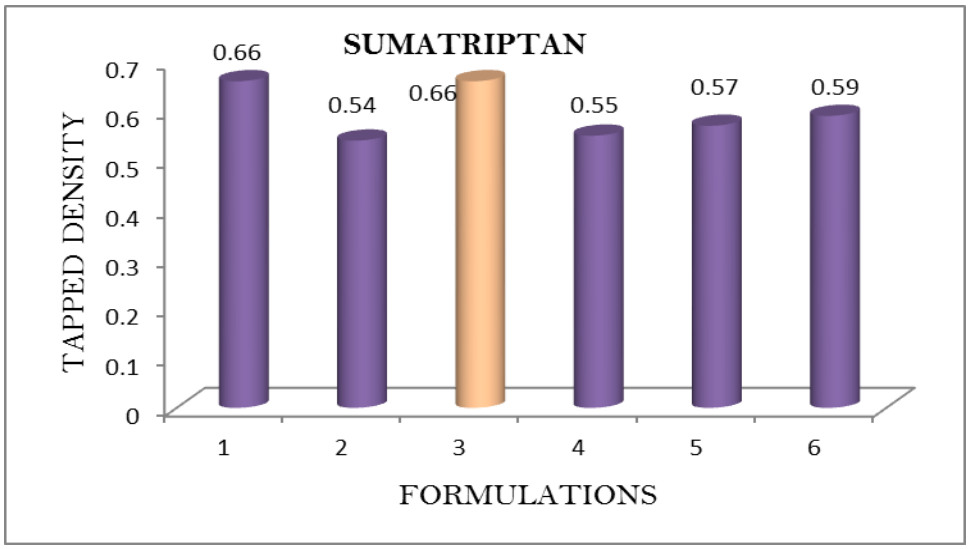


Fig 4.1 g: Tapped density of Sumatriptan SR tablets

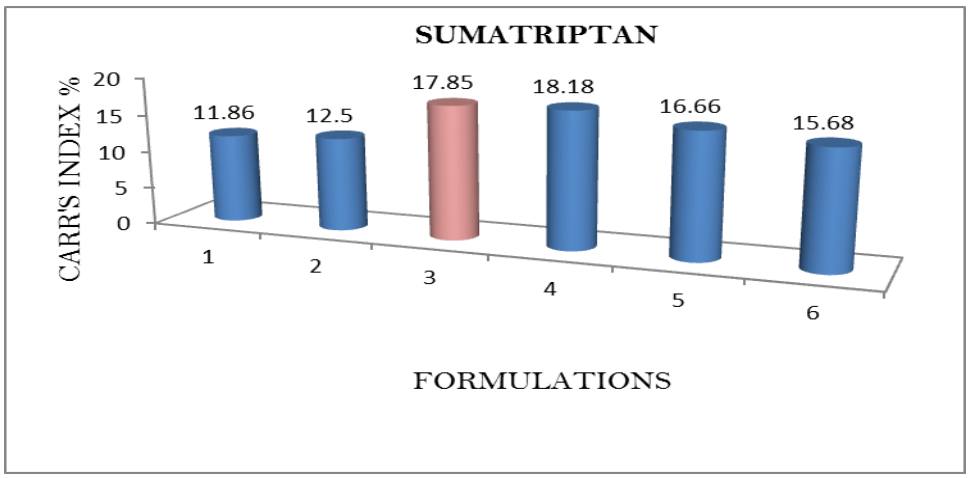


Fig 4.1 h : Carrs index of Sumatriptan SR tablets

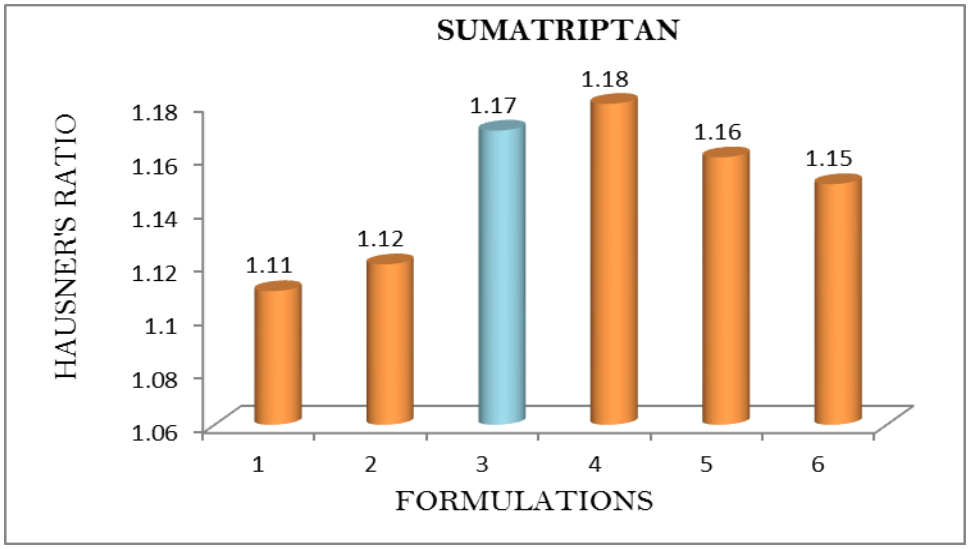


Fig 4.1 i: Hausners ratio of Sumatriptan SR tablets

DISCUSSION: Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48 to 0.59 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.66 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration for Sumatriptan Layer

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 15mg concentration showed less floating lag time of 2 min and the tablet was in floating condition for more than 12 hours.

4.2 EVALUATION OF POST COMPRESSION PARAMETERS

A. EVALUATION TESTS FOR VARIOUS FORMULATIONS OF IMMEDIATE RELEASE LAYER OF NAPROXEN

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
IR1	195.5	2.5	0.52	3.5	99.76
IR2	202.4	2.0	0.54	3.3	97.45
IR3	197.6	2.4	0.51	3.1	98.34
IR4	199.6	2.5	0.55	3.4	99.87
IR5	202.4	2.4	0.56	3.2	99.14
IR6	200.7	2.2	0.45	3.4	97.56

Table 4.2 a: Post compression data of Naproxen IR tablets

All the parameters for IR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

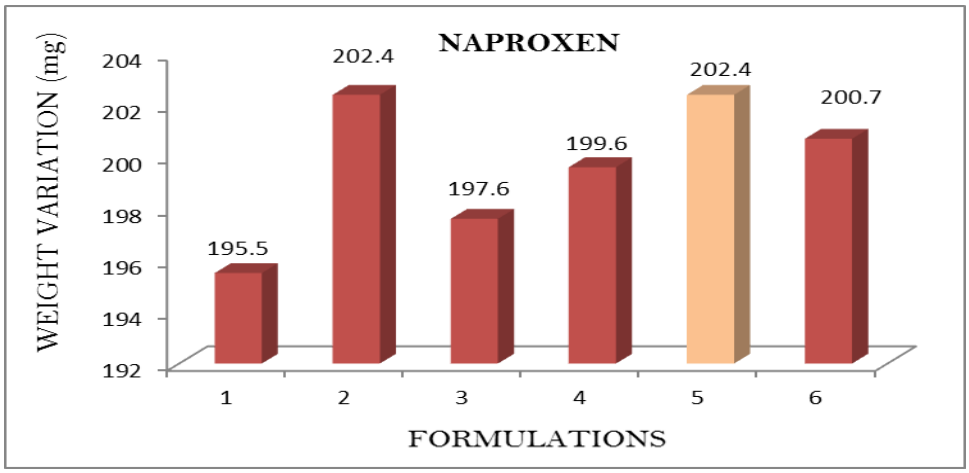


Fig 4.2.a: weigtht varitaion of Naproxen IR tablets

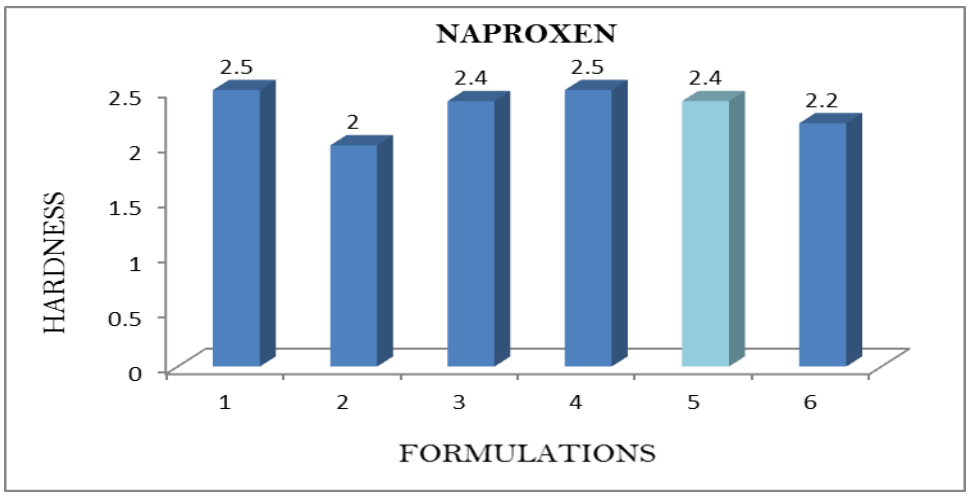


Fig 4.2.b: Hardness of naproxen IR tablets

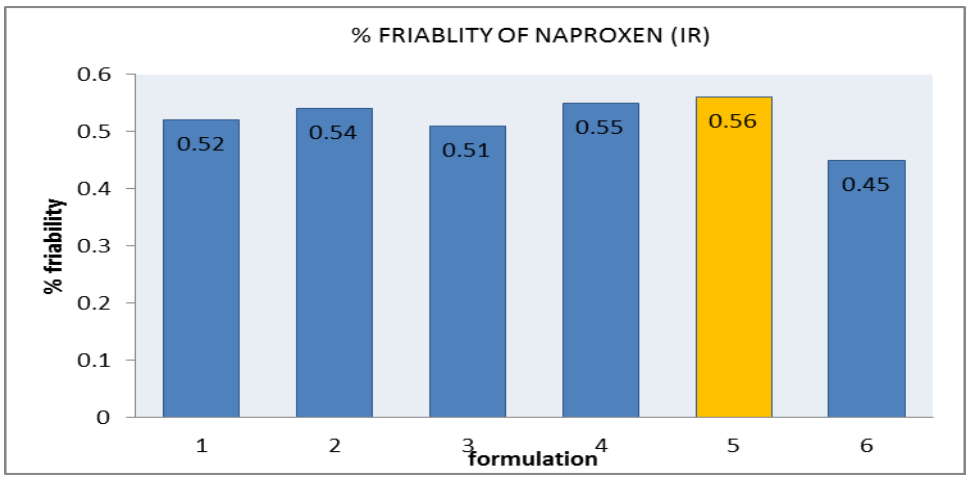


fig 4.2.c: % Friability of Naproxen IR tablets

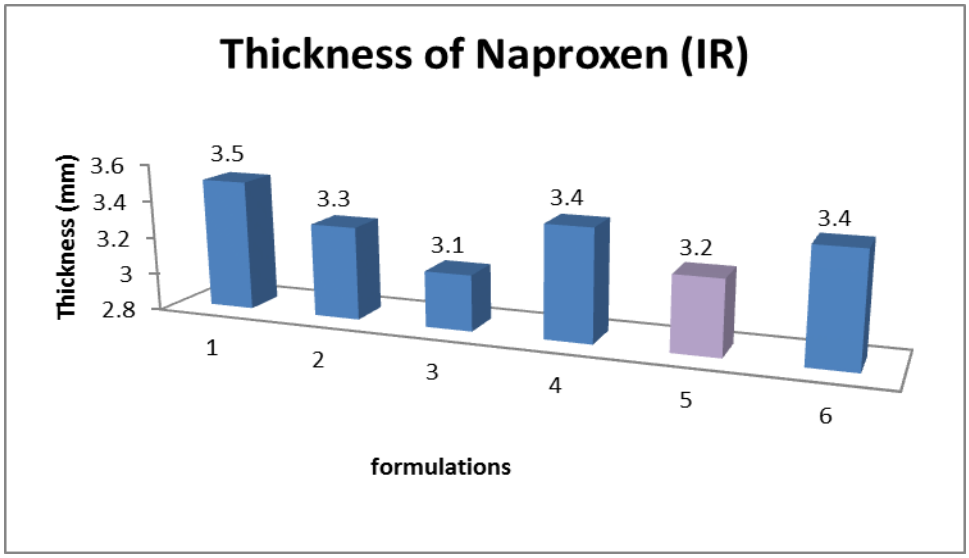


Fig 4.2.d: Thickness of Naproxen IR tablets

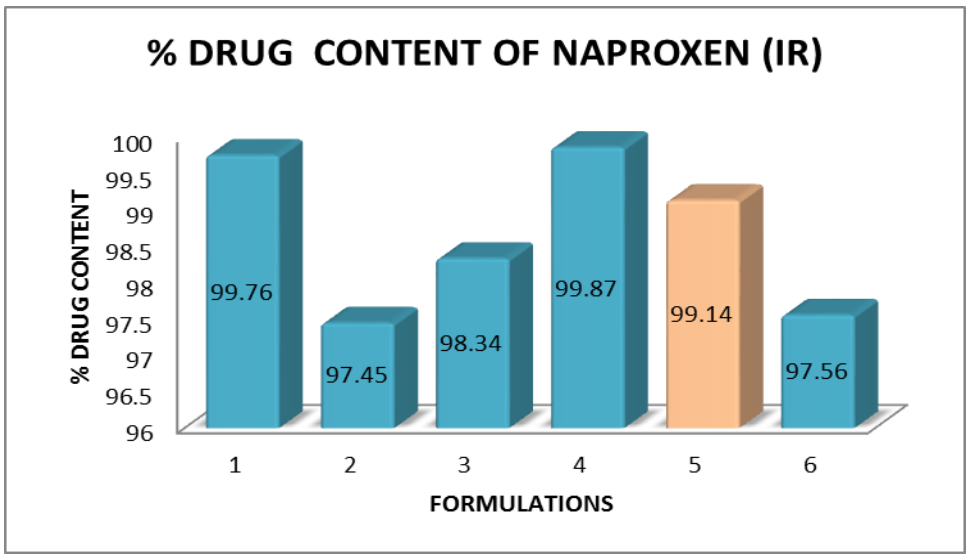


Fig 4.2.e: % Drug content of Naproxe IR tablets

B. EVALUATION TESTS FOR VARIOUS FORMULATIONS OF SUSTAINED RELEASE LAYER OF SUMATRIPTAN

Table 4.2.b: Post compression data of Sumatriptan SR tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
SR1	198.4	3.1	0.61	3.3	98.42	3.5
SR2	199.2	3.2	0.58	3.2	99.65	2.4
SR3	201.3	3.5	0.45	3.4	99.12	2.0
SR4	196.3	3.1	0.61	3.3	98.42	4.5
SR5	198.6	3.3	0.59	3.5	99.65	3.6
SR6	202.4	3.5	0.65	3.4	99.12	3.7

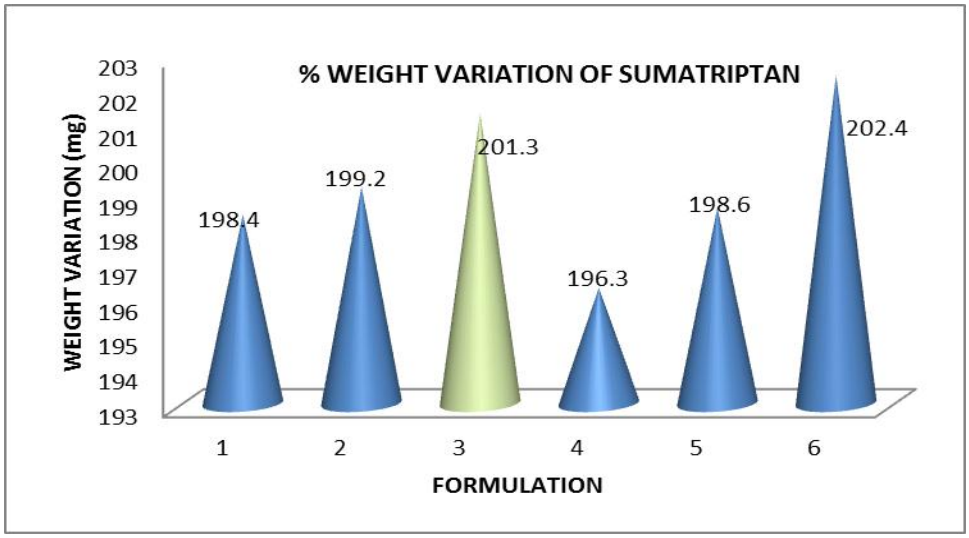


Fig 4.2.f : % weight varittion of Sumatriptan SR tablets

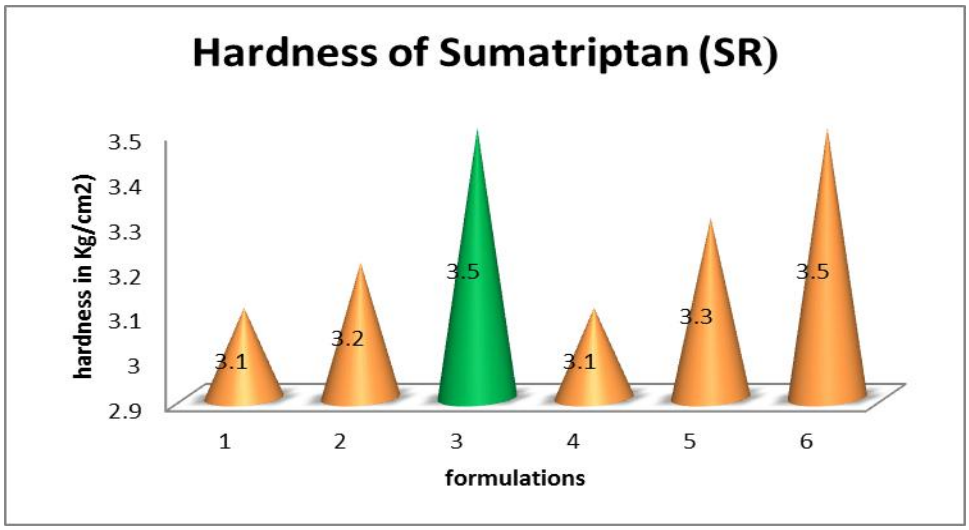


Fig 4.2.g : Hardness of Sumatriptan SR tablets

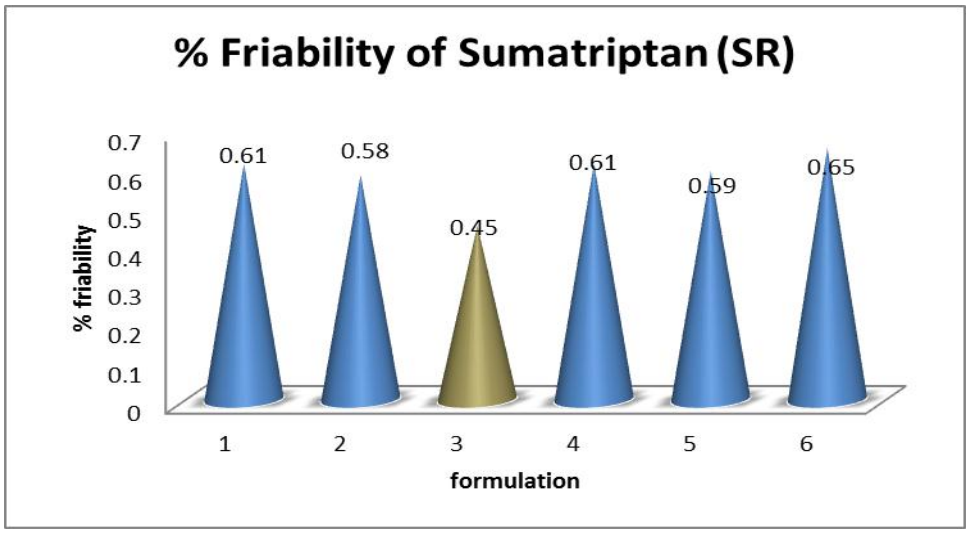


Fig 4.2.h: % friability of Sumatriptan SR tablets

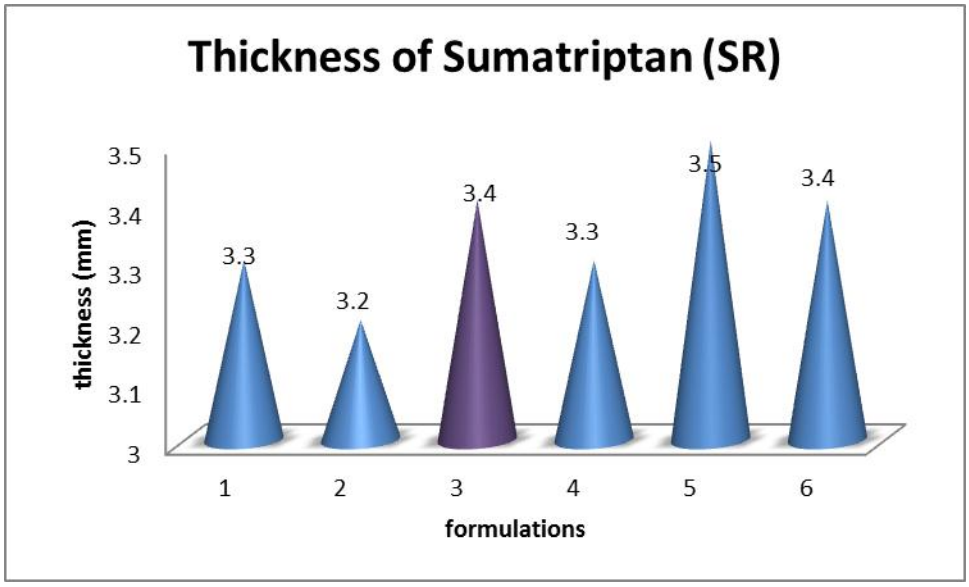


Fig 4.2.i: Thickness of Sumatriptan SR tablets

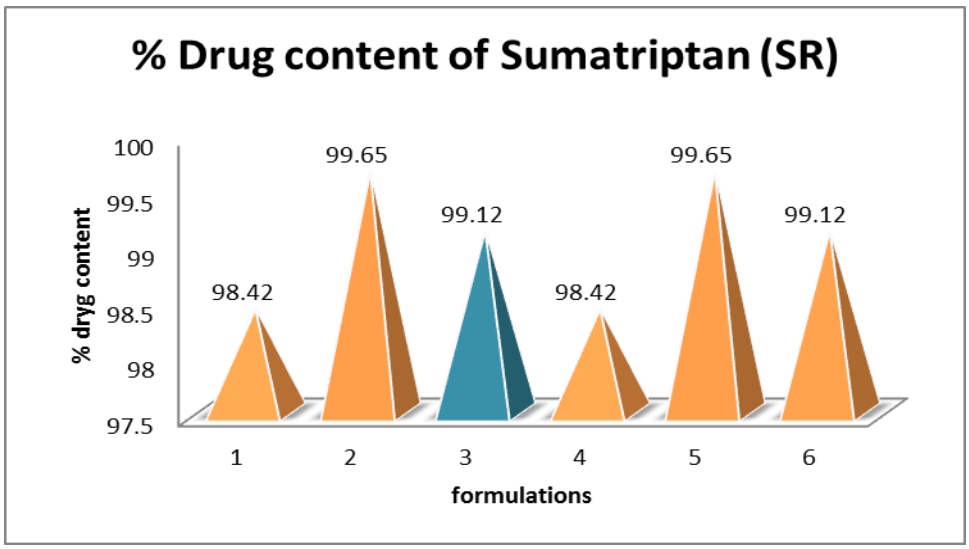


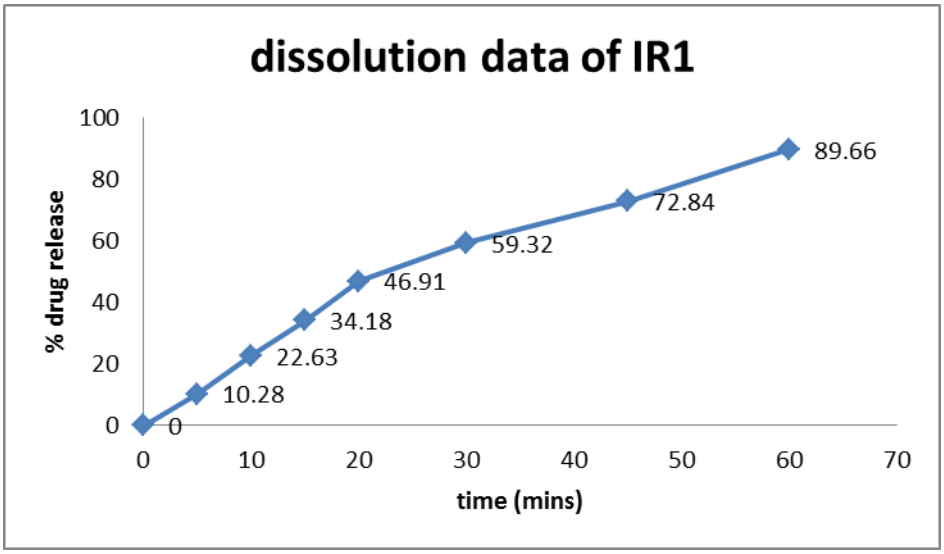
Fig 4.2.j: % Drug content of Sumatriptan SR tablets

***In Vitro* Drug Release Studies for immediate release layer Naproxen**

In-vitro drug release of Naproxen IR1 formulation

Table 4.2.c: Drug release data of IR 1 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	10.28
3	10	22.63
4	15	34.18
5	20	46.91
6	30	59.32
7	45	72.84
8	60	89.66

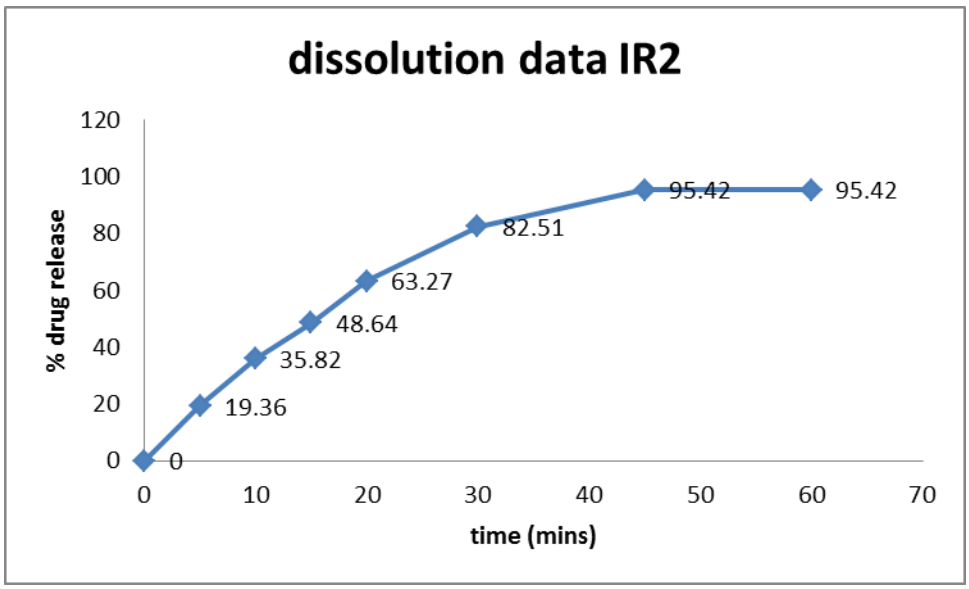


Graph 4.2ac: Drug release data of IR 1 formulation

In-vitro drug release of Naproxen IR2 formulation

Table 4.2.d: Drug release data of IR 2 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	19.36
3	10	35.82
4	15	48.64
5	20	63.27
6	30	82.51
7	45	95.42
8	60	95.42

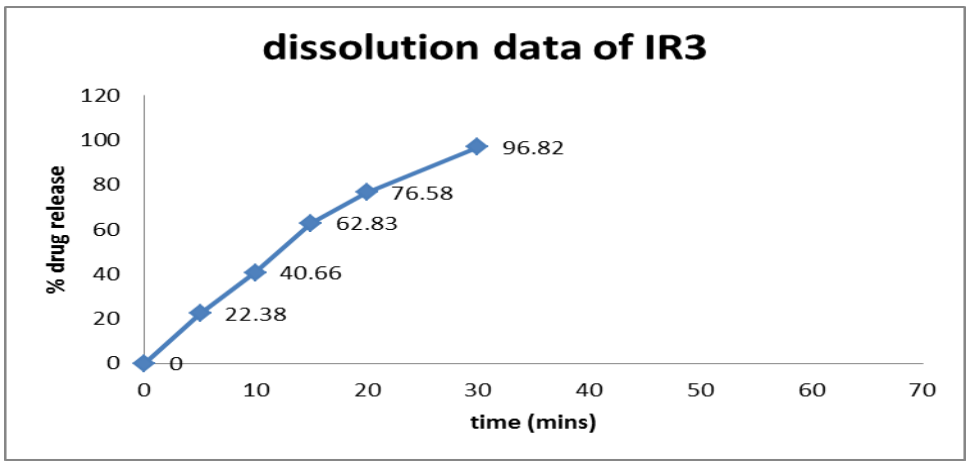


Graph 4.2.b: Drug release data of IR b formulation

In-vitro drug release of Naproxen IR3 formulation

Table 4.2.e: Drug release data of IR 3 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	22.38
3	10	40.66
4	15	62.83
5	20	76.58
6	30	96.82

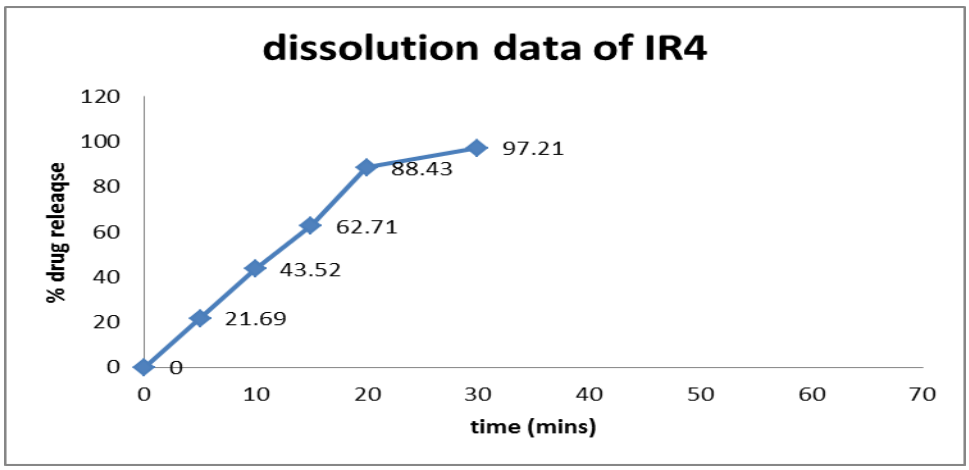


Graph 4.2.c: Drug release data of IR3 formulation

In-vitro drug release of Naproxen IR4 formulation

Table 4.2.f: Drug release data of IR4 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	21.69
3	10	43.52
4	15	62.71
5	20	88.43
6	30	97.21

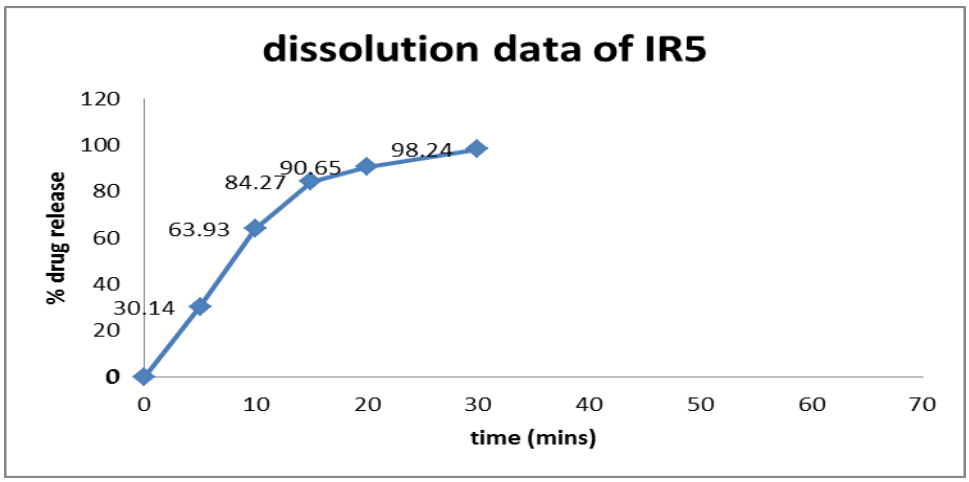


Graph 4.2.cd Drug release data of IR4 formulation

In-vitro drug release of Naproxen IR5 formulation

Table 4.2.g: Drug release data of IR 5 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	30.14
3	10	63.93
4	15	84.27
5	20	90.65
6	30	98.24

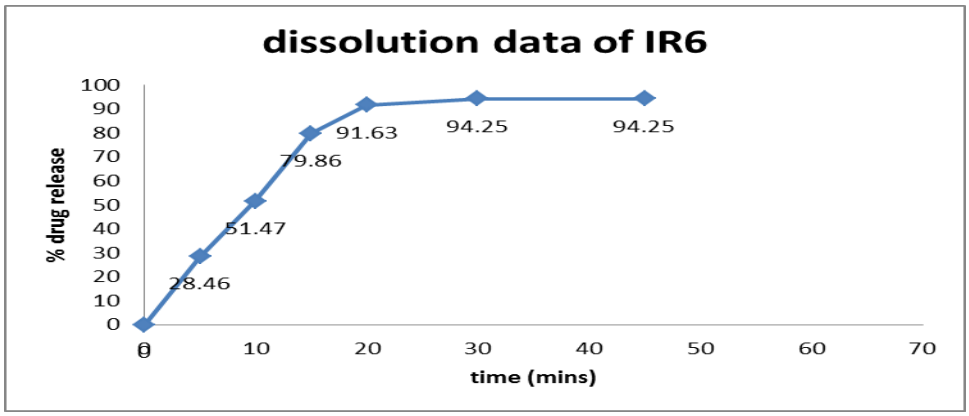


Graph 4.2.e: Drug release data of IR5 formulation

In-vitro drug release of Naproxen IR6 formulation

Table 4.2.h: Drug release data of IR 6 formulation

S.NO	Time (mins)	% Drug release
1	0	0
2	5	28.46
3	10	51.47
4	15	79.86
5	20	91.63
6	30	94.25
7	45	94.25

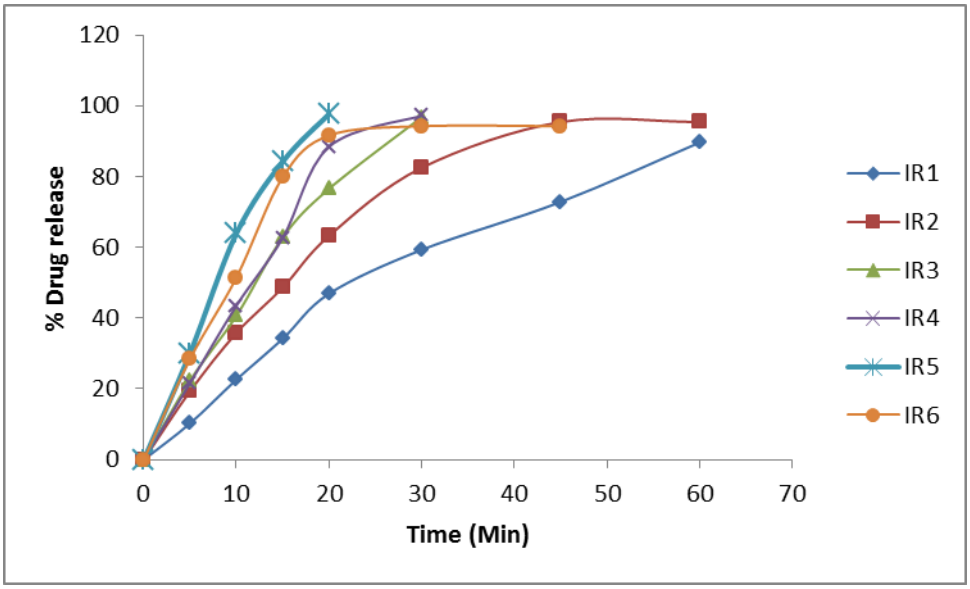


Graph 4.2.f: Drug release data of IR formulation

CUMMULATIVE % DRUG RELEASE

Table 4.2.i: Cumulative drug release data of Naproxen IR tablets

TIME(Min)	IR1	IR2	IR3	IR4	IR5	IR6
0	0	0	0	0	0	0
5	10.28	19.36	22.38	21.69	30.14	28.46
10	22.63	35.82	40.66	43.52	63.93	51.47
15	34.18	48.64	62.83	62.71	84.27	79.86
20	46.91	63.27	76.58	88.43	90.65	91.63
30	59.32	82.51	96.82	97.21	98.24	94.25
45	72.84	95.42				94.25
60	89.66	95.42				



Graph 4.2.g: Cumulative Dissolution data of Naproxen Immediate release Layer

From the dissolution data of Naproxen Immediate release Layer, IR1, IR2, IR3 formulations containing Explotab as super disintegrate revealed that increase in the concentration of Explotab shown good drug release. IR4, IR5, IR6 formulations containing Polyplasdone XL were shown good drug release compared to formulations containing Explotab.

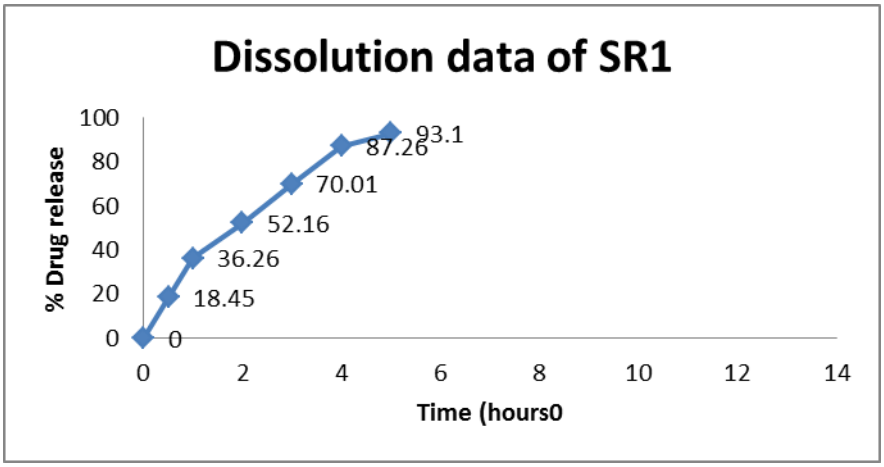
Among all IR Layer formulations, IR5 formulation was shown maximum drug release at 20min. i.e., 97.66%. Hence IR5 was concluded as optimized formulation for IR layer.

In vitro drug release studies for sustained release layer of sumatriptan

In-vitro drug release of sumatriptan sr1 formulation

Table4.2.j : Dissolution data of Sumatriptan SR1 formulation

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	18.45
3	**1**	36.26
4	**2**	52.16
5	**3**	70.01
6	**4**	87.26
7	**5**	93.1
8	**6**	
9	**7**	
10	**8**	
11	**9**	
12	**10**	
13	**11**	
14	**12**	



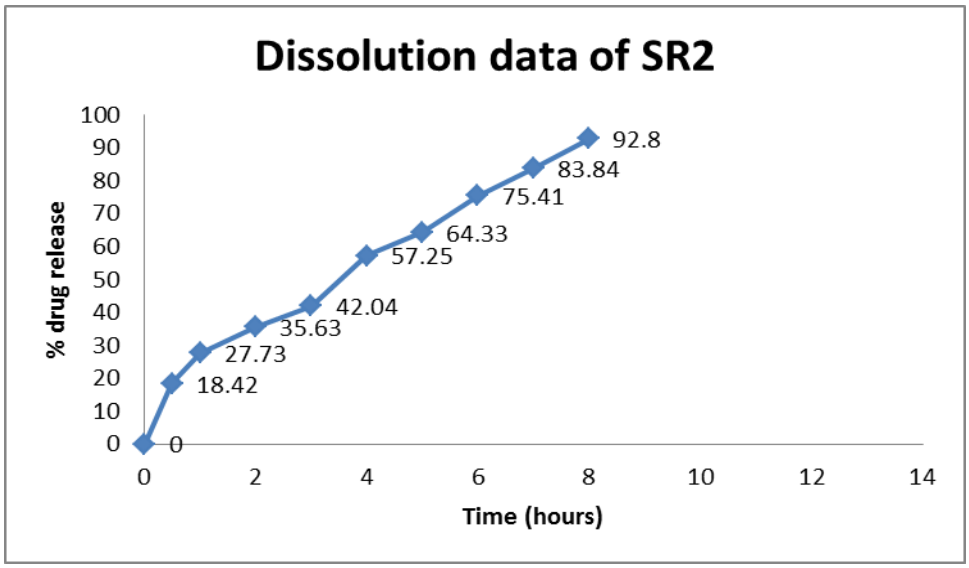
Graph 4.2.k: Dissolution data

In-vitro drug release of SUMATRIPTAN SR2 formulation

Table 4.2.k Dissolution data

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	18.42
3	**1**	27.73
4	**2**	35.63
5	**3**	42.04

6	**4**	57.25
7	**5**	64.33
8	**6**	75.41
9	**7**	83.84
10	**8**	92.8
11	**9**	
12	**10**	
13	**11**	
14	**12**	

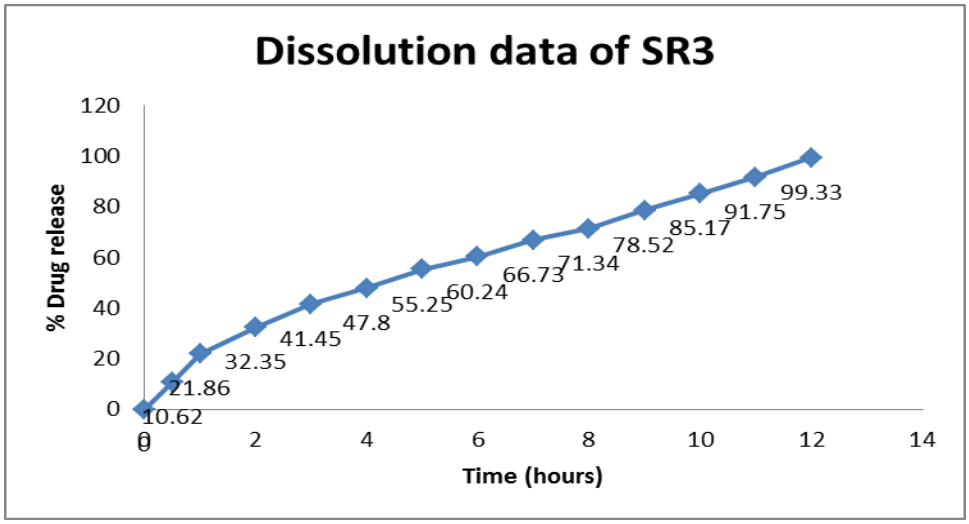


Graph 4.2.l: in-vitro drug release of SR2 Formulation

In-vitro drug release of SUMATRIPTAN SR3 formulation

Table 4.2.l Dissolution data

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	10.62
3	**1**	21.86
4	**2**	32.35
5	**3**	41.45
6	**4**	47.8
7	**5**	55.25
8	**6**	60.24
9	**7**	66.73
10	**8**	71.34
11	**9**	78.52
12	**10**	85.17
13	**11**	91.75
14	**12**	99.33

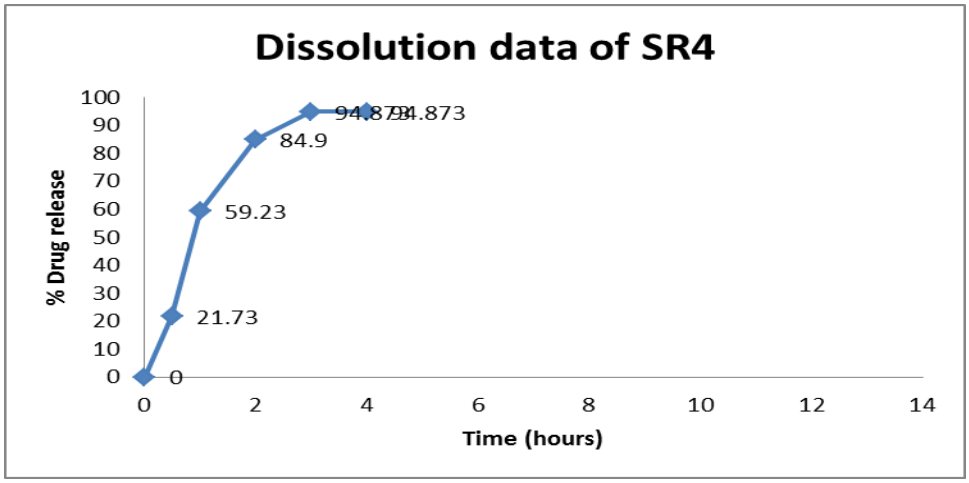


Graph 4.2.m: in-vitro drug release of SR3 Formulation

In-vitro drug release of SUMATRIPTAN SR4 formulation

Table 4.2.m. Dissoultion data

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	21.73
3	**1**	59.23
4	**2**	84.9
5	**3**	94.873
6	**4**	94.873
7	**5**	
8	**6**	
9	**7**	
10	**8**	
11	**9**	
12	**10**	
13	**11**	
14	**12**	

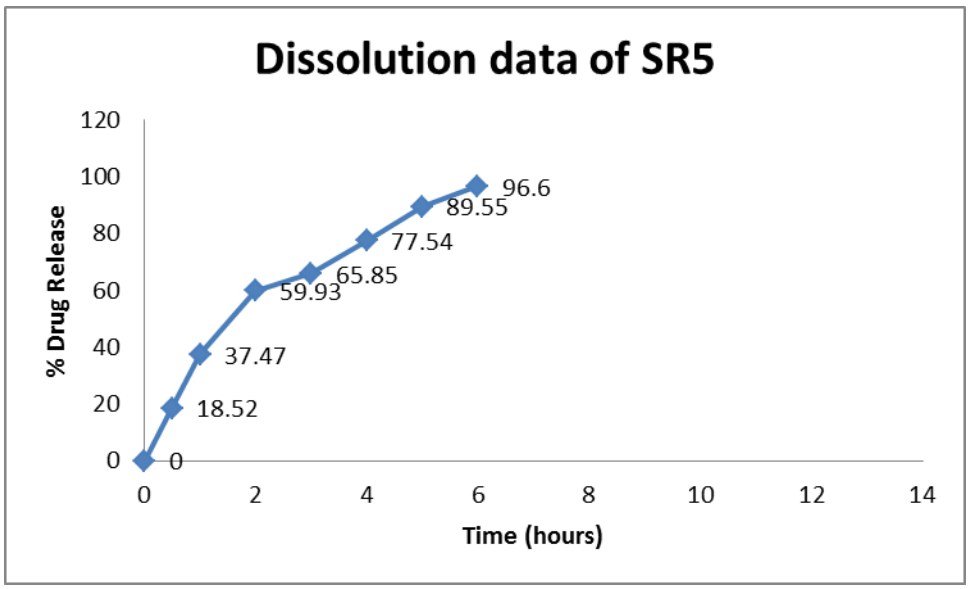


Graph 4.2.n : in-vitro drug release of SR4 Formulation

In-vitro drug release of SUMATRIPTAN SR5 formulation

Table 4.2.n Dissoultion data

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	18.52
3	**1**	37.47
4	**2**	59.93
5	**3**	65.85
6	**4**	77.54
7	**5**	89.55
8	**6**	96.6
9	**7**	
10	**8**	
11	**9**	
12	**10**	
13	**11**	
14	**12**	



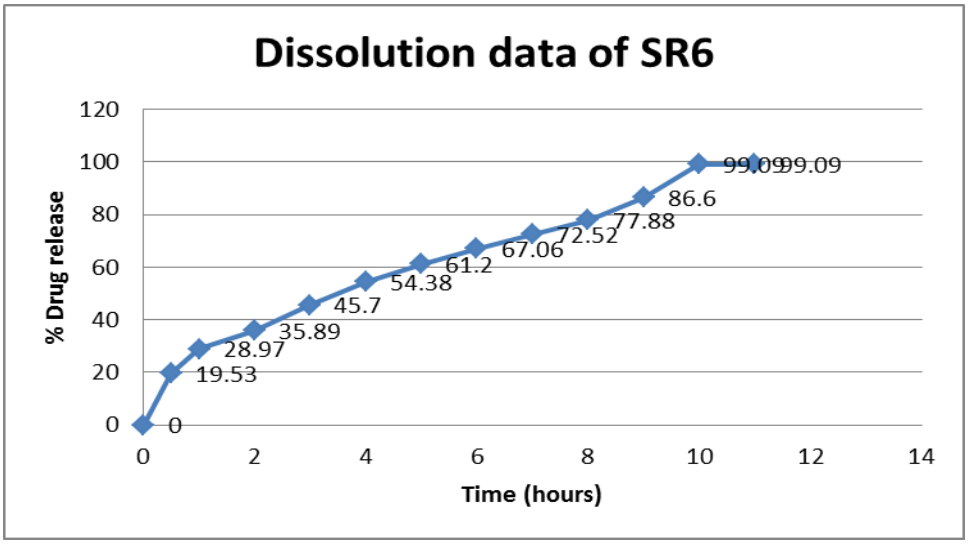
Graph 4.2.o: in-vitro drug release of SR5 Formulation

In-vitro drug release of SUMATRIPTAN SR6 formulation

Table 4.2.o. Dissoultion data

S.No	Time	% Drug release
1	**0**	0
2	**0.5**	19.53
3	**1**	28.97
4	**2**	35.89

5	**3**	45.7
6	**4**	54.38
7	**5**	61.2
8	**6**	67.06
9	**7**	72.52
10	**8**	77.88
11	**9**	96.6
12	**10**	99.09
13	**11**	99.09
14	**12**	

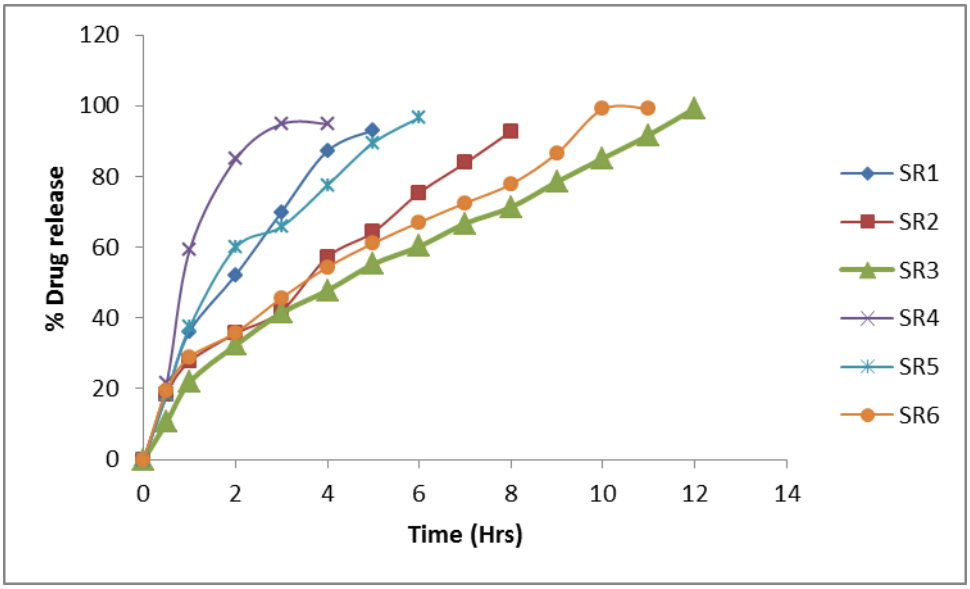


Graph 4.2.p: in-vitro drug release of SR6 Formulation

CUMMULATIVE % DRUG RELEASE OF SUMATRIPTAN

Table 4.2.p. Cumulative % drug release data of Sumatriptan SR tablets

Time	SR1	SR2	SR3	SR4	SR5	SR6
0	0	0	0	0	0	0
0.5	18.45	18.42	10.62	21.73	18.52	19.53
1	36.26	27.73	21.86	59.23	37.47	28.97
2	52.16	35.63	32.35	84.9	59.93	35.89
3	70.01	42.04	41.45	94.873	65.85	45.7
4	87.26	57.25	47.8	94.873	77.54	54.38
5	93.1	64.33	55.25		89.55	61.2
6		75.41	60.24		96.6	67.06
7		83.84	66.73			72.52
8		92.8	71.34			77.88
9			78.52			86.6
10			85.17			99.09
11			91.75			99.09
12			99.33			



Graph: 4.2.q Cummulative Dissolution data of Sumatriptan Sustained release Floating Layer

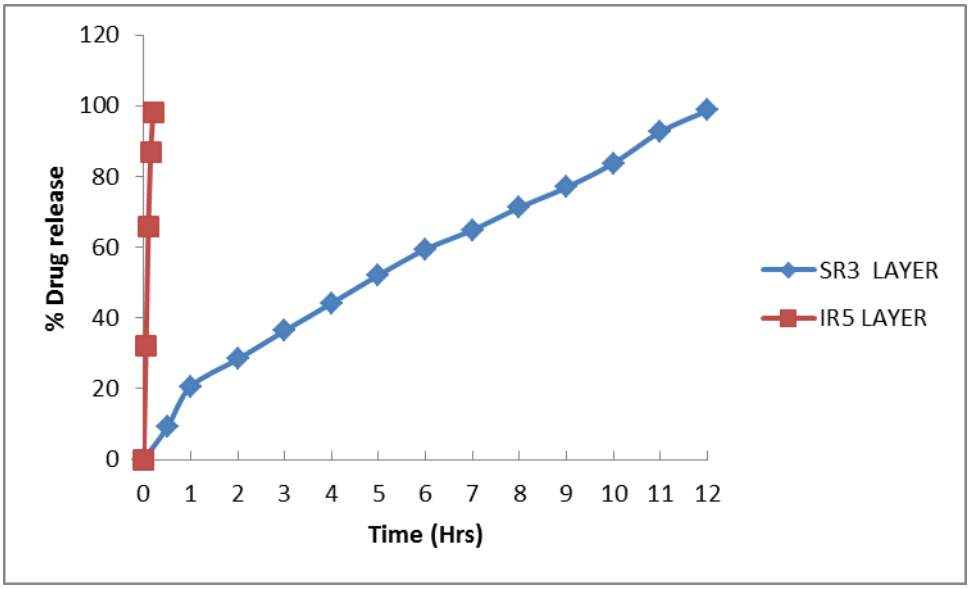
From the dissolution data of SR floating Layer formulations, formulations containing sodium alginate SR4, SR5, SR6 were not retarded the drug release up to 12 hours. Hence those formulations were not taken into consideration.

Among all formulations SR3 formulation containing Methocel as Sustained release polymer was retards the drug release up to 12 hrs. Hence SR3 SR floating layer was concluded as optimized formulation.

***IN VITRO* DRUG RELEASE STUDIES FOR BILAYER TABLETS**

Table 4.q.m: In- vitro drug release of Bilayer tablets

TIME(Min)	IR5 LAYER	TIME(Hrs)	SR3 LAYER
0	0	**0**	0
0.05	32.18	**0.5**	9.14
0.1	65.91	**1**	20.62
0.15	86.93	**2**	28.35
0.2	98.24	**3**	36.41
0.5		**4**	44.18
		5	52.16
		6	59.42
		7	64.88
		8	71.26
		9	76.91
		10	83.76
		11	92.64
		12	98.67

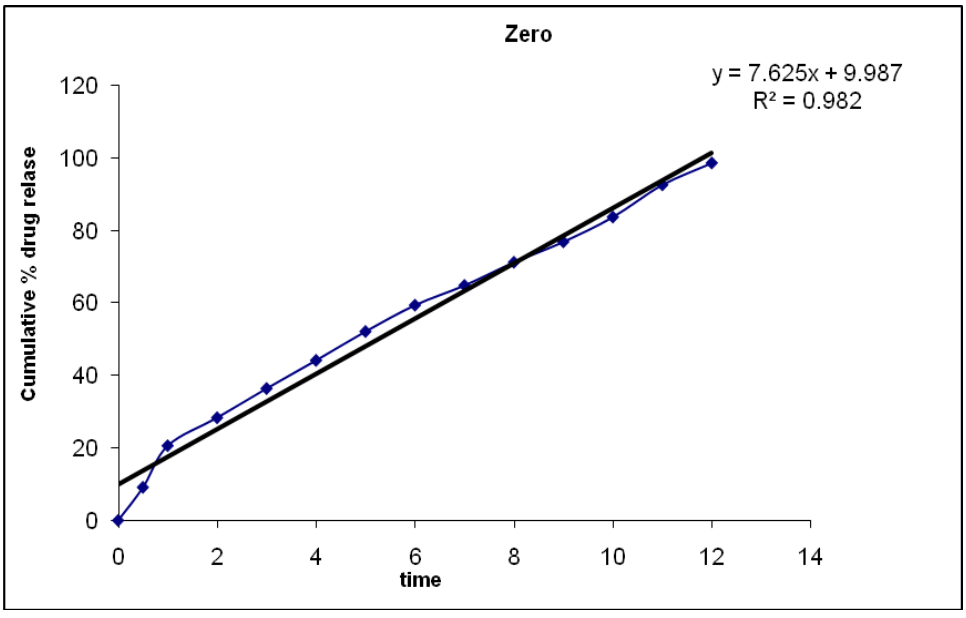


Graph4.2l. DRUG RELEASE STUDIES FOR BILAYER TABLETS

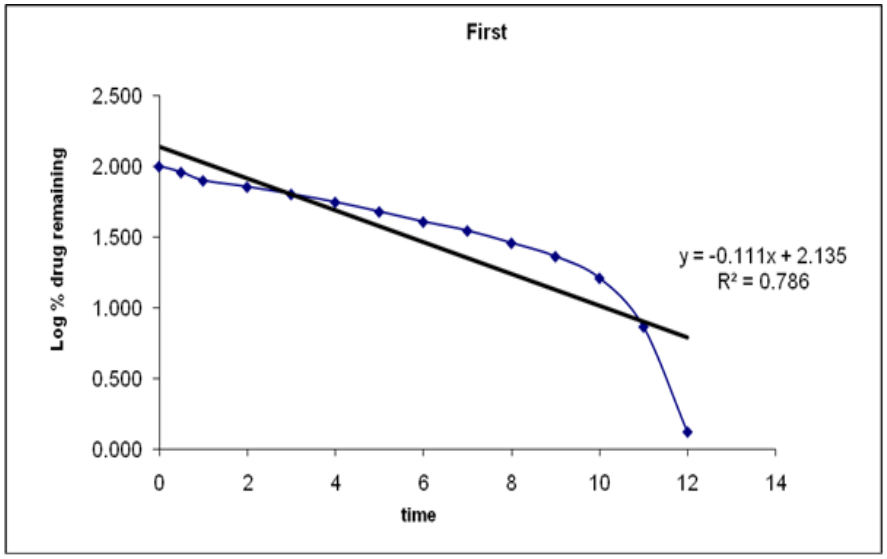
Application of Release Rate Kinetics to Dissolution Data

Table 4.2.r; kinetic model

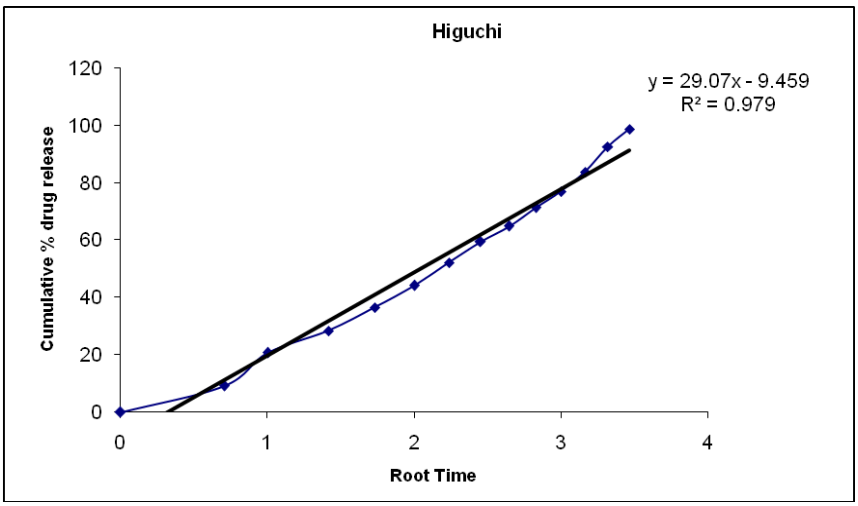
	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.625	0.111	29.07	0.697
Intercept	9.987	2.135	9.459	1.232
R 2	0.982	0.786	0.979	0.989



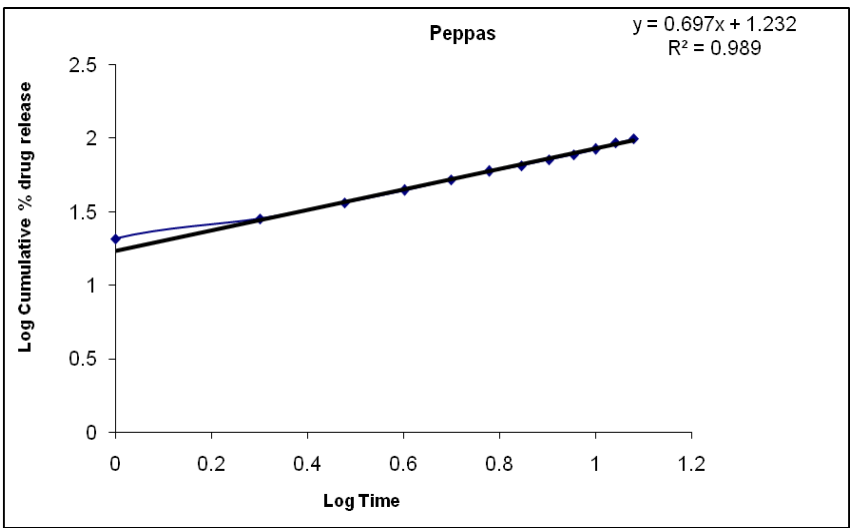
Graph 4.2.m zsero order kinetics



Graph 4.2.n first order kinetics



Graph 4.2.o Higuchis order of kinetics



Graph 4.2.p korsmeyer peppas order kinetics

5. CONCLUSIONS

The following conclusions can be drawn from the results obtained in the study.

- Gastroretentive Bilayered Floating Tablets of Naproxen and Sumatripotan were developed by using different concentrations of super disintegrants (explotab, polyplasdone XL) in the IR layer of Naproxen, similarly sustained release layer of Sumatriptan was developed using methocel (sustained release polymer), MCC was used as a diluent and Sodium Bi Carbonate used as gas generating agent.
- Preformulation studies were performed for both IR layer and SR layer formulations which showed the flow properties as good.
- FT-IR Spectroscopic studies indicated that the drug is compatible with the polymer and co-excipients in both the layers and also in Bilayer tablets of Naproxen and Sumatriptan.
- All the tablets of IR and SR layer were evaluated for post compression parameters or physicochemical parameter and they were formed well within acceptable limits of IP norms.
- The drug content was uniform and well within the accepted limits indicating uniform distribution of the drug within the prepared IR and SR layer tablets of Naproxen and Sumatriptan.
- The prepared BLFT of Naproxen and Sumatriptan showed excellent In-vitro floating properties.
- The In-Vitro dissolution profiles of all the prepared formulations of SR layer Sumatriptan tablets were found to extend the drug release over a period of 12 hours.
- All the prepared Bilayered tablets were found to be good without chipping, capping and sticking.
- In order to optimize, the best formulation for both IR and SR layer was selected on the basis of their dissolution profiles. IR layer tablets IR5 containing 10mg of polyplasdone was found to be optimum and released 98.24% of Naproxen in 30mins. The floating SR layer tablet of Sumatriptan (SR3) containing methocel 50mg released 98.67% of drug in 12 hours.
- The optimised Bilayer tablet of Naproxen and Sumatriptan was formulated and evaluated for various evaluation parameters. All the results of evaluations was found to be within limits and the final Optimised bilayer formulation released 98.27% of Naproxen in 30 mins and 98.67% of Sumatriptan in 12hrs. The optimised formulation was fitted in kinetic models and it followed korsmeyer peppas kinetic model and the release mechanism was

Case II Non- fickian refers to a combination of both diffusion and erosion controlled-drug release.

- Thus the optimised Bilayer floating tablets of Naproxen and Sumatriptan appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate the clinical safety of these Bilayered Floating tablets in suitable animals and human models.

Finally, it may be concluded that this novel drug delivery system that is Bilayered Floating Tablet offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The floating bilayered tablets of Naproxen and Sumatriptan gives promising results for curing migraine and can be further proceeded various in- vitro and in-vivo test.

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