FORMULATION AND EVALUTION OF ORAL DISINTEGRATING TABLETS OF LOFEXIDINE HYDROCHLORIDE USING NOVEL

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ABSTRACT

ODT 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 Superdisintegrants releases 99.6 % drug in just 4 minutes was found to be best formulation. Factorial design was applied to optimize the formulation. The factorial design was validated. Optimize formula taken from the design space and batch O1 was found stable for 1 month during stability study. Hence, O1 is the optimized batch.

Key words: Lofexidine HCl, CCS, SSG, ODT

1 INTRODUCTION 1.1Introduction of Drug Delivery System

Formulation of drugs into a presentable form is the basic requirement and need of today. Dosage form is a mean of drug delivery system, used for the application of drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions,

suppositories, injections, transdermal and patches having different type of drug delivery mechanisms.[1]

These classical/modern dosage forms have some advantages and disadvantages therefore the development of an ideal drug delivery system is a big challenge to the pharmacist in the presence scenario. In order to get the desired effect the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected.

1.1.1 ORAL DISPERSIBLE TABLETS:-[1]

Drinking water is mostly required for the oral administration of drugs, like tablet and capsules, in which some patients experience nuisance in swallowing bulky conventional dosage forms. In order to prevent the dysphagia and improve patient compliance, orodispersible tablets are introduced as a substitute in oral DDS, designed to disintegrate in mouth without the aid of water. So they are useful in such conditions in which water is not available, or prohibited as before operation, in kinetosis, cough episodes due to neurological stimulation or chest infections.

Different methods are adopted to manufacture the orodispersible tablets with the aim of giving fast disintegration to the dosage form as it gets in contact with saliva with good agreeable moth feeling.

These orodispersible tablets (ODT) can be administered to any patients having difficulty in swallowing. They are also recognized as mouth dissolvable, melt-in- mouth, fast dissolving, rapi-melts or porous tablets.

1.1.2 ADVANTAGES OF ODT'S -[4]

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down.

- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.

1.1.3 DISADVANTAGES OF FAST DISSOLVING TABLETS:-[4]

- Low amount of drug can be incorporated in each dose.
- Some time it possesses mouth feeling
- ODT requires special packaging for properly stabilization & safety of stable product.
- Eating and drinking may become restricted

1.1.4 Objectives of Work

- To Perform Drug: Excipients compatibility study.
- To prepare orally disintegrating tablets of Lofexidine Hydrochloride using direct compression method.
- To screen various super disintegrating agents for orally disintegrating tablets.
- To evaluate prepared orally disintegrating tablets.
- To achieve disintegration time less than 10 sec.
- To achieve more than 90 % drug release in 10 min.
- To perform stability studies on most satisfactory formulation.
- To compare optimized formulation with the marketed product.

2. MATERIAL AND EQUIPMENTS

2.1 List of Materials

Sr. No.	Materials	Function	Manufacturer
1	Lofexidine Hydrochlori de	API	Torrent, Research, Centre, Ahmedabad.
2	Croscarmello se Sodium Crospovidon e, Sodium Starch Glycolate	Super disintegrant	S.D fine chemicals, Ahmedabad
3	Acesulfa me Potassium	Sweetener	S.D fine chemicals, Ahmedabad

4	SmartEx QD-50 (L-HPC+D Mannitol+ PVA)	Novel Co-Process Excipient for Direct compression	S.D fine chemicals, Ahmedabad
5	Citric Acid	Saliva stimulant	S.D fine chemicals, Ahmedabad
6	Magnesium stearate	Lubricant	S.D fine chemicals, Ahmedabad
7	Microcrystalline Cellulose	Diluent	S.D fine chemicals, Ahmedabad

2.2 List of Equipments

Sr. No.	Equipments	Manufacturers
1.	Digital weighing balance	Reptech weighing balance ltd., Ahmadabad
2.	Tablet compression machine	Rotary Tablet compression machine, Hardik Engineering, Ahmedabad
3.	Dissolution apparatus	Electro lab ltd, Mumbai
4.	U.V. Visible spectrophotometer	Shimadzu-1601, Kroyoto, Japan.
5.	pH meter	Janki Impex Pvt. Ltd, Ahmedabad
6.	Friabilator	Electrolab, Mumbai, India
7.	Hardness Tester	Monsanto hardness tester, Mumbai.
8.	FTIR	FTIR 8400S, Shimadzu, Kroyoto, Japan.
9.	Vernier Caliber	Mitutoyo, Japan.

PRE-FORMULATION STUDIES CHARACTERIZATION OF DRUG (LOFEXIDINE HCl)

Organoleptic Characteristics:

Colour and Odor of Drug were characterized and recorded using descriptive terminology.

Flow Properties 1) Bulk density and Tapped density

An accurately weighed quantity of the API (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder was set for 100 taps and after that the volume (Vf) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.

Bulk density = W/ V0, Tapped density = W/ Vf

2) Compressibility index (CI) / Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

% Carr's index = (T.D. - B.D. ÷ T.D.) × 100

3) Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷ Bulk Density)

4) Angle of repose

Angle of repose of API powder was determined by the funnel method. Accurately weight powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ= h/r

Preparation of standard calibration curve of Lofexidine

Direct Compression Method: -

- All the ingredients weight accurately as per formula.
- Sift all the material from 40 # sieve.
- The drug was mixed with proper portion of Superdisintegrant.
- Care should be taken to confirm the proper mixing of drug and Superdisintegrant.
- Then other excipients were added.
- Then the mixture is passed through sieve (Sieve No. 40 #).
- The mixture is blended with Magnesium Stearate.
- Finally the blend is subjected for compression using tablet punching machine.

Formulation table of Lofexidine HCl ODT tablets:

Trial Batches for ODT tablets of Lofexidine prepared by using different type of Disintegrants. Avicel 102 used as diluent. Acesulfame Potassium used for giving sweetness to formulation and Here Smart Ex used as direct compressible excipient. Table 5.1 gives the formulation table of trial batches.

2.3 Formulation table of Lofexidine HCl ODT tablets

Ingredien ts (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
Sodium Starch Glycolate	2	4	8	-	-	-	-	**-**	-
Crospovidone	-	-	-	2	4	8	-	**-**	-
Croscarmellose Sodium	-	-	-	-	-	-	2	**4**	8
Acesulfame Potassium	2	2	2	2	2	2	2	**2**	2
SmartEx QD-50	40	40	40	40	40	40	40	**40**	40
Magnesium Stearate	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**

2.4 Table Formulation table for factorial batches

Ingredien ts (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
Croscarmell ose Sodium	3	3	3	4	4	4	5	5	5
SmartEx QD-50	25	35	45	25	35	45	25	35	45
Acesulfa me Potassiu m	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**

3 RESULTS & DISCUSSION

PRE-FORMULATION STUDIES

CHARACTERIZATION OF DRUG (LOFEXIDINE)

Table 3.1 Characteristic Properties of Lofexidine HCl

Sr. No.	Characteristic Properties		Observation/Result
	Organolepti c Characteristics	Colour	White to off-White Solid Powder
1		Odour	Odorless
2	Flow Properties	Bulk density (g /ml)	0.292
		Tapped density (g /ml)	0.429
		Carr's index (%)	31.93
		Hausner's ratio	1.46
		Angle of repose (θ°)	28.14º
3	Solubility	Water	Soluble (9.5 mg/ml)
		6.8 Phosphate Buffer	Soluble (8.1 mg/ml)
4	Melting Point	Capillary Method	237°C

- Based on above physical characterization of API it concluded that the API has a very poor flow itself. Hence the directly compressible grade of material is required for direct compression method.

- Further API has a good solubility in water and it's a BCS class I molecule so solubility enhancement also not require. Low dose of API easily maintains sink condition so no any issue regarding solubility.

Determination of λmax and standard calibration curve of Lofexidine The λ max of Lofexidine was found as 209 nm given in figure 6.1.

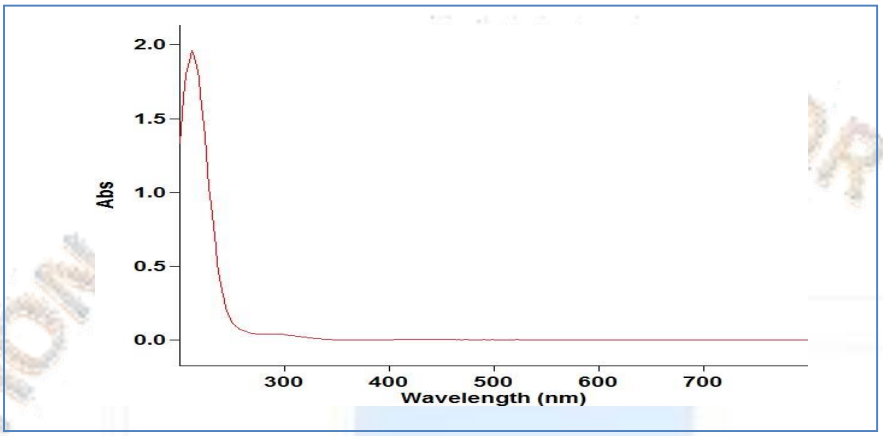


Figure 3.1. Determination of λmax of Lofexidine in phosphate buffer **Table 3.1** Standard calibration curve of Lofexidine in phosphate buffer

Sr. No.	Concentrati on (µg/ml)	Absorbanc e 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

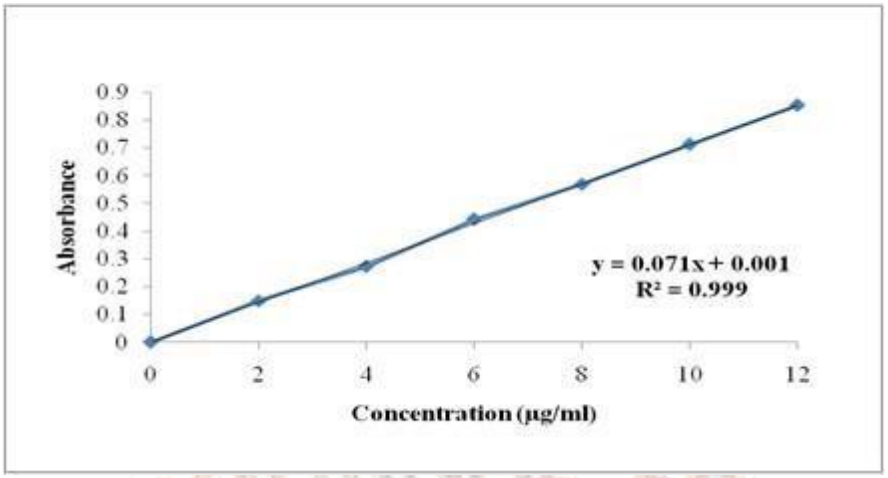


Figure 3.2 Standard calibration curve of Lofexidine in phosphate buffer

FTIR Study

Lofexidine Pure Drug and Mixture with excipients were examined for compatibility study and spectra recorded which were given below. From the spectra it concluded that no interaction observed between drug and selected excipients.

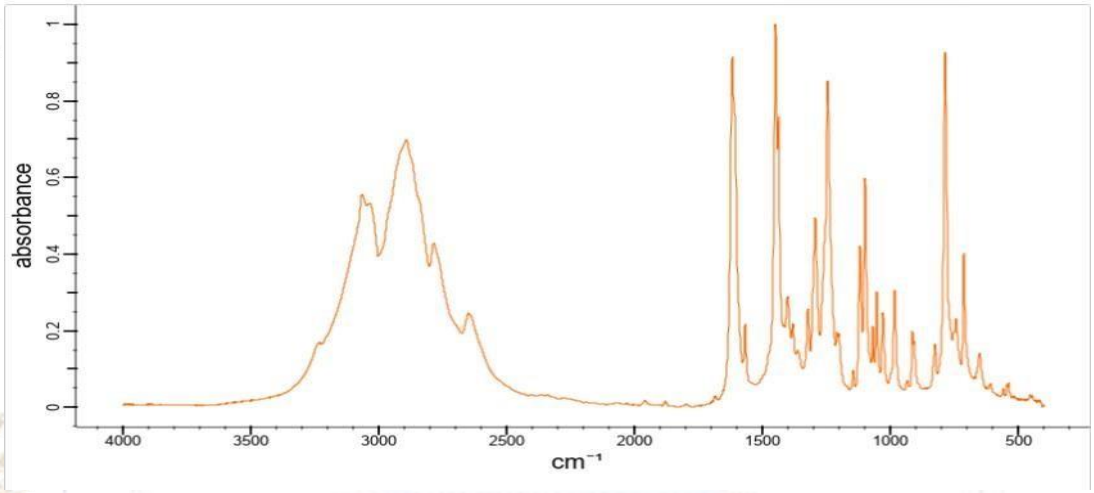


Figure 3.3 FTIR Spectra of Pure drug (Lofexidine)

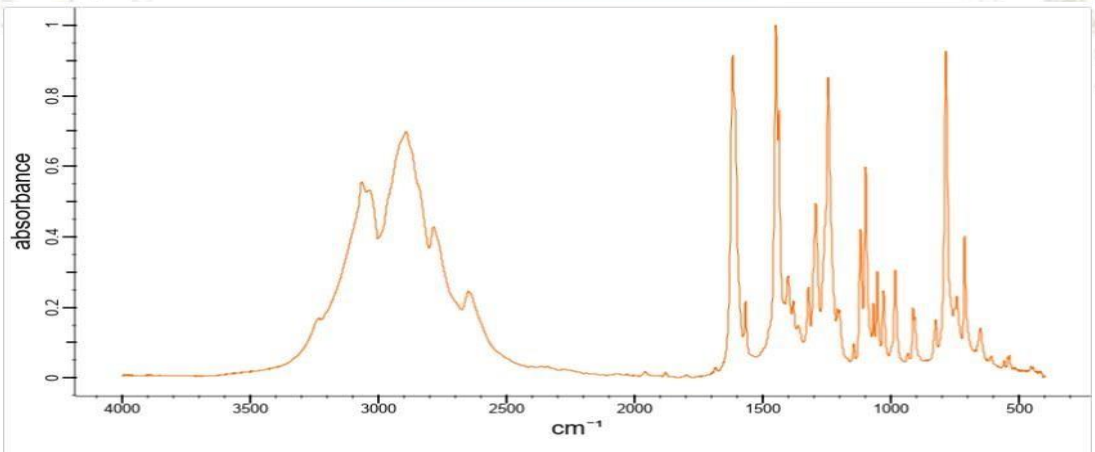


Figure 3.4 FTIR Spectra of final formulation

Table 6.3 Interpretation of FTIR spectra

	Peak of functional group [Wavelength] cm^{-1}				
	O-H Stretching	O-H Stretching	C-O	C=O Stretching	C-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

Lofexidine pure drug characteristic peak observed in final formulation also. It means that no any interaction between drug and excipients found.

So drug is compatible with excipients.

Evaluation of Lofexidine ODT Tablets

Pre compression parameters of F1-F9 trial batches were measured and results given in below table 6.3. From the results it concluded that all the batches have a good flow property and good for direct compression method.

Table 3.5 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°

Post-Compression Parameters

The tablets prepared by direct compression technique were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the F1-F9 formulations. The values are indicated in table No. 6.5. Formulation F1-F9 checked for post compression parameters. Weight variation observed within a limit. All the formulation has a good hardness and because of good hardness also passed the friability test. Friability of all formulations found below 1 %. Thickness found within limit and no any variation found in formulation. Details of results of post compression parameters of F1-F9 given in below table 6.5.

Table 3.6 Post-Compression Parameters of F1-F9 batch

Formulation Code	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

- ***In-vitro* disintegration time:**

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration ingredients are suggested to be the mechanism of disintegration.

The results are shown in table no. 6.6, which was determined as per Indian pharmacopoeial specifications for all the developed formulations. Formulations F8 showed rapid disintegration compared to other formulations.

% Drug Content

% Drug Content of F1-F9 measured and found within limit. No any formulation deviates from the limit. Results were given in table 6.6.

Content Uniformity

Content Uniformity of F1-F9 measured and found within limit. No any formulation deviates from the limit. Results were given in table 6.6.

In-vitro dissolution studies:

All the formulations were subjected for *in-vitro* dissolution studies using tablet dissolution tester USP. The dissolution medium 6.8 pH phosphate buffer was used to study the drug release.

The data obtained in the *in-vitro* release for formulations prepared by direct compression technique are tabulated in the table no. 6.6.

All the formulations showed rapid % drug release. But the rapid drug dissolution was noticed in F8 formulation compared to other formulations which release 99.63 % drug in 4 minutes. The fast dissolution might be due to quick disintegration of the tablets to form particles and rapid absorption will take place.

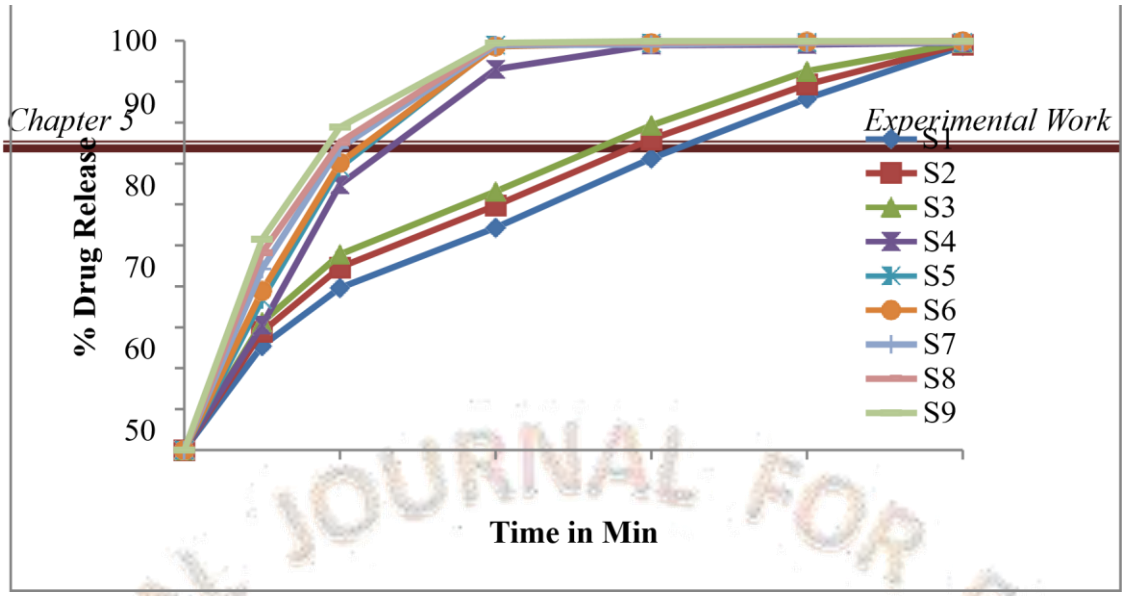
Table 3.7 Post-Compression Parameters of F1-F9 batch

Formulation code	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

F 8	**99.0 ± 1.6**	**Pass**	**26 ± 3**
F9	99.7 ± 1.1	Pass	85 ± 5

Table 3.8 *In-vitro* Dissolution Profile of the Formulations (F1F9)

Time in 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±2.5	-	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



Comparison of *In-vitro* Dissolution Profile of Facto Figure 6.6 rial Batches

Evaluation of Factorial Batches

Factorial batches S1-S9 prepared and evaluated for various parameters as discussed below; Weight variation observed within a limit. All the formulation has a good hardness and because of good hardness also passed the friability test. Friability of all formulations found below 1 %. Thickness found within limit and no any variation found in formulation.

Table 3.9 Evaluation of factorial batches S1-S9

Formulation Code	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm 2) (n=3)	Friability %
S1	101 ± 1.9	3.05 ± 0.02	3.80 ± 0.36	0.66
S2	100 ± 1.4	3.06 ± 0.03	3.78 ± 0.32	0.70
S3	102 ± 1.3	3.08 ± 0.02	3.80 ± 0.25	0.64
S4	100 ± 1.7	3.10 ± 0.06	3.86 ± 0.14	0.65

S5	99 ± 0.9	3.08 ± 0.08	3.98 ± 0.12	0.42
S6	101 ± 1.6	3.04 ± 0.03	3.87 ± 0.20	0.59
S7	102 ± 1.5	3.05 ± 0.03	3.90 ± 0.35	0.53
S8	**101 ± 1.2**	**3.09 ± 0.01**	**3.85 ± 0.30**	**0.61**
S9	100 ± 1.2	3.20 ± 0.05	3.64 ± 0.22	0.72

Table 3.10 Evaluation of factorial batches S1S9

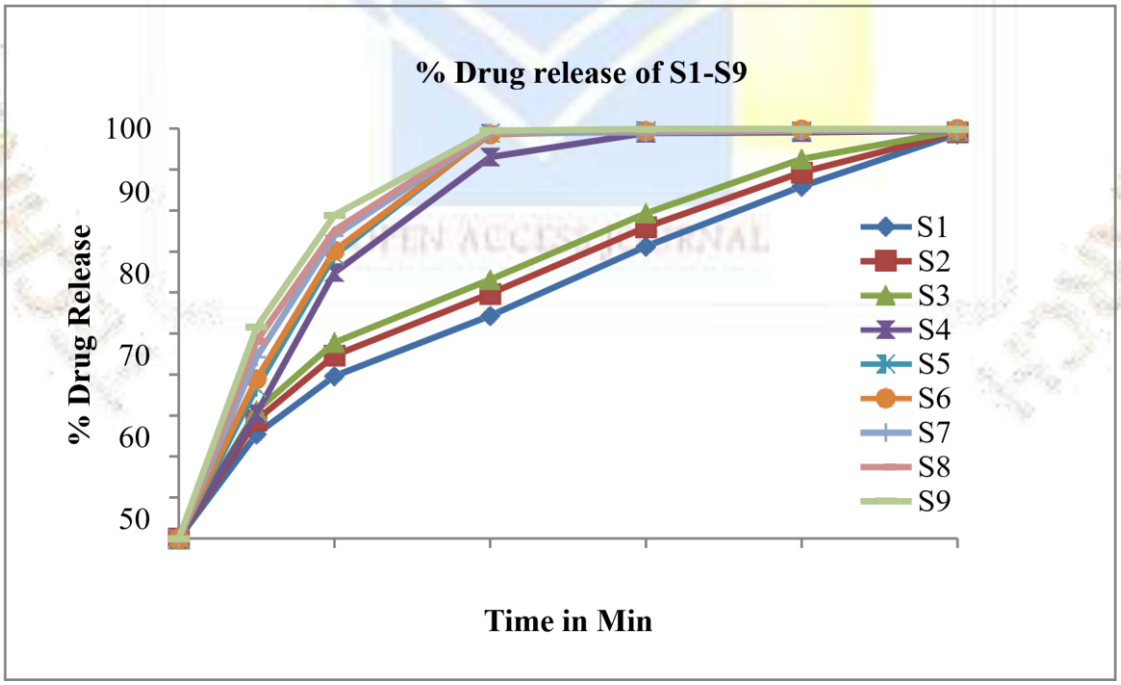
Formulation code	Wetting Time (Seconds)	*In-vitro* Disintegration time (Seconds)	Drug Content (%)
S1	59 ± 3	52 ± 5	98.4 ± 1.7
S2	53 ± 7	46 ± 3	98.9 ± 1.1
S3	47 ± 7	41 ± 2	97.5 ± 1.5
S4	35 ± 7	29 ± 4	98.2 ± 1.0
S5	32 ± 5	24 ± 2	99.1 ± 1.9
S6	30 ± 7	22 ± 2	98.7 ± 1.4

Time in min	S1	S2	S3	S4	S5	S6	S7	S8	S9
0	0	0	0	0	0	0	0	0	**0**
0.	25.	28.9	31.2	30.5	36.9	38.	44.3	48.2	**51.6**

S 7	34 ± 7	25 ± 3	97.1 ± 1.3
S 8	26 ± 7	18 ± 2	98.5 ± 1.7
S 9	19 ± 2	12 ± 1	99.0 ± 1.2

2. Table 3.11 *In-vitro* Dissolution Profile of the Factorial Batches

5	4					9			
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**



Comparison of *In-vitro* Dissolution Profile of Facto Figure 6.6 rial Batches

Regression Analysis of Factorial Design

Analysis of factorial batches data was done using Design Expert DoE software. The data compiled for the selected responses and data analysis was done. Following table was used for data analysis.

Table 3.12 Full Factorial Design Layout

Batch	Independent variable		Dependent Variables	
	X1 Croscarmellose Sodium (mg)	**X2** SmartEx QD- 50 (mg)	**Y1** Disintegration time (sec)	**Y2** (% Drug Release at 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

Stability Study

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 was found satisfactory and well within acceptable limit. The results were given in below table.

Table 3.13 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

4 CONCLUSION

ODT 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

Superdisintegrants releases 99.6 % drug in just 4 minutes was found to be best formulation. Factorial design was applied to optimize the formulation. The factorial design was validated. Optimize formula taken from the design space and batch O1 was found stable for 1 month during stability study. Hence, O1 is the optimized batch.

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