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Formulation and Evaluation of Sustained Release Matrix Tablet of Nifedipine Using Natural Polymers

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ABSTRACT

The objective of the present work was formulation and evaluation of sustained release matrix tablet of Nifedipine using natural polymers. The tablets were prepared by direct compression method using different concentrations of Guar gum and Xanthan gum as natural polymers. The prepared tablets were evaluated for pre-compression parameters such as bulk density, tapped density, the angle of repose, compressibility index, Hausner's ratio and post-compression parameters such as weight variation, hardness, thickness, friability, content uniformity, swelling index and *in vitro* dissolution studies. FTIR studies shown there was no interaction between drug and polymers. The optimum sustained release of drug around a period of 12 hr was shown by formulation F9. The 'n' value of optimized formulation indicated that the drug release follows the anomalous non-Fickian release. It was confirmed from the stability studies that the optimized formulation remained stable at 40 ^{0}C and 75% relative humidity.

INTRODUCTION

The oral route of drug delivery is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered multiple doses and therefore have several disadvantages. The rationale for the development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition.[1]

Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems.[1] Sustained release delivery systems can achieve an extended duration of activity for drugs with half-life 2-4 hrs, decreased toxicity, reduction of required dose, optimized therapy, and better patient compliance. With the aim of maximizing the bioavailability of conventional drugs with minimum side effects, new drug delivery systems continue to attract much attention. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness and broad regulatory acceptance.[2] Among the hydrophilic polymers, cellulose derivatives such as methylcellulose, hydroxypropyl, and sodium carboxymethylcellulose are generally considered to be stable and safe as release retardant excipients in the development of oral controlled release dosage forms. These semi-synthetic polymers are quite expensive when compared with natural polymers such as guar gum, xanthan gum and so forth. The natural polymers are nontoxic and easily available.[3]

Sustained release formulations can offer many pharmacokinetic and pharmacodynamic advantages over conventional dosage forms, including maintenance of constant therapeutic levels for a longer period of time and reduction of fluctuations in plasma drug concentrations. Sustained release formulations can reduce the risk of treatment failure due to inadequate dosing of antibiotics.[4]

Preparation of sustained release formulation by matrix technique is a commonly employed method because of the ease of preparation, flexibility and cost efficiency. Matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate.

Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed.[3]

Nifedipine is a 1,4-dihydropyridine calcium channel blocker. It is used for the treatment of angina pectoris, hypertension, and Raynaud's phenomenon. Nifedipine has a half-life of 2 hrs[5].

The aim of proposed work was intended to formulate and evaluate sustained release matrix tablet of Nifedipine, with a view to reducing the dosing frequency and the side effects.

The main objective of the present work was to prepare and evaluate sustained release matrix tablet of Nifedipine using natural polymers.

MATERIALS AND METHODS:

MATERIALS:

Nifedipine was supplied from Yarrow Chem Products, Mumbai. Guar gum was also supplied from Yarrow Chem Products, Mumbai. Xanthan gum was supplied from Balaji drugs. All other excipients and solvents used were of the analytical or pharmaceutical grade.

METHODS:

Preformulation studies[6]

Determination of organoleptic properties

The physical appearance of the drug was observed and compared with the pharmacopoeial specifications.

Determination of melting point

The melting point of Nifedipine was determined by the capillary method.

Solubility[7]

Small increments of Nifedipine was added to 10ml of solvent (distilled water, acetone, ethanol, diethyl ether, acetic acid) in a 25ml stoppered standard flask with vigorous shaking. Visually observed the solution, if the solution was clear and no undissolved particles were

observed if it was insoluble again another increment of particular solvent was added and the procedure was continued until undissolved Nifedipine was found.

Compatibility studies using FT-IR Spectroscopy[8, 9, 10]

The pure drug, drug, and polymer were prepared and scanned from 4000-400cm^{-1} in FTIR spectrophotometer. The FT-IR spectrum of the obtained sample of drug and drug + physical mixture were compared with the standard functional group frequencies of Nifedipine, Guar gum, and Xanthan gum respectively. The compatibility between the drug and polymer were evaluated using FTIR peak matching method.

Preparation of a standard calibration curve of Nifedipine[11, 12]

Accurately weighed 100 mg of Nifedipine was taken in a 100 ml standard flask. Added few ml of ethanol to dissolve the drug and made up to the volume with 0.1N HCl to get a stock solution of concentration 1000 µg/ml. From this stock solution, 1 ml was transferred into a 10 ml standard flask and made up to the volume with 0.1N HCl that corresponded to 100 µg/ml. From that solution, different aliquots of 0.2, 0.4, 0.6, 0.8 and 1 ml of solutions were transferred into separate 10 ml standard flasks and made up to the volume with 0.1N HCl to get concentrations 2, 4, 6, 8 and 10 µg/ml respectively. The absorbance of resultant solutions was measured at 235 nm by UV spectrophotometer. A graph of concentration Vs absorbance was plotted.

Preparation of sustained release matrix tablet of Nifedipine by direct compression method[13].

Tablets were manufactured by direct compression method employing rotary tablet compression machine. Formulations were designed with varying percentages of polymers such as Guar gum and Xanthan gum. Microcrystalline cellulose and Sodium chloride were used which helps in the slow erosion of the matrix from the tablet. All the materials were passed through 80 # screens prior to mixing. To this added weighed quantity of Magnesium stearate and Talc and all the ingredients were mixed again and compressed.

Table 1: Formulations of sustained release matrix tablet of Nifedipine

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Nifedipine	30	30	30	30	30	30	30	30	30	30	30	30
Guar gum	30	45	60	30	45	60	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-	30	45	60	30	45	60
Microcrystalline cellulose	131	121	106	-	-	-	131	121	106	-	-	-
Sodium chloride	-	-	-	131	121	106	-	-	-	131	121	106
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total Wt. (mg)	200	200	200	200	200	200	200	200	200	200	200	200

❖ **Pre-compression parameters**

Bulk density[14]

The bulk density of a powder is the ratio of the mass of the powder sample to its volume including the contribution of the inter-particulate void volume. The bulk density is expressed in grams per milliliter (g/ml) or grams per cubic centimeter (g/cm^3). The bulk volume (V_b) and weight of the powder (M) were calculated using the formula.

$$\rho_b = M/V_b$$

Tapped density[14]

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was taken. The tapped density (ρ_t) was calculated by using formula.

$$\rho_t = M/V_t$$

Angle of repose[15]

The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose (Θ) was calculated using the formula

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

where, h = height of the heap

r = radius of the heap

Compressibility Index (I)[16]

Compressibility Index is an indication of the compressibility of a powder. The Carr index is calculated by the formula

$$C = 100[(V_b - V_t)/V_b]$$

where V_b is the volume that a given mass of powder would occupy if let settled freely

V_t is the volume of the same mass of powder would occupy after "tapping down".

Hausner ratio (H_R)[17]

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula.

$$H_R = \rho_t/\rho_b$$

where ρ_b is the freely settled bulk density of the powder

ρ_t is the tapped density of the powder.

EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF NIFEDIPINE

Post-compression parameters

Physical appearance[18]

The shape of the tablet can be dimensionally described, monitored and controlled.

Organoleptic properties[19]

It includes the color and odor of the prepared tablet.

Weight variation[20]

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

Hardness test[21]

The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation, and handling before usage depends on its hardness. The hardness of the tablet is found using Pfizer tester.

Thickness[20]

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using the filling equipment. The thickness of the tablets was measured using Vernier calipers. It is expressed in mm.

Friability[21]

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets has determined by using Roche friabilator. The percentage friability is calculated by,

$$F = [(W_i - W_f)/W_i] 100$$

Where; F = friability,

W_i = initial weight,

W_f = final weight

Content uniformity[22]

Ten tablets were weighed and powdered. The powder equivalent to 100 mg Nifedipine content was determined by measuring the absorbance at 235 nm after appropriate dilution.

Swelling index[23]

The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was kept in a Petri dish containing a p^H 6.8 phosphate buffer. At the end of 1 hr tablet was withdrawn, wiped with tissue paper and weighed. Then for every 1 hr, weights of the tablets were noted and the process was continued for 12 hr. Percentage weight gain by the tablet was calculated using the formula

$$SI = (M_t - M_0) / M_0 \times 100$$

where, SI = Swelling index

M_t = weight of tablet at time 't'

M_0 = weight of tablet at time t = 0

***In vitro* dissolution studies**

Preparation of phosphate buffer (pH 6.8)[24]

Dissolved 28.80gm of Disodium hydrogen phosphate and 11.45gm of Potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Preparation of stimulated colonic fluid (p^H 7)[25]

Dissolved 0.20 gm of Potassium chloride, 8 gm of Sodium chloride, 0.24 gm of Potassium dihydrogen phosphate and 1.44 gm of Disodium hydrogen phosphate in sufficient water to produce 1000 ml.

Procedure for dissolution:

The release rate of Nifedipine from sustained release matrix tablet was determined using the United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of dissolution medium at 37± 0.50^0C and 50 rpm. 0.1N HCl was used as dissolution medium for the first 3 hr, followed by p^H 6.8 phosphate buffer for 1 hr and stimulated colonic fluid (p^H 7) for further 8 hr. A sample (5ml) of the solution was withdrawn from the dissolution medium after every hour and was replaced with an equal volume of fresh dissolution medium. Collected samples were diluted with the dissolution medium and the absorbance of these solutions was measured at 235 nm using a Shimadzu UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetics of *in vitro* drug release[26]

The results obtained from in-vitro release studies were attempted to fit into various mathematical models as follows:

1) Cumulative percent drug released Vs. Time (Zero order kinetics)

2) Log cumulative percent drug retained Vs. Time (First order kinetics)

3) Cumulative percent released Vs. The square root of Time (Higuchi model)

4) Log cumulative percent drug released Vs. Log Time (Korsmeyer- Peppas model)

In the Peppas model, the value of 'n' characterizes the release mechanism of the drug as described in Table 2.

Table 2: Interpretation of diffusional release mechanism

Release exponent (n)	Diffusion release mechanism
<0.45	Quasi – Fickian diffusion
0.45	Fickian diffusion
0.45 <n<0.89	Anomalous(Non-Fickian) diffusion
0.89 - 1.0	Case II transport (Zero order release)
>1.0	Super case II transport

Stability studies[27]

Stability testing plays a crucial role in the drug development process. The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of environmental factors such as temperature, humidity, and light to recommend shelf life for the drug product and recommended storage conditions. Stability studies were conducted according to ICH guidelines 40˚C ± 2˚C/ 75% ± 5% RH to test the physical and chemical stability of the developed formulations. The stored formulations were evaluated for hardness, drug content and *in-vitro* drug release at a predetermined time interval.

RESULTS AND DISCUSSION:

Preformulation studies

Determination of Organoleptic properties

The organoleptic properties of Nifedipine were found to be a yellow, odorless and crystalline state.

Determination of Melting point

The melting point of Nifedipine was found to be 172^0C.

Solubility

The solubility of Nifedipine in various solvents such as distilled water, ethanol, acetone, acetic acid and diethyl ether were studied and found that it was freely soluble in ethanol and acetone while it was insoluble in distilled water, sparingly soluble in acetic acid and slightly soluble in diethyl ether.

Compatibility studies

FT-IR spectroscopy of Nifedipine

The FT-IR spectrum of Nifedipine is shown in figure 5.1, complies with standard functional group frequencies.

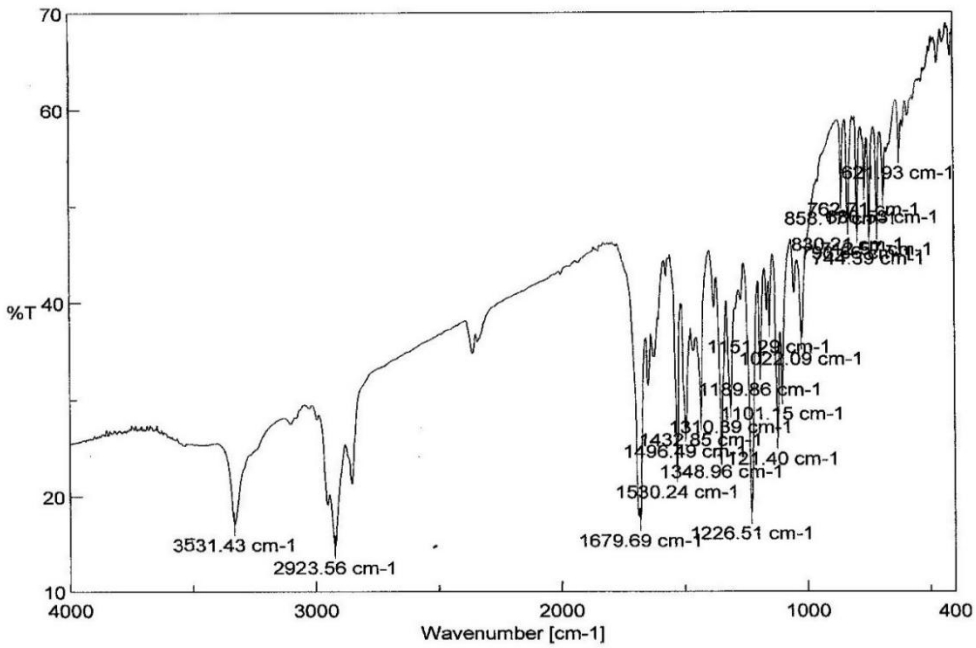

Figure 1: FT-IR spectrum of Nifedipine

Table 3: IR frequencies of Nifedipine

Functional group	Characteristic wave number(cm^{-1})	Nifedipine observed wave number (cm^{-1})
Ar-NH_2	3540 - 3460	3531.43
CH asymmetric stretching	2935 - 2915	2923.56
Conjugated C = O	1680 - 1620	1679.69
CH_3 stretching	1470 - 1430	1432.85

Compatibility between drug and polymer

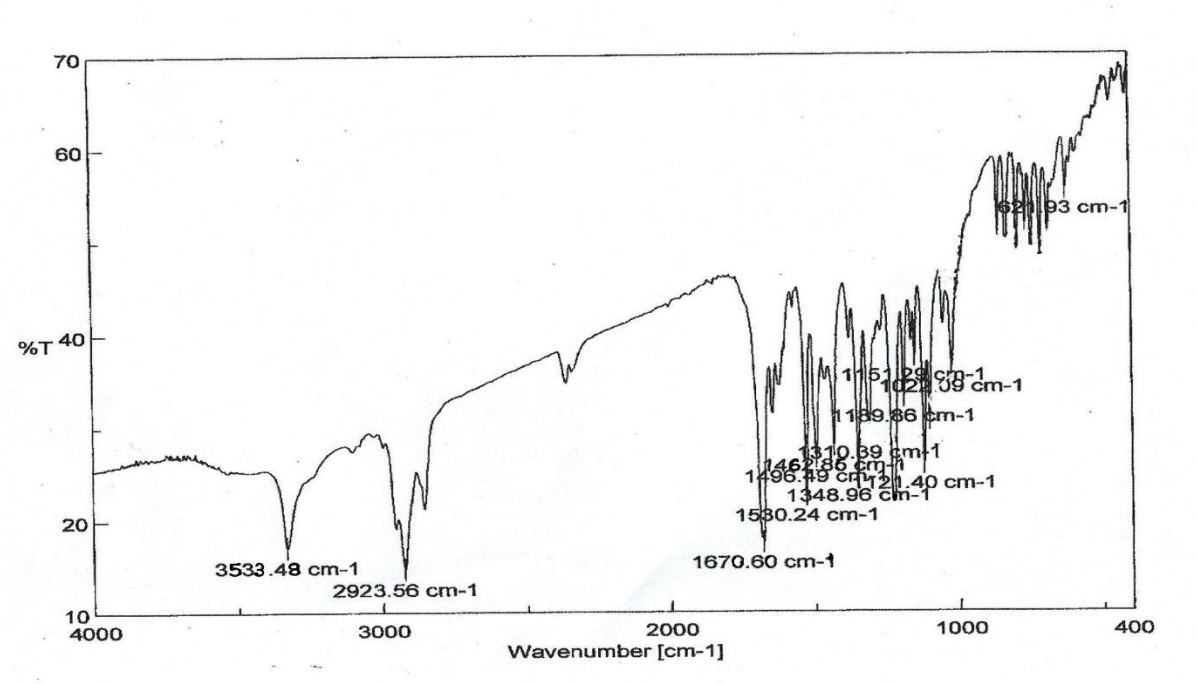

Figure 2: FT-IR spectrum of physical mixture Nifedipine + Guar gum + Xanthan gum

Table 4: IR frequencies of physical mixture Nifedipine + Guar gum + Xanthan gum

Functional group	Characteristic wave number (cm^{-1})	Nifedipine observed wave number (cm^{-1})	Nifedipine + Polymer mixture (wave number) (cm^{-1})
Ar-NH_2	3540 – 3460	3531.43	3533.48
CH asymmetric stretching	2935 – 2915	2923.56	2923.56
Conjugated C = O	1680 – 1620	1679.69	1670.60
CH_3 stretching	1470 – 1430	1432.85	1462.86

The compatibility between drug and polymer were carried out by using FT-IR peak matching method. All major peaks present in the spectrum of the pure drug were observed in the spectrum of the drug-polymer mixture. This suggests that the drug remains in its normal

structure and hence this confirmed the absence of any chemical interaction or complexation between drug and polymers.

Preparation of standard calibration curve of Nifedipine

Table 5.6: Calibration table of Nifedipine at 235nm

❖ Concentration (µg/ml)	Absorbance(nm)
2	0.126
4	0.242
6	0.364
8	0.473
10	0.596

The calibration curve was found to be linear in the range of 2-10 µg/ml at λmax 235nm

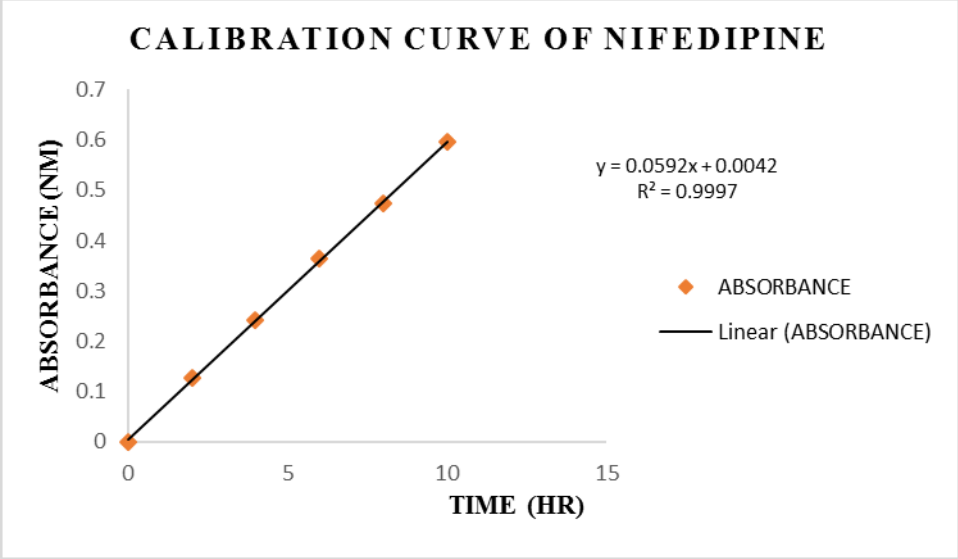

Figure 3: Calibration curve of Nifedipine at 235nm

FORMULATION OF SUSTAINED RELEASE MATRIX TABLET OF NIFEDIPINE

Method of Formulation of Sustained release matrix tablet of Nifedipine

The sustained release matrix tablets were prepared by direct compression method using varying percentages of polymers such as Guar gum and Xanthan gum. Microcrystalline cellulose and Sodium chloride was used which helps in the slow erosion of the matrix from the tablet and Talc and Magnesium stearate as lubricants.

Pre-compression parameters

Table 5: Pre-compression parameters of formulations F1 - F12

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose	Compressibility index	Hausner's ratio
F1	0.3272±0.13	0.3926±0.24	29.99^0±0.17	16.65±0.11	1.19±0.47
F2	0.2925±0.006	0.3250±0.08	26.38^0±0.11	17.69±0.28	1.13±0.15
F3	0.3288±0.24	0.4288±0.11	29.74^0±0.016	11.13±0.35	1.12±0.18
F4	0.2718±0.15	0.3322±0.52	25.82^0±0.19	18.18±0.36	1.22±0.11
F5	0.2495±0.06	0.2995±0.28	27.96^0±0.26	16.69±0.31	1.20±0.04
F6	0.30±0.46	0.3750±0.05	29.06^0±0.24	20±0.22	1.25±0.27
F7	0.2990±0.20	0.3517±0.005	26.93^0±0.06	14.98±0.22	1.17±0.46
F8	0.3266±0.002	0.3675±0.16	28.39^0±0.10	11.12±0.19	1.12±0.29
F9	0.3311±0.12	0.3725±0.31	27.75^0±0.02	11.11±0.23	1.12±0.06
F10	0.2722±0.10	0.2995±0.36	25.64^0±0.14	12.14±0.17	1.15±0.14
F11	0.2980±0.15	0.3725±0.020	26.75^0±0.25	20±0.05	1.25±0.53
F12	0.2718±0.003	0.3147±0.016	27.96^0±0.30	13.63±0.14	1.15±0.36

Post-compression parameters

Physical appearance

All the formulations F1-F12 were compressed in the round and standard convex shape.

Organoleptic properties

All the prepared formulations showed yellow in color without specific odor.

Table 6: Post-compression parameters of formulation F1 – F12

Formulation code	Average weight (mg)	Average Hardness ($kg/cm^{2)}$	Thickness (mm)	% Friability	Content uniformity (%)	Swelling index (%)
F1	202±1.14	5.4±0.13	4.5±0.05	0.49±0.16	98.89±0.06	160
F2	199±2.09	4.8±0.04	4.6±0.28	0.48±0.10	98.16±0.16	225
F3	197±1.17	4.6±0.14	4.8±0.10	0.47±0.17	96.98±0.23	261.90
F4	200±1.13	4.8±0.17	4.7±0.03	0.48±0.18	99.40±0.11	240
F5	204±2.04	5.2±0.18	4.4±0.27	0.50±0.06	95.70±0.33	247.61
F6	198±2.16	5.6±0.09	4.7±0.39	0.48±0.12	96.82±0.38	250
F7	201±1.14	4.4±.21	4.6±0.50	0.47±0.14	97.56±0.14	252.38
F8	200±1.08	4.7±0.28	4.4±0.19	0.49±0.24	99.65±0.29	257.14
F9	202±2.29	4.8±0.10	4.6±0.44	0.47±0.21	99.92±0.18	270
F10	199±1.94	4.9±0.46	4.8±0.16	0.52±0.28	95.36±0.26	238.09
F11	203±1.64	5.6±0.11	4.5±0.48	0.48±0.30	94.82±0.10	265
F12	198±1.10	4.9±0.15	4.8±0.25	0.49±0.13	96.64±0.15	266.66

***In vitro* dissolution studies**

In vitro dissolution studies of all formulations were carried out in dissolution test apparatus using 0.1N HCl, p^H 6.8 phosphate buffer for 3 and 1 hr respectively and then in the stimulated colonic fluid as the dissolution medium for 8 hr. Percentage cumulative drug release at each time interval as shown in the table and the data represented graphically.

Table 7: Percentage cumulative drug release data for Formulations F1-F4

Time hr)	F1 %CDR	F2 % CDR	F3 % CDR	F4 % CDR
0	0	0	0	0
1	58.45±0.18	43.33±0.15	37.79±0.23	44.84±0.04
2	65±0.02	60.97±0.20	46.36±0.18	55.43±0.37
3	75.58±0.10	66.51±0.18	58.96±0.29	62.48±0.29
4	89.69±0.26	79.11±0.31	65.74±0.14	68.53±0.16
5	98.26±0.22	88.18±0.56	69.54±0.60	73.06±0.41
6		97.2±0.48	73.57±0.54	77.09±0.19
7			76.59±0.19	83.64±0.08
8			79.61±0.42	88.18±0.23
9			82.92±0.78	94.73±0.19
10			84.81±0.53	99.26±0.14
11			89.65±0.31	
12			94.80±0.11	

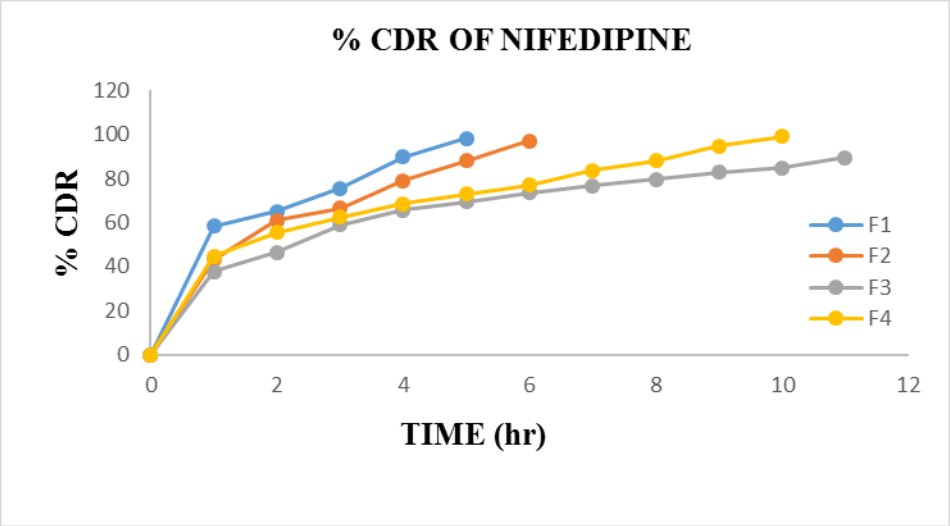

Figure 5: Percentage cumulative drug release profile of Formulations F1 – F4

Table 8: Percentage cumulative drug release data for Formulations F5-F8

Time hr)	F5 % CDR	F6 % CDR	F7 % CDR	F8 % CDR
0	0	0	0	0
1	43.84±0.34	36.78±0.26	45.35±0.16	36.27±0.17
2	48.37±0.18	44.34±0.58	63.49±0.25	47.36±0.14
3	59.46±0.46	48.75±0.84	69.54±0.03	52.85±0.27
4	63.49±0.11	57.65±0.07	78.61±0.42	65±0.13
5	67.52±0.02	61.99±0.20	85.61±0.49	71.55±0.45
6	71.55±0.08	66.53±0.43	96.24±0.85	76.04±0.14
7	74.57±0.16	69.47±0.69		80.12±0.60
8	77.60±0.19	73.69±0.92		84.65±0.38
9	81.13±0.34	75.8±0.86		88.68±0.04
10	84.65±0.62	79.58±0.37		93.72±0.10
11	86.67±0.68	85.73±0.26		99.57±0.11
12	91.88±0.57	87.98±0.13		

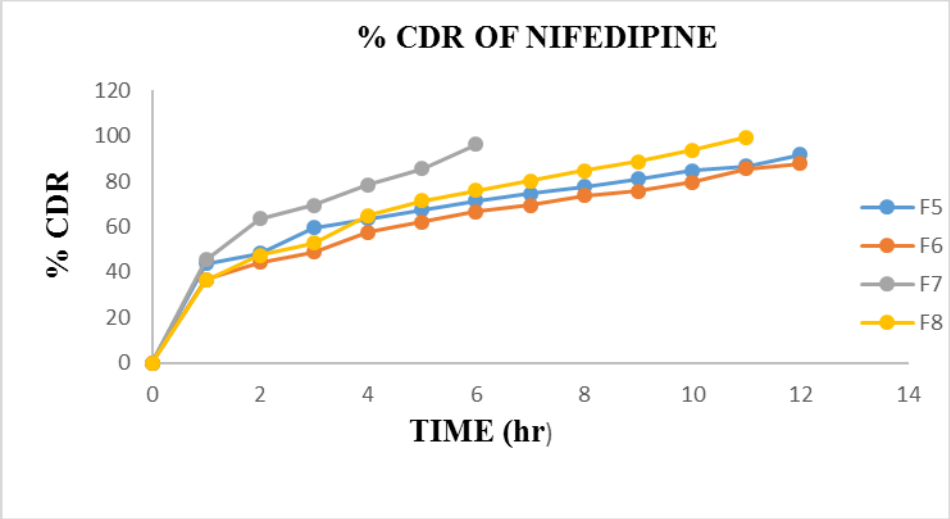

Figure 6: Percentage cumulative drug release profile of Formulations F5 – F8

Table 9: Percentage of cumulative drug release data for Formulations F9 - F12

Time hr)	F9 % CDR	F10 % CDR	F11 % CDR	F12 % CDR
0	0	0	0	0
1	31.24±0.14	35.27±0.25	37.79±0.82	34.26±0.59
2	40.31±0.46	44.34±0.19	47.36±0.26	42.32±0.40
3	44.84±0.24	51.39±0.62	54.42±0.13	49.38±0.22
4	54.92±0.72	56.43±0.16	58.95±0.10	58.45±0.26
5	61.98±0.06	65.62±0.10	64.59±0.009	60.97±0.47
6	67.52±0.18	68.53±0.29	69.03±0.27	65.5±0.56
7	75.08±0.35	73.06±0.32	73.57±0.39	69.59±0.84
8	77.60±0.84	78.61±0.09	76.09±0.56	74.07±0.21
9	84.65±0.11	83.64±0.12	79.61±0.74	78.10±0.19
10	88.18±0.50	85.66±0.20	84.65±0.15	82.13±0.01
11	91.20±0.04	88.68±0.01	87.14±0.18	84.15±0.33
12	97.75±0.17	92.95±0.45	91.25±0.10	87.68±0.53

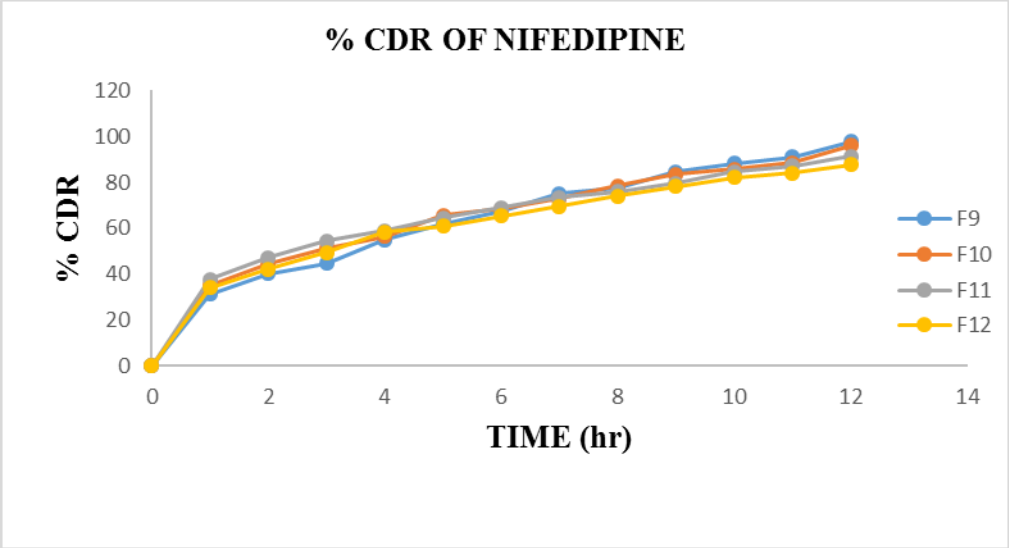

Figure 7: Percentage cumulative drug release profile of Formulations F9 – F12

From the *in vitro* drug release data of sustained matrix tablet of Nifedipine, it was observed that the percentage cumulative drug release of Nifedipine decreased as the concentration of gum increased and it was also similar when the concentration of microcrystalline cellulose and sodium chloride were decreased. The optimum sustained release of drug was shown by formulation F9 containing an increased concentration of Xanthan gum and decreased the concentration of microcrystalline cellulose. F9 released 97.75 % of the drug in 12 hrs.

Kinetics of *in-vitro* drug release

The *in vitro drug* release data were subjected to the goodness of fit by linear regression analysis, according to zero order, first-order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release.

Table 10: Kinetic study of Formulations F1-F12

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Peppas	
				n	R^2
F1	0.9870	0.8463	0.9574	0.3283	0.9322
F2	0.9839	0.8779	0.9897	0.4389	0.9890
F3	0.9362	0.9358	0.9834	0.3611	0.9893
F4	0.9884	0.8306	0.9931	0.3386	0.9887
F5	0.9672	0.9659	0.9926	0.3028	0.9857
F6	0.9782	0.9745	0.9945	0.3588	0.9888
F7	0.9732	0.8762	0.9870	0.3979	0.9881
F8	0.9696	0.9067	0.9946	0.4221	0.9937
F9	0.9838	0.8727	0.9938	0.4743	0.9883
F10	0.9749	0.9737	0.9969	0.3996	0.9944
F11	0.9761	0.9739	0.9987	0.3526	0.9969
F12	0.9711	0.9124	0.9972	0.3864	0.9955

Figure 8: Zero order plot of F9

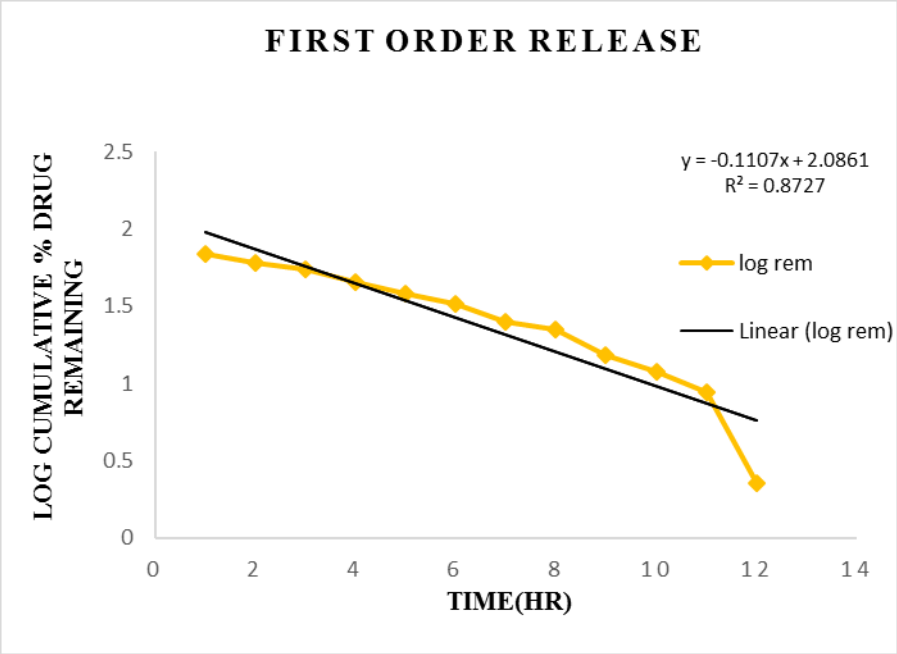

Figure 9: First order plot of F9

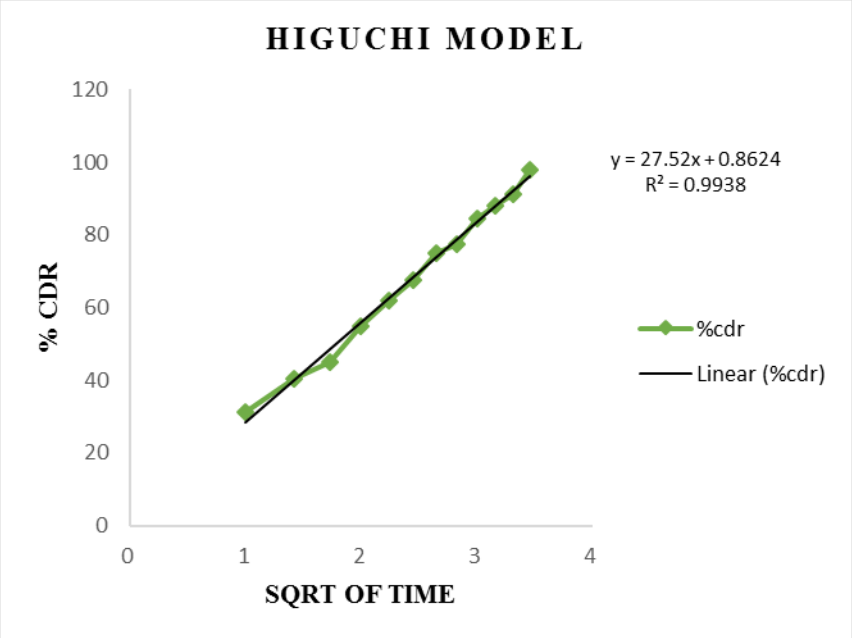

Figure 10: Higuchi model plot of F9

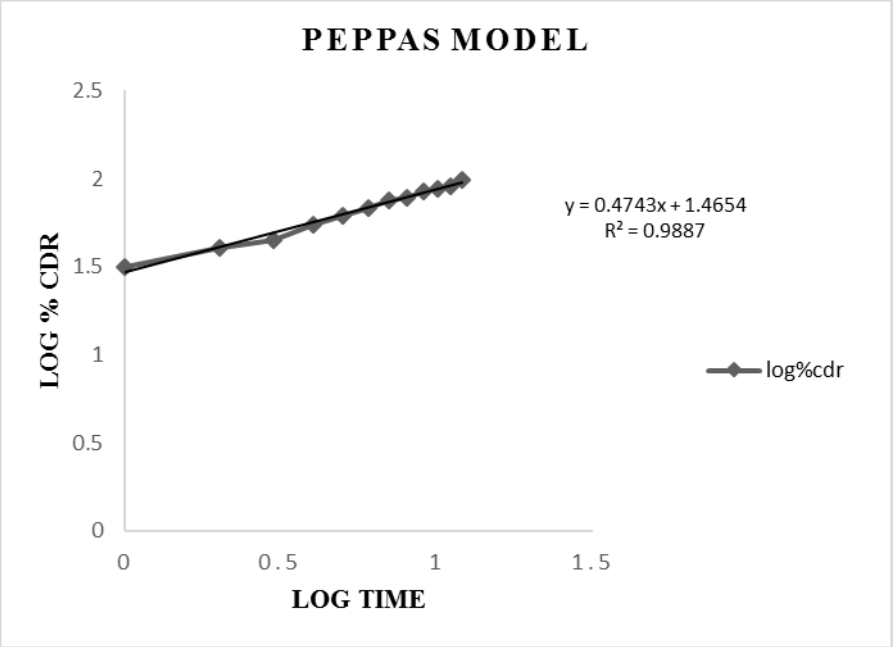

Figure 11: Peppas model plot of F9

From the above graphs, it was concluded that the formulation F9 follow zero order kinetics.

The *in-vitro* drug release data as log % CDR versus time were fitted to Korsmeyer-Peppas equation in order to understand the mechanism by which Nifedipine was released from this formulation. The value of exponent 'n' was found to be 0.3028 – 0.4743. The Korsmeyer-Peppas model yields 'n' values >0.45 indicating that the diffusion mechanism from the formulation followed Non-Fickian (Anomalous) diffusion. The 'n' value of optimized formulation F9 was found to be 0.4743 which indicated that the drug was released by zero order kinetics with anomalous (Non-Fickian) release.

Stability studies:

Stability studies were carried out on formulation F9 for a period of 3 months and comparison of the parameters before and after stability studies was represented in table 11 and 12.

Table 11: Comparison of parameters before and after stability studies

Parameters	Before stability studies	After stability studies (1month)	After stability studies (3month)
Physical changes	Yellow, Round, standard convex	No changes	No changes
% drug content	99.92	98.96	98.23
Hardness	4.8	4.76	4.7

Table 12: Drug release determination before and after stability studies

Time (min)	Before stability % CDR	After stability % CDR (1 month)	After stability % CDR (3 months)
0	0	0	0
1	31.24	30.18	28.25
2	40.31	38.26	36.62
3	44.84	40.84	39.08
4	54.92	52.36	49.96
5	61.98	58.92	56.78
6	67.52	65.82	64.57
7	75.08	71.27	70.16
8	77.60	75.20	74.02
9	84.65	80.65	78.84
10	88.18	85.48	84.52
11	91.20	89.65	88.79
12	97.75	96.89	95.28

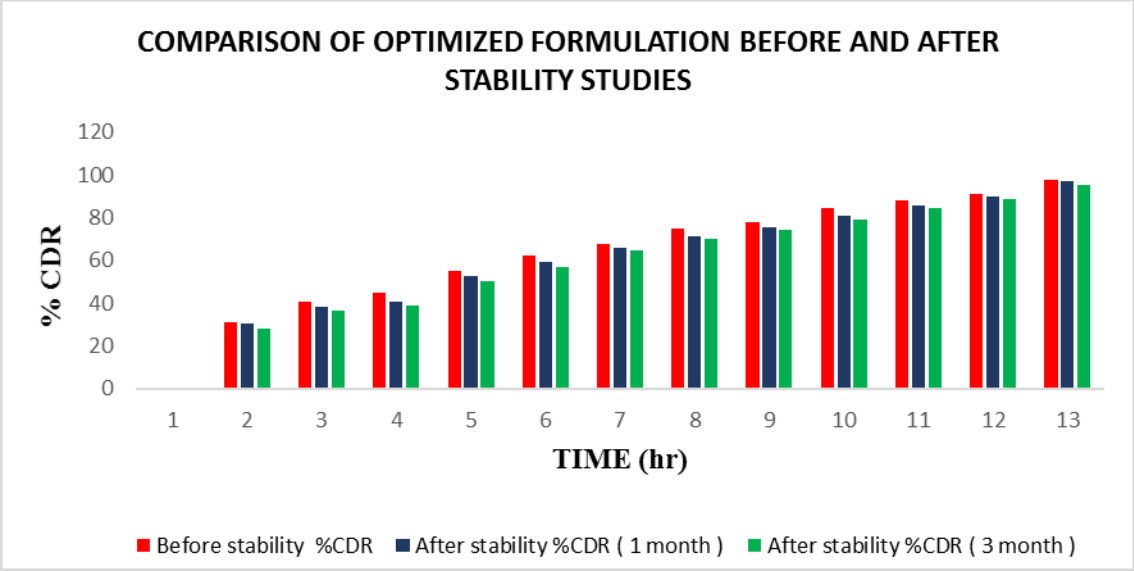

Figure 12: Percentage cumulative drug release before and after stability studies

The stability of the optimized formulation was known by performing stability studies for 2 months at accelerated conditions of 40ºC ± 75 % RH. The formulation was found to be stable with no physical changes and also shows comparable results in hardness, % drug content and *in vitro* drug release studies after the stability period. From the stability studies, it was confirmed that the formulation was stable.

CONCLUSION

The oral route of drug delivery is the most preferred route for administration of drugs. The rationale for the development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition. Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems.

Nifedipine is a 1,4-dihydropyridine calcium channel blocker. It is used for the treatment of angina pectoris, hypertension, and Raynaud's phenomenon. Nifedipine has a half-life of 2 hrs.

Organoleptic properties, melting point determination, solubility studies, FT-IR frequencies showed that the Nifedipine used was similar to the reported values. After the comparison of FTIR results, it was concluded that there was no incompatibility between drug and polymers.

Natural gums like Guar gum and Xanthan gum were chosen as polymers for the formation of sustained release matrix tablets. In this study, 12 formulations were prepared by direct compression method using different polymers at varying ratios, Microcrystalline cellulose and Sodium chloride were used which helps in the slow erosion of matrix from the tablet and Talc and Magnesium stearate as lubricants.

Each batch of the formulations was evaluated for pre-compression parameters such as bulk density, tapped density, the angle of repose, compressibility index and Hausner's ratio and the results were within the limit. The prepared formulations were also evaluated for hardness, friability, weight variation, content uniformity and *in-vitro* drug release studies. The drug content was found to be in the range of 95.36 – 99.92%. The hardness of the tablets was found to be in the range of 4.4-5.6 kg/cm^2. Friability below 1% was indicating the good mechanical resistance of tablets.

From the *in-vitro* drug release data, it was observed that the percentage cumulative drug release of Nifedipine decreased as the concentration of gum increased and it was also similar when the concentration of microcrystalline cellulose and sodium chloride were decreased. The optimum sustained release of drug was shown by formulation F9 containing an increased concentration of Xanthan gum and decreased the concentration of microcrystalline cellulose. F9 released 97.75 % of the drug in 12 hrs. The 'n' value of optimized formulation F9 was found to be 0.4743 which indicated that the drug was released by zero order kinetics with anomalous (Non-Fickian) release. The formulations F1, F2, F4, and F7 showed complete release before 12 hr, the possibility may be due to an increased percentage of microcrystalline cellulose and sodium chloride.

The swelling index was found to be highest for optimized formulation F9. The direct relationship was observed between the swelling index and gum concentration, as gum concentration increased, swelling index increased. It was observed that the cumulative percentage drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact was a slow erosion of the gelled layer from the tablets containing a higher amount of natural gums.

From the stability studies, it was confirmed that the optimized formulation remained stable at accelerated stability conditions of 40ºC and 75 % relative humidity.

Based on the above evaluation studies, it could be concluded that natural gum can be used as a suitable matrix forming agent by direct compression method for sustained release of Nifedipine over 12 hr by providing reduced dosing frequency and side effects.

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REFERENCES

1. Derle Diliprao V et al. The effects of formulation on the in-vitro release of Ambroxol Hydrochloride from Guar gum based Sustained release tablets. Journal of Pharmaceutical Research, 2007; 6(4): 222 – 225
2. Raghavendra Rao, Gandhi Sagar, Patel Tarun. Formulation and Evaluation of Sustained release matrix tablets of Tramadol Hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(1): 60 – 70
3. Nilesh V. Preparation and Evaluation of Ambroxol Hydrochloride matrix tablet using a different combination of polymers. International Journal of Pharma Tech Research , 2007; 3(1) : 309 - 313
4. Jaimini Manish, Kothari Abhay. Sustained release matrix-type drug delivery system: A review. Journal of Drug Delivery and Therapeutics, 2012; 2(6): 142 – 148
5. Nifedipine – Wikipedia; Available from en.wikipedia.org/wiki/nifedipine.
6. Preformulation Studies: Lab training. (Internet cited – May 10, 2017). Available from: labtraining.com/role-of-preformulation studies in drug development.
7. Yi Chen, Liang Zhu, Yi-Ying Gao. The solubility of Tobramycin in Methanol, Ethanol, Dimethyl sulfoxide and N, N-dimethyl formamide. Journal of Chemical Engineering Data, 2009; 54(4): 1403-1404.
8. Robert M Silverstein, Francis X Webster. Spectroscopic Identification of Organic Compounds. Wiley India, 1998; 6th edition: 79-109.
9. William Kemp. Organic Spectroscopy. Palgrave Publication, 1991; 3rd edition: 60-71.
10. V.S Kasture, D.P Belsare. Spectroscopy. Career Publications, 60-66.
11. Nifedipine Sustained Release Matrix Tablet. Indian Pharmacopoeia, 2010; Vol.II: 1751-1783.
12. Nifedipine Sustained-Release Tablets. US Pharmacopoeia-National Formulary, 2010; Vol.3: 4509-4514.
13. Eswar Kumar A, A. Vaishnavi, S. Ayesha, V. Saritha, M. Radhika. Formulation and Evaluation of Sustained release matrix tablet of Nifedipine. International Journal of Pharmacy and Analytical Research, 2015; 4(3): 219-229.
14. World Health Organisation. Bulk density and Tapped Density of Powder. Final Text for Addition to the IP, 2012; 1-6.
15. The angle of Repose – Wikipedia; Available from https://en.wikipedia.org/wiki/angle of repose.
16. Rakhi B Shah, Mobin A Tawakkul, Mansoor A Khan. Comparative Evaluation of Pharmaceutical powders and granules; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976911/
17. Hausner ratio – Wikipedia; Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976911/
18. Rita B and Suresh V. Formulation and Evaluation of Sustained release matrix tablets of Nifedipine. www.aclr.com.es.
19. Amrutha J.V. Pre and Post-Compression Studies of Tablets. Inorganic Chemistry: An Indian Journal, 2016; 11(4): 100-109.
20. Margret Chandira, B.S Venkateswarlu, Jadhav Anup Shankareao, Debjit Bhowmik, B. Jayakar, T.V Narayana. Formulation and evaluation of extended-release tablet containing Metformin hydrochloride. International Journal of ChemTech Research, 2010; 2(2): 1320-1329.
21. Deepak et al. Fast disintegrating tablets: A new era in Novel Drug Delivery System and New marketed opportunities. Journal of Drug Delivery and Therapeutics, 2012; 2(3): 74-86.

22. Lalla J K, Sharma A H. Indian drugs. 1994; 31(11): 503-508.
23. Sakthivel Deivasigamani, Arunachalam Ganesan, Shaila G Panpalia. Preparation and Evaluation of Guar gum based Extended-release matrix tablets of Aceclofenac. International Journal of Pharmaceutical and Phytopharmacological Research, 2014; 4(2): 109-112.
24. Preparation of p^H 6.8 Phosphate buffer; Available from www.pharmaguideline.com.
25. Margareth R.C. Marques, Raimar Loebenberg, May Almukainzi. Stimulated Biological fluids with possible Application in Dissolution testing. U.S Pharmacopoeia, 2011; 15-28.
26. Suvakanta Dash et al. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica Drug Research, 2010; 67(3): 217-223.
27. Kim Huynh-Ba. Chapter1-Introduction. Handbook of stability testing in Pharmaceutical development. 2011; 1st edition: 1-2.