WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 7, 1243-1271. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF NISLODIPINE USING DIFFERENT SUPERDISINTEGRANTS

B. P. Parameshwara*[1], Md. Rajdar[2], Dr. Mekkanti Manasa Rekha[3], Dr. Rinku Mathappan[4] and K. Rekha[5]

[1]Lecturer, Department of Pharmaceutics, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

[2]Student (Master of Pharmacy), Department of Pharmaceutics, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

[3]Assistant Professor, Department of Pharmacy Practice, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

[4]Principal Department of Pharmacognosy, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

[5]Lecturer, Department of Pharmaceutics, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

Article Received on
26 March 2019,

Revised on 16 April 2019,
Accepted on 06 May 2019,

DOI: 10.20959/wjpr20197-14986

***Corresponding Author**
B. P. Parameshwara
Lecturer, Department of Pharmaceutics, Gautham College of Pharmacy, R.T Nagar, Bangalore, Karnataka, India.

ABSTRACT

Hypertension (HTN) is one of the most important risks for Cardiovascular Disease, Stroke, Myocardial Infarction and end stage of Renal Disease. 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. The fast dissolving drug delivery system was chosen as the route of administration with an aim of overcoming the above mentioned difficulties. Dysphagia in Hypertension (HTN) patients is most commonly of infectious etiology. It is the medical term for the symptoms of difficulty in swallowing. Considering above clinical manifestation associated with HTN, a fast dissolving drug delivery of the proposed drug can prove to be beneficial in treating such conditions effectively. Pre formulation studies have confirmed purity of drug, lipophilicity and compatibility of drug with excipients used in the

formulation of mouth dissolving tablets. Pre-compression studies have confirmed stability of formulation blends for compression. Superdisintegrants viz. natural and synthetic were screened to obtain quick disintegration time. Formulation F18 containing mango peel powder at concentration 6% was found to have disintegration time of 18.12±0.13sec, wetting time35.19±0.58 sec. *In-vitro* studies of F18 indicated 98.916% of drug release in 45 min. Optimized formulation was found to be stable after 3 months accelerated stability studies. Hence with the proposed method, elegant MDTs of drug could be successfully formulated that would help improve the patient compliance.

KEYWORDS: Hypertension, Nisoldipine, Dysphagia, Mdts.

INTRODUCTION

Hypertension (HTN) is one of the most important risks for cardiovascular disease, stroke, myocardial infarction and end stage of renal disease. The risk of cardiovascular morbidity and mortality is directly correlated with blood pressure. The primary HTN occurs when the condition has no known cause. It cannot be cured but it can be controlled. More than 90% of individuals suffer from primary HTN and 10% of the patients suffer from secondary HTN. 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. The fast dissolving drug delivery system was chosen as the route of administration with an aim of overcoming the above mentioned difficulties. Dysphagia in Hypertension (HTN) patients is most commonly of infectious etiology. It is the medical term for the symptoms of difficulty in swallowing. Considering above clinical manifestation associated with HTN, a fast dissolving drug delivery of the proposed drug can prove to be beneficial in treating such conditions effectively. Pre formulation studies have confirmed purity of drug, lipophilicity and compatibility of drug with excipients used in the formulation of mouth dissolving tablets.

AIM: To Develop Effective Mode of Drug Delivery System to Anti-Hypertensive Drugs.

OBJECTIVES

- To enhance patient compliance and adherence to therapy
- To formulate fast dissolving tablet of Nisoldipine using superdisintegrants in different concentration by direct compression method.
- Screening of the various natural and synthetic Superdisintegrants.

- To carry out *in-vitro* evaluation of the optimized formulation.
- To carryout short term stability studies of optimized formulation.

MATERIALS AND METHODS USED

Table 1: List of Chemicals used and their Sources.

Sl.No.	CHEMICALS	SOURCE
1	Nisoldipine	Tablets
2	Mango Peel Powder	Sigma Aldrich Chemicals
3	Peritol 200- SD	RoquettePharma
4	Sacchrine	S D Fine Chemical Ltd
5	Talc	S D Fine Chemical Ltd
6	Vanilla	Himedia
7	SLS	S D Fine Chemical Ltd
8	Aerosil	Titan Biotech Ltd. Bhiwadi
9	Distilled Water	Indian Chemical Company
10	Methanol	S D Fine Chemical Ltd
11	NaOH	S D Fine Chemical Ltd
12	Potassuim Dihydrogenortho phosphate	Thomas Baker
13	n-Octanol	Thomas Baaker

Table 2: List of Instruments and Equipments used.

Sl. No.	INSTRUMENTS	SOURCE
1	Weighing balance	Shimadzu ELB 300
2	UV 1700 Spectrophotometer	Shimadzu, Japan
3	pH meter	MicroproGradmate
4	FTIR Shimadzu 8700	Shimadzu, Japan
5	Sonicator	Enertech Electronics Pvt Ltd
6	Orbital Shaker	Scigenics Biotech Pvt Ltd
7	Tablet Punching Machnine	Rimek Mini-Press- 11 SF
8	Hardness Tester	Monsanto tester
9	Friability	Electrolab
10	Dissolution Apparatus	Electrolab
11	Disintegration Apparatus	Electrolab

EXPERIMENTAL METHODOLOGY

Experimental methodology can be divided into three sections as:

- **Preformulations studies**
- **Formulation Development**
- **Evaluation**

PREFORMULATION STUDIES

Identification of drug by FT-IR: The study of pure drug IR spectrum was carried out using Shimadzu FTIR-8700 spectrophotometer. Potassium bromide disc method was employed.

The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded from 4000 to 500 cm^{-1}.

Estimation of Nisoldipine by UV method-Estimation of Nisoldipine by UV-Spectrophotometric method: A Shimadzu UV-1700 double beam UV-Visible spectrophotometer with software of UV-probe was used for all measurements. The absorption spectra were recorded over the wavelength range of 400 - 200 nm, against a solvent blank, in quartz cuvettes with a width of 1cm. For all solutions, the spectra were obtained over 400 - 200 nm range in triplicate. The linearity of the calibration curves and the adherence of the method to Beer's law are validated by the high value of the correlation coefficient.

Preparation of standard stock solution: About 100 mg of Nisoldipine (pure) was accurately weighed and dissolved in 30 mL ethanol. The solution was sonicated for 30 minutes. The solution was filtered through Whatman filter paper, volume of the filtrate made up to 100 mL with ethanol (1 mg/mL). 10 mL of the stock solution was diluted to 100mL with ethanol. Aliquots of 0.4 -2.0 mL of the diluted solution was further diluted to 10 mL with ethanol and the absorbance was measured at 237 nm using ethanol as blank and area under curve was measured between 232- 237 nm.

λmax of pure Nisoldipine: For the selection of analytical wavelength 10 µg/mL solution of Nisoldipine was prepared by appropriate dilution of standard stock and scanned using UV spectrophotometer.in the spectrum mode from 200nmto 400nm.

Standard Calibration curve: From the standard stock solution, 1ml was taken into a 10mL volumetric flask and made up to 10mL with distilled water to get concentration of 100 µg/mL. From the above working standard solution aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 1.2, 1.4, 1.6, 1.8 and 2.0mL were taken into different 10mL volumetric flasks and diluted up to mark with distilled water to get the concentration from 2–20µg/mL and the calibration curve was prepared in concentration range of 2- 20 µg/mL.

Intra - day variability: Precision studies were carried out to ascertain the reproducibility of proposed method. Intra –day precision study was carried out by preparing drug solution of same concentration and analyzing for three different times in a day. Concentration of

Nisoldipine in each replicate was calculated. The standard deviation was calculated from the concentration of Nisoldipine. The result reported as percent relative standard deviation (% RSD). For a good reproducibility % RSD should be ≤ 3**.**

Inter - day variability: Inter-day studies were carried out by preparing drug solution of same concentration and measured the absorbance for three different days to determine inter-day precision. The results were reported as % RSD. For a good reproducibility % RSD should be ≤ 3.

Partition Coefficient: Partition Coefficient was determined in n-octanol-water using flask shake method. Equal volumes of n-octanol and water (10 mL) were taken in separating funnel and shaken for 1 hour. To this known amount of Nisoldipine was added. The funnel was equilibrated for 2 hrs at constant temperature with intermittent shaking at regular intervals. Then, the aqueous and n-octanol layers were allowed to separate. From the aqueous layer 1 mL solution was pipetted and assayed by UV at appropriate wavelength after dilution with methanol. Organic layer was evaporated to dryness in a china dish and the residue was diluted up to 10 mL with methanol and was analyzed spectrophotometrically against the blank.

The partition co-efficient is calculated using the following equation:

$$Partition\ co-efficient = \frac{conc.of\ the\ drug\ in\ Organic\ Layer}{conc.of\ the\ drug\ in\ Aqueous\ Layer}$$

In-vitro **Permeation Studies of Nisoldipine:** Permeation studies of the pure drug was carried out using cellophane membrane (soaked in 0.1M HCl for 10 hr). The modified Franz diffusion cell assembly was used. Throughout the study the whole assembly was kept at 37°C ±2°C. The medium in the donor compartment was drug solution dissolved in pH 6.8 phosphate buffer solution, and the medium used in acceptor compartment was pH 7.8 buffer solution, which was continuously stirring by placing on a magnetic stirrer. The samples were withdrawn at predetermined, regular time intervals and an equal amount of fresh medium was replaced. Amount of drug in the withdrawn samples was determined spectrophotometrically. Permeability co-efficient is defined as the volume of an incompressible fluid that flows in unit time through a unit cube of a porous substance across which a unit pressure difference is maintained. Permeability Co-efficient is calculated by Potts-guy equation:

Log KP = -2.7+0.71×log K o/w -0.0061×mol.wt.

Solubility studies of pure Drug in Different Solvents: Solubility measurements were performed using method reported by Higuchi and Connors. An excess amount of Nisoldipine was added to each of 25 ml of water, pH 1.2, pH 6.8 and pH 7.4 buffer respectively in Schott Durran bottles. The bottles were placed in holder and shaken for 24hrs at room temperature in water bath shaker. The samples were filtered through Whatmann filter paper No.1. The filtrate was suitably diluted and analyzed spectrophotometrically against blank at appropriate wavelength.

Drug-Excipients compatibility study: Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of dosage form.

FT-IR Compatibility studies: The study of pure drug and physical mixture of drug and excipients IR spectrum were carried out using Shimadzu FTIR-8700 spectrophotometer. Potassium bromide disc method was employed and spectrum was recorded from 4000 to 500 cm^{-1}

FORMULATION OF MTDs

Formulation of Mouth dissolving Tablets (MDTs) Of Nisoldipineby Using Synthetic Superdisintegrants: Before the formulation of tablets, the best synthetic super disintegrant among sodium starch glycolate (SSG), Kyron T-314 and croscarmellose sodium (CCS) at different concentration was screened out. After selecting a suitable super disintegrant using perlitol-200 SD as a diluent, which will provide soothing effect as well as comply with MDT's properties.

Table 3: Formulation of MDTs using synthetic Super disintegrants.

SI.No.	SCREENING STAGE								
	INGREDIEN-TS	FORMULATION CODE							
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Nisoldipine (mg)	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
2	Crosscarmellose (mg)	6	8	10						
3	Sodium starch Glycolate (mg)				6	8	10			
4	Kyron T-314(mg)							6	8	10
5	Aerosil (mg)	5	5	5	5	5	5	5	5	5
6	SLS (mg)	2	2	2	2	2	2	2	2	2
7	Perlitol-200 SD (mg)	175.8	172.8	170.8	173.8	172.8	170.8	174.8	172.8	170.8
8	Talc (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
9	Saccharin (mg)	2	2	2	2	2	2	2	2	2
10	Vanilla (mg)	1	1	1	1	1	1	1	1	1

Formulation of Mouth Dissolving Tablet (MDTs) Of Nisoldipineby Using Natural super disintegrants: Before the formulation of tablets, the best natural super disintegrants among mango powder, banana powder, and guar gum at different concentration was screened out. After selecting a suitable super disintegrants using Perlitil-200SD as a diluent, which will provide soothing effect as well as comply with MDT's properties. The best natural super disintegrants were then used to prepare final formulation.

Table 4: Formulation of MDTs using natural Superdisintegrants.

SI. No.	INGREDIENTS	SCREENING STAGE								
		FORMULATION CODE								
		F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Nisoldipine (mg)	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
2	Guar gum (mg)	4	8	12						
3	Banana powder (mg)				4	8	12			
4	Mango peel pectin (mg)							4	8	12
5	Aerosil (mg)	5	5	5	5	5	5	5	5	5
6	SLS (mg)	2	2	2	2	2	2	2	2	2
7	Perlitol-200 SD	175.8	171.8	167.8	175.8	171.8	167.8	175.8	171.8	167.8
8	Talc (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
9	Saccharin (mg)	2	2	2	2	2	2	2	2	2
10	Vanilla (mg)	1	1	1	1	1	1	1	1	1

PRE-COMPRESSION EVALUATION

Bulk density (ρb) and tapped density: It is the ratio of total mass of powder and the bulk volume of powder. It was determined by the commonly used method, where accurately weighed quantity of the blended mixture (10gm) was carefully poured into the graduated cylinder and the bulk volume was recorded with and without tapping. The untapped (Du) and tapped bulk densities (Dt) were calculated from the following formula, weight of blended mixture/ untapped volume and weight / tapped volume, respectively. It is expressed in gm/ml.

Carr's index (I) or Percentage compressibility: An important measure that can be obtained from bulk density is the determination of percent compressibility or Carr's index, which is defined as: $I = \frac{Dt-Du}{Dt} x\ 100$, Where, Dt is the tapped bulk density of the powder and Du is the untapped bulk density of the powder. In theory, a blended mixture having an 'I' value of less than 25% is defined to have more free flowing property and good compressibility.

Hausner's Ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the formula: $H = \frac{Dt}{Du}$ Where, D*u* is the freely

settled bulk density of the powder, and D*t*is the tapped density of the powder. The Hausner ratio is used as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Angle of Repose: It may be defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height h above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. Value of θ are rarely less than 20° and values up to 40° indicates good flow potential. The angle of repose was then calculated using the formula. $\mathrm{Tan}\theta = \frac{h}{r}$ Where, θ= Angle of Repose**,** h= Height of Pile (cm), r = Radius of the base of the pile (cm).

TABLET COMPRESSION: Following the evaluation of the powder blend, the powder was compressed using a Rimek Tablet punching machine. The drug-excipients mixture was then punched using 8 mm single-punch machine to produce convex-faced tablets weighing 200 mg each. The composition of different batches and optimization stages with formulation codes from F1 to F18 is shown in the Table-11 and Table-12. Compressed tablets were further subjected to post compression evaluation.

POST COMPRESSION EVALUATION

Hardness test: The Monsanto hardness tester was used which consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and zero reading is taken. The upper plunger is then forced against a spring by turning threaded bolt until the tablet breaks. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of break is recorded and zero force reading is deducted from it.

Friability: Tablets were tested for friability using Electrolab (EF2) Friabilator. Twenty tablets were weighed initially and transferred to the friabilator. The instrument was set to 25 rpm for 100 rotations. The resulting tablets were reweighed and percentage loss was calculated using the formula: $\%\ \mathrm{Friability} = \frac{\text{Initial Wt.} - \text{Final Wt.}}{\text{Initial Wt.}} \times 100$

Wetting time: This is carried out to measure the time, which is required for the complete wetting of tablet formulations.

Method: Wetting time of tablet was determined using a simple procedure. A piece of double folded tissue paper was placed in a petri dish containing 6 mL of water. The tablet was placed on the paper and the time for complete wetting of upper surface of the tablet was measured in seconds.

***In-vitro* Disintegration test:** The *in vitro* disintegration time was determined using Electro lab- USP Disintegration apparatus. The limit for disintegration should not be more than 60 seconds at 37°C.

Method: Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed on it. The disintegration time was determined in simulated salivary fluid (pH 6.8) with temperature maintained constant at 37°C ± 1°C.

Drug content: Three tablets were weighed and powdered. Powder equivalent to 10 mg of Nisoldipine was dissolved in 25ml of 0.1 N HCl filtered and the filtrate was suitably diluted with methanol. The samples were analyzed by UV at appropriate wavelength.

***In-vitro* dissolution studies**

Dissolution medium : Simulated gastric fluid (pH1.2)
Dissolution volume : 900mL
Dissolution apparatus Type : Type II (paddle method)
RPM : 75 RPM
Temperature : 37°C ± 0.5°C
Samples withdrawn : 5ml

Dissolution was carried out for 1hr. Initially samples were withdrawn at 2 min interval for first 10 minutes. Further the samples were withdrawn at 15th, 20th, 25th, 30th, and 45th minute. At each interval 5mL of samples were withdrawn and filtered through Whatman filter paper No. 1, the initial volume of dissolution medium was maintained by adding 5mL of fresh dissolution medium. From the 5mL withdrawn sample, 1mL was taken and volume was made up to 10mL with 6.8 pH phosphate buffer and analyzed using by UV-Visible spectrophotometer. From absorbance values, percent drug dissolved at various time intervals was determined.

Weight Variation: 20 tablets of optimized batch F18 were weighed individually; the average weight was calculated and compared with the individual tablet weight. The tablets meet the

test if not more than two tablets are outside the percentage limit and none of the tablet differs by more than two times the percentage limit. The weight variation tolerance for uncoated tablets differs depending on average weight of the tablets.

Drug Release Kinetic Studies: In order to analyse the drug release mechanism, *in-vitro* release data for the optimized formulation F18 were fitted into zero order, first order, Higuchi matrix, Hixson-Crowell cube root law and Kormeyers-Peppas model.

Stability studies: Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Method: The final formulation (tablets) were filled in screw capped, labeled bottles and stored for 3 months at 40°C ± 2°C/75% RH ± 5% RH. The tablets were evaluated for any changes in the physical characteristic, friability, *in-vitro* drug release studies and drug content.

RESULTS

PREFORMULTION STUDY OF MODEL DRUG

Description: The drug was yellow, crystalline and odourless powder.

Table No 5: Standard calibration curve plot data of in Ethanol.

SL.NO	CONCENTRATION	ABSORBANCE
1	0	0
2	2	0.115
3	4	0.182
4	6	0.271
5	8	0.323
6	10	0.442
7	12	0.521
8	14	0.635
9	16	0.722
10	18	0.831
11	20	0.945

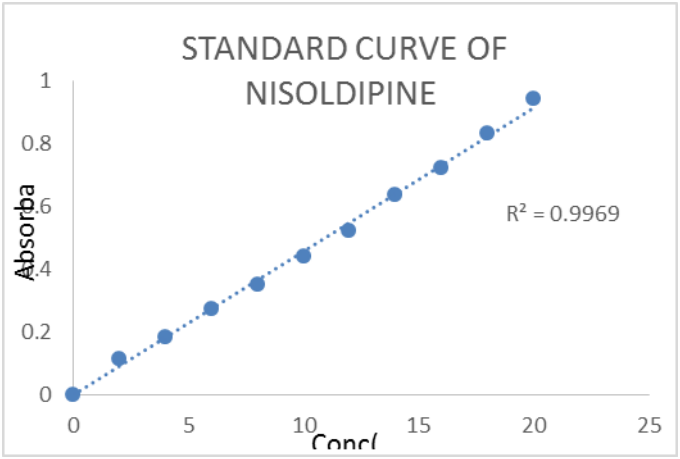


Fig No 1: Standard curve of drug in Ethanol.

Table No 6: Intra-Day Variability of Nisoldipine.

		Absorbance				
Sl.No	**Conc**	**Abs-1(10am)**	**Abs-2(1Pm)**	**Abs-3(4Pm)**	**Avg**	**%SD**
1	0	0	0	0	0	0
2	2	0.107	0.117	0.123	0.1157	0.0081
3	4	0.172	0.189	0.197	0.1860	0.0128
4	6	0.248	0.267	0.282	0.2657	0.0170
5	8	0.348	0.354	0.345	0.3490	0.0046
6	10	0.441	0.458	0.469	0.4560	0.0141
7	12	0.528	0.523	0.532	0.5277	0.0045
8	14	0.625	0.637	0.648	0.6367	0.0115
9	16	0.71	0.722	0.736	0.7227	0.0130
10	18	0.822	0.831	0.843	0.8320	0.0105
11	20	0.923	0.954	0.961	0.9460	0.0202

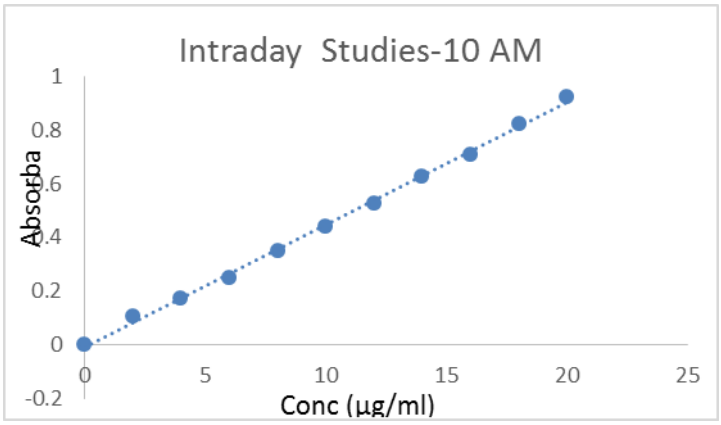


Fig no 2: Intra-day variability studies of Nisoldipine (Reading 1).

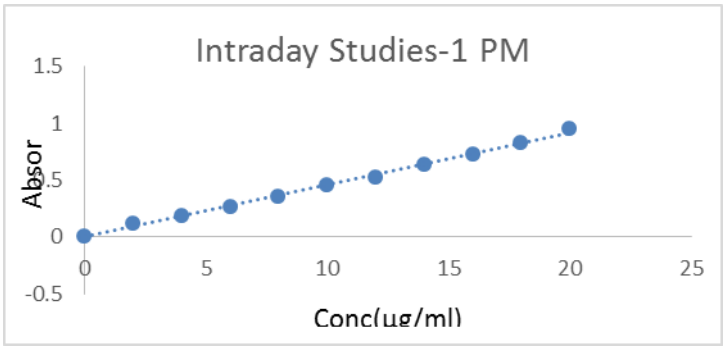


Fig no 3: Intra-day variability studies of Nisoldipine (Reading 2).

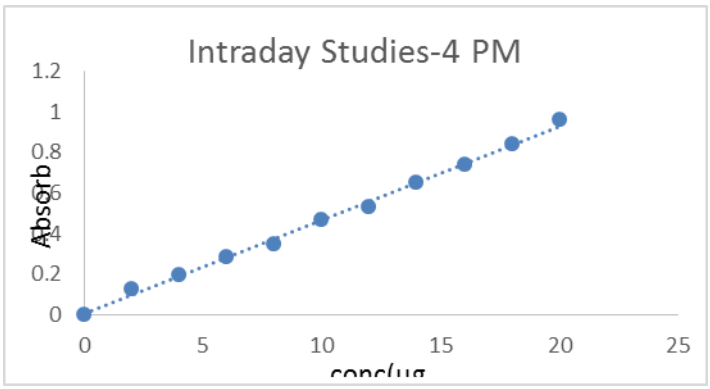


Fig no 4: Intra-day variability studies of Nisoldipine (Reading 3).

Table No 7: Inter-Day Variability of Nisoldipine.

		Absorbance				
Sl.no	**Conc**	**Abs(Day-1)**	**Abs(Day-2)**	**Abs(Day-3)**	**Avg**	**%SD**
1	0	0	0	0	0	0
2	2	0.102	0.115	0.119	0.1120	0.0089
3	4	0.161	0.182	0.187	0.1767	0.0138
4	6	0.234	0.271	0.286	0.2637	0.0268
5	8	0.323	0.323	0.338	0.3280	0.0087
6	10	0.421	0.442	0.456	0.4397	0.0176
7	12	0.517	0.521	0.532	0.5233	0.0078
8	14	0.614	0.635	0.643	0.6307	0.0150
9	16	0.702	0.722	0.732	0.7187	0.0153
10	18	0.817	0.83	0.842	0.8297	0.0125
11	20	0.914	0.945	0.956	0.9383	0.0218

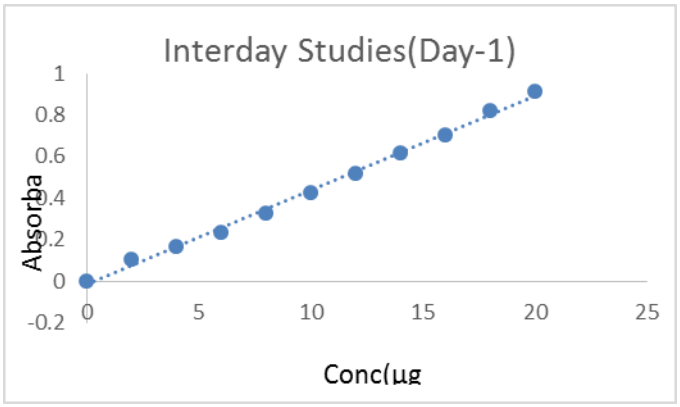


Fig 5: Inter-day variability studies of Nisoldipine (Day 1).

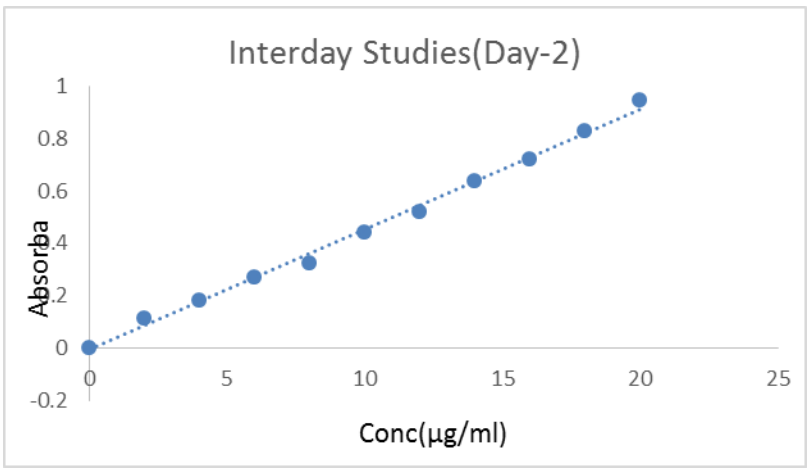


Fig 6: Inter-day variability studies of Nisoldipine (Day 2).

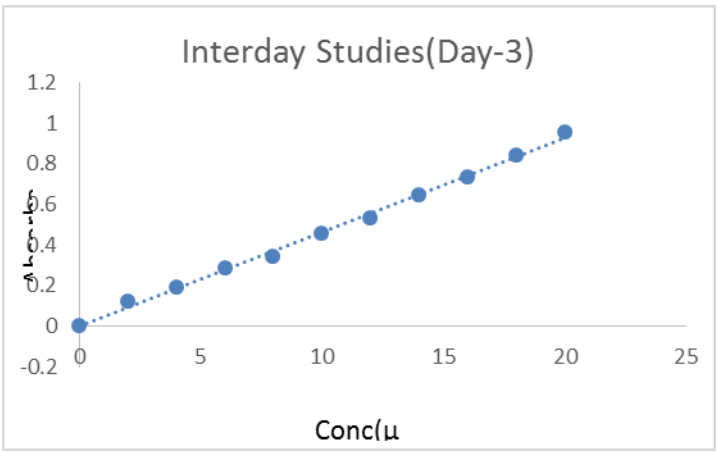


Fig no 7: Inter-day variability studies of Nisoldipine (Day 3).

Partition co-efficient: Partition co-efficient of nisoldipine was found to be 3.26 by Shake-Flask method.

***In-Vitro* PermeationStudies of Nisoldipine**

Table 8: *In-vitro* permeation studies data of Nisoldipine.

Time (hrs)	%CPR	%CPR	%CPR	AVG±SD
0	0	0	0	0
1	3.261	3.262	3.261	3.261±0.000577
2	9.880	9.880	9.870	9.877±0.005774
3	15.174	15.174	15.175	15.174±0.000577
4	20.085	20.585	20.085	20.251±0.288675
5	25.589	25.589	25.689	25.622±0.057735
6	40.965	40.965	40.665	40.765±0.173205
7	55.396	55.396	55.410	55.400±0.008033
8	69.742	69.742	69.741	69.742±0.000577
9	81.004	81.004	81.204	81.071±0.11547
24	98.957	98.957	98.896	98.196±0.035143

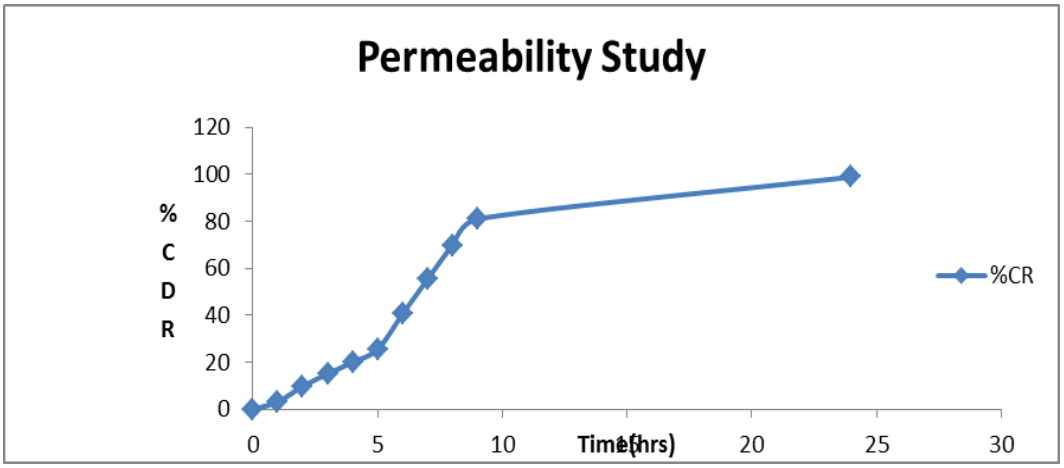


Fig no 8: Permeability Study of Nisoldipine.

Permeability coefficient: The permeability co-efficient of pure Nisoldipine was found to be -3.1, calculated by Potts-guy equation: **Log K_p = -2.7+0.71×log K o/w -0.0061×mol.wt.** Where, Log K o/w = 0.342, Mol. wt= 441.36g/mol.

Log K_p = -2.7+0.71×0.342-0.0061×441.36

Log Kp = -3.1

Solubility: Drug was soluble in ethanol. The solubility of the drug was also examined in various buffers. The results are shown in Table. 10**.**

Table No 9: Solubility of Drug.

Sl. No.	Solvent	Solubility (mg/ml)
1.	Purified water	5.5
2.	pH 1.2 buffer	37.9
3.	pH 3.0 Acetate buffer	9.7
4.	pH 4.5 Acetate buffer	6.0
5.	pH 6.8 phosphate buffer	13.0
6.	pH 7.2 phosphate buffer	20.2

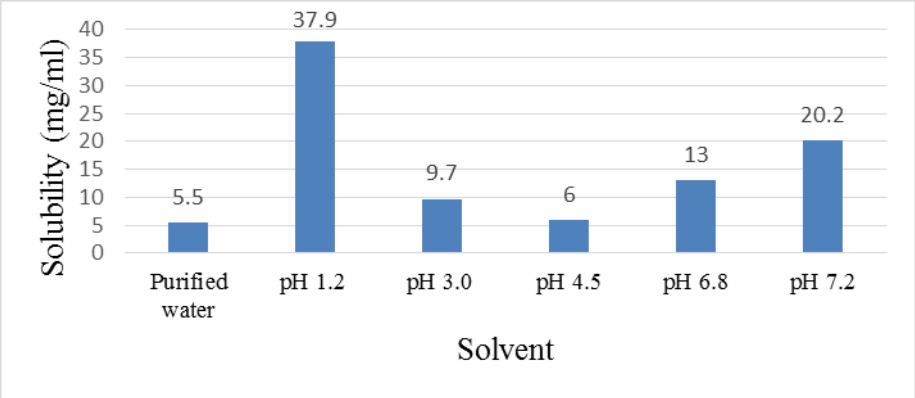


Fig No 9: Solubility of Drug Sample.

Fourier Transform Infrared Spectroscopy (FT-IR) study for model drug: The IR spectrum of model CCB drug and confirms the presence of the characteristic functional groups was in good agreement with the literature findings.

Table No 10: FT-IR spectrum data.

Functional groups	IR Absorption Band (cm^{-1}) (observed)
N-H Stretching	3350 cm^{-1}
C-H Stretching(Aromatic)	2800 cm^{-1}
C-H Stretching(Aliphatic)	3250 cm^{-1}
NO2 Stretching	1531 cm^{-1}
C=C Stretching(Aromatic)	1493 cm^{-1}
C-O Stretching	1215 cm^{-1}

COMPATABILITY STUDIES Compatibility studies by FT-IR

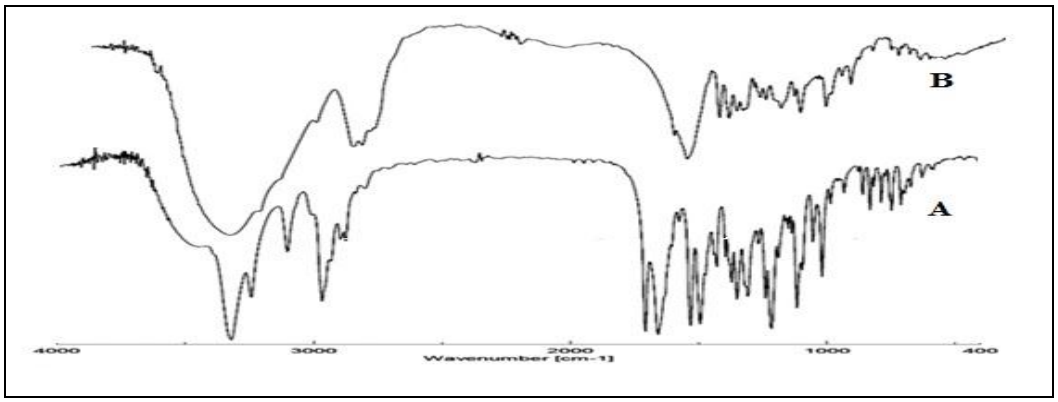


Fig No 10: FTIR Spectrum of API (A) and API + Excipients (B).

FORMULATION OF MTD

Formulation of Mouth dissolving Tablets (MDTs) Of Nisoldipine by using different Synthetic and natural Superdisintegrants is done. All the raw materials were passed through a #40sieve prior to mixing. Drug and the superdisintegrants(Sodium Starch Glycolate/Croscarmellose Sodium/ Kyron T-314), saccharin, (1%) vanilla flavour and Pearlitol SD 200 (as much as required) were blended. The powder blend was lubricated with 0.1% Talc and 1% SLS. The powder blend was mixed properly and subjected for pre-compression evaluation parameters.

PRE-COMPRESSION EVALUATION

Table no 11: Evaluation of the powder blend of MDTs of Nisoldipine with Synthetic superdisintegrants.

SI no.	Evaluated parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Untapped density* (g/mL) ± S.D	0.544± 0.001	0.537± 0.001	0.536± 0.001	0.468± 0.001	0.468± 0.002	0.463± 0.001	0.462± 0.001	0.412± 0.002	0.408± 0.001
2	Tapped density* (g/mL) ± S.D	0.576± 0.004	0.566± 0.005	0.568± 0.005	0.530± 0.004	0.529± 0.004	0.530± 0.006	0.440± 0.007	0.439± 0.006	0.437± 0.006
3	% Compressibility* ± S.D	12.76± 0.419	12.36± 0.426	11.25± 0.526	12.18± 0.450	12.67± 0.425	12.63± 0.550	11.65± 0.236	12.89± 0.289	11.99± 0.415
4	Hausner's ratio*±S.D	1.136± 0.01	1.145± 0.04	1.114± 0.06	1.144± 0.07	1.145± 0.02	1.069± 0.02	1.083± 0.05	1.062± 0.03	1.058± 0.06
5	Angle of Repose* ±SD	26°01'± 0.278	26°96'± 0.287	25°83'± 0.184	25°89'± 0.148	27°36'± 0.294	26°19'± 0.318	27°12'± 0.298	26°50'± 0.283	27°35'± 0.243

Screening of Natural Superdisintegrants

Table no 12: Evaluation of the powder blend of MDTs of Nisoldipine with natural superdisintegrants.

SI no.	Evaluated parameters	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Untapped density* (g/mL) ± S.D	0.545± 0.001	0.527± 0.001	0.586± 0.001	0.463± 0.001	0.462± 0.002	0.423± 0.001	0.452± 0.001	0.452± 0.002	0.438± 0.001
2	Tapped density* (g/mL) ± S.D	0.676± 0.004	0.666± 0.005	0.518± 0.005	0.520± 0.004	0.529± 0.004	0.510± 0.006	0.540± 0.007	0.459± 0.006	0.447± 0.006
3	% Compressibility*± S.D	12.86± 0.419	12.26± 0.426	11.15± 0.526	12.38± 0.450	12.57± 0.425	12.53± 0.550	11.25± 0.236	12.39± 0.289	12.99± 0.415
4	Hausner's ratio*±S.D	1.126± 0.01	1.545± 0.04	1.154± 0.06	1.144± 0.07	1.145± 0.02	1.059± 0.02	1.013± 0.05	1.002± 0.03	1.018± 0.06
5	Angle of Repose* ±SD	26.21± 0.278	26.06± 0.287	25.23± 0.184	25.59± 0.148	27.46± 0.294	26.49± 0.318	27.52± 0.298	26.90± 0.283	27.45± 0.243

TABLET COMPRESSION

The optimization of superdisintegrants is done by direct compressiontechnique in order to study the effect of the different concentrations of synthetic superdisintegrants (Sodium Starch Glycolate, KyronT-314, and Croscarmellose Sodium) and natural superdisintegrants (Mango peel powder, Banana powder, Guar gum) on thedisintegration time, wetting time, and percent of friability.

POST COMPRESSION EVALUATION

Table 13: Evaluation of the MDTs of Nisoldipine with Synthetic superdisintegrants.

SI no.	Evaluated parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Hardness (kg/cm^2)±S.D	5.5± 0.21	5.6± 0.32	5.0± 0.12	5.1± 0.22	5.5± 0.43	5.4± 0.13	5.3± 0.23	5.5± 0.22	5.6± 0.20
2	Friability (%)±S.D	0.47± 0.032	0.38± 0.013	0.45± 0.041	0.31± 0.06	0.48± 0.014	0.50± 0.021	0.54± 0.026	0.31± 0.025	0.42± 0.023
3	Wetting time (sec)±S.D	71.17± 0.43	70.18± 0.56	69.19± 0.54	65.13± 0.65	63.24± 0.58	61.19± 0.60	55.14± 0.62	52.12± 0.56	48.19± 0.58
4	Disintegration Time (sec)±S.D	64.49± 0.72	60.77± 0.82	57.84± 0.70	44.90± 0.68	41.20± 0.51	38.18± 0.45	28.12± 56	26.03± 0.61	24.12± 0.13
5	Drug Content (%) ± S.D	89.51± 0.032	87.25± 0.030	90.14± 0.032	85.12± 0.031	85.56± 0.032	89.74± 0.032	89.99± 0.030	92.14± 0.032	93.01± 0.031

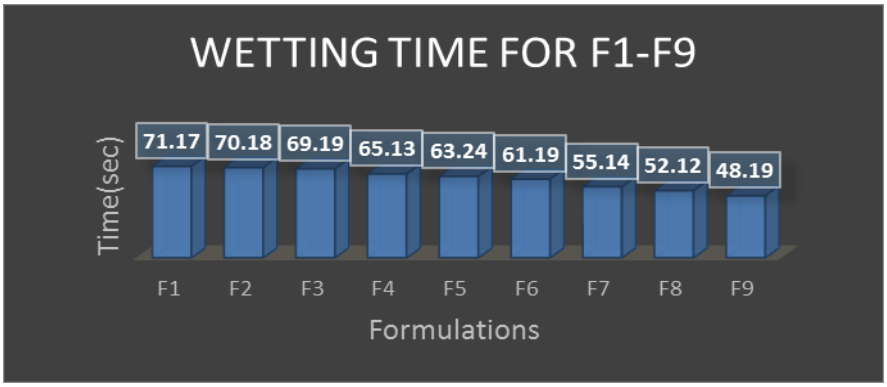


FIG no 11: Graphical representation of wetting time for F1-F9.

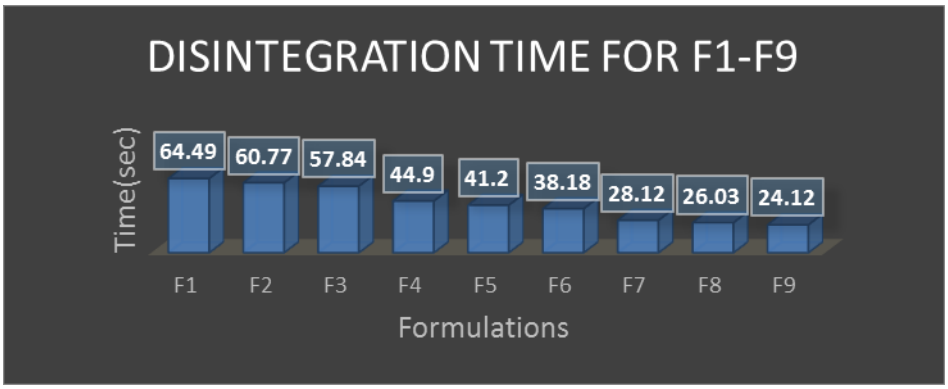


FIG no 12: Graphical representation of disintegration time for F1-F9.

Table 14: Evaluation of the MDTs of Nisoldipine with natural superdisintegrants.

SI no.	Evaluated parameters	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Hardness (kg/cm^2)±S.D	5.5± 0.21	5.6± 0.32	5.5± 0.12	5.1± 0.22	5.5± 0.43	5.4± 0.13	4.3± 0.23	4.5± 0.22	4.6± 0.20
2	Friability (%)±S.D	0.46± 0.032	0.48± 0.013	0.55± 0.041	0.31± 0.06	0.48± 0.014	0.50± 0.021	0.44± 0.026	0.31± 0.025	0.42± 0.023
3	Wetting time (sec)±S.D	74.14± 0.43	73.18± 0.56	71.19± 0.54	75.13± 0.65	71.24± 0.58	68.19± 0.60	38.14± 0.62	36.12± 0.56	35.19± 0.58
4	Disintegration Time (sec)±S.D	68.49± 0.72	55.77± 0.82	52.84± 0.70	44.90± 0.68	41.20± 0.51	38.18± 0.45	28.12± 56	24.03± 0.61	18.12± 0.13
5	Drug Content (%) ± S.D	89.45± 0.030	90.45± 0.032	93.56± 0.032	92.14± 0.031	91.78± 0.032	92.88± 0.032	91.74± 0.033	92.45± 0.032	95.65± 0.031

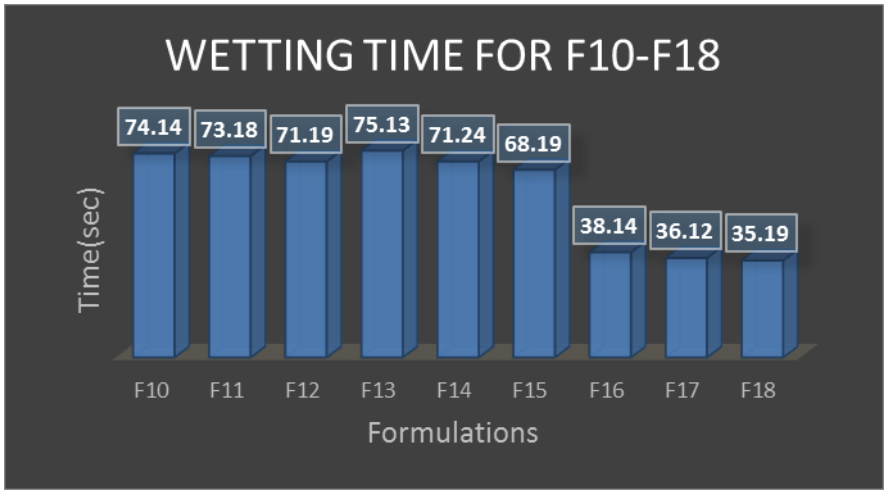


FIG 13: Graphical representation of wetting time for F10-F18.

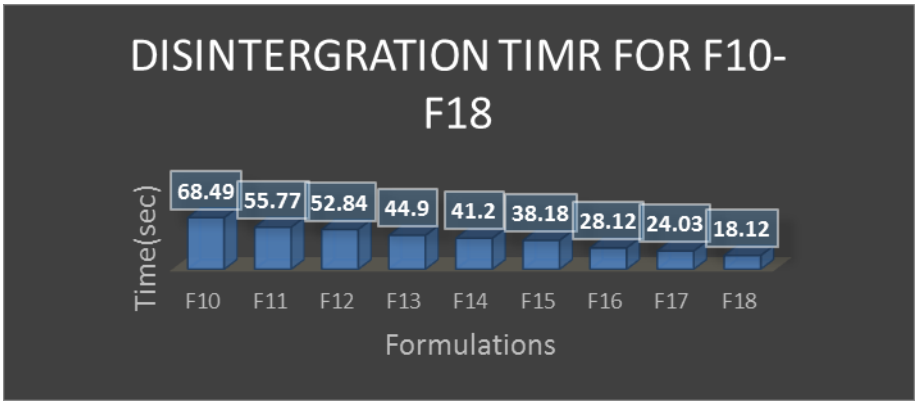


FIG no 14: Graphical representation of disintegration time for F10-F8.

***In-vitro* Drug Release Studies**

Table 15: *In-vitro* Drug Release of the MDTs of Nisoldipine with Synthetic superdisintegrants.

TIME(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	36.14	35.45	38.46	40.76	41.17	42.1	43.01	45.96	47.86
4	54.12	53.86	55.93	55.38	58.56	58.73	57.14	58.99	54.29
6	63.58	60.13	61.23	62.86	65.18	67.19	65.19	68.26	67.16
8	68.16	65.66	66.59	68.76	69.18	69.89	67.19	69.18	69.36
10	69.99	68.15	70.16	72.16	74.16	75.19	74.18	76.59	79.66
15	71.28	73.58	74.89	75.86	79.15	80.46	79.49	80.19	81.79
20	73.44	75.56	76.59	77.49	79.99	81.09	81.16	83.79	83.19
25	75.12	76.99	77.16	78.23	80.46	82.17	82.46	84.77	85.76
30	76.76	77.13	78.12	79.16	81.14	83.46	84.66	85.49	87.76
45	78.02	79.1	79.89	80.22	82.46	84.86	85.16	87.59	89.99

Table 16: *In-vitro* Drug Release of the MDTs of Nisoldipine with natural superdisintegrants.

TIME(min)	F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0	0
2	48.96	47.47	47.07	30.76	31.96	35.76	40.99	40.13	43.05
4	59.36	58.73	58.03	45.77	44.76	54.12	59.16	58.13	60.898
6	67.59	66.49	66.19	48.18	47.18	63.58	71.45	70.16	76.881
8	67.49	67.99	66.01	51.14	53.18	65.12	77.16	79.16	84.902
10	75.18	76.18	75.86	56.73	57.23	66.58	86.12	88.19	90.892
15	80.91	81.67	80.17	58.17	58.99	69.13	89.66	90.17	92.921
20	82.75	83.17	82.73	61.93	63.47	70.16	90.16	91.18	96.882
25	85.71	84.79	84.18	65.73	66.76	71.64	91.01	92.66	98.86
30	87.71	87.49	85.73	67.14	69.76	72.05	92.11	94.67	98.912
45	88.12	89.01	89.89	70.18	71.73	73.66	92.86	95.64	98.916

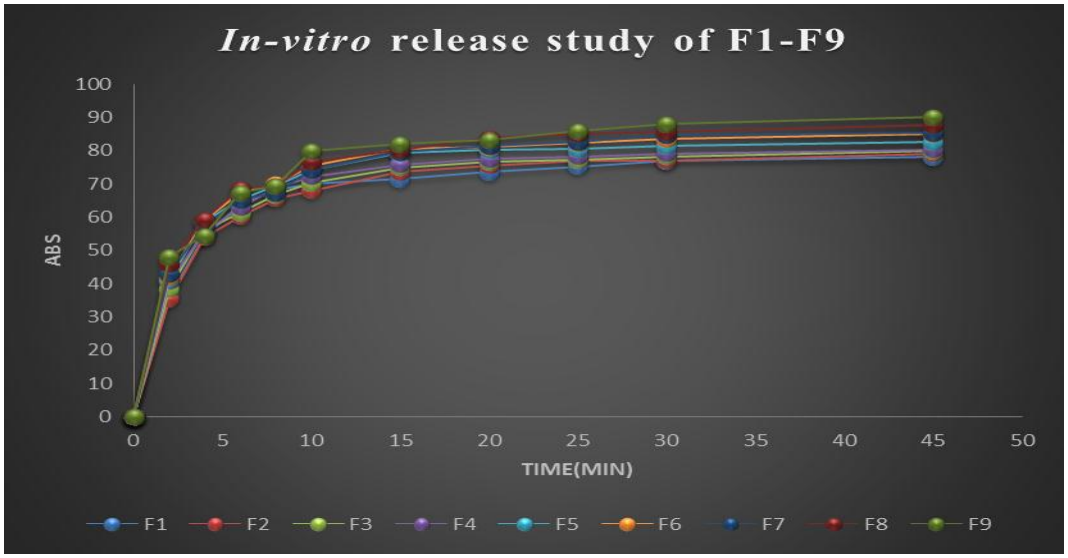


FIG no 15: *In-vitro* release study of F1-F9.

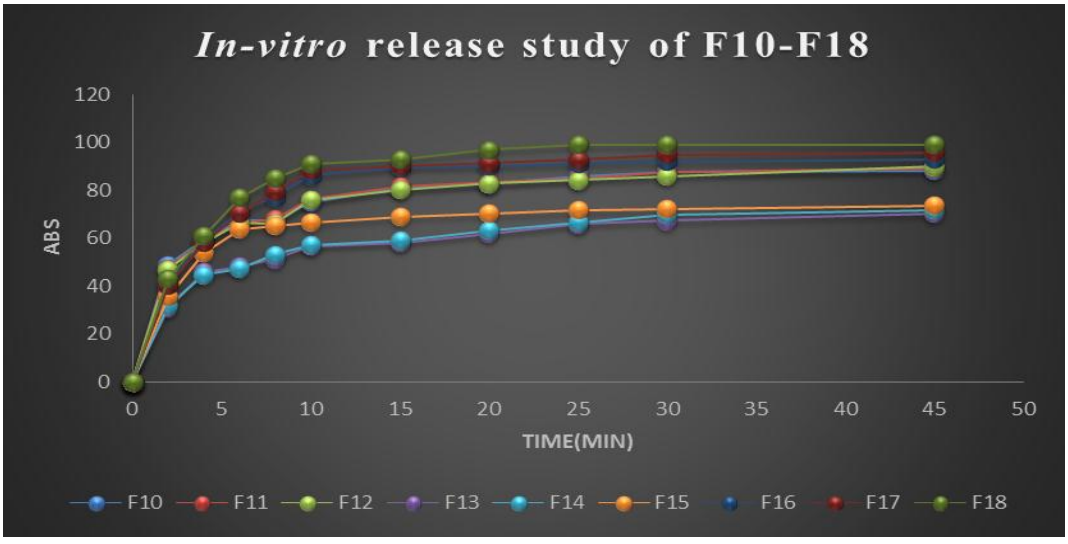


FIG no 16: *In-vitro* release study of F10-F18.

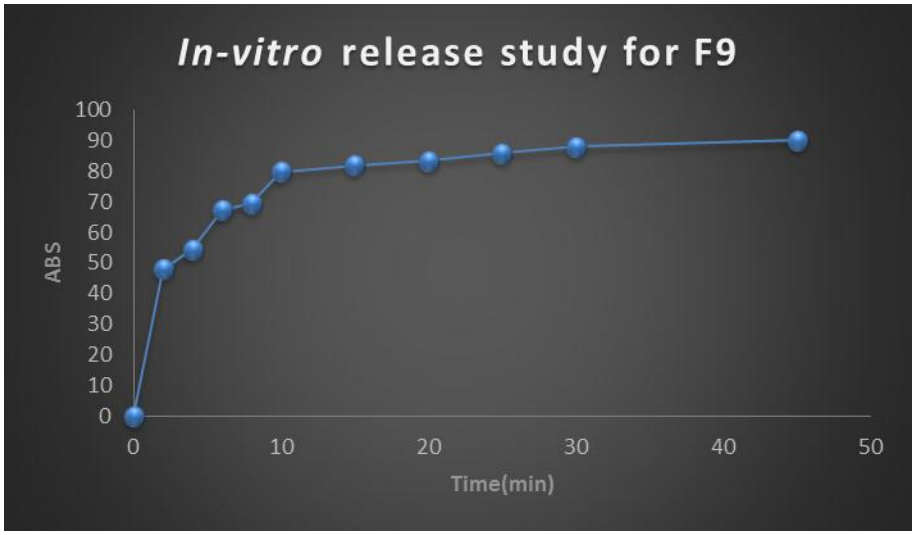


FIG no 17: *In-vitro* release study for F18.

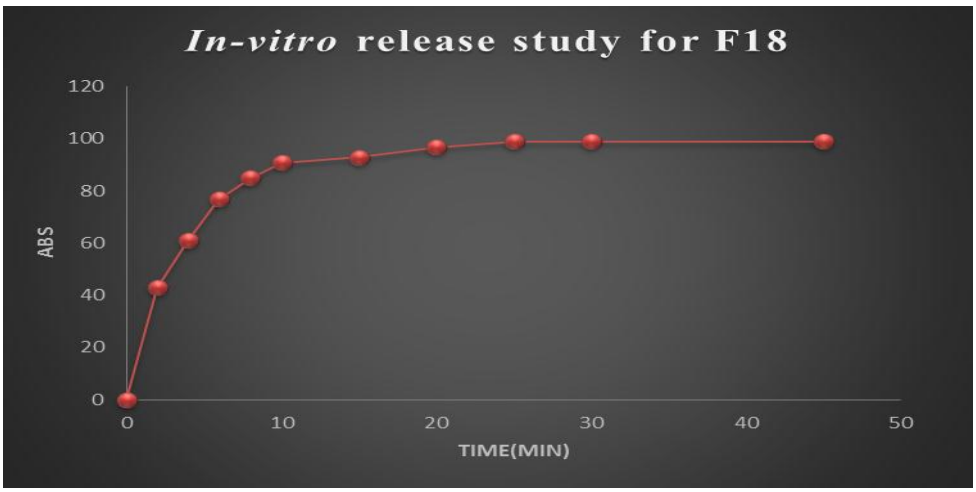


FIG no 18: *In-vitro* release study for F18.

Weight Variation: 20 tablets

Table no 17: Evaluation of weight variation of 20 tablet.

SI No.	Weight of Tablet (mg) (A)	Mean (Y)	(A-Y)	% Deviation
1	201	201.05	0.05	0.024
2	202		0.95	0.472
3	200		1.05	0.522
4	203		1.95	0.969
5	203		1.95	0.969
6	200		1.05	0.522
7	201		0.05	0.024
8	200		1.05	0.522
9	200		1.05	0.522
10	202		0.95	0.472
11	201		0.05	0.024

12	201		0.05	0.024
13	200		1.05	0.522
14	203		1.95	0.969
15	203		1.95	0.969
16	200		1.95	0.522
17	201		1.05	0.024
18	203		0.05	0.969
19	203		1.95	0.969
20	200		1.05	0.522

DRUG RELEASE KINETICS DATA ANALYSIS

The percentage release data of optimized formulation F18 is subjected to mathematical modeling.

FIG 19: Zero order model for F18.

FIG no 20: First order model for F18.

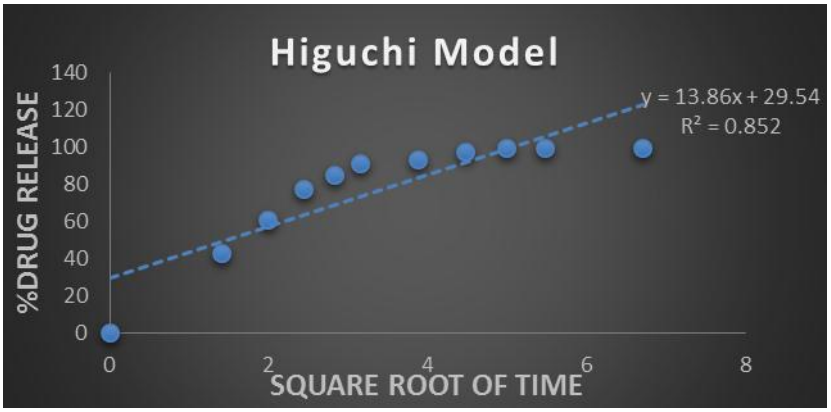
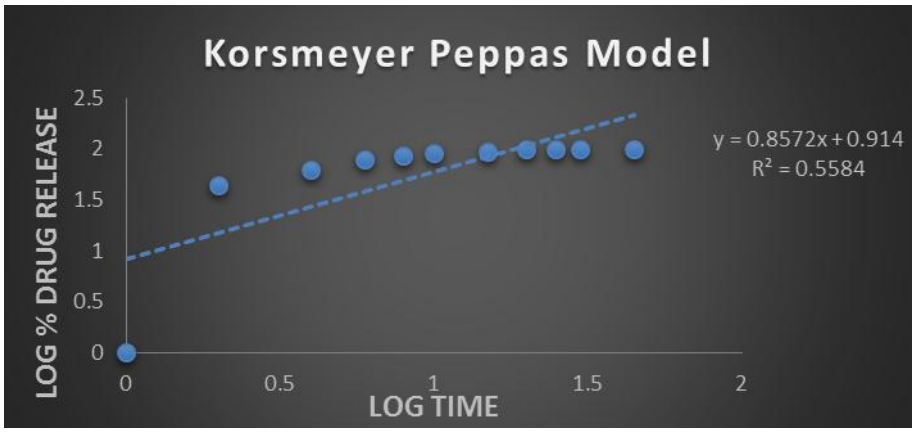


FIG no 21: Higuchi model for F18.



FIGno 22: Korsmeyer Peppas Model.

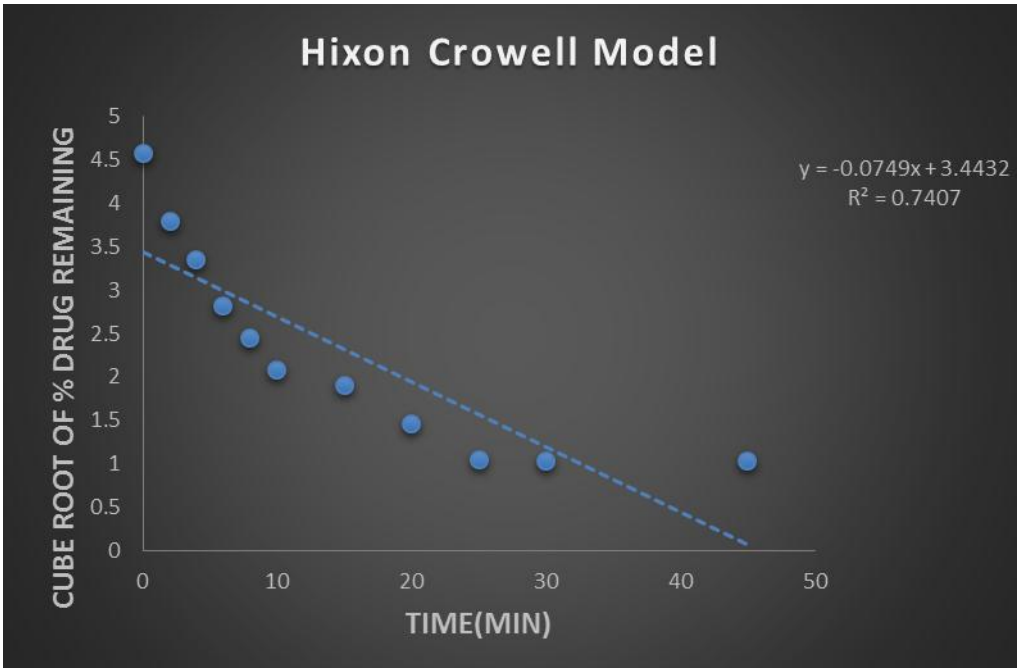


FIG no 23: Hixon Crowell Model.

Table 18: Drug Release kinetics.

R^2 value	Zero order	First order	Higuchi model	Hixon crowell	Korsmeyer peppas model	Best fit model
F18	0.4694	0.2239	0.852	0.7407	0.5584	Higuchi model

Short Term Stability Studies

Table 19: Short term stability.

Sl.no	Formulation F18	0 month ± SD	1 Month ± SD
1	Physical Appearance	White to off- white, Oval shape tablet.	White to off- white, Oval shape tablet.
2	Drug Content (%)	95.65 ±0.031	95.59±0.031
3	CPR (%) at 20 min.	96.882 ±0.0020	96.882 ±0.0020
4	CPR (%) 45 min.	98.916 ±0.0058	98.916 ±0.0058

DISCUSSION AND CONCLUSION

FAST DISSOLVING DRUG DELIVERY SYSTEMS: These dosage forms have achieved a prominent acceptance as an important novel method for administering commonly used drugs. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would request their doctors for prescription of ODTs (70%), purchase ODTs (70%), or prefer ODTs over regular tablets or liquids (>80%) pointing towards the increasing demand of ODT's over the conventional forms. These responses to a great extent can be attributed to known ODT advantages such as convenient dosing, ease of administration, pleasant taste and mouth feel and the availability of several flavors. In addition, several business needs are driving ODT technology development which primarily focuses on the commercialization of new products such as the need for expansion of the product lines, improved life-cycle management, extended patent life and marketing edge over the prevalent competitors.

SELECTION OF DRUG: Nisoldipine is a 1,4- dihydropyridine calcium channel blocker. Commercially it is available in the form of oral tablets, controlled release, Nanoaerosol, Solid dispersions. This work aimed to formulate Nisoldipine as Fast dissolving tabletsoral tablets to improve the patient compliance. The Fast dissolving tablets property could help in the management of hypertension.

PREFORMULATION STUDIES: Pre formulation studies of pure Nisoldipine were carried out by performing various parameters viz. determining the solubility profile, plotting standard curve in ethanol, pH 1.2 HCL buffer, intra and inter day studies, and compatibility studies.

Identification of drug by FT-IR: FTIR studies of pure drug, and pure drug-excipients physical mixture were carried out to see possible interaction and degradation. The IR spectrum of model CCB drug confirms the presence of the characteristic functional groups and was in good agreement with the literature findings. (Fig:-) 3350 cm^{-1} **N-H Stretching,** 2800 cm^{-1} **C-H Stretching(Aromatic)**, 3250 cm^{-1} **C-H Stretching(Aliphatic)**, 1531 cm^{-1} **NO2 Stretching,** 1493 cm^{-1} **C=C Stretching(Aromatic).** The spectrum of the pure drug shows strong absorption band at 3350cm^{-1} due to the stretching of the N–H group of dihydropyridine (DHP) moiety. The bands between 2800 and 3250 cm^{-1}can be due to the stretching of aromatic and aliphatic C–H bond. The two strong absorption bands at 1655 and 1706 cm^{-1} can be attributed to the carbonyl groups of the two side chain in the structure of DHP. The NO2 stretching produced two bands, one at 1531 $cm^{-1}$and the other at 1348 cm^{-1}. The band at 1493 cm^{-1} is for aromatic C=C bond. The two bands at 1215 and 1116 cm^{-1} are due to C–O stretching. The FTIR spectrum of the excipient revealed the main absorption bands of the drug. The recorded spectrum indicated no significant interaction between the drug and excipients.

Estimation of Nisoldipine by UV method-Absorption maxima of Nisoldipine: Nisoldipine absorption maxima was determined by preparing any concentration in ethanol and Ph 1.2 HCL buffer and analyzing the solution Spectrophotometrically using (ShimadzuUV-1700 double beam spectrophotometer) at 232-237 nm range. Absorption maxima was found to be: 237 nm which consents with that literature review.

Standard Calibration curve for Nisoldipine: Calibration of Nisoldipine was developed by UV spectrophotometry in ethanol and pH 1.2 HCL buffer which was used as the solvent for dissolving the drug. Appropriate dilutions were carried out with the buffer and absorbance was measured at λ_{max} of237 nm to get the Beer Lambert's range of 2- 20µg/ml. The regression coefficient value was found to be 0.9983. The regression values of Intra-day and Inter-day variability studies negligible difference hence revealed that the drug did not undergo any reaction or degradation.

Intra - day variability: The regression values of Intra-day variability studies and % RSD value less than 3 revealed that the drug did not undergo any reaction or degradation within a day.

Inter - day variability: The regression values of Inter-day variability studies and % RSD value less than 3 confirmed that the drug did not undergo any reaction or degradation within three days.

Partition Coefficient: The partition coefficient of Nisoldipine conducted by Shake- Flask method gave a value of k= 2.2indicating its lipophilic behaviour.

***In-Vitro* Permeation Studies of Nisoldipine:** Permeation studies of pure drug were conducted for 24 hours across activated cellophane membrane. At the end of the 24th hour 98.19 % of the drug diffused through the cellophane membrane suggesting high permeability of the drug. The permeability co-efficient of pure drug determined by applying Potts-Guy equation was found to be -3.372, which suggests high permeability of the drug through lipid membranes.

Solubility Studies of pure Drug in Different Solvents: From the solubility profile of Nisoldipine in various media (Table-) it was found that the drug was freely soluble in ethanol and pH1.2 HCL buffer. The solubility of the drug was also examined in various buffers. Hence the drug has more soluble in polar solvent that the non-polar solvents.

Drug Excipient Compatibility Studies-FT-IR Compatibility studies: Results of IR spectrum of the pure drug Nisoldipine and powder mixture of pure drug and excipients are represented in FIG and FIG respectively. The Nisoldipine has indicating presence of all specific absorption peaks suggesting that the all functionalities are also present in the powder mixture. Hence, it is concluded that, drug present in Free State in powder mixture and not in the form of reaction product. Thus,. FT-IR spectrum of pure NISOLDIPINE and physical mixture of drug with excipients did not show any major peak change hence no interactions between drug and excipients confirming compatibility.

FORMULATION OF MTD: The formulation of Mouth dissolving Tablets (MDTs) Of Nisoldipine by using Synthetic and natural Superdisintegrants is done. The powder blend for each formulation was mixed properly and subjected for Pre-compression evaluation parameters.

PRE-COMPRESSION EVALUATION-Evaluation of the powder blends: The Tableting excipients were mixed thoroughly to obtain a powder blend which was then passed through sieve no.40. The powder blends with synthetic and natural super disintegrants were evaluated

for flow properties like the bulk density and tapped density, Carr's index, Hausner's ratio and angle of repose. The Tapped density of synthetic and natural super disintegrants powder blends was in between 0.437-0.576gm/mL and 0.676-0.447gm/mL respectively, whereas the untapped density was in the range of 0.408-0.544gm/mL and 0.545-0.438gm/mL. The compressibility values varied from 11.99%- 12.76%% and 12.86%-12-99%. The Hausner's ratio values of the formulations were in between 1.058-1.136 and 1.126-1.018. The angle of repose values of the formulations varied from 26°01' to 27°35' and 26°21' to 27°45'. From these values, it was evident that these powder blends had good flow properties and can subjected for direct compression.

TABLET COMPRESSION: The formulation of ODTs was achieved by direct compression method. Different synthetic superdisintegrants (Kyron T-314, Sodium starch glycolate and crosscarmellose sodium) in different concentration of3%, 4%, and 5% and natural superdisintegrants(Guar gum, Banana powder, Mango peel powder) in different concentration of 2%, 4%, and 6% were screened for their effects on weight variation, hardness, friability, wetting time and *in-vitro* disintegration studies. The most suitable synthetic superdisintegrants was found to be Kyron T-314 and natural superdisintegrants was found to be mango peel powder due to its excellent swelling nature, resulting in rapid disintegration. Thus, Kyron T-314 and mango peel powder tablets gave satisfactory results as it showed better hardness, friability *in-vitro* disintegration and a good texture.

POST COMPRESSION EVALUATION: All the formulations prepared with synthetic and natural super disintegrants had hardness within the range of 4.6-5.6. Friability was within limits of <1% for the MDTs prepared with Perlitol-200 SD as diluent. Drug content for all the formulation was within limits of ± 5% of total drug**.** Formulation F18containing mango peel powder as super disintegrants and Perlitol-200 SD as diluent showed least wetting time of 35.19±0.43 sec. Formulation F18 showed the best disintegration time of 18.12+0.72 sec. Hence mango peel powder was selected as the super disintegrants, whereas Perlitol-200 SD was selected as the suitable diluent blend for further optimization studies. Formulation F18 with mango peel powder were optimized as best formulations and subjected to weight variation test and drug release kinetics.

Evaluation of the final optimized MDT Formulation (F-18): The weight variation results of 20 tablets indicated that all the tablets are within the range. The hardness, friability and drug content were found to be 4.06+0.20kg/cm2, 0.42+0.023% and 95.65+0.031%

respectively, hence were within the specified range. The wetting time and disintegration time were found to be 35.19sec and 18.12sec respectively. *In-vitro* dissolution studies carried out in pH 6.8 and F18 gave a better release 98.916%.

Drug Release Kinetic Studies: F18 was subjected to mathematical modelling such as Zero order, First order, Higuchi matrix, Hixon-Croswell cube root law and Kormeyers- Peppas model. And the best fitted model for F18 was found to be Higuchi matrix model having n=13.86 with R^2 0.852 which indicates that the drug release is dependent on polymer.

Stability Studies: Short term stability studies were performed on final optimized MDT formulation for period of 1 month. At the end of 1 month F18 was evaluated for physical appearance, drug content and CPR at 20^{th} and 45^{th} min and formulation was found to be stable.

REFERENCES

1. Tanira M, Al Balushi K. Genetic variations related to hypertension: a review. J Hum Hypertens, 2004; 19(1): 7-19.
2. Siyad.A.R. hypertension. Hygiea journal for drugs and medicine, 2011; 3(1): 1-16.
3. Ilyas M. Hypertension in adults. Southern sudan medical journal, 2(3).
4. G:\Website\Drug Classess\Drug Classes Final Copy Dec 2008\Calcium Channel Blockers.doc.
5. Ozawa Y, Hayashi K, Kobori H. New Generation Calcium Channel Blockers in Hypertension Treatment, Curr Hypertens Rev., 2006 May 1; 103-111. doi:10.2174/157340206776877370.
6. Vasanthan M, Narayanasamy D. Development of Fast Dissolving Tablets of Nisoldipine by Solid Dispersion Technology using Poloxamer 407 and Polaxamer 188. J Young Pharm, 2016; 8(4): 341-349.
7. Kumar S K, Ramarao T, Bikshapathi D.B.R.N and Jayaveera K.N. Controlled Release Formulation Development and Evaluation of Felodipine Matrix Tablets By Using Hydrophobic Polymers. IJPRS, 2013; 4(1): 506-511.
8. Rathore A S, Jat R.C, Sharma N, Tiwari R. An Overview: Matrix Tablets as Controlled Drug Delivery System, Jun-Jul, 2013; 2(4): 482-492.
9. Sonje A, Yadav A, Chandra A, Jain D.A. Formulation and evaluation of immediate release tablet of antihypertensive drugs according to BCS system INT J Ther Appl., 2012; 7: 18-24.

10. Gupta M.M, Mahinda M. Formulation development and evaluation of Immediate release tablet of anti-hypertensive drug Olmesartan medoxomile. Pharma Inno J., 2013; 1(3): 180-196.