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DEVELOPMENT AND CHARACETIZATION OF CALCIUM CHANNEL BLOCKER (NIFEDIPINE) BY SUBLINGUAL DRUG DELIVERY SYSTEM

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ABSTRACT

Sublingual tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. The focus of present investigation was to improve solubility, bioavailability and to achieved rapid onset action sublingual tablets of Nifedipine were prepared by direct compression technique. Eight Formulations were formulated using sodium starch glycolate and crosscaramellose as superdisintegrants on Friability, Disintegration time. In addition, the prepared tablets were also evaluated for weight variation, thickness, diameter, friability, content uniformity, wetting time and drug release studies. Formulation reveals fast dissolution and disintegration rate of optimized Nifedipine sublingual tablet, which is prerequisite for rapid management of angina.

Keywords: Nifedipine, direct compression technique, FTIR studies, Excipient, Drug release studies.

INTRODUCTION

Oral Drug delivery system

Conventional oral drug formulations, such as solid unit dosage form like tablets and capsules. They are prepared and release the active drug quickly after oral administration, to produce speed and total systemic drug absorption. After organization of medication it go into the fundamental flow after that medication will be assimilated from the tablets or container measurement shape is finished, groupings of medication plasma decrease as indicated by the medication's pharmacokinetic profile. At last, tranquilize plasma focuses dip under the base powerful plasma fixation (MEC), bringing about loss of remedial action. Before it spans to the point, additionally dosage is normally given if a maintained restorative impact is be disperate.[1] A capricious to work additionally measurements is to utilize a dose shape that will supply controlled medication discharge, and accordingly keep up plasma sedate fixations. Changed discharge measurements characterized as the readiness in which arrival of medication quality obviously time and/or are acknowledged helpful destinations not offered by ordinary dose frame, for example, arrangement, balms. Different kinds of expanded medication discharge items are recognized:[1,2]

Foundational drug releases through the sublingual transmit offer prompt beginning of remedial activity. Trouble in gulping is associated with all age gatherings, particularly elderly, kids, and patients who are rationally impede, uncooperative, disgusted patient. The dynamic pharmaceutical fixing solutes are immediately retained through uninvolved component into the reticulated vein of sublingual which lies underneath the oral mucosa, and transported through the facial veins and inward jugular vein lastly reaches to fundamental dissemination. The ingestion of the medication through the sublingual course is 3 to 10 times more noteworthy than oral course. For these planning, the little volume of salivation is every now and again enough to outcome in strong measurements shape breaks in the oral hole. Sublingual assimilation is basically speedy in real life, yet in addition short acting in length. *Advantages of sublingual drug delivery system* [3,4:] No trouble of course to

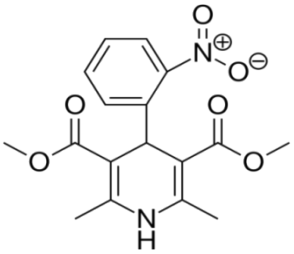
patients who decrease to swallow a tablet, for example, pediatric, geriatric patients and mental patients. Liver is skirted and furthermore dynamic fixing is shielded from corruption because of pH and stomach related compounds of the center gastrointestinal tract. This system has diverse cutoff points like not appropriate to SDS, pharmaceutical can't be utilized when a patient is uncooperative or oblivious and this course is inadmissible for delayed organization.

Sublingual glands

These are also distinguished for their authoritative and greasing up capacities, and sublingual organ discharge makes the nourishment tricky and effectively swallowable. Salivation discharge assumes a noteworthy job in molding the guideline physiological condition of oral cavity as far as pH, liquid volume and organization. Salivation discharge has been advanced by 3 noteworthy salivary organs which are-parotid, submaxillary, sublingual organs. Salivation directs oral microbial vegetation by keeping up the oral pH and catalyst movement. Around 0.5-2.0L of spit has been emitted by salivary organ. The stream rate of spit which thusly relies upon 3 factors, for example, the season of day, the kind of improvement and the level of incitement. Life structures and physiology of mucosa: The thickness of mucosa is 100-200 µm. Mucosa is made out of impartial yet polar lipid e.g. cholesterol sulfate, glucosyl ceramide. The salivation is made out of 99.5 % water, proteins, glycoprotein, high potassium (7X Plasma), bicarbonate (3X plasma), calcium, phosphorous, chloride, low sodium (1/10X Plasma). The sublingual organ contain 5% salivation. The pH of salivation is 5.6-7.0. *Advantages of sublingual drug delivery system*[5]*:* No difficulty of direction to patients who decline to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients. Liver is bypassed and also active ingredient is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

DRUG PROFILE[6,7]

NIFEDIPINE



Molecular weight: 346.46 g/mol
chemical formula: $C_{17}H_{18}N_2O_6$
Description: Nifedipine has been formulated as both a long- and short-acting 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, nifedipine prevents calcium-dependent myocyte contraction and vasoconstriction. A second proposed mechanism for the drug's vasodilatory effects involves pH-dependent inhibition of calcium influx via inhibition of smooth muscle carbonic anhydrase. Nifedipine is used to treat hypertension and chronic stable angina

Uses: Nifedipine is in a group of drugs called calcium channel blockers. It works by relaxing the muscles of your heart and blood vessels. Nifedipine is used to treat hypertension (high blood pressure) and angina (chest pain). Nifedipine may also be used for purposes not listed in this medication guide.
Materials and Equipments: Nifedipine- AR chemicals, Crosscaramellose- AR chemicals, Sodium starch glycolate- AR chemicals, PVP k 30- AR chemicals, microcrystalline cellulose- AR chemicals, Magnesium Stearate- R chemicals, Talc- AR chemicals
Equipments and Suppliers: Electronic Balance- Mettler Tolido&Sartorius, Compression Machine- Rimetek mini press-II, Mechanical Sieve Shaker- Retsch , Germany, Tap Density Tester- Electrolab, Mumbai, Disintegration Tester- Electrolab, Mumbai, Hardness Tester- Pfizer, Friabilator- Electrolab, Hyd, Thickness Tester- Sams Techno Mumbai, Dissolution Apparatus USP II- Labindia,Disso 8000

METHODOLOGY

Preformulation studies [8,9] Methods of API characterization
Physical properties: The color odour, taste of the drug was recorded using descriptive terminology.
Solubility studies: Solubility study of Nifedipine was performed in DMSO, methanol, ethanol, chloroform, and insoluble in water.
Determination of melting point: Melting point of Nifedipine was determined by capillary method.

Preparation of calibration curve of Nifedipine:
A] Preparation of phosphate buffer pH 6.8: About 28.80g of disodium hydrogen phosphate, 11.45 g of potassium dihydrogen phosphate was taken in volumetric flask and volume was made with water to produce 1000ml
B] Determination of λ_{max} for Nifedipine: Stock solutions of Nifedipine was prepared by dissolving Nifedipine in 100 ml of phosphate buffer solution pH (6.8), solutions were further diluted and analyzed spectrophotometrically.
Result: The λ_{max} of Nifedipine was found to be 275nm.
C] Preparation of standard calibration curve of Nifedipine: The calibration curve was plotted within the concentration range of 10-50 µg/ml of the Nifedipine . Appropriate dilutions were prepared and absorbance was measured for each solution at 275 nm since maximum absorbance was observed at this wavelength. Graph was plotted for absorbance Vs concentration.

Drug excipient compatibility studies[9]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 60^0 C and 40^0C/75 %RH for 90 days and LDPE bags were exposed to 40^0C±75 %RH for 90 days. Samples were observed periodically for any physical change.

Formulation table

Preparation of tablets by Direct compression method[10]

Different matrix embedded formulations of Nifedipine were prepared by direct compression method using varying proportion of superdisintegrants either alone or in combination. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, Various Super disintegrant agent and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 5–6 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Table 1: Formulation table for Nifedipine sublingual tablets

S.No.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Nifedipine	100	100	100	100	100	100	100	100
2	Cross caramellose	2.5	5	7.5	10	-	-	-	-
3	Sodium starch glycolate	-	-	-	-	2.5	5	7.5	10
4	Povidone	10	10	10	10	10	10	10	10
5	Lactose	81.5	79	76.5	74	81.5	79	76.5	74
6	Saccharrine sodium	1	1	1	1	1	1	1	1
7	Magnesium stearate	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2
9	Total	100	100	100	100	100	100	100	100

Evaluation of tablet[11-13]

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness: Twenty tablets were randomly selected from each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

Content Uniformity: Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Nifedipine. Dissolve the weighed quantity of powder into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask.

In vitro disintegration test

In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for the sublingual dosage form. The test was carried out using a tablet disintegration apparatus. Distilled water was used as the disintegrating medium at 24 ± 0.2°C. The time required to obtain complete disintegration of all the tablets was noted.

Wetting time

The tablet was placed at the center of two layers of absorbent paper fitted into a petridish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37⁰1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask. The diluted samples were assayed.

Kinetics of drug release[14]

To study kinetices data obtained from invitro releasae were plotted in various kinetic models.

Zero-order equation: %R = Kt, This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

First order equation: Log% unreleased = Kt / 2.303, This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

Higuchi equation: %R=Kt$^{0.5}$ This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

Korsmeyer-Peppas equation: $\%R=Kt^{n}$, This model is widely used, when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms as:

N	Mechanism
0.5	Fickian diffusion(Higuchi matrix)
0.5<n<1	Anomalous transport
1	Case- II transport(zero order release)
n>1	Super case- II transport

Stability studies[15]

The success of an effective formulation can be evaluated only through stability studies. The prepared sublingual tablets of Nifedipine were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2ºc and refrigerator 2-8ºc for a period of 3 months.

RESULTS & DISCUSSION

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physico-chemical parameters, in vitro release studies and stability studies.

Preparation of standard curve of Nifedipine

Standard curve of Nifedipine was determined by plotting absorbance V/s concentration at 275 nm. Using solution prepared in pH 6.8 at 275 nm. And it follows the Beer's law. The R^{2} value is 0.997.

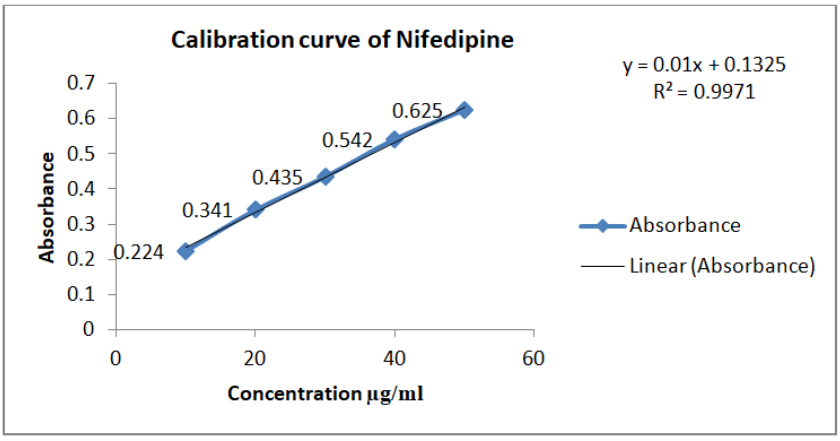


Fig 1: Calibration curve of Nifedipine

FT-IR Spectrum of Nifedipine

FT-IR Spectra of Nifedipine and F6 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Nifedipine and polymer. It also confirmed that the stability of drug during microencapsulation process.

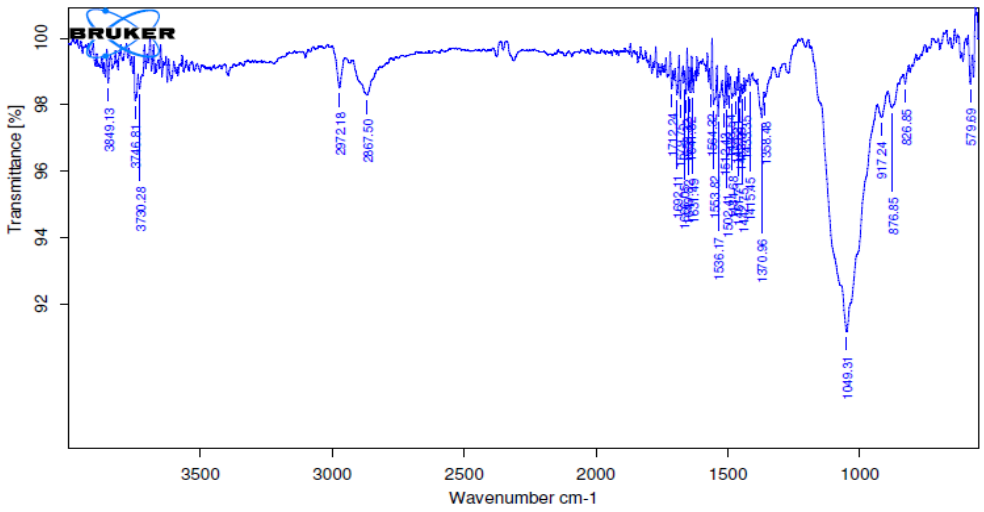


Fig 2: FTIR Studies of Nifedipine

Table 2: Characteristic Peaks for Nifedipine

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	2972.18
2	OH Bending	1000-1500	1049.31
3	C-H stretching	3000-2500	2867.50
4	C=O stretching	2000-1500	1692.11

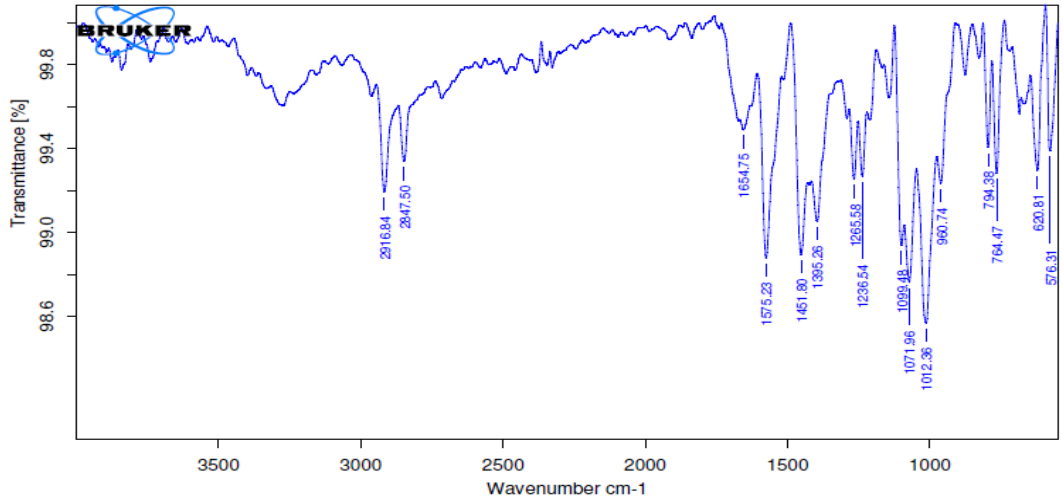


Fig 3: FTIR Studies of optimized formulation

Table 3: Characteristic Peaks for optimized formulation

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3000-2500	2916.84
2	OH Bending	1100-1070	1071.96
3	C=O stretching	2000-1500	1575.23

Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.431-0.471

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.515-0.563.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to31^0

c) Compressibility index: Compressibility index was carried out, it found between 10% to 14.90 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table 4: Pre compression parameters of Nifedipine sublingual tablets

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.431	0.522	17.43	1.21	29^{0}c
F2	0.471	0.563	16.34	1.19	29^{0}c
F3	0.463	0.524	11.64	1.13	30^{0}c
F4	0.455	0.515	11.65	1.13	30^{0}c
F5	0.462	0.531	12.99	1.14	31^{0}c
F6	0.458	0.534	14.23	1.16	29^{0}c
F7	0.449	0.521	13.81	1.16	31^{0}c
F8	0.451	0.530	14.90	1.17	30^{0}c

Post compression parameters

Weight variation: All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ⌖7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness: Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 2.3 mm to 2.6 mm.

Hardness: The measured hardness of tablets of each batch ranged between 3.24 to 3.46 kg/cm^2. This ensures good handling characteristics of all batches.

Friability: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity: The percentage of drug content for F1 to F8 was found to be between 95.20% and 98.55% of Nifedipine, it complies with official specifications.

Disintegration Time: In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 2.25 s, while the longest greatly exceeded 2.81 sec.

Wetting Time: The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The shortest registered wetting time was 1.25 s, while the longest greatly exceeded 1.52 sec.

Table 5: Evaluation parameters of Nifedipine sublingual tablets

F. No.	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content(%)	Disintegration time(sec)	Wetting time(sec)
F1	99	2.3	3.24	0.52	96.10	54	125
F2	98	2.4	3.26	0.45	95.20	53	134
F3	100	2.6	3.28	0.54	98.55	51	155
F4	97	2.4	3.46	0.51	97.50	49	152
F5	100	2.5	3.40	0.53	96.58	45	128
F6	100	2.6	3.28	0.54	98.55	51	155
F7	97	2.4	3.46	0.51	97.50	49	152
F8	100	2.5	3.40	0.53	96.58	45	128

Dissolution studies

All the eight formulation of Nifedipine sublingual tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table 6: Dissolution Profile of formulation F1 to F8

	% Drug Release							
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
2	25.36	26.39	25.98	24.59	26.79	23.40	24.80	23.85
4	35.26	36.29	37.59	39.65	34.56	32.71	33.10	32.71
6	50.26	49.67	50.26	49.99	48.26	48.56	46.29	47.36
8	62.35	59.66	61.29	64.26	63.54	65.30	59.80	60.55
10	70.26	70.98	71.29	73.29	72.59	72.28	70.60	73.60
15	79.36	81.26	82.29	83.96	83.85	82.10	81.90	82.26
20	86.26	87.26	88.99	90.26	89.56	89.25	90.64	88.25
30	93.26	95.35	94.68	93.48	94.56	98.48	95.51	90.58

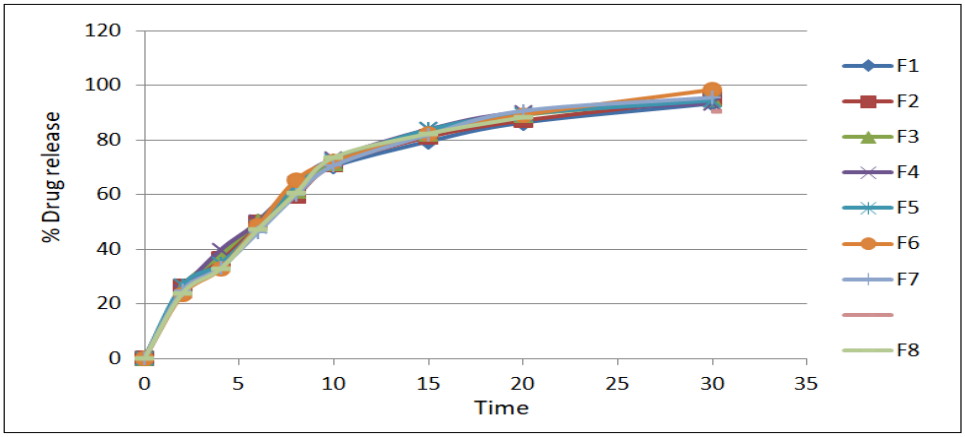


Fig 4: Percentage drug release of all formulations

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 6 months. Parameters quantified at various time intervals were shown.

Table 7: Stability studies of all formulations

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25^{0}C/60%RH % Release**	98.48	98.46	98.42	98.41	**Not less than 85 %**
F-6	**30^{0}C/75% RH % Release**	98.48	98.45	98.45	98.40	**Not less than 85 %**
F-6	**40^{0}C/75% RH % Release**	98.48	98.46	98.44	98.42	**Not less than 85 %**

CONCLUSION

The design, prepare and characterization of the sublingual tablets of the Nifedipine by using direct compression technique. In this formulation development first undergo for the pre formulation studies such as the color, odour, taste and solubility studies are done. The API and polymers compatability studies are done by the FTIR studies. For formulation studies the used excipients are the croscaramellose, sodium starch glycolate and lactose and talc were used. The eight formulations are done in this F6 formulation are release the drug up to the 8 hrs. It is compared to innovator it release the drug. The post compression parameters are also done. Such as the weight variation, friability, thickness, disintegration are done. All parameters are come within range of limits. The stability studies are done for 90days.The kinetic profile data is calculated it is fallow the zero order and higuchi model.

REFERENCES

1. Chasseaud LF, Darragh A, Doyle E, Lambe RF, Taylor T. Isosorbide dinitrate plasma concentration and bioavailability in human subjects after administration of standard oral and sublingual formulations. J Pharm Sci. 1984;73(5):699-701. doi: 10.1002/jps.2600730530, PMID 6737249.
2. Jiménez-castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993;19(1-2):143-94. doi: 10.3109/03639049309038765.
3. Labhade S, Malode C, Rawal V, Rupvate S.et al. Review article on sublingual drug delivery system. 2019;9(3): https://doi.org/10.22270/jddt.v9i3.2684
4. Lachman L, Liberman A, King JL. Tablets: the theory and practice of industrial pharmacy. Varghese publishing house. 1987. 3rd ed: pp. 296-300.
5. Sanada H, Yonezawa Y, Danjo K. Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity [Chemistry Pharma bulletin]. 1996;44(1):2121-7.
6. Biradar SS, Bhagavaati ST, Kuppasad IJ. Fast dissolving drug delivery systems: a brief overview. Int J Pharmacol. 2006;4(1):22-7.
7. Bhanji NH, Chouinard GA, Margolese HC. A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia. Eur Neuropsychopharmacol. 2004;14(2):87-92. doi: 10.1016/S0924-977X(03)00109-3.
8. Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorder. Can J Psychiatry. 2004; 49(10):701-3. doi: 10.1177/070674370404901009, PMID 15560318.
9. Sherwood BE et al., design, prepare and in vitro evaluation of tablets. Pharm Res. 1996;13(9):S197.
10. Smart JD, Formulated sublingual tablets. Rev. 2004; 56:481-9.
11. Susanne B, Margareta D, Bo L, Hans L, Anders P, Marie W et al.. design, prepare and characterization of acyclovir sublingual tablets. IJPASR sci. 2003;20:327-34.
12. Vanjan MR. Research article on sublingual tablets of Rosiglitazone J. Pharm Sci. 2012; 1973(62).
13. Vaasu EM et al. development of sustained release of Atenelol sublingual tablets. Drug Dev Ind Pharm. 1980;6:291-309.