WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 8, 428-452 Research Article ISSN 2278 – 4357

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING FILM OF PROPRANOLOL HYDROCHLORIDE

Patil Jyoti N.*, Rajdeo Archana V., Patil Samruddhi S. and Gavitre S. B.

Department of Quality Assurance Shri Bhagwan College of Pharmacy, Aurangabad, Maharashtra, India.

Article Received on
26 May 2018,

Revised on 16 June 2018,
Accepted on 06 July 2018

DOI: 10.20959/wjpps20188-11992

***Corresponding Author**
Patil Jyoti N.
Department of Quality Assurance Shri Bhagwan College of Pharmacy, Aurangabad, Maharashtra, India.

ABSTRACT

The aim of the current study is to prepare fast dissolving film of propranolol hydrochloride to provide rapid onset of action and incrse bioavailability of drug. Propranolol is a nonselective beta adrenergic blocker and is almost completely absorbed following oral administration. Fast dissolving film were prepared by solvent casting method using hydroxyl propyl methyl cellulose (HPMC E15) and natural polymers like maltodextrin. Propranolol is bitter in taste so asprtame is used as sweetening agent in combination with menthol cooling effect of which also help to mask bitter taste of propranolol. All formulations were evaluated for their weight variation, thickness, folding endurance, tensile strength, & percentage elongation, surface pH, percentage drug content, in vitro disintegration time, dissolution. Formulations F8 and F9 formulations release 97.21% and 96.89% of drug in 12min & F1, F2 and F5 formulation less than 90% of drug release in 12 min.

KEYWORDS: Fast dissolving oral film, HPMC, Maltodextrin, polymers, solvent casting method.

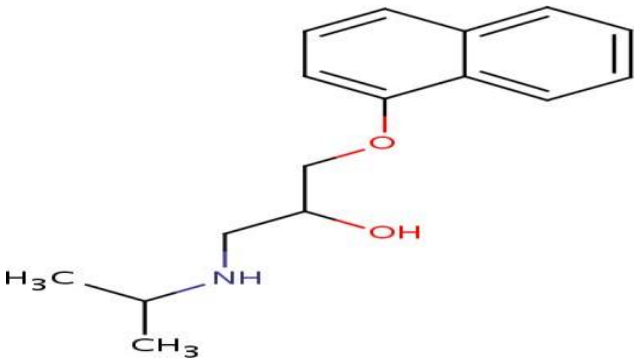
INTRODUCTION

Propranolol hydrochloride[i,ii] physicochemical properties

Molecular Formula: $C_{16}H_{21}NO_2$, HCl.

Molecular weight: 295.8

Structure



It is chemically, 1-((1-Methylethyl)amino)-3-(1-naphthalenyloxy)-2-propanol hydrochloride.

Category: Antihypertensive Agents Anti-Arrhythmia Agents Vasodilator Agents Adrenergic beta-Antagonists.

Description: It is a white powder soluble in water, methanol, ethanol, chloroform.

Melting Point: 163-165^{0}C.

Storage: Should be preserved in air tight container. Protect from moisture.

Pharmacokinetic Data

Oral Bioavailability: 25%

Bound in Plasma: Binding to serum proteins is approximately 90%.

Volume of distribution: 4 liters/kg.

Half Life: 3-6 hrs.

Peak concentration: 10 to 100 mg/l **Total plasma clearance:** 800 mL/minute **Total renal clearance:** 12 mL/kg/minute 20 mL/minute (in dialysis).

Absorption, Fate and Excretion

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first pass metabolism by the liver and on average, only about 25% of Propranolol reaches the systemic circulation.

Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. Propranolol is extensively metabolized with most metabolites appearing in the urine.

Mechanism of action

Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.

Side effects: Abdominal or stomach pain and tenderness, congestion, constipation, difficulty with breathing.

Uses: For the management of Hypertension and prophylaxis treatment of angina pectoris and heart failure, migraine.

Dose: Commence with 2.5 mg, or 5 mg/day upto 10 to 20 mg. Dose reduction in renal impairment.

Contraindications: Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; and 4) in patients with known hypersensitivity to Propranolol hydrochloride.

Marketed dosage forms

Tablets- Ciplar, Inderal, Apo-Propranolol Capsules- Inderal La.

MATERIALS AND METHOD

Table 1: Name of Materials and Manufacturers/Suppliers.

Sr No.	Name of chemical	Manufacturer/ Supplier
1	Propranolol Hydrochloride	Ipca laboratories Ltd. Aurangabad
2	Aspartame	Research Lab Fine Chem Industries, Mumbai.
3	HPMC E15	Lupin Research Park (Lupin Ltd)
4	Maltodextrin	Lupin Research Park (Lupin Ltd)
5	PG	Research Lab Fine Chem Industries, Mumbai.
6	Crossprovidone	Research Lab Fine Chem Industries, Mumbai
7	SLS	Research Lab Fine Chem Industries, Mumbai.

Table 2: Name of Instrments/Equipments and Makers.

Sr. No.	Instrument / Equipment	Make
1	Weighing Balance	Citizen
2	Differential scanning Calorimeter	Shimadzu TA-60WS
3	I.R. spectrometer	IR200 Star Lab. V.10
4	U.V. spectrophotometer	Shimadzu
5	Dissolution test apparatus	VDA-6DR USP Stds., Veego.
6	Digital Vernier caliper	Veego
7	Melting point apparatus	Labtronics
8	Digital pH meter	Electron Lab.
9	Tensile strength mesearment assembly	Assembled in college

Method

Preparation method for Fast dissolving Propranolol Hydrochloride oral film:

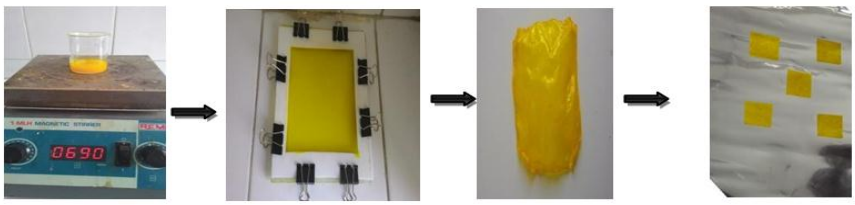


Figure 1: Preperation Method For Fast Dissolving Film.

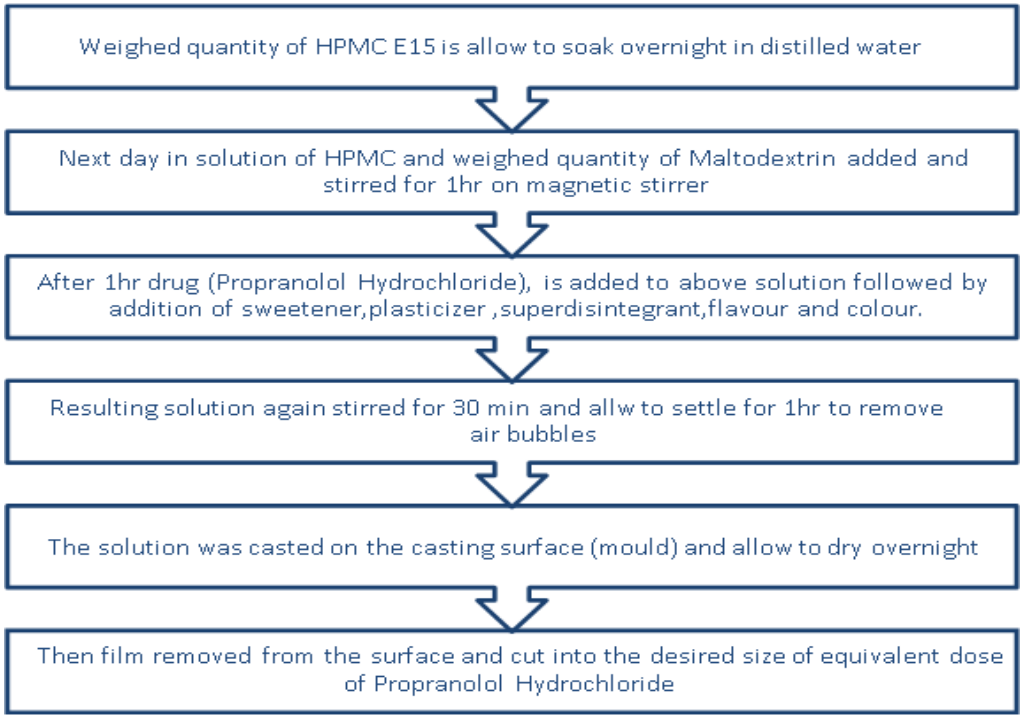


Figure 2: Steps for for formulation of afast dissolving film Screening of Film forming polymer.

The different film forming polymer was screened for their film forming capacity and removable property. The clear solution of the film forming polymer (500mg in 10ml distilled water) was made with manual shaking in the beaker and poured on the Petri plate. Then this Petri plate was kept for air drying at room temperature for 10 hours.

Table 3: Screening Of Film Forming Polymers.

Formulation	HPMC E3	HPMC E5	HPMC E15	HPMC E15+ PVA	HPMC E15+ Malt	PVA	Gelatin	HPMC E15+ MCC	Sodium Alginate	Water
A1	500mg	-	-	-	-	-	-	-	-	10 ml
A2	-	500mg	-	-	-	-	-	-	-	10 ml
A3	-	-	500mg	-	-	-	-	-	-	10 ml
A4	-	-	-	400mg + 100mg	-	-	-	-	-	10 ml
A5	-	-	-	-	400mg + 50mg	-	-	-	-	10 ml
A6	-	-	-	-	-	500 mg	-	-	-	10 ml
A7	-	-	-	-	-	-	400 mg	-	-	10ml
A8	-	-	-	-	-	-	-	400mg + 100 mg	-	10 ml
A9	-	-	-	-	-	-	-	-	400Mg	10ml

Screening of casting surface

The HPMC E15and maltodextrin is used for the screening of the casting surface with different concentration. The HPMC E15 and maltodextrin with different concentration are taken in beaker and then clear solution was made by using 10 ml distilled water with manual shaking. After formation of the clear solution the solution casted on different surfaces and allowed to kept for drying at room temperature for 10 hours.

Table 4: Screening of casting surface with different concentration.

Formulation	Surface	HPMCE15+ Maltodextrin(mg)	Distilled water (up to 10 ml)
B1	Plastic	100+50	10
B2	Glass	100+50	10
B3	Teflon	100+50	10
B4	Plastic	200+100	10
B5	Glass	200+100	10
B6	Teflon	200+100	10

B7	Plastic	300+100	10
B8	Glass	300+100	10
B9	Teflon	300+100	10
B10	Plastic	400+50	10
B11	Glass	400+50	10
B12	Teflon	400+50	10

Preparation of mould for selected casting surface material

The molds of Teflon sheet are prepared in four numbers. The area of the prepared mold is 100cm^2 (10cm x 10 cm). In 100 cm^2 area the 25 film were casted with area of 4cm^2 (2cm x 2cm) of each film.

Figure 3: Prepared Teflon Mould for Film Casting.

Optimization of polymer concentration

Film forming polymer

Optimization of the film forming polymer concentration was done with different concentration of the HPMC E15 and maltodextrin and fixed concentration of Drug. Then film was evaluated for their mechanical property. The trial formulation is given in following table no.09.

Table 5: Preliminary trial batches of HPMC E15+maltodextrin

Composition	C1	C2
HPMC E15+ Maltodextrin	300 mg +150mg	400 mg +50mg
Drug	175 mg	175 mg
Distilled Water up to	10 ml	10 ml

Drug Calculation

Optimum dose of Propranolol Hydrochloride = 10mg

So, 3cmx2cm=6 cm^2 containing10mg of Propranolol Hydrochloride Now, the area of Teflon mould = 100cm^2 6cm^2 containing 10mg of Propranolol Hydrochloride Therefore 100cm^2 containing? 10x100/6 = 175mg

Therefore 175 mg of Propranolol Hydrochloride is taken for Preparation of film.

Sweetening Agent

The sweetening agent used for the masking of the slightly bitter taste of Propranolol Hydrochloride The concentration trials are performed with starting of 10 mg of aspartame and taste of formulated film was checked by putting the film on tongue of one volunteer.

Table 6: Preliminary Trial Batches of Sweetening Agent.

	Formulations						
	D1	***D2***	***D3***	***D4***	***D5***	***D6***	***D7***
HPMC E5 +Maltodextrin	*400+50*	*400+50*	*400+50*	*400+50*	*400+50*	*400+50*	*400+50*
Drug (mg)	175	175	175	175	175	175	175
Aspartame (mg)	10	20	*30*	*40*	*50*	*60*	*70*
Distilled water(ml)	10	10	10	10	10	10	10

Saliva stimulating agent

The saliva stimulating agent used to increase the secretion of the saliva when film kept on tongue. The concentration trials are performed with starting of 3 mg of citric acid and surface pH of formulated film was checked by Digital PH meter. The concentration of citric acid was selected based on dropping of pH below 6 was rejected.

Table 7: Preliminary Trial Batches of Saliva Stimulating Agent.

Formulation	HPMC E15+Maltodextrin(mg)	Drug (mg)	Aspartame (mg)	Citric acid(mg)	Distilled Water up to (ml)
C1	400+50	175	50	4	10
C2	400+50	175	50	8	10
C3	400+50	175	50	12	10
C4	400+50	175	50	16	10
C5	400+50	175	50	20	10
C6	400+50	175	50	24	10
C7	400+50	175	50	28	10

Plasticizer

Plasticizer play important role in maintaining the mechanical properties of the film. The plasticizer selected from formulation of film was Propylene Glycol (PG). The PG was added

in formulation in increasing amount of 10 mg. The final concentration of PG was selected based on the folding endurance of the film. The concentration which markedly increases the folding endurance was selected and markedly decreases the folding endurance or film forming capacity was rejected.

Table 8: Preliminary Trial Batches of Plasticizer.

Formulation	HPMC E15+Maltodextrin (mg)	Drug (mg)	Aspartame (mg)	Citric acid (mg)	PG (ml)	Glycerin (ml)
P1	400+50	175	50	18	1	-
P2	400+50	175	50	18	2	-
P3	400+50	175	50	18	3	-
P4	400+50	175	50	18	4	-
P5	400+50	175	50	18	5	-
G1	400+50	175	50	18	-	-
G2	400+50	175	50	18	-	1
G3	400+50	175	50	18	-	2
G4	400+50	175	50	18	-	3
G5	400+50	175	50	18	-	4
G6	400+50	175	50	18	-	5

Factorial batches preparation

A factorial design is used to evaluate two or more factors simultaneously. The word “optimize” means to make as perfect, effective, as possible. Optimization is not a screening tool. Actually optimization techniques provide both a depth of understanding and an ability to explore and defend ranges for formulation and processing factors. The advantages of factorial designs over one factor at a time experiments are that they are more efficient and they allow interactions to be detected.

Full factorial design

A 3^2 full factorial design was used in the present study. For factorial design the solvent casting method was selected. In this design 2 factors were evaluated each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of polymer-1 HPMC E15 (X1) and amount of polymer-2 Maltodextrin (X2) were selected as independent variables and each factor being studied at -1, 0, +1 level. Percent drug release was selected as dependent variable.

The following table lists the design variables with its coded values and actual values, and second table provides the factorial design layout i.e. all possible 9 combinations respectively.

Table 9: Design Variables.

Coded values	Actual values (mg)	
	X1	X2
-1	350	25
0	400	50
+1	450	75

Table 10: Full Factorial Design Layout.

Formulation code	Variable level	
	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 11: Factorial Batches Composition.

	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	175	175	175	175	175	175	175	175	175
Hpmc (mg)	350	350	350	400	400	400	450	450	450
Maltodextrin (mg)	25	50	75	25	50	75	25	50	75
Aspartame (mg)	50	50	50	50	50	50	50	50	50
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Sls (mg)	20	20	20	20	20	20	20	20	20
Crossprovidone	20	20	20	20	20	20	20	20	20
Pg (ml)	1	1	1	1	1	1	1	1	1
Menthol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Colour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Factorial batches Evaluation

Weight Variation

The weight variation test is determined by measuring the weight of the individual film of 3cm x2 cm area. For the measurement of the weight digital analytical balance was used. The weight of three films was measure and mean is taken.

Thickness

The thickness of strip was measured by digital vernier caliper at different locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the

accuracy of dose in the strip.

Folding endurance

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

Tensile strength

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip (3 × 2 cm^2) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly. Measurements were done in triplicate for each batch. The mechanical properties tensile strength and % elongation were calculated for the fast dissolving film from the above measurements. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross sectional area of the fractured film as a mean of three measurements and described in the equation-

$$Tensile\ strength = \frac{\text{Load at failure} \times 100}{\text{Strip Thickness} \times \text{Strip Width}}$$

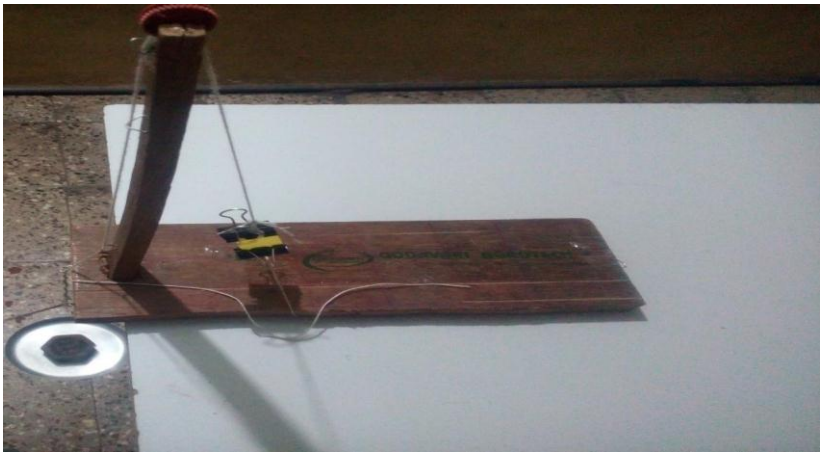


Figure 4: Tensile strenghth Measurement Assembly.

Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

$$\% \, elongation = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

P^{H} Value

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH value.

Drug content

For determination of the drug content Propranolol Hydrochloride oral film equivalent to dose of 10 mg was dissolved in 100ml of 0.1N HCl. The solution was sonicated for 10 minutes and then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipients. 1ml of filtrate was diluted to 100 ml with0.1N HCl. The absorbance of resultant solution was measured using U. V. spectrophotometer at 289 nm and drug content was calculated.

Disintegration time[iii]

Figure 5: How to take disintegration?

The disintegration for orally disintegrating tablets described in CDER guidance can be applied to oral film. Although, no official guidance is available for FDOF, this may be used as a qualitative guideline for quality control test or at development stage. But for the present work disintegration was measured by taking the 25 ml of distilled water in 50 ml beaker and individual film is dipped into that solution and disintegration time was recorded.

In *Vitro* Dissolution study[iv]

The in vitro release of drug from all formulations was determined using USP apparatus type I

(Basket method). The following conditions were followed to study the in-vitro dissolution study of Film.

USP dissolution apparatus: Type I apparatus is used. Dissolution media is taken in flask 900 ml. speed of disso apparatus set to 50 rpm. And temperature adjusted to 37±0.50 C. Dissolution medium selected is Simulated saliva (pH 6.75). then sample withdrawn at interval 2 min and quantity of sample withdrawn 5ml.

Aliquots of dissolution medium of 5 ml were withdrawn at 2 min interval for 12 min. The volume withdrawn was replaced by fresh volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 289 nm and absorbance was noted. Cumulative percent drug release was calculated.

RESULTS AND DISCUSSIONS

Organoleptic properties

Propranolol Hydrochloride is White or almost white, slightly hygroscopic powder, with slightly bitter taste.

Melting Point

The melting point of Propranolol Hydrochloride by capillary method was found to be 165^0C, which is in good agreement with reported melting point of 163-165ºC.

Bulk Characterization of Propranolol Hydrochloride

Table 12: Bulk Characterization of pure Drug.

Sr. No	Parameter	Observed	Reference
1	Bulk Density	0.277 g/cc	-
2	Tapped Density	0.33g/cc	-
3	Carres index	16.8%	Good compressibility
4	Hausner's Ratio	1.202	Poor
5	Melting point	165°c	163-165˚c
6	Solubility	4.2mg /ml	Freely Soluble

UV Spectra

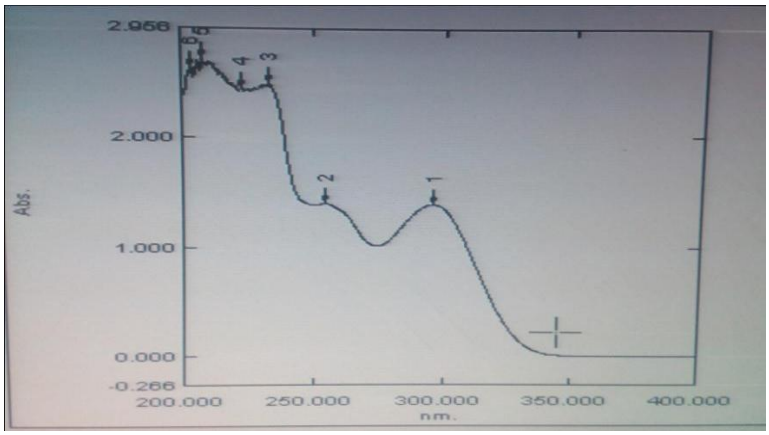


Figure 6: UV spectrum of propranolol Hydrochloride.

The UV Spectrum of Propranolol Hydrochloride solution (50 µg/ml) exhibited wavelength of absorbance maximum and linearity at 289 nm. Literature reported the wavelength maximum of 289 nm at U.V. detector for analysis of Propranolol Hydrochloride by UV Spectrophotometer.

U. V. method development

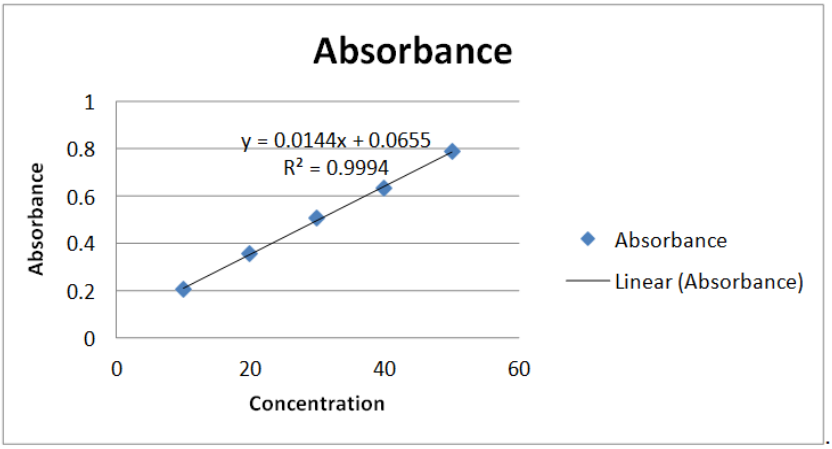


Figure 7: Calibration Curve of Propranolol Hydrochloride.

Table 13: Calibration curve preparation.

Sr. no.	Concentration (µg/ml)	Absorbance
1	10	0.206
2	20	0.356
3	30	0.505
4	40	0.635
5	50	0.787

The standard solutions of Propranolol Hydrochloride showed linear curve with correlation coefficient of 0.998. The equation of line is y = 0.02041x+0.007.

Method validation

Developed method was validated and validation parameters are listed in Table no14.

Table 14: Validation Parameter.

Parameter	Limit	Results
Accuracy	97.5-102%	100.74
Intraday precision	%RSD < 2	1.23
Inter day precision	%RSD < 2	0.49, 1.19, 1.55
Linearity	R2 > 0.999	0.999
Range	-	10-50µg/ml
LOD	-	0.00521 µ/ml
LOQ	-	2.133µ/ml

Thus from the above observation it was revealed that the analytical method complies with the validation parameters.

Drug Excipients Compatibility study Infra-red studies

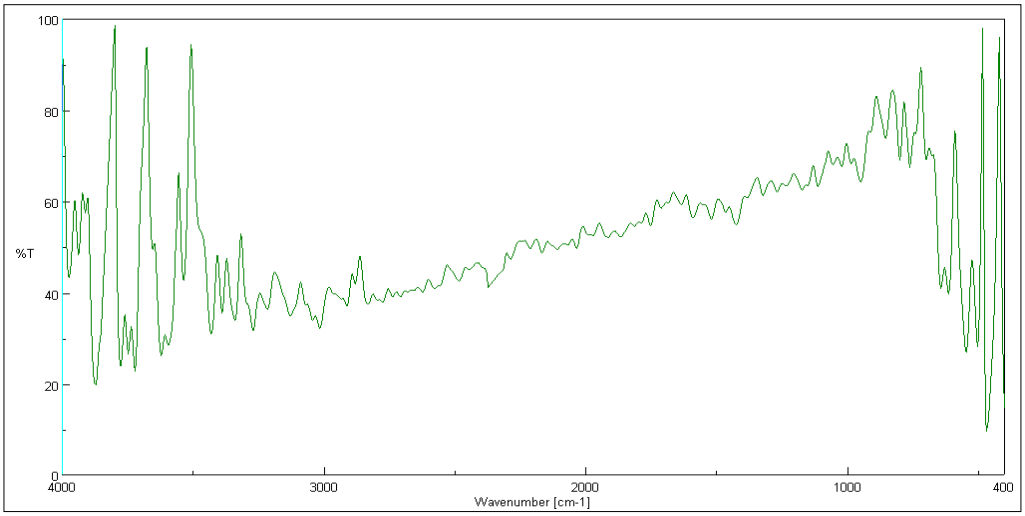


Figure 8: IR Spectrum of Propranolol Hydrochloride.

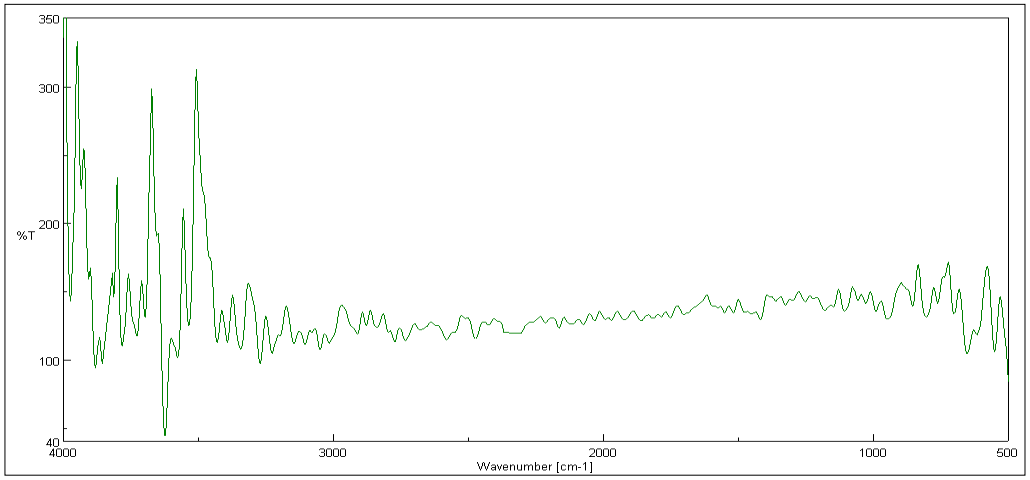


Figure 9: IR Spectrum of Propranolol Hydrochloride and Polymers.

Table 15: Infrared Spectral assignment for Propranolol Hydrochloride.

Type	Pure Drug	Formulation
C-O Stretching	1110.8	1106.94
N-H stretching	3390.24	3394.96
O-H stretching	3536.81	3647.09
Napthalene Ring	798	763

IR spectrum of Propranolol Hydrochloride and physical mixture was recorded, and it was in accordance with the reported peaks. It is shown in Following Figure.no.08. The IR spectra of Propranolol Hydrochloride comply with its chemical structure and show peaks for principal group's. The structural assignments for the characteristics absorption bands are listed in Table no.16.

In physical mixtures of drug and polymers, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra. So it was concluded that drug and HPMC E 15, and Maltodextrin were compatible with each other.

1.1.1 Differential Scanning Calorimetry

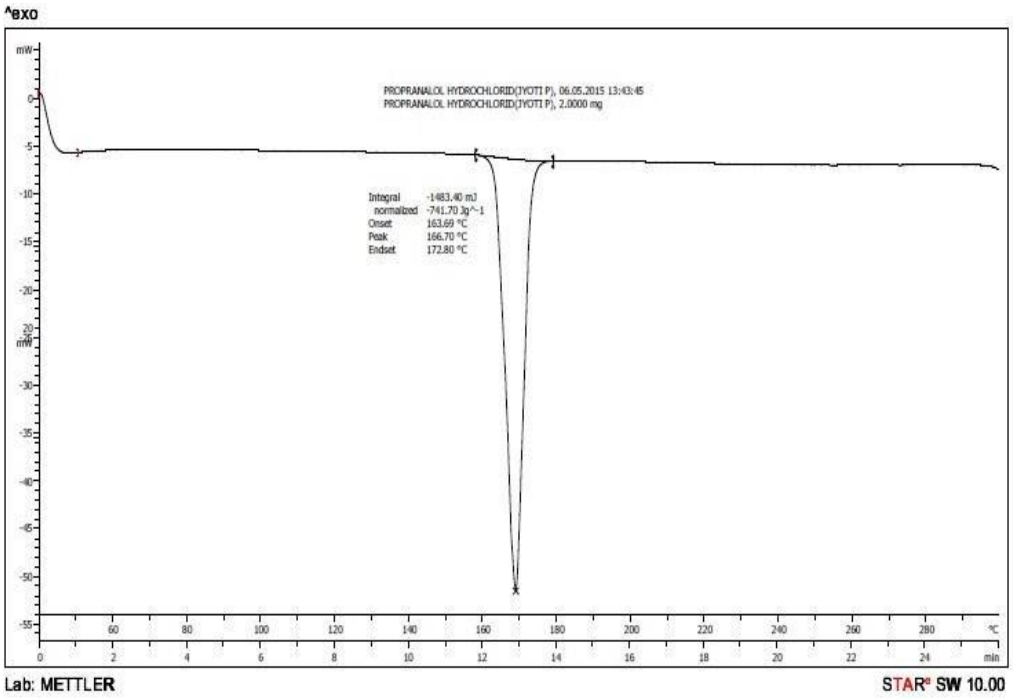


Figure 10: DSC Thermogram of Propranolol Hydrochloride.

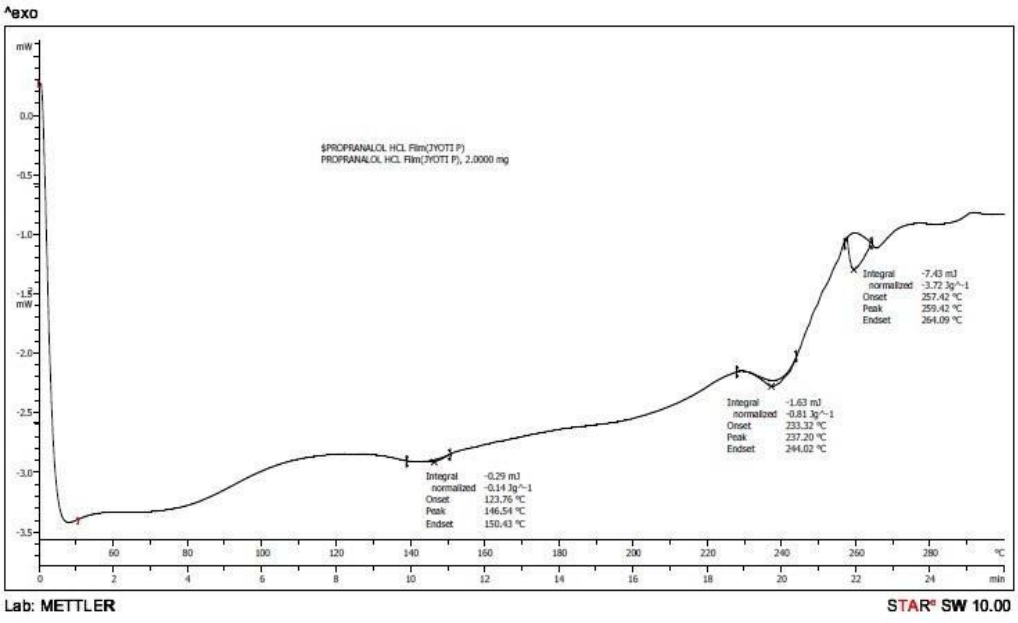


Figure 11: DSC Thermogram of Propranolol Hydrochloride + Polymers.

DSC thermogram of Propranolol Hydrochloride showed endothermic peak of fusion, having peak maximum of 166.70^{0}C. The onset temperature was 163.69^{0}C. DSC thermogram has shown in Following Figure. The melting point obtained with DSC was in good agreement with reported melting point of 163-165ºC and with melting point determined using melting point apparatus i.e.165ºC.

The possible interaction between Propranolol Hydrochloride with excipients was studied by differential calorimeter (DSC). There was no considerable change in DSC endothermic values, compared to pure Propranolol Hydrochloride and with the excipients (maltodextrin, HPMC E15). Peak value for combination was obtained at…150.43^{O}C. As pure drug shows peak value at. 166.70^{0}C, hence it shows that there was no interaction between the drug and excipients.

Factorial Batches

Screening of Film forming polymer

Table 16: Screening of film forming polymer evaluation.

Formulation	*Film forming capacity	Appearance
A1	+	Transparent
A2	++	Transparent
A3	++	Transparent
A4	++	Transparent
A5	+++	Very Transparent
A7	+	Transparent

+not removed

++removed

+++easily removed

From the screening of the film forming polymer it was concluded that the film formed by HPMC E15 is very transparent and their film forming capacity was also good. Therefore HPMC E15 was selected as film forming polymer for formulation and development of oral wafer.

Screening of casting surface with different polymers concentration

For the better film separation it was necessary to check the separation capacity of casting surface. In many literatures there was use of glass Petri dish for film formulation. But it was observed that there is difficulty during first point removal in film separation by using glass Petri dish.

Therefore screening of different polymer concentration with different casting surfaces (Glass, Plastic, and Teflon) was done and it is observed that Teflon surface with HPMC E15 300 mg and maltodextrin 100 mg gives better film separation along with desired thickness. The desired thickness was selected by selecting marketed formulation of on dissolve film.

Optimization of polymer concentration

Further study was done by selecting 300 mg HPMC E15 and 150 mg maltodextrin concentration and Teflon as casting surface. In this study drug was added in polymer solution and film was formulated. By addition of drug the film forming capacity decrease and film is not formed uniformly due to brittleness of film. Further trial was done by increasing polymer concentration. It was observed that 400 mg HPMC E15 and 50 mg maltodextrin concentration gives satisfactory result. The final film has good film forming capacity but folding endurance is less than five.

Trials for Sweetening Agent

From the trial by using the sweetening agent it was observed that by addition of 70 mg aspartame easily mask bitter taste of drug which is checked by placing the film on tongue but the drug is slightly bitter therefore 50 mg is sufficient for mask the drug's bitter taste.

Trials for Saliva stimulating agent

From the trial by using the saliva stimulating agent it was observed that by increase in concentration of citric acid the pH of the solution increases. The final concentration of the citric acid as saliva stimulating agent was selected 20 mg because the concentration range of citric acids between 3mg to 20 mg is acceptable and pH of the solution was between 6.7 to 5.9. Fuerther increasing concentration of citric acid the pH of solution drops below 5 which is not near to pH of saliva.

Trials for Plasticizer

From the trials study of the plasticizer it was concluded that by addition of the 4 ml of glycerin in the film, film removed partially with folding endurance between 25-75 and further addition of 5ml of plasticizer the film removed easily with greater folding endurance which lies between 25- 150 but after addition of 50mg glycerin the sticky film was formed. The film formed with glycerin will not be remains stable compared to that of the PG hence it was rejected in final formulation study.

FACTORIAL BATCHES EVALUATION

Appearance

The appearance of all batches was transparent film with smooth surface.

Weight Variation

Table 17: Weight of F1-F9 Batches.

Batches	Weight (mg)
F1	36.2±1.2
F2	41±2
F3	35.2±1.2
F4	38±2
F5	41.4±2.4
F6	43.8±0.8
F7	38.4±1.4
F8	**35±2**
F9	43.2±2.2

The weight of all batches observed between 35 to 45.8 mg with standard deviation less than 1.6% for all batches which indicates uniformity in the weight.

Thickness

Table 18: Thickness.

Batches	Thickness (mm)
F1	0.048±0.008
F2	0.066±0.006
F3	0.088±0.008
F4	0.038±0.008
F5	0.068±0.008
F6	0.007±0.01
F7	0.088±0.008
F8	**0.40±0.01**
F9	0.096±0.006

The thickness of the film lies between 0.04 to 0.096mm. With uniformity in the thickness. It was observed that increase in the polymer concentration the thickness of film increases with 0.01 mm.

Folding Endurance

Table 19: folding Endurance.

Batches	Folding Endurance
F1	138±6
F2	55.66±3.6
F3	86.66±4.6
F4	253±8
F5	117.33±5.3
F6	132±9
F7	220.66±5.6
F8	**131.33±9.3**
F9	182±7

The folding endurance of all batches observed between 55-254. For the batches F4, F7, F9 the folding endurance observed 254,227,175 respectively. From the evaluation of folding endurance it was concluded that with increase in polymer concentration folding endurance decreases **Tensile strength and % elongation.**

Table 20: Tensile strength and % Elongation.

Batches	Tensile Strength (kg/mm^2)	%Elongation at break
F1	0.444±0.005	4.67±0.003
F2	0.457±0.003	5.12±0.003
F3	0.471±0.001	5.23±0.001
F4	0.554±0.004	6.12±0.00
F5	0.412±0.001	5.63±0.003
F6	0.434±0.002	4.79±0.004
F7	0.510±0.00	4.86±0.001
F8	**0.469±0.003**	**5.10±0.002**
F9	0.457±0.005	5.59±0.001

Tensile strength was found in range 0.432±0.007 to 0.554±0.004 kg/mm^3. There is no significant change in the tensile strength of all prepared formulations. The nature of polymer affects tensile strength and % elongation. Soft and brittle polymer increases TS and decreases % elongation, while hard and tough polymer increases TS and % elongation. The % elongation is found in range of 4±0.004 to 6.12±0.001.

Surface pH

Table 21: surface P^H.

Batches	Surface pH^a
F1	6.54±0.12
F2	6.62±.03
F3	6.64±.09
F4	6.49±.07
F5	6.49±.035
F6	6.53±.073
F7	6.71±.020
F8	**6.87±.020**
F9	6.77±.015

The Surface pH of all formulation observed between 6 to 6.8. It was observed that after addition of the plasticizer the pH moves slightly towards basic pH. The pH between 6 to 6.8 indicates the pH of formulation near to ph of saliva.

% Drug content

Table 22: % Drug content.

Batches	%Drug Content
F1	91.04
F2	83.20
F3	90.95
F4	81.55
F5	90.13
F6	86.18
F7	91.77
F8	**98.77**
F9	84.55

The percent drug content observed between 80-99%. The values ensure good uniformity in the drug content in Fast Dissolving Film of Propranolol Hydrochloride

In Vitro Disintegration Time

Table 23: In vitro disintegration time.

Batches	In-vitro disintegration time[a] (s)
F1	22±00
F2	20±2.08
F3	30±1.15
F4	29±0.00
F5	23±1.00
F6	13±2.64
F7	24±1.5
F8	**6±1.52**
F9	12±2.00

The in vitro disintegration time for all batches measured between 9 to 15 seconds which indicated faster disintegration time as compared to the mouth dissolving tablet which have normal disintegration time 30 seconds in many reported literature.

DISSOLUTION STUDY

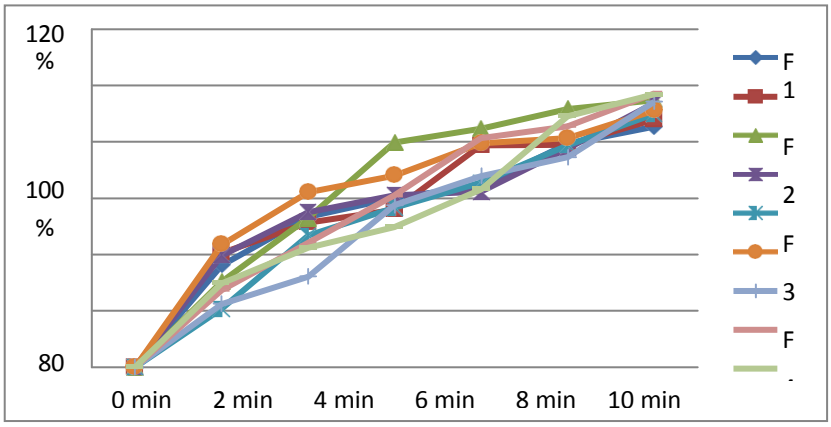


Figure 12: Dissolution profile of batches F1 to F9.

Table 24: % Drug Release of F1-F9 Batches.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0 min	0%	0%	0%	0%	0%	0%	0%	0%	0%
2 min	36.15%	40.58%	30.24%	39.69%	20.7%	43.49%	22.42%	27.38%	29.82%
4 min	53.35%	51.36%	52.90%	55.05%	46.73%	62.15%	32.16%	44.20%	42.36%
6 min	60.06%	55.98%	79.76%	61.05%	56.58%	68.03%	57.49%	61.02%	49.77%
8 min	64.33%	78.79%	84.66%	62.29%	65.56%	79.45%	67.83%	81.29%	63.06%
10 min	79.39%	79.06%	91.66%	77.62%	78.86%	81.28%	74.52%	85.57%	89.08%
12 min	85.41%	87.94%	94.76%	93.74%	89.94%	91.11%	94.20%	97.21%	96.89%

The *in-vitro* drug release from film of all formulation was performed in triplicate using USP apparatus II (paddle method). Dissolution study was performed in simulated saliva.

In case of F4 and F9 formulations about 99% and 98.85% of drug was released in 2.5 min. In case of F1, F7 formulation about 94.35% and 94.2% of drug released in 2.5 min. This drug release pattern indicates that the increased concentration of polymer decreases drug release and increased concentration of plasticizer increases drug release**.**

Shows that drug release decreases with increasing concentration of independent variables HPMC E15 (A) and decreasing concentration of Maltodextrin (B). The possible reason which may be attributed to this drug release is ability due to its hydrophilic nature.

SUMMARY AND CONCLUSION

The Propranolol Hydrochloride fast dissolving oral film was formulated. The given film disintegrates within six second which release drug rapidly and gives antihypertensive action. As compared to that of conventional dosage form Fast Dissolving Oral Film has rapid onset of action.

For the formulation of Fast dissolving film of Propranolol Hydrochloride, HPMC E15 and Maltodextrin used as film forming agent. HPMC E15 is synthetic water soluble polymer and Maltodextrin is natural polymer, obtained from natural resources. Other agents used are citric acid as saliva stimulating agent, aspartame as sweetening agent and Propylene Glycon as plasticizer. Menthol as a flavouring agent.

The conclusion drawn from formulation and development of Fast Dissolving Oral film were summarized as below

As compare to Plastic And Glass, *Teflon* surface gives the best result for the film removable property.

HPMC E15: Maltodextrin in the concentration of 400 mg:50mg suitable for the 175 mg drug loading for twenty films as compared with 300 mg and 150 mg as it gives brittle film and not removed easily.

From preformulation study were concluded that drug procured from company is in pure form. Drug-Excipient compatibility study shows that drug is compatible with excipient.

Suitable analytical method based on UV visible spectrophotometer was developed for Propranolol Hydrochloride by using Distilled water.

The Fast dissolving oral film was evaluated for their mechanical property as per literature review.

The 3^2 factorial can be successfully applied for the optimization of the batches. The selected independent variable exhibits significant effect on dependent variable i.e. percent drug release. It was observed that the increase in polymer concentration decreases the drug release.

The film rapidly disintegrates and disperses in saliva which gives rapid absorption of drug.

In case of F8 and F9 formulations about 97.21% and 96.89 % of drug was released in 12 min. In case of F1, F2 and F5 formulation less than 90% of drug release in 12 min This drug release pattern indicates that the increased concentration of polymer decreases drug release.

AKNOWLEGMENT

At first, I consider it as a great privilege to express my hurtful gratitude and sincere thanks to Guide Dr. S. J. Jaybhaye and Ms. V. A. Chavan for his valuable suggestion, encouragement, motivation, guidance, and co- operation during my thesis work. I wish to extend my gratitude to Mr. S. R. Lahoti Mr. N. A. Tribhuvan, Mr. D. D. Gadade. Mr. P. T. Deshmukh, Mr. N. B. Dharbale. The Faculty, Shri Bhagwan College of Pharmacy, for their kind co-operation in resolving analytical problems, & immense help whenever required in Project. Words are not sufficient to express my gratitude to friends for their priceless support and encouragement,

REFERENCES

1. *United state pharmacopoeia*, 2007.
2. Indian Pharmacopia, seventh edition, 2007; III: 995-996.
3. Guidance For Industry, August, Orally disintegrating tablets U.S. Department of Health

and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 1997: 1-6.

4. Guidance For Industry, August, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 1997; 4-17.
5. Parmar, D., Dr. Patel, U., Orally Fast Dissolving Film As Dominant Dosage For Quick Releases, *International Journal of Pharmaceutical Research And Bio Science*, 2012; 1(3): 24-41.
6. Siddiqui, N., Garima, G., Sharma, P.K., A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents", *Advances in Biological Research*, 2011; 5(6): 291-303.
7. Dixit, R.; Puthli, S., Oral strip technology: Overview and future potential, *Journal of Controlled Release*, 2009; 139: 94–107.
8. Saini, S., Nanda, A., Dhari, J., Formulation, development & evaluation of oral fast dissolving anti-allergic film of levocetrizine dihydrochloride, *J Pharm. Sci. & Res*., 2011; 3(7): 1322- 1325.
9. Borsadia, S.B., Quick-Dissolving Films - A Novel Approach to Drug Delivery, *Drug Delivery Technology*, 2003; 3(3). Posted On: 3/28/2008[Accessed on 10/6/2014).
10. Patel, A.R., Prajapati, D.S., Raval, J.A., Fast Dissolving Films As A Newer Venture In Fast Dissolving Dosage Forms, *International Journal of Drug Development & Research*, 2010; 2(2): 232-246.
11. Thakur, N. Bansal, M.; Sharma, N., Yadav, G., Khare, P. Overview "A Novel Approach of Fast Dissolving Films and Their Patents", *Advances in Biological Research*, 2013; 7(2): 50-58.
12. Makwana, P., Dr. H. V. Patel., Dr. V. A., Patel, *International journal of pharmacy and integrated life sciences*, Fast dissolving films: An innovative drug delivery system2- (i2), 2014; 43-63.
13. Dinge, A.; Nagarsenkar, M.; Formulation and Evaluation of Fast Dissolving Films for Delivery of Triclosan to the Oral Cavity, *American Association of Pharmaceutical Scientists Pharm Sci Tech*, 2008; 9(2): 349-356.
14. Dahiya, M., Saha, S., Shahiwala, A., A review on mouth dissolving films, *Curr. Drug Deliv.*, 2009; 6(5): 469-76.
15. Kaur, R., Bala, R., Malik, D., A novel approach in oral fast dissolving drug delivery system – a review, *American Journal of Pharm Tech Research*, 2012; 2(1): 2249-3387.

16. Patil, S., Mahaparale, P., Shivnika, M., Tiwari, S., Pawar, K., Sane, P. Fast dissolving oral films: an innovative drug delivery system, *International Journal of Research and Reviews in Pharmacy and Applied science*, 2012; 2(3): 482-496.
17. Ghodake, P., Karande, K., Osmani, R., Bhosale, R., Harkare, B., Kale, B., Mouth Dissolving Films: Innovative Vehicle for Oral Drug Delivery, *International Journal of Pharma Research & Review*, 2013; 2(10): 41-44.
18. Kaur, M., Rana A., Seth, N., Fast Dissolving Films: An Innovative Drug Delivery System, *International Journal of Pharmaceutical Research & Allied Sciences*, 2013; 2(1): 14-24.
19. Ketul, P., Patel, K., Patel, M., Patel, N., Fast Dissolving Films: A Novel Approach to Oral Drug Delivery, *International Journal of Pharmacy Teaching & Practices*, 2013; 4(2): 655-661.
20. Saini, S., Nanda, A., Hooda, M., Fast Dissolving Films (Fdf): Innovative Drug Delivery System, *Pharmacologyonline*, 2011; 2: 919-928.
21. Bhura, N., Sanghavi, K., Pate,l U., Parmar, B., Patel, D., A Review on Fast Dissolving Film, *International Journal of Pharmaceutical Research and Bio-Science*, 2012; 3: 66-89.
22. Patel, A.R., Prajapati, D.S., Raval, J.A., Fast Dissolving Films As A Newer Venture In Fast Dissolving Dosage Forms, *International Journal of Drug Development & Research*, 2010; 2(2): 232-246.
23. Patil, S., Mahaparale, P., Shivnika, M., Tiwari, S., Pawar K., Sane P., Fast dissolving oral films: an innovative drug delivery system, *International Journal of Research and Reviews in Pharmacy and Applied science*, 2012; 2(3): 482-496.
24. www.odftechnology.com (Accessed on 24/2/2013) 25.www.umangopharmatech.com (Accessed on 24/2/2013).