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Development of Bilayer Fast Dissolving Film of Lidocaine HCl and Choline Salicylate to Treat Localised Moderate to Severe Oral Pain

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A B S T R A C T

Aim: In this study, we aimed to the development of bilayer fast-dissolving film of Lidocaine HCl (LH) and Choline salicylate (CS) to treat localised moderate to severe oral pain.

Methods: Three film-forming agents (HPMC E15, HPMC 15cps, and HPMC K4M) were evaluated for their film-forming properties, and HPMC E15 was selected as the optimal agent and PEG 400 as a plasticizer. 32 full factorial design was applied to the selected trial batch for further optimization of the formulation. Two factors X1 (HPMC E15) and X2 (PEG 400) were studied at three levels against three responses R1 Disintegration time (DT), R2 Tensile Strength (TS), and R3 %drug released within 1 minute using Design® Expert software. All 9 factorial batches were evaluated for physical appearance, thickness, weight, folding endurance, %elongation, TS, DT and %drug released within 1 minute. Based on these evaluations, Derived models were further validated using two checkpoint batches and the final optimized formulation was derived by applying the desirability function.

Results: The optimized formulation achieved quality criteria: 5-second DT, highest TS, and drug release within 1 minute. More plasticizers increased TS and reduced DT, while less film-forming polymer enhanced drug release. This bilayer film aids in managing severe oral pain, improving patient compliance and enhancing the quality of life.

Conclusion: The bilayer fast-dissolving film of LH and CS for treating localized oral pain was successfully developed and optimized using a 3^2-full factorial design.

Keywords: Lidocaine, Choline salicylate, Bilayer fast dissolving film, Severe oral pain.

1. Introduction

Buccal drug delivery has emerged as a recent and promising approach, offering an effective and safe alternative to conventional routes of drug administration. It allows for local or systemic effects, especially suitable for drugs affected by gastric inactivation and gastrointestinal irritation. Available formulations like gels, chewable tablets, and mouthwashes face challenges of poor retention and high cost. The dental gel can be easily rinsed out, affecting compliance due to taste, texture, administration difficulties, forgetfulness and side effects [1]. Drug delivery technologies adjust drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient compliance. The oral route of administration is considered the most common route for drug systemic actions owing to its flexibility, ease of use and painlessness, as well as patient compliance. Bilayer fast-dissolving films (BFDF) are the most advanced solid dosage form in terms of their flexibility. The formulation of BFDF is composed of materials such as strip-forming polymers, plasticizers, active pharmaceutical ingredients (API), sweetening agents, saliva stimulating agents, flavouring agents, colouring agents, surfactants, permeation enhancers and super disintegrants. The delivery system consists of a very thin oral strip, which is placed on the patient's tongue or any oral mucosal tissue. The strip is instantly wet by saliva and the film rapidly hydrates and disintegrates and dissolves to release the medication for oral mucosal absorption. The ideal BFDF is a thin film of 1-10 mm thickness, with an area of 1-20 cm2 of any geometry. Drugs can be incorporated up to a single dose of about a maximum of 15 mg. The immediate dissolution in the saliva is due to a special matrix made from water-soluble polymers. It has usually low tack for easy handling and application. The flexibility and strength of films are selected to facilitate the manufacturing process and processes like rewinding, die cutting and packing [2]. Oral films are the newer technologies in the manufacturing of oral disintegrating dosage forms. They are elegant thin films of edible water-soluble polymers of various sizes and shapes like squares, rectangles, or discs. The stripes may be flexible or brittle, opaque or transparent. BFDF have a large specific surface area for disintegration. A major limitation of these dosage forms is low drug loading capacity and limited taste masking options [3].

A dissolvable oral film medication offers a convenient and patient-friendly solution for mentally ill disabled and uncooperative individuals, providing ease of administration without the need for water, overcoming unpleasant taste, leaving minimal residue in the mouth and allowing for rapid disintegration and release of the medication [4]. Dissolvable oral films face challenges of dose uniformity, limited incorporation of high Doses and the need for specialized packaging to ensure product stability and safety, which are considered disadvantages of this dosage form [5]. The formulation offers immediate

relief by rapidly releasing the drug into the bloodstream upon ingestion, making it beneficial for patients experiencing severe pain or discomfort associated with oral cancer or other mouth conditions that may alter taste perception or pose challenges in tolerating certain medications, with the inclusion of non-steroidal anti-inflammatory drugs (NSAIDs) commonly used for managing severe cancerous pain and dental pain [6].

Lidocaine hydrochloride is a widely used medication in oral healthcare, with a chemical formula of C14H22N2O and a molecular weight of 234.3373 grams/mole. It is a white crystalline solid that melts at a temperature of 68.5°C. LH serves as a drug of choice in various oral conditions such as tooth decay, periodontal disease, tooth loss, and lip and oral cavity cancer. LH effectively reduces pain by temporarily anaesthetizing the nerve endings located on the surfaces of the oral mucosa. Its mechanism of action involves blocking the sodium channels' ionic fluxes necessary for the initiation and conduction of nerve impulses. This inhibition prevents pain signals from reaching the brain, leading to the alleviation of pain sensations experienced by the patient [7]. Choline salicylate, with a chemical formula of C12H19NO4 and a molecular weight of 241.287 grams/mole, is a liquid with a melting point of 49.5-50.0°C, functioning as a local analgesic by blocking the effect of chemical messengers that cause pain and inflammation and in combination with LH, it provides relief for severe pain [8] [9].

2. Materials and Methods

2.1. Materials

HPMC E15 [9004-65-3], HPMC K4M [9004-65-3], HPMC 15 cps [9004-65-3], Sodium Saccharin [6155-57-3], PEG 400 [25322-68-3], Citric acid, [77-92-9], SSG [9063-38-1], Peppermint oil [8006-90-4] were procured from SRL chemicals. The laboratory was equipped with various instruments, including a Shimadzu UV spectrophotometer, Kent's Scientific analytical balance, a magnetic stirrer from 1-MLH, Remi Motor LTD., Mumbai, Maharashtra, India, a pH meter from Model 111, EI Products, Techno Instruments, Bangalore, Karnataka, India, a bath sonicator from D-150, Trans-o-Sonic, Mumbai, Maharashtra, India, and a dissolution apparatus from ECD-6, Electro Lab, Ahmedabad, Gujarat, India.

2.2. Preformulation Studies

2.2.1. Spectrophotometric Estimation

This chapter shows the development of a simple UV spectrophotometric method for the analysis of LH and CS.

2.2.2. Preparation of Standard Solution of Lidocaine HCl

An accurately weighed quantity of LH (100 mg) was added into a 100 mL volumetric flask and made up the volume with phosphate buffer pH 6.8 solution. The flask was sonicated for 20 minutes to dissolve LH completely. The concentration obtained stock solution was 1000 µg/ml. This stock solution was scanned spectrophotometrically between 200-400 nm in a UV/Visible Double beam spectrophotometer to determine the absorption maxima (λmax) of LH.

2.2.3. Construction of Calibration Curve of Lidocaine HCl

from the above stock solution, Aliquots (1,2,3,4,5,6 and 7ml) of the appropriate volume of stock solutions were taken into a 10 mL volumetric flask and made up with phosphate buffer pH 6.8 solution to separate the final strength of 100, 200, 300, 400, 500, 600, and 700 µg/ml. The standard curve was taken by scanning the test solution against pH 6.8 phosphate buffer as blank. All the prepared samples were subjected to measurement of absorbance at their respective λmax values. The values of absorbance were plotted against their respective concentrations as per Beer-Lambert's law.

2.2.4. Preparation of Standard Solution of Choline Salicylate

An accurately weighed quantity of CS (2 ml) was added into a 100 mL volumetric flask and made up the volume with phosphate buffer pH 6.8 solution. The flask was sonicated for 20 minutes to dissolve CS completely. The concentration obtained stock solution was 1000 µg/ml. This stock solution was scanned spectrophotometrically between 200 - 400 nm in a UV/Visible Double beam spectrophotometer to determine the absorption maxima (λmax) of CS.

2.2.5. Construction of Calibration Curve of Choline Salicylate

From the above stock solution, Aliquots (0.5,1,1.5,2,2.5,3,3.5,4 and 4.5 ml) ml of the appropriate volume of stock solutions were taken into a 10 mL volumetric flask and made up with phosphate buffer pH 6.8 solution to separate final strength of 50, 100, 150, 200, 250, 300, 350, 400 and 450 µg/ml. The standard curve was taken by scanning the test solution against pH 6.8 phosphate buffer as blank. All the prepared samples were subjected to measurement of absorbance at their respective λmax values. The values of absorbance were plotted against their respective concentrations as per Beer-Lambert's law.

2.3. Drug Identification

2.3.1. Fourier-Transform Infrared Study

IR spectra of the pure drugs (LH, CS) were obtained by an FTIR spectrometer. IR spectroscopy was employed to determine the probable interaction between the drug and excipients. The samples were dispersed in a KBr pellet and scanned using Shimadzu IR Spectrophotometer between 4000-400 cm-1 with a resolution of 4 cm-1. IR spectra can be used to study the formation of new intermolecular interactions as well as changes in existing ones.

2.3.2. Drug–Excipients Compatibility Study

For checking the drug and excipients compatibility, the FTIR Study of the physical mixture of the drug with excipients was performed. The samples were dispersed in a KBr pellet and scanned using Shimadzu IR Spectrophotometer between 4000-400 cm-1 with a resolution of 4 cm-1. IR spectra can be used to study the formation of new intermolecular interactions as well as changes in existing ones. The FTIR Spectrum thus obtained was compared with that of the Reference Standard Drug and excipient to determine any significant shifts in the characteristic peaks of the drug.

2.4. Formulation and Development of Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast-Dissolving Film by solvent casting method

Fast dissolving films are ideally formulated by the solvent casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution and the drug along with different excipients is dissolved in a suitable solvent then both the solutions are mixed and stirred and lastly casted into the Petri plate and dried [1].

2.4.1. Screening Study to Select Film Forming Agent

In our screening study to develop a bilayer fast-dissolving film, we utilized three different film-forming agents, namely HPMC E15, HPMC 15cps, and HPMC K4M. We evaluated the film-forming properties of each agent by preparing solutions of the desired concentration, applying them to suitable surfaces, and testing the resulting films for thickness, flexibility, and transparency. We also measured the dissolution properties of each film by placing them in contact with simulated saliva and assessing the time it took for them to completely dissolve. The data obtained from these tests will enable us to select the most suitable film-forming agent and optimize the formulation to achieve the desired properties for our specific application.

2.4.2. Screening Study to Select the Appropriate Composition Ranges for Film Forming Agent and Plasticizer

In our composition screening study to develop a fast-dissolving film, we used HPMC E15 as the film-forming agent and PEG 400 as the plasticizer. We prepared different formulations by varying the concentration of each component and tested the resulting films for their properties such as thickness, TS, disintegration time, folding endurance and transparency. The data obtained from these tests will enable us to select the optimal composition with the desired properties for our specific application.

2.4.3. Dose Calculation (Amount of Drugs to be Poured Per Plate)

- Length of glass plate = 10cm
- Width of glass plate =10 cm
- Area of the plate=100 cm2
- No. of 4 cm2 films present whole plate =100/4 =25 films
- Each film contains 16 mg of LH and 0.069 ml of CS drug.
- 25 films contain 400mg LH (25×16) and 1.725 ml of CS drug (25×0.069)

2.4.4. Preparation of Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast-Dissolving Film

2.4.4.1. Prepare The First Layer of Film (Lidocaine loaded)

Dissolve the appropriate amount of water-soluble film-forming agent (HPMC E15) and plasticizer (PEG 400) in distilled water in a 50 ml Beaker and stir for 2 hours in a magnetic stirrer (150 rpm). Remove all air bubbles entrapped by placing them in a sonicator and keep them aside. On the other hand, Dissolve the required amount of excipients (citric acid, sodium saccharine) and drug (LH) in distilled water and stir well for 30 minutes using a magnetic stirrer (150 rpm). Mixed both solutions and cast the solution into a suitable Petri plate to form the first layer of the film. Dry the film by placing it in the hot air oven at 60 c for 1 hr [10].

2.4.4.2. Prepare The Second Layer of Film (Choline Salicylate loaded)

Dissolve the water-soluble film-forming agent (HPMC E15) and plasticizer (PEG 400) in distilled water in a 50 ml Beaker and stir for 2 hours in a magnetic stirrer (150 rpm). Remove all air bubbles entrapped and keep them aside. On the other hand, Dissolve the excipients (citric acid, sodium saccharine) and drug (CS) in distilled water and stir well for 30 minutes using a magnetic stirrer (150 rpm). Mixed both solutions and cast the solution on the LH-loaded film petri plate. Dry the film by placing it in the hot air oven at 60 c for 1 hr. Peel it carefully and collect the bilayer film [10].

2.5. Preliminary Studies

Preliminary studies were carried out to optimize various parameters like the type and concentration of film-forming agents and plasticizers. These preliminary studies provide information about how these parameters affect the quality of the final formulation of bilayer fast-dissolving film. These preliminary screening studies for film-forming agents in three different film forming agents and also screening studies to select the appropriate composition ranges for film forming agent, plasticizer and super disintegrant.

Table 1: Preliminary Screening Study Batches B1 to B15

INGREDIENTS	**BATCHES**														
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**
HPMC K4M (mg)	300	400	500	300	400	-	-	-	-	-	-	-	-	-	-
HPMC E15 (mg)	-	-	-	-	-	300	400	500	300	400	-	-	-	-	-
HPMC 15 cps (mg)	-	-	-	-	-	-	-	-	-	-	300	400	500	300	400
Sodium Saccharin(mg)	125	125	125	125	125	125	125	125	125	125	125	125	125	125	125
Citric acid(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
PEG 400 (ml)	0.5	1	1.5	0.5	1	0.5	1	1.5	0.5	1	0.5	1	1.5	0.5	1
SSG (mg)	-	-	-	150	200	-	-	-	150	200	-	-	-	150	200
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

2.6. 3^2 Full Factorial Design for Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast Dissolving Film.

3^2 full factorial designs were generated by keeping HPMC E15 (X1) and PEG 400 (X2) as factors and then further levels were also selected. Three levels were chosen to get linear correlations. As per the 3^2 designs, a total of nine batches were prepared. The three levels (-1, 0, +1) were selected for both the factors [HPMC E15 (X1) and PEG 400 (X2)] by keeping their concentration different. Levels and design are in following tables 2 and 3.

Table 2: The Layout of 3^2 Full Factorial Experimental Design

Formulation Code	**X1**	**X2**
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Table 3: Factors and Levels of 3^2 Full Factorial Design

Variables/Levels	-1 (Low)	0 (Medium)	1 (High)
X1 (HPMC E15) (mg)	300	400	500
X2 (PEG 400) (ml)	0.5	1	1.5

For each batch of factorial design, the dependent variables selected were disintegration time, TS and %cumulative drug release within 1 minute.

2.7. Evaluation Parameters of Film

2.7.1. Appearance

The physical appearance was checked with a visual inspection of the film and texture by feel or touch [11].

2.7.2. Thickness

A micrometre screw gauge was used to measure the film thickness. To obtain uniformity of the film, the thickness was measured at 5 different locations and the average value was recorded. The study was repeated in triplicate [11].

2.7.3. Weight Variation

Ten films were randomly selected, and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation. The study was repeated in triplicate [12].

2.7.4. Folding Endurance

To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. The study was repeated in triplicate [13].

2.7.5. Percentage Elongation

When stress is applied, a strip sample stretches and this is referred to as a strain. Strain is the deformation of the strip divided by the original dimension of the sample. The study was repeated in triplicate [14].

$$\text{Percentage Elongation} = \text{Increase in length of the strip}/\text{The initial length of the strip} * 100$$

2.7.6. Tensile Strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula. The study was repeated in triplicate [15]

Tensile strength (N / cm2) = Fmax/A

Where,

Fmax is the maximum force at the break.

A is the initial cross-sectional area of the film.

2.7.7. Disintegration time

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva. The study was repeated in triplicate [16].

2.7.7.1. Petri Dish Method:

2 ml of distilled water was placed in the petri dish and one film was added to the surface of the water and the time was measured until the oral film was dissolved completely.

2.7.8. In-vitro Dissolution Study

250 ml of buffer (6.8 pH) was used as a medium, at was maintained at 37 +0.5 °c while the basket was set at 50 rpm. A film sample of 4 cm2 (2×2 cm) was cut and taken into the basket. 5 ml of the sample was taken every 10 seconds and the same amount was replaced with fresh buffer (6.8 pH). The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 263 nm for LH and 238 nm for CS. As a reference solution was used 6.8 pH phosphate buffer. The study was repeated in triplicate [17].

2.7.9. Drug Content

This test was performed by dissolving a 4 cm2 area of film in 50 ml of buffer (6.8 pH) with stirring. This solution was filtered using a Whatman filter paper (0.45 microns), and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using a UV spectrometer. The study was repeated in triplicate [18].

2.7.10. Stability Study

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimize formulation was sealed in Aluminum packing laminated with polyethylene. Samples were kept at 40c and 75%RH for 30 days. At the end of the study period, the formulation was observed for change in physical appearance, colour, drug content and drug release characteristics. The study was repeated in triplicate [19].

3. Results and Discussion

3.1. Spectrophotometric Estimation

3.1.1. Calibration Curve of Lidocaine HCl

The λmax value for the UV Spectrum of LH in phosphate buffer pH 6.8 was found to be 263 nm. The prepared aliquots (100-700 µg/ml) were evaluated for absorbance at their respective λmax value and the calibration curve was prepared as per Beer- Lambert's law [20].

Table 4: Data for Calibration Curve of Lidocaine HCl in pH 6.8 Phosphate Buffer Solution

Sr. No.	Concentration (µg/ml)	Absorbance ± S.D.*
1	100	0.126 ± 0.015
2	200	0.254 ± 0.023
3	300	0.435 ± 0.037
4	400	0.593 ± 0.016
5	500	0.784 ± 0.033
6	600	0.908 ± 0.042
7	700	1.07 ± 0.040

*The results are mean±SD, (n=3)

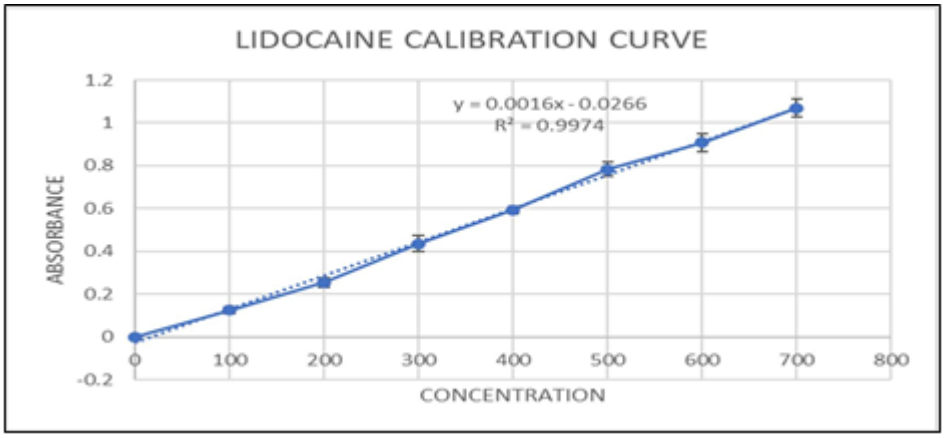

Figure 1: Calibration Curve of Lidocaine HCl in pH 6.8 Phosphate Buffer Solution

3.1.2. Calibration Curve of Choline Salicylate

The λmax value for the UV Spectrum of CS in phosphate buffer pH 6.8 was found to be 238 nm. The prepared aliquots (150-450 µg/ml) were evaluated for absorbance at their respective λmax value, and the calibration curve was prepared as per Beer- Lambert's law [21].

Table 5: Data for Calibration Curve of Choline Salicylate in Phosphate Buffer pH 6.8 Solution

Sr. No.	Concentration (µg/ml)	Absorbance ± S.D.*
1	150	0.198 ± 0.019
2	200	0.302 ± 0.018
3	250	0.356 ± 0.018
4	300	0.453 ± 0.018
5	350	0.504 ± 0.011
6	400	0.602 ± 0.060
7	450	0.690 ± 0.030

*The results are mean ± SD, (n=3)

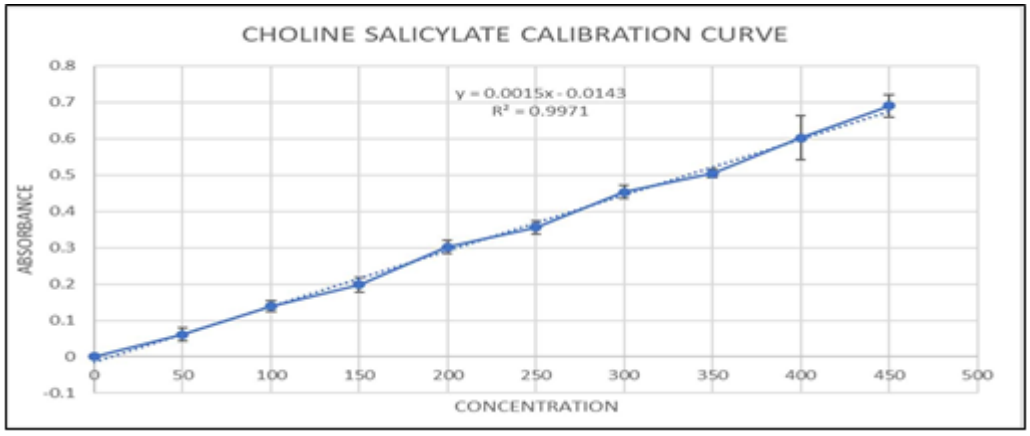

Figure 2: Calibration Curve of Choline Salicylate in pH 6.8 Phosphate Buffer Solution

3.2. Fourier-Transform Infrared (FTIR) Study

FTIR spectra of pure drug LH and CS are shown in Figure 3 and Figure 4 respectively

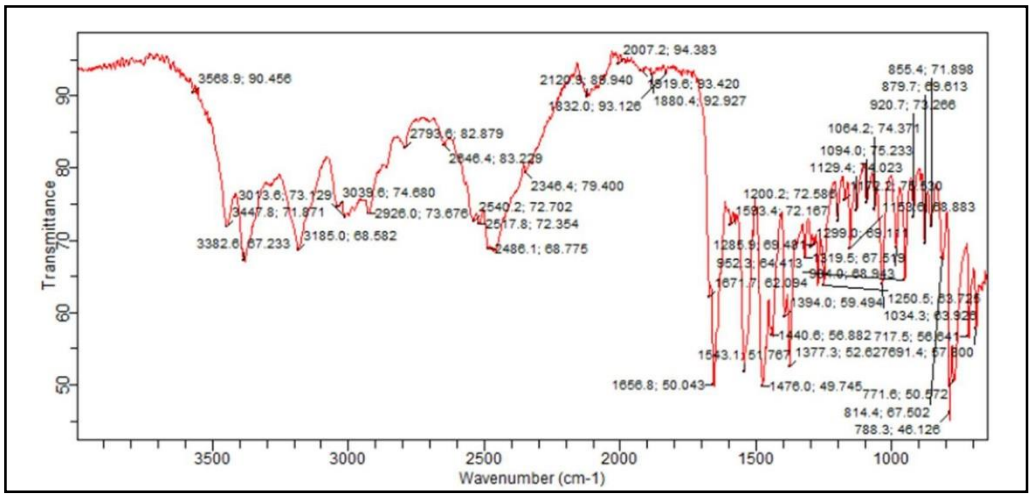

Figure 3: FTIR Spectrum of Drug Lidocaine

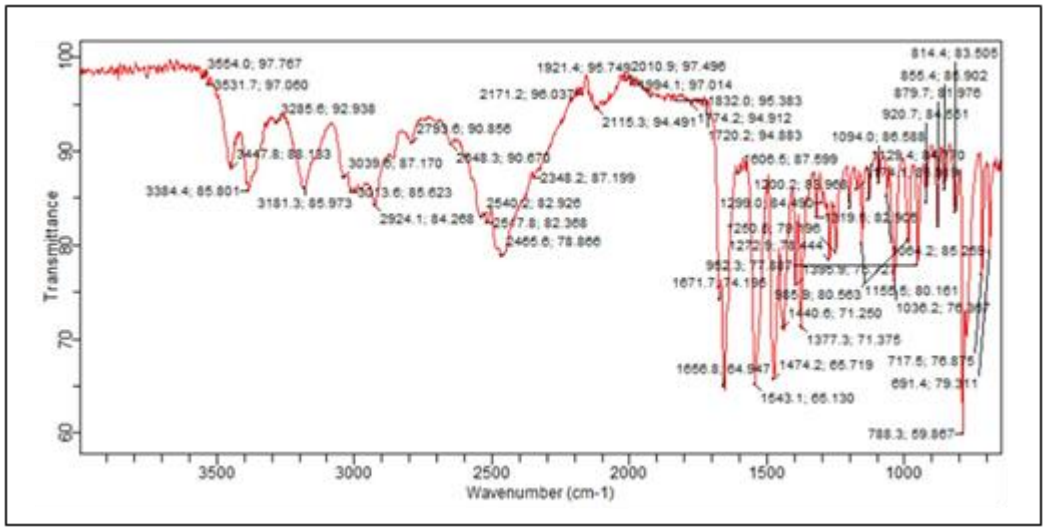

Figure 4: FTIR Spectrum of Drug Choline Salicylate

The FTIR spectra of pure drugs showed characteristic peaks. The obtained spectrum of the pure drug was compared with standard FTIR spectra of LH and CS which agree with the reported values of LH and CS. As shown in Tables 6 and 7 the functional group matches with standard spectra of the drug [22] [23].

Table 6: Characteristic Peak Observed in FTIR of Drug Lidocaine HCl

Sr. No.	Functional group showing peak	FT IR spectra of the drug (LH)	FTIR spectra of Reference Standard Drug
1	N-H	3382	3383
2	C-H	3013	3011
3	Amide I C=O	1656	1654
4	Amide II C≡N	1476	1472

Table 7: Characteristic Peak Observed in FTIR of Drug Choline Salicylate

Sr. No.	Functional group showing peak	FTIR spectra of drug (CS)	FTIR spectra of Reference Standard Drug
1	-OH	3384.4	3400-3200
2	C=O	1094	1088
3	C≡N	855.4	860
4	C=C	1474	1487

3.2.1. Drug-Excipient Compatibility Study

From the study of FTIR of pure drug and physical mixture of drug & excipients, it was found that peaks of functional groups of the drug remain almost the same in the physical mixture of drug and excipients. From the observation and identification of peaks, it was found that drug and excipients are compatible. Although some peaks overlapped due to similar chemical moieties, the absorption bands that corresponded to specific moieties were unchanged [24] [25] [26].

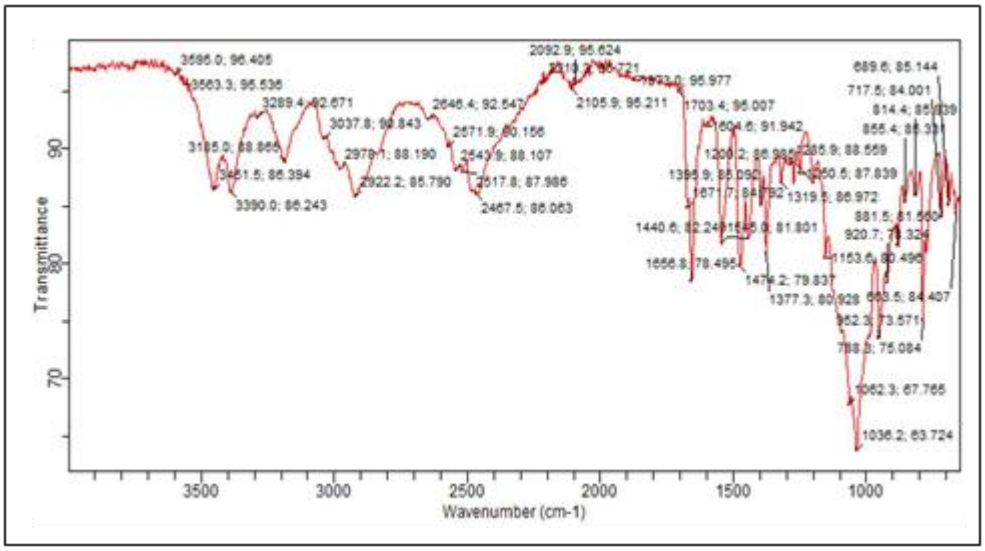

Figure 5: FTIR Spectra of the Physical Mixture of Lidocaine HCl + HPMC E15

Table 8: FTIR Compatibility Study

Sr. No.	Functional group showing peak	FTIR spectra of the drug (LH)	FTIR spectra of the physical mixture (LH + HPMC E15)
1	N-H	3383	3390
2	C-H	3011	3037
3	Amide I C=O	1654	1656.8
4	Amide II C≡N	1472	1474.2

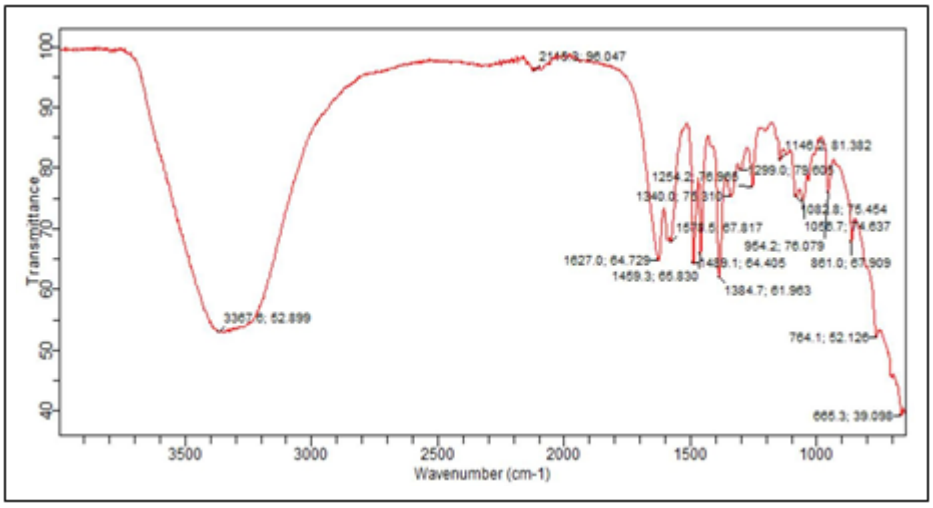

Figure 6: FTIR Spectra of the Physical Mixture of Choline Salicylate + HPMCE 15

Table 9: FTIR Compatibility Study 4

Sr. No.	Functional group showing peak	FTIR spectra of drug (CS)	FTIR spectra of the physical mixture (CS+HPMC E15)
1	-OH	3384.4	3367.6
2	C=O	1094	1082.8
3	C≡N	855.4	861.0
4	C=C	1474	1459.3

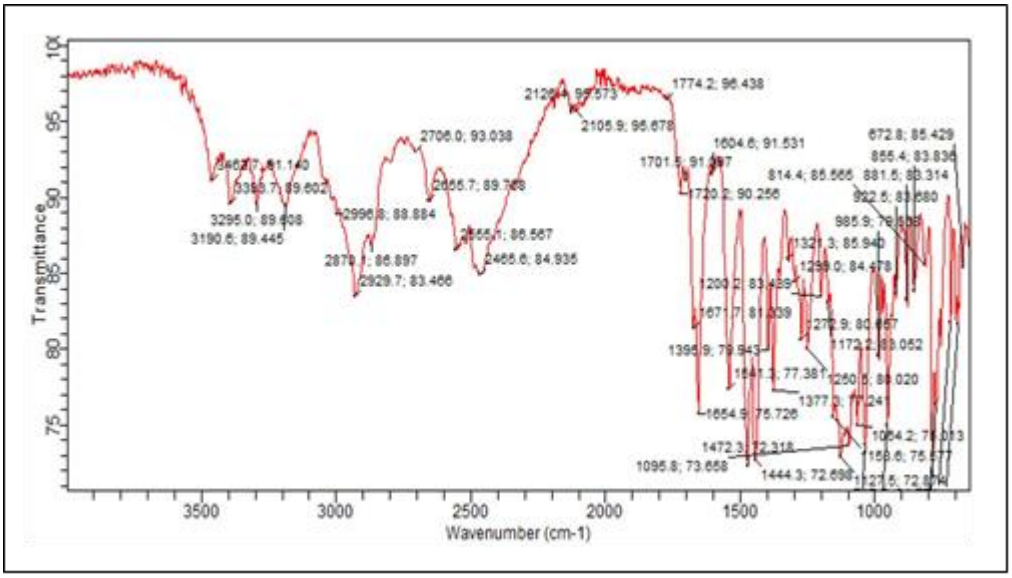

Figure 7: FTIR Spectra of Physical Mixture of Lidocaine HCl + Citric Acid

Table 10: FTIR Compatibility Study

Sr. No.	Functional group showing peak	FTIR spectra of the drug (LH)	FTIR spectra of the physical mixture (LH + CA)
1	N-H	3383	3393
2	C-H	3011	2996
3	Amide I C=O	1654	1654
4	Amide II C≡N	1472	1472

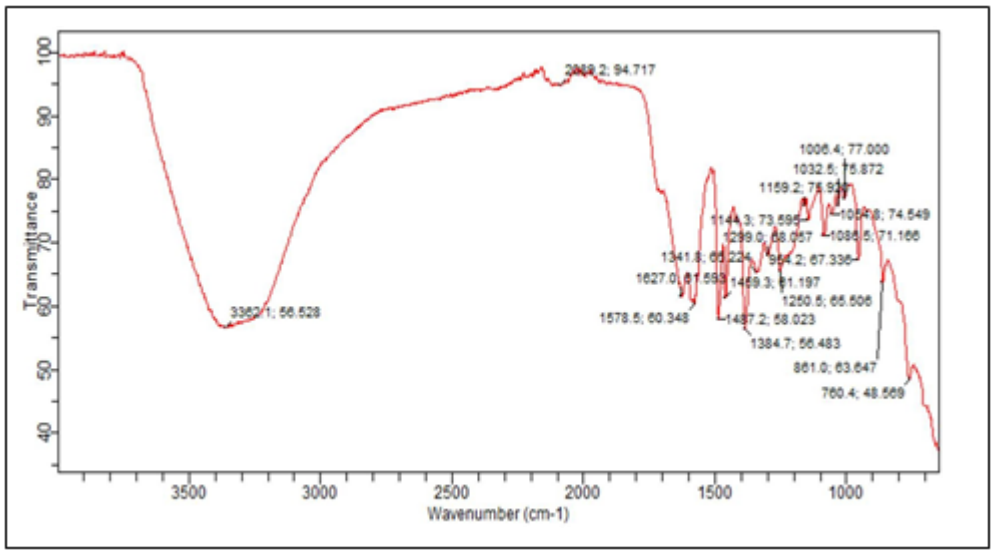

Figure 8: FTIR Spectra of Physical Mixture of Choline Salicylate + Citric Acid

Table 11: FTIR Compatibility Study

Sr. No.	Functional group showing peak.	A characteristic peak in FTIR spectra of drug (CS)	FTIR spectra of the physical mixture (CS+CA)
1	-OH	3384.4	3362
2	C=O	1094	1086.5
3	C≡N	855.4	861.0
4	C=C	1474	1487

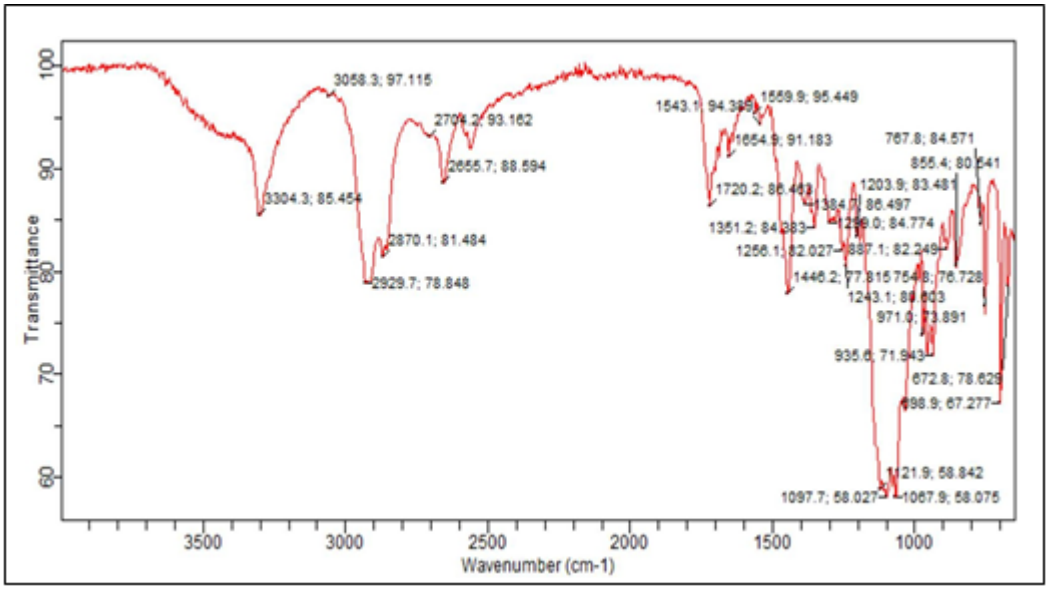

Figure 9: IR Spectra of Physical Mixture of Lidocaine HCl + PEG 400

Table 12: FTIR Compatibility Study

Sr. No.	Functional group showing peak.	FTIR spectra of the drug (LH)	FTIR spectra of the physical mixture (LH + PEG 400)
1	N-H	3383	3304
2	C-H	3011	3058
3	Amide I C=O	1654	1654
4	Amide II C≡N	1472	1446

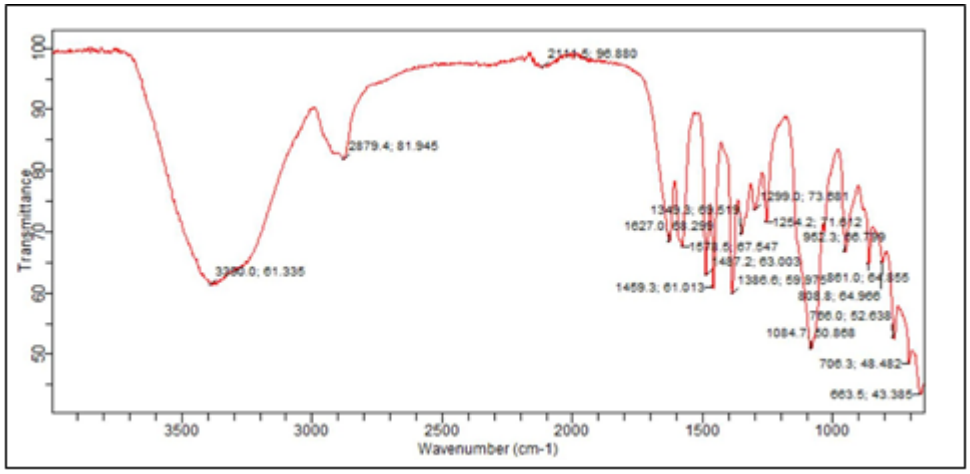

Figure 10: FTIR Spectra of Physical Mixture of Choline Salicylate +PEG 400

Table 13: FTIR Compatibility Study

Sr. No.	Functional group showing peak	FTIR spectra of drug (CS)	FTIR spectra of the physical mixture (CS + PEG 400)
1	-OH	3384.4	3380
2	C=O	1094	1084.7
3	C≡N	855.4	808.8
4	C=C	1474	1487

3.3. Formulation and Optimization of Bilayer Fast-Dissolving Film [Trial Batches]

Trial batches B1-B15 were characterised by specific evaluation parameters: Physical appearance, Thickness, weight, Folding endurance, % Elongation, TS and Disintegration time. The results of these evaluations were satisfactory. However, to achieve specific quality parameters such as a disintegration time of 5 seconds, the highest TS, and enough thickness. Based on the results of all parameters we are selecting HPMC E15 (Film-forming agent) and PEG 400 (Plasticizer) for final formulation Evaluation results for the same are shown in Table 14.

Table 14: Evaluation Results of Trial Batches B1 to B15

Sr. No	**Test**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**
1	Thickness (mm)	0.071 ± 0.01	0.08± 0.02	0.09± 0.01	0.07± 0.03	0.08± 0.01	**0.07± 0.02**	0.08± 0.01	0.09± 0.01	0.07± 0.03	0.08± 0.02	0.07± 0.01	0.08± 0.01	0.09± 0.01	0.07± 0.02	0.08± 0.01
2	Weight (mg)	17 ± 1	20±1	22±1	16±2	18±1	**17±2**	19±1	21±1	15±2	16±2	18±1	20±3	22±2	17±2	18±1
3	Folding Endurance	96 ± 1	94±1	93±2	91±1	90±2	**105±1**	104±1	102±1	99±1	98±1	95±1	94±1	93±2	90±2	89±2
4	% Elongation	12.5 ±1.5	15.5 ±1.9	13.75 ±2.5	14.5 ±1.8	12.5 ±0.5	**20±0.5**	17.5± 1.0	16.25 ±2.2	15±1.5	12.5 ±1.5	15±1.5	12.5 ±1.8	17.5± 0.7	20±1.6	16.25 ±1.3
5	TS (N/cm2)	1.470 ±0.30	1.34 ±0.20	1.300 ±0.30	1.545 ±0.30	1.447 ±0.25	**1.667 ±0.30**	1.593 ±0.25	1.447 ±0.30	1.470 ±0.25	1.545 ±0.20	1.347 ±0.30	1.300 ±0.20	1.592 ±0.30	1.667 ±0.20	1.545 ±0.15
6	DT (Sec)	8±1	9±2	10±1	12±1	11±1	**5±2**	6±2	7±2	9±1	8±1	9±1	10±1	11±1	13±1	12±1

3.4. Formulation and Optimization of Bilayer Fast-Dissolving Film [Factorial Batches]

To achieve specific quality parameters such as less disintegration time, the highest TS and % drug release within 1 minute. further study, optimization of the formulation is necessary. For this purpose, we plan to use the design of experiment software to identify the optimal formulation that meets these specific quality criteria. Formulated factorial batches F1-F9 were evaluated for various evaluation parameters. A summary of evaluation results is shown in Table 15.

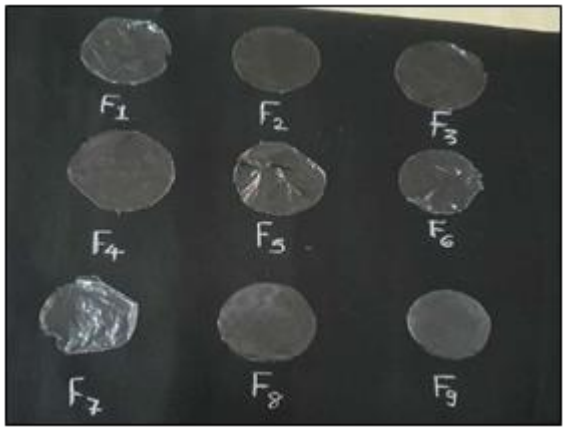

Figure 11: Factorial Batches

Table 15: Results of 32 Full Factorial Design Batches of Lidocaine HCl and Choline Salicylate loaded Bilayer Fast Dissolving Film

Sr. No	**Test**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Thickness(mm)	0.07± 0.02	0.08± 0.01	0.09± 0.03	0.07± 0.01	0.09± 0.02	0.11± 0.01	0.07± 0.03	0.12± 0.01	0.13± 0.02
2	Weight (mg)	17±1	16±2	15±1	16±3	17±2	18±1	17±1	18±2	19±1
3	Folding endurance	96±2	95±1	94±3	99±2	98±1	97±2	105±1	104±1	102±2
4	% Elongation	13.75 ±1.5	12.5 ±1.8	12.25 ±2.2	13.5± 1.5	14.5 ±0.5	13.75 ±1.7	20± 2.2	17.5± 1.5	16.25 ±1.2
5	TS (N/cm2)	1.407 ±0.30	1.347 ±0.20	1.300 ±0.30	1.545 ±0.30	1.470 ±0.25	1.447 ±0.20	1.715 ±0.30	1.667 ±0.25	1.592 ±0.20
6	DT (sec)	5±1	6±2	9±1	8±2	11±1	12±3	6±1	10±1	14±1

7	% CDR within 1 minute	88.30 ±0.11	85.54 ±0.13	78.78 ±0.19	98.50 ±0.18	96.03± 0.16	93.52 ±0.13	99.90 ±0.15	97.42 ±0.13	95.30± 0.15
8	% Drug content	87.02 ±0.48	87.20 ±0.52	86.63 ±0.32	89.60 ±0.48	89.73 ±0.64	88.50 ±0.39	97.63 ±0.40	95.96 ±0.53	94.30 ±0.47

The results are mean±SD, (n=3)

3.4.1. In-Vitro Drug Release Study of Factorial Batches

A study of in-vitro drug release was carried out in a 6.8 pH phosphate buffer. The dissolution data of Batch F1 to F9 in phosphate buffer (6.8 pH) at 37±0.5˚C are presented in Table 16. The dissolution profile of Batch F1 to F9, with LH and CS as a control, was evaluated for 60 seconds in a defined medium. Figure 12 shows the dissolution of Batch F1 to F9 in 250 ml of phosphate buffer (6.8 pH). % drug release of the two drugs LH and CS which was measured at 263nm and 238nm respectively, was calculated by taking the average % drug release of both the drugs.

Table 16: Result of In-Vitro Drug Release Study of Factorial Batches F1 to F9

Time (sec)	**% Drug Release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
10	42.19 ±0.18	22.81 ±0.15	17.37 ±0.11	56.32 ±0.17	47.58 ±0.13	48.18 ±0.18	58.63 ±0.12	38.23 ±0.13	42.46 ±0.11
20	50.05 ±0.15	38.37 ±0.12	29.71 ±0.15	71.50 ±0.16	68.34 ±0.11	62.51 ±0.12	73.61 ±0.16	49.12 ±0.11	53.07 ±0.18
30	65.43 ±0.16	55.01 ±0.16	45.32 ±0.12	85.88 ±0.15	79.37 ±0.12	75.76 ±0.17	88.68 ±0.18	71.5± 0.16	72.29 ±0.11
40	81.69 ±0.15	68.43 ±0.11	55.63 ±0.18	96.6± 0.13	91.31 ±0.15	85.91 ±0.16	97.66 ±0.11	85.88 ±0.17	83.81 ±0.16
50	85.14 ±0.12	75.52 ±0.17	69.35 ±0.16	97.88 ±0.12	95.77 ±0.17	92.89 ±0.15	98.91 ±0.12	96.60 ±0.18	94.75 ±0.13
60	88.30 ±0.11	85.54 ±0.13	78.78 ±0.19	98.50 ±0.18	96.03 ±0.16	93.52 ±0.13	99.90 ±0.15	97.42 ±0.13	95.30 ±0.15

*The results are mean ± SD, (n=3)

In vitro, drug release profiles of prepared factorial batches are shown in **Figure 12** below. Immediate drug released in 1 minute.

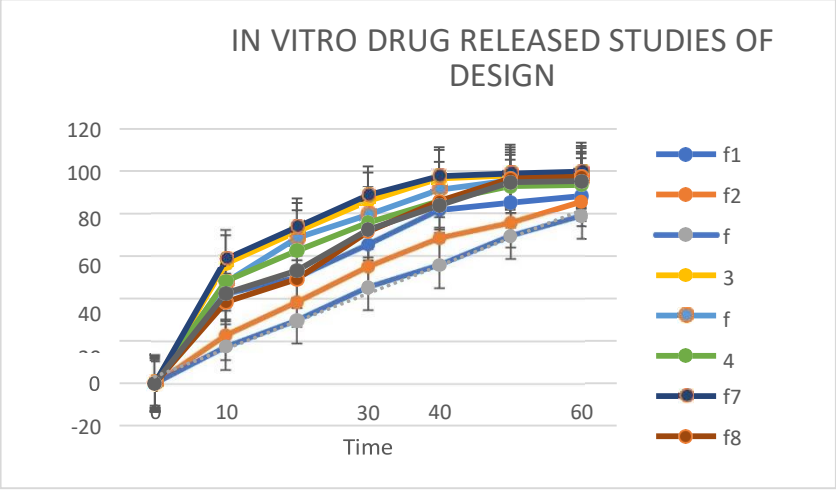

Figure 12: In vitro drug release profiles of factorial batches

3.5. 3^2 full factorial design for lidocaine HCl and choline salicylate loaded bilayer fast-dissolving film.

The present study involved only two factors X1- the amount of HPMC E15 and X2- PEG 400 at three levels and each was employed to develop LH and CS-loaded bilayer film formulations.

Table 17: Actual Levels of 3^2 Full Factorial Designs For Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast Dissolving Films.

Coded Values	Actual Values	
	X1	**X2**
-1	300	0.5
0	400	1
1	500	1.5

X1: Amount of film-forming agent (HPMC E15) in w/w%, X2: Amount of plasticizer (PEG 400) in w/w%, The actual values of each chosen factor have been shown against respective coded values in Table 17.

Table 18: Results of 3^2 Full Factorial Designs For Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast-Dissolving Film.

Code	DT (sec)	TS (N/cm2)	%CDR
F01	5±1	1.407±0.25	88.30±0.11
F02	6±1	1.347±0.20	85.54±0.13
F03	9±2	1.300±0.15	78.78±0.19
F04	8±1	1.545±0.30	98.50±0.18
F05	11±2	1.470±0.25	96.03±0.16
F06	12±2	1.447±0.20	93.52±0.13
F07	6±1	1.715±0.30	99.90±0.15
F08	10±1	1.667±0.25	97.42±0.13
F09	14±3	1.592±0.30	95.30±0.15

The results are mean±SD, (n=3),

DT: Disintegration time, TS: Tensile strength, %CDR: Percentage Cumulative drug release

The results of responses like Disintegration time, TS, and Percentage Cumulative drug release for experimental design batches of LH and CS-loaded BFDF have been illustrated in Table 18. For all nine batches of the chosen dependent variable, disintegration time revealed a wide variation of 5 to 14 sec. TS and percentage cumulative drugs release study also showed variation from 1.300 to 1.715 N/cm2 and 88.31 to 99.90%, respectively as per shown in the table. 18.

The data suggested a strong influence of chosen factors (X1 and X2) on the responses (R1, R2, and R3). A stepwise multivariate linear regression analysis was carried out to evaluate the observations. The equation representing the quantitative effect of the formulation variables on the measured responses is shown below:

Disintegration time, (R1) = +10.33+2.67 * A+1.67 * B+1.00 * A * B+0.000 * A2-2.00

* B2

Tensile strength, (R2) = +1.48-0.055 * A+0.15 * B-4.000E-003 * A * B+6.333E-003

* A2+0.017 * B2

Cumulative drug release within 1 min, (R3) = +95.39-2.49 * A+7.20 * B+1.76 * A * B-0.86 * A2-3.42 * B2

Table 19: The Results of ANOVA*

Response Disintegration time	**Regression**				
	df	**SS**	**MS**	**F**	**R2**
FM	5	71.33	14.27	Fcal:12.14	0.9640
RM	2	59.33	29.67	Ftab:16.05	0.8018
Response TS	**Regression**				
	df	**SS**	**MS**	**F**	**R2**
FM	5	0.16	0.032	Fcal:155.48	0.9962

RM	2	016	0.079	Ftab:350.33	0.9915
Response percentage cumulative drug release	**Regression**				
	df	**SS**	**MS**	**F**	**R2**
FM	5	384.90	76.98	Fcal:24.88	0.9877
RM	2	347.76	173.88	Ftab:48.25	0.8924

*ANOVA indicates the analysis of variance, DT: Disintegration time, TS: Tensile strength, %CDR: Cumulative drug release, FM: full model, RM: reduced model.

All the responses were subjected to ANOVA to explore the significance of the individual and combine the effects of the two factors. It was observed that all the independent variables had a significant effect on the responses ($p<0.05$). The large value of the F-ratio indicates that most of the variation in the response can be explained by the regression equations. All determination coefficients (R2) are larger than 0.9 that indicated over 90% of the variation in the response could be explained by the model

(A) Influence of Formulation Composition Factor on Disintegration Time (R1)

Disintegration time, as seen from the equation and graph, it was found that relative increase in the disintegration time with an increase in the amount of Film-forming polymer (HPMC E15) and Plasticizer (PEG 400) that might be due to the greater thickness of the film. The lowest Disintegration time of the film was found with Batch 1 (5 sec) [27].

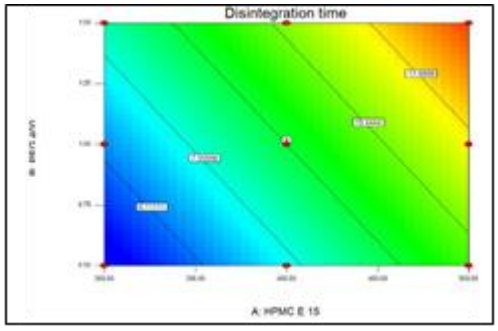

Figure 13: Contour Plot of Disintegration Time

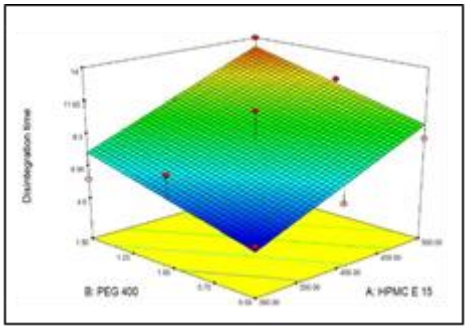

Figure 14: Surface Plot of Disintegration Time

B) Influence of Formulation Composition Factor on Tensile strength (R2)

Tensile Strength, as seen from the equation and graph, it was found that there is an increase in the TS with the increase in the amount of Plasticizer and a decrease in the amount of polymer. From the equation and graph, it was observed that the co-efficient of X2(Amount of Plasticizer) was higher than the co-efficient of X1(Amount of film-forming polymer). This means that the effect of X2 is a much more significant effect on TS than X1 [27].

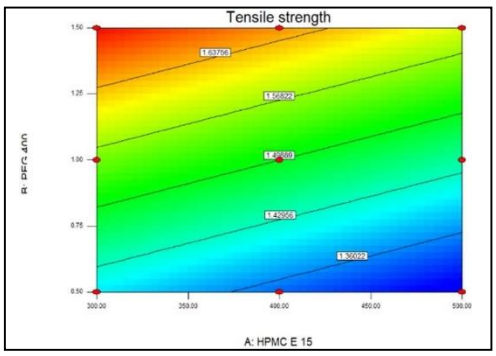

Figure 15: Contour Plot of TS

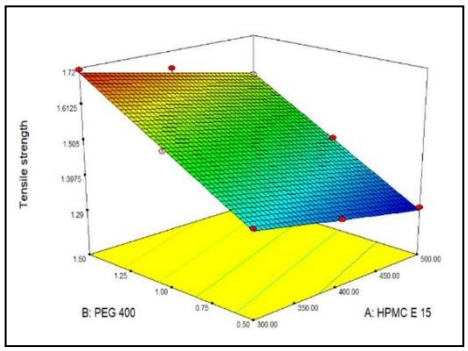

Figure 16: Surface Plot of TS

C) Influence of Formulation Composition Factor on Cumulative Drug Release (R3)

% Drug Release at 1 min, as seen from the equation and graph, it was found that there is an increase in the % Drug Release within 1 min with the decrease in the amount of Film-forming polymer and an increase in the amount of Plasticizer. From the equation and graph, it was concluded that the coefficient

of X1 (Amount of Film-forming polymer) was higher than the X2 (Amount of Plasticizer). This means that effect of X1 is much more significant on % drug released at 1 min. than X2 [28].

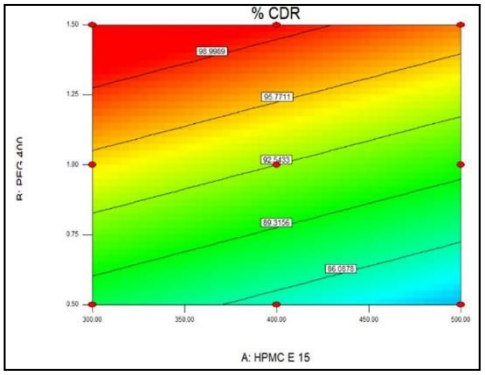

Figure 17: Contour Plot of % CDR

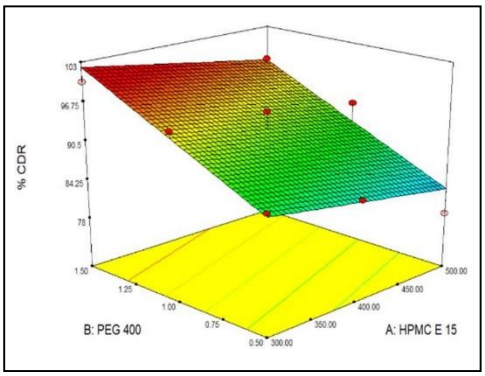

Figure 18: Surface Plot of % CDR

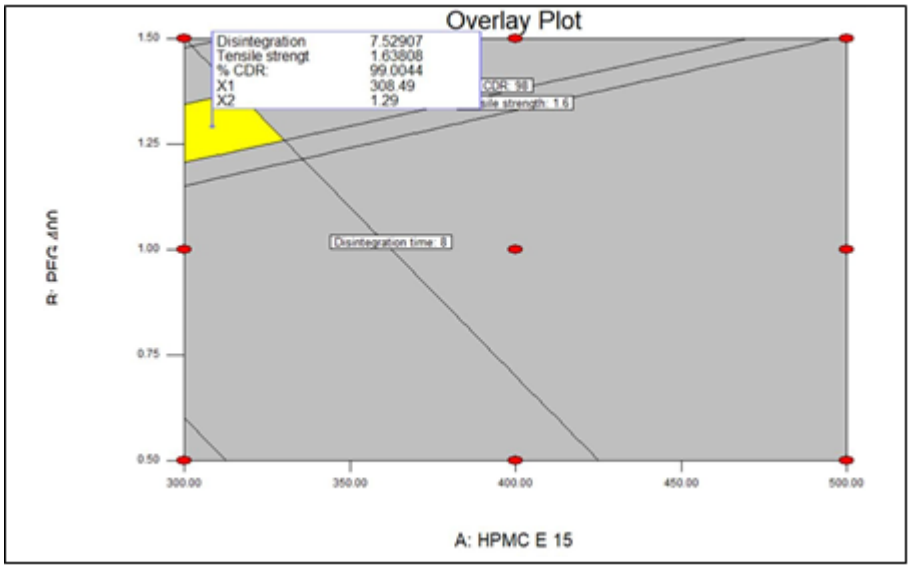

Figure 19: Overlay Plot with Checkpoint Batch for Lidocaine HCl and Choline Salicylate Loaded Bilayer Fast-Dissolving Films.

Based on the criteria for a desired response, the following batch was formulated to measure the reliability of the evolved equations. Checkpoint/optimized batch of LH, and CS loaded bilayer film formulations. were formulated practically according to levels of the factors illustrated in Figure 19. The experimental values and predicted values of each response are shown in Table 20. The percentage relative error of each response was calculated using the following equation.

Percentage relative error = Predicted value − Experimental value/ Predicted value × 100

Table 20: Results of Checkpoint Batch

Response	**Predicted Value**	**Experimental Value [mean ± SD, (n=3)]**	**%Relative Error**
DT (sec)	7.52907	7	6.91
TS (N/cm2)	1.63808	1.540	5.84
% CDR	99.0044	97.65	1.36

Table 21: Formulation and Composition of Optimized Batch

Name of component	**Amount**
HPMC E15 (mg)	308.49

PEG 400(ml)	1.29

The percentages of relative errors for the checkpoint batch were in the range of acceptance. It was concluded that the experimental values were in good agreement with theoretical values. This proved the validity of equations and selected 32 full factorial designs (Table 21).

3.6.1. Appearance

The prepared films were found to be smooth, uniform in thickness, mass, and drug content without any visible cracks or folds. The physical appearance was checked with a visual inspection of films and texture by feel or touch. Appearances of all the films were transparent, all were having smooth surfaces and were elegant enough for appearance.

3.6.2. Thickness

Film thickness as all the formulations contain a different concentration of (HPMC E15) and (PEG 400), the thickness gradually increased with the amount of polymers. All the film formulations were found to have a thickness in the range of 0.07±0.02 to 0.13±0.02 mm. the results are mean± SD, (n=3). The results of the above evaluation parameters were found to be in the standard range of 5-200µm.

3.6.3. Weight

Weight variation Three films each of 4 cm2 were cut at three different places from the casted film, and weight variation was determined. Weight variation varies from 15±1 to 19±1 mg. The results are mean± SD, (n=3).

3.6.4. Folding Endurance and Tensile Strength

Folding endurance helps in determining the mechanical strength of films. The higher the value of folding endurance, the higher the mechanical strength of the film. All the medicated films had satisfactory folding endurance. It was noticed that, as the concentration of PEG 400 increased, the folding endurance of the film also increased indicating that it affects the overall flexibility of the film. A direct relation

exists between mechanical strength and the folding endurance of films. As mechanical strength is governed by plasticizer concentration, it is evident that plasticizer concentration also indirectly affects folding endurance value. the highest folding endurance was found to be 105±1 F7 formulation and TS was found to be 1.300±0.30to to 1.715±0.30 for F7 formulation. the results are mean± SD, (n=3).

3.6.5. % Elongation

it was calculated by formula. Generally, the elongation of the strip increases as the plasticizer content increases. formulations were found to have a percentage elongation in the range of 12.25±2.2 to 20±2.2 %. the results are mean± SD, (n=3)

3.6.6. Disintegration Time

in vitro Disintegration time study was performed by the petri dish method. it was found that a relative increase in the disintegration time with an increase in the amount of Film-forming polymer (HPMC E15) and Plasticizer (PEG 400) might be due to the greater thickness of the film. The lowest Disintegration time of the film was found with F1 (5 sec). the results are mean± SD, (n=3). The results of the above evaluation parameters were found to be in the standard range of 5-30 sec.

3.6.7. % Drug Release at 1 Minute

In vitro drug release study Being a highly water-soluble polymer, it provides rapid disintegration and dissolution of the film. This characteristic helps in the rapid onset of action of the formulation, as the drug quickly diffuses from the oral mucosa and reaches systemic circulation. The in vitro drug release profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition. Being the fast-disintegrating formulations, the release rates of all the formulations were nearly rapid. highest dissolution of 99.9±0.130 % was seen in F7 formulation within 1 min. the results are mean± SD, (n=3)

3.6.8. Drug Content

The drug content of the film was between 86.63±0.32 and 97.63±0.40% w/w, indicating an almost uniform drug loading in all medicated batches. the results are mean± SD, (n=3)

3.6.9. Stability Study

The stability studies were carried out according to ICH to assess the drug formulation stability. film formulation was sealed in Aluminum packing laminated with polyethene. Samples were kept at 40°C and 75% RH for 30 days. At the end of the study period, the formulation was observed for change in physical appearance, thickness, folding endurance, TS, disintegration time and drug release within 1 minute. It is found to be all the physical and chemical parameters are satisfactory based on initial stability data. It is found to be all the physical and chemical parameters are satisfactory based on initial stability data. As per Table 22.

Table 22: Stability Studies [Condition (40°C/75%RH)]

Parameters	**Initial**	**15 days**	**30 days**
Thickness (mm)	0.07±0.01	0.07±0.01	0.07±0.02
Folding endurance	105±2	105±2	102±1
TS (N/cm2)	1.715±0.30	1.715±0.25	1.715±0.20
in-vitro disintegration time (sec)	6±2	6±2	7±1
in-vitro dissolution (%)	99.9±0.10	99.9±0.10	99.25±0.16

4. Conclusion

In conclusion, the development of a BFDF of LH and CS for the treatment of localized moderate to severe oral pain was successfully achieved through the optimization of the formulation. The use of the design of experiment software enabled the identification of the optimal formulation that met specific quality criteria, including a less disintegration time, the highest TS, and drug release within 1 minute. The results showed that the amount of film-forming polymer (HPMC E15) and plasticizer (PEG 400) significantly influenced the disintegration time, TS, and drug release of the formulation. Formulation F7 disintegrated in 6 seconds, %drug released 99.9% of the drug within 1 minute, TS 1.715 N/cm2, thickness measured 0.07mm, the weight of film was 17mg, folding endurance was 105 and % elongation calculated at 20 and was considered as the best formulation. Increasing the amount of plasticizer led to an increase in TS and a decrease in disintegration time while decreasing the amount of film-forming polymer increased drug release. These findings suggest that the BFDF formulation offers a promising approach for managing oral pain associated with various conditions, including oral cancer pain and other mouth disorders severe pain. The taste-masking advantage and rapid drug release of the formulation may improve patient compliance and outcomes, ultimately enhancing the quality of life for patients suffering from oral pain.

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