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DEVELOPMENT OF NIOSOMAL SUBLINGUAL FILMS FOR ENHANCED PRAZOSIN HCL BIOAVAILABILITY: A HYBRID DRUG DELIVERY SYSTEM

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ABSTRACT
In order to improve the bioavailability of Prazosin HCl, a selective alpha-1 adrenergic receptor antagonist with low oral bioavailability because of substantial first-pass metabolism, this study focuses on the development and assessment of niosomal sublingual films. In order to get around this restriction, niosomes were created using the thin-film hydration technique and non-ionic surfactants (Span 60 & cholesterol). Pre-formulation studies verified that the drug was compatible with the chosen excipients, guaranteeing that there would be no major interactions, and they optimized the vesicle size, zeta potential, and encapsulation efficiency. In order to promote quick drug absorption through the sublingual mucosa, these niosomes were subsequently added to sublingual films made using biocompatible polymers. When compared to conventional formulations, the formulated films showed a significantly higher drug release profile, confirming the hybrid drug delivery system's potential to improve bioavailability. The films were characterized for thickness, weight variation, disintegration time, folding endurance, and in-vitro drug release behavior. The findings demonstrate that niosomal sublingual films offer a viable strategy for boosting Prazosin HCl's therapeutic effectiveness by offering a non-invasive, patient-friendly substitute with enhanced bioavailability and a quick beginning of action.

KEYWORDS: Prazosin hydrochloride, Antihypertensive, Span 60, Cholesterol, Niosomal film.

1. INTRODUCTION

One of the main causes of premature death globally and a substantial risk factor for cardiovascular disease is hypertension. Due to its lack of obvious signs, it is frequently referred to as the "silent killer" and causes over 9.4 million deaths annually.[1] The World Health Organization (WHO) reports that the prevalence of hypertension is lower in the United States at 35%, whereas it is higher in Africa, where 46% of persons aged 25 and over suffer from the condition.[2]

Prazosin, initially developed as a centrally acting α1-adrenergic receptor antagonist for managing hypertension, was later recognized for its effectiveness in alleviating trauma-related nightmares and enhancing sleep quality in individuals with PTSD.[3],[4]

Microscopic, lamellar structures called niosomes are made up of cholesterol and non-ionic surfactants that have been hydrated in an aqueous solution. Depending on how they are prepared, these bilayered vesicles can be either unilamellar or multilamellar. The stability and affordability of niosomes make them a popular choice over liposomes. They are a promising drug delivery system that can be used parenterally, topically, or in ophthalmic applications.[5] The ether injection method, thin film hydration (handshaking method), sonication, micro fluidization, multiple membrane extrusion, reverse-phase evaporation, transmembrane pH gradient (remote loading), and the "Bubble" method are some of the methods that can be used to create niosomes.[6]

The kind of surfactant, medication choice and concentration, charge, cholesterol content, osmotic stress resistance, and membrane composition are some of the variables that affect niosomal formulations. Therapeutic drugs are delivered to their target site via niosomes, which are drug carriers made of non-ionic surfactant vesicles.[7],[8] They usually have an aqueous phase enclosed in a well-structured bilayer of non-ionic surfactant, either with or without cholesterol and dicetyl phosphate, and range in size from 10 to 1000 nm. Both hydrophilic and hydrophobic medications can be entrapped by these vesicles.[9] Because of their non-ionic nature, low toxicity, biodegradability, improved drug availability at the target site, and superior intrinsic penetrating ability, niosomes are preferred over other vesicular systems.[10],[11]

Fast dissolving sublingual films

In order to improve absorption and overcome the drawbacks of conventional oral dose forms, sublingual films have been created, which will maximize therapeutic results. Because of their versatility, fast-dissolving sublingual films are the most sophisticated solid dosage type. They are more effective than orally disintegrating tablets because they dissolve quickly in the oral cavity with little contact with saliva, increasing the potency of the active pharmaceutical ingredient (API).[12],[13]

A quick onset of pharmacological activity is the goal of the sublingual route for systemic medication delivery. All age groups are concerned about swallowing problems (dysphagia), but older people, children, people with mental disabilities, people who are recalcitrant, people who are sick, or people who are on a restricted liquid intake are especially at risk.[14],[15] By putting the drug under the tongue, it can enter the bloodstream through the floor of the mouth and the ventral surface of the tongue. This is known as sublingual drug administration. The reticulated vein beneath the mouth mucosa is where the medication solutes are rapidly absorbed. From there, they are carried into the systemic circulation by the internal jugular vein, brachiocephalic vein, and facial veins.[16]

The main way that drugs are absorbed through the oral mucosa is by passive diffusion into the lipoidal membrane. Second only to hypodermic injection, the sublingual method has an absorption rate that is three to ten times greater than the oral route. For these formulations, a tiny quantity of saliva is usually enough to cause the tablet to dissolve in the oral cavity.[17],[18]

2. MATERIALS AND METHODS

2.1 Materials

Onex Life Science in (Chennai) provided a complimentary sample of prazosin hydrochloride. Loba Chemie PVT LTD in (Mumbai) is the source of hydroxypropyl methyl cellulose, Polyethylene Glycol 400, Span 60, cholesterol, and microcrystalline cellulose. High- performance liquid chromatography (HPLC) grade methanol was used. Every other solvent and reagent were of analytical reagent quality.

2.2 Preparation of stock solution

A standard stock solution (100µg/ml) was prepared by dissolving 10mg of Prazosin hydrochloride in 100 ml of methanol to obtain a standard stock solution (100µg/ml).

Preparation of working standard solution

From Standard stock solution (100µg/ml) take 1ml and dilute to 10ml of methanol to get 10µg/ml. From 10µg/ml – serial dilutions of 1ml…….5ml (concentration – 1 µg/ml……5 µg/ml)

Determination of wavelength

The wavelength was determined for 1µg/ml concentration in the range of 200 to 400nm in UV spectrophotometer using methanol as blank. The absorption maximum was found to be 251nm.

Instrument used

UV-Visible spectrophotometer – Jasco V 730

Construction of calibration curve for drug

The concentrations 1, 2, 3, 4, and 5 µg/ml were obtained by transferring aliquots of the working standard solution of prazosin hydrochloride (1µg/ml) 1, 2, 3, 4, and 5 ml into a series of 10 ml volumetric flasks and make up the volume with methanol. Methanol is used as a blank, the absorbance of each solution was measured at 251 nm. Plotting the corresponding absorbance against concentration in µg/ml produced the calibration curve.

2.3 Compatibility Studies

IR spectroscopy can be used to analyse and predictions of physio-chemical interactions between different components in a formulation. It can be applied to the selection of suitable chemically compatible excipients. The aim of present study was to test whether there is any interaction between the polymer & drug. The IR spectroscopy was recorder for following compounds. Prazosin HCL, Span 60, Cholesterol, HPMC, MCC.

The compatibility of the medication with the polymers was investigated using FT-IR spectroscopy. To create a clear pellet, weighed amounts of the medication and polymer were combined with potassium bromide (dried at 40–50 degrees Celsius) in a 1:10 ratio. The mixture was then compressed in a hydraulic press for 30 minutes at 10-ton pressure. The pellet was placed in the sample holder and scanned in the Jasco V 530 FT-IR Spectrophotometer between 4000 and 400 cm-1. It was then contrasted with the initial spectrum. IR spectra were compared and examined for functional group non-involvement and any shifting of functional peaks.

2.4 Preparation of Prazosin hydrochloride loaded niosomes

Thin film hydration was used to create niosomes filled with prazosin hydrochloride. In a round- bottom flask, 10 milliliters of a 2:1 v/v chloroform and methanol mixture were used to dissolve span 60 and cholesterol in various concentrations. Before being introduced to the surfactant combination, 120 mg of prazosin hydrochloride was separately dissolved in 5 ml of a 2:1 v/v chloroform and methanol mixture. In a rotary evaporator set at 120 rpm and vacuumed at 40°C, the solvents were evaporated until a thin, smooth layer developed on the flask wall.[16]

The surfactant film was hydrated using 10 ml of distilled water at 60°C ± 2°C with mechanical agitation to create a niosomal suspension after the volatile solvents had been completely removed. Multilamellar niosomes were formed by sonicating the resultant niosomal suspension for five to ten minutes. The resulting niosomal

suspension was refrigerated for future research after being allowed to mature overnight at 2°C to 8°C. [12]

2.5 Evaluation of Niosomes

1. Determination of Entrapment Efficiency (EE)

Centrifugation at 5,000 rpm for 60 minutes was used to separate the prazosin hydrochloride- containing niosomes from the free drug. After each separation, the supernatant was measured using spectrophotometry at 251 nm. By deducting the amount of free drug from the overall amount of drug, the amount of entrapped drug was determined. Equation was then used to get the entrapment efficiency (EE%) percentage.

EE% = Amount of entrapped drug / Total drug amount ×100

2. Particle sizes determination

A Malvern Instruments dynamic light scattering laser was used to quantify the generated niosomes dispersion's mean particle size (nm) and polydispersity index. Better drug penetration and absorption are guaranteed by niosomes that are smaller (<500 nm).

Zeta potential determination

Using the same Malvern Instruments, photon correlation spectroscopy was used to determine the associated zeta potentials (mV). By measuring the surface charge of niosomes, zeta potential establishes stability; for optimal stability, it should be between +/-20 and 30 mV.

3. Scanning electron microscopy (SEM)

Shape, size, and surface morphology were assessed using scanning electron microscopy. Various magnification powers are used to capture SEM micrographs. Surface morphology aids in the disintegration and release of the therapeutic substance from the matrix of the microsphere and is crucial for media absorption at the intended location.

2.6 Preparation of Fast dissolving niosomal films

Solvent casting was used to create fast-dissolving films. HPMC were employed as polymers for film formation. As a plasticizer, polyethylene glycol 400 was employed. Avicel, or microcrystalline cellulose, was employed as a super disintegrant.

Following levigation with the necessary volume of the plasticizer, the calculated amount of super disintegrant was added to the polymeric solutions after the specified weight of the film-forming polymer had first been dissolved in 20 mL of the casting solvent (warm distilled water). Prior to adding the super disintegrant, the necessary quantity of prazosin hydrochloride was introduced straight to the polymeric solution and thoroughly dissolved in order to create medicated films (which include free drug).[16]

The chosen polymeric solution was carefully combined with a predetermined amount of the chosen niosomal dispersion (which corresponded to the necessary dosage of prazosin hydrochloride) to create the niosomal film. Distilled water was used to bring the final volume down to 25 mL. A magnetic stirrer was used to gently agitate the casting fluid for two hours.[12] A Petri dish was filled with 25 mL of the casting solution. The film was taken out of the Petri dish and left to dry in a desiccator for at least 48 hours prior to examination after the solvent had evaporated for 72 hours.

2.7 Evaluation of fast dissolving films

Physical appearance

The physical appearance was checked with texture and visual inspection of film.

Thickness

At various points throughout each formulation, thickness was measured using a micrometre screw gauge, and the mean values were computed.

Weight variation

Ten randomly chosen 4 cm2 patches for each formulation (made in separate batches) were weighed individually in order to investigate weight variance using an electronic analytical balance.

Disintegration time

In vitro disintegration time test was determined visually in a Petri dish containing 25 mL of phosphate buffer (pH 6.8) gently agitate every 10 seconds. The disintegration time is the time recorded when the film starts to shatter or disintegrate.

Folding Endurance

Folding endurance was determined by repeated folding of the film at the same location till the strip breaks. The number of times the film is folded without breaking was determined as the folding endurance value.

In-vitro drug release studies

After removing the previously produced film from the plate, it was sliced into a 4 cm2 piece and weighed using an analytical balance. Prazosin hydrochloride was released from the produced films using the beaker method in beakers with 100 mL of phosphate buffer at pH 6.8. A shaking water bath with 370C and 50 rpm was used to hold the beakers. At predetermined intervals, 1 mL of samples were taken out, centrifuged, and the supernatant was filtered and examined with a UV-visible at 251 nm. Samples were replaced by equal quantities of new buffer to maintain the same volume in the flasks. Three duplicates of the experiment were carried out. Each time interval's medication release amount was computed.

3. RESULTS AND DISCUSSION

3.1 Description of prazosin hydrochloride

Table 1: Appearance of Prazosin HCL.

S.NO	DESCRIPTION	OBSERVATION
1	Colour	White
2	Oduor	Odorless
3	Nature	Crystalline

3.2 Solubility of the drug

Table 2: Solubility of Prazosin HCL.

DRUG	SOLUBILITY
Prazosin hydrochloride	Freely soluble (methanol)
	Sparingly soluble (ethanol)
	Insoluble (water)

3.3 Pre-formulation and Compatibility Studies

FT-IR spectra confirmed the absence of interactions between drug and excipients.

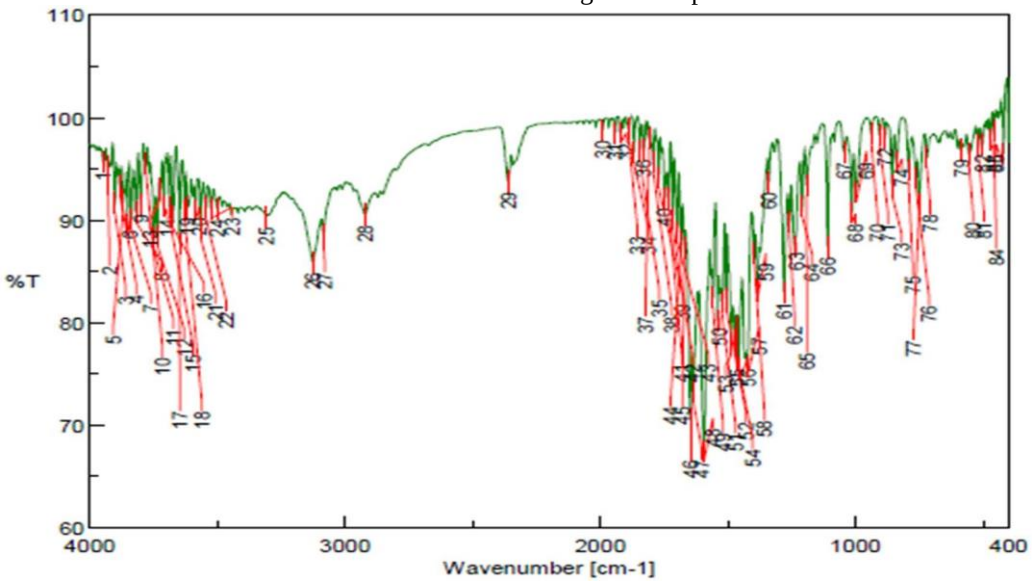

Figure 1: FTIR spectrum of prazosin hydrochloride.

Table 3: IR spectrum analysis.

S.no	Functional group	Type of vibration	Test absorption (cm^{-1})
1	N-H	Stretching	3309.25 cm^{-1}
2	C-H	Stretching	3126.04 cm^{-1}
3	C≡N	Stretching	2360.44 cm^{-1}
4	C=O (Ketone)	Stretching	1732.73 cm^{-1}
5	C=C	Stretching	1593.88 cm^{-1}
6	C-N	Stretching	1279.54 cm^{-1}
7	C-O	Stretching	1190.83 cm^{-1}

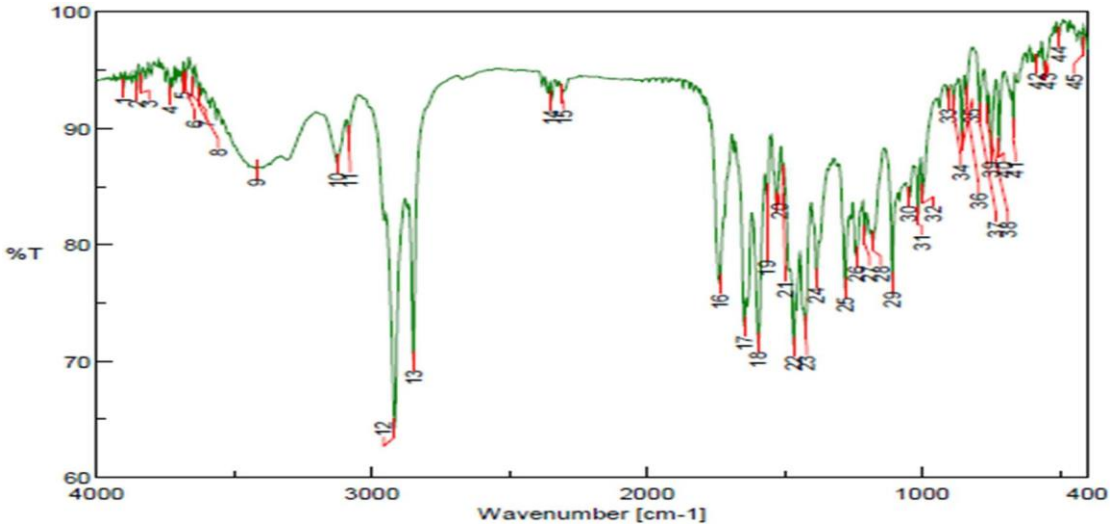

Figure 2: FTIR spectrum of Prazosin HCL +Span60.

Table 4: IR spectrum analysis.

S.no	Functional group	Type of vibration	Test absorption (cm^{-1})
1	N-H	Stretching	3126.04 cm^{-1}
2	C-H	Stretching	3084.58 cm^{-1}
3	C≡N	Stretching	2347.91 cm^{-1}
4	C=O (Ketone)	Stretching	1735.62 cm^{-1}
5	C=C	Stretching	1595.81 cm^{-1}
6	C-N	Stretching	1280.50 cm^{-1}
7	C-O	Stretching	1209.15 cm^{-1}

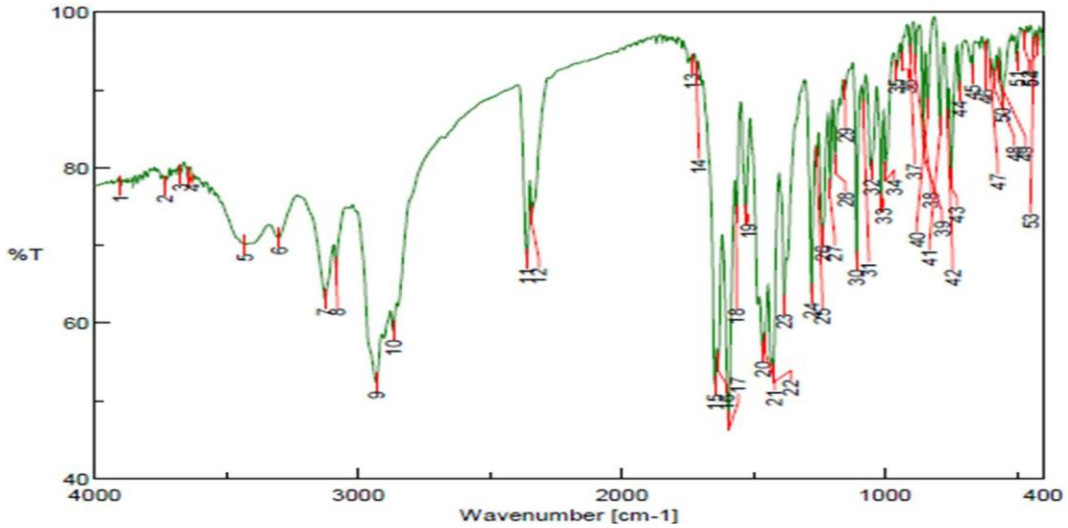

Figure 3: Prazosin HCL + Cholesterol.

Table 5: IR spectrum analysis.

S.no	Functional group	Type of vibration	Test absorption (cm^{-1})
1	N-H	Stretching	3126.04 cm^{-1}
2	C-H	Stretching	3084.58 cm^{-1}
3	C≡N	Stretching	2360.44 cm^{-1}
4	C=O (Ketone)	Stretching	1733.69 cm^{-1}
5	C=C	Stretching	1594.84 cm^{-1}
6	C-N	Stretching	1279.54 cm^{-1}
7	C-O	Stretching	1190.83 cm^{-1}

3.4 UV Spectroscopy

λmax of Prazosin HCl was found at 251 nm. A standard curve was established between 1–5 µg/mL with linear absorbance.

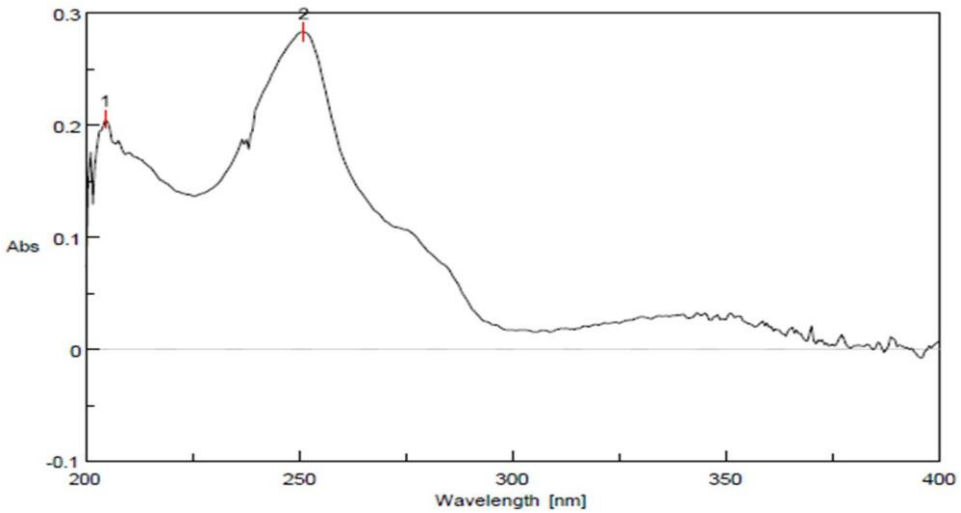

Figure 4: UV spectrum of Prazosin HCL Standard graph of prazosin hydrochloride.

The concentrations 1, 2, 3, 4, and 5 µg/ml were obtained by transferring aliquots of the working standard solution of prazosin hydrochloride (1µg/ml) 1, 2, 3, 4, and 5 ml into a series of 10 ml volumetric flasks and adjusting the volume with methanol. Using methanol as a blank, the absorbance of each solution was measured at 251 nm. Plotting the corresponding absorbance against concentration in µg/ml produced the calibration curve. Correlation coefficient = 0.9989,

Table 6: Standard graph data of Prazosin HCL.

Concentration (µg/ml)	Absorbance (at 251nm)
1	0.2714
2	0.4632
3	0.6786
4	0.8881
5	1.0906

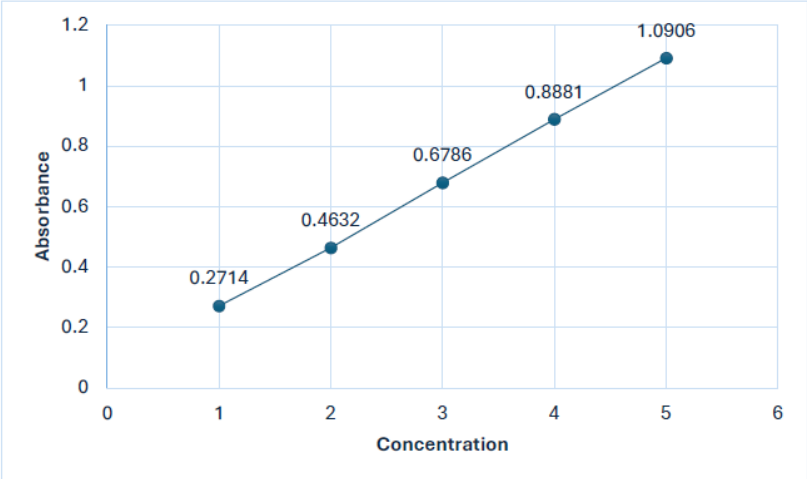

Figure 5: Standard curve of Prazosin HCl.

3.5 Evaluation of Niosomes Determination of Entrapment Efficiency

Centrifugation at 5,000 rpm for 60 minutes was used to separate the prazosin hydrochloride- containing niosomes from the free drug. After each separation, the supernatant was measured using spectrophotometry at 251 nm. By deducting the amount of free drug from the overall amount of drug, the amount of entrapped drug was determined. Equation was then used to get the entrapment efficiency (EE%) percentage.

EE% = Amount of entrapped drug / Total drug amount ×100

Table 7: %Entrapment efficiency for F1 to F8

Formulation	Drug (mg)	Span 60 (mg)	Cholesterol	EE%
F1	60	66.6	33.3	99.83
F2	80	66.6	33.3	99.87
F3	100	66.6	33.3	99.90
F4	120	66.6	33.3	99.92
F5	140	66.6	33.3	99.92
F6	100	99.9	33.3	99.89
F7	100	99.9	66.6	99.88
F8	100	133.2	33.3	99.89

3.6 Zeta potential

The zeta potentials (mV) were determined by photon correlation spectroscopy by using the Malvern Instruments. Zeta potential determines **stability** by measuring the surface charge of niosomes, 25.4 mV ensure good stability).

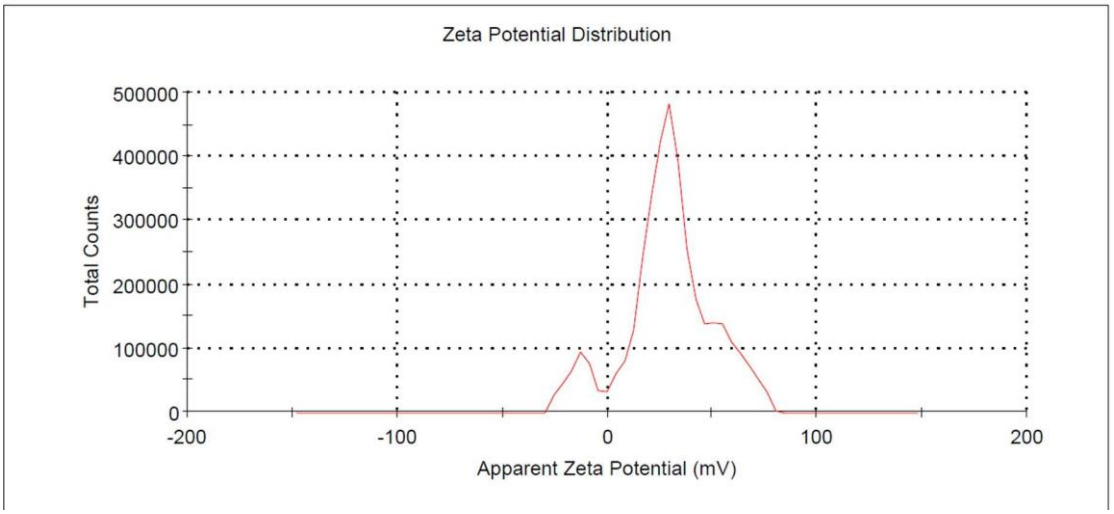

Figure 6: Zeta potential result.

3.7 Particle Size

The particle size (nm) and polydispersity index (PDI) of the prepared Prazosin HCL niosomes dispersion were measured by dynamic light scattering laser by using a Malvern Instruments Smaller niosomes (288.9 nm) ensure better drug penetration and absorption.

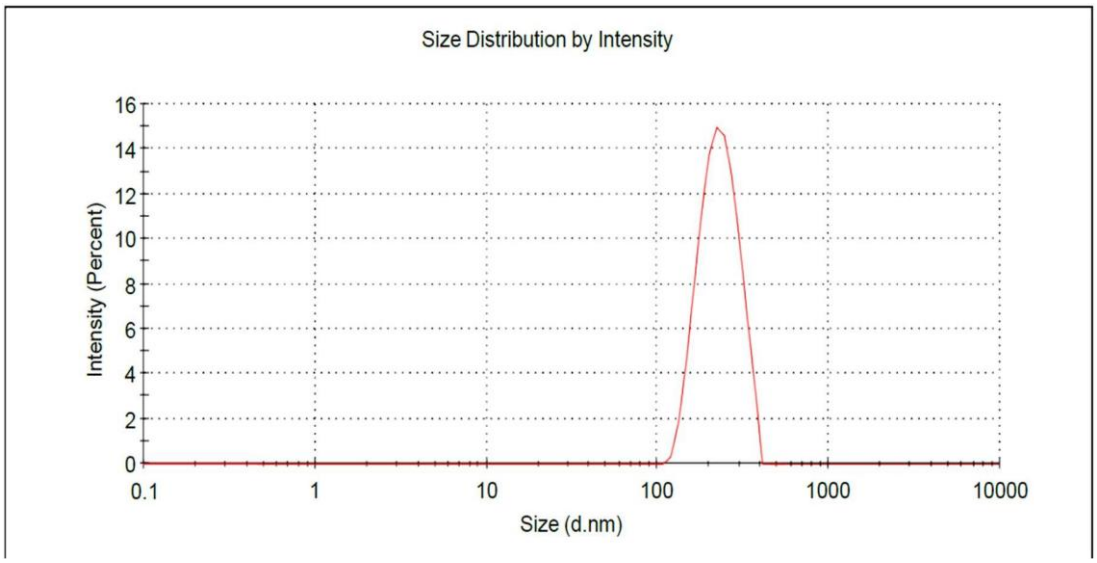

Figure 7: Particle size result.

3.8 Scanning Electron Microscopy

Shape, size, and surface morphology were assessed using scanning electron microscopy. Various magnification powers are used to capture SEM micrographs. Surface morphology aids in the disintegration and release of the therapeutic substance from the matrix of the microsphere and is crucial for media absorption at the intended location, slight rough surface was observed in the SEM image, and no aggregates were formed.

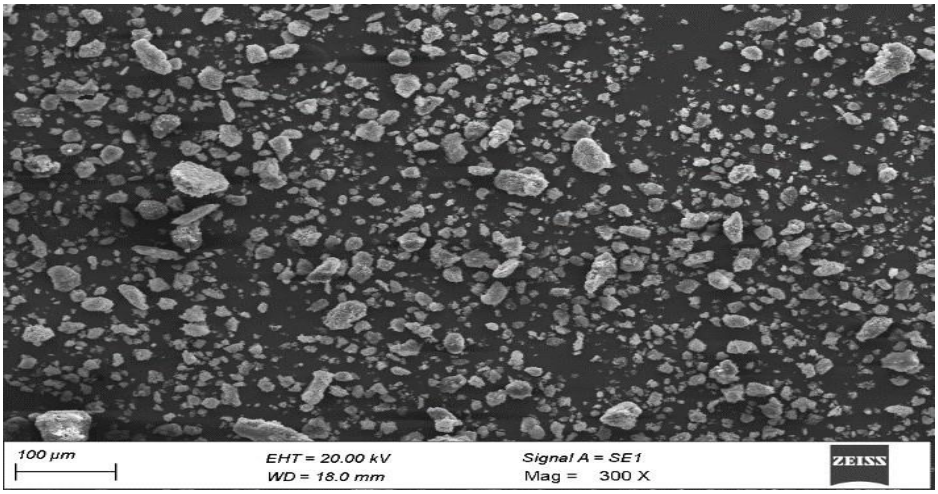

Figure 8: Scanning electron microscope.

3.9 Evaluation of Niosomal Films.

Table 8: Results of evaluation parameters of F1 to F4.

Formulation	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Disintegration time (sec)
F1	0.20 mm	60	>300 folds	90
F2	0.16 mm	51	>250 folds	24
F3	0.19 mm	56	>300 folds	85
F4	0.14 mm	49	>100 folds	24

Table 9: Result of %drug release of F2.

Time(min)	Cumulative Drug Release	%Drug Release
0.3	0.1042	53.40%
1	0.1305	78.50%
2	0.1455	92.80%
3	0.1478	95.40%
4	0.1491	96.30%
5	0.1501	97.20%

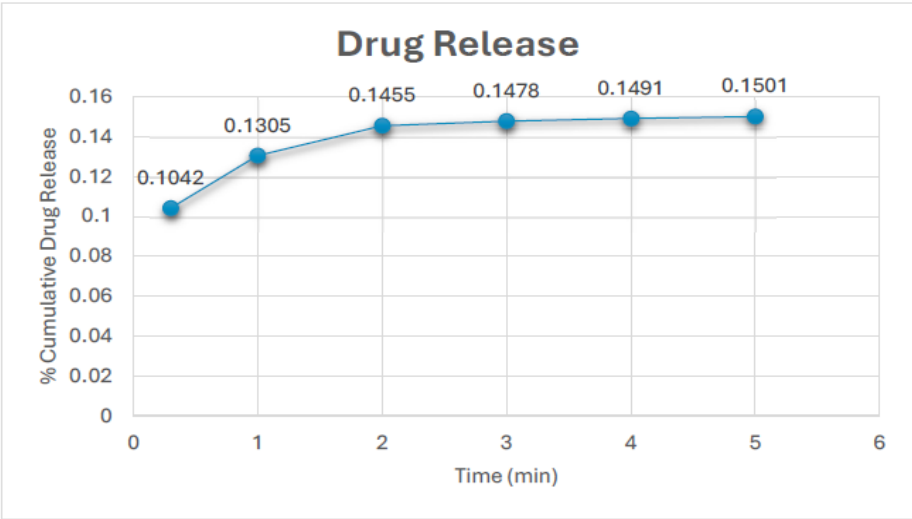

Figure 9: Result of % cumulative drug release of F2.

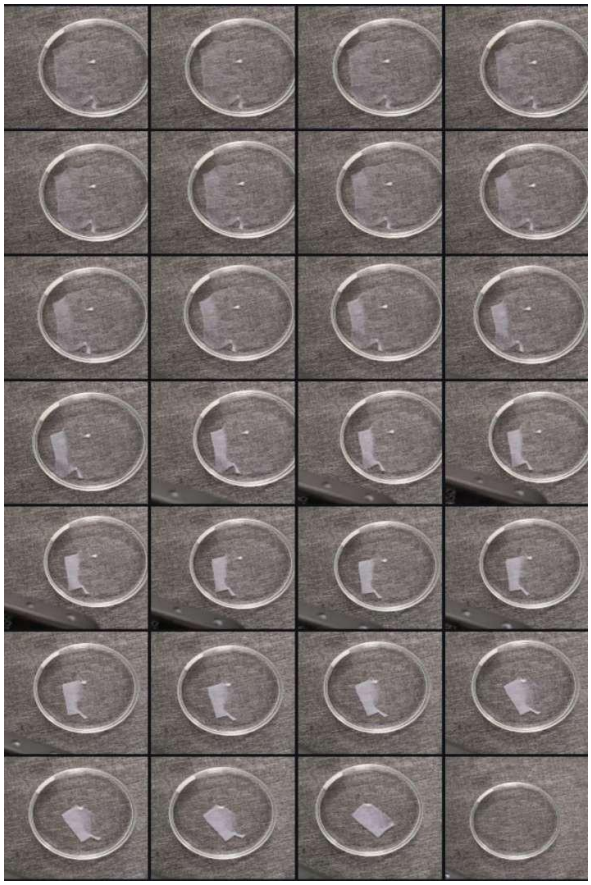

Figure 10: Result of Disintegration of sublingual film.

3.10Discussion of Fast dissolving sublingual films

Physical appearance: All the sublingual films were visually inspected for colour, clarity, flexibility.

a. Weight of the film

Films (2x2 cm2) coated with drugs were examined for weight homogeneity. The films were discovered to be consistent. The film's average weight was determined to be between 51 ± 1.00 and 56 ± 1.20 mg. The patch's weight grew in tandem with the polymer content.

b. Thickness of the film

The thickness of each film is consistent throughout. It was determined that the average thickness was between 0.14 ± 0.005 and 0.19 ± 0.010 mm. The patch gets thicker as the amount of polymeric material rises.

c. Folding endurance

Folding endurance gauges a film's resistance to rupture. Even after folding more than 300 times, the patch showed no signs of cracking. It was therefore regarded as the conclusion.

d. Disintegration time

The disintegration time ranged from 24 ± 2 to 45 ± 3 seconds on average. Higher viscosity and film strength caused the disintegration time to increase in tandem with the polymer concentration.

e. *IN-VITRO* drug release

The movies have a profile of quick release. Within 5 to 10 minutes, the cumulative drug release was determined to be between 85.0 ± 2.5% and 98.5 ± 1.8%. The creation of a denser polymer matrix, which regulated the drug's diffusion, caused the drug release rate to drop as the polymer content rose.

4. SUMMARY AND CONCLUSION

Niosomes were prepared and evaluated for their abilities to enhance bioavailability of Prazosin hydrochloride, as compared to administration of oral tablets. FTIR Studies revealed that excipients were compatible with the drug. Pre-formulation study for the drug surfactant compatibility by FTIR gave conformation about their purity and showed no interaction between drug and selected surfactant various formulations were developed by using non-ionic surfactants (cholesterol, span 60) these are thin film hydration. Developed niosomes were evaluated for size and shape, surface morphology, drug entrapment efficiency. It was concluded that, Prazosin hydrochloride was successfully encapsulated into niosomes. Prazosin HCL was first entrapped in different niosomal formulations, and drug-loaded niosomes with small size, low polydispersity, and high EE were selected for incorporation into different fast dissolving films, which were then evaluated for different physical characteristics, folding endurance, weight variation, In vitro characterizations of the drug-loaded films were performed. 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 Prazosin HCL, thus improving the patient compliance by eliminating the need for frequent dosing of the drug.

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