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FORMULATION AND *IN-VITRO* EVALUATION OF SOLID LIPID NANOPARTICLES CONTAINING NADOLOL

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Keywords:

Nadolol, Oral films, Oral fast-dissolving films, SLN fast dissolving films

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ABSTRACT: The solid lipid nanoparticles are sub-micron colloidal carriers (50-100 nm) that are composed of physiological lipid dispersed in water or in aqueous surfactant solution. Nadolol-loaded SLNs were prepared by modified high shear homogenization. It was observed that all formulations contain a good product yield. The highest drug content was found in formulation F5 98.37%. Entrapment efficiency for formulation F5 (98.58 %) was maximum. F5 formulations have lowest particle size (151.76) and the lowest PDI value (0.12) good Zeta potential (-28.8). The dissolution data of Nadolol solid lipid Nanoparticles F5 formulation was shown maximum drug release at 30 min. *i.e.,* 99.04%. Hence, F5 was concluded as an optimized formulation for solid lipid nanoparticles (Nadolol-loaded SLNs F5 formulation). The present work aimed at preparing oral film with a quick onset of action, which is very convenient for oral administration. Oral fast-dissolving films of Nadolol SLN were prepared using HPMC (E5) as film-forming polymer and PEG 400 as a plasticizer by solvent casting method. Dissolution of prepared oral films of Nadolol was performed using USP type II apparatus using pH 6.8 phosphate buffer medium at 50 rpm at temperature 37±0.5ºC temperature. The films prepared were evaluated for various parameters, which showed satisfactory results. In conclusion, the development of fast dissolving oral films using HPMC E5 300 mg polymer gives rapid drug delivery and rapid onset of action. F2 oral fast dissolving film was optimized in, which it showed a drug release of 97.36% after 30 min compared with other batch formulations.

INTRODUCTION: A solid lipid nanoparticle is typically spherical with -an average diameter between 10 to 1000 nanometers. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules [1-2]. The lipid core is stabilized by surfactants (emulsifiers).

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The term lipid is used here in a broader sense and includes triglycerides (*e.g.,* tristearin), diglycerides (*e.g.,* glycerol bahenate), monoglycerides (*e.g.,* glycerol monostearate), fatty acids (*e.g.,* stearic acid), steroids (*e.g.,* cholesterol) and waxes (*e.g.* cetyl palmitate) [3-4].

All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics [5]. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could hold

great promise for attaining the bioavailability enhancement along with controlled and site-specific drug delivery [6]. Solid lipid nanoparticles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in the submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components [7-9]. These are made of biocompatible and biodegradable materials that incorporate lipophilic and hydrophilic drugs. Orally fast-dissolving film is a new drug delivery system for the oral delivery of the drugs [10]. It was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue; instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application [11]. It then rapidly disintegrates and dissolves to release oromucosal and intragastric absorption medication. Normally these films are soluble in water at room temperature and will break up in 30 sec and disappear in one minute [12]. The faster the drug goes into the solution, the quicker its absorption and onset of clinical effect. The oral dissolving films contain active ingredients, flavors, sweeteners and other ingredients; these materials are released as the film dissolves [13-15].

MATERIALS: Nadolol was procured from Mylan pharmaceuticals Ltd, India. Glyceryl tri palmitate was procured from Lipoid GMPH, Germany. Soya lecithin was purchased from Merck Ltd, Mumbai. Poloxamer 407 was purchased from SD Fine-chem Ltd, Mumbai. Chloroform was purchased from Loba Chemie Pvt Ltd, Mumbai. Methanol and HPMC E5 were purchased from SD Fine-chem Ltd, Mumbai. PEG-400 was purchased from Merck Ltd, Mumbai. Aspartame and Ascorbic Acid was purchased from SD Fine-chem Ltd, Mumbai.

METHODOLOGY:

Analytical Method Development:

Preparation of 6.8 Phosphate Buffer: 6.8g of potassium di hydrogen orthophosphate was weighed and diluted up to 1000 ml with distilled water and adjust the pH with Sodium hydroxide solution up to 6.8 Ph [16].

Determination of Absorption Maxima of Nadolol: Absorption maxima is the wavelength at which maximum absorption occurs. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure:

Working Standard: 100 mg of accurately weighed drug and dissolved in 100ml of methanol (1mg/ml).

Dilution 1: Further, 1ml of the stock solution was pipette out into a 100 ml volumetric flask, and the volume was made up of phosphate buffer (6.8 pH).

Dilution 2: From this stock solution, pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer [17].

Standard Calibration Curve in Phosphate Buffer pH 6.8 Solution Procedure:

Working Standard: 100 mg of accurately weighed drug and dissolved in 100ml of methanol (1mg/ml).

Dilution 1: Stock solution (1 mg/mL) of Nadolol was prepared in methanol, and subsequent working standards (4, 8, 12, 16 and 20 mg/ml) were prepared by dilution with phosphate buffer of pH-6.8. These solutions were used for the estimation Nadolol by UV method. The whole procedure was repeated three times, and the average peak area was calculated. A calibration plot was drawn between concentrations and peak area. The calibration equation and R^2 value are reported [18].

Fourier Transform Infrared (FTIR) Spectroscopy: The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during preparation. FTIR analysis of the Pure drug and optimized formulation was carried out using an FTIR spectrophotometer (Bruker FT-IR - GERMANY) [19-20].

Preparation of Nadolol Loaded Solid Lipid Nanoparticles: The hot homogenizing method of drug-loaded solid lipid particles was prepared. Nadolol (drug 20 mg), solid lipid (50-300mg), and soya lecithin (50-200mg) were dissolved in 10 mL mixture of chloroform and methanol (1:1). Organic solvents were completely removed using a rotary evaporator. A drug-embedded lipid layer was melted by heating at 5°C above the melting point of the lipid. The aqueous phase was prepared by

dissolving polaxamer 407 (1.5% w/v) in double-distilled water (sufficient to produce 10 mL of preparation) and heated to the same temperature as the oil phase. A hot aqueous phase was added to the oil phase, and homogenization was carried out (at 12,000 rpm) using a Diax 900 homogenizer for 10min. Coarse hot oil in water emulsion obtained was ultrasonicated (12T- probe) using Vibracell probe sonicator (Bandelin, Germany) for 20 min. Nadolol-loaded solid lipid nanoparticles were obtained by allowing hot nanoemulsion to cool to room temperature. The quantity of ingredients used for the preparation of SLNs of Nadolol is given in **Table 1** [21].

TABLE 1: COMPOSITION OF SOLID LIPID NANOPARTICLES FORMULATIONS F1-F9

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nadolol (mg)	20	20	20	20	20	20	20	20	20
Glyceryl tri palmitate (mg)	50	100	200	300	50	100	200	300	200
Soya lecithin(mg)	50	50	50	50	100	100	100	100	200
Poloxamer 407 (%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Double distilled water (Ml)	10	10	10	10	10	10	10	10	10
Chloroform: Methanol (1:1)(mL)	10	10	10	10	10	10	10	10	10

Characterization of Preparing Solid Lipid Nanoparticles:

Particle Sizes, PDI, Zeta Potential: The mean particle length and polydispersity index (PDI), that's a degree of the distribution of nanoparticles population, was decided the usage of dynamic light scattering (Delta Nano C, Beckman counter) and Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK). Samples were diluted with the distilled water before measurement and measured at a hard and fast angle of 165^0c for the particle size and polydispersity index (PDI) analysis. For the Zeta ability measurement, Samples were diluted as 1; 40 ratios with filtered water (v/v) before analysis. Average particle size, PDI and zeta potential have been then measured in triplicate [23-25].

Drug Content: Nadolol content in solid lipid nanoparticles was assayed by a UV-visible spectrophotometer. Solid lipid nanoparticles (100mg) were dissolved in 10ml methanol by shaking the mixture for 5 min. One ml of the resultant solution was taken and diluted to 10ml with methanol. Then, aliquots were withdrawn, and absorbance was recorded at 270 nm using a UV-visible spectrophotometer [26].

Yield of Solid lipid Nanoparticles: After complete drying, the solid lipid nanoparticles powders were collected and weighed accurately. The yield of solid lipid nanoparticles was calculated using the formula [27].

% Yield = Total weight of solid lipid nanoparticles x 100 / total weight of drug + weight of added materials

Entrapment Efficiency: Entrapment Efficiency (EE) of the Nadolol-loaded SLNs changed determined by measuring the awareness of uninterrupted drugs in an aqueous medium by centrifugation method. The nanoparticles had been centrifuged during a high-space cooling Centrifuge (C-24.Remi) using nano step centrifuge tubes with ultra-filter out having a relative molecular mass cutoff 100KD (Pall existence sciences-India) at 5000rpm for 15min at 4^oC, and therefore the supernatant was separated. The amount of Nadolol inside the supernatant changed to determining the usage of a UV-Visible spectrophotometer (U-1800, Hitachi) at lambda max 270 nm after suitable dilution [28]. The percent entrapment efficiency (%) changed into calculated using the usage of the subsequent formula:

% EE = Total drug content-Free drug x 100 / Total drug content

Percentage of Drug Release from Semi-Permeable Membrane: Franz diffusion cell was used for the *in-vitro* drug release studies. Semi-permeable membrane was placed between donor and receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared 30ml 6.8 PH phosphate buffer. SLN equivalent to 1gm was placed on semi permeable membrane.

The franz diffusion cell was placed over a magnetic stirrer (REMI 1ML) with 500rpm and the temperature was maintained at 37±1°C. 5ml of samples were withdrawn periodically and replaced

with fresh buffer [29]. The withdrawn samples were periodically diluted and analyzed for drug content using UV visible spectrophotometer (Lab India 3200) at 270 nm.

SEM (Scanning Electron Microscope) Studies: The layered sample's surface morphology was examined using SEM (Hitachi, Japan). The small amount of powder was manually dispersed onto a carbon tab (double-adhesive carbon-coated tape) adhered to an aluminum stub. These sample stubs were coated with a thin layer (30Å) of gold by employing POLARON-E 3000 sputter coater[30]. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

Preparation of Oral Fast Dissolving Film Containing SLN Nadolol: The fast-dissolving films of Nadolol were prepared by solvent casting technique. **Table 2** it shows that the fast-dissolving films were prepared using polymers like HPMC (E5). Polyethelene glycol-400 (PEG400) was used as a plasticizer. The calculated amount of polymer was dispersed in the solvent with continuous stirring using a magnetic stirrer, and the homogenous solution is formed.

Then 6 drops of plasticizer and sweetener were added to the above dispersion under continuous stirring. After stirring, the optimized SLN preparation was incorporated under a homogenizer at 1000 rpm. Then the solution was kept in a sonicator for degassing. Then the bubble-free solution was cast on to petriplate. The dried film is then cut into the desired shape and size (1cm x 1cm) for the intended application [31-33].

TABLE 2: COMPOSITION OF NADOLOL ORAL DISSOLVING FILMS

Ingredients(mg)	F1	F2	F3	F4
Nadolol SLN equivalent to dose	180.8	180.8	180.8	180.8
HPMC E5 (mg)	250	300	400	500
PEG-400 (drops)	6	6	6	6
Methanol (ml)	2	2	2	2
Aspartame (mg)	25	25	25	25
Ascorbic Acid (mg)	5	5	5	5

Total amount of the drug =180.0 mg per petriplate

Evaluation of Oral Films / Fast Dissolving Films:

1. Thickness: As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by a micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations [34]. The thickness was measured at three different spots of the films, and the average was taken.

2. Tensile Strength: Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The applied load calculates it at rupture divided by the cross-sectional area of the strip as given in the equation below

Tensile strength = Load at breakage/ Strip thickness × Strip Width

3. Percent Elongation: When stress is applied, a strip sample stretches, and this is referred to as strain. Strain is basically the deformation of a strip divided by the original dimension of the sample. Generally, elongation of the strip increases as the plasticizer.

% Elongation = Increase in length ×100 / Original length

4. Folding Endurance: Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value [36].

5. Physical Appearance and Surface Texture of Film: These parameters were checked simply with visual infection of films and by feel or touch.

6. Weight Uniformity of Films: Film (size of 1 cm^2) was taken from different areas of film. The weight variation of each film is calculated [37].

7. Drug Content Uniformity or Assay of Film: The films were tested for drug content uniformity using the UV Spectrophotometrical method. Films of 1cm x 1cm square size were cut from three different places from the casted films. Each patch

was placed in 10 ml volumetric flask and dissolved in 6.8 phosphate buffer. The absorbance of the solution was measured at 270 nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph, and the same procedure was repeated for all the formulations [38].

***In-vitro* Disintegration time:** The *in-vitro* disintegration time of fast dissolving films was determined visually in a glass dish of 8 ml 6.8 pH phosphate buffer with swirling action. The disintegration time is when a film starts to break or disintegrate [39]. The *in-vitro* disintegration time was calculated for different patches of the same film, and the average value was taken.

***In-vitro* Dissolution Study:** *In-vitro* dissolution of Nadolol oral dissolving films was studied in paddle-type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used as a dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of the dissolution medium was maintained at 37±0.5 ºC throughout the experiment. Samples of dissolution medium (5ml) were withdrawn by means of a syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 270 nm [40]. The volume withdrawn at each time interval was replaced with a fresh quantity of dissolution medium. Percentage drug release was calculated and plotted against time.

Drug Release Kinetics: Diffusion data of the above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using the Higuchi equation.

Zero-Order Kinetics: Zero-order as the cumulative amount of Percentage drug released vs. time

$$C = K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First Order Kinetics: First order as cumulative log percentage of log (%) cumulative drug remaining vs. time,

$$\text{Log } C = \text{Log } Co - k\,t / 2.303$$

Where C0 is the initial concentration of the drug, k is the first order constant, and t is the time.

Higuchi Model: Higuchi's model as cumulative percentage of drug released vs. square root of time

$$Q = K\,t^{1/2}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, the drug release rate is proportional to the reciprocal of the square root of time.

Kors Meyer Peppas Equations: Korsmeyer Peppas equation is used to determine the mechanism of drug release from the polymer matrix of the tablet. Log cumulative percentage of drug released vs. Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt / M\infty = Kt\,n$$

Where Mt /M∞ is the fractional solute release, t is the release time, K is a constant kinetic characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release [41].

Stability Studies as Per ICH Guidelines: Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Table 3 shows stability studies were performed at a temperature of 25± 2 °C / 60±5% RH & 30±2°C / 65±5% RH, over a period of three months (90 days) on the promising MDT of Amiodarone formulation. A sufficient number of tablets were packed in the amber-colored screw-capped bottles and kept in a stability chamber maintained at 40±2°C / 7 5±5% RH. Samples were taken at monthly intervals for drug estimation. At the end of a three-month period, dissolution studies were

performed to determine the drug release profile per ICH guidelines.

Note: ∗ It is up to the applicant to decide whether long-term stability is performed at 25±2°C/60±5% or 30±2°C/65±5%. ∗If 30±2°C/65±5% is the long-term condition, there is no intermediate condition.

TABLE 3: STORAGE CONDITIONS AS PER ICH GUIDELINES

Study	Storage condition	Duration
Short term	40 ± 2°C at 75 ± 5%RH	3 months
Intermediate	30 ± 2°C/65 ± 5%RH	6 months
Long term	25 ± 2°C /60 ± 5 % RH	12 months

RESULTS AND DISCUSSIONS:

Drug-Excipient Compatibility studies by FTIR Studies: IR spectral analysis was carried out using FT-IR, and the results showed that there were no /interactions between drugs and excipients.

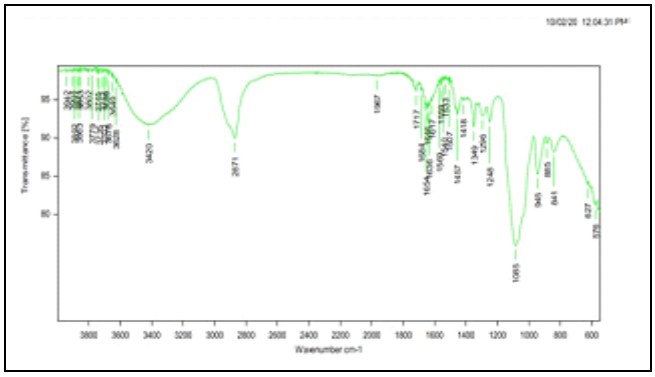


FIG. 1: FTIR SPECTRUM OF PURE DRUG

TABLE 4: INTERPRETATION OF FTIR OF PURE DRUG NADOLOL

Materia materials	Functional group	frequency	Observed peak
Pure API	C-O	1085-1050	1085
	C-H	2000-1650	1967
	N-H	3350-3310	3420

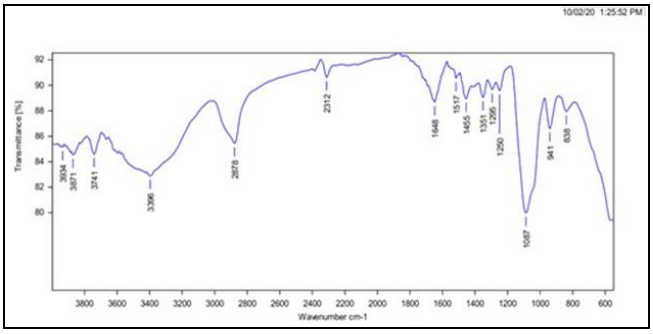


FIG. 2: FTIR SPECTRUM OF PURE DRUG WITH EXCIPIENTS

DISCUSSION: Fig. 1 and **2** show that the pure drug and its combination with excipients were subjected to FTIR studies. It was observed that there were no appearances or disappearance, or shifts in the peak position of Nadolol.

This proved that drug and excipients were compatible and the study of spectra indicated no chemical reaction.

Analytical Method Development:

Determination of λ_{max} of Nadolol (IP):

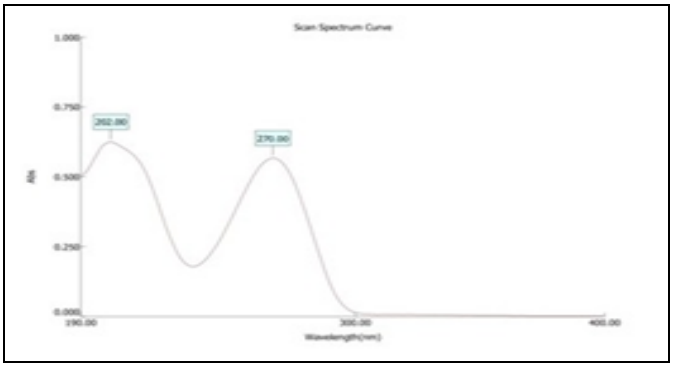


FIG. 3: GRAPH INDICATING λ_{max} OF NADOLOL (I.P)

Discussion: In **Fig. 3** it shows that Pure drug nadolol was scanned over a range of 200-400 nm, the peak was observed at the 270 nm confirm the identification of nadolol in p^H 6.8 phosphate buffer.

Preparation of Standard Calibration Curve of Nadolol (I.P):

TABLE 5: STANDARD CALIBRATION CURVE VALUES OF NADOLOL

Concentration (µg/ml)	Absorbance λ_{max} =270nm
0	0
4	0.156±0.02
8	0.290±0.03
12	0.454±0.02
16	0.611±0.01
20	0.740±0.03

All the values are expressed in S.D (n=3)

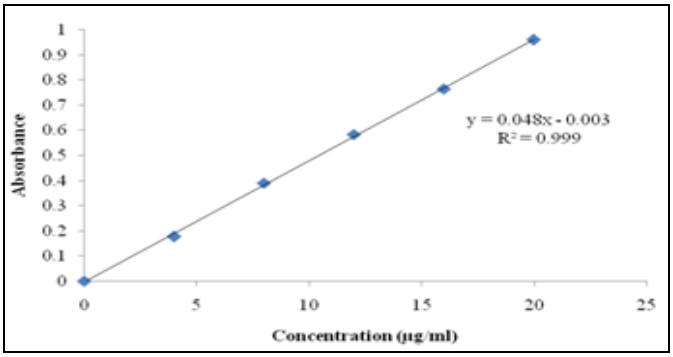


FIG. 4: CALIBRATION CURVE OF NADOLOL IN PH 6.8 PHOSPHATE BUFFER AT λ_{max} =270 nm

Discussion: In **Fig. 4** it shows that Standard graph of nadolol has shown good linearity with R2 value 0.999 and shows the slope of 0.074 in pH 6.8 phosphate buffer; indicating that it obeys Beer's law in the concentration range of 2-12 µg/ml.

Characterization of Solid Lipid Nanoparticles:

TABLE 6: PERCENTAGE YIELD, DRUG CONTENT, ENTRAPMENT EFFICIENCY OF ALL SOLID LIPID NANOPARTICLES FORMULATIONS

Formulation	%yield	Drug Content	Entrapment Efficiency
F1	90.23±0.02	90.11±0.01	89.23±0.02
F2	96.07±0.03	94.29±0.02	94.35±0.03
F3	93.56±0.02	91.33±0.01	92.71±0.02
F4	92.77±0.01	90.23±0.03	90.08±0.01
F5	99.12±0.01	98.37±0.02	98.58±0.01
F6	94.38±0.02	91.92±0.03	89.47±0.02
F7	93.19±0.01	92.46±0.01	91.28±0.03
F8	97.07±0.03	93.21±0.02	93.56±0.01
F9	98.47±0.02	95.69±0.01	96.28±0.02

All values are expressed in S.D (n=3)

Percentage Yield of All Formulations:

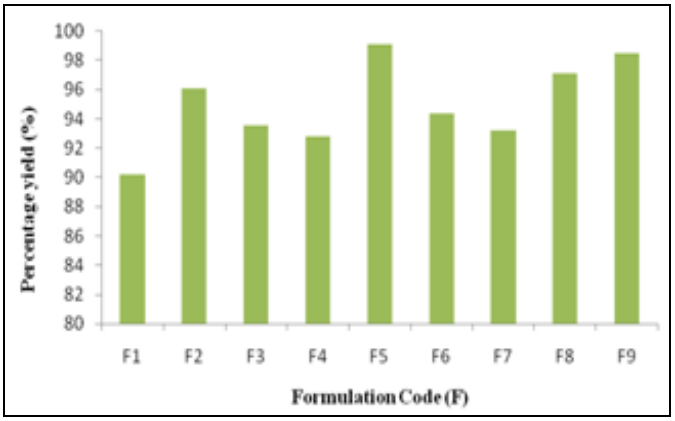


FIG. 5: PERCENTAGE YIELD OF ALL FORMULATIONS

Drug Content of All Formulations:

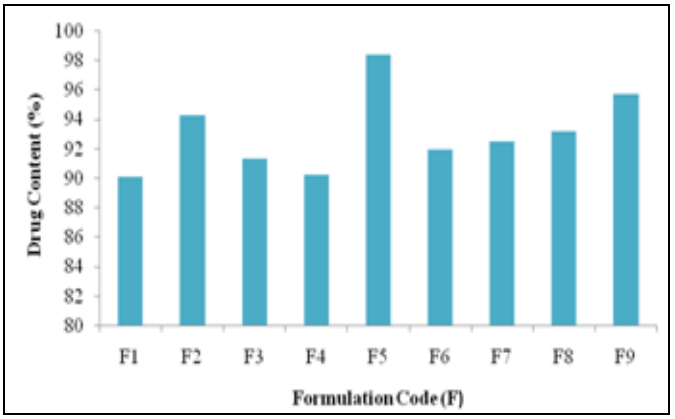


FIG. 6: DRUG CONTENT OF ALL FORMULATIONS

Entrapment Efficiency of All Formulations:

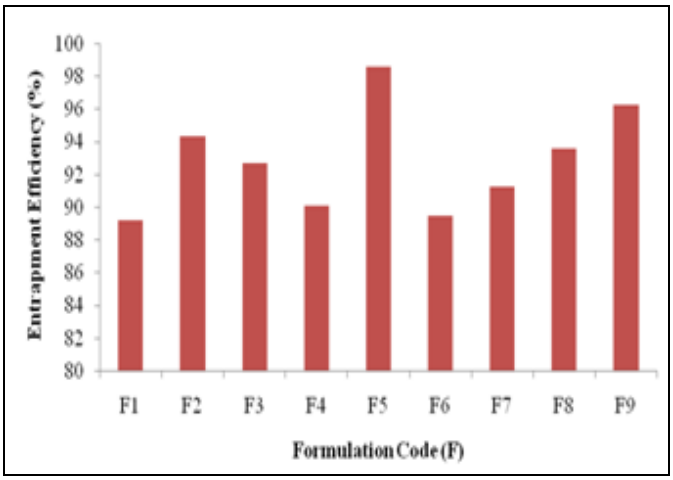


FIG. 7: ENTRAPMENT EFFICIENCY OF ALL FORMULATIONS

Discussion: In **Fig. 5**, the percentage yield was found to be in the range of 90 to 99% for solid lipid nanoparticles containing Glyceryl tri palmitate and Soya lecithin as lipid.

It was observed that as the all most all formulations contain the highest product yield. The highest drug content was found in formulation F5 98.37%.

In **Fig. 7** it shows that the percentage entrapment efficiency of Glyceryl tri palmitate and Soya lecithin nanoparticles were as given in **Table 6** for batch F1 to F9.

Entrapment efficiency for formulation F5 (98.58 %) was maximum and minimum for formulation F1 (89.23%).

It was observed that use of Soya lecithin increased the entrapment efficiency of Nadolol.

TABLE 7: PARTICLE SIZES, PDI, ZETA POTENTIAL OF ALL SOLID LIPID NANOPARTICLES FORMULATIONS

Formulation	Particle Size(nm)	PDI	Zeta Potential (mV)
F1	230.95±2.0	0.73	-15.7±0.32
F2	160.23±1.60	0.36	-21.9±0.2
F3	192.11±1.88	0.21	-18.6±1.00
F4	200.42±1.55	0.23	-25.4±0.42
F5	151.76±0.90	0.12	-28.8±0.15
F6	220.23±1.52	0.35	-13.2±0.30
F7	260.73±0.90	0.44	-18.2±0.51
F8	242.79±0.91	0.57	-14.9±0.87
F9	290.52±0.95	0.69	-23.2±0.54

All the values are expressed in S.D (n=3)

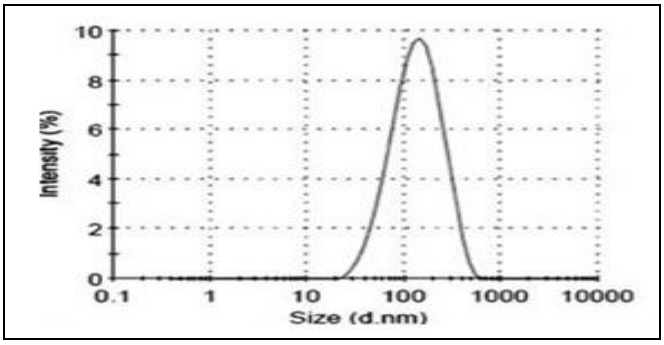


FIG. 8: PARTICLE SIZE DISTRIBUTION OF F5

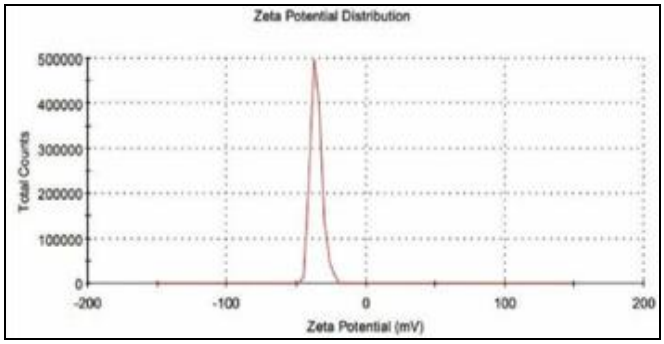


FIG. 9: ZETA POTENTIAL OF F5 FORMULATION

Discussion: Table 7 shows that the particle size of Nadolol-loaded solid lipid nanoparticles were directly proportional to the concentration of Soya lecithin. Present investigation suggests that increasing the Soya lecithin concentration in the continuous medium increases the particle size of solid lipid nanoparticles. The particle size distribution and polydispersity index (PDI) of lipid-based nanocarriers are important physical characteristics to consider when creating food-grade or pharmaceutical-grade products. F5 formulation has the lowest particle size (151.76). PDI is a number calculated from a two-parameter fit to the correlation data (the cumulants analysis). Lowest PDI value (0.12) for F5 formulation. More Zeta potential is useful for the good stable product. In **Fig. 9** it shows that Hence F5 formulation had high zeta potential (-28.8), and it was considered as a good stable product.

TABLE 8: *IN-VITRO* DISSOLUTION STUDIES OF F1-F9 SLN FORMULATIONS IN PERCENTAGE

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	60.75 ±0.01	70.88 ±0.03	65.86 ±0.02	62.65 ±0.02	75.65 ±0.01	70.41 ±0.02	64.81 ±0.01	65.82 ±0.03	50.90 ±0.02
10	68.90 ±0.02	75.54 ±0.02	72.13 ±0.02	68.21 ±0.01	80.27 ±0.02	77.32 ±0.01	70.46 ±0.02	71.27 ±0.02	58.98 ±0.01
15	73.66 ±0.03	82.27 ±0.01	80.46 ±0.01	72.88 ±0.02	86.31 ±0.03	82.18 ±0.02	78.97 ±0.03	76.59 ±0.01	64.12 ±0.02
20	80.42 ±0.02	90.09 ±0.02	85.99 ±0.03	77.35 ±0.03	91.22 ±0.02	87.24 ±0.01	83.60 ±0.01	80.12 ±0.03	70.59 ±0.02
30	85.29 ±0.01	95.32 ±0.03	90.42 ±0.02	82.46 ±0.01	99.04 ±0.03	92.21 ±0.03	86.02 ±0.02	83.76 ±0.02	75.27 ±0.03

All values are expressed in S.D (n=3)

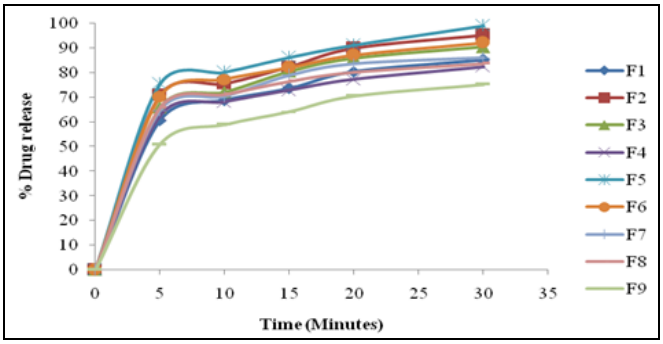


FIG. 10: COMPARATIVE *IN-VITRO* DRUG RELEASE OF DIFFERENT FORMULATIONS

Discussion: In table 8 the dissolution studies were conducted by using dissolution media, pH 6.8. The results of the *in-vitro* dissolution studies of formulations F1 to F9 are shown in table. The plots of cumulative percentage drug release Vs time.

Fig. 10 shows the comparison of % CDR for formulations T F1 to F9. The formulations F1, F2, F3 and F4 containing Soya lecithin (50mg) along with Glyceryl tri palmitate showed a maximum release of 85.29%, 95.32%, 90.42% and 82.46% after 30 minutes, respectively. The formulations F5, F6, F7 and F8 containing Soya lecithin (100mg) and Glyceryl tri palmitate showed a maximum release of 99.04%, 92.21%, 86.02%, and 83.76% after 30 minutes, respectively. The formulation F9 containing Soya lecithin (200mg) along with Glyceryl tri palmitate (200mg) showed a maximum release of 75.27%. From the dissolution data of Nadolol solid lipid Nanoparticles F5 formulation was shown maximum drug release at 30 min. *i.e.,* 99.04%.

Hence F5 was concluded as an optimized formulation for solid lipid Nanoparticles. The optimized F5 formulation Nanoparticles are incorporated into the Films (as dose equivalent). Films are further evaluated in different parameters.

Scanning Electron Microscopy (Sem):

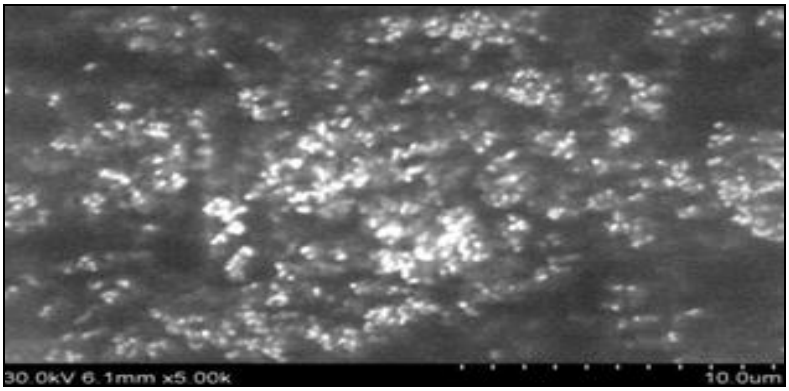


FIG. 11: SCANNING ELECTRON MICROSCOPY GRAPH F5 SOLID LIPID NANOPARTICLES OPTIMIZED FORMULATION

Discussion: SEM studies showed that the Nadolol loaded solid lipid nanoparticles had a spherical shape with a smooth surface, as shown in **Fig. 11.**

Evaluation of Fast Dissolving Films:

TABLE 9: PHYSICAL EVALUATION PARAMETERS OF ALL FORMULATIONS

Formulation Code	Thickness (mm)	Weight variation (mg)	isintegration time (sec)	Drug content (%)
F1	0.134±0.02	31.07±0.01	24±0.02	98.33±0.01
F2	0.131±0.01	30.33±0.02	18±0.01	99.01±0.02
F3	0.136±0.02	32.80±0.01	20±0.02	97.93±0.03
F4	0.142±0.03	33.41±0.03	28±0.03	98.76±0.02

All the values are expressed in S. D (n=3)

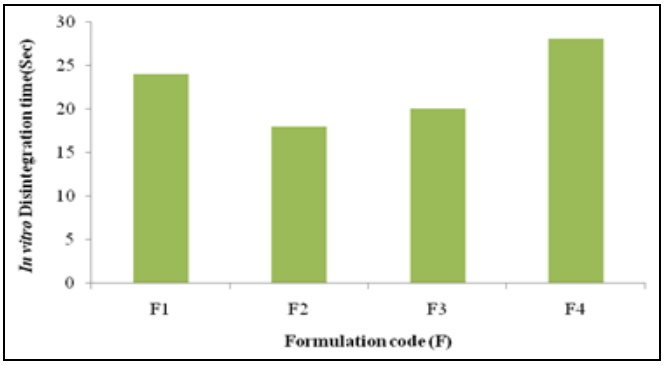


FIG. 12: *IN-VITRO* DISINTEGRATION TIME OF ALL F1-F4 FORMULATIONS

Discussion: The thickness of the films from F1-F4 formulations ranged from 0.131 to 0.143. F2 formulation had the less and optimum thickness values in all the formulations. From the thickness values,, it is concluded that thickness also increased as the polymer concentration increases. Weight uniformity of films was carried out for all the formulations and weight variation varies from 31.07 to 33.41 mg. The disintegration time is the time when a film starts to break or disintegrate. The *in-vitro* disintegration time was calculated for all the formulations and it ranges from 15sec to 30 sec disintegration time of the films was increased with increase in concentration of the polymer, as more fluid is required to wet the film in the mouth. F2 formulation was quickly disintegrated that is in 18 sec. The drug content uniformity of the films from F1-F4 formulations were ranged from 98.33% to 97.76%. F2 formulation had the maximum drug content uniformity and F3 formulation had the lowest values in all the formulations.

TABLE 10: MECHANICAL PROPERTIES OF ALL FORMULATIONS

Formulation Code	Tensile Strength(kg)	% Elongation	Folding Endurance
F1	1.396±0.03	20.76±0.01	94.0±0.76
F2	1.466±0.01	24.05±0.02	151.0±0.71
F3	1.515±0.02	25.46±0.03	154.6±0.74
F4	1.529±0.01	27.54±0.01	159.5±0.86

All the values are expressed in S.D (n=3)

Discussion: The tensile strength of the films from F1-F4 formulations ranged from 1.396 to1.529 kg. F2 formulation had the maximum and sufficient tensile strength. From the tensile strength values, it is concluded that as the polymer concentration increases, tensile strength and percentage elongation also increase. The folding endurance value of the films from F1-F4 formulations ranged from 90 to 160. In HPMC containing formulations, as polymer concentration increases, folding endurance values were also increased, as shown in **Table 10.**

TABLE 11: *IN-VITRO* DRUG RELEASES FOR F1 TO F4 FORMULATIONS

Time (min)	(%) Cumulative drug release			
	F1	F2	F3	F4
0	0	0	0	0
5	79.00±0.01	77.07±0.02	72.05±0.01	70.99±0.02
10	81.27±0.02	79.41±0.01	77.82±0.02	77.69±0.01
15	89.02±0.03	88.34±0.03	83.25±0.03	82.90±0.01
20	92.51±0.01	92.10±0.02	89.60±0.02	87.21±0.03
30	98.12±0.02	97.36±0.01	94.13±0.03	95.55±0.01

All the values are expressed in S.D (n=3)

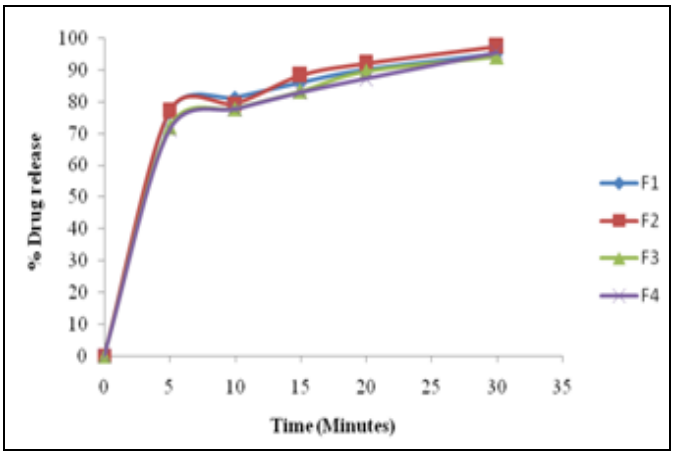


FIG. 13: COMPARISON CURVE OF IN VITRO DRUG RELEASE FOR F1- F4FORMULATIONS

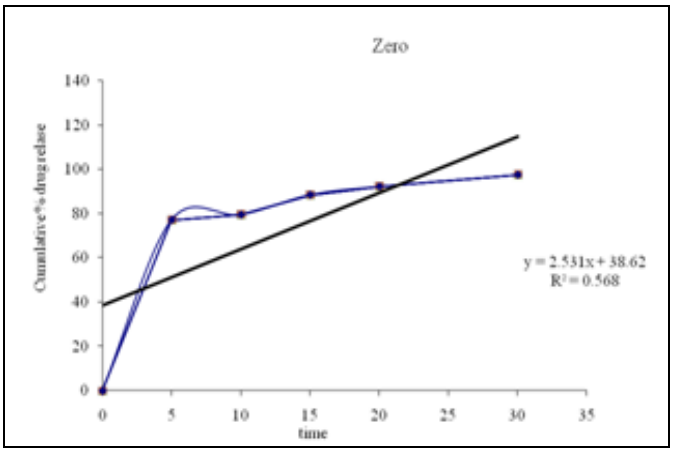
Discussion: **Table 11** shows *in -vitro* dissolution study of F1-F4 formulations were showed different drug releases of 98.12%, 97.36%, 94.13%, and 95.55%, respectively, within 30 min.

Among the formulations,, F2 showed better dissolution property than others, but because of better folding endurance, tensile strength, and % elongation, F2 is optimized. Small differences were observed in the dissolution of the drug from the different formulations of the film.

Present study reveals that maximum all formulated films showed satisfactory film parameters. F2 was optimized based on dissolution, folding endurance, tenstile strength, and % elongation from all formulations.

F2 formulation contains 300 mg of HPMC E5 as film-forming polymer. So, oral fast dissolving film containing 300 mg of HPMC E5 was optimized in, which it showed a drug release of 97.36% compared with other batch formulations, as shown in **Fig. 13.**

Kinetic Studies for Optimized Formulation:



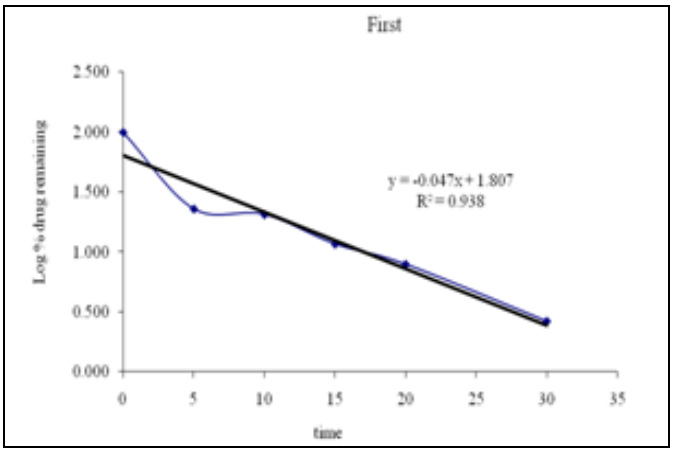


FIG. 14: ZERO-ORDER PLOT FOR F2 FORMULATION FIG. 15: FIRST ORDER PLOT FOR F2 FORMULATION

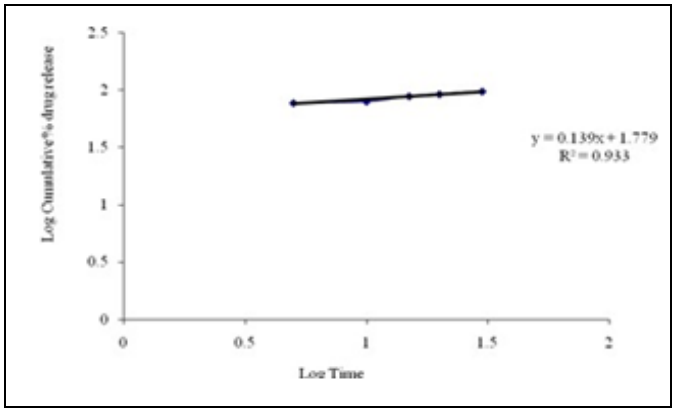


FIG. 16: HIGUCHI PLOT FOR F2 FORMULATION

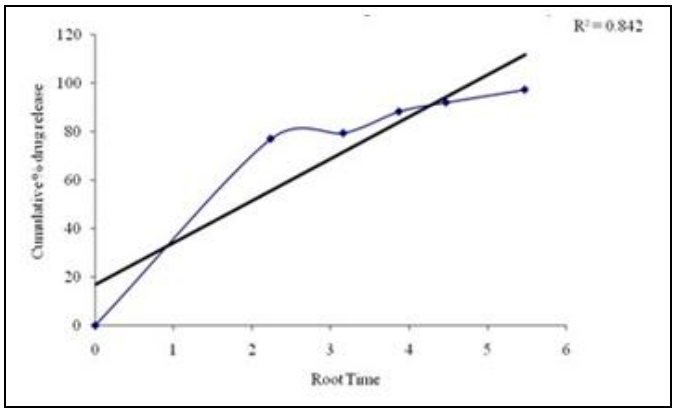


FIG. 17: PEPPAS PLOT FOR F2 FORMULATION

Discussion: The release rate kinetic data for the F2 is shown in **Table 11**. Drug release data of nadolol loaded SLN-oral disintegrating films follows the FIRST order equation. The plots showed the linearity $r^2 = 0.938$ for the first order and r2 = 0.564 for zero-order as shown in **Fig. 14, 15, 16, 17.**

TABLE 12: R^2 VALUES FOR ALL FORMULATIONS

Formulation Code	Zero Order	First Order	Higuchi	Peppas
F1	0.672	0.922	0.921	0.813
F2	0.568	0.938	0.933	O.842
F3	0.542	0.91O	0.927	0.836
F4	0.342	0.926	0.924	0.824

Discussion: The release rate kinetic data for the F2 is shown in the table. Drug release data of nadolol loaded SLN-oral disintegrating films follows the first order equation., as the plots showed the linearity $r^2 = 0.938$ for first order and $r^2 = 0.564$ for zero order.

Stability Studies Best Formulation: Selected formulation F2 was packed and stored at 25±2°C / 65±5% RH and 30°C ± 2°C / 65% ± 5% RH or a period of 2 months. **Table 13** shows that samples were analyzed after storage for 3 months and evaluated.

TABLE 13: STABILITY STUDIES FOR OPTIMIZED FORMULATION F2

Formulat ion code	Appearance	Thickness (mm)	Weight variation	Folding endurance	% Assay	Disintegration time(sec)	% Drug released	
							25±2°C / 65±5%RH	40±2°C / 75±5%RH
First day	Smooth and Transparent	0.131	3.0±0.01	151	99.01	18	99.52	99.52
30 days	Smooth and Transparent	0.131	3.0±0.01	151	98.90	19	99.50	99.51
60 days	Smooth and Transparent	0.131	3.0±0.02	151	98.88	19	99.48	99.50
90 days	Smooth and Transparent	0.131	3.0±0.02	151	98.88	19	99.48	99.50

CONCLUSION: The project's main aim was to prepare and evaluate solid lipid nanoparticles incorporated in oral films. Solid lipid nanoparticles (SLN), because of their lesser particle size, surface area helps better absorb low soluble and low permeable drugs. Since Nadolol lower permeability attempt was made to SLN for better absorption. This SLN was incorporated in the oral film by solvent casting method. Oral disintegrating film is suitable for ease of administration and better patient compliance. F1-F9 Nine formulations of solid lipid nanoparticles were prepared using soy lecithin, glyceryl tri palmitate, and poloxomer 407. F5 formulation was optimized for its better particle size (151.76), PDI (0.12), and better zeta potential (-28.8). F5 formulation was incorporated in oral dissolving films using HPMC E5 as a film-forming agent, PEG 400 as a plasticizer, aspartame as a sweetening agent, and ascorbic acid was used as sialogogue. F1-F4 four formulations of oral films

were prepared by solvent casting method. F2 was optimized for its better dissolution (97.36), in 6.8 phosphate buffer, tensile strength (1.46), % elongation (24.05) and folding endurance (151). The release kinetics showed that dosage form follows first order (0.938) *i.e,* drug release depends upon concentration further it shows drug release is by Higuchi model *i.e* drug release depends upon diffusion since (n>5) it was found that drug release follows non-fickian mechanism. Stability studies show that SLN in oral films was stable after 3 months in 25°C /60±5%RH and 30°C/65±5%RH. Hence, further research work can be carried out for further investigations.

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