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FORMULATION AND EVALUATION OF NIFEDIPINE FAST DISINTEGRATING SUBLINGUAL TABLETS USING SUBLIMATION METHOD

P. Venkata Anudeep[1*], Y. Prapurnachandra[2], S. K. Ameer,[3] S. Supraja[3], P. Bhavana[3], K. Viswa Roopa[3] and T. Lavanya[3]

[1]Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore Dt.524346 A.P., India.

[2]Department of Pharmacology, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore Dt.524346 A.P., India.

[3]Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore Dt.524346 A.P., India.

***Corresponding Author: P. Venkata Anudeep**

Assistant Professor, Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore Dt.524346 A.P., India. **Email Id:** anudeeppadavala9@gmail.com

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ABSTRACT

Nifedipine, a commonly prescribed calcium channel blocker, is essential for managing hypertension and angina, yet its rapid release in traditional formulations poses challenges. This study explores a novel approach, utilizing sublimation technique, to formulate immediate-release Nifedipine tablets using direct compression method. The study systematically formulates Nifedipine tablets with varying concentrations of Croscarmellose sodium(CS), starch, and microcrystalline cellulose (MCC), meticulously optimizing disintegration and dissolution kinetics. The resulting tablets demonstrate uniformity in weight and drug content, aligning seamlessly with pharmaceutical standards. Additionally, FTIR analysis validates the compatibility between the drug and polymer, without any undesirable chemical interactions. Overall, this study unveils a promising avenue for enhancing Nifedipine therapy for hypertension and angina through the development of immediate-release tablets. Such optimized formulations hold the potential to significantly improve treatment outcomes for patients.

KEYWORDS: Nifedipine, FTIR analysis, Croscarmellose sodium, microcrystalline cellulose.

1. INTRODUCTION

Hypertension emerges as the foremost health risk factor within the Indian context, assuming a profound role in shaping the nation's disease burden and mortality landscape.[1-3] The staggering toll amounts to a daunting 1.6 million deaths annually, predominantly stemming from ischemic heart disease and stroke complications. The oral route of drug delivery stands as the foremost, most coveted, and widely embraced method for the administration of therapeutic agents aimed at producing systemic effects.[4] This preference is rooted in its inherent naturalness, convenience, and cost-effectiveness, all of which contribute to its status as the gold standard for drug delivery mechanisms.[5,6] Orally disintegrating dosage forms are used in the formulation of a wide range of pharmaceutical products, including analgesics, antiemetics, antihistamines, cardiovascular agents, and psychiatric medications.[8,9] These dosage forms are particularly well-suited for drugs intended for acute or emergency treatment, where rapid onset of action is desirable. Orally disintegrating tablets.[15-21] (ODTs) have gained popularity as a patient-friendly dosage form due to their ease of administration and rapid disintegration in the oral cavity without the need for water. The preparation of ODTs involves various techniques aimed at achieving quick disintegration, enhanced drug dissolution, and improved patient compliance. In this comprehensive review, we explore the different techniques used for the preparation of ODTs, including direct compression, freeze-drying, spray drying, and other innovative methods. Sublimation utilizes volatile substances, such as camphor or menthol, to create pores in the tablet matrix, facilitating rapid disintegration upon exposure to moisture.

The study systematically formulates Nifedipine tablets with varying concentrations of Croscarmellose sodium(CS), starch, and microcrystalline cellulose (MCC), meticulously optimizing disintegration and dissolution kinetics. Nifedipine[8-10] acts by inhibiting the influx of calcium ions through L-type calcium channels in arterial smooth muscle cells. By inhibiting the initial influx of calcium, nifedipine disrupts the contractile processes of smooth muscle cells, leading to arterial dilation. Ultimately, the vasodilatory effects of nifedipine contribute to an overall decrease in blood pressure. Croscarmellose, Sodiumcross-linking reduces water solubility while still allowing the material to swell

(like a sponge) and absorb many times its weight in water. As a result, it provides superior drug dissolution and disintegration characteristics, thus improving formulas′ subsequent bioavailability by bringing the active ingredients into better contact with bodily fluids. Camphor is an Antioxidant that improves skin permeability. Microcrystalline celluloseserves as a bulking agent, binder, disintegrant, lubricant, and flow enhancer in tablet and capsule formulations, where it imparts desirable properties such as hardness, friability, disintegration, and flowability.

2. MATERIALS AND METHODS

Nifedipine and all other excipients were procured in analytical grade and utilized as received, The equipment employed for both the preparation and evaluation of the tablet formulations are outlined, other excipients were of analytical research grade and contain the highest purity.

Table 1: List of chemicals.

S.No.	Name of Ingredıents	Name and Grade
1	Nifedipine	Mylan research laboratories, India
2	Croscarmellose sodium	Divya Pharmaceuticals Pvt. Ltd.
3	Starch	Nice chemicals private limited
4	Lactose	Sigma Aldrich, AR grade
5	MCC	Sigma Aldrich, AR grade
6	Aspartam	Sigma Aldrich, AR grade
7	Camphor	Sigma Aldrich, AR grade

Table 2: List of equipments used for the formulation and evaluation of tablet.

S.No.	EQUIPMENTS	MANUFACTURER
1.	UV Visible Spectro Photometer1800	Shimadzu, Japan
2.	Digital weighing balance	Dhona 160D, India
3.	Dissolution apparatus	Labindia disso 2000
4.	Friabilator	PCI Analytics Limited, India
5.	Varnier caliper	Remi Equipment
6.	Monsanto hardness tester	Remi Motors Ltd
7.	Cadmuch punching machine (Single station)	CMB4 D-27, Cadmach Engg, Ahmedabad, India

2.1 Calibration Curve of Nifedipine

The standard curve of Nifedipine was prepared by using 6.8pH phosphate buffer.

Spectrophotometric method for the estimation of Nifedipine

The standard curve of Nifedipine was prepared in 0.1NHCl (PH1.2) at 237nm.

Standard Solution

Stock solution of 100µg/ml was prepared by dissolving accurately weighed quantity of10mgNifedipinein 10mlof ethanol.

Working Solution

From the stock solution aliquots of 0.5, 1, 1.5, 2and 2.5ml of stock solution were pipetted out into 10ml volumetric flask. The volume was made up to the mark with of 0.1 N HCl (PH 1.2). These dilutions give 2,4,6,8 and 12, 5µg/ml concentration of Nifedipine respectively. The absorbance of prepared solutions of Nifedipine was measured at 237nm in UV-spectrophotometry against an appropriate blank. The standard calibration curve yields a straight line, which shows that drug follows Beer's law in the concentration range of 2 to 12 µg/ml. A standard graph was plotted by keeping the known concentration on X-axis and obtained absorbance on Y-axis.

2.2 Formulatıon of Sublıngual Tablets

The preparation of Nifedipine tablets involves meticulous steps to ensure the uniform distribution of both the active ingredient and superdisintegrants, namely Croscarmellose sodium (CS), starch, and microcrystalline cellulose (MCC), at various proportions. Initially, Nifedipine and the selected superdisintegrants are weighed and sieved through a #80 mesh screen to achieve a fine particle size and uniformity. These screened substances are then carefully transferred into a mortar where they are thoroughly mixed using a pestle to achieve intimate blending. Subsequently, the powder blend is compacted into tablets using a single punch tablet machine. This step involves compressing the powder blend under high pressure to form tablets of uniform size and weight. The tablets are then subjected to drying at 60°C for 8 hours to facilitate the sublimation of camphor, an ingredient used to induce porosity in the tablet structure.

Table 3: Formulation of Nifedipine (100mg) and their composition (mg).

Ingredients	Batches					
	F1	F2	F3	F4	F5	F6
Nifedipine	10	10	10	10	10	10
Croscarmellose sodium	20	15	10	5	10	-
Starch	5	10	15	10	10	10
MCC	5	5	5	15	10	20
Aspartame	5	5	5	5	5	5
Camphor	5	5	5	5	5	5
Lactose	10	10	10	10	10	10

2.3 Preformulation study

The significance of the pre-formulation study is to strengthen the formulation under regulatory guidance and gather enough data to develop a chemically stable product containing a better therapeutic effect. This study also helps to enhance the product quality, safety, and standard and minimize toxicity. Regarding the same FTIR and DSC studies have been performed. This result helps to determine the chemical composition and physical state of the drug and polymers used in the formulation.

2.4 Evaluatıon Of Tablets

The compressed tablets were evaluated for the important parameter that affects the release of the drug such as weight variation, thickness, hardness, friability, drug content and dissolution test for all formulations.

Thıckness

Tablet thickness was measured by using Vernier callipers. Control of physical dimensions of the tablets such as thickness is essential for consumer acceptance and tablet-to-tablet uniformity. These dimensional specifications were measured using digital micrometer callipers. The thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter. Tablet thickness was tried to control within 5% variation of the standard value.

Weıght Varıatıon Test

Weighed 20 tablets individually and their average was calculated and compared with the weight of each tablet. The tolerance in weight variation was allowed according to IP.

Hardness Test

Hardness was determined by Monsanto Hardness Tester. The hardness of all the formulation is determined.

Frıabılıty Test

Weighed 10 tablets and were placed in the Roche's friabilator for 4 minutes /100 rpm. Then the weight after the test was calculated. The difference in the weight is noted and expressed as percentage. It should be less than 1%.

Drug Content Estımatıon

Randomly selected 10 tablets from each formulation were weighed individually, crushed and hydrated in water. The solution was filtered by whatman no.42 (2.5 µm) filter paper and the drug content was determined by UV spectrophotometer (Jasco V-670, Japan) at 237 nm with a suitable dilution.

In-Vıtro Dıssolutıon Test

Drug release studies for all formulations were carried out by using single bucket USP type- I basket apparatus (Secor India Lab), at 100rpm bearing 900 ml of pH 2 or pH 6.8 medium at 37 ± 0.5°C. The samples (5ml) were withdrawn at required intervals of time and replaced by same amount of fresh solution (pH 2 or pH 6.8). Absorbance was determined by UV Visible spectrophotometer at 237 nm.

Stability Studies

Selected formulations were kept tapped with vials in an incubator maintained at 40±2^{o}C and75±5% RH for three months (Nighute and Bhise 2009). Changes in the appearance, particle size, drug content and release profile of these stored microspheres were investigated at regular timeintervals (1, 2 and 3months).

3. RESULTS AND DISCUSSION

3.1 Calıbratıon Curve of Nefıdıpıne

The standard curve of Nifedipine was prepared by using 0.1N HCL (PH 1.2).

Table 4: Calibration values of Nifedipine.

Sl. No.	Concentration	Absorbance
1	0	0
2	2	0.09
3	4	0.17
4	6	0.26
5	8	0.343
6	12	0.430

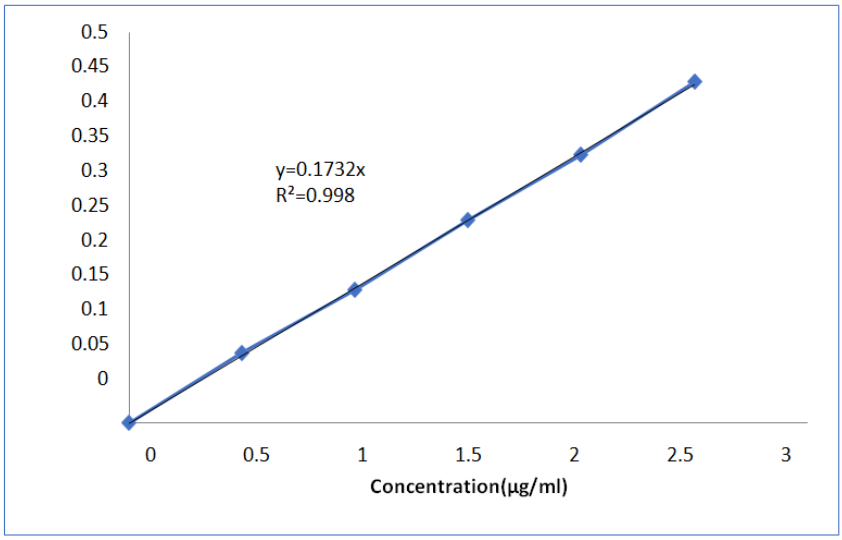

Fig 1: Calibration curve of Nifedipine.

3.2 Pre-Evaluatıon of Mıxture

The bulk density ranged from 0.33 to 0.41 gm/ml, while the tapped density ranged from 0.39 to 0.45 gm/ml. The angle of repose, which indicates how well the powder flows, was between 21.02 to 27.11. Carr's index, a measure of powder flowability, ranged from 5.12 to 25.64, and Hausner's ratio, which assesses powder compressibility, ranged from 1.05 to 1.34. Overall, the results were within acceptable limits, indicating excellent flowability of the formulations.

Table 5: Pre-formulation studies for Nifedipine SLTs (Formulation F1-F6).

Pre-Compression Parameter	F1	F2	F3	F4	F5	F6
Bulk density	0.33±0.11	0.36±0.08	0.35±0.11	0.36±0.02	0.39±0.07	0.41±0.99
Tapped density	0.39±0.73	0.40±0.12	0.41±0.91	0.40±0.13	0.44±0.78	0.45±0.61
Angle of repose	25.11±0.1	23.03±0.41	27.2±0.04	21.02±0.13	26.09±0.13	27.11±0.1
Carr's index	25.64±0.1	11.11±0.01	24.44±0.01	5.12±0.21	6.97±1.11	10.86±0.01
Hausner's ratio	1.34±0.01	1.12±0.03	1.32±0.03	1.05±0.02	1.07±0.01	1.12±0.04

3.3 Post-Evaluation of Tablets

Drug Content Uniformity

Randomly selected tablets from each formulation were crushed and dissolved in pH 6.8. The solution was filtered and the drug content was determined by UV spectrophotometer (Jasco V-670, Japan) at 237 nm with a suitable dilution. Nifedipine tablets (Formulation F1-F6) were evaluated for their drug content properties that play a vital role in the drug release pattern. The drug content for different formulations was found to be within the standard limit of 97.17 to 99.95% shown in Table 7.3. The formulated tablets are stable for further study. Nifedipine tablets (Formulation F1-F6) were evaluated for their physicochemical properties that play a vital role in the drug release pattern.

Table 6: Physical properties of Nifedipine SLTs (Formulation F1-F6).

Formulation	Tablet Weight variation (mg)	Tablet Thickness (mm)	Tablet Hardness (kg/cm2)	Tablet Friability (%)	Drug Content (%)
F1	58.13+1.31	3.17+1.13	3.73+0.01	0.62+0.51	98.63+1.31
F2	59.11+1.46	2.93+0.51	3.51+0.3	0.71+0.09	98.71+1.16
F3	60.73+1.31	2.88+0.77	3.09+0.28	0.63+0.12	99.21+1.71
F4	59.09+1.21	2.96+0.09	3.91+0.12	0.61+0.54	99.61+1.11
F5	58.27+0.11	3.11+0.71	3.83+0.17	0.68+0.11	97.17+1.47
F6	59.79+1.27	3.19+0.48	3.79+0.25	0.71+0.37	99.95+1.37

Results are expressed as of mean ±SD (n=3)

3.4 Drug Compatibility Using FTIR

The FTIR spectrum of individual drug (Nifedipine) and drug with other excipients. Obtained result reveals that individual polymers and nifedipine shows different spectra which are different from each other. Whenever nifedipine and polymers combination has been taken observed that there is no shifting or change in nifedipine spectra. Obtained result concludes that individual

polymers and their different weight ratios are compatible with the drug nifedipine. From the FTIR results it has been formulations.

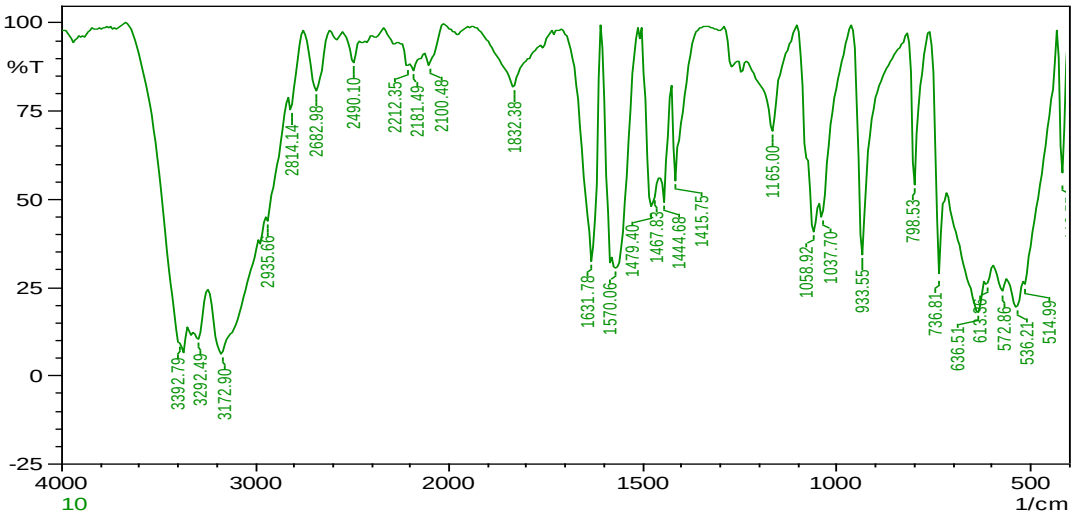

Fig 2: FTIR spectrum of Nifedipine.

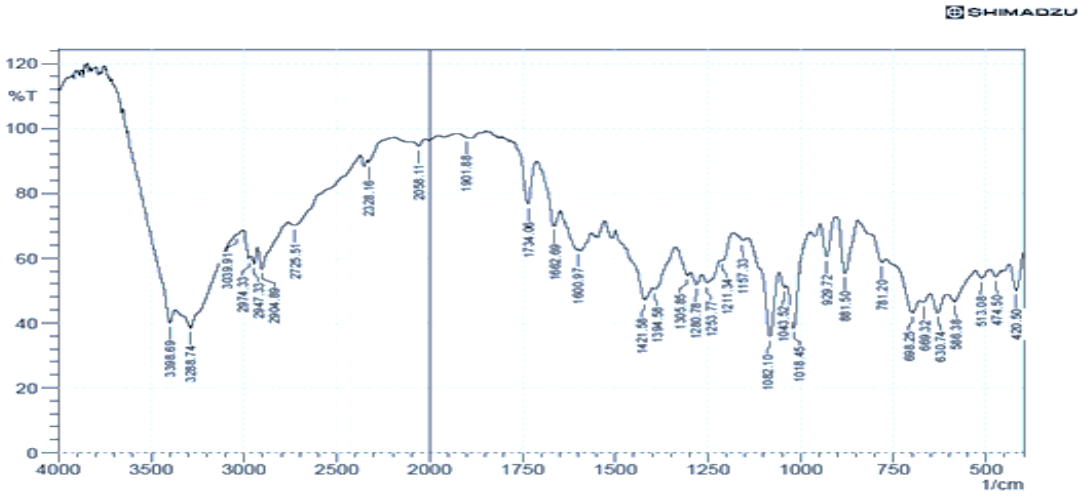

Fig 3: FTIR spectra of croscarmellose sodium.

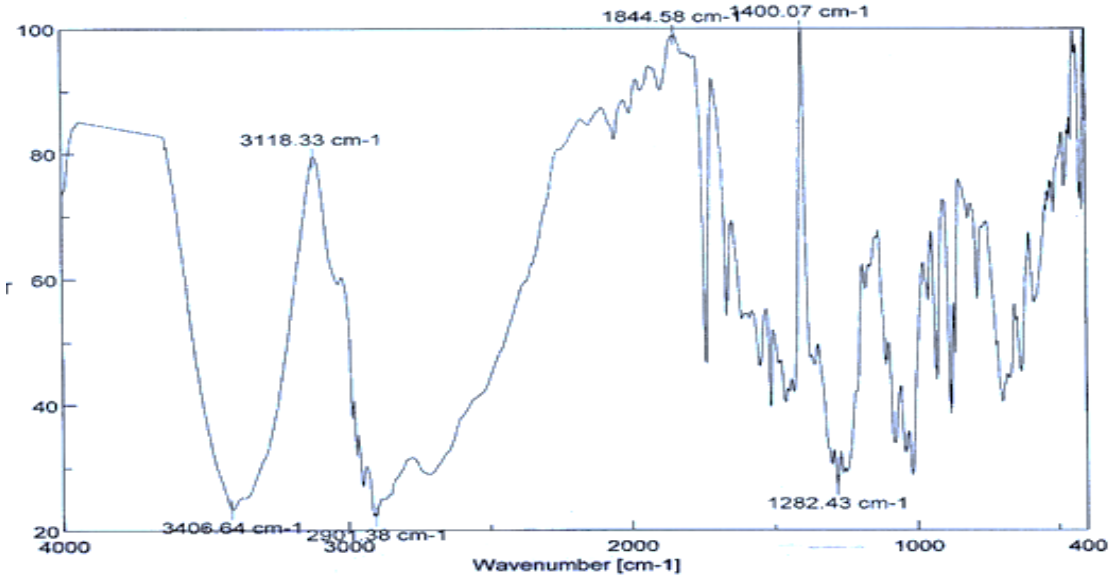

Fig 4: FTIR spectra of starch.

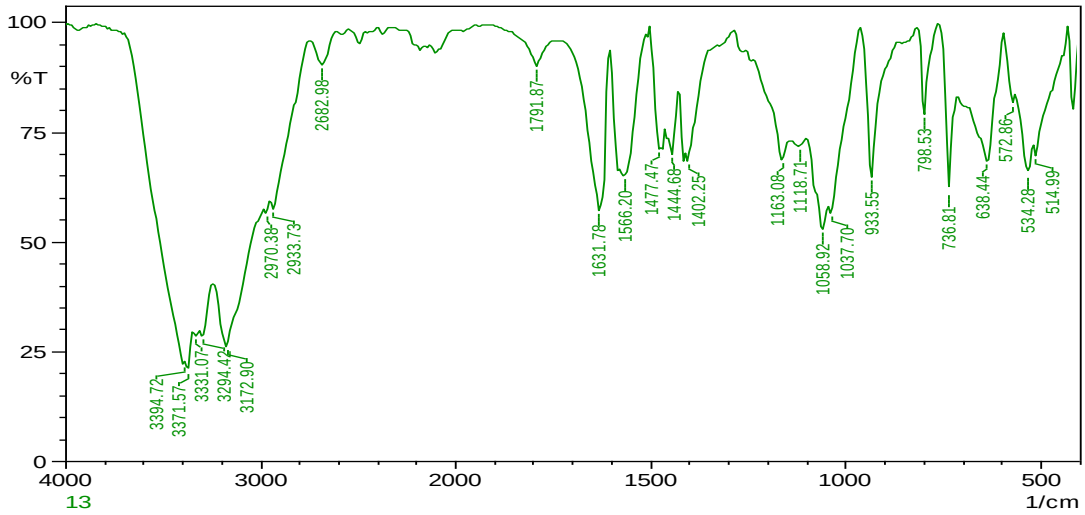

Fig 5: FTIR spectrum of Nifedipine and Croscarmellose sodium.

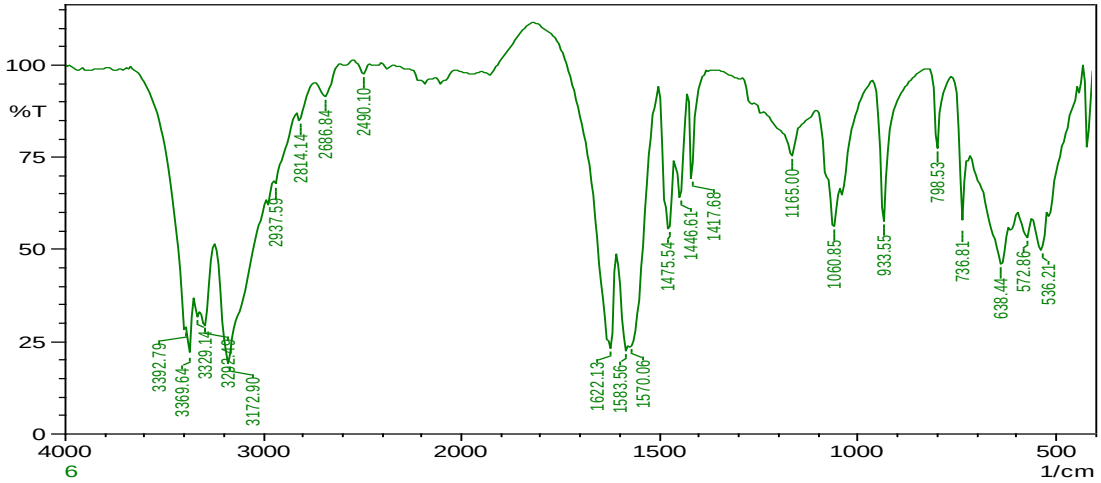

Fig 6: FTIR spectrum of Nifedipine and Starch.

3.5 Drug Release Profile

In Vitro Dissolution Study

Drug release studies for all formulations (F1-F6) were determined using multi bucket USP basket apparatus (Secor India Lab) at 100rpm containing 900 ml of pH 6.8 medium at 37 ± 0.5°C. The variation in dissolution time observed for formulations F1 to F6 tablets, ranging from 5 to 12 minutes, can be attributed to the characteristics of the polymers and their viscosity. Conversely, formulations containing starch and microcrystalline cellulose (MCC) as disintegrating agents, such as formulation F6, exhibit slower disintegration and drug release due to their lower disintegrating capabilities. For instance, F4 achieves 98.79% drug release at 8 minutes, F5 achieves 97.86% release at 10 minutes, and F6 achieves 98.99% release at 12 minutes. Overall, the observed results highlight the importance of selecting appropriate disintegrating agents and optimizing their concentrations to achieve desired drug release kinetics and enhance tablet disintegration in sublingual formulations.

Table 7: In-vitro dissolution profile for nifedipine SLTs (Formulation F1-F6).

Formulation	1min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	11 min	12 min
F1	31.31	32.98	51.11	77.72	99.31	-	-	-	-	-	-	-
F2	30.31	48.91	57.21	66.54	78.21	86.21	99.35	-	-	-	-	-
F3	27.23	33.41	45.72	56.71	68.29	76.73	81.32		-	-	-	-
F4	28.79	37.86	46.92	58.98	67.72	78.45	87.31	98.79				
F5	19.75	29.62	39.63	47.69	54.82	60.79	68.32	73.79	84.81	97.86	-	-
F6	8.73	14.44	19.21	23.74	30.32	39.85	49.73	57.22	64.92	76.57	87.57	98.99

Results are expressed as of mean ±SD (n=3)

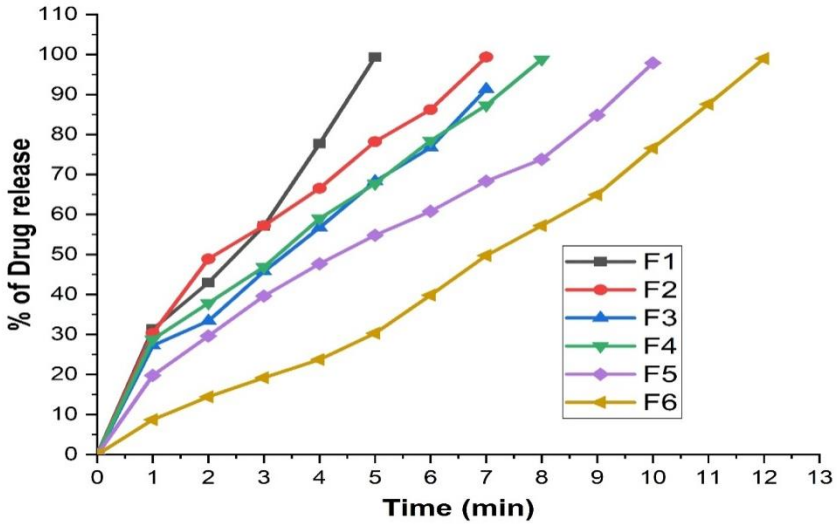

Figure: 7 In-vitro dissolution profile of nifedipine tablets (Formulation F1-F6).

3.6 Stability Studies

The results of stability studies indicated that there was no significance change observed in stability study for formulations F1 during the test period and the results are mentioned in below. Physical stability characteristics of selected formulations.

Evaluation Parameter	Formulation code	1st Month	2nd Month	3rd Month
Drug content	F1	98.63	98.1	97.92
Drug Release		99.31	98.74	98.08

4. CONCLUSION

The formulation of sublingual tablets (SLTs) containing Nifedipine was explored using Croscarmellose sodium (CS), starch, and microcrystalline cellulose (MCC) as disintegrating agents. The tablets were prepared using a direct compression method, with the addition of camphor for sublimation to create pores and enhance tablet disintegration. Various formulations were developed with different ratios of superdisintegrants and disintegrating agents, and their properties were evaluated. The pre-compression studies revealed satisfactory characteristics of the formulated SLTs. The post-evaluation results of SLTs exhibiting uniformity in weight and drug content. In vitro dissolution studies demonstrated varying release profiles for formulations F1 to F6, ranging from 5 to 12 minutes. The high concentration of CS in formulations facilitated rapid tablet disintegration and drug release, while formulations containing starch and MCC exhibited slower disintegration kinetics. The optimized formulations offer rapid and efficient drug release, potentially improving patient compliance and treatment outcomes. Further studies, including in vivo evaluations and clinical trials, are warranted to validate the efficacy and safety of these formulations for therapeutic use.

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