Available online on 15.02.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Preparation and evaluation of fast dissolving sublingual film of lisinopril

Swathi Palepu*, T. Sathyanarayana, Mudigiri Ravali, P. Dakshyani, Ubbala Sirisha, Pathipati Divya Sri, Madupalli Srinu

Mother Teresa pharmacy College, kothuru, Sathupally-507303, Khammam Dist.,Telagana, India

ABSTRACT

Fast-dissolving drug-delivery systems (FDDS) serve a major benefit over the conventional dosage forms because the drug gets disintegrated rapidly and dissolves in the saliva without the use of water. Lisinopril is the lysine analog of enalapril which was used to treat hypertension and symptomatic congestive heart failure, to improve survival in certain individuals after myocardial infarction and to prevent the progression of renal disease in hypertensive patients with diabetes mellitus and microalbuminuria or overt nephropathy. The drug is found to be absorbed slowly and incompletely from the gastrointestinal tract (oral) bioavailability of the drug is ~25% in order to increase bio availability lisinopril was formulated as fast dissolving sublingual film A total of 10 formulations of Fast dissolving sublingual film of lisinopril was prepared by using different polymers like HPMC E15, HPMCE5, HPMC E3, HPMC K 15, PVP, PEG 400 as plasticizer, SSG as a super disintegrant. Among them F10 formulation containing HPMC E 3 and PVP in combination of 4:1 ratio with SSG as a super disintegrant showed 95.69 % drug released in 10 minutes and which was disintegrated in 95 sec .

Keywords: FDDS, Lisinopril, HPMC, SSG

Article Info: Received 29 Nov 2018; Review Completed 24 Jan 2019; Accepted 29 Jan 2019; Available online 15 Feb 2019

Cite this article as:

Palepu S, Sathyanarayana T, Ravali M, Dakshyani P, Sirisha U, Divya Sri P, Srinu M,, Formulation and evaluation of fast dissolving sublingual film of lisinopril, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):101-106

DOI: http://dx.doi.org/10.22270/jddt.v9i1-s.2342

***Address for Correspondence:**

Swathi Palepu, Assistant professor, Dept of Pharmaceutics, Mother Teresa Pharmacy College, Sathupally, Khammam Dist, T.S., India

INTRODUCTION

Fast dissolving sublingual films

The concept of sublingual films has been introduced to overcome the problems associated with conventional oral dosage forms and improve bioavailability there by optimization of therapy.

Fast dissolving films are most advance form of solid dosage form due to flexibility. It improve efficacy of active pharmaceutical ingredient [API] dissolving in short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.[1]

Ideal characteristics for a drug to formulate it into sublingual film[2]:

- The drug should have pleasant taste.
- The drug that is incorporated should have low dose up to 40mg.
- The drug with smaller and moderate molecular weight is preferable.
- The drug should have good stability and solubility in water as well as in saliva
- It should be have partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissues.

Advantages of sublingual film [3, 4, 5]:

- No risk of chocking.
- Convenient dosing or accurate dosing.
- No need of water to swallow or chew.
- Rapid onset of action.
- Easy of handling & transportation.
- Enhanced stability.
- Taste masking.

Half life of Lisinopril is 12 hr. The daily doses ranges from 20 to 80 mg. The systemic bioavailability of Lisinopril is approximately 25%. In view of these facts this drug can be considered as a suitable candidate for fast dissolving oral film. In this study an attempt is made to investigate the feasibility of fast dissolving oral films as a medium for the

fast delivery of Lisinopril with better bioavailability and enhanced patient compliance.

MATERIALS

All the materials used in this study (Lisinopril, HPMC E15, HPMCE5, HPMC E3, HPMC K 15, PVP, SLS, SSG, PEG 400, Sucralose, Peppermint oil, Citric acid) were obtained from Sree srinivasa scientifics, Hyderabad

METHODOLOGY

Preparation of fast dissolving sublingual films[6-10]:

Fast dissolving sublingual film was prepared by solvent casting method. A total of 10 formulations were prepared by using different polymers, super disintegrating agent, plasticizer in combination. Total water was divided into two parts in one part drug is dissolved and in other part polymer, plasticizer, super disintegrant and flavouring agents were dissolved. Part one is added to the part two with stirring and sonicated for 10 mins to remove the entrapped air, the solution was poured into petridish and an inverted funnel was placed over it. Kept for evapouration for 24 hours. The formed patch was removed and analyzed.

Table 1: Formulation Design

Excipient	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug (mg)	40	40	40	40	40	40	40	40	40	40
HPMC E15(mg)	500	-	-	-	-	-	-	-	-	-
HPMCE5 (mg)	-	500	-	-	300	-	400	-	-	-
HPMC E3 (mg)	-	-	500		-	300	-	400	400	400
HPMC K 15 M(mg)	-	-	-	500	-	-	-	-	-	-
PVP (mg)	-	-	-	-	200	200	100	100	100	100
SLS (mg)	2	2	2	2	2	2	2	2	2	2
SSG (mg)	-	-	-	-	-	-	-	10	20	30
PEG 400 (ml)	2	2	2	2	2	2	2	2	2	2
Sucralose (mg)	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Peppermint oil (ml)	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml	0.3ml
Citric acid (mg)	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg
Water upto (ml)	15	15	15	15	15	15	15	15	15	15

Evaluation studies

Preparation of standard solution:

Method:

The pure drug of about 10 mg was weighed and transferred in to a 10ml volumetric flask. The drug was dissolved completely in a few ml of 0.1N NaOH and made up to the final volume with NaOH to get a stock solution of concentration 1000µg/ml. Aliquots of standard stock solution were pipette out and diluted suitably with water to get the final concentration of standard solutions.

Absorption maxima method:

The solutions were scanned in the range of 400-200 nm against 0.1N NaOH as reference, and the peaks were observed in the spectra at 218nm. The wavelength selected for analysis of drug was 218nm. The drug obeys the lamberts law in the range of 2-12 µg/ml. By using linearity plot the quantification was carried out.

Compatibility studies by FTIR

The drug and excipient compatibility studies were carried out by FTIR study.

Thickness:

The thickness of the patch was measured using digital VernierCalliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

Weight variation:

Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated

Folding endurance:

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

Tensile strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

Tensile strength = Load at failure ×100/ Film thickness × film width

Percent elongation:

Film sample stretches when stress is applied and it is referred to as strain.Strainis basically the deformation of film divided by original dimension of the sample. Elongation of film increases as the plasticizer content increases.

*Percent Elongation= L * 100/ Lo*

Where, L = Increase in length of film,

Lo = Initial length of film.

Surface pH:

The film to be tested was placed in a petri dish and was moistened with0.5ml of distilled water and kept for 30sec.The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equlibriation for 1min. The average of three determinations for each formulationwas done.

Uniformity of drug content

This parameter was determined by dissolving one film of dimension 2 x 2 cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. . From this, 10 ml was diluted to 50 ml with simulated salivary fluid. The absorbance was measured using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations and average values were recorded.

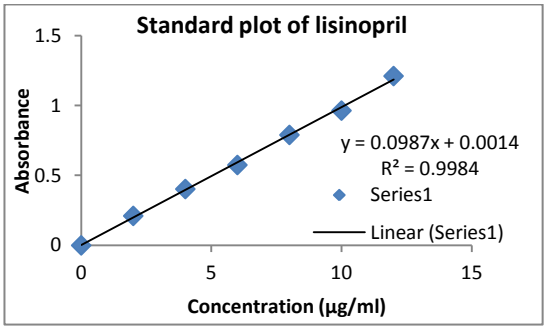
***In Vitro* permeation studies through egg membrane:**

Permeation studies were carried using the modified Franz diffusion cell of internal diameter of 2.5 cm. The egg membrane was separated by using concn HCL then washed in isotonic phosphate buffer of pH 6.8 and used immediately. The egg membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 25 mL of isotonic phosphate buffer of pH 6.8. Which was maintained at 37 ± 0.2ºC and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One film of dimensions 2 x 2 cm, previously weighed, was placed in intimate contact with the mucosal surface of the membrane that was previously moistened with a few drops of simulated saliva. The donor compartment was filled with 1 mL of simulated saliva of pH 6.8. Samples

RESULTS AND DISCUSSION

Table 2: Standard graph of lisinopril pure drug

Concentration (µg/ml)	Absorbance
0	0
2	0.211
4	0.403
6	0.575
8	0.790
10	0.964
12	1.211

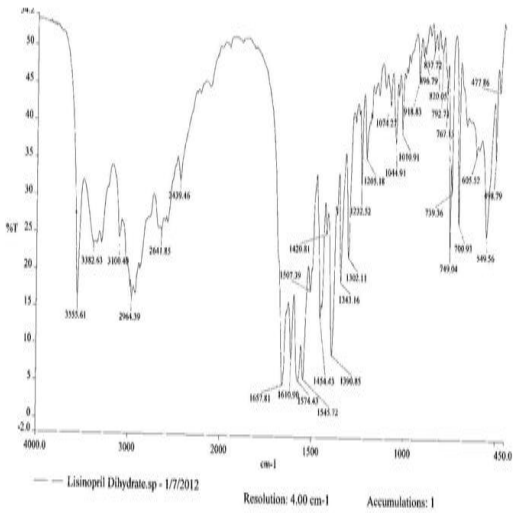


Compatibility studies by FTIR:

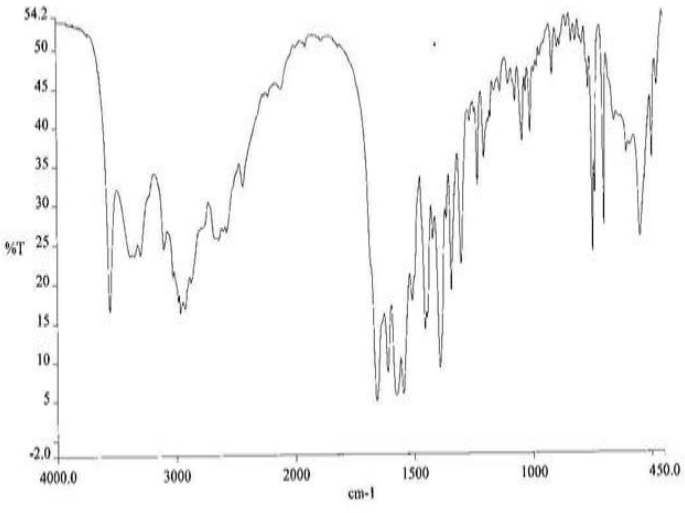
The study showed peaks for the corresponding functional groups in Lisinopril. When the study was carried out with the combination of Lisnopril and polymers, there were no major changes in the peaks. Hence there was no interaction with the polymers. The results were shown below

Table 3: Results of FTIR studies

Ftir spectra	Peak of Functional groups [Wave length (cm-1)]				
	C-H Stretching (alkane)	C-H Bending (aromatic)	C=O Stretching (Phenols)	C=O Stretching (Amide)	C=C Stretching (Aromatic)
Pure drug	2925.3	749.27	1395	1656.38	1590
Final Formulation	2900	750	1400	1659.12	1590



FTIR of lisinopril of pure drug



FTIR of Final formulation

Preparation of Fast dissolving sublingual patches:

Initially fast dissolving sublingual patches were optimized with an intention to get good physical properties by employing plasticizer in different concentrations. Film forming polymers used in the present investigation were HPMC and PVP different grades in different concentrations. The plasticizer Propylene glycol (10, 15, 20&25%W/W) were studied. Propylene glycol (20%) W/W Concentration gave good physical properties like flexibility, elasticity and transparency. Plasticization with Propylene glycol provided higher strength and better elongation characters to the films. The reason attributed to this is as the major parts of the films were HPMC which is hydrophilic polymer, the hydrophilic plasticizer Propylene glycol could reduce the glass transition temperature of the film. After getting a desired flexible film different concentration of super disintegrants was employed in order to achieve fast dissolution.

Table 4: Result of Evaluation Parameters of Batch F1-F10

Formulation Code	Thickness (mm)	Weight (mg)	Folding endurance	Tensile strength (N/ mm2)	% Elongation	% Moisture content
F1	0.10 ± 0.020	51 ± 1.00	> 300	5.2 ± 0.03	28.5 ± 0.11	3 ± 0.957
F2	0.12 ± 0.005	53 ± 1.00	> 300	6.8 ± 0.01	32.3 ± 0.08	4 ± 0.942
F3	0.11 ±0.011	52 ± 1.00	> 300	7.1 ± 0.05	35.0 ± 0..16	3 ± 0.642
F4	0.09 ± 0.005	49 ± 1.00	152	4.2 ± 0.10	18.0 ± 0.12	5 ± 0.744
F5	0.16 ± 0.010	56 ± 1.40	209	3.6 ± 0.13	19.0 ± 0.32	4 ± 0.956
F6	0.15 ± 0.005	55 ± 1.15	>300	8.6 ± 0.04	40.6 ± 0.10	4 ± 0.749
F7	0.10 ± 0.005	51 ± 0.57	124	4.0 ± 0.10	12.1 ± 0.13	7 ± 0.442
F8	0.12 ± 0.010	54 ± 1.00	> 300	4.4 ± 0.10	27.3 ± 0.09	6 ± 0.882
F9	0.15 ± 0.005	54 ± 1.53	> 300	5.9 ± 0.06	29.4 ± 0.14	5 ± 0.242
F10	0.12 ± 0.05	56 ± 1.20	> 300	7.1 ± 0.05	35.0 ± 0..16	4 ± 0.603

Table 5: Result of Evaluation Parameters of Batch F1-F10

Formulation Code	Surface pH	Disintegration time (s)	Drug content (%)
F1	6.63 ± 0.05	192 ± 3.00	85.67
F2	6.61 ± 0.04	162 ± 1.00	90.23
F3	6.63 ± 0.02	168 ± 2.00	91.38
F4	7.01 ± 0.01	160± 2.00	87.96
F5	6.68 ± 003	130 ± 1.40	89.59
F6	7.04 ± 0.01	202 ± 1.15	90.42
F7	6.53 ± 0.03	177 ± 5.00	91.5
F8	7.08 ± 0.02	125 ± 2.00	92.91
F9	6.41 ± 0.03	121 ± 5.00	92.82
F10	6.63 ± 0.02	95 ± 2.53	95.69

Discussion of evaluation parameters of Fast dissolving sublingual films;

Physical appearance: All the sublingual films were visually inspected for colour, clarity, flexibility.

a. Weight of the film

Drug loaded films (2x2 cm2) were tested for uniformity of weight. The films were found uniform. The average weight of the film was found to be in the range of 51 ± 1.00 to 56 ± 1.20mg. as the polymer content increase, the weight of the patch also increased.

b. Thickness of the film

All the films have uniform thickness throughout. Average thickness was found to be in the range of 0.10 ± 0.005 to 0.16 ± 0.010 mm. As the polymeric content increases, the thickness of the patch also increases.

c. Moisture content

Moisture content in F1 to F10 were found to be in the range of 3 to 7%.

d. Drug content determination

It was determined for all formulation by UV spectrophotometer method shown in table. The data obtained from triplicate studies were analyzed for mean and standard deviation. The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 85.67 to 95.69 %.

e. Tensile strength

Ideal sublingual film should be flexible, elastic and strong enough to withstand breakage due to stress caused during its residence in the mouth. The tensile strength shows the strength and elasticity of the film. A soft and weak polymer is characterized by low TS; a hard and brittle polymer is defined by a moderate TS, a soft and tough polymer is characterized by a moderate TS, whereas a hard and tough polymer is characterized by high TS. Tensile Strength increased with the increase in polymeric content. Maximum TS was exhibited by F6 batch (8.6 ± 0.04 kg/cm2) and minimum was exhibited by F5 batch (3.6 ± 0.13 kg/cm2).

f. Folding endurance

Folding endurance measures the ability of film to withstand rupture. Patch did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point.

Folding endurance did not vary when the comparison was made between plain patch and drug loaded patch.

In-vitro diffusion studies:

The percentage amount of drug diffusion is plotted against time to obtain the diffusion profile. It was found that in 10 min, the entire quantity of the released drug from the formulation diffused completely and hence indicated a good diffusion coefficient, which is essential for faster onset of action. Formulation F4 showed minimum drug release (41.71 %) and F10 Formulation showed a maximum drug release of (95.69%).

Table 6: *In-vitro* drug diffusion data

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
2	40.12	54.5	56.5	15.9	58.5	55.6	59.6	60.12	62.8	65.9
4	65.3	67.5	75.5	27.5	68.2	70.12	72.15	74.5	78.5	80.5
8	74.7	80.5	89.5	30.31	80.81	81.5	86.5	87.5	88.5	90.12
10	85.67	90.23	91.38	41.71	89.59	90.42	91.5	92.91	92.82	95.69

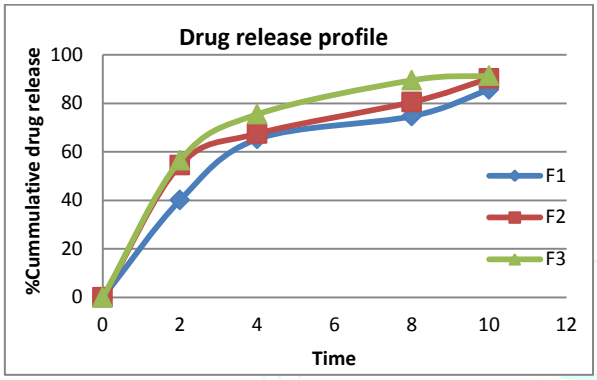


Figure 1: Comparisons of drug release of formulations F1,F2,F3

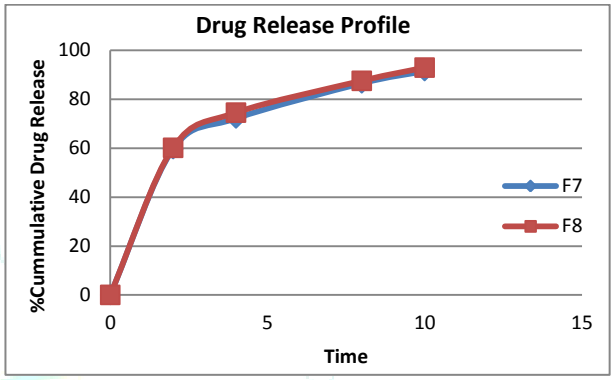


Figure 3: Comparisons of drug release of formulations F7,F8.

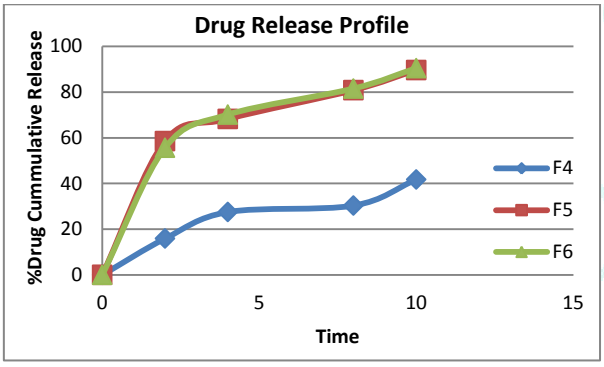


Figure 2: Comparisons of drug release of formulations F4,F5,F6

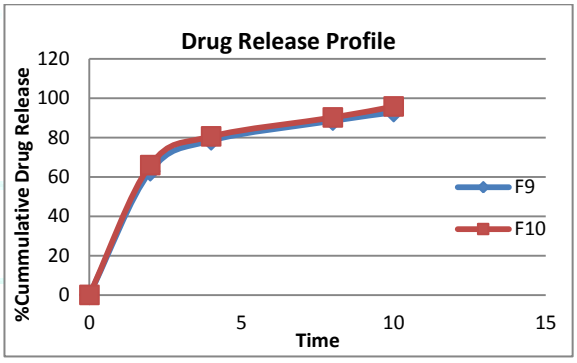


Figure 4: Comparisons of drug release of formulations F9,F10

Stability studies:

Stability studies were carried out for 45 days at 2-8°C (45% RH) and 25-30°C (60% RH). The films were observed for physical changes, the percentage drug content and the percentage drug release. Fast-dissolving films of lisinopril were found to be physically and chemically stable and showed no significant change in terms of physical characteristics, the percentage drug content and the percentage drug release.

Table 7: Stability studies data

S.No	Time in Days	Appearence	In –Vitro disintegration time	%CDR
1	Intial (0 Days)	Transparent and Acceptable	95 ± 2.53	95.69
2	1 month (30 Days)	Transparent and Acceptable	95 ± 4.25	94.98
3	3 months (90 days)	Transparent and Acceptable	95 ± 5.46	94.85

CONCLUSION

Fast-dissolving drug-delivery systems (FDDS) serve a major benefit over the conventional dosage forms because the drug gets disintegrated rapidly and dissolves in the saliva without the use of water. Lisinopril is the lysine analog of enalapril which was used to treat hypertension and symptomatic congestive heart failure, to improve survival in certain individuals after myocardial infarction and to prevent the progression of renal disease in hypertensive patients with diabetes mellitus and microalbuminuria or overt nephropathy. The drug is found to be absorbed slowly and incompletely from the gastrointestinal tract (oral) Bioavailability of the drug is ~25% inorder to increase bio availability lisinopril was formulated as fast dissolving sublingual film .A total of 10 formulations of Fast dissolving sublingual film of lisinopril was prepared by using different polymers like HPMC E15, HPMCE5, HPMC E3, HPMC K 15, PVP, plasticizer PEG 400, SSG as a super disintegrant .Among them F10 formulation containg HPMC E 3 and PVP in combination of 4:1 ratio with SSG as a super disintegrant showed 95.69 % drug released in 10 mins and which was disintegrated in 95 sec. The optimized formulation was kept for stability studies no significant changes were observed after 3 month in the disintegration time and drug content.

REFERENCES

1. Jain NK. Controlled and Novel Drug Delivery, *CB Publishers and Distributors*, New Delhi, 1997; 1:52-81.
2. Rajesh B. Gandhi and joseph R. Robinson. Oral Cavity as a site for bioadhesive drug delivery. *Advdrug Del Rev.* 1994; 13:43-74.
3. David Haris and Joseph R. Robinson Buccal drug delivery via the mucous membrane of the oral cavity**.** *Journal Pharm Sci*. 1992; 81(1):1-9
4. Pramod Kumar TM, Shivakumar HG Desai KG. Oral Transmucosal drug delivery system. *Indian Drugs*2004; 41(2):63-67
5. Swarbrickjames. Bioadhesive Drug Delivery Systems. *Marcel Dekker Inc*, NewYork, 1999, 541-562
6. Patel R et al, development and characterization of mucoadhesive buccal patches of Solbutamol Sulphate, *current drug delivery*, 2004; 140 -144.
7. Panchal MS, Patel H, Bagada A, Vadalia KR, Formulation and Evaluation of Mouth Dissolving Film of Ropinirole Hydrochloride by Using Pullulan Polymers, International Journal of Pharmaceutical Research &Allied Sciences, 2012; 1(3):60-72.
8. Qadir KA, Charyulu RN, Prabhu P, Bhatt S, Shastry CS, Formulation and evaluation of fast dissolving film of loratidine for sublingual use, International research journal of pharmacy, 2011; 3(7):157-162.
9. Bhyan B, Jangra S, Kaur M, Sing H. Orally fast dissolving films: innovations in formulation and technology. International Journal of Pharmaceutical Sciences Review and Research, 2011; 9:50-56.
10. Tomar A, Sharma K, Chauhan NS, Mittal A, Bajaj U, Formulation and Evaluation of Fast Dissolving Oral Film of Dicyclomineas potential route of Buccal Delivery., International Journal of Drug Development & Research, 2012; 4 (2):408-417