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FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF LOFEXIDINE HYDROCHLORIDE

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ABSTRACT
In the present research work, sublingual tablets of Lofexidine were developed and evaluated analytically by FTIR Spectra for drug absorption and bioavailability. Lofexidine was chosen as a model drug because its water solubility is good and belongs to BCS class I. The peak plasma concentration occurs after 2-5 hours of oral administration and sublingual formulation has not been developed yet. Pre-formulation studies were carried out to optimize the required quantity for polymers and excipients. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipient's interactions. A total of nine batches of sublingual of Lofexidine were prepared by direct compression technique, using polymers such as SSG, Cross povidone, cross carmellose sodium in different combinations with other standard excipients like Sucralose, Starcap 1500, Aerosil 200 and citric acid. Tablets were evaluated for physical parameters viz. hardness, friability, thickness, weight variation and stability studies. Further, tablets were evaluated *in-vitro* for drug release. All results were found to be in acceptance criteria; hence it was concluded that sublingual tablet of Lofexidine can be formed as marketed formulation also.

KEYWORDS: Lofexidine, SSG, HPMC, Crospovidone, Croscarmellose sodium, Sucralose, Sublingual tablet.

INTRODUCTION TO SUBLINGUAL DRUG DELIVERY SYSTEM
Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularizing, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first- pass metabolism in the liver. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through ventral surface of the tongue and floor of the mouth. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route.[1]

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane. The Absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration.

Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia.)

ADVANTAGES AND DISADVANTAGES OF SUBLINGUAL TABLET[2]
Advantages
- Produces immediate systemic effect.
- Dose gets reduced.
- Onset of action is very fast.
- Improved bioavailability.
- Effective in disease like nausea, vomiting, migraine, schizophrenia.
- Provides sustained drug delivery.
- Easy to administer.
- Bypass GI tract and hepatic portal system, therefore it increases the bioavailability of orally administered drugs that otherwise undergo hepatic first pass metabolism.

Disadvantages[3]
- Less area for absorption.

- Unsuitable for bitter drugs.
- Poor patient compliance.
- Administration of highly ionic drug is not allowed.
- Administration of high dose is not possible. Techniques used in preparation of sublingual tablet[4]:
- Direct Compression Technology
- Fast melting technology
- Sublimation
- Lyophilization Introduction to Lofexidine[5-9]

Lofexidine is a white to off white crystalline powder. It is centrally acting α2 adrenergic agonist. It possesses molecular weight of 259.132 g/mol. It is freely soluble in water, methanol and ethanol. Lofexidine peak plasma concentration occurs after 2-5 hours of oral administration. About 30% of the administered dose of lofexidine is lost during first-pass metabolism. The protein binding of lofexidine is determined to be moderate and it represents about 55% of the administered dose. It is metabolized mainly by the activity of CYP2D6 and in a minor degree by CYP1A2 and CYP2C19.With the half-life of 11 hours, the elimination of Lofexidine is primarily through the renal system and it represents 94% of the administered dose while elimination in feces corresponds to only 0.93%.

Lofexidine is indicated for mitigation of symptoms associated with acute withdrawal from opioids and for facilitation of the completion of opioid discontinuation treatment. It is the first non- opioid medication for the symptomatic management of opioid discontinuation. Lofexidine is a potent alpha2-adrenergic receptor agonist with some moderate agonistic affinity towards Alpha-1A adrenergic receptor and 5-HT1a, 5-HT7, 5HT2c and 5HT1d receptors.

MATERIALS AND METHODS

Materials: The active drug Lofexidine was obtained from Torrent Research Centre, Ahmedabad, India. Other excipients such as Croscarmellose Sodium Crospovidone, Sodium Starch Glycolate, Starcap 1500, Sucralose, Aerosil 200, Citric acid, avicel pH 102 were purchased from S.D. Fine Chemicals, Ahmedabad. All other solvents and ingredients used were of analytical grade.

METHODS

Formulation of sublingual Tablets: Sublingual tablet containing 0.18 mg Lofexidine were prepared by direct compression method (Lachman et al, 1991). Lofexidine was mixed with required quantity of Croscarmellose Sodium Crospovidone, Sodium Starch Glycolate, Starcap 1500, Sucralose, Aerosil 200, Citric acid and avicel pH 102 by geometric mixing in mortar and pestle for 10 min. The blend was compressed into tablets using single punch. A total of nine batches were prepared with varyingcomposition of excipients.

Preparation of standard calibration curve of Lofexidine: Accurately weighed 10 mg Lofexidine was dissolved in 100 ml of pH 6.8 phosphate buffer solution. Take 10 ml of this solution in a 100 ml of volumetric flask and make up the volume with phosphate buffer (pH 6.8) solution to get working stock- solution having concentration 100 µg/ml. From this stock-solution aliquots of 1ml, 2ml, 3ml, 4ml and 5ml were pipetted out into a series of 10 ml volumetric flasks and make up to mark with pH 6.8 phosphate buffer solution in order to get a concentration within the Beer's range from 10-50 µg/ml. Theabsorbance of the resulting solution was then measured at 209 nm using UV Spectrophotometer againstrespective parent solvent as a blank (i.e., pH 6.8 buffer solutions). The standard curve was obtained by plotting absorbance V/s concentration in µg/ml.

Pre-Compression Parameters: Angle of repose

The angle of repose of Lofexidine was determined by fixed funnel method. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder.

Carr's index: The Carr's index or Carr's Compressibility Index is an indication of the compressibility of a powder. It can be calculated by formula.

$$\text{Carr's Index} = \frac{(\text{tapped density} - \text{bulk density}) \times 100}{\text{tapped density}}$$

Hausner's ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It can be calculated by formula.

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Thickness: Thickness of tablets was determined using Vernier calipers. Three tablets from each batch were used, and average values were calculated.

Average weight: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

Drug content: Ten tablets were randomly selected, accurately weighed and average weight per tablet calculated. The tablets were ground individually to fine powder. Accurately weighed tablet powder transferred to 100 ml volumetric flask. Add 6.8 phosphate buffer up to the spot. After few minutes the solution was filtered; rejecting first few ml of the filtrate analyzed spectrophotometrically at 209 nm.

Hardness: The ability of tablets to resist breakage, under conditions of shipping or storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability: The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). 6.5-gram weight equivalent tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by,

$$\text{Percent loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

***In vitro* Release Studies:** Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II. A total volume of 500 ml of 6.8 phosphate buffer was taken in dissolution apparatus, which was maintain at 37°C ± 0.5°C at 50 rpm. Ten milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 2-minute intervals and filtered by Whatman filter paper. Samples were analyzed spectrophotometrically at 209 nm.

***In vitro* disintegration studies:** In- vitro Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temp were 37±2°C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

Content Uniformity: Ten tablets were randomly selected from each batch. Assay of each tablet was measured as per drug content method. The Assay value of each tablet is reported and based on that the Acceptance value was calculated as per USP. The Acceptance value will be not more than 15.

Stability Study: The optimized batch will be subjected for stability study. Tablets will be suitably packed in aluminum foil. The Tablets was exposed at 40° C/75% RH condition. At the end of 1 month, the sealed Tablets was opened and evaluated for critical parameters.

Statistical data analysis: Statistical data analysis of independent variables and Response variables can be adequately characterized by polynomial equation. Specific effects (main, interaction) of independent variables on responses also can be explained from polynomial equation. For estimating of significance of the model, the analysis of variance (ANOVA) was determined as per provision of Design Expert software.

RESULT AND DISCUSSION

The reported melting point values for Lofexidine was in the range of 221°C-223°C which was in agreement with literature. The absorption maxima of the standard solution were scanned between 200- 350 nm regions on Shimadzu 1800 spectrophotometer. The absorption maxima were found to be 209 nm. FTIR study was performed with the supplied sample of Lofexidine. This FTIR spectrum was found concordant with the FTIR of Lofexidine reported in official monograph and the peaks matched with the standard peaks of pure Lofexidine. The infrared spectrum of physical mixture of excipients and Lofexidine was studied and confirmed that there was no interaction with each other. So, the drug is compatible with excipients.

The powder mixtures of all the formulations were tested by various studies including angle of repose (ranging from 26.52° to 39.08°), bulk density (ranging from 0.200 to 0.348 gm/cm^3), tapped density (ranging from 0.350 to 0.697 gm/cm^3), Hausner's ratio (ranging from 1.23 to 1.72) and Carr's index (ranging from 28.69 to 33.57 %). All the results showed poor flow property. The thickness of prepared tablet batches from F1 to F9 was measured by Vernier calipers and was found to vary between 2.96 ± 0.01 to 3.04 ± 0.03 mm. The hardness of formulations F1 to F9 was measured by Monsanto tester and was found to assume values between 3.54 ± 0.30 and 3.67 ± 0.14 kg/cm^2. The friability of all the formulations was measured by Roche friabilator and was found to be in the range of 0.6% to 0.9%, well within the permissible limits.

The weight variation for different formulations (F1 to F9) was found to be ranging in between 498 to 500 mg, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. Drug content was in the range of 99 ± 2.10 to 101 ± 2.01.

The results of *in-vitro* disintegration and dissolution studies are given in table. All the tablet formulations showed more than 12 % release within 15 minutes, but F8 formulation showed maximum 99.6% drug release within 4 minutes.

In ANOVA for quadratic model (disintegration time), Factor coding is Coded. Sum of squares is Type III – Partial. The Model F-value of 98.85 implies the model is significant. There is only a 0.16% 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 A, B, A² are significant model terms. 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 model.

For validation of optimized formulation, a checkpoint batch was designed accordance to the desirability function, as shown in table and figure. To assess the validity of prediction, a checkpoint batch C1 and C2 was prepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with that of required data.

Stability study of optimized batch O1 was performed for 1 month. The stability study data revealed that the O1

formulation found stable over the period of 1 month. The evaluation parameters after 1 month were found satisfactory and well within acceptable limit.

Table 1: Formulation table of Lofexidine HCl Sublingual tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lofexidine HCl	0.2	0.2	0.2	0.2	0.2	0.2	0.2	**0.2**	0.2
SSG	2	4	8	-	-	-	-	-	-
Crospovidone	-	-	-	2	4	8	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	2	**4**	8
Sucralose	2	2	2	2	2	2	2	**2**	2
Starcap 1500	40	40	40	40	40	40	40	**40**	40
Aerosil 200	1	1	1	1	1	1	1	**1**	1
Citric Acid	4	4	4	4	4	4	4	**4**	4
Avicel pH 102	50.8	48.8	44.8	50.8	48.8	44.8	50.8	48.8	44.8
Total weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 2: Coded levels translated in actual units.

Coded level	Actual value	
	X1 (mg)	X2 (mg)
-1	3	25
0	4	35
+1	5	45

Table 3: 3^2 full factorial design layouts.

Sr. No	Batch No	X1	X2
1.	S1	-1	-1
2.	S2	-1	0
3.	S3	-1	+1
4.	S4	0	-1
5.	S5	0	0
6.	S6	0	+1
7.	S7	+1	-1
8.	S8	+1	0
9.	S9	+1	+1

Table 4: Formulation table for factorial batches.

Ingredients (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
Lofexidine HCl	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Croscarmellose Sodium	3	3	3	4	4	4	5	5	5
Starcap 1500	25	35	45	25	35	45	25	35	45
Sucralose	2	2	2	2	2	2	2	2	2
Aerosil 200	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric Acid	5	5	5	5	5	5	5	5	5
Avicel pH 102	61.9	51.9	41.9	60.9	50.9	40.9	59.9	49.9	39.9
Total weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 5: Standard calibration curve of Lofexidine in phosphate buffer.

Sr. No.	Concentration (µg/ml)	Absorbance Average ± SD
1	0	0
2	2	0.149 ± 0.003
3	4	0.273 ± 0.002
4	6	0.443 ± 0.003
5	8	0.569 ± 0.002
6	10	0.712 ± 0.003
7	12	0.853 ± 0.003

Table 6: Interpretation of FTIR spectra.

IR Spectra	Peak of functional group [Wavelength] cm^{-1}				
	O-H Stretching	C-O Stretching	C=O	C-C Stretching	N-H Bend
Lofexidine	2862.89	1152.16	1715.12	1441.93	1612.82
Formulation	2942.16	1149.79	1719.03	1459.16	1612.84

Table 7.1: Pre-Compression Parameters of F1-F9 batch.

Formulation	Bulk density±SD (g/ml) (n=3)	Tapped density± SD(g/ml) (n=3)	Carr's index ± SD (%) (n=3)	Hausner's ratio± SD (n=3)	Angle of repose (Ɵ) ± SD(n=3)
F1	0.49 ± 0.07	0.57 ± 0.04	13.88 ± 0.05	1.16 ± 0.08	28.2º
F2	0.46 ± 0.06	0.53 ± 0.01	12.55 ± 0.08	1.14 ± 0.03	21.8º
F3	0.52 ± 0.05	0.59 ± 0.02	11.41 ± 0.09	1.13 ± 0.04	28.5º
F4	0.52 ± 0.10	0.60 ± 0.08	13.04 ± 0.07	1.15 ± 0.05	27.4º
F5	0.51 ± 0.09	0.57 ± 0.07	11.15 ± 0.04	1.13 ± 0.06	29.8º
F6	0.46 ± 0.04	0.52 ± 0.06	12.21 ± 0.06	1.14 ± 0.04	26.2º
F7	0.47 ± 0.03	0.53 ± 0.04	11.32 ± 0.03	1.13 ± 0.02	28.3º
F8	**0.51 ± 0.03**	**0.60 ± 0.09**	**15.00 ± 0.03**	**1.18 ± 0.07**	**26.9°**
F9	0.54 ± 0.09	0.59 ± 0.06	8.47 ± 0.05	1.09 ± 0.08	29.8°

Table 7.2: Pre-Compression Parameters of F1-F9 batch.

Formulation	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %
F1	100 ± 2.36	3.07 ± 0.02	3.70 ± 0.36	0.5
F2	99 ± 2.36	3.04 ± 0.03	3.76 ± 0.32	0.4
F3	100 ± 2.05	3.04 ± 0.02	3.86 ± 0.25	0.8
F4	101 ± 2.78	3.20 ± 0.06	3.67 ± 0.14	0.6
F5	98 ± 2.72	3.06 ± 0.08	3.96 ± 0.12	0.4
F6	100 ± 2.46	3.06 ± 0.03	3.84 ± 0.20	0.3
F7	101 ± 2.30	2.96 ± 0.03	3.77 ± 0.35	0.6
F8	**99 ± 2.10**	**2.96 ± 0.01**	**3.54 ± 0.30**	**0.9**
F9	101 ± 2.01	3.02 ± 0.05	3.88 ± 0.22	0.3

Table 7.3: Pre-Compression Parameters of F1-F9 batch.

Formulation	Drug Content (%)	Content Uniformity	*In-vitro* Disintegration time (Seconds)
F1	98.9 ± 1.5	Pass	398 ± 52
F2	97.1 ± 1.6	Pass	311 ± 26
F3	99.5 ± 1.9	Pass	239 ± 17
F4	98.6 ± 1.2	Pass	99 ± 10
F5	97.3 ± 1.4	Pass	89 ± 2
F6	99.1 ± 1.3	Pass	80 ± 8
F7	99.6 ± 1.8	Pass	108 ±15
F8	**99.0 ± 1.6**	**Pass**	**26 ± 3**
F9	99.7 ± 1.1	Pass	85 ± 5

Table 8: In-vitro Dissolution Profile of the Formulations (F1-F9).

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.4±1.4	19.4±1.8	15.8±1.6	20.8±2.3	48.5±1.9	15.8±2.8	7.2±1.6	28.5±2.2	33.7±2.8
2	19.8±2.1	24.3±2.9	20.8±1.8	65.7±2.8	78.8±2.8	50.7±1.6	50.4±2.9	55.7±1.9	67.8±1.6
3	26.7±2.2	32.3±1.3	45.6±2.9	94.8±1.4	86.9±1.3	83.2±2.5	63.9±1.5	71.2±2.6	90.5±1.4
4	33.4±1.8	51.8±1.2	68.9±2.7	99.7±1.9	95.2±2.4	97.8±1.6	74.2±2.3	99.6±1.3	99.7±2.2
5	45.8±2.3	61.4±1.1	90.7±1.4	99.7±2.3	97.8±1.1	99.4±1.4	86.9±2.54	-	99.8±1.2
8	52.0±1.9	95.8±2.4	92.8±1.6	99.7±1.8	99.4±1.2	99.5±2.7	98.4±1.8	-	99.9±2.6
10	66.5±1.4	96.7±1.3	99.7±2.5	99.7±2.2	99.8±1.3	99.5±2.9	99.7±2.7	-	99.9±1.1
12	97.3±2.8	99.4±2.8	99.8±1.6	99.7±2.1	99.8±2.9	99.5±1.8	99.7±2.3	-	99.9±2.1
15	99.8±2.3	99.7±1.9	99.9±2.8	99.7±1.4	99.9±1.8	99.5±1.6	99.8±2.2	-	99.9±2.3

Table 9: Evaluation of factorial batches S1-S9.

Formulation	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %
F1	101 ± 1.9	3.05 ± 0.02	3.80 ± 0.36	0.66
F2	100 ± 1.4	3.06 ± 0.03	3.78 ± 0.32	0.70
F3	102 ± 1.3	3.08 ± 0.02	3.80 ± 0.25	0.64
F4	100 ± 1.7	3.10 ± 0.06	3.86 ± 0.14	0.65
F5	99 ± 0.9	3.08 ± 0.08	3.98 ± 0.12	0.42
F6	101 ± 1.6	3.04 ± 0.03	3.87 ± 0.20	0.59
F7	102 ± 1.5	3.05 ± 0.03	3.90 ± 0.35	0.53
F8	**101 ± 1.2**	**3.09 ± 0.01**	**3.85 ± 0.30**	**0.61**
F9	100 ± 1.2	3.20 ± 0.05	3.64 ± 0.22	0.72

Table 10: Evaluation of factorial batches S1-S9.

Formulation	Wetting Time(Seconds)	*In-vitro* Disintegration time(Seconds)	Drug Content(%)
S1	59 ± 3	52 ± 5	98.4 ± 1.7
S2	53 ± 7	46 ± 3	98.9 ± 1.1
S3	47 ± 7	41 ± 2	97.5 ± 1.5
S4	35 ± 7	29 ± 4	98.2 ± 1.0
S5	32 ± 5	24 ± 2	99.1 ± 1.9
S6	30 ± 7	22 ± 2	98.7 ± 1.4
S7	34 ± 7	25 ± 3	97.1 ± 1.3
S8	26 ± 7	18 ± 2	98.5 ± 1.7
S9	19 ± 2	12 ± 1	99.0 ± 1.2

Table 11: In-vitro Dissolution Profile of the Factorial Batches.

Time in min	S1	S2	S3	S4	S5	S6	S7	S8	S9
0	0	0	0	0	0	0	0	0	0
0.5	25.4	28.9	31.2	30.5	36.9	38.9	44.3	48.2	51.6
1	39.6	44.6	47.8	64.9	69.1	70.2	73.9	75.2	78.9
2	54.3	59.7	63.2	93.1	98.9	98.6	98.9	99.4	99.5
3	71.2	75.9	79.4	98.9	99.5	99.4	99.1	99.6	99.9
4	85.9	89.3	92.6	99.1	99.6	99.8	99.5	99.7	99.9
5	98.7	99.1	99.5	99.5	99.6	99.9	99.6	99.8	99.9

Table 12: 3^2 Full Factorial Design Layout.

Batch	Independent variable		Dependent Variables	
	X1 Croscarmellose Sodium (mg)	**X2 Starcap 1500 (mg)**	**Y1 Disintegration time (sec)**	**Y2 (% Drug Releaseat 1 min)**
S1	3	25	52	39.6
S2	3	35	46	44.6
S3	3	45	41	47.8
S4	4	25	29	64.9
S5	4	35	24	69.1
S6	4	45	22	70.2
S7	5	25	25	73.9
S8	5	35	18	75.2
S9	5	45	12	78.9

Table 13: ANOVA for Quadratic model- Disintegration time.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1446.11	5	289.22	98.85	0.0016	significant
A-Croscarmellose Sodium	1176.00	1	1176.00	401.92	0.0003	
B-Starcap 1500	160.17	1	160.17	54.74	0.0051	
AB	1.0000	1	1.0000	0.3418	0.5999	
A^2	107.56	1	107.56	36.76	0.0090	
B^2	1.39	1	1.39	0.4747	0.5403	

Residual	8.78	3	2.93			
Cor Total	1454.89	8				

Table 14: ANOVA for Quadratic model- Disintegration time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1726.09	5	345.22	312.15	0.0003	significant
A-Croscarmellose Sodium	1536.00	1	1536.00	1388.88	< 0.0001	
B-Starcap 1500	57.04	1	57.04	51.58	0.0056	
AB	2.56	1	2.56	2.31	0.2255	
A^2	130.14	1	130.14	117.68	0.0017	
B^2	0.3472	1	0.3472	0.3140	0.6144	
Residual	3.32	3	1.11			
Cor Total	1729.41	8				

Table 15: Check point batch.

Batch	**C1**	**C2**
Croscarmellose Sodium (mg)	4.2	3.2
Starcap 1500 (mg)	39.1	40.0
Predicted Disintegration time (sec)	19	35
Observed Disintegration time (sec)	20	34
% Difference	0.95	1.02
Predicted % Drug release at 1 min	73.2	54.8
Observed % Drug release at 1 min	74.5	53.9
% Difference	0.98	1.01

Table 16: Composition of Optimized batch formulation (O1)

Ingredients (mg)	**O1**
Lofexidine HCl	0.2
Croscarmellose Sodium	4.8
Starcap 1500	44.2
Sucralose	2
Aerosil 200	0.6
Citric Acid	5
Avicel pH 102	40.7
Total weight (mg)	**100**

Table 17: Results of optimized batch O1.

Evaluation Parameters	**Results**	
Appearance	White colour round tablets plain on both side	
Weight variation (mg)	100.6 ± 1.9	
Thickness (mm)	3.08 ± 0.02	
Hardness (kg/cm^2)	3.96 ± 0.03	
Friability (%)	0.45	
Drug Content (%)	99.2 ± 1.4	
Wetting Time (sec)	20 ± 4	
Disintegration time (sec)	12 ± 1	
% Drug Release	**Time (Min)**	**% Drug Release**
	0	0
	0.5	53.8 ± 3.9
	1	79.8 ± 3.1
	2	98.4 ± 2.3
	3	99.6 ± 1.1
	4	99.9 ± 0.4
Ex-vivo Permeability Study	**Time (Min)**	**% Drug Release**
	0	0
	2	21.2 ± 3.5

	4	40.1 ± 3.3
	6	59.3 ± 2.9
	8	78.1 ± 2.6
	10	86.5 ± 1.6

Table 18: Comparison with marketed product.

Time (Min)	% Drug Release	
	O1	Marketed Product
0.5	53.8 ± 3.9	9.1 ± 3.9
1	79.8 ± 3.1	15.4 ± 3.2
2	98.4 ± 2.3	19.6 ± 3.6
3	99.6 ± 1.1	26.8 ± 3.0
4	99.9 ± 0.4	32.9 ± 2.6
5	99.9 ± 0.2	39.2 ± 2.2

Table 19: Stability study of optimized batch O1.

Evaluation Parameters	Initial	After 1 month
Appearance	Complies	Complies
Drug Content (%)	99.2 ± 1.4	99.0 ± 1.8
Disintegration time (sec)	12 ± 1	13 ± 2
% Drug Release at 5 min	99.9 ± 0.4	99.2 ± 0.2

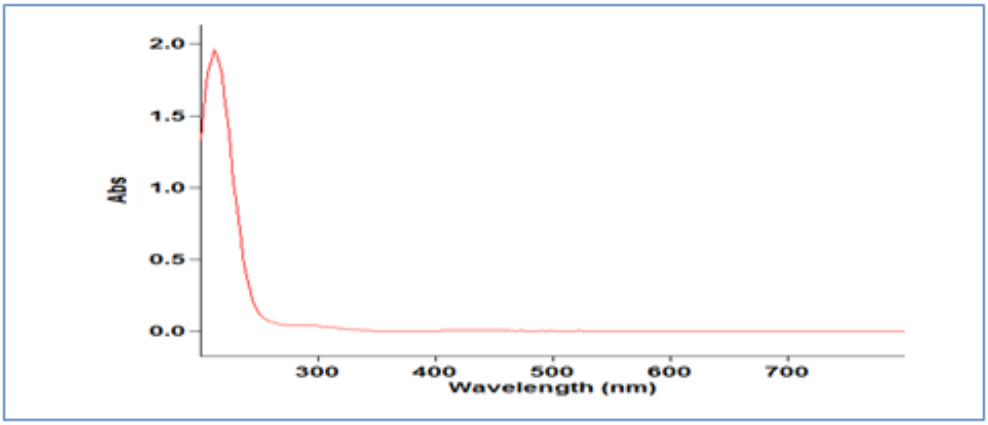

Figure 1: Determination of λmax of Lofexidine in phosphate buffer.

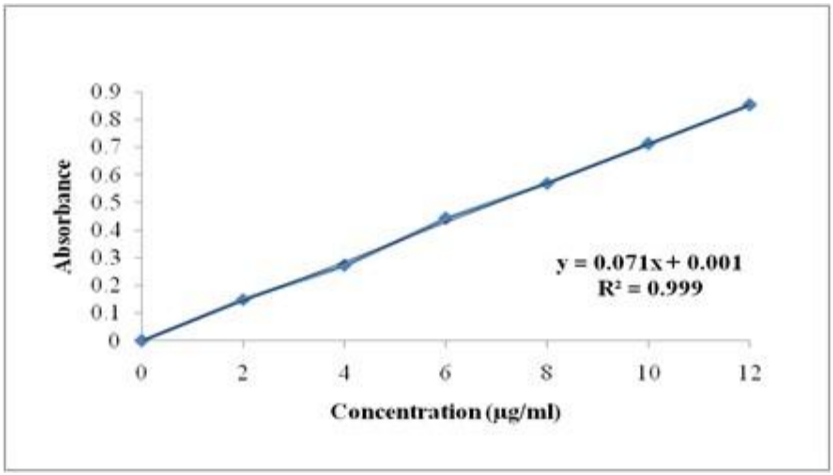

Figure 2: Standard calibration curve of Lofexidine in phosphate buffer.

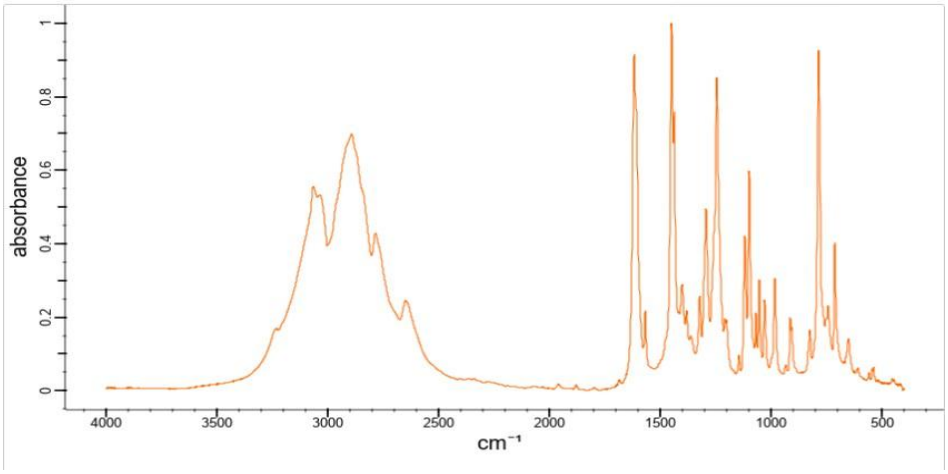

Figure 3: FTIR Spectra of Pure drug (Lofexidine).

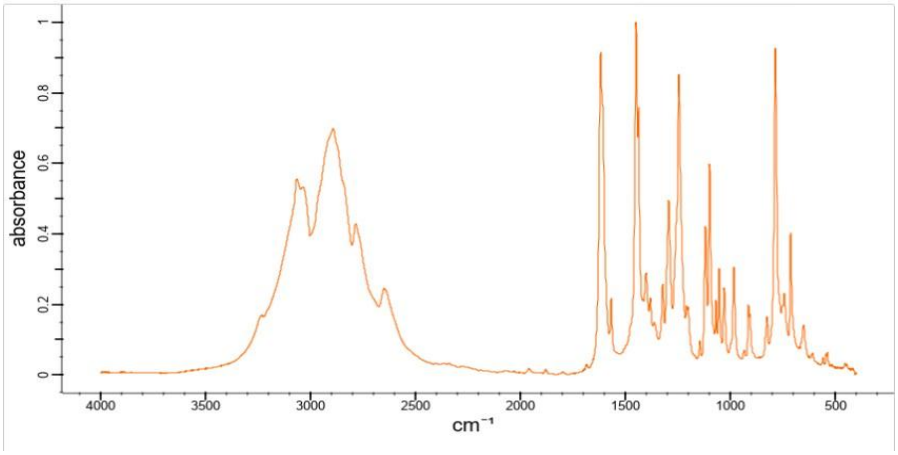

Figure 4: FTIR Spectra of final formulation.

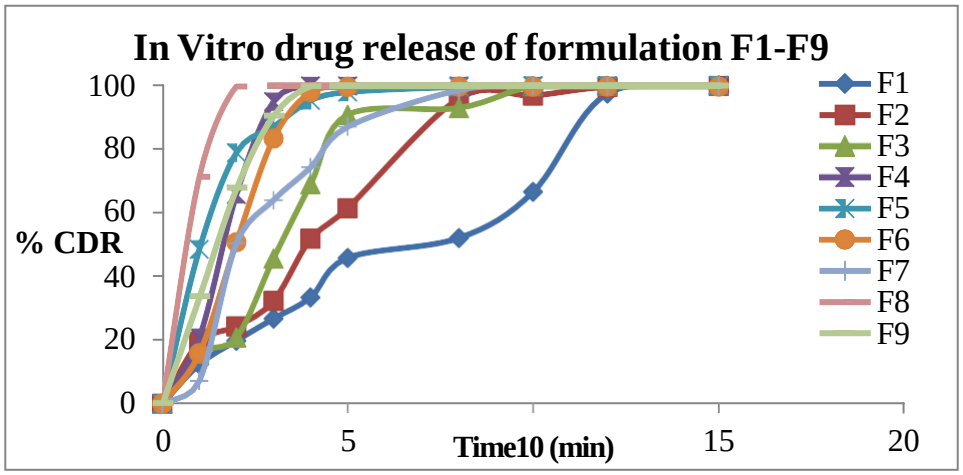

Figure 5: Comparison of *In-vitro* Dissolution Profile of the Formulations F1-F9.

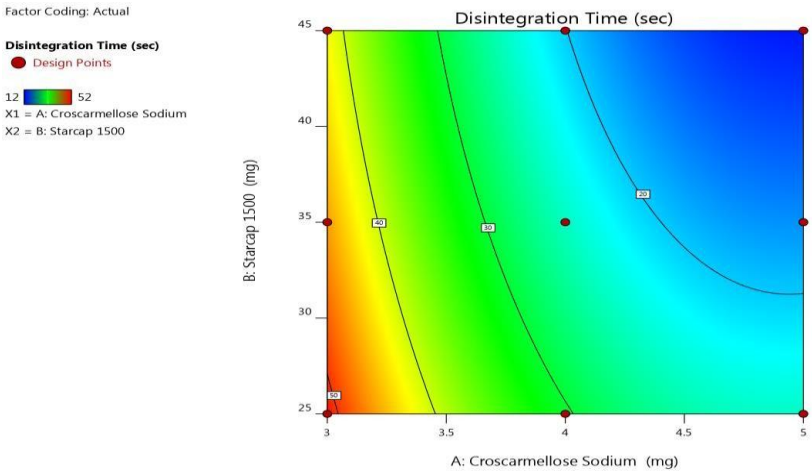

Figure 6: Surface plot for Disintegration time.

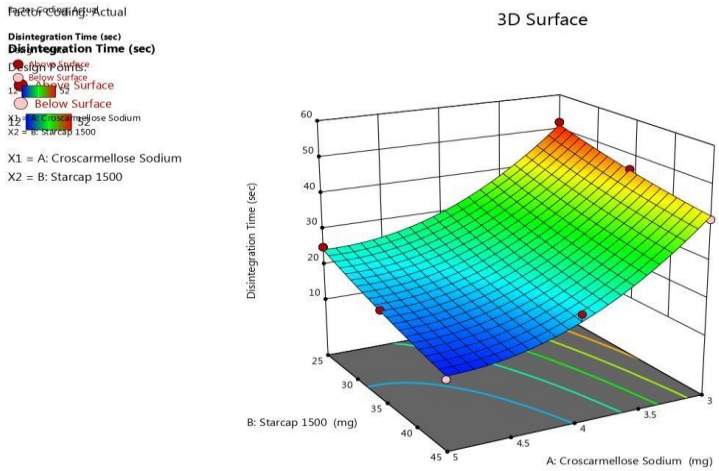

Figure 7: Contour plot for Disintegration time.

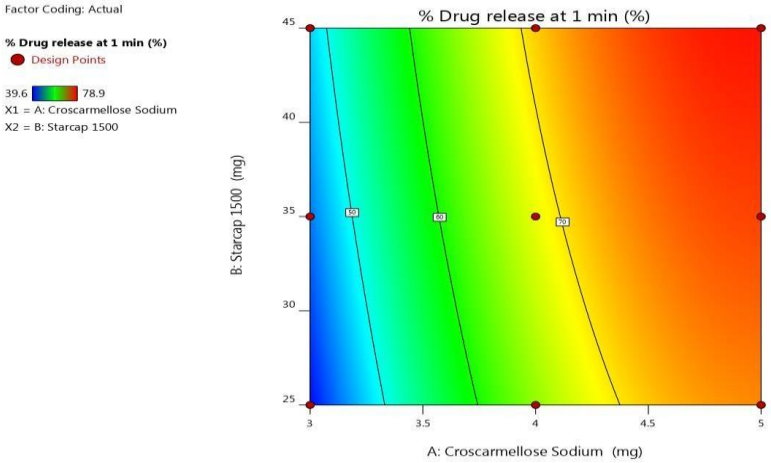

Figure 8: Contour plot for % Drug release.

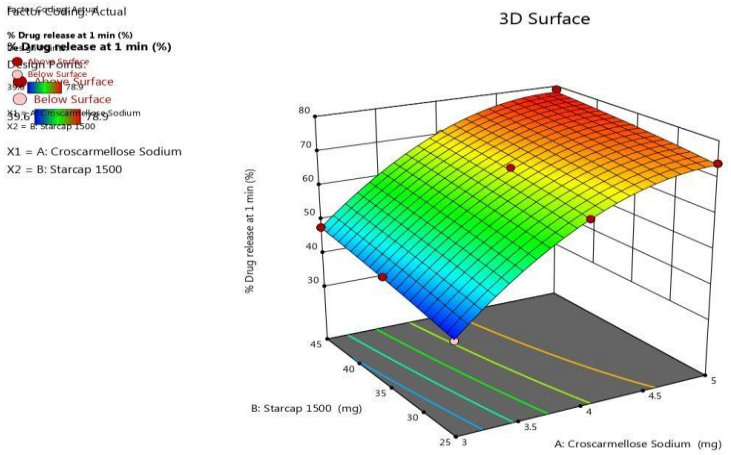

Figure 9: Surface plot for % Drug release.

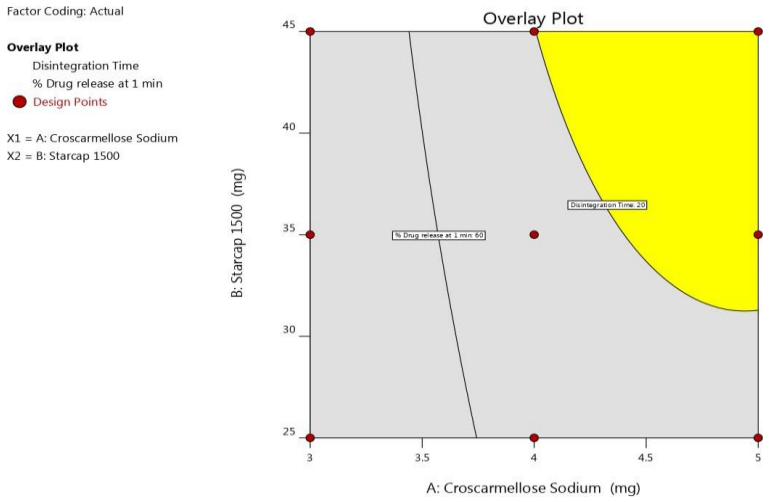

Figure 10: Overlay plot.

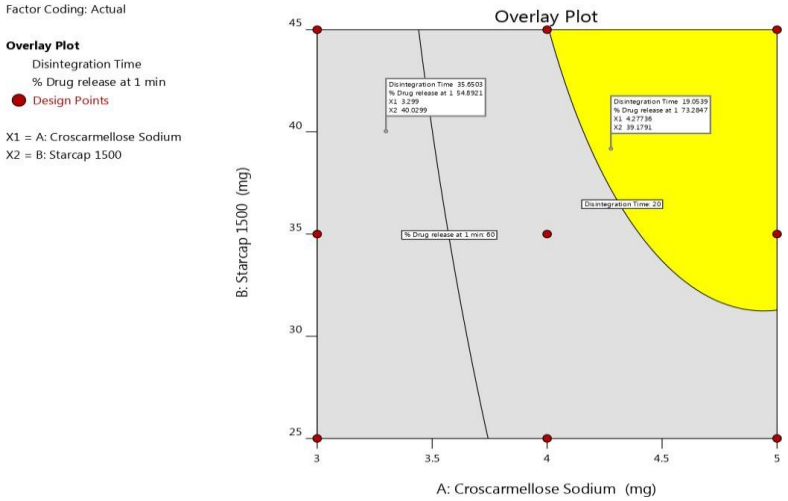

Figure 11: Overlay plot of check point batch.

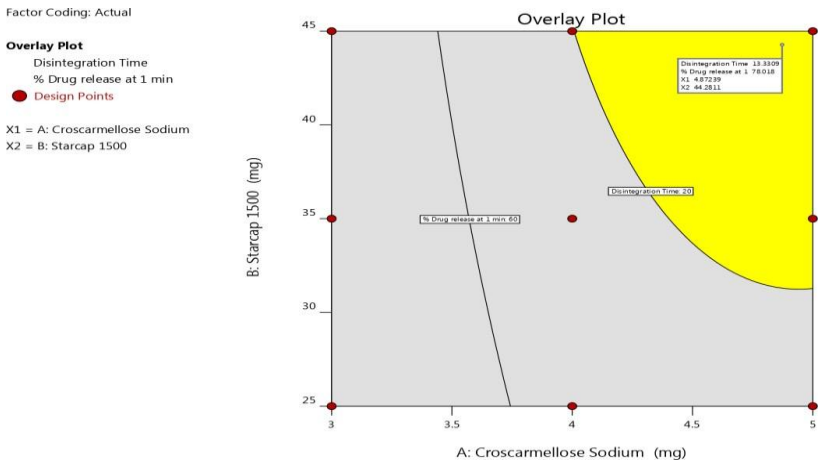

Figure 12: Overlay plot of optimized batch.

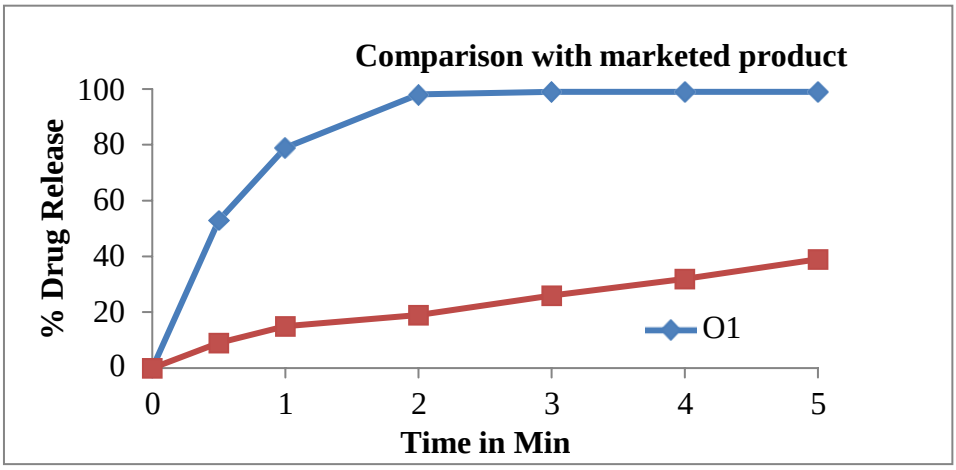

Figure 13: Comparison with Marketed Product.

CONCLUSIONS

Sublingual tablets of Lofexidine HCl were successfully formulated by employing direct compression method. Evaluation parameters like hardness and friability indicated good mechanical resistance of the tablets for all the formulations. Percentage weight variation and drug content uniformity were found to be within the approved range for all the formulations. The in-vitro release studies showed 90% of drug release in less than 8 minutes except for F1 formulations prepared by direct compression method. Overall, in the formulations prepared by direct compression method, F8 which contain 4% CCS as Super disintegrants releases 99.6 % drug in just 4 minutes was found to be best formulation.

REFERENCES

1. Nagaraju P, Subhash C, Ravi G, Damineni S, Valluru R. A Review on Current status of Buccal drug delivery system. Res J Pharm. and Tech, 2020; 13(6): 2954-2962.
2. Budhrani A, Shadija A. Mucoadhesive Buccal Drug Delivery System: A Review. Amer Journ of Pharm Tech Res, 2020; 10: 275-285.
3. Pawar P, Ghorpade H, Kokane B. Sublingual route for systemic drug delivery. Journ of Drug Discov and Therapeu, 2018; 8(6-s): 340-343.
4. Shaikh S, Shaikh Z, Khan G, Patel M. A Review on buccal mucoadhesive drug delivery system. Euro Journ of Pharma and Med Res, 2017; 4(11): 247-252.
5. Drug Information, December 2021, https://go.drugbank.com/drugs/DB04948.
6. Drug Information, December 2021, https://www.rxlist.com/lucemyra-drug.htm.
7. Drug Information, December 2021, https://pubchem.ncbi.nlm.nih.gov/compound/Lofexidine-hydrochloride.
8. Drug Information, December 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209229s000lbl.pdf.
9. Drug Information, December 2021, https://www.drugs.com/lofexidine.html.