ejpmr, 2017,4(05), 340-345

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF CHLORPHENIRAMINE MALEATE FAST DISSOLVING FILM AS AN ANTI ALLERGIC MEDICATION.

Tekade B. W.*, Jadhao U. T., Patil V. R. and Sumit Dhanwade

Department of Pharmaceutics, TVES's Honorable Loksevak Madhukarrao Chaudhari College of Pharmacy, Faizpur, (India).

***Corresponding Author: Dr. Tekade B. W.**

Department of Pharmaceutics, TVES's Honorable Loksevak Madhukarrao Chaudhari College of Pharmacy, Faizpur, (India).

Article Received on 22/02/2017 **Article Revised on 15/03/2017** **Article Accepted on 05/04/2017**

ABSTRACT

In the present work, aimed to prepare and evaluate the fast dissolving films containing Chlorpheniramine Maleate, as an anti-allergic drug using different ratios of polymers, Hydroxypropyl methylcellulose E15, Pectin and Aloe Vera gel. The film was prepared by solvent casting technique using Glycerin as a plasticizer, Aspartame as a sweetener. The study examines about the effect of polymers ratio on physicochemicalProperties and drug release potential of films. All the films formulations (F1-F9) were evaluated for their thickness, weight variations, tensile strength, percentage elongation, folding endurance, surface pH, in -vitro disintegration, drug content, *In-Vitro* drug release. The formulation, (F7) consisting of 200 mg of HPMC E-15 , 100 mg of Pectin, 75 mg of Aloe Vera gel was found to be suitable in the form of fast dissolving film based on the in vitro evaluation studies. The (F7) showed optimum disintegration time and faster drug release 29.00 ±0.60 & 96.49 ± 0.36 respectively.

KEYWORD: polymers, Hydroxypropyl methylcellulose E15, Pectin and Aloe Vera gel.

INTRODUCTION

Oral drug delivery system it is widely used drug delivery system as it provides more compliance to the patients.Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It rapidly disintegrates and dissolves to release the medication for oral and intra-gastric absorption. Since the drug is directly absorbed into the systemic circulation, degradation in the GI tract and first pass effect can be avoided.[1]

Allergies, also known as allergic diseases, are a number of conditions caused by hypersensitivity of the immune system to something in the environment that usually causes little or no problem in most people.[2] Chlorpheniramine is an antihistamine used to relieve symptoms of allergy, hay fever, and the common cold. These symptoms include rash, watery eyes, itchy eyes / nose / throat / skin, cough, runny nose, and sneezing. Histamine is an inflammatory biochemical that causes skin redness, swelling, pain, increased heart rate, and blood pressure drop when it binds to one of many H1 receptors throughout the body. Histamine is a very important mediator of allergy in humans; hence a spectacular array of different antihistamines has proliferated. Chlorpheniramine maleate is typically administered 2 to 3 times daily. The drug is readily and rapidly absorbed from the G.I. tract and is usually effective within an hour. The half-life may be as long as 24 hours. The drug is largely inactivated in the liver and excreted as metabolites in the urine. In conventional tablets the onset of action is slow. So there is need to formulate dosage forms which give fast relief from allergic conditions and at the same it should minimize the first pass effect so that it improves the bioavailability.[3]

The preset investigation was undertaken with the objective of formulating FDFs of CPM to be potentially useful for treatment of allergic conditions and enhance the convenience and compliance by the pediatric and geriatric patients and enhance bioavailability and rapid onset of action. Chlorpheniramine Maleate a H_1 antagonist It is a first- generation alkylamine antihistamine used in the prevention of the symptoms of allergic conditions such as rhinitisand urticaria. Its sedative effects are relatively weak compared to other first-generation antihistamines. Chlorpheniramine(CPM) is one of the most commonly used antihistamines. Although not generally approved as an antidepressant or anti-anxiety medication, Chlorpheniramine appears to have these properties as well.[4, 5] CPM has oral bioavailability of 25-50% due to hepatic first pass metabolism. The present study investigated the possibility of developing Chlorpheniramine Maleate fast dissolving films allowing fast drug dissolution in the oral

cavity, thus bypassing first pass metabolism to provide rapid onset of action of the drug.[6, 7]

MATERIALS AND METHODS

Materials

Chlorpheniramine Maleate was obtained as a gift sample from Cipla. HPMC E-15, Pectin obtained from Rankem chemicals, Aloe Vera Gel obtained from Patanjali Haridwar. Glycerine, Aspartame, Citric acid purchased from Rankem chemicals. All the reagents and materials were of analytical or pharmacopoeia grade.

Formulation and development of fast dissolving film

Fast-dissolving films of Chlorpheniramine Maleate were prepared by the solvent-casting method. Thewater soluble polymers were soaked in half quantity of distilled water for overnight to obtain a uniform dispersion. Aqueous solution I was prepared by adding plasticizer to above polymeric solution and wasallowed to stir for 4 hours and kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution II was prepared by dissolving the Chlorpheniramine Maleate, aspartame in specific proportion in remaining amount of distilled water. Both aqueous solutions I and II were mixed and stirred for 1 hourand kept for 30 min for sonication. Then the mixture solution was casted onto a plastic Petri dish having surface area of 78.5cm2 and it was dried in the oven at 50°C for 24 hour. The film was carefully removed from the Petri dish, checked for any imperfections, and cut according to the size required for testing(2×2cm2). The various ratios of polymer and excipients given in Table No.1.

Table No: 1 Composition of Formulations.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorpheniramine Maleate	78.5	78.5	78.5	78.5	78.5	78.5	78.5	78.5	78.5
HPMC E15	100	125	175	250	300	350	200	250	325
Pectin	100	125	150	100	125	150	100	125	150
Aloe Vera Gel	75	100	125	75	100	125	75	100	125
Glycerin	90	120	150	90	120	150	90	120	150
Citric acid	50	50	50	50	50	50	50	50	50
Aspartame	60	60	60	60	60	60	60	60	60
Pineapple flavor	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Water(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Evaluation Parameter of Fast Dissolving Film.

TensileStrength.

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS) can be calculated by dividing the maximum load bythe original cross-sectional area of the specimen and it is expressed in force per unit area (N/mm^2).[8]

Folding Endurance

Folding endurance was determined by repeatedly folding the film at the same place till it break .The numbers of times the film can be folded at the same place without breaking give the value of folding endurance.[9]

Thickness offilm.

The thickness of each sample was measured using a micrometer at five locations (center and four corners), and the mean thickness calculated.[10]

Weight variation.

Four centimeter square (2 X 2 cm) 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.[11]

Percent Elongation at break(%E).

Percent elongation at break (%E) is calculated by dividing the extension at the moment of rupture of the specimen by the initial gage length of the specimen and multiplying by100.[12]

Drug contentuniformity.

The film unit of the dimensions 2 cm× 2 cm wasplaced in 100 ml of distilled water.After complete solubilization, the solution was diluted appropriately, filtered and analyzed by UV method. The average of three films was taken as the content of drug in one film unit.[13]

Disintegration Time.

In vitro disintegration time was determined visually in a petridish containing 25 ml of pH 7.2 artificial saliva with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.[14,15]

In Vitro Dissolution Study.

The dissolution study was carried out using USP paddle apparatus (Model TDT-00T, Electrolab, Mumbai, India), at $37^0c \pm 0.5^0c$ using 900 ml of simulated saliva (pH 6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. In order to sink the film, each prepared film of the dimensions 2 × 2 cm^2 was affixed to a paper clip and put into the vessel at initial time. Sampling was done after 5 minutes. The sample was filtered through Whatmann filter paper, diluted suitably if required and analyzed by UV method. An equal volume of the fresh dissolution media, maintained at the same temperature was added after withdrawing the sample to maintain the volume.[16]

Surface pH

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.[17]

Differential scanning Calorimetry (DSC) study.

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the Preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC TA- 60WS) allows the fast evaluationof possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipientsandoptimizedfilmwererecorded.

Thethermalanalysiswasperformedina nitrogen atmosphere at a heating rate of 100C/min over a temperature range of 40^{0C} to 300^{0C}. DSC study was performed for Chlorpheniramine Maleate and physical mixture of all ingredients ofoptimized film.

Infrared spectroscopy

The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR- 8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400cm-1.

RESULTS AND DISCUSSION

Thickness of mouth dissolving film depends on the concentration of polymer. Thickness of all mouth dissolving film was measured with micrometer screw gauge. All the mouth dissolving formulations of different polymers are show thickness value in the range of 0.06 ± 0.01 to 0.27 ± 0.01 mm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film. A result showed that as the concentration of polymer increases weight of film also increases.Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.2 to 6.9 pH, which was close to the neutral pH. Result were shown in table no.2.

Table No: 2 Evaluation Parameter of Fast Dissolving Film.

Formulation Code	Thickness (mm)	Weight (mg)/4cm^2	Surface pH
F1	0.06 ± 0.01	33.67 ± 1.50	6.23 ± 0.06
F2	0.08 ± 0.02	39.51 ± 0.70	6.38 ± 0.08
F3	0.11 ± 0.01	44.47 ± 0.23	6.43 ± 0.03
F4	0.13± 0.01	49.33 ± 0.68	6.50 ± 0.10
F5	0.15 ± 0.00	53.26 ± 1.53	6.38 ± 0.13
F6	0.17 ± 0.02	57.50 ± 0.50	6.51 ± 0.05
F7	0.21 ± 0.01	63.40 ± 0.77	6.46 ± 0.22
F8	0.24 ± 0.00	68.00 ± 0.38	6.53 ± 0.15
F9	0.27 ± 0.01	71.96 ± 0.21	6.85 ± 0.03

n=6±SD

Folding endurance gives an indication of brittleness of the film. A result showed that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film increases.In vitro disintegrating time for mouth dissolving film of CPM was ranges from 19.67 ± 0.58 to 37.00 ± 0.00 sec. All the formulations found to gave minimum disintegration time. Result were shown in table no.3.

Table No.3: Evaluation Parameter of Fast Dissolving Film Batch F1 to F9

Formulation Code	Disintegration Time in Sec	Folding Endurance
F1	19.67 ± 0.58	145.33 ± 3 .21
F2	22.33 ± 1.52	150.67 ± 3.05
F3	24.00 ± 0.00	164.00 ± 2.15
F4	25.33 ± 0.57	178.00 ± 1.00
F5	26.00 ± 0.57	183.33 ± 3.51
F6	26.70 ± 0.00	189.67 ± 2.52
F7	29.00 ± 0.60	192.33 ± 1.64
F8	31.66 ± 0.58	197.00 ± 1.82
F9	37.00 ± 0.00	204.12 ± 2.30

The tensile strength was found to increase with increase with concentration of HPMC E 15. Formulation F8 was found maximum 22.33g/mm^2.The percentage elongation of all the batches ranges from 9-18.94 mm elongation. It increased upon polymer as shown by the formulations. Formulation F9 had highest percentage elongation. The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory showing drug content as per labeled amount. Result were shown in table no.4.

Table No.4: Evaluation Parameter of Fast Dissolving Film Batch F1 to F9.

Formulation Code	Tensile Strength (g/mm^2) ± S.D.	Elongation (mm) ± SD	Drug Content (%) ± S.D.
F1	8.19 ± 0.122	9.24 ± 1.20	94.21 ± 0. 48
F2	11.33 ± 0.142	14.29 ± 0.88	96.36 ± 0.21
F3	12.53 ± 0.098	11.10 ± 0.14	92.37 ± 0.56
F4	14.11± 0.091	12.59 ± 0.29	92.53 ± 0.37
F5	15.82± 0.119	13.78 ± 0.45	95.37 ± 1.25
F6	16.03 ± 0.137	17.05 ± 0.30	92.25 ± 0.81
F7	18.21 ± 0.155	12.24 ± 0.75	97.06 ± 0.67
F8	20.60 ± 0.085	15.69 ± 0.81	91.59 ± 0.26
F9	22.33 ± 0.121	18.94 ± 0.91	90.43 ± 0.13

Dissolution Study

In vitro drug release profiles of the formulations in pH 6.8 artificial saliva show A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Chlorpheniramine Maleate within 10 minutes. The formulations F1 to F9 showed approximately 90 to 98% drug release within 10 minutes. It was also observed that HPMC E-15 was able tomodulate the Chlorpheniramine Maleate release as lower amount of HPMC E-15 resulted in release of drug a faster rate.

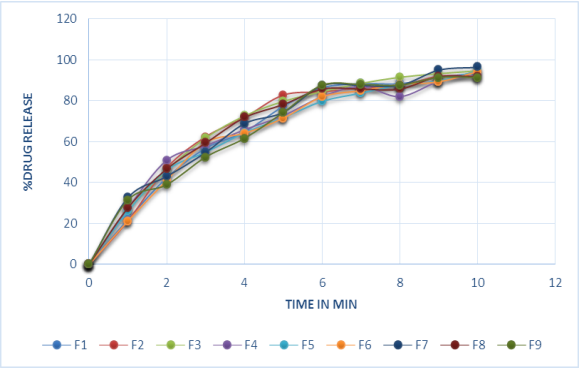

Figure No.1-In-vitro Dissolution Profile of Formulation Batch F1 to F9.

The result FTIR spectra of drug polymers mixture it was found that drug and excipients were compatible with each other there was no interference of peaks or existence of extra prominent peaks. Theresults of DSC and FTIR study of drug polymers mixture are given in figure 23 & 24 DSC thermo gram showed endothermic peak of Chlorpheniramine Maleate at 135.35°C.Thermo gram of HPMC E 15 showed peak at 112.24°C. There was no change in the melting point of drug when prepared in the form of film. The evaluation of the thermo gram obtained from DSC and FT-IR revealed no interaction between the polymer and the drug in the film.IR spectra for Chlorpheniramine Maleate, Pectin, HPMC E-15 and physical mixture of Chlorpheniramine Maleate and ethyl cellulose are given in fig.1-3. Majorfunctional groups of Chlorpheniramine Maleate N-H Stretching in (Amines) at 3545.28, C-H Stretching in methyl or aromatic at 2985.91, C=C Stretching in aromatic nuclei at 1683.91, C-H deformation in methyl at 1417.73, C-H deformation in –CH3 at1394.58, C-N Stretching at 1124.54 can be seen in spectra of individual drugs as well as in spectra of physical mixture. So there is no interaction between.

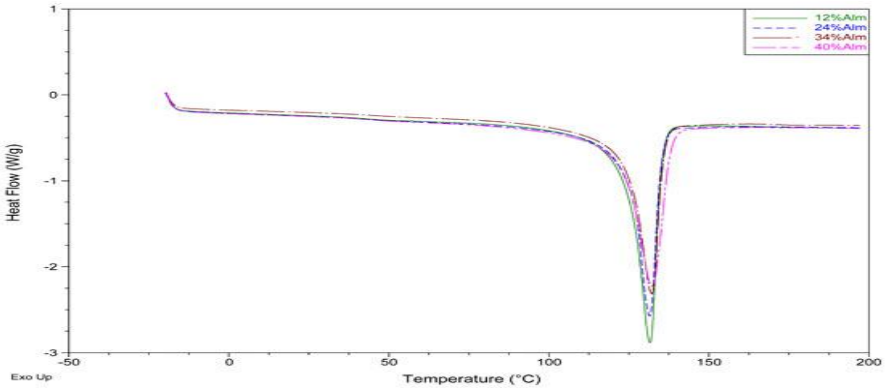

Figure No.2:-DSC Chlorpheniramine Maleate(Pure Drug)

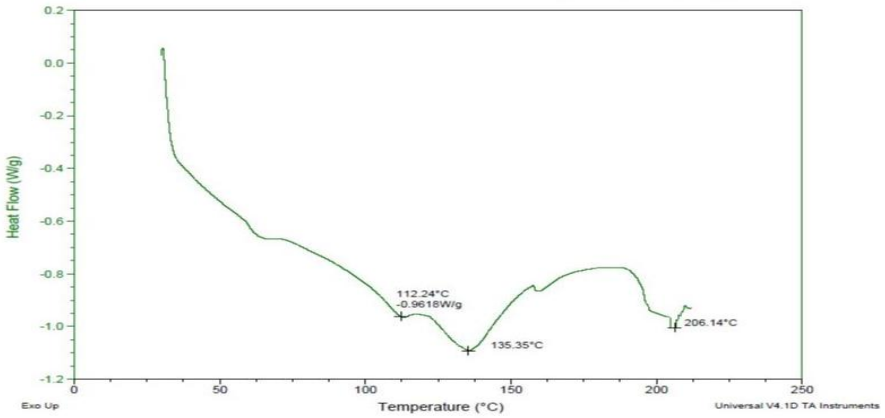

Figure No.3: DSC curve for Optimized Formulation F7

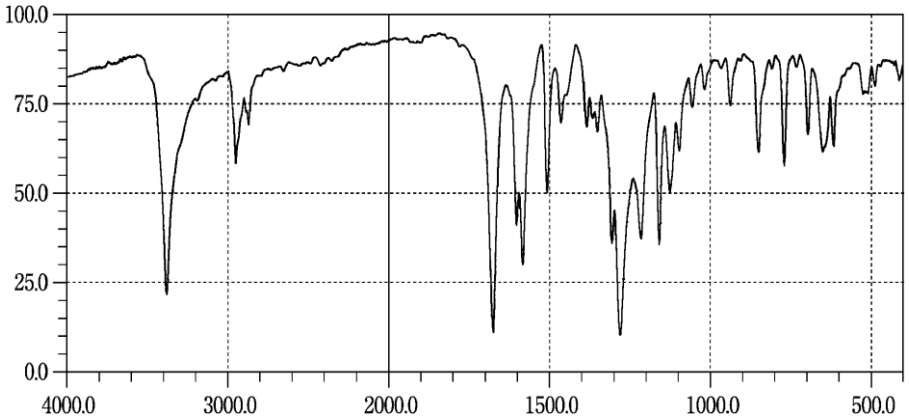

Figure No.4:- FT-IR spectra of Pure Chlorpheniramine Maleate (CPM).

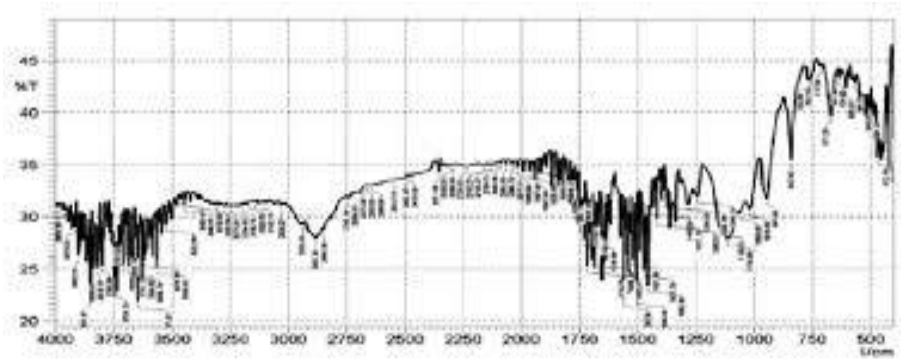

Figure No.5: FT-IR Spectra for Optimized Formulation F7.

Stability Study

The stability study of the formulation F1 and F9 was carried out at accelerated conditions for period of three month. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for up to three month. Dissolution time of the films after the stability study was also not found to be affected. Result were shown in Table No.4.

Table No.4: Evaluation of optimized batch F7 during stability studies

Stability Conditions	Sampling Time	Observations					
		Folding Endurance	Invitro DT (in Sec.)	Visual appearance	Drug Content	Surface pH	% CDR
Accelarated condition (40±2) and 75+5%RH)	0 DAY	192.3±1.64	29	Clear, homogeneous transperant film	97.06±0.67	6.46	96.49±0.36
	30 DAY	189.33±1.44	31		96.46±0.67	6.43	95.98±0.36
	60 DAY	182.33±1.38	33	Clear, homogeneous film	95.97±0.17	6.4	95.91±0.77
	90 DAY	179.33±1.25	34		95.06±0.52	6.34	95.19±0.17

CONCLUSION

Allergy it is generalized as rest condition. People who suffer with allergy and/or trouble in remaining sleeping even if there's chance are recognized to have the condition.Chronic Allergic conditions are serious disease so patients need to take medicine for preventive measure daily, now dosage form which don't need water and which can be consumed anywhere without water will make it easy for patient. Chlorpheniramine Maleate is an Anti-Histamine agent, widely used in the acute and chronic treatment of Allergy. In market, Chlorpheniramine Maleate tablets available. Fast dissolving film have got all advantages of tablets, but in addition to it, it is easy to swallow and preferable for pediatric and geriatric patients (ease of application).It leads to precise dosing, rapid onset of action, easy application (no need of water), easy to carry. The fast dissolving film of Chlorpheniramine Maleate obtained by the solvent casting method showed acceptable mechanical properties and satisfactory drug release after 3 minute. The prepared film was transparent with smooth surface without any drug excipients interaction.

REFERENCES

1. Priyanka Nagar, Iti Chauhan and Mohd Yasir. Insights into Polymers: Film Formers in Mouth Dissolving Films. Drug Invention Today, 2011; 3(12): 280-289.
2. McConnell, Thomas H. The nature of disease: pathology for the health professions.Baltimore, Mar.: Lippincott Williams & Wilkins, 2007. 159. *ISBN 978-0-7817-5317-3*
3. Murrell W. Nitroglycerin as a remedy for insomnia. Lancet, 1879; 1(80): 113,225,284,642-46.
4. Carlsson, Arvid; Lindqvist, Margit. "Central and peripheral monoaminergic membrane-pump blockade by some addictive analgesics and antihistamines". Journal of Pharmacy and Pharmacology. Retrieved 1 December 2013.
5. Gruetter CA, Lemke SM, Anestis DK, Szarek JL, Valentovic M "Potentiation of 5-hydroxytryptamine-induced contraction in rat aorta by chlorpheniramine, citalopram and fluoxetine". Eur J Pharmacol (Department of Pharmacology, 1992; 217: 109–18.
6. Tekade, B.W. Jadhao U. T. Thakare V. M.,Formulation and evaluation of diclofenac sodium effervescent tablet. IPP, 2014; 2(2): 350-358.
7. Thakare V. M., Tekade, B.W. Jadhao U. T. Development of Metoclopramide Hydrochloride Orodispersibal tablets using taste masking tulsion 339 journal of Advanced Pharmacy Education & Research;2013.;2(3)480-486.
8. Frey, P., Film strips and pharmaceuticals, pharma mfg. & packag. Sourcer, winter; 2006. 92-93.
9. Chang, R., Goo, X., Burnside, B., Fast-dissolving tablets, Pharm Tech., 2000; 24(6):.52-58.
10. Browhn, G., Formation of films from polymer dispersions. J Polym Sci., 1956; 22(102): 423-434.
11. Chandak, C., Master of Sci. Thesis, "Orally dissolving film of selegiline hydrochloride" London Island University, May 2009. 123.
12. Gandhi, R., Robinson, J., Oral cavity as a site for bioadhesive drug delivery. Advanced Drug Delivery Reviews, 1994; 13: 43-74.
13. Aulton ME, Razzak MH, Hogan JE. The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems: The influence of solid inclusions. Drug Dev Ind Pharm., 1981; 7:649-68.
14. Hoogstraate, A., Verhoef, J., Tuk, B., and Pijpers, A., In-vivo buccal delivery of fluoresce in is othiocyanate dextran 4400 with glycodeoxycholate as an absorption enhancer in pig. J Pharm Sci., 1996; 8: 457-460.
15. Rajput N., Thakare V.M., Formulation And Evaluation Of Fast Dissolving Tablet By Inclusion Complexation. Asian J Pharm. Sci. & tech., 2014; 4(1): 15-20.
16. Chen M, Tirol G, Bass C, Corniello C, Watson G, Sanchez I. Castable Edible Pharmaceutical Films. Poster presented at theAnnual Meeting and Exposition of the American Association of Pharmaceutical Scientists, San Diego, California, 2007; 11–15.
17. Chaudhari K. P., Jadhao U. T., Chaudhari C. D., Thakare V. M., Tekade B. W., Formulation and evaluation of fast dissolving sublingual tablets of amlodipine besylate.Der Pharmacia Sinica, 2014, 5(4):1-9
18. Tekade B. W., Jadhao U. T., Thakare V. M., Liquisolid System to Imorove Dissolution Rate of Aceclofenac. *2015 JIRMEPS, 5(2): 94-101,*