

FORMULATIONS AND EVALUATION OF NISOLDIPINE SUSTAINED RELEASE MATRIX TABLETS

¹Srinivasarao Mande, ²Lalitha Repudi, ³Kumaraswamy Gandla, ⁴Sravanthi Gandu, ⁵Gangavarapu.Nadia Psalms

^{1,2,3,5}Department of Pharmacy, Chaitanya Deemed to be university, Gandipet, HimayathNagar, Hyderabad.

⁴Department of Pharmaceutical Analysis, Trinity College of Pharmaceutical Sciences, Peddapalli.

Corresponding author: Gangavarapu Nadia Psalms, Assistant Professor

Abstract- The Present study was undertaken with an aim to formulate and evaluate Nisoldipine sustained release matrix tablets, a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. It is used as an adjunct in the symptomatic treatment of musculoskeletal conditions associated with painful muscle spasm. Preformulation studies were carried and results were found to be satisfactory. The compatible excipients were selected for the formulation development. Experiment was performed by using both dry and wet granulation techniques based on the flow properties of API. In order to increase the flow property of the tablets, wet granulation was chosen for further formulation and found to be satisfactory. During development of formula, in-process tests such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were evaluated for granules and hardness, friability, weight variation, thickness and disintegration were evaluated for the core tablets. Core tablets were coated with coating suspension. Finished products were evaluated for hardness, friability, weight variation, thickness, disintegration, dissolution and drug content. The developed trials were tested for in-vitro dissolution profile and compared with the reference product Carisoma. Stability studies performed at 45°C /75% RH, 25°C /60% RH for 2 months. Stability samples were evaluated initially and after 2 months. The results were compared with the pre-determined specifications. All the results were found to be satisfactory.

Keywords: Nisoldipine; sustained release matrix tablets; Stability studies; formulate and evaluate.

Introduction

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. Advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. One of the interesting results of pharmaceutical research is the fact that absorption rate of a drug can be decreased by reducing its rate of release from the dosage form. The product so formulated are designated as sustained action, sustained release, delayed action, prolonged action, depot, respiratory, retarded release and timed release medication. Over the past 30 years, as the expense and Complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by

continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems.

To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs. Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

POTENTIAL ADVANTAGE OF SUSTAINED RELEASE DOSAGE FORM

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improved bioavailability of some drugs.
- Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.
- Economy.
- Overall, administrations of sustained release form enable increased reliability of therapy.

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM

- If there requires immediate change during the therapy or if any significant adverse effect is noted and prompt termination of therapy is needed, sustained release does not permit immediate termination of therapy.
- More costly process and equipment are needed in manufacturing of SRDDS.
- Physician has less flexibility in adjusting dosage regimen as this is fixed by design of dosage form. Risk of dose dumping, usually SRDDS contain drug amount that is 3-4 times more than conventional formulations. Sometimes this large quantity of drug may get rapidly released leading to toxicity.
- Reduced drug absorption may delay onset of action. The effect of food on drug absorption.
- Kinetics may differ markedly from one SR formulations to another.
- Drug absorbed at specific time in GIT cannot be formulated in SRDDS.
- Increased potential for first pass clearance.
- In case of accidental failure of the product effective antidote may be difficult to employ.

Aim: Formulation and evaluation of the Nisoldipine sustained release matrix tablets.

Objectives:

- The sustained release tablets are formulated by the direct compression method.
- The development of this Nisoldipine tablets by applying various polymers
- The pre-compression studies such as the bulk density, tap density, angle of repose, hausners ratio, compressability index. .
- The post-evaluation parameters are done prepared tablets.
- In-vitro drug release studies are done for sustained release tablets.
- For optimized formulation stability studies done for 90days
- The kinetic profile data is calculated.

WORK:**1. LITERATURE SURVEY****2. PREFORMULATION STUDIES**

- Preformulation study of Nisoldipine
- Organoleptic Properties
- Melting point of drug
- Determination of solubility
- Drug – Excipient Compatibility studies

3. EVALUATION OF BLENDS OR PRE-COMPRESSSION STUDIES

- Bulk density
- Tapped density
- Carr's Index (Compressibility Index)
- Hausner's Ratio
- Angle of repose

4. PREPARATION OF MATRIX TABLETS BY USING VARIOUS CONCENTRATIONS OF MATRIX FORMING POLYMERS

- By direct compression Technique

5. EVALUATION OF MATRIX TABLETS (POST COMPRESSION STUDIES)

Thickness

Hardness

Weight variation

Friability

Assay

In-vitro drug release study

Comparison with Kinetic models

6. NEED FOR THE STUDY

- Nisoldipine sustained release matrix tablets work by helping to relax the muscles.
- The Nisoldipine sustained release matrix tablets are formulating as the sustained form for release the drug over longer period of time.
- The enhance the bio availability of a drug
- To develop the sustained tablets by using different sustained release polymers to increase the drug release.
- To perform the stability studies for the selected formulation.

7. DRUG PROFILE:**NISOLDIPINE**

Description: Nisoldipine is a 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nisoldipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction. Nisoldipine may be used in alone or in combination with other agents in the management of hypertension.

Chemical name: C₂₀H₂₄N₂O₆

Molecular weight: Average:388.41

Structure formula:

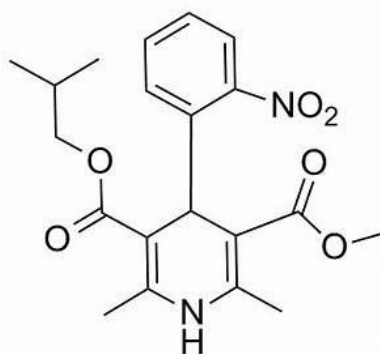


Figure.no.1: Structure of Nisoldipine

Solubility. It is slightly soluble in water, alcohol, chloroform, acetone

Appearance: white, crystalline powder

IUPAC:

3-methyl 5-(2-methylpropyl) 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Pharmacodynamics:

Nisoldipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Nisoldipine is similar to other peripheral vasodilators. Nisoldipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload

Pharmacokinetics:

Absorption:

Relatively well absorbed into the systemic circulation with 87% of the radiolabeled drug recovered in urine and feces. The absolute bioavailability of nisoldipine is about 5%.

Half-life: The terminal half-life is approximately 2 hours.

Metabolism:

Pre-systemic metabolism in the gut wall, and this metabolism decreases from the proximal to the distal parts of the intestine. Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. The major biotransformation pathway appears to be the hydroxylation of the isobutyl ester. A hydroxylated derivative of the side chain, present in plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolite and has about 10% of the activity of the parent compound. Cytochrome P450 enzymes are believed to play a major role in the metabolism of nisoldipine. The particular isoenzyme system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P450 IIIA4

Protein binding: 99%

Route of elimination:

Although 60-80% of an oral dose undergoes urinary excretion, only traces of unchanged nisoldipine are found in urine.

Mechanism of Action:By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Nisoldipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

Uses:

For the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

8. EXCIPIENT PROFILE

8.1 CROSPVIDONE (Kollidon CL) [88]

Nonproprietary Names

- **BP:** Crospovidone
- **PhEur :** Crospovidonum
- **USPNF:** Crospovidone

Synonyms

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; PolyplasdoneXL-10; polyvinylpyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer. 71

Chemical Name and CAS Registry Number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight: (C₆H₉NO) *n*>1 000

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 72 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, freeflowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)

Density: 1.22 g/cm³

Density (bulk): 0.35 g/cm³

Density (tapped): 0.45 g/cm³

Moisture content : Maximum moisture sorption is approximately 60%.

Particle size distribution: 50% greater than 50 μm and maximum of 3% greater than 250 μm

Solubility: Practically insoluble in water and most common organic solvents.

Specific surface area: 1.0 m²/g

Storage Conditions: 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.

8.2 HYDROXYPROPYL METHYL CELLULOSE

Nonproprietary names:

B.P: Hypromellose 2208,

Ph. Eur: MethylHydroxyPropylCellulosum,

USP: Hydroxy

Propyl Methylcellulose

Synonyms:

Cellulose, Hydroxy propyl methyl ether; culminal MHPC; E-464; HPMC; Methylcellulose propylene glycol ether;

Methyl hydroxy propyl cellulose; Metolose;

Pharmacoat.

Structure:

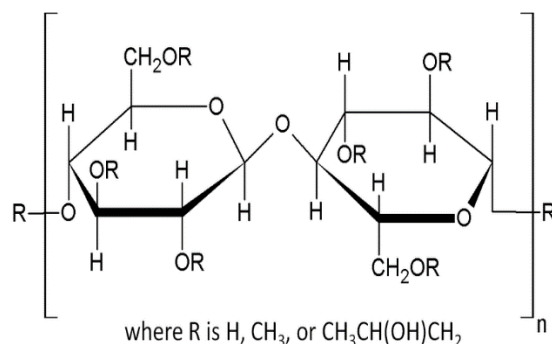


Fig.no:2. Structural image of HPMC

Chemical Name: Cellulose, 2-Hydroxypropyl-methyl ether.

Molecular weight: Molecular weight is approximately 10,000 – 1, 50,000.

Functional category:

Coating agent, film former, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

APPLICATIONS

Hydroxy propyl methyl cellulose is widely used in oral and topical pharmaceutical formulation. In oral product, hydroxy propyl methylcellulose is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix.

Description: Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy white colored fibrous or granular powder.

PHARMACOPOEIAL SPECIFICATIONS

PH (1% solution):5.5-8.0.

Apparent viscosity: 3000-5600 cps.

Typical Properties:

Acidity/alkalinity:pH 5.5 – 8 (for a 1% aqueous solution).

Density (tapped):0. 50-0.70 g/ml.

Specific gravity:1.26.

Solubility:Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether.

8.3. TALC

Nonproprietary names

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial;

Luzenac Pharma;

Chemical name and CAS registry number

Talc [14807-96-6]

STRUCTURE:

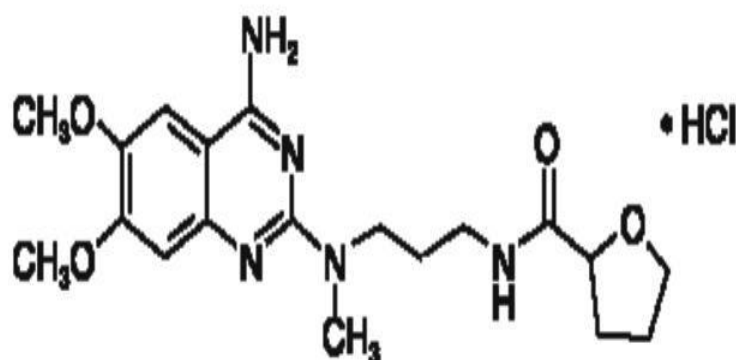


Fig.no:3. Structural image of the talc

Structural formula

$Mg_3Si_4O_{10}(OH)_2$

Functional category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Talc was once widely used in oral solid compounds such as a lubricant and dilents. However, it is widely used to break down in development in controlled-release Products.

8.4 MICROCRYSTALLINE CELLULOSE (MCC-KG 100)

Chemical name: Cellulose

Empirical formula and molecular weight: $(C_6H_{10}O_5)_n$ (36000)

Functional category:

Adsorbant, Suspending agent, tablet and capsule diluent, tablet disintegrant

Description

The key to the compatibility of the Ceolus KG grades lies in their needle-like particle shape. Needle-like particles, once compressed, have less elastic recovery and more particle-to-particle entanglements to provide greater tablet hardness. It is commercially available in different particle size & moisture grades that have different properties and application. It is incompatible with strong oxidizing agent.

Structure

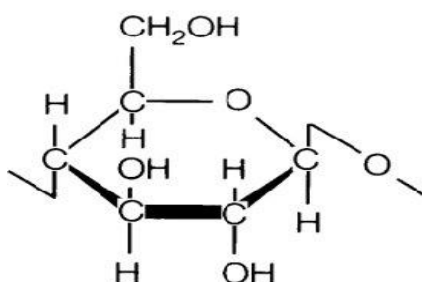


Fig.no: 4. Structural images of MCC

Applications

It is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a diluent in capsule and tablet manufacturing.

7.5 MAGNESIUM STEARATE

Synonyms:

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid and magnesium salt.

Chemical Formula: Octadecanoic acid magnesium salt. $C_{36}H_{70}MgO_4$.

Molecular weight: 591.34.

Functional Category: Tablet and capsule lubricant.

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 the touch and readily adheres to the skin.

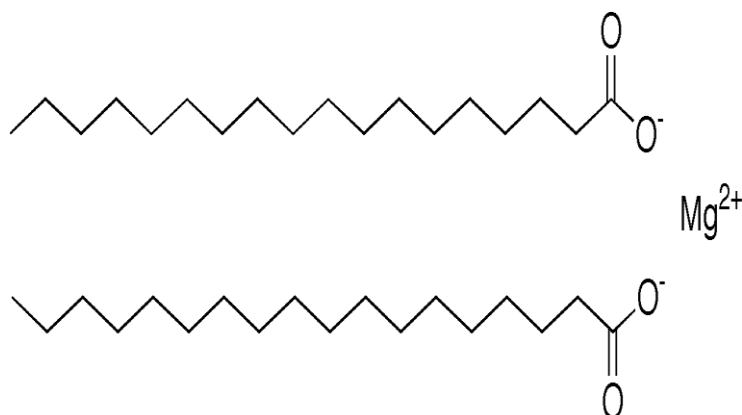
Structure:

Fig.no:5 Structural image of the Magnesium stearate

Solubility:

Practically insoluble in ethanol, ether, and water, slightly soluble in warm benzene and warm ethanol.

Stability and storage conditions:

Magnesium stearate is stored in a well closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salt.

Applications:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

8. MATERIALS AND METHODS:**8.1. MATERIALS USED IN TABLETS PREPARATION**

Table no.1: Materials used to be formulated

S.No.	MATERIALS	SOURCE
1.	Nisoldipine	RA chem Pharma
2.	HPMCK4M	Clariant pharma
3.	Stearic acid	Shinetsu company
4.	Cross povidone	Evonik company
5.	Mcc	Evonik company
6.	Talc	Laxmi chem. Pvt.ltd
7.	Magnesium stearate	Laxmi chem. Pvt.ltd

8.2.EQUIPMENTS USED

Table.no.2 : Equipments used

S.No	NAME	MFG & MODEL NO
1	Electronic Weighing Balance	Essae DS-852

2	Mechanical Stirrer	REMI Electrotechnik RQ1291D
3	Tablet punching Machine	Karnavati
4	Dissolution Apparatus	Lab india 8000plus
5	Friability apparatus	Roche fraibilator
6	Hardness tester	Faizer
7	Disintegration tester	REMI Electrotechnik RQ1291D

9. METHODOLOGY:

9.1. PREFORMULATION STUDIES:

9.1.1. ORAGANOLEPTIC CHARACTERS:

The pre formulation studies such as the colour, odour, taste can be done by visually.

9.1.2. SOLUBILITY STUDIES:

The solubility studies are done by using various solvents such as the ethanol, methanol, acetone, and other organic solvents.

9.1.3. DRUG AND EXCIPIENT COMPATABILITY STUDIES:

The drug and excipient compatibility studies are done by FTIR Studies by using Kbr pellet method. First the 1 gm of the drug powder is taken under kept for the FTIR studies. The 1gm of drug and polymer take and kept under FTIR studies the peaks which are came for drug product the nearer to the drug the polymer peaks will come. If they are not came the drug and excipients are in compatible with each other.

9.1.4. CONSTRUCTION OF CALIBRATION CURVE IN 6.8 BUFFER:

To take 10mg of Nisoldipine active substance it is going to disperse in 10ml of water in volumetric it is 1000ppm. From 1000ppm to take 1 ml and it is disperse in 10ml of volumetric flask it is 100ppm. From that take 1 ml and make up to 10 ml in volumetric flask it is 10ppm. To check absorbance at 10ppm if the absorbance is high undergo for serial dilutions like 1,2,3,4,5, ml and check the absorbance at 280 nm by using U.V visible spectroscopy.

9.1.5. CONSTRUCTION OF CALIBRATION CURVE IN ETHANOL:

To take 10mg of Nisoldipine active substance it is going to disperse in 10ml of ethanol in volumetric it is 1000ppm. From 1000ppm to take 1 ml and it is dispersing in 10ml of volumetric flask it is 100ppm. From that take 1 ml and make up to 10 ml in volumetric flask it is 10ppm. To check absorbance at 10ppm if the absorbance is high undergoing for serial dilutions like 1,2,3,4,5, ml and check the absorbance at 315nm by using U.V visible spectroscopy.

9.2. PRECOMPRESSION PARAMETERS:

9.2.1. BULK DENSITY

The pre formulation studies such as the bulk density. The bulk density is defined as the certain amount powder is taken into the measuring cylinder. The Bulk density is the ratio of the weight of a powder to the volume it occupies.

It is expressed as gm/ml.

Bulk density = W / V_o

Where,

W = weight of the powder

V_o = initial volume

9.2.2. TAPPED DENSITY

The tap density is defined as the amount of powder will take in the measuring cylinder the measuring cylinder is closed with lid. The tap density apparatus under kept and set for 500 tapings. The powder particles will settle down in the measuring cylinder the powder will decrease. The process is continued for the both consecutive readings were equal.

$$\text{Tapped density} = W / V_F$$

Where,

W = weight of the powder

V_F = final volume

9.2.3. ANGLE OF REPOSE

The angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. For determining of the angle of repose the funnel method is used. The certain amount of powder taken in to the glass funnel by closing the funnel orifice. The glass funnel is fixed at 2cm from horizontal plan. The finally the closed orifice will opened the powder flows through the funnel and form a pile. The height of the pile is noted. A Circumference was drawn with a pencil on a graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculation.

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

Where h = height of pile.

r = radius of the base of the pile.

θ = angle of repose.

Angle of repose below 25 indicates an excellent powder flow.

Table.no.3: Relationship between angle of repose (a) & powder flow

S. No.	Angle of repose (a) degrees	Flow
1	< 25	Excellent
2	25-30	Good
3	30-40 *	Passable
4	40 & above	Very poor

9.2.4. COMPRESSIBILITY INDEX

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder.

Table.no. 4 : Compressibility Index Range

S. No.	% compressibility index	Flowability
1	5-15	Excellent
2	12-18	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very Very Poor

Compressibility index were calculated using the formula:

$$\text{Compressibility index} = T.D - B.D / T.D * 100$$

9.2.5. HAUSNER RATIO:

It indicates the flow property of the powder and Measured by the ratio of tapped density to bulk density

Table .no.5 : Hausner ratio values

Hausner ratio	Properties
0 -1.11	Free flowing
1.2 -1.6	Cohesive powder

Hausner ratio= $T.D \backslash B.D$

Where,

T.D= Tapped density, B.D= Bulk density

9.3. FORMULATION TABLE OF NISOLDIPINESUSTAINED RELEASE TABLETS**Table.no.6 : showing formulation table of Nisoldipine**

Ingridients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Nisoldipine	50	50	50	50	50	50	50	50	50	50
HPMCK4M	5	-	5	10	-	10	20	-	20	20
Stearic acid	-	5	5	-	10	10	-	20	20	-
Cross povidone	5	5	5	10	10	10	10	10	10	10
Mcc	236	236	231	226	226	216	216	216	196	206
Talc	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Total wt	300	300	300	300	300	300	300	300	300	300

NISOLDIPINE TABLETS PREPARED BY USING DIRECT COMPRESSION METHOD:

Dispensing: The drug and all ingredients are dispensed above mentioned in table.

Mixing: All ingredients are mixing except adding Mg.Strate and talc

Seiving: The drug and all ingredient's undergo for sieving in sieve no:40

Mixing: After sieving the drug and expect Mg. Stearte and talc all ingredients are mixed together.

Compression: After mixing the all along with mg.stearte and talc they undergo for punching in a multi compression mission.

9.4. POST COMPRESSION PARAMETERS:**9.4.1. WEIGHT VARIATION TEST:**

The post compression parameters in that weight variation study is done. The weight variation is done by the taking 20 tablets. First to take the individual weight for 20 tablets. Finally to take final weight of the group of 20 tablets by

using the Essae electronic balance. None of the individual Tablet weight should be less than 90% and more than 110% of the average weight.

Calculated by using the following formula;

$$\text{Weight variation} = \frac{(\text{Weight of Tablet}-\text{Average weight})}{\text{Average weight of Tablet}} \times 100$$

9.4.2. HARDNESS:

The after formulation of the tablets the post compression parameter such as the hardness was done by using the Monsanto hardness tester. Hardness defined as the it indicates the capability of a tablet to withstand mechanical shocks while handling. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

9.4.3. THICKNESS:

The thickness of the tablets is done by using Digital venirecalipers. By using this the diameter of the tablets are done. Five tablets were used, and average values were calculated.

9.4.4. FRIABILITY TEST:

The formulated tablets are under kept for the friability test. The friability can be done by the using friability apparatus that is Roche Friabilator (USP EF-2 Electrolab.). It is expressed in percentage (%). The friability is done by the taking 10 tablets and they first weight that is initial weight of the tablets. After that the tablets are kept in the friabilator. The friability operator started the rpm set for 4mins at 50 rpm about to 100 revaluations.

$$\%F = 100 (1-W_0/W) \%$$

Friability of tablets less than 1% are considered acceptable.

9.4.5. IN-VITRO DRUG RELEASE STUDIES:

The In-vitro drug release studies are performed by the using USP type II apparatus paddle method. For In -vitro drug release studies 6.8 buffer is used the dissolution volume is 900ml. The room temperature is 37±5°C. The time interval is 10mins. The drug will release up to the 10 hrs The 1ml of sample is taken into the bowl it is replaced by the fresh sample for maintain of the sink conditions. The sample is analysed in U.V visible spectroscopy at 315nm.

9.5. STABILITY STUDIES

Stability studies protect the maintenance of product quality, safety and efficacy throughout the shelf life are contemplated as pre-requisite for the acceptance and approval of any pharmaceutical substance. These studies are appropriate to be conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies. Importance of different technologies followed for stability testing of pharmaceutical substances, guidelines issued for stability testing and other aspects.

10. RESULTS:

10.1. ORGANOLEPTIC CHARACTERS

Table.no.7: showing results of organoleptic characters

Properties	Results
Description	crystalline powder
Taste	bitter taste
Odour	mild, characteristic odor
Colour	White

10.2. SOLUBILITY STUDIES

Table.no.8 : Solubility of the Nisoldipine in various solvents

Solvent	Solubility properties of drug
Water	Slightly Soluble
Alcohol	Soluble
chloroform	Soluble
Acetone	soluble

10.3. CALIBRATION CURVE OF THE NISOLDIPINE IN PH 6.8 BUFFER

Table.no.9 : showing calibration values of Nisoldipine

Concentration (µg/ml)	Absorbance in pH 6.8 buffer
0	0
1	0.177
2	0.392
3	0.563
4	0.741
5	0.921

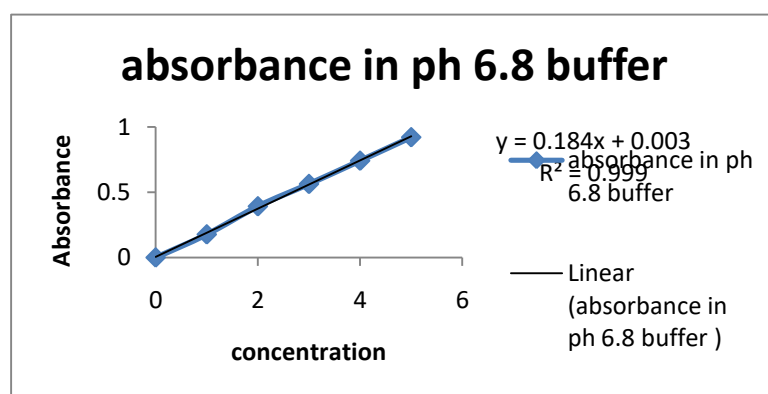


Fig.no.6: showing picture of the calibration plot in 6.8 buffer

10.4. CALIBRATION CURVE OF THE NISOLDIPINE IN METHANOL

Table.no.10 : showing calibration values in methanol

Concentration (µg/ml)	Absorbance in methanol
0	0
1	0.14
2	0.29
3	0.45

4	0.63
5	0.78

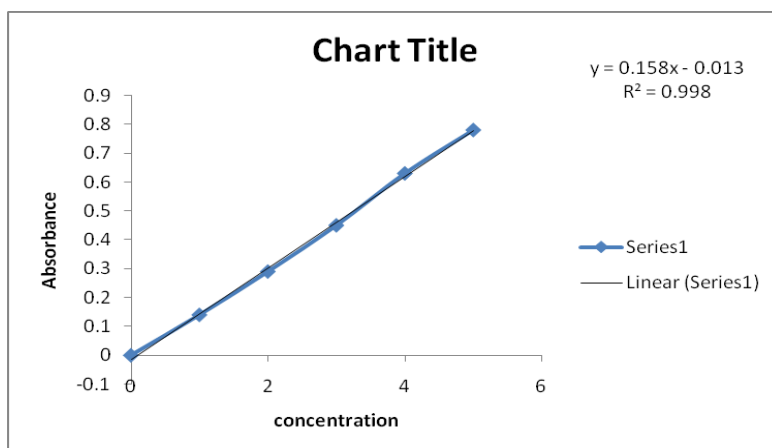


Fig.no.7: showing calibration plot in methanol

10.5. FTIR STUDIES:

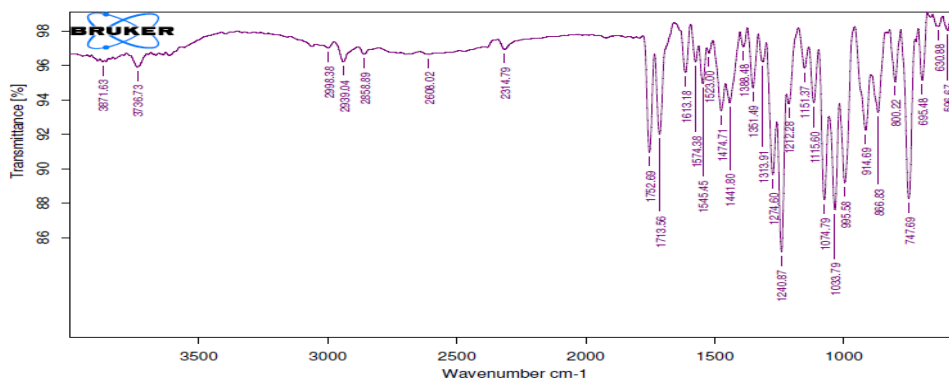


Fig.no.8: pure spectra of the Nisoldipine

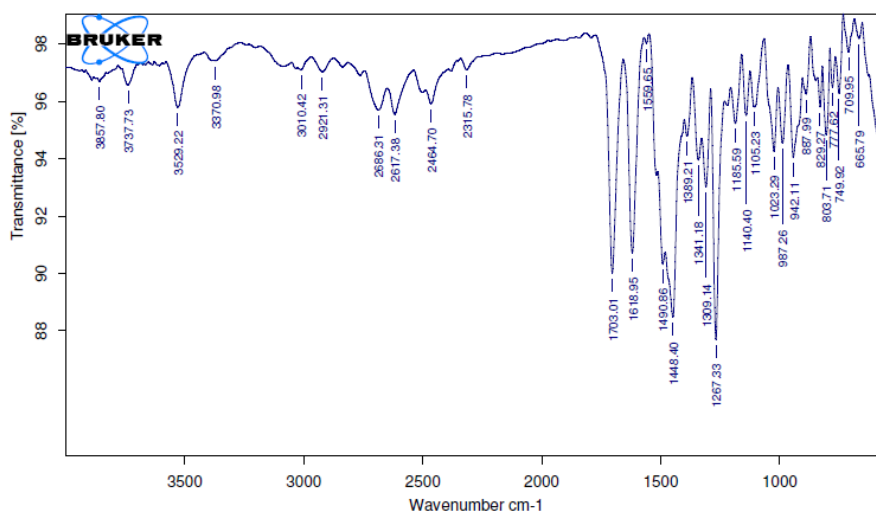


Fig.no.9: The fig shows the FTIR spectra of the drug and polymer blend

10.6. PRE-COMPRESSION PARAMETERS**Table.no.11: showing values of the pre compression parameters**

Formulation	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	25.38 \pm 0.13	0.40 \pm 0.02	0.50.02	20 \pm 0.13	1.25 \pm 0.01
F2	22.52 \pm 0.28	0.44 \pm 0.02	0.56 \pm 0.04	20 \pm 0.04 1.	1.27 \pm 0.01
F3	27.19 \pm 0.19	0.44 \pm 0.00	0.54 \pm 0.01	18.61 \pm 0.11	1.22 \pm 0.02

Formulation	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F6	24.38 \pm 0.13	0.38 \pm 0.02	0.48.02	20.83 \pm 0.13	1.26 \pm 0.01
F7	23.52 \pm 0.28	0.39 \pm 0.02	0.47 \pm 0.04	17.02 \pm 0.04 1.	1.20 \pm 0.01
F8	24.19 \pm 0.19	0.39 \pm 0.00	0.45 \pm 0.01	13.33 \pm 0.11	1.15 \pm 0.02
F9	22.51 \pm 0.16	0.40 \pm 0.01	0.44 \pm 0.01	9.09 \pm 0.15	1.1 \pm 0.01
F10	23.60.21	0.40 \pm 0.01	0.46 \pm 0.00	13.04 \pm 0.05	1.15 \pm 0.02
F4	28.51 \pm 0.16	0.45 \pm 0.01	0.55 \pm 0.01	18.33 \pm 0.15	1.22 \pm 0.01
F5	23.60.21	0.41 \pm 0.01	0.50 \pm 0.00	18 \pm 0.05	1.21 \pm 0.02

Discussion: The all the F1-F5 formulations pre compression parameters such as the angle of repose,bulk density,tap density,husners ratio,compressability index all comes under the within range of limits. All the formulations follow the good flow.

Table.no.12: showing values of the pre compression parameters**Discussion:**

The all the F6-F10formulations pre compression parameters such as the angle of repose, bulkdensity, tap density, husners ratio, compressability index all comes under the within range of limits. All the formulations follow the good flow.

POST COMPRESSION PARAMETERS FOR F1-F5 FORMULATIONS**Table.no.13: showing post compression parameters of F1-F5**

Formulation	Weight variation	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)	Disintegration (mins)
F1	299 \pm 1.02	2.50 \pm 0.01	3.2 \pm 0.06	0.232	87.24 \pm 0.22	35
F2	298 \pm 0.08	2.6 \pm 0.00	3.8 \pm 0.06	0.246	89.57 \pm 0.42	38
F3	298.002	2.5 \pm 0.01	3.71 \pm 0.00	0.386	90.43 \pm 0.13	30
F4	299 \pm 0.003	2.00 \pm 0.01	3.65 \pm 0.06	0.326	92.83 \pm 0.42	28
F5	299 \pm 0.08	2.10 \pm 0.01	3.65 \pm 0.10	0.446	92.86 \pm 0.32	28

POST COMPRESSION PARAMETERS FOR F6-F10 FORMULATIONS

Table.no.14 : showing post compression parameters of F1-F5

Formulation	Weight variation	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)	Disintegration (mins)
F6	299±1.02	2.40±0.01	3.4±0.06	0.232	93.24±0.22	25
F7	298±0.08	2.2±0.00	3.1±0.06	0.256	94.57±0.42	26
F8	301.002	2.3±0.01	3.2±0.00	0.226	96.43±0.13	25
F9	300±0.003	2.00±0.01	3.0±0.06	0.226	99.83±0.42	24
F10	300±0.08	2.50±0.01	3.1±0.10	0.256	96.86±0.32	25

10.8. IN –VITRO DRUG RELEASE STUDIES FOR ALL FORMULATIONS

Table.no.15: showing in—vitro drug release studies

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	10.23	12.65	15.89	18.56	20.56	22.32	22.52	21.65	22.15	23.21
3	18.35	25.65	28.36	30.56	35.62	40.53	41.53	42.62	45.15	48.65
4	75.35	50.36	55.68	56.12	57.65	57.65	56.72	58.56	59.12	58.52
6	89.35	60.78	64.65	68.42	70.56	70.55	71.62	72.62	78.32	79.22
8	100.33	80.41	70.42	74.74	79.56	80.18	81.43	82.65	92.63	89.23
10	105.65	85.96	80.75	82.23	85.65	89.83	89.53	89.65	98.65	96.23

10.9. ALL COMPARATIVE GRAPH

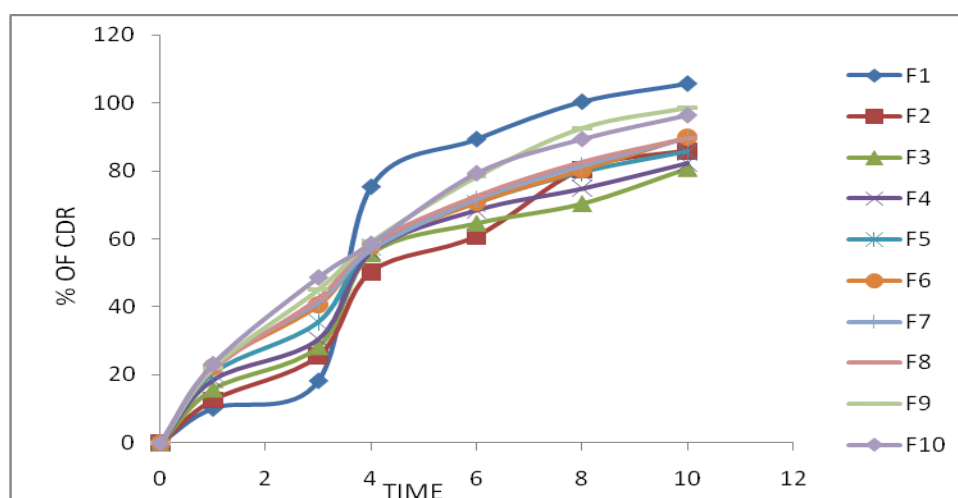
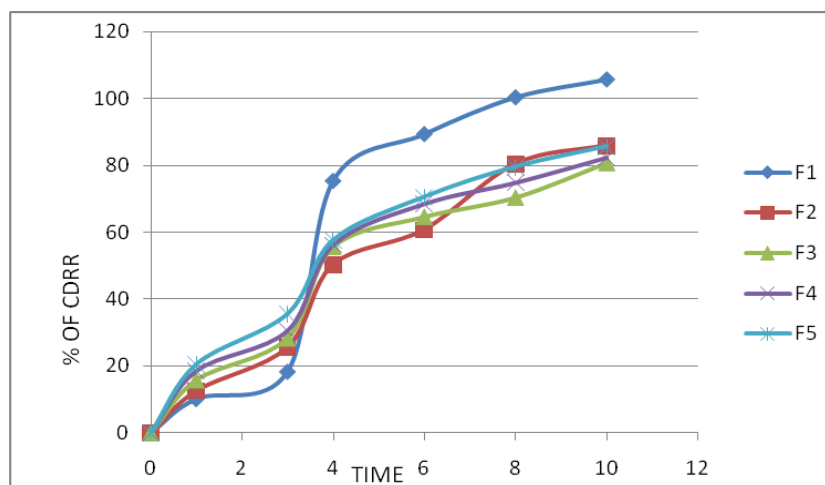


Fig.no.10: showing picture of in vitro drug release studies comparative graph

Table.no.16: COMPARATIVE GRAPHS FOR F1-F5:

Time in hrs	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	10.23	12.65	15.89	18.56	20.56
3	18.35	25.65	28.36	30.56	35.62
4	75.35	50.36	55.68	56.12	57.65
6	89.35	60.78	64.65	68.42	70.56
8	100.33	80.41	70.42	74.74	79.56
10	105.65	85.96	80.75	82.23	85.65

**Fig.no.11: Picture showing all Comparative drug release profile F1-F5****COMPARATIVE GRAPHS FOR F6-F10:****Table.no.17: COMPARATIVE GRAPHS FOR F6-F10**

Time in hrs	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	22.32	22.52	21.65	22.15	23.21
3	40.53	41.53	42.62	45.15	48.65
4	57.65	56.72	58.56	59.12	58.52
6	70.55	71.62	72.62	78.32	79.22
8	80.18	81.43	82.65	92.63	89.23
10	89.83	89.53	89.65	98.65	96.23

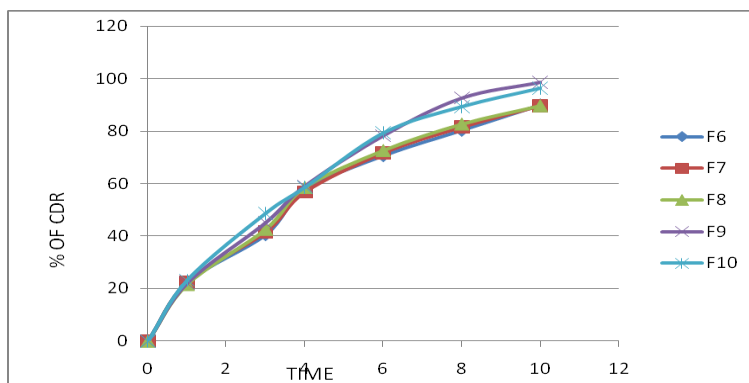


Fig.no.12: Picture showing all Comparative drug release profile for F6-F10

KINETIC PROFILE DATA:

KINETIC STUDIES:

Table.no.18: table showing kinetic studies

Time	%cdr	Log T	\sqrt{T}	Log%cdr	ARA	Log%ARA
0	0	1	0	0	100	2
1	22.15	0	1	1.34537373	77.85	1.89125862
3	45.15	0.47712125	1.73205081	1.65465775	54.85	1.73917663
4	59.12	0.60205999	2	1.77173443	40.88	1.61151089
6	78.32	0.77815125	2.44948974	1.89387268	21.68	1.33605928
8	92.63	0.90308999	2.82842712	1.96675166	7.37	0.86746749
10	98.65	1	3.16227766	1.99409709	1.35	0.13033377

ZERO ORDER REACTION

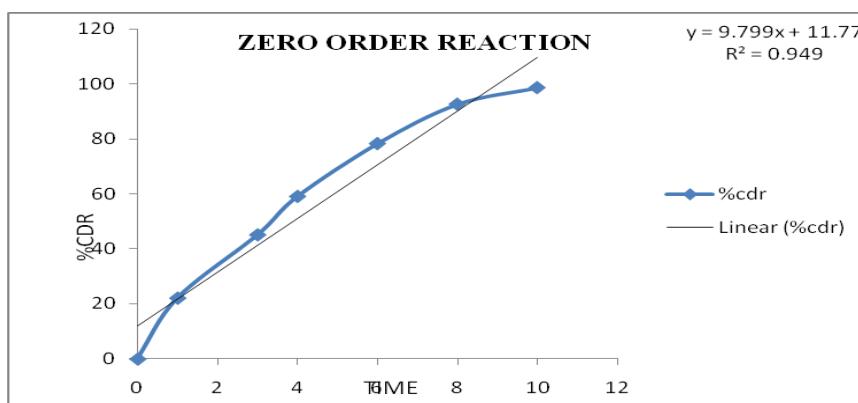


Fig.no.13: showing picture of zero order reaction

FIRST ORDER REACTION

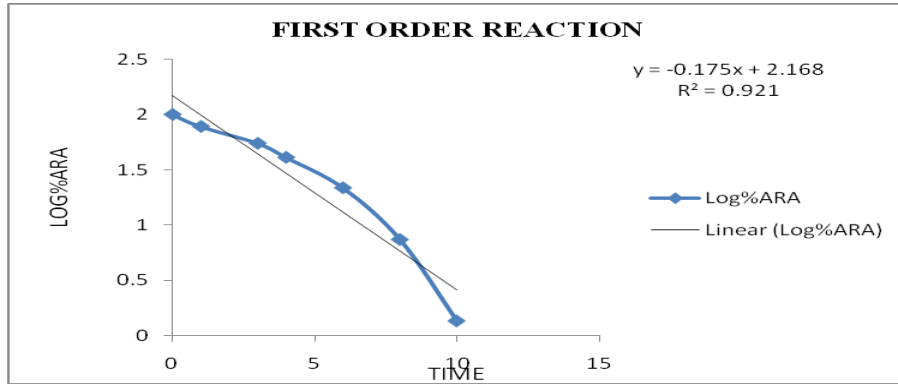


Fig.no.14: showing picture of First order Reaction

HIGUCHI EQUATION

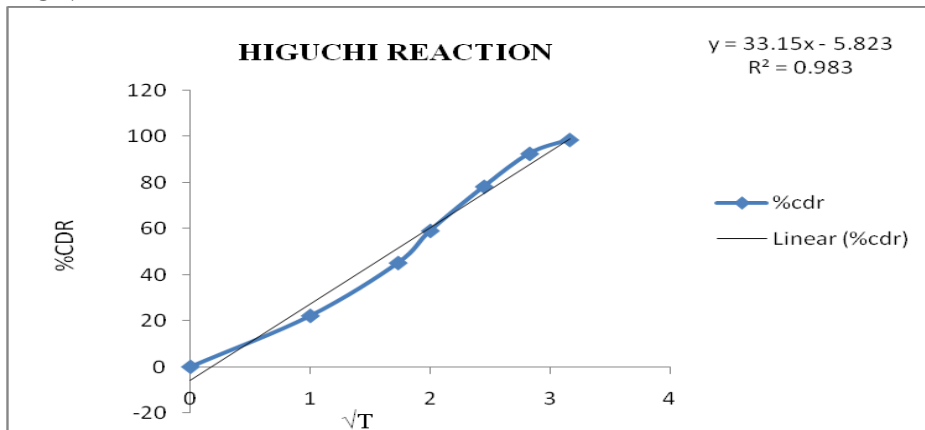


Fig.no.15: showing picture of higuchi

KROSS MAYER PEPPAS

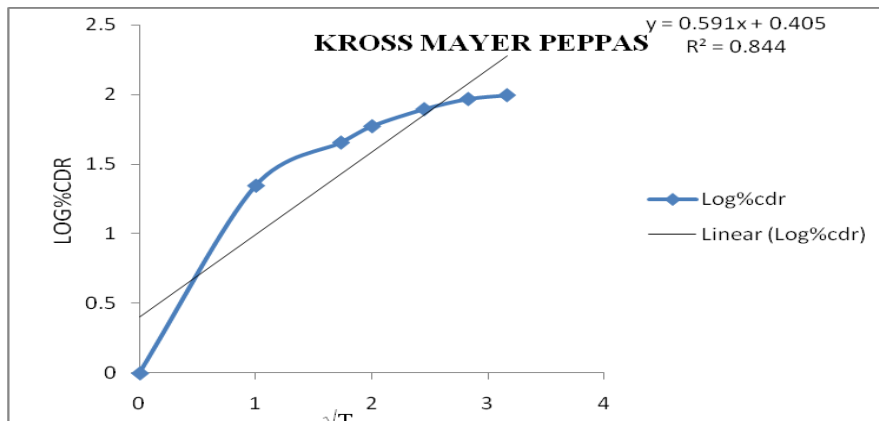


Fig.no.16: showing picture of krossmayer peppas

10.10. STABILITY RESULTS:

10.10.1.) STABILITY SAMPLES ARE STORED AT

- Accelerated: 40±2⁰C/75±5% RH
- Intermediate: 30±2⁰C/65±5% RH
- Long term: 25±2⁰C/60±5% RH

10.10.2.) TESTING INTERVALS

- Accelerated: Initial, 3 months.

Table.no.19: Results of stability studies of optimized formulation F-9

Formulation Code	Parameters	Initial	1 st month	2 nd month	3 rd month	Limits as per Specifications
F-9	25°C/60%RH % Release	98.65	99.7	97.56	99.53	Not less than 85 %

Discussion: It was concluded that stability studies of the optimized F9 was carried out using the samples at temperatures $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\% \text{RH}$ for a period 3 month the Nisoldipine tablets are observed and there is no significant change in the release characteristics and physicochemical properties.

SUMMARY

Formulation and evaluation of the sustained release tablets of the Nisoldipine. For development of the tablets different excipients are used. The used various excipients are the HPMC K4M, Xanthin gum, pvpk30, Mg.sterate, Talc, MCC used as the diluents, Mg.sterate used as the lubricants. Talc is used as Glidant.

For formulation design the literature review is carried out. The drugs selection and the polymer selection is based on the collection of review literature. The polymers choosing also carried out by the review literature.

Before going to development the pre formulation studies are done such as the color, odor, taste, solubility studies. The drug and the excipient compatibility studies are done by using the FTIR studies.

The formulation is developed by the using direct compression method. The formulation is prepared by using different excipients. The excipients are hpmc and xanthin gum in various compositions for drug to release in 10hrs. The pre compression parameters are done such as the bulk density, tap density, compressability index, Hauners ratio, Angle of repose. The all parameters are come under within range good flow. The post compression parameters are done such as the harness, thickness, weight variation, friability, disintegration.

The evaluation parameters of the optimised formulation F9 tablets values:

The weight variation of matrix tablets, 300mg

The hardness of the matrix tablets, $3.1(\text{Kg}/\text{cm}^2)$

Thickness of the matrix tablets, 2.50mm

Disintegration of the matrix tablets, 25 mins

Friability of the matrix tablets, 0.256 %

In-vitro drug dissolution studies of the oral dispersible tablets, 98.65%

The all parameters come under acceptable criteria within range of limits. The In-vitro drug release studies are done by USP-II apparatus paddle method. The optimised formulation F9 gives the prolong release upto 10hrs the drug release

CONCLUSION

Formulation and evaluation of the sustained release tablets of the Nisoldipine. The before going to formulate the tablets the preformulation studies are carried out such as FTIR, calibration, organoleptic characters. The formulation is developed by using different types of the super disintegrates such as the hpmc and xanthin gum in different trails. The pre compression parameters such as angle of repose, bulk density, true density, compressability index, these are found to be within the limits. The oral dispersible tablets of Nizatidine tablets are prepared by the direct compression method. The talc used as glidant and lactose used as lubricant mcc used as filler. The after development of oral dispersible tablets are undergo for evaluation parameters. Such as weight variation, thickness, friability, drug content, disintegration, and In vitro dissolution studies. They all are found in within range of limits. The in vitro drug release studies carried out by USP-II apparatus. The buffer medium 6.8. The optimised formulation undergoes for stability studies for 3 months. In stability studies the drug content and drug release studies carried out. These no degradation takes place in the drug content and drug release studies.

REFERENCES:

27. Roser BJ, Blair J. Rapidly Soluble Oral Dosage Forms, Method of making same and Compositions Thereof. US patent No. US 5762961, 1998.
28. Koizumi KI, et al. New Method for Preparing High-Porosity Rapid Saliva-Soluble Compressed Tablets Using Mannitol with Camphor a Subliming Material. Int. J. Pharm 1997; 152: 127-31
29. Makino T, Yamada M, Kikuta JI. Fast- Dissolving Tablet and its Production. US patent No. US 5720974, 1998.

4. 30. Gohel M, Patel M, Agarwal R, Amin A, Dev R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPS Pharm. Sci. Tech* 2004; 5(36): 1-6.
5. 31. Sreenivas SA. Orodispersible tablets: New-fangled drug delivery system- A Review. *Indian J.Pharm.Educ.Res* 2005; 39(4): 177-81.
6. 32. Chein YW. *Oral Drug Delivery and Delivery systems*, 2nd ed., New York: Marcel Dekker, 1992.
7. 33. Rakesh RK. Orally Disintegrating Tablets novel tablets novel approach to drug delivery. *Pharma Review* 2004; 2(12): 34- 6.
8. 34. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets: a novel drug delivery system. *Pharma Times* 2003; 35: 1-8
9. 35. Brown D. Orally disintegrating tablets – taste over speed. *Drug Delivery Technology*. [Http://www.drugdeliverytech.com/cgi-bin/articles.cgi?Idarticle=164](http://www.drugdeliverytech.com/cgi-bin/articles.cgi?Idarticle=164).
10. 36. Klauke J. Dissolution testing of orally disintegrating tablets. Retrieved from www.dissolutiontech.com.
11. 37. Harmon TM. Orally Disintegrating Tablets: a valuable life cycle Management Strategy”. *Pharmaceutical commerce*, march 2007, available online www.pharmaceuticalcommerce.com.
12. 38. Biradar SS, Bhagavati ST. Fast dissolving Drug Delivery System: A brief overview. *The Internet Journal of pharmacology* 2006; 4(2):1531-2972.
13. 39. Slowson M, Slowson S. What to do when patients cannot swallow their medications”. *Pharm. Times* 1985; 51: 90-6.
14. 40. Seager H. Drug-deliver Products and the Zydis Fast-dissolving Dosage Form. *J. Pharm. And Pharmacol* 1998; 50: 375-82.
15. 41. Reddy LH, Ghose, B., Rajneesh. *Indian J. Pharm. Sci* 2002; 64(4): 331- 36.
16. 42. Harmon TM. Beyond the first generation of Orally Disintegrating Tablets. *Emerging technology. Tablets and capsules*, 3rd Sep 2006.
17. 43. Dobbetti L. Fast- Melting Tablets: Developments and Technologies: *Pharmaceutical Technology. Drug Delivery* 2001 (Supplement): 44-50.
18. 44. Technology Catalysts International, “Oral Fast- Dissolving Drug delivery: Technologies, Market Analysis, & Business Opportunities.” August 2003.
19. 45. Hamilton E, Lutz E. Orally Disintegrating tablets. *Drug Delivery Technology*. January 2005.
20. 46. Indurwade NH, Rajyaguru TH, Nakhat PD. *Indian Drugs* 2002; 39(8): 405-09
21. 47. Rish RK. A review on fast dissolving tablets techniques. *The Pharma Review* 2004; 2: 32.
22. 49. Kahoka BS, Badhan AC, Mahajan HS. Mouth Dissolving Tablets: A Novel Drug Delivery System. *Pharma Times* 2003; 35: 7-14.
23. 50. Vanscoik KG. Solid pharmaceutical dosage in tablet triturates form and method of producing the same. US patent No. 5, 082, 667.
24. 51. Kogawa AC, Salgado HRN (2016) Optimization of Microbiological Method by Turbidimetry for Quantification of Rifaximin Tablets: Validation, Application and Evaluation of Degraded Compounds. *Pharm Anal Acta* 7: 518.
25. 52. Vargas M, Villarraga EA (2016) Bioequivalence Study of Two Formulations Containing Bosutinib 500 mg Tablets in Healthy Colombian Volunteers. *J Bioequiv Availab* 9: 299-301.
26. 53. Sravya I (2016) Tablets Manufacturing Methods and Granulation Techniques. *Research & Reviews: Journal of Pharmacology and Toxicological Studies*.
27. 54. Lachman L., Lieberman, H. A., Joseph L. K. *The Theory and Practice of Industrial Pharmacy*; Varghese Publishing House; Mumbai; Third Edition; Pp .297-321.
28. 55. Lachman L., Liberman H., and Kanig J. *The Theory and Practice of industrial pharmacy*; Third Edition: 293-345, 346-373.
29. 56. Aulton M. *Pharmaceutics: The Science of Dosage Form Design*; International student edition: 304-321, 347-668.
30. 57. Yeole PG, Galgatte UC, Babla IB and Nakhat PD. Design and Evaluation of xanthan gum based sustained release matrix tablets of diclofenac sodium. *Indian J Pharm Sci*.
31. 58. Derle DV, Kasliwal NH and Chavan N. Development and comparative evaluation of xanthan gum and guar gum based sustained release matrix tablets of tizanidine hydrochloride. *Indian drugs*. 2008;46(2):485-489.
32. 59. Basak SC, Jayakumar reddy BM and Lucas Mani KP. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. *Indian J Pharm Sci*.
33. 60. Rekhi GS, Nellore RV, Hussain AS, Tillman LG, Malinowski HJ and Augsburger LL. Identification of critical formulation and processing variables for Metoprolol tartrate extended release (ER) matrix tablets. *J Control Rel*.
34. 61. Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC and Takayama K. Once daily Propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. *Eur J Pharm Biopharm*.

35. 62. Nilesh P. Tekade^{1*}, Nitin S. Bhajipale¹, V. Ganesan², Raju R. Thenge³, Durgesh R. Dewade, Orodispersible Tablets Of Lansoprazole: Formulation, Characterization And In Vitro Evaluation, International Journal of chemtech Research CODEN(USA): IJCRGG ISSN : 0974-4290 Vol.2, No.1, pp 400-405,
36. 63. S. Ramu^{*}, P. Chandra Gopal Reddy, D. Srinivasa Rao and G. Ramakrishna, formulation and evaluation of lansoprazole delayed release pellets. International journal of pharmaceutical, chemical and biological sciences, ijpcbs 2015, 5(4), 860-878 Ramu et al. ISSN: 2249-9504
37. 64. Ref: * K.R. Vinod¹, A. Padma Sri¹, David Banji¹, S. Anbazhagan², Santhosh Vasa¹, S. Sandhya, Formulation and in vitro characterization of lansoprazole floating gastroretentive microspheres by modified non aqueous solvent evaporation method, Scholars Research Library Der Pharma Chemica, 2010, 2(5): 419-425.
38. 65. K. Satish Kumar¹, Santhosh Kumar Kasanagottu², Pendota Santhosh Kumar³, N. Nishanth Kumar⁴, P. Bharghav Bhushan, Formulation and in vitro evaluation of Ofloxacin tablets, Journal of Pharmacy Research 2011,4(9),3007-3009
39. 66. shazyatasneem^{*}, dr. K. V. Ratnamala, Formulation and Evaluation of Metformin Hydrochloride Immediate Release Tablets by Using Low-Density Excipients,ijppr, December 2017 Vol.:11, Issue:1
40. 67. Ref: Nagar Bhanu^{*}, Sheorey Sonali, Agrawal Vipul, Shah Nirmal, Shah Jainam, formulation and evaluation of orodispersible labetalol tablet for hypertensive crisis, Journal of Drug Delivery & Therapeutics; 2013, 3(6), 106-112
41. Ref: Srikant Pimple^{*}, Pravin Maurya, Akash Joshi, Mohan Salunke, Ruby Singh, formulation and evaluation of immediate release tablets of s (-) metoprolol succinate using roller compaction approach, world journal of pharmacy and pharmaceutical sciences sjif Impact Factor 5.210 Volume 4, Issue 07, 1551-1561. Research Article ISSN 2278 – 4357
42. Ref: Aher Smita^{1*}, Saudagar Ravindranath¹, Chaudhari Dhanshri², formulation and evaluation of taste masked fast dissolving tablet of prazosin hydrochloride, Journal of Drug Delivery and Therapeutics, Journal of Drug Delivery & Therapeutics. 2018; 8(4):263-271