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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF ARIPIPRAZOLE

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A B S T R A C T

The oral route is the most preferred route, though preoral administration of drug has disadvantage like hepatic first pass metabolism ana enzymatic degradation within the GI tract however trans mucosal routes of drug delivery (i.e.Mucosal lining of nasal, rectal, ocular & oral cavities) offer distinct advantage over preoral administration.Aripiprazole is an antipsychotic also primarily used in the treatment of schizophrenia and bipolar disorder. Fast dissolving sublingual films of Aripiprazole were prepared by solvent casting technique. HPMC E-15 was selected as polymer because of its good water solubility. Polyvinyl pyrrolidone K-30(PVP K-30) as superdisintegrant and Polyvinyl alcohol as film forming agent. Mannitol as sweetner and saliva stimulating agent used in the formulation. Chitosan as permeability enhancer. The compatibility of the drug in the formulation was confirmed by FTIR studies. A various concentration of polymers was conducted in order to optimize API concentration of the new dosage form. The FDSF was characterized for weight, thickness, folding endurance, tensile strength and dissolution using *In-vitro* experimentations. The effect of PVA and PVP K-30 on drug release profile and film forming properties was investigated. Estimation of drug content of films was performed and the results were satisfactory. *In-vitro* dissolution studies revealed higher drug release from formulation F7 batch.

INTRODUCTION

The oral cavity has been investigated as a site for drug delivery for a long period of time. In 1847 Sobrero found that nitroglycerine was absorbed from the oral cavity. Since then various active substances have been investigated for local or systemic use[10]. Buccal drug delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route for administration[18]. United States Food and Drug Administration (USFDA) define orally disintegrating tablets as "A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue". US Food and Drug Administration Center for Drug Evaluation And Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue (USFDA)[20]. European Pharmacopoeia described orally disintegrating tablets (ODT'S) as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 min (EU Patents)[21]. By above definition, a solid dosage forms that dissolve or disintegrate quickly in the oral cavity; resulting in solution or suspension without the need of water for the administration, is known as oral fast dispersing dosage form. Fast dissolving drug delivery were developed in the late 1970's as a alternative to the capsules, tablets and syrups for paediatric and geriatric patients who experience difficulty in swallowing traditional oral solid-dosage forms[19]. The novel technology of oral fast dissolving dosage forms is known as fast dissolve, rapid dissolve, rapid melt, quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. Dysphasia associated with many medical conditions, including stroke, Parkinson's disease, AIDS, thyroidectiomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy[18].

The Anatomy and Physiology of Oral Mucosa

Oral transmucosal drug delivery can be subdivided into:

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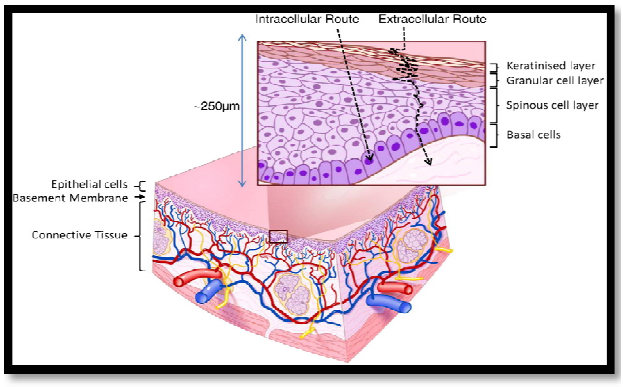
- sublingual drug delivery: via the mucosa of the ventral surface of the tongue and the floor of the mouth under the tongue;
- buccal drug delivery: via the buccal mucosa – the epithelial lining of the cheeks, the gums and also the upper and lower lips.



Various physiological differences between the buccal and sublingual regions (described below) mean that the types of dosage forms appropriate for these two routes are very different[14].

MATERIALS AND METHODS

Aripiprazole was obtained as a gift sample from Ajantha pharmaceuticals, Mumbai. HPMC E-15 was procured from LOBA CHEME, Mumbai, PVP K-30 obtained from Evonik, Kolkata. Mannitol from Research Lab Fine Chem Industry, Mumbai, and PVA was obtained from Reliance Cellulose. All other reagents and chemicals were of analytical grade.

Formulation of Fast Dissolving Sublingual Films

Fast Dissolving Sublingual Films of Aripiprazole were prepared by solvent casting technique using film forming polymer. In this method, three portions were made. In first portion the drug was dissolved in sufficient quantity of Ethanol, and in second portion weighed amount of PVP K-30, HPMC E-1, mannitol and chitosan were added in ethanol[8]. In third portion, the weighed quantity of PVA was dissolved in sufficient amount of distilled water with continuous stirring on magnetic stirrer[4]. Now, this third portion was mixed with shaking in above two portions. At last calculated amount of PEG400 and flavours were added to this drug polymeric solution. This solution was mixed thoroughly to obtain homogeneous solution. Ethanol was finally added to make up the final volume. The homogeneous solution was put in to mould prepared from aluminium or glass (size 4-5 $cm^{2)}$ and dried at 40-50^0 C. The optimization of batch was carried out by 3^2 full factorial designs.

Different formulation codes were assigned to all batches containing ratios of PVA and PVP K-30[10].

Evaluation of Fast Dissolving Sublingual Films

Weight variation

Weight variation is studied by individually weighing 10 randomly selected filmstrips and calculating the average weight should not deviate significantly from average weight. According to specifications given in I.P.2007 for 30 mg film standard deviation should not more than 10 %.

Film thickness

The thickness of the drug loaded films was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each film. Mean SD is calculated. The standard range for film thickness should not be less than 5 %. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of dose[6].

Surface pH

The film formulation has to be kept in the oral cavity, pH of the saliva ranging from 5.5-7.5. So, to dissolve and solubilise the drug in saliva present in the oral cavity the pH of film should keep near to neutral. Since acidic or alkaline pH may leads to irritation to the buccal mucosa[7]. The surface pH of the film is calculated in order to investigate any side effects *in vivo*. A combined pH electrode was used for this purpose. The film preparation to be tested was placed in nesseler cylinder and was slightly moistened with o.5 ml distilled water introduced drop wise. The pH is measured by bringing the electrode in contact with the surface of the oral film and allowing equilibrating for 1 min[5]. The study performed on three films of each formulation and mean ±SD calculated.

Folding endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at the same place till until it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance[7]. This test should be performed on three films of each formulation and mean ±SD calculated.

Drug content

The films were tested for content uniformity. Films of size 4 cm^2 is placed in 100 ml volumetric flask and dissolved in methanol, volume is made upto 100 ml with methanol (100µg/ml). Samples were suitably diluted by using methanol[8]. The absorbance of the solution was measured at 230 nm in UV spectrophotometer. The acceptance value (AV) of the preparation 85-115%.

Table 1 Formulation of fast dissolving sublingual film of Aripiprazole

	Aripiprazo-le (mg)	Polyvinylp-yrrolidone K-30 (mg)	Polyvinyl Alcohol (mg)	Hydroxypr-opylmethylcellulose E-15 (mg)	Mannitol (mg)	Chitosan (mg)	PEG-400 (ml)
F1	10	3	3	10	3.5	6	0.015
F2	10	3	4	10	2.5	6	0.015
F3	10	3	5	10	1.5	6	0.015
F4	10	4	3	10	4.5	6	0.015
F5	10	4	4	10	3.5	6	0.015
F6	10	4	5	10	2.5	6	0.015
F7	10	5	3	10	5.5	6	0.015
F8	10	5	4	10	4.5	6	0.015
F9	10	5	5	10	3.5	6	0.015

In-vitro disintegration time

In vitro disintegration time was determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds[9]. The test was performed in triplicate for each formulation. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate. All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia limits for disintegration is 1-3 min for fast dissolving dosage forms.

In-vitro dissolution studies

The in vitro dissolution study was carried out in freshly prepared deionised simulated saliva solution pH 6.8 phosphate buffer using USP paddle apparatus at 37±0.5°C. Percent drug release was calculated for each formulation[5]. Samples were withdrawn at every 1 min time interval within 5 min dissolution study. Samples were diluted by phosphate buffer pH 6.8 solution and analysed by UV-Visible spectrophotometer.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile testing of the film was determined with digital tensile tester, which consists of two load cell grips[10]. The lower one is fixed and upper one is movable. The test film of specific size was fixed between cell grips and force was gradually applied till the film breaks. Tensile strength is calculated by Formula;

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of film in mm}^2}$$

Percent elongation

It is calculated by the distance travelled by pointer before the break of the film on the graph paper.

When stress is applied, a film strip sample stretches and this is referred to as strain. Strainis basically the deformation of film strip divided by original dimension of the sample[17]. Generally elongation of strip increases as the plasticizer content increases. It is calculated as;

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original Length}} \times 100$$

RESULT AND DISCUSSION

Weight variation of film: The weight of each filmstrip is taken on Electronic analytical balance and the weight variation is calculated as mean SD. Weight variation varies from 27.15±2.1 to 29.83± 0.13. The results are given in the Table 2.

Thickness of the film: The thickness of the drug loaded films F-1 to F-9 formulations was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each films. Mean SD is calculated. Film thickness should be controlled within a ± 5 % variation of standard value. This is essential to assure uniformity in the thickness of the film as this is directly related to the accuracy of dose and other mechanical properties of the film.Thickness of a single film varies from 0.61±0.21 to 0.69±0.04 mm. The results are reported in the Table 2.

Surface pH

The film formulations have to be kept in the oral cavity, pH of saliva ranging from 5.5-7.5. So, to dissolve and solubilize the drug in the saliva present in the oral cavity the pH of the film should keep near to neutral. If it is acidic it can leads to irritation of the buccal mucosa. Surface pH of all Aripiprazole fast dissolving films are reported in Table 2.

Surface pH of the formulations does not show considerable variations in pH.

Table No. 2

Evaluation of fast dissolving sublingual film

Formulation code	Tensile Strength (kg/mm^2) Mean±SD	Percentage elongation at break Mean±SD	Thickness(mm) Mean±SD	Weight variation(mg) Mean±SD	Folding endurance Mean±SD
F1	1.7619±0.110	0.25±0.06	0.61±0.148	28.05±2.9	148±5.2
F2	1.8695±0.037	0.39±0.002	0.63±0.523	27.56±1.7	161±3.2
F3	1.456±0.271	0.63±0.04	0.68±0.618	29.83±0.13	187±2.9
F4	1.4954±0.313	0.25±0.02	0.61±0.214	28.12±0.16	145±3.3
F5	1.525±0.129	0.32±0.03	0.66±0.183	29.07±0.24	156±2.2
F6	1.3278±0.159	0.59±0.08	0.68±0.084	27.42±0.33	175±3.2
F7	1.8715±0.071	0.24±0.03	0.69±0.041	27.15±2.1	143±2.0
F8	1.2354±0.501	0.31±0.03	0.67±0.169	26.09±0.52	151±3.1
F9	1.8994±0.029	0.45±0.04	0.65±0.029	29.19±0.43	163±1.7

All formulations show acceptable pH range 6.17-6.63. This study also reflects the influence of concentration of PVA in the formulation. As there is increase in proportion of PVA, pH of the formulation also increases as PVA is more alkaline than PVP. The highest surface pH was observed for F9 batch 6.63±0.17. There is a marginal pH difference between all the formulations.

Folding endurance of the films

The number of times the film fold until it breaks is reported. The studies reflex the influence of concentration of PVA in the formulation. As the concentration of PVA is increased, folding endurance is also increased. Formulation F3, F6 and F9 shows the largest folding endurance. Folding endurance of all Aripiprazole sublingual films are reported in Table 2. It is also found that increase in conc. of PVP K-30 decreases folding endurance. The F3 formulation shows highest folding endurance at 187 ± 2.9 as it contains highest percentage of film former and lowest percentage of PVP K-30.

Formulation code	Surface pH	% Drug Content	Disintegration time (sec)
F1	6.17±0.13	96.09±0.011	61±2.42
F2	6.28±0.18	96.30±0.012	63±1.85
F3	6.45±0.12	97.18±0.015	65±1.84
F4	6.29±0.15	96.50±0.057	54±1.21
F5	6.34±0.11	97.44±0.020	55±2.67
F6	6.23±0.07	97.90±0.026	58±1.71
F7	6.17±0.02	98.66±0.043	43±1.80
F8	6.36±0.06	96.15±0.060	48±2.29
F9	6.63±0.17	98.36±0.043	50±1.89

Drug content

Drug content of optimized batches are calculated by using film containing 5 mg of Aripiprazole3.Three trials from each formulation are analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranging from 96.09±0.01 to 98.66±0.04. The results indicated that in all the formulations the drug content is uniform. The studies also show that uniformity of content is within the specifications range 85-115%. The results are as shown in Table 2.

In-vitro Disintegration Test

In-vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate. PVP is incorporated as a superdisintegrant. All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia limits for disintegration are 1-3 min. The *In-vitro* disintegration time of all Aripiprazole films are reported in Table 2.

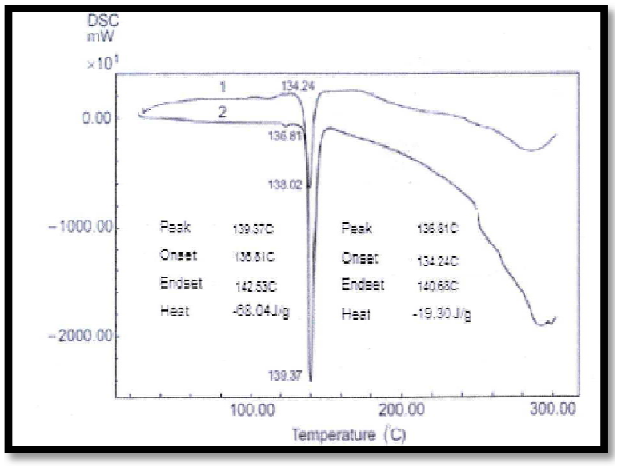
The studies show that as there is increase in concentration of PVP, disintegration time of the film decreases. It is also found that as the concentration of PVA increases in film, the disintegration time decreases. The lowest disintegration time 43±1.80 found for F7 formulation as it contains highest proportion of PVP K-30 and lowest proportion of PVA.

Tensile strength

Mechanical properties of the films are evaluated using Instron TA.XT2 texture analyzer equipment equipped with a 50 N load cell. Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. From the results it clears that when the concentration of the polymer increases, the tensile strength of the film also increases. The formulation F7 shows the maximum tensile strength. Presence of PEG 400 as a plasticizer imparts the flexibility to the Polymers. Tensile strength measures the ability of the film to with stand rupture. The Formulation F9 shows the maximum strength1.8994 ±0.0296, shown in Table 2. This might be due to formation of strong hydrogen bonds between polymer and plasticizer thereby imparting flexibility to withstand rupture, but formulation F9 also shows comparable tensile strength as compared to F7 formulation.

Percentage elongation of the films

The film of 03 inch X 10 mm was taken for the studies. Percentage elongation was found to be increased as increase in concentration of film former polymer in the film. Data is reported in Table 2. It is also found that increase in concentration of PVP K-30 decreases percentage elongation. The F3 formulation shows highest percentage elongation at 0.63±0.04, as it contains highest percentage of film former polymer and lowest percentage of PVP K-30.



DSC Spectra of Sublingual film of Aripiprazole

The DSC spectrum of sublingual film containing drug is shown in figure.18.Sublingual film of Aripiprazole showed an endothermic peak at 140.88. Studies show that heat of solution i.e -68.04 J/g is low as compared to pure drug i.e -19.30 j/g, which indicates that low energy is needed to solublise the drug when administered as a sublingual film. A study also showed that drug is totally embedded within the polymer matrix of the film which indicates that stability of drug would be good.

In-vitro Drug release study

In-vitro dissolution study shows maximum release i.e. 97.45% for F7 formulation this could be attributed to higher concentration of PVP and lower concentration of PVA in the formulation. In-vitro drug release data is shown in Table 8. F7 formulation also shows highest drug release within 1 min. i.e. 73.69% as compared to the other formulation.

The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug release. It was found to be near to one which indicating good estimation of the coefficient. Similarly Ri-squared was near to zero which led to good model. The values of Prob>F were less than 0.0003, which indicated model terms were

Table 3 *In-vitro* drug release study of all formulations

Time in	Cumulative drug release (%) ±SD								
Min	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	60.30±0.31	58.33±0.45	55.32±0.3	65.48±0.8	64.13±0.8	60.47±0.6	73.69±0.8	68.32±0.9	67.13±0.4
2	66.31±0.7	64.25±0.6	65.17±1.3	71.26±0.7	69.76±0.72	66.14±0.52	81.33±0.7	75.32±0.001	71.36±0.6
3	72.35±0.7	70.31±0.65	67.36±0.003	76.54±1.0	74.66±0.8	71.23±0.5	86.79±0.8	79.86±0.03	77.19±0.30
4	77.13±0.31	76.51±0.79	70.18±0.05	83.79±0.25	81.56±0.26	79.12±0.45	92.62±0.6	82.47±0.08	82.25±0.42
5	84.21±0.8	81.46±0.7	78.34±0.7	87.32±0.82	87.12±0.65	85.46±0.34	97.45±0.9	89.13±0.05	87.34±0.25

Optimization : Statistics was applied to the results obtained from general factorial design in which two independent variables varied namely polyvinyl pyrrolidone (X1) and polyvinyl alcohol (X2) and their effect is recorded on dependent variable namely % drug release (Y1). Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Table 4 shows ANOVA for the dependent variable % drug release. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Variable caused significant change in the responses. From this data optimum concentration of polyvinyl pyrrolidone 10 mg and polyvinyl alcohol 15 mg was found.

Table 4 ANOVA for % drug release (Y1)

Source	Degree of Freedom	F value	P-value	Inference
Model	212.16	228.30	0.0057	Significant
A-PVP K-30	154.13	46.96	0.0005	
B-PVA	58.03	17.18	> 0.0057	

std.dev. = 0.63
R-Squared = 0.9151

significant. The linear model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots were generated using Design Expert 8.0.4 software presented in figure. 21 to observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial design was choosen using linear design mode. The range was set from minimum 75.26 to maximum 100.91. The 9 run was performed for the response % drug release and model was found to be linear.

Accelerated stability study

Formulation F7 at 40°C temperature is found to be stable upto 3 months. There is no significant change in drug content, visual appearance i.e. change in colour and disintegration time. All films stored at elevated temperature showed slight change in pH, other parameters are found to be unchanged.

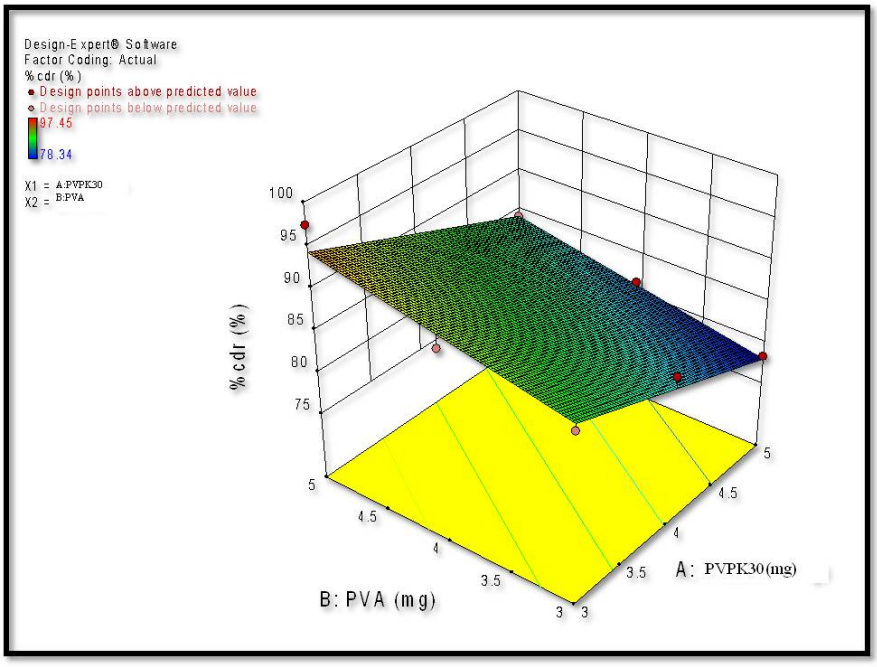


Fig.No.1 Surface Response plot showing effect of polyvinyl pyrrolidone K-30 and polyvinyl alcoholo release
Stability studies[16]

Table 5 Stability data for F7 formulation

Sr. No	Observations	Before Accelerated Stability Testing	After Accelerated Stability Testing		
			30 days	60 days	90 days
1	Drug content	98.50%	97.18%	97.90%	98.66 %
2	Visual appearance (Colour changes)	White to off-white	White to off-white	White to off-white	White to off-white
3	pH	6.17	6.2	6.3	6.3
4	Disintegration time	43 Sec	44 Sec	41 Sec	41 Sec

This change in pH is due to presence of PVA which is alkaline in nature, but it does not affect stability of drug within the film.

CONCLUSION

Films were prepared with different film formers such as, PVA (low viscosity), in combination with PVP as a super disintegrant by solvent casting method. The method of casting of film on the petri plates was found to be satisfactory. This shows suitability of drug for administered as a mouth dissolving dosage form. The nine preliminary trial batches arranged/prepared by using the 3^2 factorial design lead to the final optimized concentration of the factors. Dissolution profile was taken as the response for study, which was found to be within the expected range. The optimized concentrations of polyvinyl alcohol and polyvinyl pyrrolidone obtained by applying polynomial equation of 3^2 factorial designs were 3 mg and 5 mg respectively. Surface pH was determined for all formulations show acceptable pH range 6.17-6.63. This study also reflects the influence of concentration of PVA on the pH of formulation. The increase in proportion of PVA greater is the pH of the formulation. Disintegration time study shows that there is increase in concentration of PVP disintegration time of the film decreases. The formulations shows fairly uniform drug content ranging from 96.09 to 98.66 % with minimum batch to batch variation. Drug release study was conducted to determine the % drug release with formulation F7 it shows the highest drug release i.e. 97.45% up to 5min.

Finally it is concluded that the drug release from the sublingual film was increased by using the increased concentration of superdisintegrant thus assisting in faster disintegration in the buccal cavity. As the drug is having low solubility, fast disintegration may lead to more drug availability for dissolution, resulting in faster absorption in systemic circulation. Increased systemic availability of drug may lead to quick onset of action, which is a prerequisite for psychotic patient optimized formulation fulfils all necessary attributes required for sublingual film and can become a promising alternative to present marketed tablet.

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References

1. M. Renuka, A. Avani, Formulation and Devlopment of taste mask rapidly dissolving films of Cetrizine Hydrochloride. *Pharmaceutical technology*; 2009; 368; 105-111
2. N. A. Nafee, F.A. Ismail, N. A. Borale, L.A. Mortada, Mucoadhesive buccal patches of miconazole nitrate: In vitro in vivo performance effect of ageing, *Internayional J Pharma* 2003; 264; 1-14
3. K. D. Tripathi, Antipsychotics drugs, essentials of pharmacology, ed 6th, Jaypee medical publications; 2009, 423-438.
4. P. Seeman, Dopamine receptors and the dopamine hypothesis of Schizophrenia; Synapse; 1987; 1(2); 133-52
5. G. Ponchel, Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive material; Ad drug delivery reviews; 1993; 13; 75-87.
6. USP NF, Vol 2, (2015), The Official compendia of standards, The United States Pharmacopoeial convention, 2280-2281
7. Indian Pharmacopoeia (2014) Addendum 2015, A publication of the I.P. commission, Ministry of Health & Family Welfare Government of India, Published by I.P. commission, Gaziabad, 734, 3803-3804.
8. Indian Pharmacopoeia (2014) Vol. II, A publication of the I.P. commission, Ministry of Health & Family Welfare Government of India, 7th edition; Published by I.P. commission, Gaziabad, 1081-82.
9. British pharmacopoeia 2009, Published by B.P., Commission Office,vol-II, 1172-73.
10. K. Vinod Kumar, B. Pragati Kumar, Formulation and Evaluation of Orodispersible tablets of Aripiprazole by direct compression technique. I.*J.Res. in Pharmacy and Biotec*.2010; 2(6): 1473-1480.
11. H. P. Rang, M.M. Dale, J. M. Ritter, R. J. Flower, Antipsychotic drugs, pharmacology, ed 6th Edinburgh; New York; Churchill Living stone, 2003,87-111.
12. F.S.K Barar, Psychopharmacological agents, essentials of pharmacotherapeutics, ed 4th , S.Chand publishers, 138-150
13. P. G. Strange, Antipsychotic drugs; importance of dopaminereceptors for metabolism of therapeutic actions and side effects; *pharmacology Rev*. 2001; Mar,53(1); 119-33
14. P. G. Busatto, R. W. Kerwin, perspectives on role of serotonin mechanisms in thepharmacology of schizophrenia; *J psychopharmacology*; 1997; 11(1);3-12
15. H.L. Klawans, C.M. Tanner, C.G. Goetz; Epidemiology and pathophysiology of tardive dyskinesias. *Adv Neurol*; 1988; 49, 185-97
16. Martindale; The extra pharmacopoeia; The royal pharmaceutical society; edited by J.E.F Reynolds; London; 1996; 909.
17. D.E.Casey; Tardive dyskinesia pathophysiology; 1995; In Bloom F.E.; Kupter D.J.(eds) psychopharmacology; a fourth generation of progress; Raven press; New York; 4-10

18. Goodman & Gilman's the pharmacological basis of therapeutics; chapter 11, 5Hydroxytryptamine (Serotinin): Receptor Agonists and Antagonists; 11 ed. (2006), 308-315.
19. G.J.Tortora, B. Derrickson, Principles of Anatomy and physiology,cp-17th special senses, ed 11th; 2007, 101-107.
20. J.M. New comer, Abnormalities of glucose metabolism associated with atypical antipsychotic drugs; *J clinical psychiatry*;65th Suppli.18; 2004; 36-46
21. A. Wagh, A.Grant, Ross and Wilson anatomy and physiology in health and illness. 10ed, London: Churchill livingstone; 2006, 206-213.
22. IW Kellaway, In vitro test methods for the measutrment of mucoadhesion. In: R.Gunny, HE Junginger. Bioadhesion possibilities and future trends; Wissenshaftliche Verlagsgesell-schaft; mbH. 1990; 886-92
23. S.C. Nitesh, Alka Tomar *et al,* Formulation and Evaluation of Fast Dissolving Oral Film of Diclomine as potential route of buccal delivery; *Inter. J. Of Drug Development and research*; April-June 2012;4(2); 408-417
24. B.B. Suresh, Quick Dissolving Films-A Novel Approach to Drug Delivery, Drug Delivery Technology 2003: 3(3), Pg no. 1-6
25. US Food and Drug Administration, CDER Data Standards Manual
26. European Pharmacopoeia. 5th ed. Strasbourg, France:2006; 628
27. M.D. Nehal Siddiqui *et al*, A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents; *Advances in Biological Research;* 2011; (6); 291-303
28. A. Ganem-Quintanar, Y.N.Kalia, F.Falson-Rieg, Buri P., Mechanism of penetration enhancement, *International J Pharm* 1997; 156; 127-142
29. Y.W.Chien; Oral Drug Delivery and Delivery systems. 2nd Ed. New York: Marcel Dekker; 1992. 139-145
30. V.F.Patel, Liu Fang, B.B.Brown *et al*; *Journal of Controlled Release*; (2011); 153; 106-116

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