ijlpr 2020; doi 10.22376/ijpbs/lpr.2020.10.2.P1-8

International Journal of Lifescience and Pharma Research

Research Article

Pharmaceutics for effective drug dosage

Formulation, Evaluation and Optimization of Sublingual Tablet of Clonidine Hcl

Ashok Mahajan*, Parmar Jayendra, Priyal Patel, Shailesh Koradiya and Falgun Mehta

Babaria Institute of Pharmacy, BITS edu. Campus Vadodara-Mumbai NH#8, Varnama, Vadodara-391 240, Gujarat

Abstract: Clonidine hydrochloride (CHL) is a centrally acting alpha two adrenergic agonist. It crosses the blood brain barrier and acts in hypothalamus to induce a decrease in blood pressure. The objective of the present study was to develop and evaluate sublingual tablet of Clonidine Hcl for rapid action and to improve patient compliance to therapy. Wet granulation method was used to prepare sublingual tablet of Clonidine HCL. 3^2 factorial designs were used to study the effect of binder concentration on dependent variables such as friability disintegration time and wetting time. The prepared formulations were evaluated for various parameters such diameter, thickness, weight variation, hardness, friability, wetting time, drug content, in vitro disintegration time and stability studies Results (Hausner's ratio 1.24, Carrs index less than 13% and angle of repose $29^?$) revealed that all pre compression parameters meet the standard values indicating good flow properties. The average weight, friability and hardness were within compendial limits which showed that all formulations possessed good mechanical strength. The formulation F8 containing 5 % binder and 6 % disintegrant showed minimum disintegration time and wetting time, good friability, drug content and rapid drug release. Prepared sublingual tablets of Clonidine Hcl, were able to provide rapid drug release (94% drug release in 10 minutes) which is a prerequisite for the treatment of hypertension.

Keywords: Sublingual tablet, Clonidine Hcl, Hypertension, SSG, Optimization

***Corresponding Author**

Ashok Mahajan* , Babaria Institute of Pharmacy, BITS edu. Campus Vadodara-Mumbai NH#8, Varnama, Vadodara-391 240, Gujarat

Recieved On 05 December 2019
Revised On 19 December 2019
Accepted On 08 January 2020
Published On 03 April 2020

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Ashok Mahajan*, Parmar Jayendra, Priyal Patel, Shailesh Koradiya and Falgun Mehta , Formulation, Evaluation and Optimization of Sublingual Tablet of Clonidine Hcl.(2020).Int. J. Life Sci. Pharma Res.10(2), 1-8 http://dx.doi.org/10.22376/ijpbs/lpr.2020.10.2.P1-8

1. INTRODUCTION

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children and patients who are mentally restarted, uncooperative, nauseated or on reduced liquid intake/diet have difficulties in swallowing these dosage forms[1,2]. The sublingual tablet, in comparison to the other conventional dosage forms have increased bioavailability, which may be attributed to direct absorption of drug into systemic circulation via sublingual blood vessels and lymphatic system, which bypasses the liver[3]. Systemic hypertension is a common disorder that, if not effectively treated, results in a greatly increased probability of coronary thrombosis, strokes and renal[4]. Clonidine is an imidazoline-derivative hypotensive agent is a centrally-acting alpha two adrenergic agonist. It is the first choice for the treatment of hypertension and also used in the treatment of ADHD (Attention Deficit Hyperactivity Disorder). It crosses the blood-brain barrier and acts in the hypothalamus to induce a decrease in blood pressure. Clonidine is having higher solubility as well as permeability[5,6]. Oral bioavailability of Clonidine Hcl is 25-48%[7]. About 50% of the absorbed dose is metabolized in the liver orally[8]. Also many geriatric patients suffering from hypertension, face difficulty in swallowing tablets and hard gelatin capsules, therefore do not take medication as prescribed by physicians[9]. Hence there is a need to develop a Clonidine sublingual tablet which will have following advantages immediate response, escape from first pass metabolism, improvement in bioavailability and also reduced manufacturing difficulty and cost effectiveness. Moreover, sublingual tablet overcomes the shortfalls of conventional quick dispersing /dissolving intraoral tablets and overcome patent impediments. Hence the aim of the present investigation is to formulate, evaluate and optimize sublingual tablet of Clonidine Hcl.

2. MATERIALS AND METHODS

2.1 Materials

Clonidine hydrochloride was received as gift sample from Alembic pharma. Mannitol, aspartame, cremophor RH 40, PVP K 30, sodium starch glycolate, Talc and Magnesium stearate were purchased from suvidhinath laboratories. All other chemicals were of analytical grade.

2.2 Methods

2.2.1 Formulation of Clonidine Hcl sublingual tablets using 3^2 factorial design

A 3^2 randomized full factorial design (as shown in Table 1) was used in the present study for the preparation of sublingual tablets[10]. In this design 2 independent factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The concentration of binder (X1) and concentration super disintegrate (X2) were chosen as independent variables in 3^2 full factorial designs. Friability (Y1), wetting time (Y2) and disintegration time (Y3) were taken as dependent variables. A statistical model was developed to evaluate the responses, where Y stands for dependent variable and b0 is arithmetic mean for all the nine runs respectively.

Table 1 Percentage composition of different factorial batches (F1 to F9)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clonidine HCl	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol	85.5	83.5	81.5	83.5	81.5	79.5	81.5	79.5	77.5
Aspartame	4	4	4	4	4	4	4	4	4
Cremophor RH 40	2	2	2	2	2	2	2	2	2
PVP K 30	3	5	7	3	5	7	3	5	7
SSG	2	2	2	4	4	4	6	6	6
Talc	2	2	2	2	2	2	2	2	2
Mg stearate	1	1	1	1	1	1	1	1	1
Total (%)	100	100	100	100	100	100	100	100	100

2.2.2 Method of preparation of sublingual tablets

The Clonidine Hcl sublingual tablets were prepared by wet granulation[11]. The ingredients were weighed accurately and passed through sieve no. 60# separately. Mannitol, aspartame and PVP K30 (concentration taken as per the factorial design) were weighed accurately and mixed in mortar. Clonidine Hcl was dissolved in water. To this cremophor RH 40 was added to prepare a solution. The powder mass was granulated with above prepared solution to prepare wet mass which was passed through 20# sieve to form the granules. The granules were dried in tray drier at 40°C. The dried granules were mixed with calculated quantity of SSG (quantity taken as per the factorial design, table 1), talc & magnesium stearate as per the formula & blended for 5 min. separately. The granules were subjected to pre-compression evaluation like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The granules were compressed using 6mm diameter punch and tablets with average weight of 60mg were prepared.

2.3 Evaluation of Clonidine HCl sublingual tablets

2.3.1 Precompression characteristic

Before compression of tablets, granules were subjected for evaluation of various micromeritics properties such as angle of repose, carr's index and Hausner ratio[12]. The bulk and tapped density were calculated using following formula:

Bulk density = W/Vp and Tapped density = W/ Vt

Where W is the mass of powder, Vp and Vt is the bulk volume and tapped volume of powder. The carr's compressibility index was determined using following equation.

Carr's index = (Vp – Vt / Vp) * 100

Hausner's ratio was calculated by following equation

Hausner ratio = Tapped density / Bulk density

2.4 Post compression evaluation[13]

2.4.1 Hardness

The hardness of three randomly selected tablets from each formulation is determined by placing each tablet diagonally between the two plungers of tablet hardness tester (monsanto type) and applying pressure until the tablet broke down into two parts completely and the reading on the scale is noted down.

2.4.2 Thickness

The thickness of three randomly selected tablets from each formulation is determined in mm using a vernier caliper. The average values are calculated.

2.4.3 Friability test

Friability was evaluated as the percentage weight loss of 20 tablets tumbled in friabilator for 100 revolutions, at 25rpm. The tablets were dedusted & the loss in weight caused by fracture or abrasion was recorded as the percentage friability.

2.4.4 Weight variation

To study weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

2.4.5 Disintegration time

The time taken for a tablet to disintegrate is measured by USP disintegration apparatus without disk using water as medium at 37°C. According to USP, all the tablets should disintegrate completely within 2 min.

2.4.6 Wetting time

Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release drug in the presence of minute volumes of saliva. The tablet was placed above absorbent paper fitted into a petri dish. After the paper is thoroughly wetted with distilled water, excess water is completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet is then recorded using a stopwatch[14].

2.4.7 In vitro dissolution

The sublingual tablets were subjected to dissolution study by using modified dissolution apparatus consisting of 50 ml beaker and magnetic stirrer. The tablet was placed in the beaker containing 30 ml phosphate buffer 6.8 as dissolution medium at 37° C. Aliquots of 5 ml were withdrawn at every 2, 4, 6, 8, 10, 12, 14 and 16 minutes. After each withdrawal the volume removed was compensated by fresh 5 ml of phosphate buffer 6.8. The drug content was analyzed spectrophotometrically at 215 nm against reagent blank[15].

2.4.8 Stability studies

Stability studies of clonidine HCl sublingual tablets were carried out according to ICH guidelines by storing the samples at 40 ± 5°C and 75 ± 5 % RH for 1 month using stability chamber. The samples were evaluated for physicochemical parameters namely hardness, friability, disintegration time, wetting time, % drug release and drug content. Similarity factor f2 was used to check the similarity between release profile of optimized formulation before and after the stability testing[16].

3. STATISTICAL ANALYSIS

Stat Ease software (Design Expert version, 7.0) was used to generate the polynomial equations for the selected dependent variables such as disintegration time (Y1), wetting time (Y2), and friability (Y3). One way ANOVA was applied to prove the significant coefficients at 95% confidence ($P < 0.05$).

4. RESULTS AND DISCUSSION

Sublingual tablets of Clonidine Hcl were prepared by wet granulation method. Mannitol was used as filler. Clonidine Hcl is a slightly bitter drug. In Clonidine HCl sublingual tablets aspartame was used as a sweetening agent. Along with sweetening agent, cremophor RH 40 was also added into the formulation which acted as a taste masking agent. In the US patent and various research articles it been reported that cremophor RH 40 is used as a taste masking agent[17,18].Cremophor RH 40 is a hydrogenated castor oil which binds and coats the taste receptors (coats the surface protein receptors) responsible for the taste masking of the drugs

4.1 Pre and post compression properties of sublingual tablets

Results of precompression properties of Clonidine HCl sublingual tablets are shown in Table 2 Bulk density and tapped density of formulation F1 to F9 was found to be in the range of 0.25-0.35 gm/ml and 0.31-0.43 gm/ml respectively. Values for angle of repose 20°-30°generally indicate good flow property. A hausner ratio of less than 1.25 and carr's index 12-20 indicate good flow and compressibility[19]. All the pre-compression parameters meet the standard values. So, all the formulations showed good flow properties.

Table 2 *Precompression properties of Clonidine HCl sublingual tablets (n=3)*

Batches	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index	Hausner's ratio	Angle of repose
F1	0.35	0.43	18.60	1.22	25.32
F2	0.34	0.41	17.07	1.20	24.68
F3	0.31	0.37	17.81	1.19	25.56
F4	0.28	0.33	15.15	1.17	24.44
F5	0.30	0.38	17.14	1.26	23.96
F6	0.27	0.35	20.01	1.18	27.15
F7	0.38	0.47	19.15	1.23	26.56
F8	0.25	0.31	13.85	1.24	29.01
F9	0.39	0.34	12.28	1.13	29.68

Table 3 shows the evaluation data of post compression properties of clonidine Hcl sublingual tablets. As we know thickness is one of the criteria for packing so the tablets should have appropriate thickness. The thickness and diameter for all the formulations were measured. It was observed that thickness ranged from 1.5-1.79mm and the diameter ranged from 6.03-6.06mm. All the formulations were tested for hardness by Monsanto type hardness tester. The hardness of all formulations was found to be in the range of 2-5 kg/cm2 which indicated good mechanical strength. The percentage drug content of all tablets was found to be between 92- 100 % which was within the acceptable limits. The average weight of the tablets was 60mg ± 2%. As the weight of the tablets was 60mg, the acceptable weight variation range is 60 mg or less (±10%). Hence all the tablet formulations were within the limits and passed the weight variation test. Result showed that as the concentration of binder increases, disintegration time increases and friability decreases due to increase in hardness. Formulation F8 shows less D.T and good friability

Table 3 *Post compression properties of Clonidine Hcl sublingual tablets(n=3)*

Batches	DT (Sec)	Friability (%)	Wetting time (Sec)	Hardness Kg/cm2	Drug Content %
F1	125	0.94	117	2.5	94.37
F2	177	0.72	168	2.5	95.93
F3	200	0.35	192	3	92.61
F4	82	0.89	73	3	96.80
F5	71	0.44	65	3.5	97.34
F6	136	0.39	128	4	95.01
F7	57	0.91	48	4	100.28
F8	54	0.53	42	4.5	98.44
F9	75	0.28	69	5	97.20

4.2 Effects of formulation variable on D.T (Y1)

Multiple linear regression analysis showed that coefficient b1 bear a positive sign and coefficient b2 bear a negative sign. The positive coefficient indicates that as the concentration of X1 (PVP K-30) increases, there is increase in the disintegration time. The negative X2 coefficient indicates that as the concentration of X2 (SSG) increases; there is decrease in the value of disintegration time. The Y1 for all batches F1 to F9 shows good correlation coefficient of 0.9586. Low disintegration time value is very important parameter for sublingual tablets. 3-D surface plot for D.T is shown in figure 1. Here, X2 variable is responsible for low disintegration time value. The fitted equation for the response Y1 is shown below.

$$Y_1 = 89.56 + 22.83X_1 - 54.33X_2 - 16.75X_1X_2 + 10.17X_1^2 + 16.67X_2^2$$

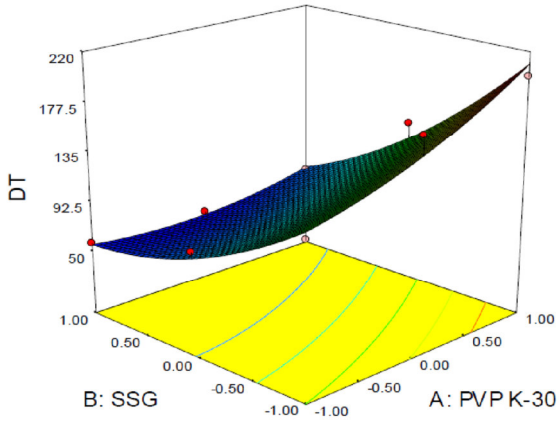

Fig 1. *3-D surface plot for D.T(Y1)*

4.3 Effects of formulation variable on Friability (Y2)

Concerning Y2, the results of multiple linear regression analysis showed that coefficient b1(it is the estimated coefficient for factor X1, negative values indicates that if we increase the PVP K-30 concentration there is decrease in the friability) bear a negative sign and coefficient b2 also bear a negative sign. The b2 coefficient indicates that as the concentration of X2 (SSG) increases, there is decrease in the friability value, but the coefficient of b2 is very low as compared to b1. 3-D surface plot for friability is shown in figure 2. The Y2 for all batches F1 to F9 shows good correlation coefficient of 0.9468. Low friability value is very important parameter for sublingual tablets. Here, X1 variable is responsible for low friability value. The fitted equation for the response Y2 is shown below.

$$Y_2 = 0.53 - 0.29X_1 - 0.048X_2 - 0.01X_1X_2 + 0.063X_1^2 + 0.048X_2^2$$

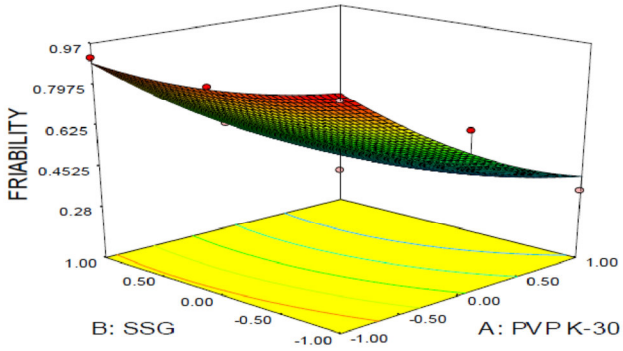

Fig 2. *3-D surface plot for Friability (Y2)*

4.4 Effects of formulation variable on Wetting time (Y3)

The b1 coefficient indicates that as the concentration of X1 (PVP K-30) increases, there is increase in the wetting time. 3-D surface plot for wetting time is shown in figure 3.The b2 coefficient indicates that as the concentration of X2 (SSG) increases, there is decrease in the value of wetting time. The Y3 for all batches F1 to F9 shows good correlation coefficient of 0.9642. Low wetting time value is very important parameter for sublingual tablets. Here, X2 variable is responsible for low disintegration time value. The fitted equation for the response Y3 is shown below

$$Y_3 = 81.67 + 22.83X_1 - 55.33X_2 - 17X_1X_2 + 10.50X_1^2 + 15X_2^2$$

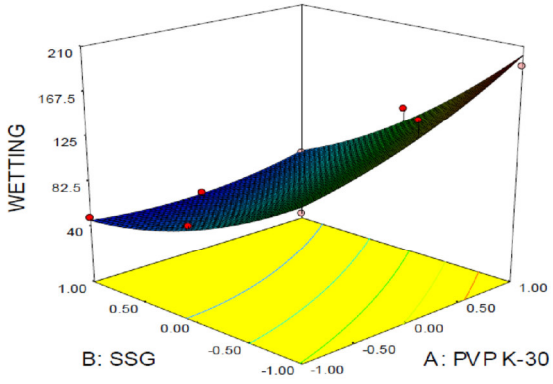

Fig 3. *3-D surface plot for Wetting time (Y3)*

The dissolution study was carried out using 30 ml of phosphate buffer 6.8 dissolution medium at 50rpm at 37°C ± 0.5 °C. It was observed that formulations F5 F7 and F8, showed rapid drug release. The percentage cumulative drug release (figure 4) of formulation F5, F7 and F8 after 8 minutes found to be more than 80 %. Results of ANOVA study for the dependent variables are summarized in Table no 4. Model ia said to be significant when p value is less than 0.05.

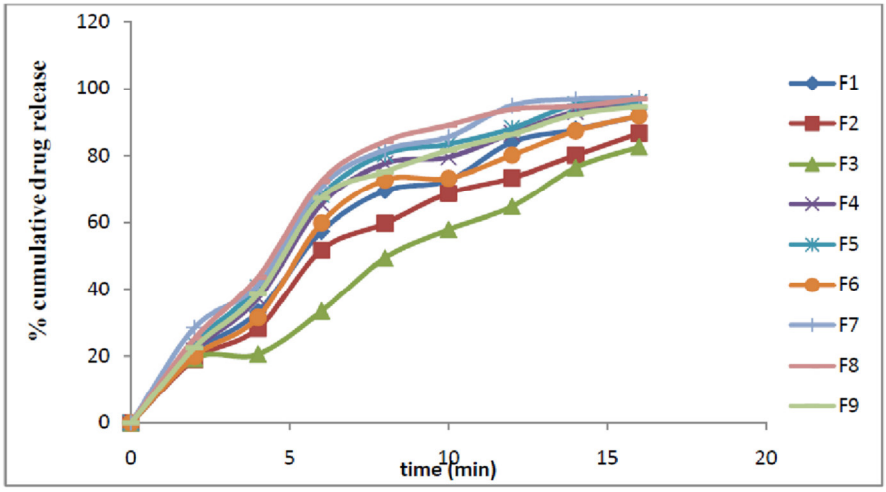

Fig 4. *Plot of %cumulative drug release versus time of batches F1 to F9(n=3)*

Table 4. Results of ANOVA study for the dependent variables

Response	Sum of square	Degree of freedom	Mean square	F value	P value
D.T (Y1)	22725	5	4545	13.90	0.0275
Friability (Y2)	0.52	5	0.10	10.67	0.0397
Wetting time (Y3)	23325	5	4665	16.15	0.0223

If P value less 0.05 then model is significant

4.5 Optimization of formulations

Optimization of sublingual tablets was done by using desirability function (by use of design expert software). The red dot on the ramp graph indicates the desired concentration of independent factors. Ramp graph (as shown in figure 5) gives desired concentration of binder (5%) and disintegrate (6%) for the desired constraint. For example in sublingual dosage desired constraint are minimum disintegration time, minimum wetting time and optimum friability. The values of the desired responses (dependent variables) are also shown in the ramp graphs which are responsible for the overall desirability of the formulation. It has been reported that, we have to choose the optimum formulation which will have desirability value closer to 1. The desirability function for formulation F8 was found to be 0.994. Hence it was selected as an optimized formulation.

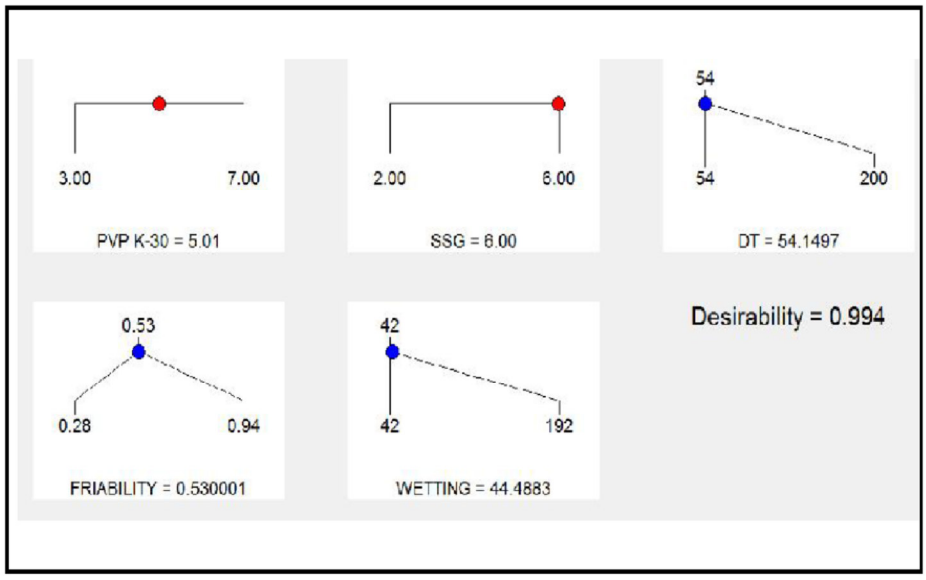

Fig 5. Ramps graph for overall desirability values

4.6 Stability studies

Results of stability studies showed (Table 4) (figure 6) that there is no significant change in the parameters like hardness, friability, disintegration time, wetting time, drug content and %CDR when stored at 40°C and 75% RH for period of one month. Similarity factor was used to calculate drug release. The curves are thought to be statistically similar if f2 value was above 50. f2 value was found to be 83.91. Results of stability studies concluded that there was no significant change in drug release when stored at 40°C and 75% RH for a period of one month.

Table 4. *Stability data of optimized formulation*

Parameters	Before	After 30 days
Hardness	4.5 kg/cm2	4.3 kg/cm2
Friability (%)	0.53	0.49
DT(sec)	54	48
Wetting time (sec)	42	35
Drug content (%)	98.44	95.84

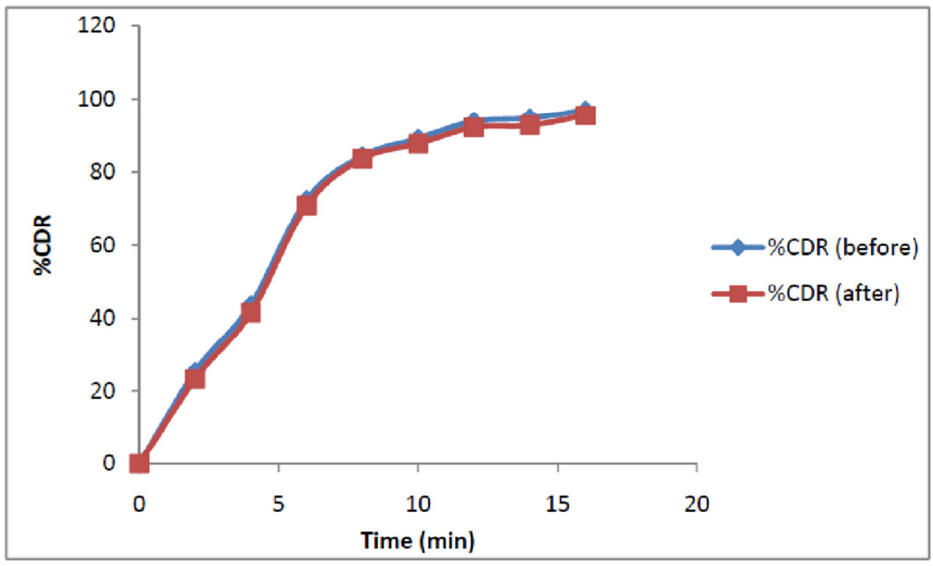

Fig 6. *Plot of Percentage Cumulative Drug Release vs Time of optimized batch before and after stability*

5. CONCLUSION

The concept of sublingual tablets containing Clonidine Hcl offers a suitable and practical approach in serving the desired objective of management of hypertension. The excipients used in the formulation were inexpensive and are easily available. Most of the excipients used in formulation are water-soluble and hence have a better patient acceptability. The optimized formulation F8 containing 5 % binder and 6 % disintegrant showed minimum disintegration time (54 sec) and wetting time (42 sec) and rapid drug release. From the study it can be concluded that, sublingual

tablets of clonidine Hcl can provide rapid drug release within a short period time which a prerequisite for the treatment of hypertension.

6. AUTHORS CONTRIBUTION STATEMENT

Dr Ashok Mahajn has conceptualized the idea and prepared the manuscript. Mr. Parmar Jayendra has gathered and done the review of literature. Dr Priyal Patel has given inputs regarding optimization of formulation by Stat Ease software. Dr Shailesh Koradiya and Dr Falgun Mehta have helped us in development of analytical method for the drug. All authors discussed the results and contributed to final manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES

1. Senel S, Comoglu T. Orally disintegrating tablets, fast-dissolving, buccal and sublingual formulations.Pharm Dev Technol. 2018;23(5):431. DOI:10.1080/10837450.2018.1462471.
2. Kraan H, Vrieling H, Czerkinsky C, Jiskoot W, Kersten G, Amorij JP. Buccal and sublingual vaccine delivery. J Control Release. 2014;28(190):580-92. DOI: 10.1016/j.jconrel.2014.05.060.
3. Guo Y, Singh AP. Emerging strategies for enhancing buccal and sublingual administration of nutraceuticals and pharamaceuticals. Journal of Drug Delivery Science and Technology. 2019;52:440-451. DOI: 10.1016/j.jddst.2019.05.014.
4. Macdougall AI, Addis GJ, Mackay N, Dymock IW, Turpie G, Ballingall LK, Maclennan WJ, Whiting B, Macarthur JG. Treatment of Hypertension with Clonidine. Br Med J. 1970; 3(5720):440-442. DOI: 10.1136/bmj.3.5720.440.
5. Dangre PV, Phad RD, Surana SJ, Chalikwar SS. Quality by Design (QbD) Assisted Fabrication of Fast Dissolving Buccal Film for Clonidine Hydrochloride: Exploring the Quality Attributes. Advances in Polymer Technology. 2019;Article ID 3682402, 13 pages. DOI:10.1155/2019/3682402.
6. Goede AL, Boedhram RR, Eckhardt M. Development and validation of a paediatric oral formulation of clonidine hydrochloride. International Journal of Pharmaceutics.2012; 433(1-2):119-120. DOI:10.1016/j.ijpharm.2012.04.055.
7. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia. 1999;54(2):146-65. DOI: 10.1046/j.1365-2044.1999.00659.x
8. Vasseur B, Dufour A, Houdas L. Comparison of the systemic and local pharmacokinetics of clonidine mucoadhesive buccal tablets with reference clonidine oral tablets in healthy volunteers: an open-label randomised cross-over trial. Adv Ther. 2017;34(8):2022–2032. DOI: 10.1007/s12325-017-0585-9.
9. Makwana S, Kharadi R. A Review on Sublingual Formulation. World journal of pharmacy and pharmaceutical sciences. 2018;7(9):1300-1306.
10. Mahajan A, Surti N, Koladiya P. Solid dispersion adsorbate technique for improved dissolution and flow properties of lurasidone hydrochloride: characterization using 3^2 factorial design, Drug Development and Industrial Pharmacy. 2018;44(3):463-471. DOI: 10.1080/03639045.2017.1397687.
11. El-Setouhy,DA Basalious,AbdelmalakNS. Bioenhanced sublingual tablet of drug with limited permeability using novel surfactant binder and microencapsulated polysorbate: In vitro/in vivo evaluation. Eur J Pharm Biopharm. 2015;94:386-92. DOI: 10.1016/j.ejpb.2015.06.006.
12. United States Pharmacopoeia and National Formulary (2002). United States Pharmacopoeia, XXIII. Rockville: U.S.P Convention Inc. Available from: http://www.who.int/medicines/areas/quality_safety/quality_assurance/resources/US_Pharmacopoeia.pdf
13. Lachman L LH. The Theory and Practice of Industrial Pharmacy 3rdEdition ed. Varghese Publishing house; 1987. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jps.2600760125
14. Patel BP, Patel JK, Rajput GC, Thakor RS. Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine. Indian J Pharm Sci. 2010;72(4):522-525. DOI:10.4103/0250-474X.73930.
15. Rachid O, Qalaji MR, Simons ER, Simons KJ. Dissolution Testing of Sublingual Tablets: A Novel In Vitro Method. AAPS PharmSciTech. 2011;12(2):544-552. DOI:10.1208/s12249-011-9615-0.
16. Duan JZ, Riviere K, Marroum P. In vivo bioequivalence and in vitro similarity factor (f2) for dissolution profile comparisons of extended release formulations: how and when do they match. Pharm Res. 2011;28:1144-56. DOI: 10.1007/s11095-011-0377-x.
17. Edible oral strip or wafer dosage form containing on exchange resin for taste masking United States Patent Application Publication. 2017/0136078A1.
18. Ezequiel M, Mariana L, Claudia S, Fabian B, Carlos B, Adriana C. Pharmaceutical optimization of lipid-based dosage forms for the improvement of taste-masking, chemical stability and solubilizing capacity of Phenobarbital. Drug Dev Ind Pharm. 2013;40:783-792. DOI: 10.3109/03639045.2013.787536.
19. Patil R, Pande V, Sonawane R. Nano and Microparticulate Chitosan Based System for Formulation of Carvedilol Rapid Melt Tablet Advanced Pharmaceutical Bulletin 5(2):169-179. DOI: 10.15171/apb.2015.024