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Research Article

Formulation, Evaluation and Comparative Study of Effects of Super Disintegrants in Sublingual Fast Dissolving Niosomal Films of Nifedipine

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ABSTRACT

The aim of the present work was to prepare and evaluate sublingual fast dissolving niosomal films containing Nifedipine with the purpose to achieve quick onset of action. Niosomes are utilized for prolonged release of the drug, and its film increases bioavailability via the sublingual route. Niosomes were prepared using span 60 and cholesterol at different drug to surfactant ratios. The niosomes were characterized for particle size and zeta-potential. The selected niosomal formulation was incorporated into polymeric films using hydroxypropyl methyl cellulose E15 and methyl cellulose as film-forming polymers and crosspovidone, croscarmelose sodium and sodium starch glycollite as superdisintegrants to produce six formulations. The physical characteristics of the prepared films were studied, in addition to evaluating the in vitro drug release and stability. The formulation F6 containing the methyl cellulose and sodium starch glycolate as good film forming polymer and superdisintegrant respectively was found to be the best formulation showing good film forming capacity, tensile strength and % cumulative drug release of 93.91±0.648% after 9 minutes. The kinetic data analysis showed that it follows zero order models by non fickian release mechanism. These results indicate that the fast dissolving niosomal film could be a promising delivery system to enhance the bioavailability and prolong the therapeutic effect of Nifedipine.

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INTRODUCTION

The oral route is considered as the ideal route for the administration of therapeutic agents. It is more acceptable from patient compliance [1]. The significant constraints with oral administration such as hepatic first pass effect and drug degradation due to enzymes. The pediatric and geriatric patients find it difficult to take solid preparations due to fear of choking [2,3,4]. Sublingual route can be considered as a novel route of administration because of immediate onset of pharmacological action. By these route drugs gets absorbed and reaches directly into the blood stream through the ventral surface of the tongue and the floor of the mouth. The sublingual area of oral cavity is more permeable than buccal area. Sublingual drug delivery can bypass the first pass metabolism and avoids drug elimination without absorption. Such factors make sublingual cavity a feasible site for achieving the systemic therapeutic effects of drug [5,6].

Fast dissolving films have recently attracted increasing interest in the pharmaceutical industry due to the improved patient compliance, accurate dosing, and rapid onset of action, pleasant taste, as well as their convenient handling and administration. These films consist of thin oral strips formulated using hydrophilic polymers that rapidly disintegrate and dissolve when placed in the oral cavity to release the medication, which becomes available for oromucosal absorption, without chewing and intake of water. However, drugs that require high doses cannot be incorporated into film strip due to its limited surface area [7,8].

Nifedipine is a calcium-channel blocker, which is used to treat hypertension and also to control angina (chest pain). It lowers blood pressure by relaxing the blood vessels so the heart does not have to pump as hard. It controls chest pain by increasing the supply of blood and oxygen to the heart. Nifedipine is a class II compound, which has poor water solubility and dissolution rate and limited absorption through the sublingual mucosa. After oral administration, Nifedipine almost completely absorbed (95%) with peak plasma concentrations achieved after 2–3 hours. It undergoes extensive first-pass metabolism by the liver that results in low and variable oral bioavailability (40%–50%). The plasma half-life is approximately 3–4 hours, which needs frequent dosing to maintain the therapeutic blood levels of the drug for a long-term treatment [6,7]. Several attempts have been attained to enhance its bioavailability by avoidance of first-pass hepatic metabolism such as intravenous, transdermal, intranasal, rectal, and bucco adhesive drug delivery systems. Other strategies with sustained drug release pattern have been developed to avoid the frequent dosing of nifedipine, including the use of floating tablets, mucoadhesive floating beads, microspheres, niosomes and proniosomes [9,10,11].

Drug delivery systems using colloidal particulate carriers have significant advantages over conventional dosage forms as the particles can act as reservoir for the loaded drug [12]. Niosomes are closed bilayer vesicles formed by self-assembly of nonionic surfactants in aqueous media. These structures are analogous to liposomes but have the ability to increase the stability of their entrapped drugs. Due to the flexibility of their structural characteristics (composition, fluidity, and size) and ease of storage and handling, these lipid vesicles can be tailored for delivery of a wide variety of drugs for drug targeting, controlled release and per-meation enhancement [13,14].

In the present study, an attempt has been made to prepare and evaluate sublingual fast dissolving film containing Nifedipine-loaded niosomes. The sublingual route of administration is expected to enhance the drug bioavailability by avoidance of first-pass hepatic metabolism. In addition, rapid absorp-tion of the drug-loaded niosomes may maintain therapeutic concentrations of the Nifedipine for prolonged time period and, thus, avoiding the frequent dosing of the drug [15,16].

MATERIALS AND METHODS

Materials:

Table 1: List of chemicals and reagents

Chemicals	Suppliers
Nifedipine	Yarrow chem products, Mumbai
HPMC E 15	Yarrow chem products, Mumbai
Methyl cellulose	Yarrow chem products, Mumbai
Poly ethylene glycol 400	Yarrow chem products, Mumbai
Micro crystalline cellulose	Yarrow chem products, Mumbai
Croscarmallose sodium	Yarrow chem products, Mumbai
Crospovidone	Yarrow chem products, Mumbai
Sodium starch glycollate	Yarrow chem products, Mumbai

Methods:

Formulation of Nifedipine-loaded niosomes

Niosomes were prepared by the conventional thin film hydration method using span 60 as a nonionic surfactant and cholesterol as an enhancer of niosomal membrane rigidity [17,18]. The drug to surfactant ratios were utilized as 1:2. The drug and cholesterol ratio was similar in all formulations. Drug, nonionic surfactant, and cholesterol were weighed and dissolved in chloroform in a round bottom flask. The solvent was evaporated at a temperature of 60°C under reduced pressure using a rotary evaporator to form a thin film on the flask wall. The resulting film was hydrated with deionized water for 30 minutes at room temperature with gentle shaking [19,20]. This film was hydrated with 10 mL of deionized water at 60°C. The resulting niosomal suspension was mixed by vortex mixing for 10 minutes and sonicated for 20 minutes at 25°C. The niosomal suspension was left overnight at 4°C and stored at refrigerator temperature (4°C–8°C) for further studies [21,22,34].

Preparation of fast dissolving niosomal films

The fast dissolving films were prepared by solvent casting technique. HPMC and MC were used as film-forming polymers. Polyethylene Glycol 400 was used as a plasticizer. Saccharine is used as a sweetener, and menthol as flavoring agent as well as to give mouth refreshment feeling. Concentrations of plasticizer, sweetener, and flavoring agents were kept constant [23,24]. Microcrystalline cellulose (Avicel), croscarmellose sodium, crospovidone and sodium starch glycolate were used as super Disintegrants. Specified weight of film-forming polymer was first dissolved in 20 mL of the warm distilled water, and sweetener and flavoring agent were dissolved in the polymeric solution. The calculated amount of super Disintegrants was incorporated into the polymeric solutions after levigation with the required volume of the plasticizer [4,25,26]. For the preparation of medicated films (containing free drug), the required amount of Nifedipine was directly added and completely dissolved into the polymeric solution before the addition of super Disintegrants [27,28]. For niosomal film, a specified volume of the niosomal dispersion (corresponding to the required nifedipine dose) was incorporated and gently mixed with the selected polymeric solution. The final volume was adjusted to 25

mL with distilled water, and the beaker was covered with aluminum foil to prevent solvent evaporation. The casting solution was subjected to gentle stirring for 2 hours using magnetic [29,30,34].

The casting solution (25 mL) was transferred into a previously cleaned and dried Teflon-coated plate. The solvent was allowed to evaporate for 72 hours, and the film was then removed from the Teflon plate and was allowed to dry in a desiccator at least 48 hours before evaluation. The patches were punched into 4 cm2 pieces containing 25 mg of Nifedipine, then wrapped in an aluminum foil (to maintain the integrity and elasticity of the films) and were finally stored in a dry place at ambient room temperature [4,31,32]. The films were subjected to evaluation within 1 week of their preparation. Composition of various formulations is provided in Table 2.

Table 2: Formulation ingredients

Component (mg)	F1	F2	F3	F4	F5	F6
HPMC E15	200	200	200	-	-	-
MC	-	-	-	200	200	200
PEG 400	150	150	150	150	150	150
Saccharine	50	50	50	50	50	50
Menthol	17	17	17	17	17	17
MCC	14	14	14	14	14	14
CCS	7			7		
CP		7			7	
SSG			7			7

Abbreviations: HPMC, hydroxyl propyl methyl cellulose; MC, methyl cellulose; MCC, microcrystalline cellulose; CCS, croscarmellose sodium; CP, crospovidone; SSG, sodium starch glycolate; PEG, polyethylene glycol.

EVALUATION

Organoleptic evaluation

Organoleptic properties of drug like Colour, appearance and Odour were observed and recorded melting point and solubility was determined.

Determination of UV Absorbance Maxima of Nifedipine

An accurately weighed quantity of 100mg Nifedipine was transferred to 100ml volumetric flask and diluted using phosphate buffer of pH 6.8 and made up to the volume. From this 10ml was transferred to 100ml volumetric flask and diluted up to the mark [33]. From the above stock solution, 0.5ml was taken and diluted to 10ml with PH 6.8 phosphate buffer, Nifedipine was scanned in the range of 200-400nm to determine the wavelength of maximum absorbance for the drug Nifedipine [34].

Preparation of Standard Calibration Curve of Nifedipine

Accurately weighed 100mg of pure Nifedipine. It was transferred to 100ml volumetric flask. Then it was dissolved in phosphate buffer of PH 6.8 and made up to the volume to 100ml. From this 10ml was transferred to 100ml volumetric flask and diluted to the mark. The resulted solution had the concentration of 100µg/ml which was labeled as “stock solution” [35]. From the above stock solution, 0.5ml was taken and diluted to 10ml with pH 6.8 phosphate buffer, which having the concentration 5µg/ml. Series of dilution were prepared with the concentration of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50µg/ml measured at 238 nm. Then, the calibration curve was plotted [36].

FTIR spectra analysis

A FT-IR spectrum of Nifedipine was recorded by Potassium bromide (KBr) palletization method. Drug was mixed with KBr and was

compressed into small thin disk, which was subsequently analyzed by FT-IR spectrophotometer [37]. Obtained spectra were analyzed for characteristic peaks corresponding to specific functional groups present in the drug molecule. These peaks were considered as a reference for further drug-excipient compatibility studies [38].

Characterization of prepared niosomes

Particle size and zeta potential

The mean particle size (nm) and polydispersity index of the prepared niosomes in both niosomal dispersion and niosomal film were measured by dynamic light scattering laser using a Zetasizer Nano ZS equipped with a 4 W helium/neon laser (λ=633 nm) and thermoelectric temperature controller. The corresponding zeta potentials (mV) were determined by photon correlation spectroscopy using the same Zetasizer Nano instrument [2,3, 4,39].

EVALUATION OF FAST DISSOLVING FILMS

Physical evaluation

- **Film forming capacity**

  It is the ability of film formers to form desired films. It is categorized according to film forming capacity such as very poor, poor, average, good, very good and excellent.

- **Appearance of films**

  It is evaluated by visual observation such as transparent or opaque.

- **Weight variation**

  The film of dimension 2×2 cm^2 was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

- **Thickness**

  The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different position of the film. The thickness was measured at five different positions of the film and average was taken and standard deviation was calculated [34].

Mechanical evaluation

- **Folding endurance**

  To determine folding endurance, a film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

- **Tensile strength**

  The Tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of the sample}}$$

- **Percent elongation**

  The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation was obtained by following equation.

$$\% \text{ Elongation} = \frac{\text{Increase in length at breaking point (mm)}}{\text{original length (mm)}} \times 100$$

- **Surface pH**

  The surface pH of fast dissolving film was determined in order to investigate the possibility of any in vivo side effect. As an acidic or alkaline pH may cause irritation of the mucosa, so the surface pH of the films was determined to check whether its neutralising or not. A pH electrode was used for this purpose. The film was allowed to swell in closed petri dish for 30 min. The pH was measured by bringing the electrode in contact with the surface of the sublingual film. The procedure was performed in

triplicate and average with standard deviation was reported.

- **In-vitro Disintegration**

The disintegration time is the time when the film starts to break or disintegrates. In *vitro* disintegration time was determined in a petri dish containing 25ml of pH 6.8 phosphate buffer at 37±0.50C with swirling every 10 sec.

- **Drug Content**

Drug content determination of the film was carried out by dissolving the film of 4 cm2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically. The determination was carried out in triplicate and average with standard deviation was recorded.

- **Scanning electron microscopy (SEM)**

The morphological characteristics of the Sublingual films were studied by scanning electron microscopy. The film sample was placed in the sample holder and the SEM micrographs were taken at 10,000x and 3000 magnification using tungsten filament as an electron source. Films were fixed onto a metallic stub with double sided conductive tape (diameter 12 mm).

- **Dissolution test**

I*n vitro* dissolution test was carried out according to the USP type II dissolution apparatus. 900ml of pH 6.8 phosphate buffer was taken as dissolution media, the temperature was maintained at 37±0.5°C with a rotation speed of 50rpm. Five ml of sample was taken at regular intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer and take the absorbance at 238 nm with the help of double beam UV-Visible spectrophotometer.

- **Drug Release Kinetic Studies**

The drug release kinetic studies were done by various mathematical models like zero order, first order, Higuchi's square root, Hixson-Crowell cube root law and Peppas equation. The model that best fits the release data is selected based on the correlation coefficient (r^2) value in various models. The model that gives high 'r^2' value is considered as the best fit of the release data.

- **Stability study**

For the prepared fast dissolving films, stability study was carried out at two different storage conditions, one was normal room conditions and the other was 40°C/75% relative humidity for 8 weeks. Each piece of the conventional medicated film formulation (F6) and the niosomal film (NF6) were packed in butter paper followed by aluminum foil and plastic tape. After 8 weeks, the films were evaluated for the physical appearance, surface pH, and in vitro drug release. Regarding the prepared niosomal dispersion, stability study was carried out at 4°C, room temperature, and elevated temperature for a period of 8 weeks. The samples of selected niosomal dispersion were sealed in a glass vial and stored at the selected temperature for 4 weeks. Samples from each batch were withdrawn at definite time intervals and evaluated for physical appearance, vesicle size, and zeta potential, as compared to the reconstituted niosomal dispersion after the niosomal film dissolution in phosphate buffer (pH 6.8)[4,34].

RESULT AND DISCUSSION

Identification of drug

Organoleptic evaluation

The organoleptic characters of the drug were evaluated and the results obtained are shown in the Table 3.

Table 3: Organoleptic character of nifedipine

Colour	Yellow powder
Odour	No characteristic Odour
Taste	Bitter taste
Melting point	175° C

Analytical method for the determination of Nifedipine

- Determination of λ max of Nifedipine = 238 nm.
- Preparation of calibration curve of Nifedipine
- 100 mcg/ml solution of Nifedipine was prepared and graph was plotted.

Table 4: Standard data of Nifedipine

S. No	Concentration (µg/ml)	Absorbance (238nm) *±SD
1	0	0
2	10	0.260 ± 0.0025
3	20	0.489 ± 0.0027
4	30	0.709 ± 0.0021
5	40	0.955 ± 0.0033
6	50	1.187± 0.0040

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Figure 1: Calibration curve of Nifedipine

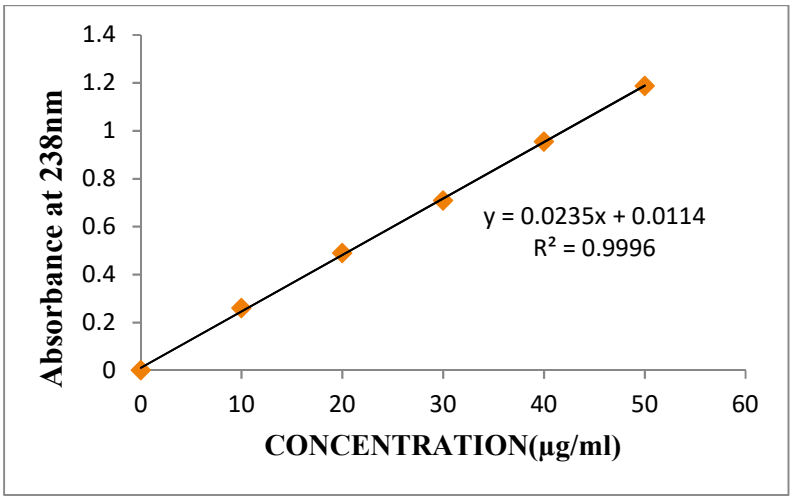


Figure 2: FTIR of NIfedipine

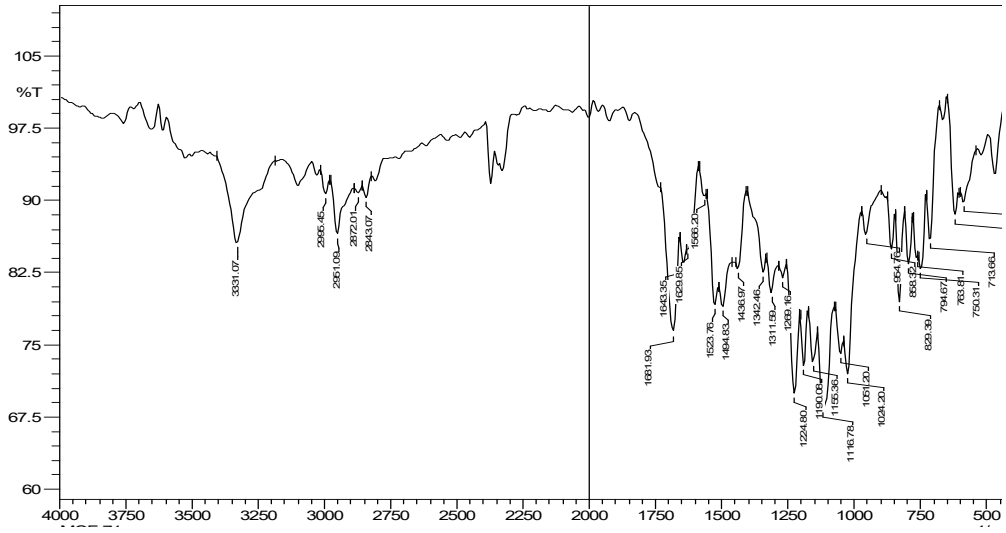
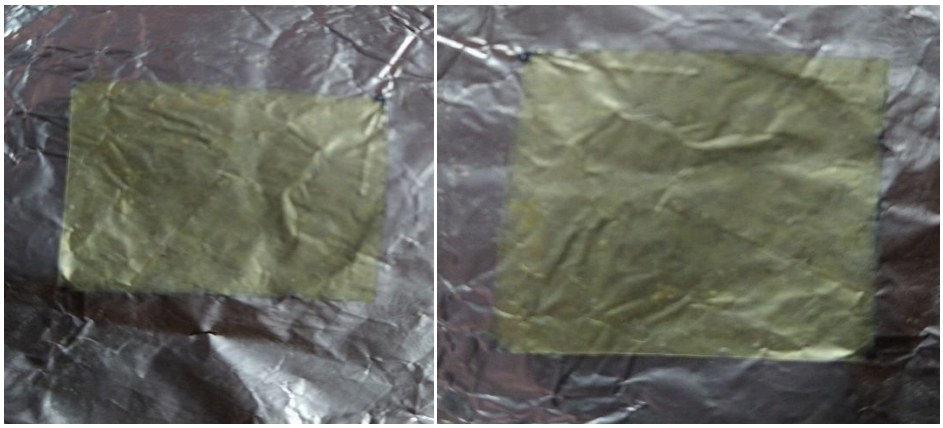


Table 5: Functional groups and their observed peak values of Nifedipine reference and standard

S.No	Functional groups	Characteristic peak range in cm^{-1}	Characteristic peak range in cm^{-1}
1	N-H Streching	3500-3300	3331.07
2	C-H Streching	2850-3000	2951.09
3	-C=C- Streching	2050-2260	2139.21
4	C=O Streching	1670-1820	1681.93

Figure 3: Nifedipine niosomal films

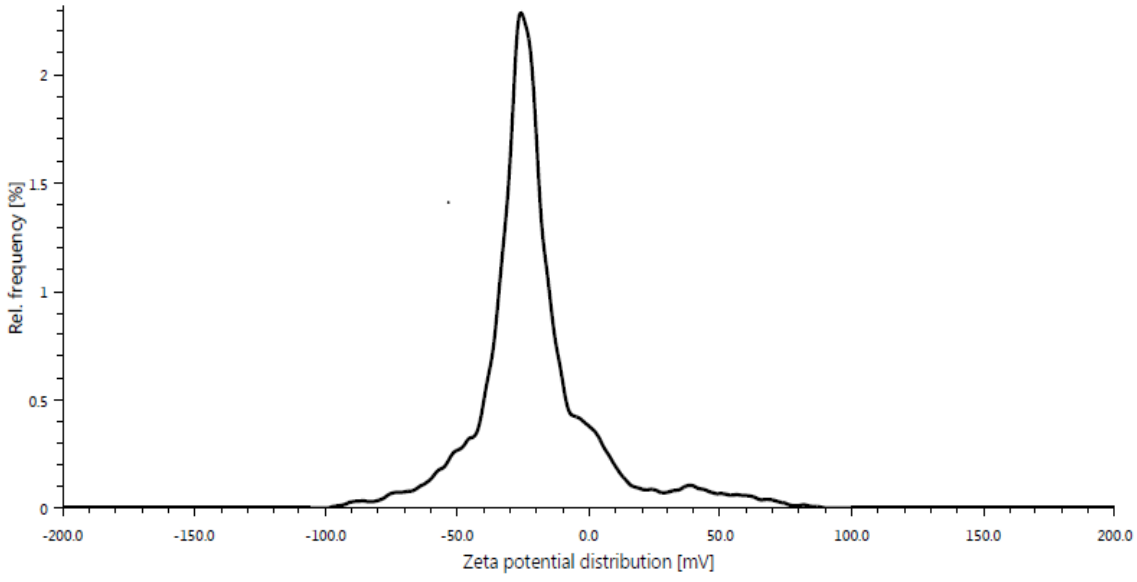


Formulation Development

Zeta Potential

The Zeta potential values of the Niosomal formulations loaded with Nifedipine were found to be negative due to the presence of free carboxyl groups in cholesterol and span 60. The Zeta potential of the formulation is -27.3 Mv(figure 4).

Figue 4: Zeta potential of Nifedipine



Evaluation Of Sublingual Film

Physical evaluation

The results of film forming capacity and appearance of the films are presented in Table 6.

Table 6: Results of film forming capacity and appearance of films

S .No	Formulation code	Film forming capacity	Appearance
1	F1	Very poor	Transparent
2	F2	Poor	Transparent
3	F3	Good	Transparent
4	F4	Average	Transparent
5	F5	Good	Transparent
6	F6	Very good	Transparent

To cut 4cm^{2}of the three films each, three different places from the casted film and weight variation was determined. Thickness of film was done in triplicate and then the standard deviation was taken. The results of the weight variation and thickness of the films are given in Table 7.

Table 7: Results of weight variation and thickness

S .No	Formulation code	Weight variation (mg) ± S.D	Thickness ± S.D
1	F1	20.53 ± 0.554	0.12 ± 0.012
2	F2	20.38 ±0.588	0.14 ± 0.015
3	F3	20.42 ±0.572	0.13 ± 0.014
4	F4	21.18 ±1.097	0.12 ± 0.013
5	F5	23.48± 1.444	0.13 ± 0.014
6	F6	22.51±1.722	0.14 ± 0.015

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Mechanical evaluation

Folding endurance of film was done in triplicate and then standard deviation was taken. Tensile testing is an indication of the strength or the toughness and elastic behavior of the film, measured by the parameters tensile strength (TS). The results of folding endurance and tensile strength are given in Table 8.

Table 8: Results of folding endurance and tensile strength

S .No	Formulation code	Folding endurance ± S.D	Tensile strength(kg/cm^2) ± S.D
1	F1	120 ± 0.387	2.28 ± 0.45
2	F2	130 ± 0.673	2.31 ± 0.56
3	F3	190 ± 0.701	2.51 ± 0.34
4	F4	215 ± 0.033	2.43 ± 0.36
5	F5	228 ± 0.408	2.52 ± 0.35
6	F6	235 ± 0.577	2.81 ± 0.28

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

The result of surface Ph are given in Table 9. The results showed that the prepared films were suitable for buccal administration as the pH of buccal region is nearly 6.5

Table 9: Results of Surface pH

Sl .No	Formulation code	Surface pH ± S.D
1	F1	7.04 ± 0.098
2	F2	7.1 ± 0.158
3	F3	6.9 ± 0.251
4	F4	7.08 ± 0.150
5	F5	6.95 ± 0.185
6	F6	6.8± 0.234

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

The prepared film formulation was assayed for drug content. Actual drug content in the prepared films was in the range of 95-105% of the claimed content. This indicates the even distribution of the drug in the prepared matrix of the films as well as the stability of drug in the procedure used for preparation. It was observed that the formulation was satisfactory in uniformity of drug as given in table 10.In-Vitro Disintegration of film was done in triplicate and then standard deviation was taken. The results of in-Vitro Disintegration are given in Table 10.

Table 10: Results of drug content and disintegration

Sl .No	Formulation code	Drug content (%) ± S.D	Disintegration time (seconds) ± S.D
1	F1	94.59 ± 2.29	180 ± 1.92
2	F2	97.98 ± 2.32	174 ± 2.302
3	F3	98.5 ± 2.54	169 ± 2.04
4	F4	95.78 ± 2.05	85 ± 3.36
5	F5	97.5 ± 2.30	63 ± 3.507
6	F6	98.6 ± 2.57	39 ± 3.83

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Figure 5: Percentage drug content

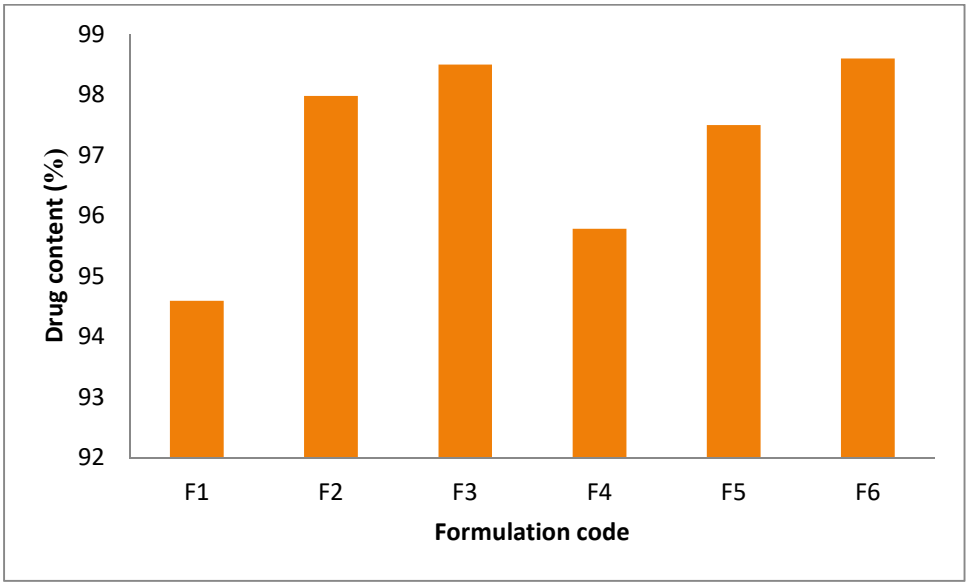
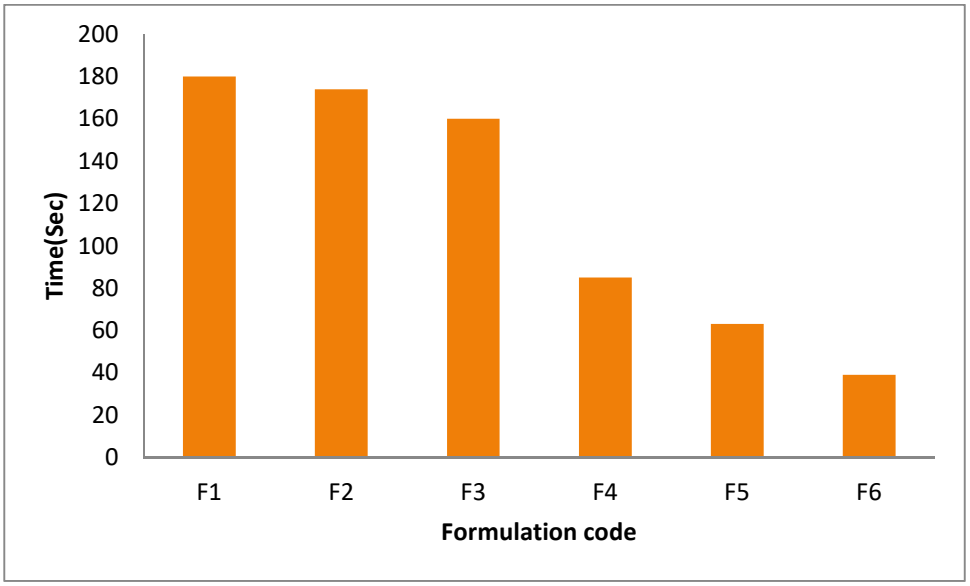


Figure 6: Disintegration time



Scanning Electron Microscopy

The resulting scanning electron micrographs are presented in Figure 7. For the selected niosomal dispersion, Figure 7A clearly demonstrates spherical shape of unilamellar vesicles in nanometer size range with good dispersibility. Similar surface morphology of the niosomes was visualized from the niosomal film micrograph (Figure 7B), which shows spherical vesicles with smooth surfaces. The vesicle size was in the nanometer range with good dispersibility. These results confirm that the incorporation of the prepared niosomes within fast dissolving film base did not show any significant changes in the morphology, shape, or dispersibility of the incorporated vesicles

Figure 7: Surface morphology of the selected fast dissolving niosomal film and niosomal dispersion.

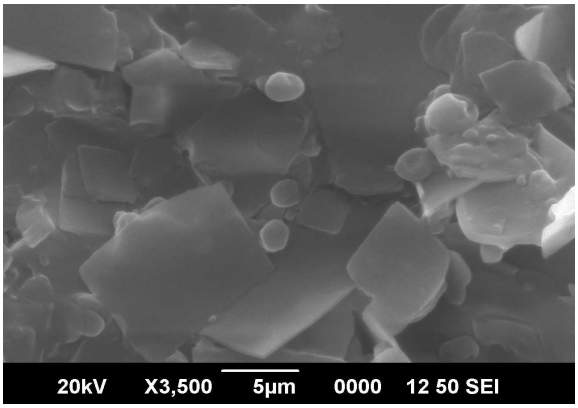


Figure 7(A)

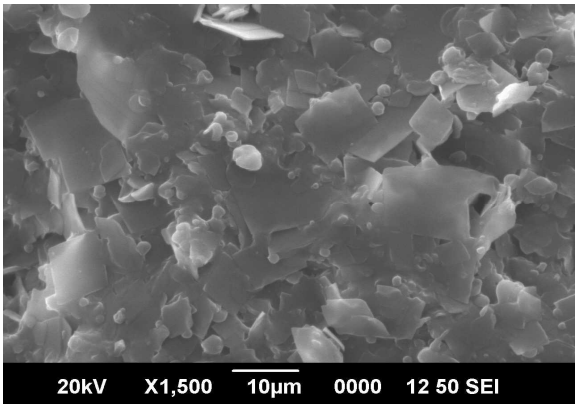


Figure 7 (B)

Notes: Scanning electron micrograph of (A) niosomal formulation and (B) niosomal fast dissolving film (NF6).

***In Vitro* Dissolution Study**

In-Vitro Dissolution of film was done in triplicate and then average and standard deviation was taken. 93.91 % of drug was released from the film within 540 sec. The results of *in vitro* dissolution are given in Table 11 and Fig 8&9

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Table 11: In vitro dissolution profile

S. No	Time (seconds)	Percentage drug release (%)± S.D					
		F1	F2	F3	F4	F5	F6
1	0	7.82±0.063	5.86±0.084	4.89±0.075	9.78±0.015	17.6±0.649	19.56±0.723
2	30	11.73±0.682	9.78±0.015	7.82±0.063	15.65±0.596	21.52±0.952	26.41±0.054
3	60	18.58±0.790	14.67±0.576	9.78±0.015	18.58±0.673	26.41±0.054	30.32±0.539
4	90	22.5±0.778	17.6±0.649	13.69±0.218	21.52±0.952	29.34±0.174	34.23±0.803
5	120	27.39±0.080	22.5±0.452	17.6±0.649	24.45±0.836	33.26±0.683	38.15±0.875
6	150	33.26±0.683	26.41±0.054	19.56±0.723	28.36±0.284	37.17±0.864	41.08±0.049
7	180	38.15±0.875	29.34±0.174	23.47±0.371	30.32±0.539	42.06±0.293	45.01±0.294
8	210	42.06±0.081	33.26±0.683	28.36±0.284	33.26±0.683	46.95±0.703	51.84±0.959
9	240	45.97±0.294	37.17±0.785	31.3±0.635	43.04±0.261	50.86±0.841	57.71±0.274
10	270	48.91±0.830	43.04±0.261	36.19±0.723	46.95±0.664	55.76±0.657	60.65±0.609
11	300	51.84±0.959	47.93±0.759	40.1±0.229	49.89±0.826	58.69±0.273	66.52±0.639
12	330	55.76±0.238	51.84±0.254	46.95±0.703	51.84±0.254	63.58±0.127	69.45±0.803
13	360	58.69±0.110	55.76±0.657	50.86±0.841	55.76±0.657	67.5±0.267	75.32±0.682
14	390	63.58±0.127	58.69±0.273	56.73±0.572	58.69±0.273	71.41±0.845	78.26±0.643
15	420	68.47±0.218	62.6±0.318	61.63±0.715	61.63±0.715	76.3±0.738	82.17±0.759
16	450	68.47±0.632	67.5±0.267	66.52±0.639	64.56±0.684	78.26±0.779	86.08±0.548
17	480	72.39±0.841	70.43±0.554	69.45±0.803	66.52±0.639	81.19±0.649	88.04±0.227
18	510	76.3±0.559	75.32±0.682	74.34±0.519	67.5±0.267	85.1±0.694	90.01±0.405
19	540	80.21±0.635	78.26±0.643	78.26±0.538	71.41±0.845	89.02±0.549	93.91±0.648

*Each reading is an average of 3 determinations ± Standard deviation (SD)

Figure 8: Comparative in-vitro dissolution of F1-F3

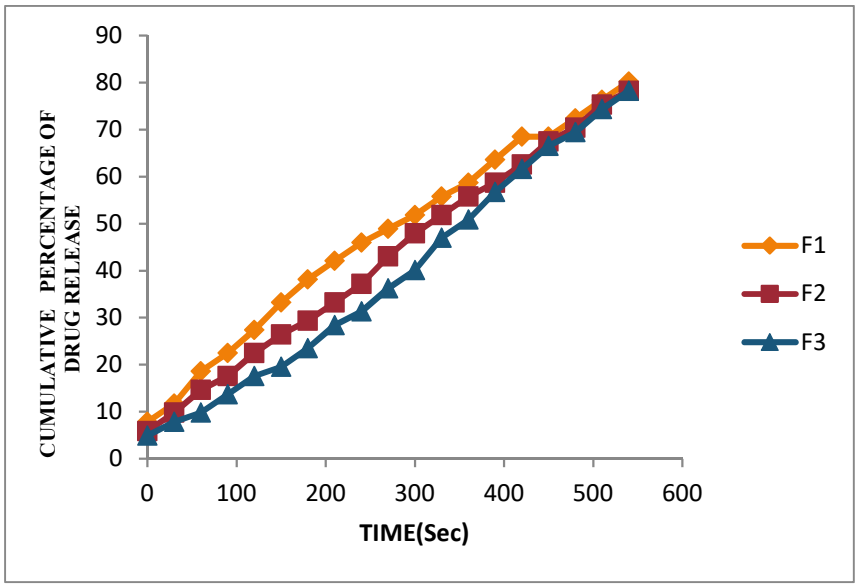

Figure 9: Comparative in-vitro dissolution of F4-F6

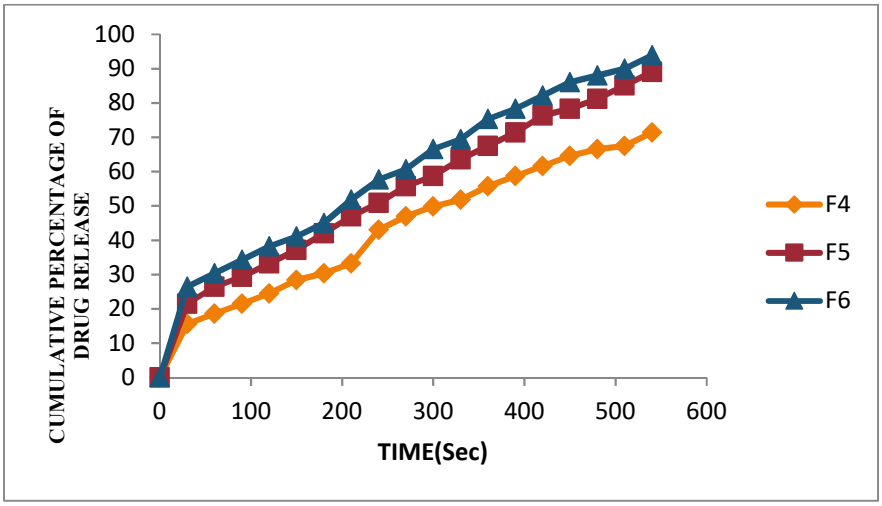

Figure 10: Zero order kinetics

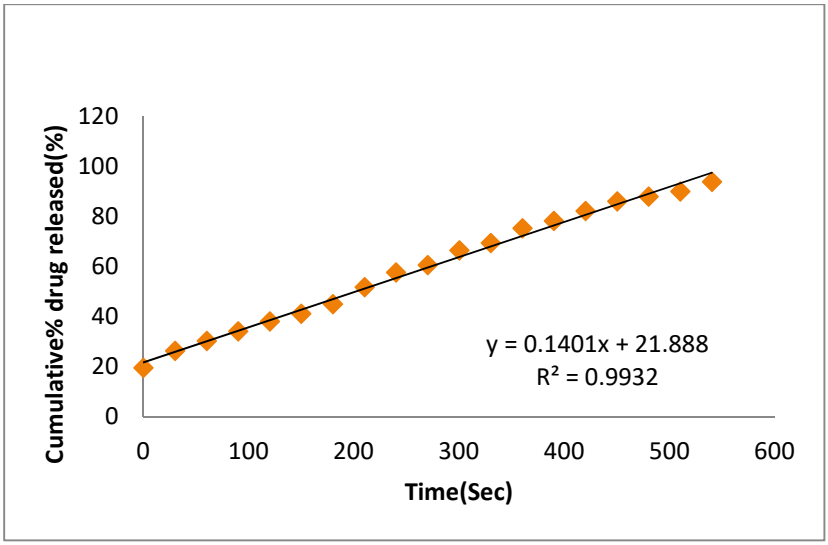

Figure 11: First order kinetics

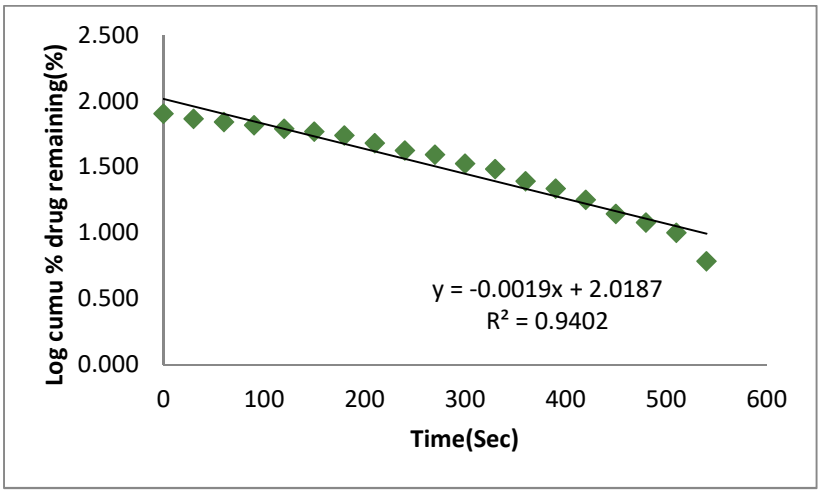

Figure 12: Higuchi plot

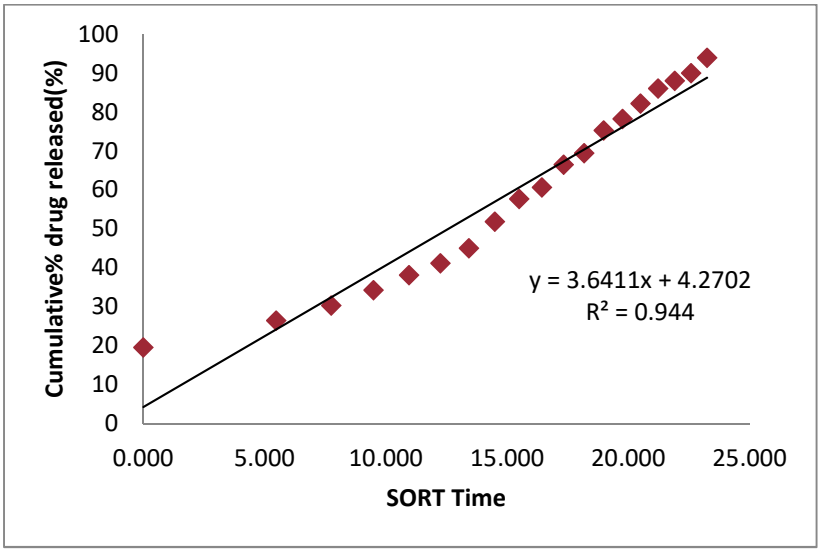

Figure 13: Korsmeye-peppas plot

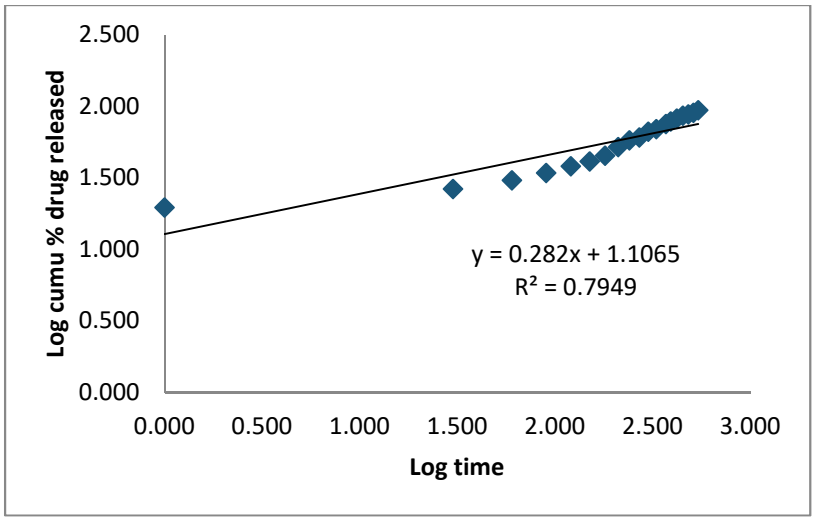

Figure 14: Hioxon croell plot

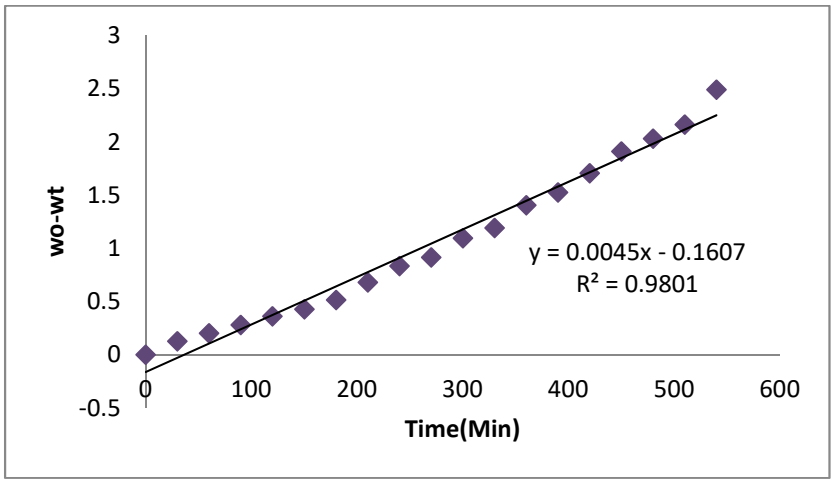

Table 12: kinetic models

Kinetic model fitting						
Formulation code	Zero order	First order	Higuchi matrix	Hixson crowell	Korsmeyer peppas	N
F6	0.993±0.482	0.940±0.395	0.944±0.351	0.980±0.497	0.794±0.836	1.106±0.59

**Each reading is an average of 3 determinations ± Standard deviation (SD)*

Kinetics of optimized formulation

Stability Studies

Stability study of the optimized formulation (F6) carried out for 0 to 90 days in two physical condition. On physical observation of the stored samples there was found that no change in physical appearance of the in-situ raft. The drug content, tensile strength, folding endurance, surface pH and *in vitro* drug release did not change significantly on storage. These studies suggest the physical and chemical stability of propranolol raft solution. The results are shown in the table no 13.

Table 13: stability studies

Time(days)	Physical appearance	Tensile strength (kg/cm^2)	Folding endurance	Surface pH	Percentage drug content (%)	Cumulative percentage drug release (%)
0	-	2.81 ± 0.28	235 ± 0.57	6.8±0.2	98.6 ± 2.57	93.91±0.648
30	No changes	2.8±0.09	235±0.57	6.8±0.24	98. 2±0.36	93.88±0.54
60	No changes	2.78±0.12	232±0.26	6.7±0.12	97.9±0.47	93.80±0.21
90	No changes	2.74±0.10	230±0.45	6.5±0.28	97.7±0.45	93.65±0.12

CONCLUSION

In this research work sublingual films that contain nifedipine -loaded niosomes were prepared and evaluated for their abilities to enhance systemic delivery of nifedipine. From all the above results, it clearly demonstrated the successful development of sublingual niosomal film of nifedipine which provides sustained release. The use of the inexpensive polymers like methyl cellulose and Sodium starch glycolate make them safer and biocampatable. Consequently, the absolute bioavailability of the drug following sublingual administration was significantly higher than that after oral tablet administration. These results indicated that the prepared sublingual fast dissolving niosomal film could have potential as an efficient delivery system to enhance the bioavailability and prolong the therapeutic effect of nifedipine, thus improving the patient compliance by eliminating the need for frequent dosing of the drug.

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