RESEARCH PAPER

Design, Formulation and Optimization of Nifedipine Sublingual Films Using 3^2 Experimental Design

Satyajit Sahoo[1]*, Sapna Desai[1], Tejas Patel[1], Rashmi Rajeghorpade[1], Archana Kaushik[1] and Shrivastav Vaishali Shashikant[1]

Pioneer Pharmacy College, Vadodara, Gujarat, India – 390019
satyajitppdc@gmail.com

Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT

Objectives: The present investigation was to formulate, develop and optimize sublingual films of Nifedipine, a BCS Class II drug, to enhance its bioavailability. The approach involved preparing solid dispersions using Soluplus polymer to improve the drug's solubility.

Experimental Work: Solid dispersions of Nifedipine and Soluplus were prepared using the solvent evaporation method. These dispersions were incorporated into sublingual films using Hydroxypropyl Methylcellulose (HPMCE5) as the film-forming polymer, Polyethylene Glycol 400 (PEG 400) as the plasticizer, and a hydroalcoholic mixture (ethanol and water) as the solvent. Preformulation studies included drug- excipient compatibility tests using FTIR, Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD).Sublingual films were assessed for various physicochemical parameters, including Thickness, Weight variation, Folding Endurance, Surface pH, Disintegration time, Drug content, In-Vitro drug release and Ex-Vivo Permeation.

Result and Discussion: The solid dispersion technique significantly improved the aqueous solubility and dissolution rate of Nifedipine. Compatibility studies indicated no major interaction between the drug and excipients. The formulated films showed uniform drug content, rapid disintegration, and excellent release profiles, confirming their potential for fast therapeutic action. The inclusion of Soluplus played a key role in the solubilization and stabilization of Nifedipine.

Conclusion: The developed Nifedipine sublingual films incorporating solid dispersions present a promising novel drug delivery approach with improved bioavailability, faster onset of action and better patient compliance for hypertension treatment.

Keywords: *Nifedipine, Sublingual Films, Solid Dispersion, rapid onset action, Bioavailability*

How to cite this article: Sahoo S, Desai S, Patel T, Rajeghorpade R, Kaushik A, Shashikant SV., Design, Formulation and Optimization of Nifedipine Sublingual Films Using 3^2 Experimental Design. Int J Drug Deliv Technol. 2026;16(7):574-586. DOI: 10.25258/ijddt.16.7.61
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Elevated arterial pressure is the hallmark of hypertension, also referred to as high blood pressure, a chronic medical condition. It dramatically raises the risk of kidney failure, heart disease, and stroke. Often termed the "silent killer," hypertension may remain asymptomatic until it leads to severe health complications. [1] Approximately 90-95% of patient suffers from primary hypertension and has no identifiable cause. [2] Blood pressure that is greater than usual is known as hypertension. A measurement of 130/80 mm Hg or higher is regarded as high blood pressure. Although the precise origin of primary hypertension is unknown, lifestyle variables (such as high-sodium diets, excessive alcohol use, physical inactivity, and obesity) and genetic susceptibility (from family history) are risk factors. [3]

High prevalence in the elderly and certain ethnic groups. An increase in cardiac output, frequently as a result of increased blood volume or sympathetic nervous activity, and an increase in peripheral vascular resistance as a result of the intricate interplay between general and environmental factors. [4] These changes may lead to endothelial dysfunction, arterial stiffening and ultimately target organ damage. Hypertension affects more than 1.13 billion individuals worldwide, two-thirds of them reside in nations with poor and moderate incomes. [5] This is an increasing problem due to ageing populations and changes in lifestyle and it may be difficult to get patients to take medicines as they are unlikely to bother about the disease present when there are no symptoms. Resistant hypertension: Blood pressure that is unresponsive to

**Author for Correspondence: satyajitppdc@gmail.com*

therapy. Blood pressure that does not respond to treatment with a combination of several anti-hypertensive.

The use of lifestyle changes and pharmacological treatment is used at present. ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics are used but they have the following limitations: First pass metabolism results in poor bioavailability of some drugs. [6] A delayed onset of action in hypertensive emergency is not desirable. The negative effects were GI discomfort. Also there could be systemic adverse events which might affect the patient compliance. [7]

A common dihydropyridine calcium channel blocker used to treat angina pectoris and hypertension is Nifedipine. In order to treat angina pectoris and hypertension, Nifedipine blocks the entrance. Nifedipine works by preventing calcium ions from entering the heart and vascular smooth muscles through L-type calcium channels. Blood pressure is lowered as a result of vasodiation and a decrease in peripheral vascular resistance. [8] Limitations of conventional oral formulations of Nifedipine: Low bioavailability, short half- life leading to frequent dosing impacting patient adherence. Furthermore, in acute settings, delayed onset agents are not suitable for fast blood pressure control. Fast-dissolving drug delivery systems are made to quickly dissolve or disintegrate in the oral cavity, allowing for quick drug absorption. [9]

These systems offer bioavailability as it bypass first pass metabolism. It improved compliance of patients especially beneficial for for young children and elderly populations. It offers rapid onset of action in critical emergencies. [10] Due to the sublingual region's high vascularization, the medication can enter the systematic circulation directly, and thus a rapid therapeutic effect. Sublingual films are thin, flexible ribbons that deliver drugs through the sublingual route. The best sublingual film should dissolve in seconds, at the contact of saliva. [11]It should have adequate mechanical strength to withstand during handling. Ensures even distribution of the drug for uniform dosing. It must be palatable so that the patients will take it. Sublingual film provides the advantage of rapid drug absorption and onset of action. It avoids gastrointestinal degradation and first-pass metabolism. It should be non-invasive and easy. [12]

A formulation technique called solid dispersion is used to improve the solubility and bioavailability of medications that are poorly soluble in water. Using this method, one or more active medicinal compounds are dispersed in an inert carrier matrix, usually in a solid state. The resulting system can improve the drug's solubility rates and, consequently, its bioavailability. [13] The classification of solid dispersion includes Eutectic Mixtures, crystalline carrier with Amorphous Precipitation, Sturdy solutions, Glass solutions and Suspensions and Carrier type based classification. Several techniques are employed to prepare solid dispersions are Solvent Evaporation, spray Drying, Hot-Melt Extrusion, Lyophilization and Fluid Supercritical Techniques. The solid dispersion approach offers several benefits such as it enhanced solubility and rate of dissolution. May increase bioavailability. It can be used to prevent the drug from recrystallizing and therefore could keep the drug soluble. It is versatility as it can be applicable to wide range of drugs and carriers. Hypertension is blood pressure which has higher than normal pressure. A person has high blood pressure if their blood pressure is 130/80 mmHg or higher. Hypertension is the term of high blood pressure. It greatly raises the chancesof having heart disease, stroke and kidney failure.

Primary hypertension occurs in 90-95% of patients, and is without known cause, whilst the remaining 5-10% of patients may have secondary hypertension which is associated with underlying disease (such as renal disease, endocrine disease or drug use). There are several risk factors such as Lifestyle (excessive alcohol consumption, a diet heavy in salt, inactivity, and obesity) and Genetic predisposition (from family history). There is age and ethnicity related prevalence rates (e.g., older ages, certain ethnicities). Nifedipine is a member of the class of medications known as calcium channel blockers that are typically used to treat angina pectoris and hypertension. By preventing calcium from entering L-type calcium channels in cardiac cells and peripheral vascular smooth muscle and cardiac cells, causing vasodilation and decreasing peripheral vascular resistance, and hence blood pressure. The limitations of traditional oral products of Nifedipine include low bioavailability, short half- life and need for frequent doses making compliance challenging. In addition, delayed onsets are unsuitable for an acute situation for rapid blood pressure control. The concept of a fast-disintegrating drug delivery system is to break down or dissolve very fast within the mouth, in order to facilitate the absorption of a drug. These systems provide better bioavailability because of its route of action (no first pass metabolism). It was useful in improving compliance in the patient, particularly in children and elderly. The sublingual is being a highly vascular substructure, with direct absorption of a drug into the blood circulation, so that a quick therapeutic impact may be obtained in an emergency. Sublingual films are extremely thin, extremely flexible strips that deliver drugs via the sublingual route.

When a good sublingual film comes into touch with saliva, it should disintegrate quickly-within seconds. [11] It should have adequate mechanical strength so that it can withstand during handling. It assures a constant distribution of the drug; it is dosed evenly. It should be palatable and if not then patients will not take it. An advantage of sublingual film is that the film should have a fast absorption rate of drug and should have a fast onset of

action. It is not degraded in GI tract and first pass metabolism. Easy and non-intrusive. [12] One formulation technique for improving the water-solubility and bioavailability of medications that are insoluble in water is solid dispersion. It is an approach to disperse one or more active pharmaceutical ingredient(s) I an inert carrier matrix, typically a solid matrix. There are various good dispersion classifications including: Eutectic Mixtures, Amorphous precipitations in solid solutions and crystalline carriers, Glass Solutions and Suspensions and Carrier Type Based Classification. Several techniques are employed to prepare solid dispersions are Solvent Evaporation, Lyophilization, Spray Drying, Hot-Melt Extrusion, and Supercritical Fluids Methods. The Solid dispersion approach offers several benefits such as it enhanced solubility and rate of dissolution. It may increase the bioavailability. It may be used to help prevent recrystallization and continue to maintain the solubility advantage, it may be used to stabilize and amorphous forms. It is versatility as it can be applicable to a wide range of drugs and carriers. [14]

MATERIALS AND METHODS

Nifedipine and Soluplus were received as a generous gift sample from Ami Lifesciences Pvt. Ltd., Vadodara, Gujarat and BASF Corporation, Mumbai, India respectively. Hydroxypropyl ethylcellulose (HPMC E5), Polyethylene Glycol (PEG 400) were purchased from SAVA fine chemical, Mumbai. All other ingredients used during formulation were of either pharmaceutical or analytical grade.

Preparation of Solid Dispersion

Nifedipine and Soluplus were accurately weighed in a 1:1 proportion and mixed in ethanol (10 mL) to form a clear and homogenous solution. Initially, the polymer was completely solubilized in the solvent, gradually added with Nifedipine up to 45 minutes with continuous stirring. The resultant solution was kept under normal temperature conditions to allow complete evaporation of the solvent. Dried solid dispersion mass was collected, powdered using mortar and pestle and sieved for getting uniform powder form. Drug loaded solid dispersion was kept in desiccator until next use.[15]

Formulation Method for Sublingual Films

Method of preparation of sublingual films was prepared using solvent casting method. The exact amounts of solid dispersion, plasticizer (PEG 400) and film- forming polymer (HPMC E5) were weighed and dissolved in an appropriate solvent system. The solution was stirred until a homogenized viscous solution was obtained. It was then poured onto a flat glass or Petri dish and dried in a hot air oven for 24 hours at 40-45°C. The films were then removed from the oven and cut into strips of 2cm*2cm in size containing the desired amount of Nifedipine per film. [16] The various formulas are given in table 1.

Preliminary Screening of Polymers for Sublingual Films

Initial investigation was conducted on various polymers to assess their influence on the drug release pattern of mouth-dissolving formulations. Nine trail batches, labeled TB1 through TB9, were prepared and tested for disintegration time, tensile strength, and cumulative drug release percentage at the 5-minurte mark, along with their respective compositions. [17] The results are given in Table 1.

Table 1: Composition of Preliminary Trial Batches of Solid Dispersion of Nifedipine with different polymer ratio in Sublingual Film

Batch Code	Polymer Used	Drug: Polymer Ratio	Percentage Yield (%)	Drug Content (%)	Saturation Solubility (mg/mL)
TB1	Soluplus	1:1	89.3	96.1	0.045
TB2	Soluplus	1:2	91.5	98.4	0.061
TB3	Soluplus	1:3	94.2	99.4	0.078
TB4	PVPK30	1:1	88.7	96.7	0.038
TB5	PVPK30	1:2	90.1	97.8	0.046
TB6	PVPK30	1:3	93.2	98.9	0.054
TB7	SSG	1:1	87.4	95.5	0.031
TB8	SSG	1:2	89.9	96.9	0.039
TB9	SSG	1:3	92.3	97.5	0.047

Experimental Design of Sublingual film

A 3^2 full factorial design was employed in this study [18]. Based on a comprehensive review of the literature, the quantities of HPMC E5 (X_1) and PEG 400 (X_2) were selected as independent variables within the 3^2 factorial framework, while tensile strength and percentage cumulative drug release (% CDR) were designated as the response variables. To obtain a formulation exhibiting the desired tensile strength and % CDR, various combinations of HPMC E5 and PEG 400 were systematically evaluated and optimized using this experimental design.

Full factorial design

This approach is appropriate when a thoroughly examination of higher-order interactions between factors is necessary. It involves conducting experiments. It involves conducting experiments at every possible combination of factor levels. Because the number of required runs grows quickly with the number of factors, full factorial designs are typically applied when only a small number of known influential factors are involved, or when gathering extensive data is practical. This method provides rich information efficiently and allows effects to be estimated with high precision. The total number of experimental runs depends directly on the number of chosen independent variables, and the response (Y) is recorded for each run.

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11}X_1^2 + b_{22} X_2^2$$

In the 3^2 full factorial designs, two independent factors were assessed, each at three levels, resulting in 9 experimental conditions. The design structure for this 3^2 full factorial setup is presented in Table 1 and Table 2. The two selected independent variables were:

X1 = HPMC E5

X2 = PEG 400

Table 2: Variables with coded and exact values for 3^2 full factorial design

Independent Variables	Low	Medium	High
Coded values	**-1**	**0**	**+1**
X1 = HPMC E5	200	300	400
X2 = PEG 400	0.2	0.3	0.4
Dependent Variables			
Y_1 = Tensile strength			
Y_2 = % CDR			

Drug-Excipients Compatibility Study:

Interactions between the active drug and Excipients are crucial for ensuring the stability of the final dosage form. Fourier transform infrared spectroscopy (FTIR) was employed to assess both physical and chemical compatibility between the Drug and Excipients. The FTIR spectra of Nifedipine, HPMC K15M, and their physical mixture were obtained using the KBr pellet method on an FTIR spectrometer. [19]

EVALUATION OF NIFEDIPINE SUBLINGUAL FILMS

Film Thickness

The film thickness was determined using a vernier caliper and the average thickness across all samples was computed [20].

Weight Uniformity of the Film

Five individual sections, each one square inch in size, were cut from different areas of the cast film. The weight of each section was recorded and variations in weight were assessed. [21]

Surface pH

This test evaluates the surface acidity or alkalinity of the film to ensure it is unlikely to cause irritation, inflammation, or harm upon contact with sensitive tissues or food. Measurements were taken using a pH meter. [20]

Tensile strength

The tensile strength of the film was measured using a digital tensile testing machine equipped with two grips-one fixed at the bottom and the other movable at the top. A film sample of defined dimensions (2*2 cm) was clamped between the grips, and a steadily increasing force was applied until the film fractured. The tensile strength value, recorded in kilograms, was then obtained from the device [20,22].

$$\text{Tensile strength (Nmm}^2) = \frac{Force\ at\ break\ \ x\ 9.8}{Initial\ cross\ sectional\ area\ of\ sample}$$

Folding endurance

The film's resistance to folding was assessed by repeatedly folding a narrow strip of the material at the same location until it fractured. The average folding endurance across all film samples was then calculated [21,22].

Disintegration time

The CDER guidance specifies disintegration time limit of 30 seconds or less for orally disintegrating tablets, a benchmark that may also serve as a reference for sublingual films, despite the absence of official guidelines specific to this dosage form. This criterion can be used quantitatively during product development or for quality control purposes. The disintegration test can be conducted using a standard Pharmacopoeial disintegration apparatus. Typical disintegration times for films range between 5 and 50 seconds. In testing, a 2*2 cm film sample is placed in the basket of the apparatus, which is then moved up and

down at a rate of approximately thirty cycles per minute [23].

***In-vitro* drug release**

In-vitro dissolution testing was performed using 300 ml of simulated saliva fluid. The experiments were carried out with a USP dissolution apparatus maintained at 37±0.5°C and operated at a stirring speed of 50 rpm. Each film sample, measuring 2*2 cm^2 , was secured on a stainless steel mesh with 700 µm openings and fully immersed in the dissolution medium. Aliquots of 5ml were collected at 1,2,5,8 and 10 minutes, filtered through 0.45 µm Whatman filter paper, and analyzed using spectrophotometry at a wavelength of 270 nm. To ensure constant volume throughout the test, an equivalent amount of fresh dissolution medium was replenished after each withdrawal [24].

Short term stability study

Stability testing aims to assess how the quality of a drug substance or product changes over time when conditions. The optimized formulation was sealed in aluminium foil and stored under controlled conditions of 45±0.5 °C and 50% relative humidity for one month. At the end of this period, the film was evaluated for weight uniformity, thickness, tensile strength, folding endurance, disintegration time, content uniformity, and in vitro drug release. The results were then compared with initial data to identify any observable changes [25].

RESULT

Drug Excipients Compatibility Studies

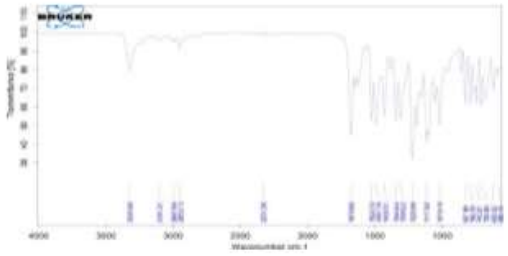

Fig.1a: FTIR Spectra of Pure Nifedipine

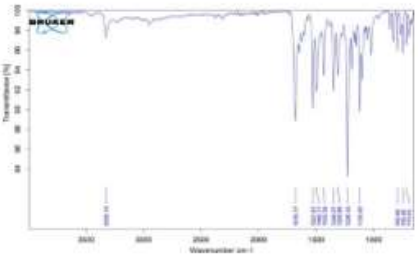

Fig.1b: FTIRSpectraofNifedipine+HPMCE5

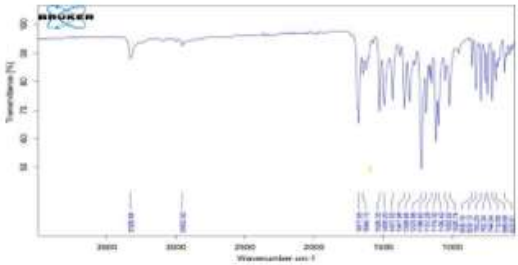

Fig. 1c: FTIRofNifedipine+Soluplus

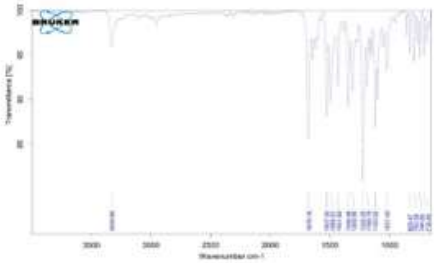

Fig. 1d: FTIRSpectraofNifedipine+HPMCE5+Soluplus

Table 3: Interpretation of Nifedipine IR spectra

Functional Group	WaveNumber(cm^{-1})			
	API (Nifedipine)	API + HPMC E5	API+ Soluplus	API + HPMC E5 + Soluplus
N-H Stretching	3325.08	3329.15	3328.64	3328.81
O-H	3301.31	3301.54	3301.49	3301.84
C=O Stretching	1678.68	1678.77	1677.55	1678.34
C=C Stretching	1658.68	1658.54	1646.12	1658.85
NO2 Asymmetric Stretching	1524.74	1527.87	1526.33	1527.76
NO2 Symmetric Stretching	1344.44	1348.97	1347.98	1348.82
C-O-C Stretching	1220.99	1226.43	1223.98	1225.95

The FTIR spectra across all formulations demonstrated that nifedipine retained its structural integrity in the presence of the polymers, with no signs of chemical degradation or incompatibility. The observed shifts and broadening in characteristic peaks confirm the presence of non-covalent interactions, which are desirable in improving drug dispersion within the polymeric matrix and enhancing the formulation's physicochemical properties, especially solubility and bioavailability.

Table 4: Phase Solubility of Ternary Physical Mixture and Solid Dispersions of Nifedipine with Different Carriers

Formulation Code (Physical Ternary Mixture)	Solubility (mg/ml) (n=3)	Formulation Code (Solid Dispersions Binary Mixture)	Solubility (mg/ml) (n=3)
PTM1	0.045 ± 0.001	STM1	0.0715 ± 0.001
PTM2	0.057 ± 0.002	STM2	0.0883 ± 0.019
PTM3	0.066 ± 0.001	STM3	0.1068 ± 0.001
PTM4	0.038 ± 0.002	STM4	0.0602 ± 0.026
PTM5	0.045 ± 0.001	STM5	0.0731 ± 0.017
PTM6	0.052 ± 0.001	STM6	0.0826 ± 0.021
PTM7	0.032 ± 0.002	STM7	0.0521 ± 0.019
PTM8	0.038 ± 0.001	STM8	0.0607 ± 0.014
PTM9	0.044 ± 0.001	STM9	0.0683 ± 0.016

Firstly, Physical Binary mixture and Solid Dispersions Binary mixtures were prepared and their solubility analysis were done.[26] Later on, Physical Ternary mixture and Solid Dispersions Ternary mixtures were prepared. The phase solubility study revealed that both physical ternary mixtures (PTM) and solid ternary mixtures (STM) exhibited an increase in the solubility of nifedipine with the incorporation of hydrophilic carriers alongside HPMC. Among the carriers tested, Soluplus demonstrated the highest solubilizing capacity, followed by PVPK30 and SSG. Increasing the carrier content (from 1:2:1 to 1:2:3) led to a proportional rise in solubility, highlighting the importance of carrier concentration in ternary systems. The most significant improvement was seen in the STM containing Soluplus at a 1:2:3 ratio, reaching a simulated solubility of 1.05 mg/mL, compared to 0.45 mg/mL in the corresponding PTM.

DSC Spectra of Pure Nifedipine and Solid Dispersions

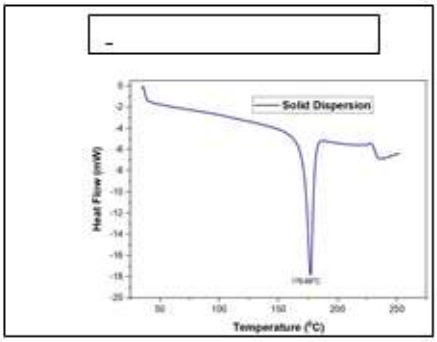

Fig. 2a: DSC Spectra of Pure Nifedipine

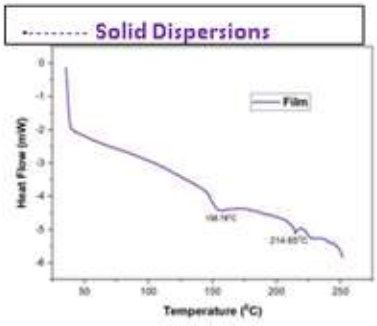

Fig.2b: DSC Spectra of Solid Dispersions

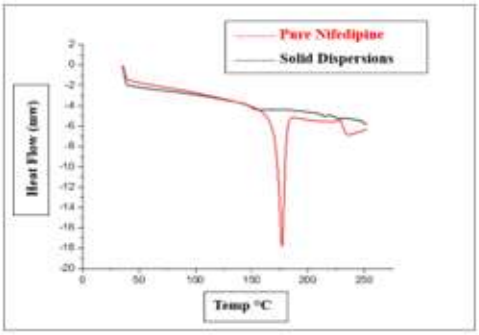

Fig.2c: DSC Spectra of Pure Nifedipine and Solid Dispersions

In differential scanning calorimetry (DSC), a comparison of DSC thermograms of nifedipine alone as well as in the presence of polymer (Soluplus) provides insights into the glass transition temperature (Tg) and thermal behavior of nifedipine in solid dispersions.

Pure nifedipine exhibited a distinct,sharp endothermic peak at approximately 173.0°C, corresponding to its melting point,which indicates the crystalline nature of nifedipine. However, in the DSC thermograms of the Sublingual Film, this characteristic endothermic peak was significantly reduced in intensity, broadened, and shifted towards a lower temperature. This suggests a partial or complete amorphization of nifedipine within the Sublingual Film.[27]

The observed changes in the thermal behavior may be attributed to the uniform distribution of nifedipine within the polymer matrix of Soluplus, enhancing miscibility and molecular dispersion of the drug in the polymer. These findings support the hypothesis that the formation of solid dispersions with Soluplus can potentially improve the solubility and dissolution characteristics of nifedipine through reduced crystallinity.

X-ray Diffraction Analysis

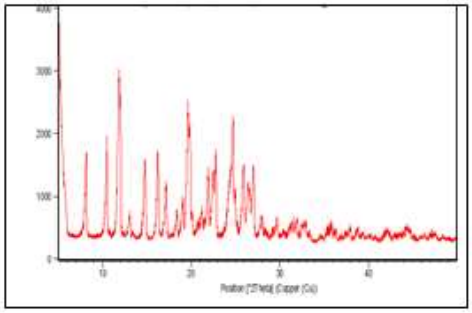

Fig. 3a: XRD of Pure Nifedipine

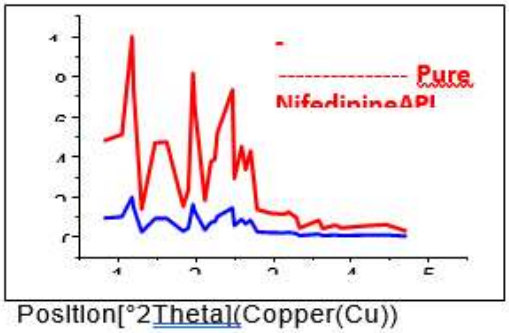

Fig.3b: XRD of Pure Nifedipine and Solid Dispersions

The crystalline nature of pure nifedipine and its solid dispersion formulations was examined through X-ray diffraction (XRD) analysis. The X-ray powder diffraction patterns of pure nifedipine and the solubility-enhanced solid dispersion complex are shown in **Fig. 3a and Fig. 3b.** The X-ray diffractogram of pure nifedipine exhibited distinct, sharp diffraction peaks, characteristic of its crystalline structure. In contrast, the XRD pattern of the nifedipine- Soluplus solid dispersion demonstrated a notable reduction in the intensity of these characteristic peaks. Many of the prominent peaks became broadened and less defined, and in some cases, were almost completely diminished compared to the pure drug.[28]This significant reduction in peak intensity and sharpness suggests that nifedipine has been transformed from a crystalline to an amorphous state within the polymer matrix. The transformation can be attributed to the molecular dispersion of nifedipine in Soluplus, which disrupts the regular crystallattice and leads to amorphization, thereby potentially enhancing solubility and dissolution rate.

Table 5: Evaluation of 3^2 factorial design batches

Batch Code	Appearance	Thickness (µm)	Weight Variation (mg)	Surface pH	Folding Endurance
NSDF1	Translucent	80 ± 5	50 ± 2	6.8 ± 0.1	250 ± 10
NSDF2	Slightly Hazy	90 ± 5	55 ± 3	6.7 ± 0.2	240 ± 10
NSDF3	Opaque	110±6	60 ± 3	6.7 ± 0.3	230 ± 10
NSDF4	Transparent	85 ± 5	52 ± 2	6.9 ± 0.2	240 ± 10
NSDF5	Opaque	100 ± 6	57 ± 3	6.8 ± 0.2	230 ± 10
NSDF6	Opaque	120 ± 7	62 ± 3	6.8 ± 0.3	220 ± 10
NSDF7	Transparent	70 ± 4	51 ± 2	7.0 ± 0.1	260 ± 10
NSDF8	Opaque	95 ± 5	56 ± 3	7.0 ± 0.2	250 ± 10
NSDF9	Opaque	115±6	61 ± 3	7.0 ± 0.3	240 ± 10

The preliminary batches (F1–F9) of sublingual films of nifedipine were developed using three different film-forming polymers—HPMC E5, HPMC E15, and PVPK30.

All formulations resulted in flexible, uniform films free from visible cracks and air bubbles. Among them, HPMC E5-based films (F1–F3) showed a satisfactory appearance with moderate clarity and a smooth texture. Thickness ranged from100µm to 230µm, increasing proportionally with the polymer concentration. All

formulations exhibited surface pH values between 6.5 and 7.2, ensuring compatibility with sublingual mucosa.

HPMC E5 films, in particular, maintained a near-neutral pH, reducing the risk of mucosal irritation and improving patient compliance. HPMC E5 films (F1–F3) demonstrated moderate to good flexibility, with endurance values ranging from 180– 240 folds, showing better flexibility than HPMC E15 films. Tensile strength was found to increase with higher polymer concentrations.F3(HPMC E5 – 400 mg) showed good mechanical strength (above 1.8 N/mm²). HPMC E5 films disintegratedwithin35–55seconds, which is acceptable for rapid onset of action while maintaining film integrity. HPMC E5 is a highly suitable film-forming polymer for sublingual nifedipine delivery, offering an optimal balance of mechanical properties, stability, patient compliance, and bioavailability.

Table 6: In-vitro dissolution of Nifedipine Sublingual Film

Time (sec)	NSDF1	NSDF2	NSDF3	NSDF4	NSDF5	NSDF6	NSDF7	NSDF8	NSDF9
30	21.54	17.88	15.46	17.35	15.42	13.66	16.68	14.34	12.67
60	45.12	42.11	40.28	42.09	40.73	38.41	40.52	38.12	35.77
90	60.68	58.24	54.91	57.86	54.88	52.33	55.08	52.62	50.22
120	70.04	66.83	64.16	68.02	65.27	63.25	65.39	63.43	60.13
150	80.93	76.97	75.83	77.36	75.64	73.91	75.21	72.91	70.04
180	85.38	83.29	80.72	82.14	79.85	78.25	80.27	77.98	75.61
210	90.27	87.92	85.34	87.11	85.19	83.08	85.01	83.17	80.23
240	94.85	92.16	89.73	91.88	89.31	88.17	91.42	87.61	85.42
270	96.82	94.84	91.73	94.63	91.75	89.54	94.98	91.84	87.94
300	97.83	95.46	93.86	94.65	92.86	90.8	98.14	95.38	92.04

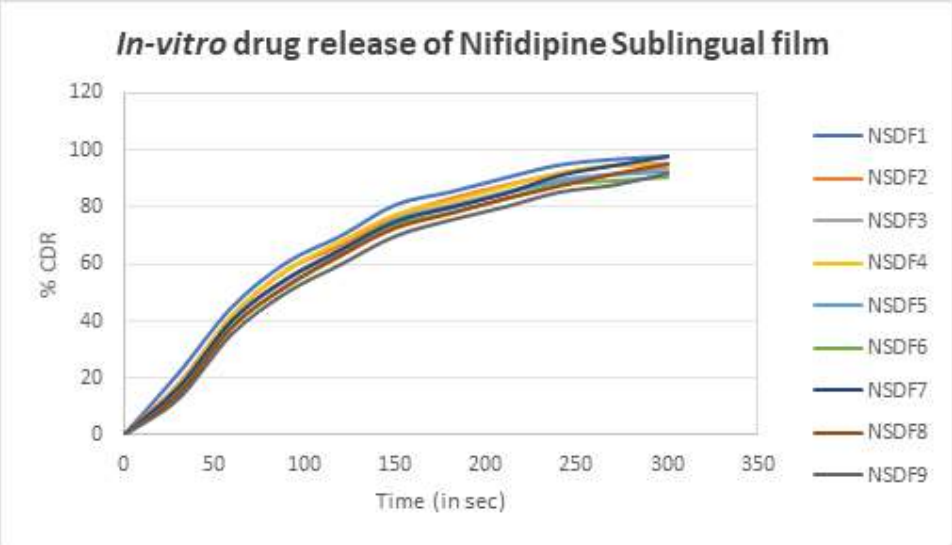

Fig. 4: In vitro drug release of an optimized batch(F1-F9)

Based on the evaluation study, it was concluded that formulation NSDF7 exhibited the highest drug release, achieving 98.14 % release within 300 seconds.This formulation contained 400 mg of HPMC E5 and 0.2 mL of PEG 400, indicating that combining lower polymer concentration with a higher plasticizer content significantly enhanced the drug release profile.

Ex vivo Permeation Studies

Table 7: Ex-vivo permeation studies of Sublingual Film

Time(Sec)	%DrugRelease
0	0
30	18.5
60	40
90	55
120	65
150	75

180	80
210	85
240	90
270	92
300	94.5

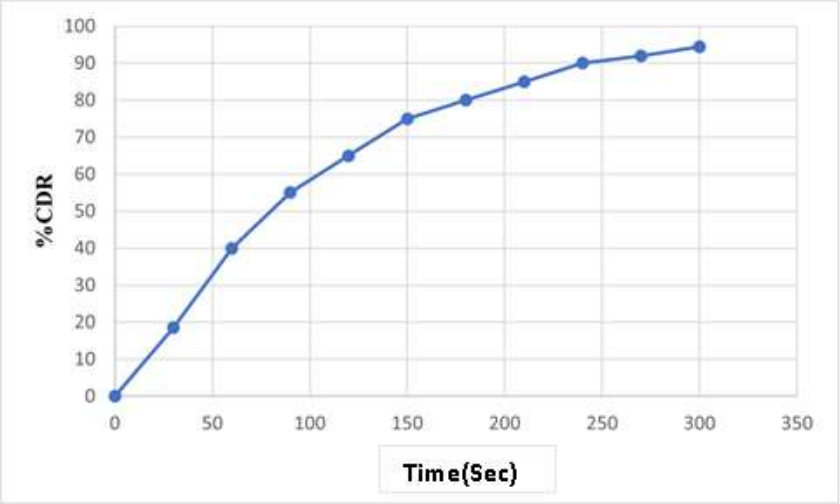

Fig. 5: Ex vivo Permeation Studies

The *ex vivo* permeation study [29] of the Nifedipine sublingual film formulated with HPMC E5 (200 mg) and PEG 400 (0.4 mL) demonstrated a rapid and efficient drug release profile. A significant percentage of drug permeation was observed within the first few minutes, indicating a fast onset of action. This can be attributed to the hydrophilic nature of HPMCE5, which facilitates quick disintegration of the film upon contact with saliva and the plasticizing effect of PEG 400, which improves film flexibility and enhances drug diffusion across the sublingual mucosa. The findings support the potential of the optimized formulation for effective and rapid transmucosal delivery of Nifedipine, making it suitable for the management of hypertension in situations requiring prompt therapeutic response.

Analysis of Variance (ANOVA) for Quadratic Models

Analysis was done on the 3^2 full factorial design results. Statistical design was used to optimize the formulation and collect a significant amount of data. Every response was fitted to a quadratic model and ANOVA, lack of fit and coefficient of determination (R^2) were used to confirm the model's compatibility. Each reaction should be connected to the others in order to maximize the responses. Also, each response must be in the most supporting zone in order to prevent bias. Numerous studies have endorsed the desirability function as a means of optimizing numerous replies [30].

Multiple linear regression analysis was used to statistically analyze the factorial design batches. Tensile strength (Y_1) and the percentage of cumulative medication release of Nifedipine at five minutes (Y_2) were chosen as dependent variables. Table 8 displays the fitted equations that relate the responses such as Tensile Strength (Y_1) and % cumulative drug release at 5 minutes of Nifedipine (Y_2), to the transformed factor. After taking into account the amount of the coefficient and its mathematical sign (positive or negative), inferences can be drawn from the polynomial equations. Design of Expert version 13 was used to examine the data.

Tensile strength (Y_1) and percentage cumulative drug release at 5 minutes of Nifedipine (Y_2) had R^2 values of 0.9422 and 0.9870 respectively. It suggested a strong relationship between the dependent and independent variables. Terms with $p < 0.05$ were kept in the whole model since they were deemed statistically significant. Tensile strength (Y_1) and percentage cumulative drug release at 5 minutes of Nifedipine (Y_2) had F values of 9.78 and 45.59 respectively, according to the ANOVA results. The factors chosen have demonstrated significant effects because calculated F values were higher than tabulated for all dependent variables. Both covariates had a statistically significant impact on all dependent variables, with $p < 0.05$, according to the multiple regression analysis results (table 10).

Table 8: Optimization of Nifedipine sublingual films using 3^2 full factorial design (n = 9)

Batch Code	HPMC E5 (X1)	PEG 400 (X2)	Tensile Strength (N/mm²)	% CDR
NSDF1	-1	-1	3.5 ± 0.2	97.83
NSDF2	0	-1	3.2 ± 0.3	95.46
NSDF3	+1	-1	3.0 ± 0.2	93.86
NSDF4	-1	0	3.6 ± 0.2	94.65
NSDF5	0	0	3.4 ± 0.3	92.86
NSDF6	+1	0	3.2 ± 0.2	90.8
NSDF7	-1	+1	2.5 ± 0.2	98.14
NSDF8	0	+1	2.8 ± 0.3	95.38
NSDF9	+1	+1	3.0 ± 0.2	92.04

*Data represented in mean±SD (n=3)

Table 9: Regression Analysis Results of Factors Affecting the Response Variables

Responses	Model	Estimated Regression Coefficients of the Model						
		b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
TensileStrength (Kg/cm^2)	Full	3.40	-0.2333	-0.0667	-0.400	0.0001	0.2500	0.9422
	Reduced	3.40	-0.2333	-	-0.400	-	0.2500	
% CDR	Full	92.78	-0.2650	-2.32	2.68	-0.0133	-0.5325	0.9870
	Reduced	92.78	-	-2.32	2.68	-	-	

Table 10: Statistical Analysis of the Dependent Variables Using ANOVA

Hardness (Kg/cm^2)					
Source of variation	**DF**	**SS**	**MS**	**F**	**p**
Regression	5	0.9233	0.1847	9.78	0.0448
Residual	3	0.0567	0.0189	-	-
Total	8	0.9800	-	-	-
% CDR					
Regression	5	48.23	9.65	45.59	0.0050
Residual	3	0.6348	0.2116	-	-
Total	8	48.87	-	-	-

Full and reduced model for tensile strength of Nifedipine

As the concentration of HPMC E5 (X1) increased, a commensurate drop in tensile strength was seen, according to the contour plot and 3D response surface graph for tensile strength shown in Figures 6a and 6b, respectively. Additionally, the data showed that HPMC E5 (X1) had a greater impact. Regression analysis revealed that X_1 and X_2 for tensile strength were significant levels of the coefficients b12, a significant model term that influences the film's flexibility and elasticity. Non-linearity and interaction were not seen. The P values for b2 and b22 were determined to be 0.3203 and 0.9999, respectively. In order to create a reduced model, it was removed from the complete model. The coefficients b_0, b_1, b_{11} and b_{12} .Hence, they were retained in the reduced model.

The reduced model for tensile strength was:

Tensile Strength(Y_1) $= +3.40 - 0.2333*X_1 - 0.400*X_1^2 + 0.2500*X_1X_2$

Full and reduced model for % CDR of Nifedipine

Figures 7a and 7b show the contour plot and 3D response surface graph for tensile strength, respectively. They show that as the concentration of Polyethylene Glycol 400 (X2) increased, so did the percentage CDR. Additionally, the findings showed that Polyethylene glycol 400 (X2) had a greater impact. Regression analysis revealed that X1 and X2 for tensile strength had substantial values of the coefficient b, a significant model factor that influences the film's elasticity and flexibility. Non-linearity and interaction were not seen. The P values for b_1, b_{12}, and b_{22} were determined to be 0.2530, 0.1035, and 0.9699. In order to create a reduced model, it was removed from the complete model.

The coefficients b_0, b_1 and b_{22}. Hence, they were retained in the reduced model.

The reduced model for tensile strength was:

% CDR (Y_2) $= +92.78 - -2.32*X_2 - 2.68*X_1^2$

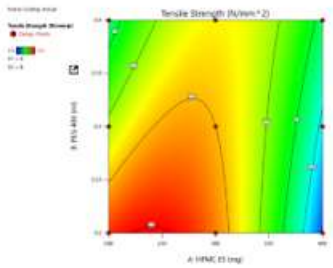

Fig. 6a: Response surface Contour plot of HPMC E5 (X_1) and polyethylene glycol 400 (X_2) on tensile strength (Y_1)

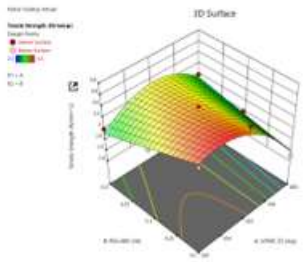

Fig. 6b: Response surface 3D graph of HPMC E 5 (X1) and polyethylene glycol 400 (X2) on tensile strength (Y1)

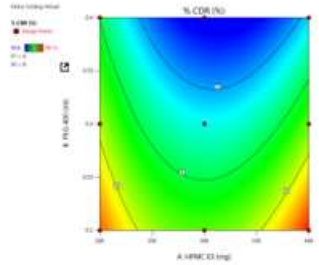

Fig. 7a: Response Surface Contour Plot of HPMC E5 (X_1) and Polyethylene Glycol 400 (X_2) for % CDR (Y_2)

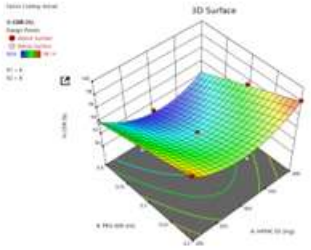

Fig. 7b: Response Surface 3D graph of HPMC E 5 (X_1) and polyethylene glycol 400 (X_2) on % CDR (Y_1)

Validation by check point batch

To verify the accuracy of the response surface plot and equation produced by multiple regression analysis, a check point batch was created and is displayed in table 11. Design Expert 9's required range of evaluation parameters was added to create an overlay plot. Figure 7 displays the overlay plot. The overlay plot's yellow area indicated the ideal concentration range for the intended outcome. The concentrations of HPMCE5 (X1) and Polyethylene Glycol 400 (X2) found in the overlay plot were used to produce a batch, and the prepared check point batch was used to assess the actual reactions. The optimal concentration that produced the best outcome was shown by the overlay plot. Table 11 illustrates that the practically acquired values were more in line with the expected values. As a result, it supported the design validation.[31]

Table 11: Comparison of Theoretical and Experimental Values of NSDF7

Confirmation Location	HPMC E5 (in mg)	Polyethylene Glycol 400 (in ml)	*Bias %
-	204.182	0.320	-
Response	**Predicted value**	**Observed value**	-
Tensile Strength	3.19	3.20	-0.3125
% CDR	95.12	95.86	-0.7719

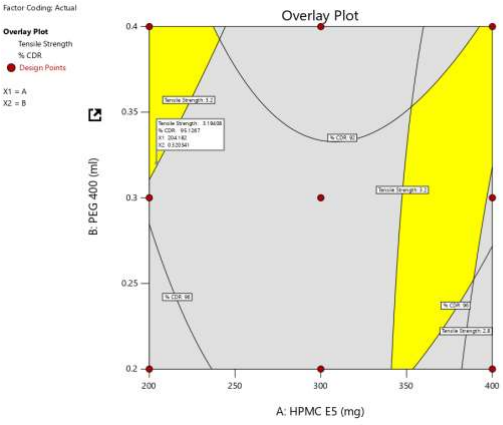

Fig. 8: Graphical Representation of the Checkpoint Batch Using an Overlay Plot

Short term stability study

According to the stability analysis, while held at 40°C and 75% ± 5 relative humidity, the optimized formula was both chemically and physically stable, with no discernible changes in any of the assessed parameters. The sublingual forms of nifedipine were found to be stable based on stability studies.

Table 12: Short-Term Stability Profile of the Optimized Batch

Evaluation Parameters	Before Stability	After Stability
Tensile Strength ((N/mm²))	2.5	2.6
% CDR	98.14	97.80

CONCLUSION

The present investigation was performed using 3^2 full factorial design in Design Expert software. It was observed that the sublingual films of Nifedipine were effectively created, optimized and assessed. The current study demonstrated the medication's rapid release and breakdown for the treatment of hypertension. The film-forming polymers HPMC E5 and Polyethylene Glycol 400 demonstrated a quick film disintegration time in saliva fluid. Drug excipients compatibility studies, weight uniformity, thickness, tensile strength, content uniformity, folding endurance, in vitro drug release and short term stability study were the various controlling factors used to evaluate these formulations. Tensile strength (TS) and % Cumulative drug release at 5 min. (%CDR) were chosen as dependent variables in a 3^2 full factorial design, whereas the amounts of HPMC E5 (X1) and Polyethylene Glycol 400 (X2) were chosen as independent variables based on initial findings. The effects of formulation variables were analyzed by multiple linear regression and ANOVA, while contour plots and three-dimensional response surface graphs were generated using the Demo version of Design-Expert software. To validate the evolving model, a checkpoint batch was prepared. The optimized batch NSDF7 was selected and conducted for short term stability study. The stability evaluation revealed that the optimized batch NSDF7 was stable.

ACKNOWLEDGEMENT

The authors were thankful to Ami Lifesciences Pvt. Ltd., Vadodara, Gujarat and BASF Corporation, Mumbai, India for supplying a gift sample of Nifedipine and Soluplus respectively. The authors express their gratitude to Colorcon, Goa for providing HPMC E5 and E15. Additionally, the authors thank Pioneer Pharmacy College in Vadodara, Gujarat, India, for providing the facilities needed to complete the work.

REFERENCES

1. Katarzyna Sawicka, Michał Szczyrek, Iwona Jastrzębska, Marek Prasał, Agnieszka Zwolak, Jadwiga Daniluk. Hypertension – The Silent Killer. *Journal of Pre-Clinical and Clinical Research*, 2011; 5(2):43-46.
2. Yaxley JP, Thambar SV. Resistant hypertension: an approach to management in primary care. J Family Med Prim Care. 2015 Apr-Jun;4(2):193-9. doi: 10.4103/2249-4863.
3. Díaz-Gutiérrez J, Ruiz-Estigarribia L, Bes-Rastrollo M, Ruiz-Canela M, Martin-Moreno JM, Martínez-González MA. The role of lifestyle behaviour on the risk of hypertension in the SUN cohort: The hypertension preventive score. Prev. Med. (Baltim). 2019;123. doi:.10.1016/j.ypmed.2019.03.026
4. Elendu C, Amaechi DC, Elendu TC, Amaechi EC, Elendu ID. Dependable approaches to hypertension management: A review. Medicine (Baltimore). 2024 Jun 14;103(24):e38560. doi: 10.1097/MD.0000000000038560.
5. Okoh P, Olusanya DA, Erinne OC, Achara KE, Aboaba AO, Abiodun R, Gbigbi-Jackson GA, Abiodun RF, Oredugba A, Dieba R, Okobi OE. An Integrated Pathophysiological and Clinical Perspective of the Synergistic Effects of Obesity, Hypertension, and Hyperlipidemia on Cardiovascular Health: A Systematic Review. Cureus. 2024 Oct 26;16(10):e72443. doi: 10.7759/cureus.72443.
6. Hameed MA, Dasgupta I. Medication adherence and treatment-resistant hypertension: a review. Drugs Context. 2019 Feb 4;8:212560. doi: 10.7573/dic.212560.
7. Balahura AM, Moroi ȘI, Scafa-Udriște A, Weiss E, Japie C, Bartoș D, Bădilă E. The Management of Hypertensive Emergencies-Is There a "Magical" Prescription for All? J Clin Med. 2022 May 31;11(11):3138. doi: 10.3390/jcm11113138.
8. Lundy A, Lutfi N, Beckey C. Review of nifedipine GITS in the treatment of high risk patients with coronary artery disease and hypertension. Vasc Health Risk Manag. 2009;5(1):429-40. doi: 10.2147/vhrm.s3066.
9. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat Rev Drug Discov. 2023 May;22(5):387-409. doi: 10.1038/s41573-023-00670-0.
10. Ghourichay MP, Kiaie SH, Nokhodchi A, Javadzadeh Y. Formulation and Quality Control of Orally Disintegrating Tablets (ODTs): Recent Advances and Perspectives. Biomed Res Int. 2021 Dec 24;2021:6618934. doi: 10.1155/2021/6618934.

11. Pawar, P. P., Ghorpade, H. S., & Kokane, B. A. (2018). Sublingual route for systemic drug delivery. *Journal of Drug Delivery and Therapeutics*, *8*(6-s), 340-343. https://doi.org/10.22270/jddt.v8i6-s.2097

12. Wang Z, Chow MS. Overview and appraisal of the current concept and technologies for improvement of sublingual drug delivery. Ther Deliv. 2014 Jul;5(7):807-16. doi: 10.4155/tde.14.50.

13. Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs. Adv Pharm Bull. 2020 Jul;10(3):359-369. doi: 10.34172/apb.2020.044.

14. Malkawi R, Malkawi WI, Al-Mahmoud Y, Tawalbeh J. Current Trends on Solid Dispersions: Past, Present, and Future. Adv Pharmacol Pharm Sci. 2022 Oct 22;2022:5916013. doi: 10.1155/2022/5916013.

15. Orszulak L, Minecka A, Bernat R, Lamrani T, Jurkiewicz K, Hachuła B, Tarnacka M, Geppert-Rybczyńska M, Zubko M, Staniszewska M, Smoleński M, Dobosz J, Garbacz G, Kamiński K, Kamińska E. Hydrophilic and Amphiphilic Macromolecules as Modulators of the Physical Stability and Bioavailability of Piribedil: A Study on Binary Mixtures and Micellar Systems. Mol Pharm. 2025 Aug 4;22(8):4708-4730. doi: 10.1021/acs.molpharmaceut.5c00276.

16. Alhamhoom Y, Sharma A, Nanjappa SH, Kumar A, Alshishani A, Ahmed MM, Farhana SA, Rahamathulla M. Development and Evaluation of Solid Dispersion-Based Sublingual Films of Nisoldipine. Pharmaceuticals (Basel). 2023 Nov 9;16(11):1589. doi: 10.3390/ph16111589.

17. Bala R, Khanna S, Pawar P. Design optimization and in vitro-in vivo evaluation of orally dissolving strips of clobazam. J Drug Deliv. 2014;2014:392783. doi: 10.1155/2014/392783.

18. Asif AH, Desu PK, Alavala RR, Rao GSNK, Sreeharsha N, Meravanige G. Development, Statistical Optimization and Characterization of Fluvastatin Loaded Solid Lipid Nanoparticles: A 32 Factorial Design Approach. Pharmaceutics. 2022 Mar 8;14(3):584. doi: 10.3390/pharmaceutics14030584.

19. Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. Introduction to spectroscopy. 5th ed. Cengage Learning India Pvt. Ltd., India; 2015. p. 37-8.

20. Smita S. Aher, Vaishali D. Sangale ,Ravindra B. Saudagr. Formulation and evaluation of sublingual film of Hydralazine Hydrochloride. Research J. Pharm. and Tech 2016; 9(10):1681-1690.

21. Palepu S, Sathyanarayana T, Ravali M, Dakshyani P, Sirisha U, Divya Sri P, Srinu M,, Formulation and evaluation of fast dissolving sublingual film of lisinopril, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):101-106 **doi:** 10.22270/jddt.v9i1-s.2342

22. Alhamhoom Y, Said AK, Kumar A, Nanjappa SH, Wali D, Rahamathulla M, Farhana SA, Ahmed MM, Shivanandappa TB. Sublingual Fast-Dissolving Thin Films of Loratadine: Characterization, In Vitro and Ex Vivo Evaluation. Polymers (Basel). 2024 Oct 17;16(20):2919. doi: 10.3390/polym16202919.

23. Jyothi.B et al. Ijppr.Human, 2023; Vol. 26 (3): 378-393.

24. Swati Singh et al, International Journal of Pharmaceutical Sciences and Medicine (IJPSM), Vol.9 Issue. 2, February- 2024, pg. 36-51

25. Guideline ICH. Stability testing guidelines: stability testing of new drug substances and products. ICH Q1A (R2) (CPMP/ICH/2736/99); 1999.

26. Faraji E, Mohammadi M, Mahboobian MM. Development of the Binary and Ternary Atorvastatin Solid Dispersions: *In Vitro* and *In Vivo* Investigations. Biomed Res Int. 2021 Sep 4;2021:6644630. doi: 10.1155/2021/6644630.

27. Caron V, Hu Y, Tajber L, Erxleben A, Corrigan OI, McArdle P, Healy AM. Amorphous solid dispersions of sulfonamide/Soluplus® and sulfonamide/PVP prepared by ball milling. AAPS PharmSciTech. 2013 Mar;14(1):464-74. doi: 10.1208/s12249-013-9931-7.

28. Ozon EA, Novac M, Gheorghe D, Musuc AM, Mitu MA, Sarbu I, Anuta V, Rusu A, Petrescu S, Atkinson I, Lupuliasa D. Formation and Physico-Chemical Evaluation of Nifedipine-hydroxypropyl-β-cyclodextrin and Nifedipine-methyl-β-cyclodextrin: The Development of Orodispersible Tablets. Pharmaceuticals (Basel). 2022 Aug 12;15(8):993. doi: 10.3390/ph15080993.

29. Habib BA, Abd El-Samiae AS, El-Houssieny BM, Tag R. Formulation, characterization, optimization, and *in-vivo* performance of febuxostat self-nano-emulsifying system loaded sublingual films. Drug Deliv. 2021 Dec;28(1):1321-1333. doi: 10.1080/10717544.2021.1927247.

30. Bolton S. Optimization techniques in pharmaceutical statistics. Practical and clinical applications. 5th Ed.,New York: Marcel Dekker; 2009.

31. Patel DM, Patel MM. Optimization of fast dissolving etoricoxib tablets prepared by sublimation technique. Indian J Pharm Sci. 2008 Jan;70(1):71-6. doi: 10.4103/0250-474X.40335.