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FORMULATION AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM LOADED BUCCAL FILM OF BCS CLASS II DRUG

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ABSTRACT

The pharmaceutical industry faces significant challenges in drug development, with approximately 40% of new drugs exhibiting low solubility, leading to challenges in achieving adequate bioavailability. One such drug affected by this issue is Darifenacin Hydrobromide (DH), an Anti-muscarinic agent crucial for treating conditions like Overactive Bladder and frequent urination. Despite its therapeutic potential, DH's oral administration suffers from poor bioavailability due to its inherently lipophilic nature and susceptibility to extensive first-pass metabolism. Utilizing a regular 2^3 Full Factorial Design, we investigated the influence of formulation variables, including the concentrations of HPMC E4M, PVA, and Glycerol, on critical parameters such as disintegration time and % drug content. This systematic approach allows us to develop an optimized oral film, designated as L_STF-9, which exhibits superior characteristics in terms of thickness, folding endurance, and in-vitro drug release performance. The culmination of our research efforts yields promising results, demonstrating the successful formulation of DH-LSEDDS and its integration into buccal films. By circumventing hepatic first- pass metabolism, our approach not only enhances DH solubility but also improves its dissolution profile, patient compliance, and safety. This innovative drug delivery strategy holds considerable potential for addressing the challenges associated with low solubility drugs, paving the way for the development of more effective pharmaceutical formulations.

KEYWORDS: Self emulsifying drug delivery system, Darifenacin hydrobromide, Full factorial design, Buccal film.

1. INTRODUCTION

1.1 SELF EMULSIFYING DRUG DELIVERY SYSTEM {SEDDS}

The self-emulsifying drug delivery system (SEDDS) emerges as a promising strategy for enhancing solubility in pharmaceutical formulations. Approximately 40% of drug candidates fall into the Biopharmaceutical Classification System (BCS) Class II category, characterized by low solubility and high permeability. Due to their high lipophilic nature, these drugs often exhibit decreased solubility. SEDDS offer a solution by increasing the solubility and bioavailability of poorly soluble drugs. SEDDS formulations consist of an isotropic mixture of oil, surfactants, and co-solvents, which rapidly form fine oil-in-water emulsions upon exposure to aqueous media under conditions mimicking gentle agitation or digestive motility encountered in the gastrointestinal tract (GIT).[1][2][3]

1.2 MECHANISM OF SELF EMULSIFICATION

Self-emulsification occurs when the entropy shift supporting dispersion surpasses the energy needed to expand the surface area of the dispersion. In a traditional emulsion formulation, the free energy is directly influenced by the energy necessary to establish a new surface boundary between the oil and water phases and can be described by following equation

$$\Delta G = \sum N_i \prod r_i^2 \sigma$$

Where ‘n’ is the free energy associated with the process, ‘N’ is the number of droplets, ‘r’ is the radius of the droplets, ‘s’ is the interfacial energy.[4][5]

1.3 OVERACTIVE BLADDER

Overactive bladder (OAB) manifests as a sense of urgency to urinate, sometimes accompanied by leakage, increased frequency, and night time awakenings to urinate. A "stable" bladder denotes the ability to tolerate increasing urine volumes without involuntary contractions of the bladder muscle. Around urinary bladder, there are two types of muscarinic acetylcholine receptors M2 and M3. M3 receptors are specifically involved in the contraction of detrusor muscle when bladder is filled with urine. Normal bladder function allows for gradual filling during the storage phase with minimal pressure changes. Sensory signals from the bladder inform the brain's micturition center when it's about half full, triggering the sensation of needing to urinate at around 75% capacity. In OAB, even when the bladder isn't substantially filled, acetylcholine stimulates receptors leading to detrusor muscle contraction

and frequent urination. Involuntary contractions typically occur at volumes exceeding 200 ml but can happen at any level of bladder filling.[6][7]

Fig no. 1.1: Schematic representation of Normal Bladder V/s Overactive Bladder.

1.4 NEED OF THIS STUDY

The significance of this study lies in addressing the persistent challenge of low solubility among BCS class II drugs, exemplified by Darifenacin hydrobromide (DH), a crucial treatment for overactive bladder symptoms such as urinary incontinence and frequent urination. . This research focuses on developing a Self Emulsifying Drug Delivery System (SEDDS), which is renowned for its ability to significantly enhance the solubility of lipophilic drugs, thereby improving their absorption through the oral route and potentially increasing therapeutic efficacy. By optimizing DH delivery through SEDDS in buccal films, this study aims to maximize therapeutic outcomes, offering a promising alternative for managing overactive bladder conditions effectively.

1.5 OBJECTIVES

1. Preformulation studies of DH to assess its physical and chemical properties.
2. Formulation, development and Optimization, Characterization and Evaluation of Darifenacin hydrobromide (DH) Liquid SEDDS loaded fast dissolving Buccal films using various concentrations of water-soluble polymers and plasticizer incorporating Optimized DH-loaded Liquid SEDDS.
3. To formulate a Solid Self Emulsifying Drug Delivery System (S-SEDDS) of Optimized Liquid SEDDS and assess the solubility of Darifenacin hydrobromide (DH), comparing it with the solubility of the pure drug in various solvents
4. To optimize the buccal film formulation using Response Surface Methodology (design of experiments approach).
5. In-vitro dissolution testing and study the release kinetics of DH.
6. Stability studies on the optimized DH Self Emulsifying Buccal Film (SEBF) formulation.

1.6 REVIEW OF LITERATURE

RESEARCH WORK DONE ON DARIFENACIN HYDROBROMIDE

Ishraq K. Abbas et al., (2019) developed and assessed the effectiveness of fast-dissolving buccal films (FDBF) containing Darifenacin hydrobromide for treating Overactive Bladder (OAB).

K. Latha et al., (2017) formulated and evaluated Darifenacin hydrobromide-loaded nano-liposomes for prolonged drug release. Compatibility studies confirmed no interactions between the drug and excipients.

G. Venkata Sudarsan et al., (2017) aimed to develop an extended-release formulation of Darifenacin hydrobromide using a multiparticulate drug delivery system (MUPS) to improve consistency in gastrointestinal transit time.

2. MATERIAL AND METHODOLOGY

2.1 Pre-formulation studies

a) Characterization study

a) General appearance

b) Melting point determination

c) Identification by FTIR

b) Compatibility studies between Drug and excipients.

a) FTIR spectroscope

2.2 Analytical study of drug.

a) Determination of λmax of Darifenacin hydrobromide.

b) Calibration curve of Darifenacin hydrobromide.

Selection of solvents in formulation of SEDDS.

a) Solubility studies for oils, surfactants and co-solvents.

b) Screening of surfactants

c) Screening of Co-solvents.

Conducting stability studies on the optimized buccal film (LsTF-9).

2.3 LIST OF EQUIPMENTS, MATERIALS AND REAGENTS

All materials, including DH and excipients, were supplied by their respective providers and

used as received without additional purification.

2.4 Preformulation involves studying the physical and chemical properties of a drug that could impact its performance before the compounding process begins.

2.4.1 IDENTIFICATION TEST

2.4.2 General Appearance: The DH powder was examined for physical appearance such as colour and texture.

2.4.3 Melting Point

The melting point of DH powder was assessed by filling the drug into a capillary sealed at one end and placing it into a melting point apparatus. The average melting point was determined based on three samples.[10][11]

2.4.4 FT-IR studies

Pure DH was subjected to Fourier transform Infrared for its characterization. The spectrum was obtained by scanning the samples at 4000-400 cm^{-1}.

2.4.5 COMPATIBILITY STUDIES

Fourier transform infrared analysis was employed to examine changes in characteristic peaks by scanning samples within the range of 4000-400 cm^{-1}.

2.4.6 FTIR Spectroscopy analysis

The infrared spectra of pure DH and the physical mixtures of DH with excipients used in formulating SEDDS (such as sunflower oil, Tween 20, and ethanol) and in preparing liquid SEDDS-loaded buccal films (such as HPMC E4M and PVA) were recorded separately using an FTIR spectrophotometer.[11][12]

2.4.7 FORMULATION OF SEDDS

The drug, accurately weighed, is added to a beaker containing the predetermined amount of oil. The beaker is then placed in a water bath at 40-45°C until the drug completely dissolves. Subsequently, the surfactant and co-solvent are added to the beaker, and the solution is stirred at 200 rpm until a homogeneous mixture is achieved. The solution is then allowed to cool to room temperature and observed for any signs of phase separation. It is then ready for further use in subsequent steps of the formulation process.

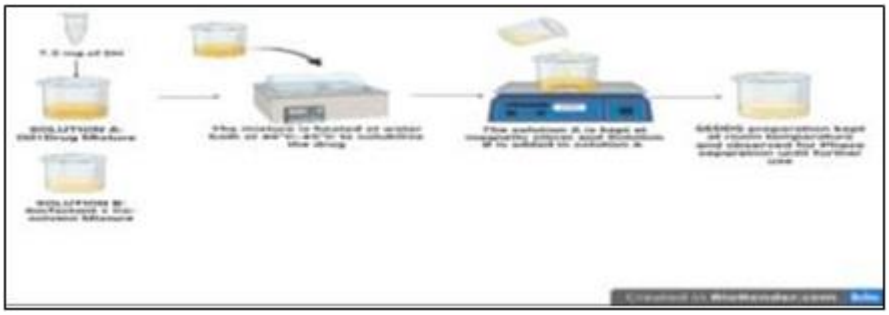

Fig no 2.1: Schematic representation of Formulation of SEDDS.

2.5 EVALUATORY TEST

2.5.1.1 pH of the Solution

The pH meter was used to measure the pH of the solution for buccal delivery of film.[13]

2.5.1.2 Particle Size Analysis & Polydispersity Index

Droplet size analysis and polydispersity index were conducted using a Malvern Particle Size analyzer. The solution was diluted 100 times with distilled water before measurements. The analysis was performed in triplicate, and the results are presented as mean size ± standard deviation (SD).[14][15]

2.5.1.3 Zeta Potential Measurement

Zeta potential determination of the liquid was performed using Dynamic Light Scattering after dilution with distilled water. The measurements were conducted in triplicate, and the results are presented as mean ± SD.[16][17]

2.5.1.4 Self-Emulsification Time

The self-emulsification time was determined using a USP Dissolution Apparatus II. The temperature of the water bath was maintained at 37 ± 0.5°C, and the dissolution vessel was filled with 500 ml of distilled water. The apparatus was set to rotate at 50 rpm to provide gentle agitation, and the time taken for self-emulsification was recorded. The observations could be:

Grade A: Rapid forming Clear/bluish appearance

Grade B: less clear emulsion /bluish appearance

Grade C: Fine milky emulsion that is formed within 2 min.

2.5.1.5 Optical Clarity

The SEDDS were diluted with distilled water, and the absorbance of the diluted SEDDS was measured at three time points: 0 h, 12 h, and 24 h, indicating the stability of the droplets over

time.

2.5.1.6 Thermodynamic Stability Studies

The thermodynamic stability studies were conducted at 3 stages

2.5.1.6.1 Robustness to dilution

One drop of the prepared SEDDS formulation was diluted with 50 ml of distilled water and phosphate buffer of pH 6.8. The dilutions were observed for any signs of phase separation.

2.5.1.6.2 Centrifugation test

In this test, the diluted SEDDS formulations were centrifuged at 6000 rpm for 15 min. The solution is observed for phase separation and turbidity.

2.5.1.6.3 Freeze thaw Stress test

The freeze thaw cycles are usually performed to check the effect of elevated temperatures.3 cycles of freeze-thaw were executed at 3ºC, room temperature and +40ºC. Each formulation was stored at each temperature for a minimum of 48 hours, and its stability was observed.

2.6 OPTIMIZATION OF ORAL FILM USING DoE

A 2^3 factorial design was employed to optimize the composition of an oral film. Combinations of two hydrophilic polymers were used in the formulation. The independent variables were the concentrations of hydrophilic polymer (HPMC E4M), second hydrophilic polymer (PVA), and plasticizer (Glycerol). The films were formulated and evaluated based on two dependent variables: disintegration time and in-vitro drug release. A total of 8 experimental runs were conducted. Using the data from these variables, the system generated the formula for the optimized oral film (L_STF-9).

2.6.1 FORMULATION OF PURE DRUG SUSPENSION ORAL FILM

The preparation of Darifenacin hydrobromide oral film suspension began with soaking HPMC E4M and polyvinyl alcohol separately in distilled water overnight. After hydration, all required excipients were added to the polymer solutions, followed by thorough stirring for 2 hours to ensure homogeneity. Dropwise addition of the Darifenacin hydrobromide drug solution into the polymeric mixture facilitated uniform distribution. The resulting suspension was then poured into a petri dish and dried in an oven to remove the solvent, yielding a pure drug suspension film. This film, serving as the control sample, is crucial for subsequent studies to evaluate drug release characteristics and ensure formulation consistency and efficacy. [18]

2.6.2 FORMULATION OF DARIFENACIN HYDROBROMIDE LIQUID SELF EMULSIFYING DRUG DELIVERY SYSTEM LOADED ORAL FILM

As per the 8 runs generated by the Design of Experiments (DoE) software, DH-LSEDDS-loaded oral films (L_STF-1 to L_STF-8) were prepared using the solvent casting method, Polymers HPMC E4M and polyvinyl alcohol were soaked overnight in 10 ml of distilled water. Glycerol, sodium starch glycolate (25 mg), citric acid anhydrous (20 mg), and dextrose (20 mg) were added in suitable quantities of ethanol, and this solution was added to the polymeric solution. The mixture was stirred at 200 rpm on a magnetic stirrer for 1 h. After 1 h, an accurately weighed quantity of DH-LSEDDS equivalent to 7.5 mg of the drug per 2 x 2 cm^2 oral film was added and stirred for another hour to ensure uniform distribution. The resulting casting solution was allowed to stand for 10 min to remove air bubbles. Finally, the solution was poured into a petri plate and dried overnight at 60ºC in a hot air oven. The dried film was then cut into suitable sizes for evaluation tests.

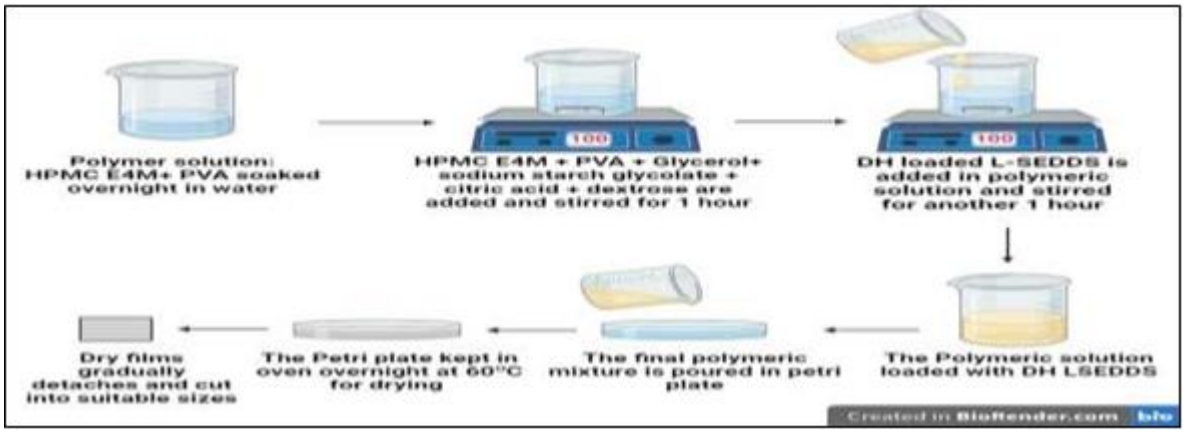

Fig no. 2.2: Schematic representation of preparation of liquid SEDDS loaded oral fil.

3. RESULTS AND DISCUSSIONS

3.1 OPTIMIZED FORMULA FOR DH-LSEDDS LOADED BUCCAL FILM

The system generated an optimized formula (LsTF-9) for Darifenacin hydrobromide Liquid SEDDS loaded buccal film using statistical modelling and a desirability factor with 95% confidence. Subsequently, the optimized Darifenacin hydrobromide SEOF (LsTF-9) was formulated, and its performance was evaluated based on the dependent variables, Disintegration time and % Drug Content. The results were assessed against the upper and lower response limits defined by the system to ensure they meet predefined criteria for efficacy and consistency.

3.1.1 re-formulation Studies

3.1.2 Physical Characterization of BM

3.1.3 Color - white powder

Odor- odorless

Melting point –227.33 ± 0.57735

Solubility – water = 0.0811 ± 0.0056

3.2 EVALUATION OF THE OPTIMIZED DH LIQUID SEDDS THIN FILM (LsTF-9)

3.2.1 ORGANOLEPTIC PROPERTIES. The DH liquid SEDDS loaded buccal film (LsTF- 9) exhibited a smooth, white appearance.

3.2.1.1 THICKNESS

The thickness of the DH SEDDS loaded buccal film was measured at three different locations on each film using Vernier caliper, with measurements taken in triplicate (n=3). The results showed a mean thickness of 0.197 ± 0.012 mm, indicating uniformity across the film.

3.2.1.2 WEIGHT VARIATION

The weight variation test is crucial for ensuring dosage consistency, which is essential for patient safety and acceptance of pharmaceutical products. Data is typically recorded in triplicate (n=3) to ensure accuracy and reliability. Upon analysis, the mean weight and standard deviation were calculated to be 43.26 ± 0.003 mg,

3.2.1.3 FOLDING ENDURANCE

The folding endurance test for the DH SEBF (Darifenacin hydrobromide Self-Emulsifying Buccal Film) was conducted in triplicate (n=3), yielding a mean value of 345.98 ± 5.05.

3.2.1.4 TENSILE STRENGTH

The tensile strength of the buccal film was measured in triplicate, yielding a mean value of 0.05 ± 0.0025 kg/cm².

3.2.1.5 PERCENT ELONGATION

The % elongation was measured in triplicate, with a mean value of 18.33 ± 7.637 %.

3.2.1.6 SURFACE pH

The optimized Darifenacin hydrobromide Self-Emulsifying Buccal Film (DH SEBF) was

found to have a pH of 7.2. This pH level aligns well with the physiological pH of the buccal mucosa, indicating that the film is well-suited for application in the oral cavity without adverse effects on mucosal integrity.

3.2.1.7 PERCENT MOISTURE LOSS

The percent moisture loss of the buccal film was measured over a span of 3 days and found to be 1.216 ± 0.610% (n=3), indicating its good stability.

3.2.1.8 DRUG CONTENT

Drug content testing, conducted in triplicate (n=3), and was found to have a measured drug content of 76.19 ± 4.620 %.

3.2.1.9 *IN VITRO* DISINTEGRATION TIME

The mean disintegration time was found to be 34 ± 3.60 s.

3.2.1.10 Identification by FTIR

The characterization study of drug Darifenacin hydrobromide (DH) was performed and spectrum was recorded using FTIR spectrophotometer at the range of 4000 - 400 cm^{-1}. All the characteristic peaks of DH are retained ensuring the purity of drug.

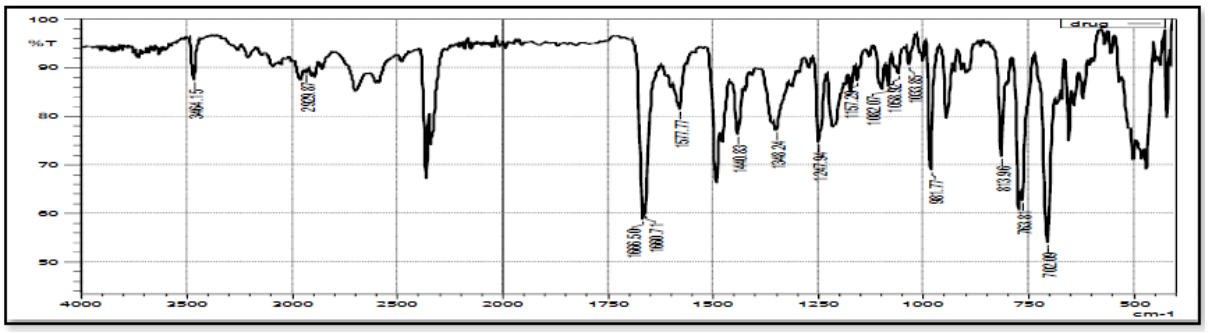

Fig no 3.1: FTIR spectrum of Darifenacin hydrobromide.

Table no 3.1: Characteristic peaks of drug Darifenacin hydrobromide.

Sr.no	Literature value peak	Type of peak	Observed peak
1	3500 – 3400 cm^{-1}	N-H asymmetric stretching of an amide group.	3464.15 cm^{-1}
2	3000 – 2840 cm^{-1}	C-H asymmetric, asymmetric stretching aliphatic methyl and methylene groups.	2929.87 cm^{-1}
3	1695-1630 cm^{-1}	C=O stretching of amide	1666.50 cm^{-1}
4	1610 - 1500 cm^{-1}	C=C stretching of an aromatic ring	1577.77 cm^{-1}
5	1450 - 1400 cm^{-1}	C-H bending of methyl and methylene groups	1440.83 cm^{-1}
6	1360-1310 cm^{-1}	C-N stretching of tertiary amine.	1348.24 cm^{-1}
7	1300-1000 cm^{-1}	C-O stretching of furam ring.	1247.94 cm^{-1}

8	1300-1000 cm^{-1}	In-plane C-H bending of an aromatic ring	1033.85, 1058.92, 1082.07 cm^{-1}
9	900 – 675 cm^{-1}	Out plane C-H bending of an aromatic ring	813.96, 763.81 cm^{-1}
10	700 – 675 cm^{-1}	C=C bending of Aromatic ring	702.09m^{-1}

3.3 COMPATIBILITY STUDIES

ANALYTICAL STUDY

3.3.1 Calibration Curve of Darifenacin Hydrobromide.

The standard calibration curve for Darifenacin hydrobromide was constructed by plotting a graph of Concentration (µg/ml) V/s Absorbance. The absorbance values corresponding to concentrations in table no 3.2. Fig no 3.2 displays the standard calibration plot, which includes the equation of the line and the regression coefficient.

Table no 3.2: Absorbance of Darifenacin hydrobromide in phosphate buffer pH 6.8

Concentration(µg/ml)	Absorbance at 289 nm
10	0.047
20	0.081
30	0.125
40	0.161
50	0.196
60	0.228
70	0.263
80	0.312

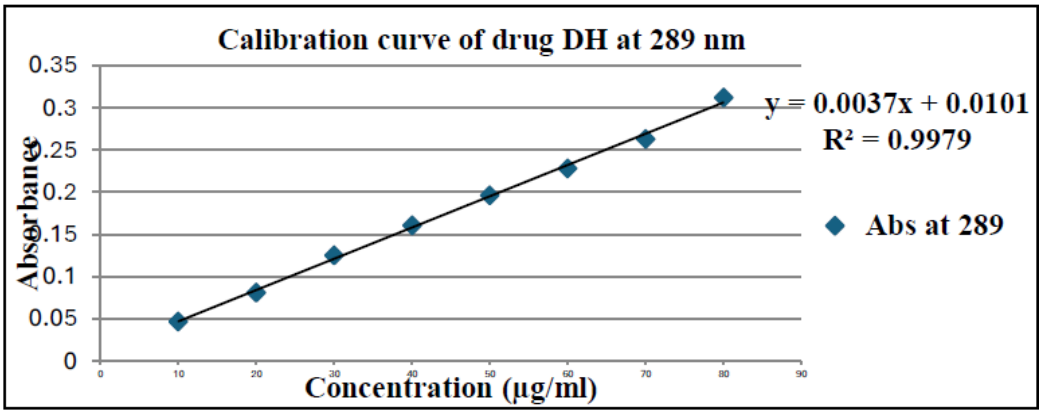

Fig. no. 3.2: Standard calibration curve of Darifenacin hydrobromide in phosphate buffer pH 6.8.

3.4 FORMULATION OF DARIFENACIN HYDROBROMIDE LIQUID SEDDS

Based on the pseudoternary phase diagrams, formulations F1 to F10 of the Self Emulsifying Drug Delivery System (SEDDS) incorporating Darifenacin hydrobromide (DH) were

successfully developed using sunflower oil, Tween 20, and Ethanol. The concentrations of oil, surfactant (Tween 20), and co-solvent (Ethanol) were determined based on the defined shaded regions Specifically, formulations F1 to F3 were prepared using a 2:1 S_{mix} ratio, formulations F4 to F6 utilized a 1:1 S_{mix} ratio, and formulations F7 to F10 were formulated with a 1:2 S_{mix} ratio. All formulations were stored at room temperature for subsequent use and evaluation.

Table no. 3.3: Percent v/v of Sunflower oil, Tween 20 and Ethanol for F1-F10 of DH Liquid SEDDS Formulations.

S_{mix} Ratio	Formulation Code	% Composition v/v		
		Sunflower Oil	Tween 20	Ethanol
2:1	F1	20%	53.2%	26.66%
2:1	F2	25%	50%	25%
2:1	F3	30%	46.66%	23.33%
1:1	F4	13%	43.5%	43.5%
1:1	F5	15%	42.5%	42.5%
1:1	F6	20%	40%	40%
1:2	F7	35%	21.66%	43.34%
1:2	F8	40%	20%	40%
1:2	F9	30%	23.33%	46.66%
1:2	F1O	27%	24.33%	48.66%

Fig no 3.3: Formulations (F1-F10) of DH Liquid Self emulsifying drug delivery system.

3.4.1 Self-emulsification Time

The self-emulsification times recorded for formulations F1 to F10. This data is pivotal in assessing how promptly each formulation achieves emulsification, which directly impacts its efficacy in delivering drugs within the body.

Table no 3.4: Comparative evaluation of DH L-SEDDS based on Phase separation & Self-emulsification time.

S_{mix} Ratio	Formulation Code	% Composition v/v			Phase separation (Yes/No)	Self emulsification time (s)
		Sunflower Oil	Tween 20	Ethanol		
2:1	F1	20%	53.2%	26.66%	Yes	Oil globules seen.
2:1	**F2**	**25%**	**50%**	**25%**	**No**	**35 s**
2:1	**F3**	**30%**	**46.66%**	**23.33%**	**No**	**40 s**
1:1	F4	13%	43.5%	43.5%	Yes	Oil globules seen
1:1	F5	15%	42.5%	42.5%	No	70 s
1:1	F6	20%	40%	40%	No	72 s
1:2	F7	35%	21.66%	43.34%	No	Milky emulsion at 60 s
1:2	F8	40%	20%	40%	Yes	75 s
1:2	F9	30%	23.33%	46.66%	No	55 s
1:2	**F10**	**27%**	**24.33%**	**48.66%**	**No**	**50 s**

Based on the tabulated data above, the top three selected Liquid Self Emulsifying Drug Delivery Systems (LSEDDS) formulations are as follows

1. **F2: Oil = 25%, Tween 20 = 50%, Ethanol = 25%**
2. **F3: Oil = 30%, Tween 20 = 46.66%, Ethanol = 23.33%**
3. **F10: Oil = 27%, Tween 20 = 24.33%, Ethanol = 48.66%**

3.5 EVALUATION FOR SELECTION OF IDEAL LIQUID DH SEDDS

The evaluatory tests focused on formulations F1(F2), F2(F3), and F3(F10), which were chosen based on the outcomes of phase separation and self-emulsification time studies. The optimal formulation of Darifenacin hydrobromide (DH) in liquid Self Emulsifying Drug Delivery Systems (SEDDS) was determined based on criteria such as achieving a low particle size, minimal zeta potential, and a low polydispersity index.

3.5.1 pH of SEDDS of DH Liquid SEDDS [F1(F2), F2(F3) & F3(F10)

The pH of all three SEDDS formulations of DH ranged from 6 to 7, indicating that they are non-irritant and fall within a slightly neutral range suitable for formulation of Self Emulsifying Buccal Films (SEBF) in the oral mucosa. This pH range ensures compatibility with the mucosal environment, minimizing the risk of irritation upon application or ingestion.

Table no 3.5: pH of DH Liquid SEDDS [F1(F2), F2(F3) & F3(F10)]

Formulation Code	pH of SEDDS
F1(F2)	6.1
F2(F3)	6.8

F3(F10)	6.9

3.5.2. Particle size and Polydispersity index of DH Liquid SEDD Particle size and Polydispersity Index (PDI) were conducted for formulations of DH Liquid Self Emulsifying Drug Delivery Systems using the Nano Plus – Zeta/Nano particle analyzer.

Table no 3.6: Particle size and Polydispersity index of DH Liquid SEDDS.

Formulation Code	Particle Size (nm)	Polydispersity Index
F1(F2)	778 nm	0.471
F2(F3)	634.2 nm	0.394
F3(F10)	432.3 nm	0.322

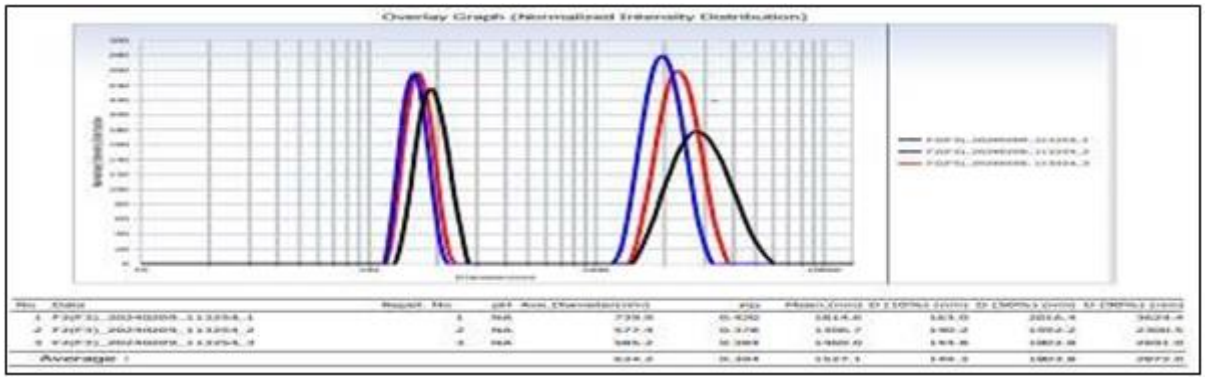

Fig no 3.4: Particle size distribution of DH Liquid SEDDS F2(F3).

3.5.3 Self emulsification time

The self-emulsification times for formulations of DH Liquid SEDDS F1(F2), F2(F10) and F3(10) ranged from 35 to 50 s, indicating their ability to quickly form emulsions and achieve self-emulsification.

Table no. 3.7: Self emulsification time of DH Liquid SEDDS [F1(F2), F2(F3) & F3(F10)]

Formulation Code	Self Emulsification Time
F1(F2)	35 s
F2(F3)	40 s
F3(F10)	50 s

Fig no. 3.5: Formation of white turbid emulsion upon dilution of pre-concentrate (self emulsification study).

3.5.4 FT-IR SPECTROSCOPY

The FTIR spectra of Optimized DH Liquid SEDDS F3 (F10) revealed the presence of all characteristic peaks of Darifenacin hydrobromide. However, Fig 3.6 shows slight changes in the intensities of these peaks, which may be indicative of interactions between the drug and the formulation excipients. The presence of oil and surfactant in the formulation likely facilitates the solubilization of the drug, potentially influencing the observed peak intensities.

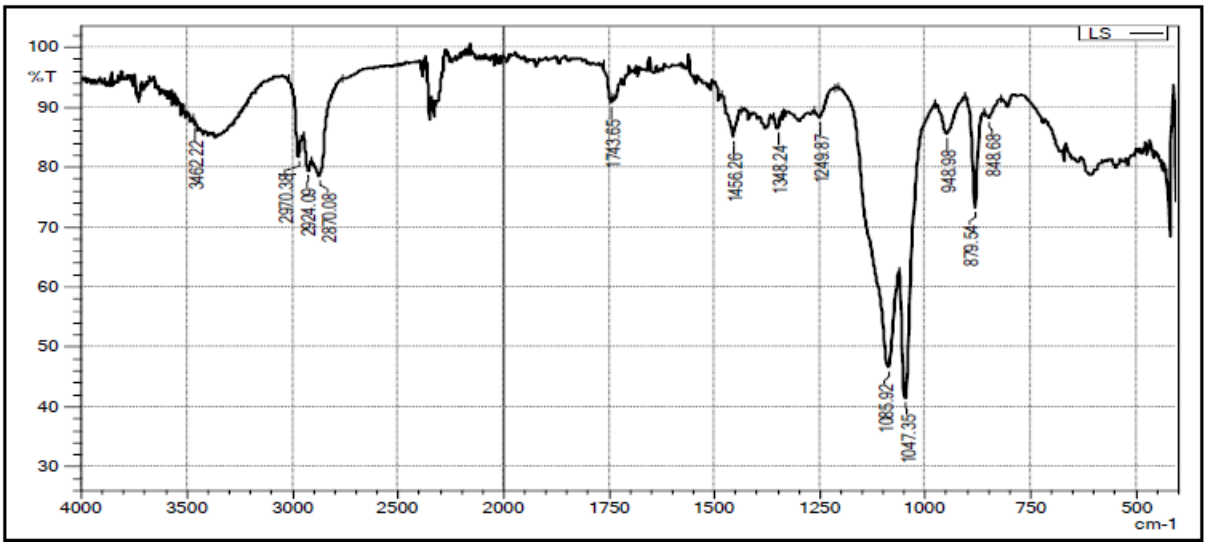

Fig no. 3.6: FTIR spectrum of Optimized DH Liquid SEDDS F3(F10) (LS).

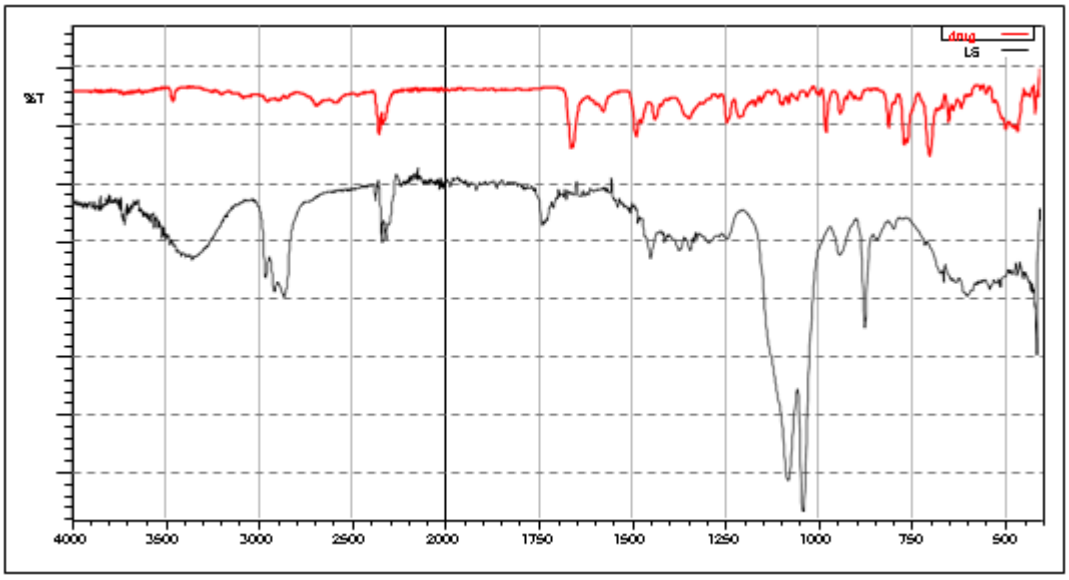

Fig no. 3.7: FTIR Overlay of DH & Optimized DH Liquid SEDDS F3(F10) (LS).

3.5 OPTIMIZATION OF BUCCAL FILM USING DoE

Table no 3.8: Optimization of SEDDS loaded buccal film by 2^3 factorial design.

Formulation Code.	Factor 1	Factor 2	Factor 3	Response 1	Response 2
	A:Conc of HPMC E4M	B:Conc of PVA	C:Conc of Glycerol	Disintegration time	% Drug Content
	mg	mg	mg	s	%
L_sTF-1	200	150	150	270	38.21
L_sTF-2	300	175	100	195	54.66
L_sTF-3	300	175	150	180	66.66
L_sTF-4	200	150	100	30	70.22
L_sTF-5	200	175	100	300	49.47
L_sTF-6	300	150	100	180	76.13
L_sTF-7	200	175	150	55	80.29
L_sTF-8	300	150	150	60	42.36

This study employed a factorial design with 8 experimental runs to optimize the formulation of Self Emulsifying Drug Delivery System (SEDDS) buccal films containing 7.5 mg of Darifenacin hydrobromide per 2 x 2 cm area. The investigation focused on three critical independent variables i.e., concentration of HPMC E4M, concentration of PVA, and concentration of ethanol The primary objectives were to evaluate disintegration time and % drug content as the dependent variables, which are pivotal for assessing the efficacy and quality of the buccal film formulations.

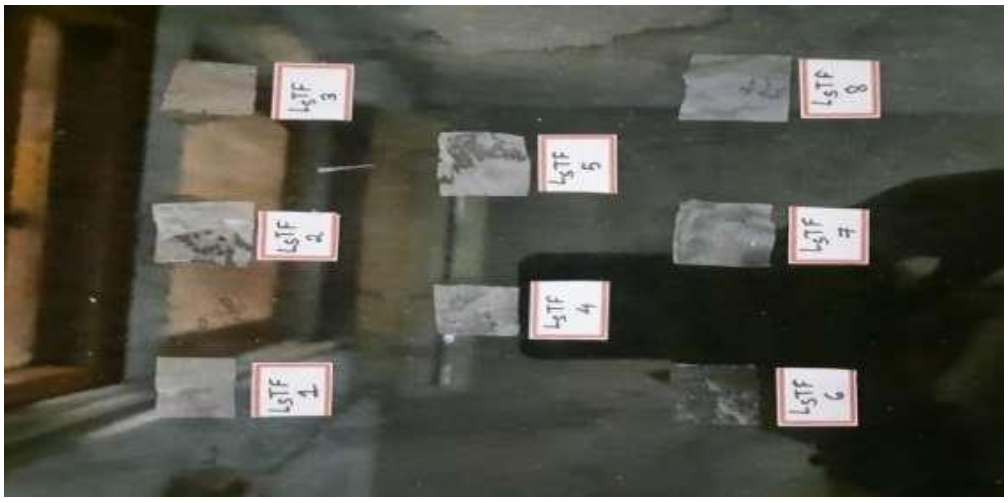

Fig no 3.8: Formulated DH liquid SEDDS thin film (L_sTF 1- L_sTF 8).

3.5.5 SELECTION OF MODEL

Based on the evaluation of DH SEDDS buccal films (LsTF 1 to LsTF 8) using the dependent variables, disintegration time (ranging from 30 to 300 s) and percent drug content (ranging from 38.21% to 80.29%), the study has derived the final optimized formulation of DH

LSEDDS buccal films. This optimized formulation represents a balanced combination of HPMC E4M, PVA, and ethanol concentrations that ensures both the desired disintegration time and accurate drug content within the specified ranges. These parameters are crucial for achieving effective delivery and therapeutic efficacy of Darifenacin hydrobromide through buccal administration,

RESPONSE 1: DISINTEGRATION TIME

Table no 3.9: Disintegration time for L_sTF 1- L_sTF 8

Formulation Code	Response 1
	Disintegration Time (s)
L_sTF-1	270
L_sTF-2	195
L_sTF-3	180
L_sTF-4	30
L_sTF-5	300
L_sTF-6	180
L_sTF-7	55
L_sTF-8	60

Table no 3.10: ANOVA for selected Factorial model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	66275.00	4	16568.75	9.27	0.0489	**Significant**
A-Conc Of HPMC E4M	200.00	1	200.00	0.1119	0.7600	
B-Conc Of PVA	4512.50	1	4512.50	2.52	0.2103	
BC	18050.00	1	18050.00	10.10	0.0502	
ABC	43512.50	1	43512.50	24.34	0.0160	
Residual	5362.50	3	1787.50			
Cor Total	71637.50	7				

Factor coding is **Coded**.

Sum of squares is **Type III – Partial**

The **Model F-value** of 9.27 implies the model is significant. There is only a 4.89% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case ABC is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

DISCUSSION

3.6 OPTIMIZED FORMULA FOR DH-LSEDDS LOADED BUCCAL FILM

Based on the results obtained from Formulations LsTF-1 to LsTF-8, the system generated an optimized formula (LsTF-9) for Darifenacin hydrobromide Liquid SEDDS loaded buccal film using statistical modeling and a desirability factor with 95% confidence. Subsequently, the optimized Darifenacin hydrobromide SEOF (LsTF-9) was formulated, and its performance was evaluated based on the dependent variables, Disintegration time and % Drug Content. The results were assessed against the upper and lower response limits defined by the system to ensure they meet predefined criteria for efficacy and consistency. These steps are crucial in refining the formulation process to achieve desired product characteristics and ensure quality control in pharmaceutical development.

Table no 3.11: Optimized formula of Conc of HPMC E4M, Conc of PVA, Conc of

Concentration of HPMC E4M (mg)	Concentration of PVA (mg)	Concentration of Glycerol (mg)
250	162.5	125

Table no 3.12: Formula for the preparation of Darifenacin hydrobromide Glycerol from 2^3 Factorial design liquid SEDDS loaded buccal film.

Sr. no	Name of Ingredients	Quantity in mg (for 2 x 2 cm film)
1	Optimized DH Liquid SEDDS [F3(F10)]	131 mg (equivalent to 7.5 mg of DH)
2	HPMC E4M	250
3	PVA	162.5
4	Glycerol	125
5	Sodium Starch Glycolate	25
6	Citric acid	20
7	Dextrose	20
8	Distilled water	q.s to 10 ml

Table no 3.13: Responses of the DH SEDDS loaded optimized Buccal film (LsTF-9)

Sr. no.	Responses	I	II	III	Mean and Std. dev.
1	Disintegration time	35 s	37 s	30 s	34 ± 3.60 s
2	% Drug Content	74.19	76.21	78.17	76.19±4.620%

Table no 3.14: Confirmation table

Analysis	Predicted Mean	Predicted Median	Observed	Std Dev	n	SEPred	95% PI low	95% PI high
Disintegration Time	158.75	158.75	34	42.2788	1	44.8435	16.038	301.462
% Drug content	59.75	59.75	76.19	5.46658	1	5.79819	41.2976	78.2024

3.7 EVALUATION OF THE OPTIMIZED DH LIQUID SEDDS THIN FILM (LsTF-9)

Fig no 3.9: Optimized Darifenacin hydrobromide Liquid SEDDS loaded buccal film (LsTF-9).

Fig no 3.10: Pure drug Darifenacin hydrobromide suspension loaded buccal film.

3.7.1 ORGANOLEPTIC PROPERTIES

The DH liquid SEDDS loaded buccal film (LsTF-9) exhibited a smooth, white appearance without any irregularities and lacked a characteristic odour. In contrast, the pure drug DH suspension film appeared transparent but had a rough surface, which suggests the presence of crystalline drug particles.

3.7.2 THICKNESS

The thickness of the DH SEDDS loaded buccal film was measured at three different locations on each film using Vernier calliper, with measurements taken in triplicate (n=3). The results showed a mean thickness of 0.197 ± 0.012 mm, indicating uniformity across the film. Table no. 4,5 presents the detailed measurements of thickness for each location of the SEOF (Self-Emulsifying Oral Film.

Table no 3.15: Thickness of DH Self Emulsifying Buccal film (SEBF).

SEOF	I	II	III	Mean ± SD
1	0.20	0.19	0.20	0.197±0.012 mm
2	0.21	0.21	0.21	
3	0.19	0.18	0.19	

3.7.3 WEIGHT VARIATION

The weight variation test is crucial for ensuring dosage consistency, which is essential for

patient safety and acceptance of pharmaceutical products. In this test, data is typically recorded in triplicate (n=3) to ensure accuracy and reliability. Upon analysis, the mean weight and standard deviation were calculated to be 43.26 ± 0.003 mg, indicating high uniformity in weight across the samples tested.

3.7.4 FOLDING ENDURANCE

Folding endurance is a critical characteristic for buccal films, reflecting their ability to withstand repeated folding without cracking or breaking. This property is essential as it ensures the films maintain integrity and flexibility during handling, facilitating easy application and removal from the buccal cavity without damage. The folding endurance test for the DH SEBF (Darifenacin hydrobromide Self-Emulsifying Buccal Film) was conducted in triplicate (n=3), yielding a mean value of 345.98 ± 5.05.

3.7.5 TENSILE STRENGTH

The tensile strength of the buccal film was measured in triplicate, yielding a mean value of 0.05 ± 0.0025 kg/cm². This result indicates that the film has a moderate tensile strength, which is important for maintaining integrity and durability.

3.7.6 PERCENT ELONGATION

Percent elongation is a crucial parameter for buccal films as it measures the film's ability to stretch before breaking. The % elongation was measured in triplicate, and the results are summarized in Table no.3.16, with a mean value of 18.33 ± 7.637 %. This finding demonstrates that the buccal films have sufficient flexibility to conform to the contours of the oral mucosa, enhancing comfort for the patient and ensuring proper adhesion.

Table no 3.16: Tensile strength of DH self emulsifying buccal film

SEOF	Initial length of film (cm)	Final length of film upon elongation (cm)	% Elongation of film	Mean ± SD
1	2	2.2	10%	18.33 ± 7.637 %
2	2	2.4	20%	
3	2	2.5	25%	

3.7.7 SURFACE pH

The buccal mucosa naturally has a slightly acidic pH, typically ranging from 6.2 to 7.4. Therefore, buccal films with a pH close to this range are less likely to cause irritation or discomfort upon application. The optimized Darifenacin hydrobromide Self-Emulsifying

Buccal Film (DH SEBF) was found to have a pH of 7.2, as measured in triplicate (n=3) as shown in Table no 3.17. This pH level aligns well with the physiological pH of the buccal mucosa, indicating that the film is well-suited for application in the oral cavity without adverse effects on mucosal integrity.

Table no 3.17: pH measurements of DH SEBF.

SEOF	pH OF SEOF	Mean ± SD
1	7.1	7.2
2	7.2	
3	7.3	

3.7.8 PERCENT MOISTURE LOSS

Buccal films are designed to be applied to the mucous membrane of the oral cavity, where maintaining appropriate moisture levels is critical for patient comfort and effectiveness. Excessive moisture loss can render films brittle or overly dry, potentially causing irritation or discomfort during application. The percent moisture loss of the buccal film was measured over a span of 3 days and found to be 1.216 ± 0.610% (n=3), indicating its good stability.

3.7.9 DRUG CONTENT

The drug content test is essential to ensure accurate dosing of the active pharmaceutical ingredient (API), thereby providing efficacy and safety to patients. The optimized DH Self-Emulsifying Drug Delivery System (SEDDS) loaded buccal film (LsTF-9) underwent drug content testing, conducted in triplicate (n=3), and was found to have a measured drug content of 76.19 ± 4.620 %.

3.7.10 *IN VITRO* DISINTEGRATION TIME

Disintegration time is a crucial parameter for buccal films, as it determines how quickly the film breaks down into smaller particles when placed in the buccal cavity. This directly impacts drug absorption and patient experience. The mean disintegration time was found to be 34 ± 3.60 s. Fig. no.3.11 illustrates the disintegration test performed using the petri plate method for DH SEBF.

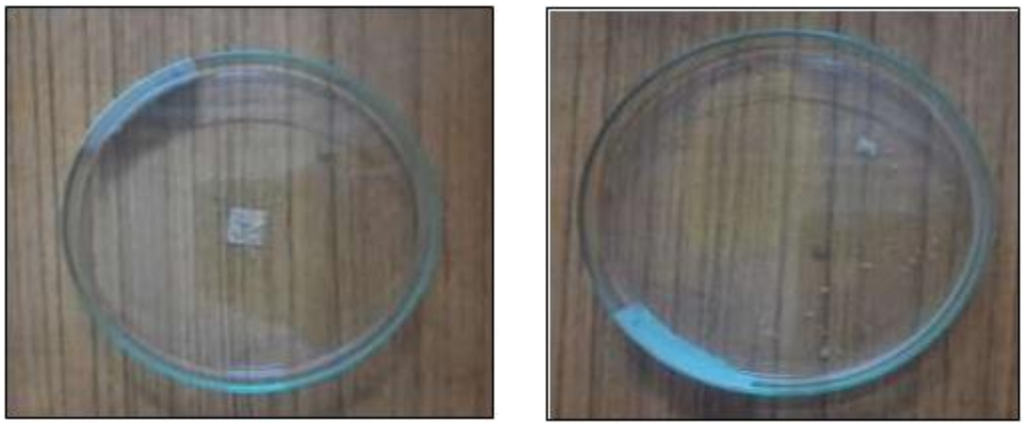

Fig no. 3.11: *In Vitro* Disintegration test performed for optimized DH self emulsifying buccal film showing before and after 34s.

3.7.11 FT-IR SPECTROSCOPY

The fig no 3.12 demonstrates the FT-IR spectrum of Formulated DH L-SEDDS loaded buccal film (L_sTF-9) and the Overlay of formulated buccal film and Pure drug.

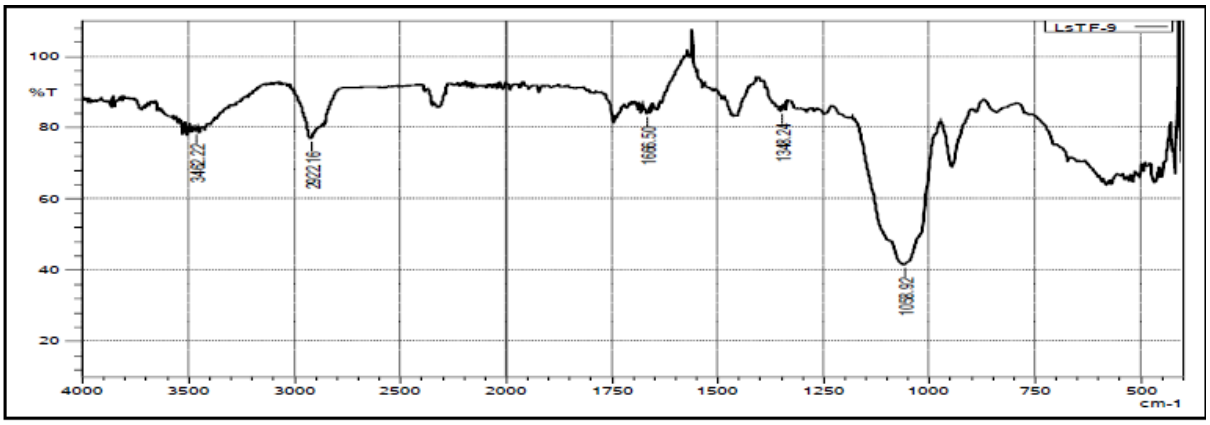

Fig no 3.12: FTIR Spectrum of Optimised DH SEOF (L_sTF-9).

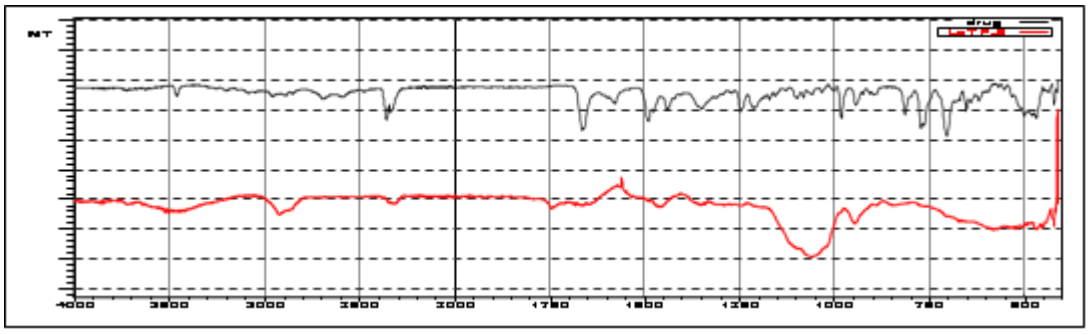

Fig no 3.13: FTIR Overlay of Pure drug DH & Optimised DH SEOF (L_sTF-9).

3.8 SCANNING ELECTRON MICROSCOPE

The SEM images of the pure drug Darifenacin hydrobromide (DH) loaded oral film (Fig no

3.14) were compared with those of the DH SEDDS loaded buccal film (Fig no 3.15). In the SEM image of the pure drug DH buccal film, crystalline drug particles were observed with a rough surface texture. In contrast, the SEM image of the DH SEDDS buccal film (L_sTF-9) showed an absence of free drug particles. The surface appeared smooth with circular points, indicating the presence of Darifenacin hydrobromide in a dissolved state within the polymer HPMC E4M.

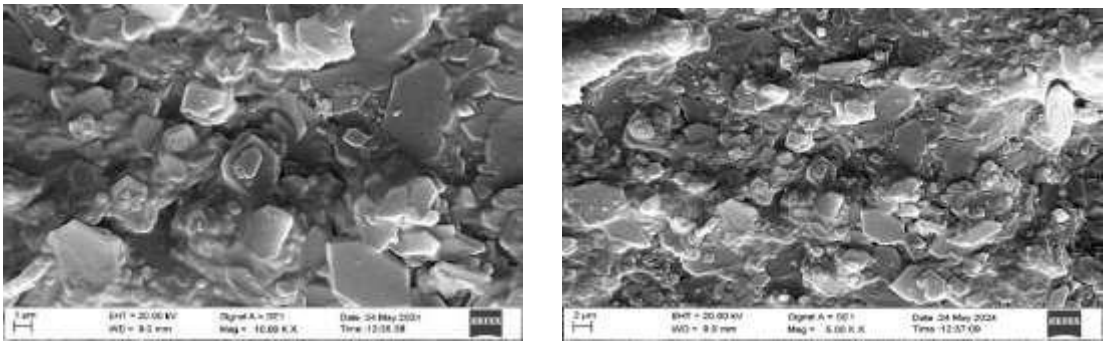

Fig no 3.14: SEM images of drug DH suspension loaded Buccal film.

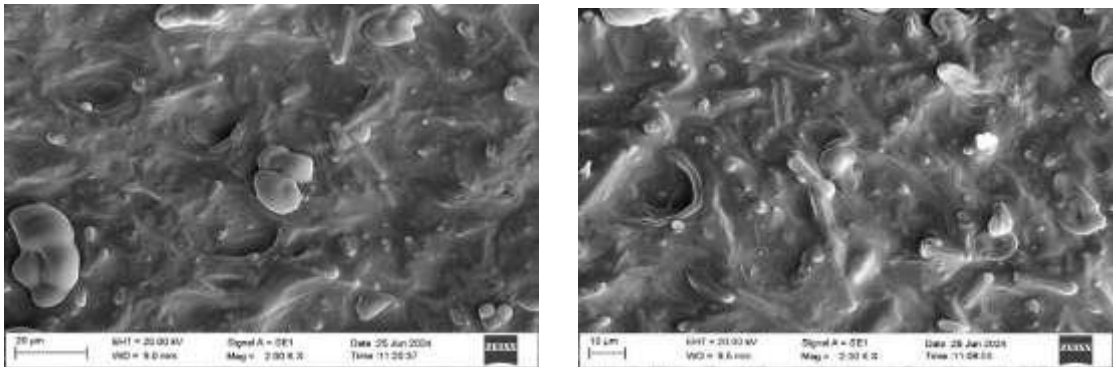

Fig no 3.15: SEM images of Optimized DH L-SEDDS loaded buccal film.

3.8.1 *IN VITRO* DISSOLUTION STUDY

The *in vitro* dissolution test provides valuable information about how a drug is released from a formulation under simulated physiological conditions. In this study, the dissolution test was conducted using a USP type I apparatus with Phosphate buffer pH 6.8 as the dissolution medium. The dissolution profiles of the optimized DH SEOF were compared with those of the pure drug DH suspension loaded oral film. The drug release profile from the optimized Darifenacin hydrobromide Self-Emulsifying Drug Delivery System (SEDDS) loaded buccal film (L_sTF-9) was compared with that from the pure drug DH suspension loaded buccal film. As depicted in Fig no.3.16, there is a clear distinction in drug release kinetics between the two formulations. The optimized DH SEDDS loaded buccal film (L_sTF-9) exhibited a higher drug

release, reaching nearly 90% release within 5 min. In contrast, the pure drug DH loaded film achieved only 58% release by the same time point.

Table no 3.8: *In- Vitro* dissolution profile of DH Liquid SEDDS loaded buccal film.

TIME IN MIN	% CDR	LOG T	SQUARE ROOT OF T	LOG %CDR	% DRUG RETAINED	LOG % DRUG RETAINED
0	0	0	0	0	100%	2
0.5	35.28%	-0.301	0.707	1.54	64.72%	1.81
1	45%	0	1	1.65	55%	1.74
1.5	48.32%	0.17	1.22	1.68	51.68%	1.71
2	61.29%	0.3	1.414	1.78	38.71%	1.58
2.5	64.54%	0.39	1.58	1.8	35.46%	1.54
3	67.78%	0.47	1.73	1.83	32.22%	1.5
3.5	71.02%	0.54	1.87	1.85	28.98%	1.46
4	74.27%	0.6	2	1.87	25.73%	1.41
4.5	80.75%	0.65	2.12	1.9	19.25%	1.28
5	90.48%	0.69	2.23	1.95	9.52%	0.97

Table no 3.9*: In-vitro* dissolution profile of Pure drug DH buccal film.

TIME IN MIN	% CDR	LOG T	SQUARE ROOT OF T	LOG %CDR			% DRUG RETAINED	LOG % DRUG RETAINED
0	0	0	0	0			100 %	2
0.5	19.13%	- 0.301	0.7	1.281			80.87 %	1.9
1	32.10%	0	1	1.506			67.9 %	1.83
1.5	35.35%	0.17	1.22	1.548	64.65%	1.81		
2	41.83%	0.3	1.41	1.621	58.17%	1.76		
2.5	48.32%	0.39	1.58	1.684	51.68%	1.71		
3	51.56%	0.47	1.73	1.712	48.44%	1.68		
3.5	51.56%	0.54	1.87	1.712	48.44%	1.68		
4	54.81%	0.6	2	1.738	45.19%	1.65		
4.5	58.05%	0.65	2.12	1.763	41.95%	1.62		
5	58.05%	0.69	2.23	1.763	41.95%	1.62		

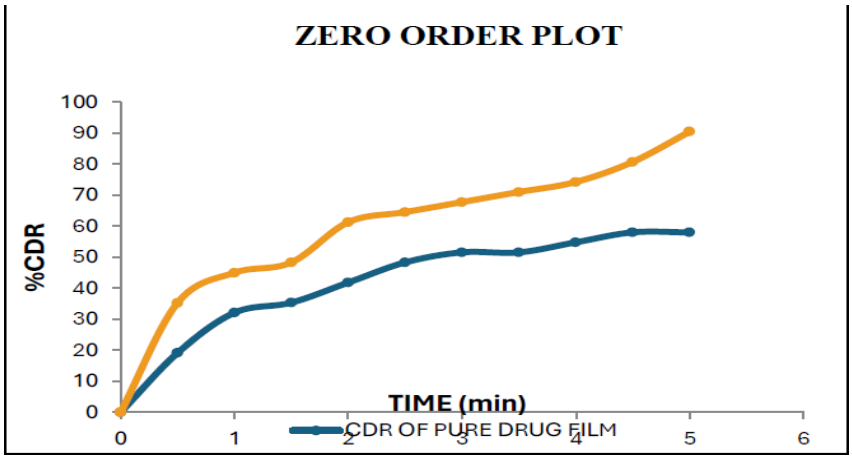

Fig no. 3.16 Optimized DH SEOF (L_sTF-9) V/s Pure drug DH film.

3.9 RELEASE KINETIC MODELS

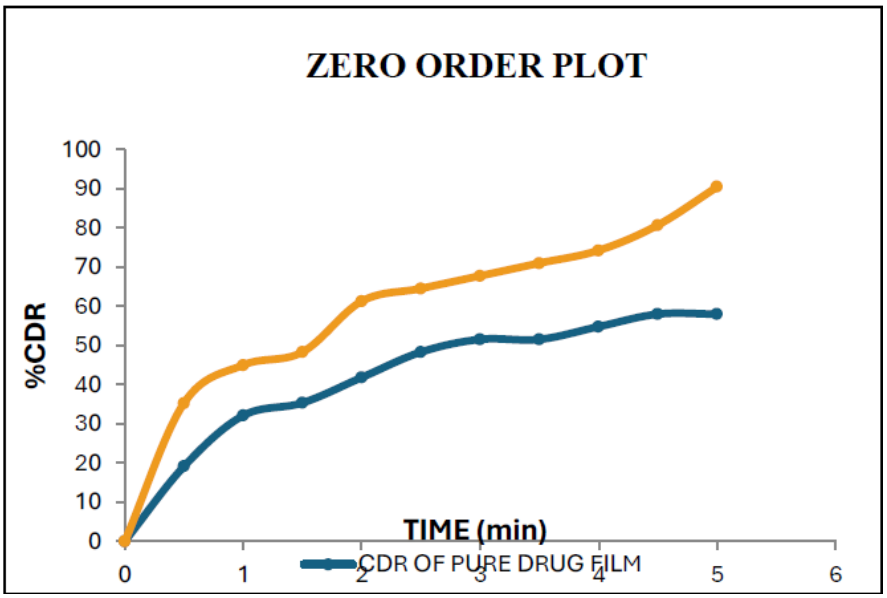

Fig no 3.17: *In-vitro* dissolution profile- Zero order plot.

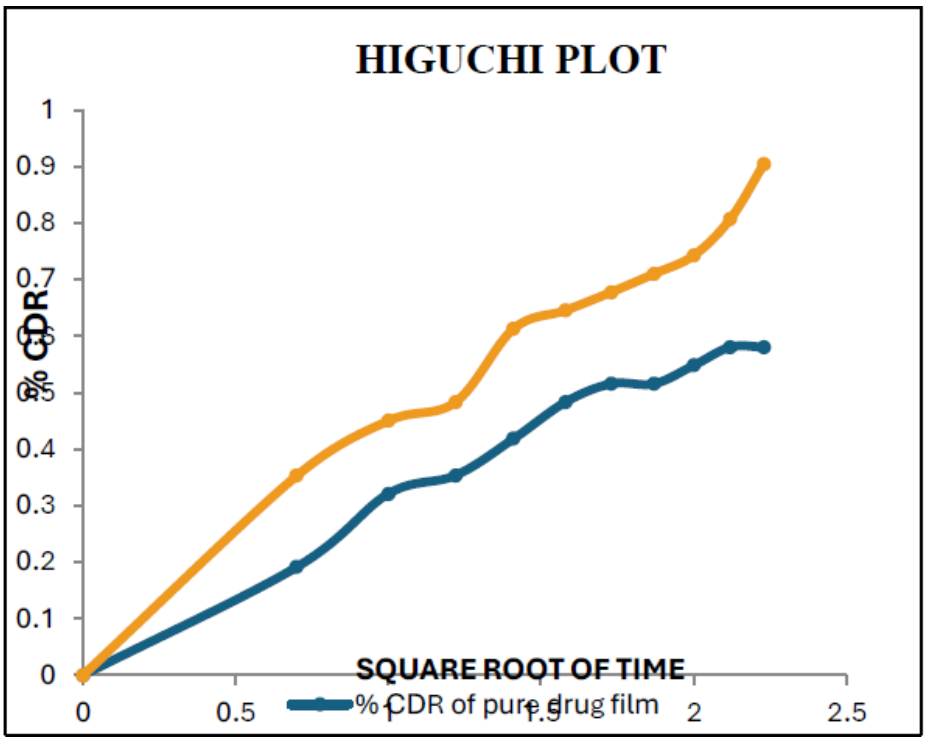

Fig no 3.18: *In-vitro* dissolution profile- Higuchi model.

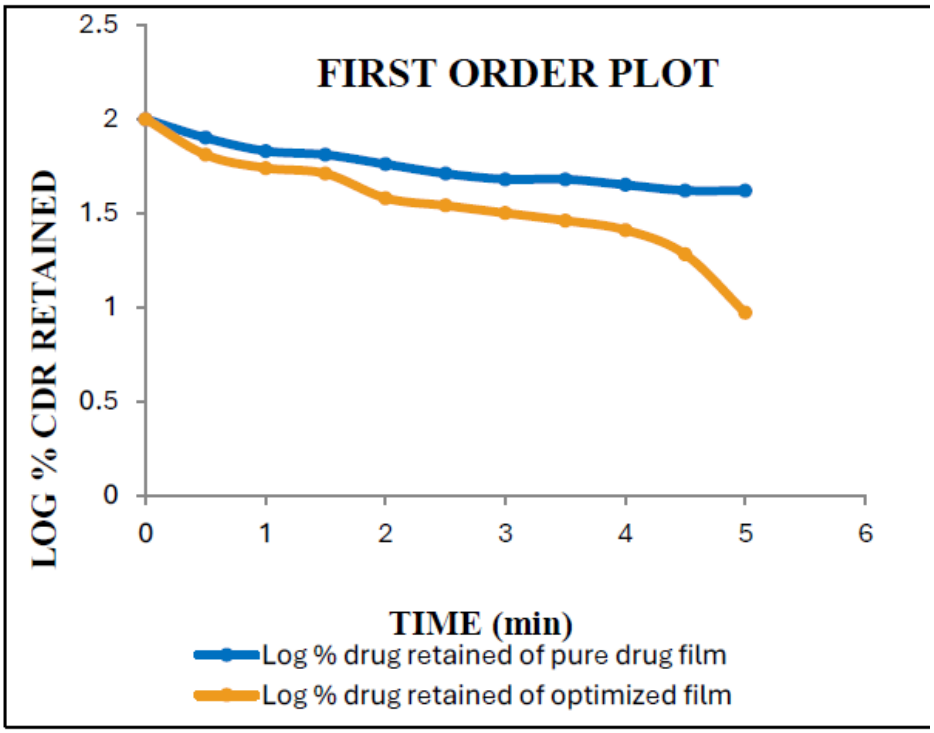

Fig no 3.19: *In-vitro* dissolution profile- First order plot.

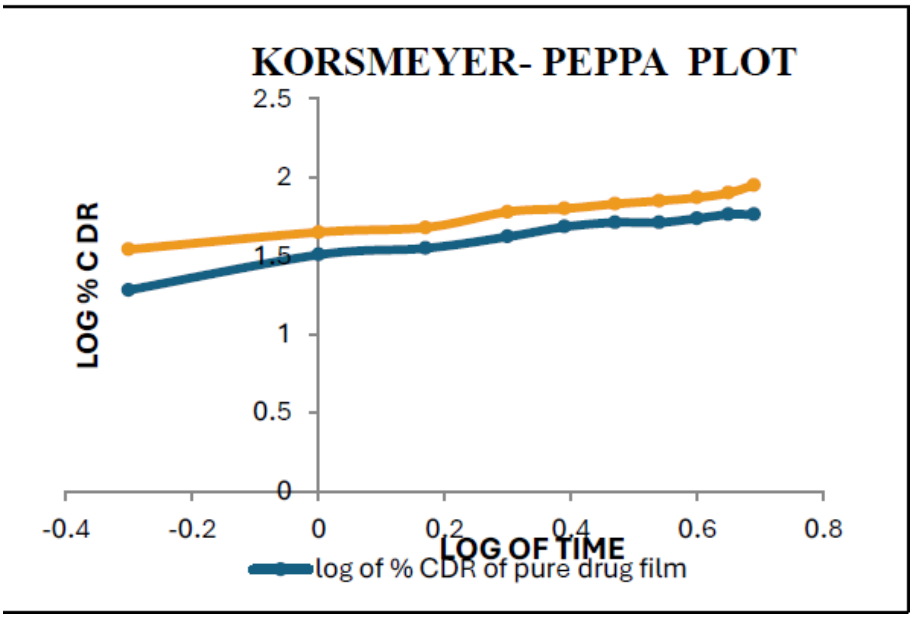

Fig no 3.20: *In- vitro* dissolution profile- Korsmeyer- Peppa.

Table no 3.10: Values of Regression Coefficient and Kinetics for formulations

FORMULATION	TYPE	SLOPE	R^2
Darifenacin hydrobromide liquid SEDDS loaded buccal film.	Zero order	14.072	0.8646
	First order	-0.1607	0.9201
	Higuchi Plot	0.3683	0.9804
	Korsemeyer Peppa's model	0.395	0.9807

	Zero order	10.106	0.8468
Pure drug	First order	-0.0709	0.92
Darifenacin hydrobromide	Higuchi Plot	0.2675	0.9813
suspension loaded buccal film	Korsmeyer Peppa's model	0.472	0.9688

3.10 Analysis of Release kinetics study

The dissolution kinetics of Optimised Darifenacin hydrobromide (DH) Liquid SEDDS loaded buccal film (LsTF-9) were comprehensively analyzed using mathematical models, revealing distinct mechanisms governing drug release. The first-order kinetic model demonstrated a strong correlation ($R^2 = 0.9201$), indicating that drug release is influenced by the concentration of dissolved drug available.

3.11 STABILITY STUDIES

After storing the optimized DH Self-Emulsifying Oral Films (SEOF) at 25 ± 2ºC and 60 ± 5% relative humidity (RH) for 60 days, several evaluations were conducted. The films were visually inspected and found to maintain a smooth appearance without any characteristic odour or discoloration, indicating stability in physical appearance. Further analysis included, checking the disintegration time and folding endurance of the films, which were found to be unchanged compared to initial values, suggesting robustness in these mechanical properties over the storage period. Fig no 3.21 presents the detailed results in graphical form, showcasing the consistency and stability of the DH SEOF after prolonged storage under controlled conditions.

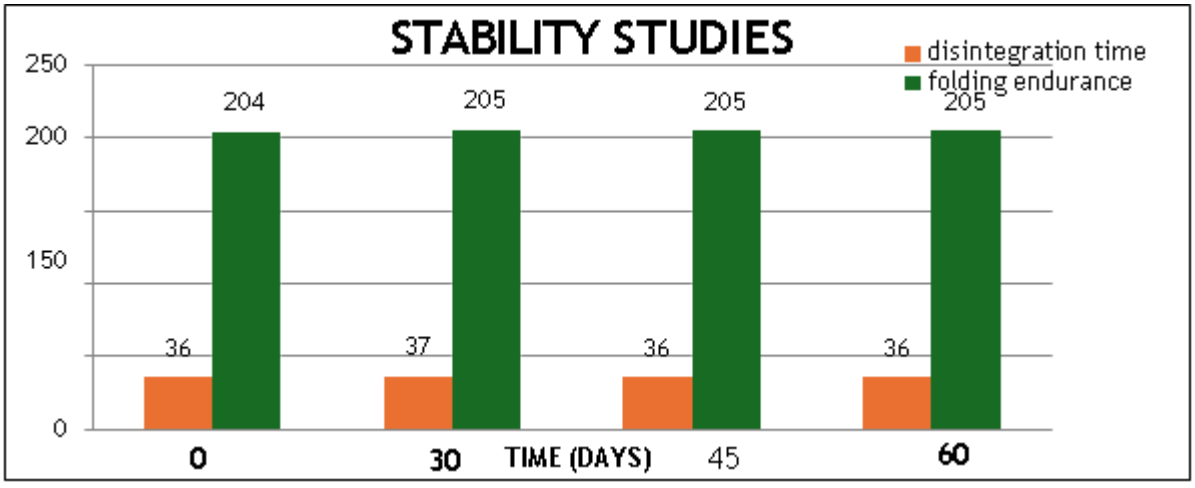

Fig no 3.21: Results of stability studies conducted for optimized DH L-SEDDS.

4.0 CONCLUSION

This research highlights the successful formulation of Darifenacin hydrobromide as a Liquid SEDDS and its subsequent transformation into fast-dissolving buccal films. These innovations not only address the drug's solubility and bioavailability challenges but also offer a promising strategy for enhancing therapeutic efficacy and patient compliance in the treatment of overactive bladder

5.0 ACKNOWLEDGEMENT

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6.0 Conflict of Interest

The authors confirm that there are no known conflicts of interest associated with this publication.

7.0 IEAC Approval number Copyright orm.

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