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FORMULATION AND EVALUTION OF FAST DISSOLVING ORAL FILM OF KETOROLAC TROMETHAMINE

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ABSTRACT

Ketorolac (KT) is currently administered orally in the form of tablets or as intramuscular injections in multiple divided doses for short term management of post-operative pain.IR spectrum of ketorolac tromethamine was recorded using Bruker spectrophotometer. Melting point of ketorolac tromethamine was determined by capillary method. UV-Visible spectral analysis of ketorolac tromethamine was done by using Elico double beam UV-Visible spectrophotometer 1800 model (Optiglass U.K Limited).Accurately weighed 100 mg of ketorolac tromethamine was taken in 100 ml volumetric flask and dissolved in q.s. 100 ml of citrophosphate pH 6.5 to prepare a stock solution of 1000 ppm. From the above stock solution aliquots of 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4 1.6 and 1.8 were transferred separately into 10 ml volumetric flasks and volume was made up to 10 ml with citrophosphate pH 6.5 to get the standard solutions of 2 to 18µg/ml respectively. Physical mixture of ketorolac tromethamine, PVP and HPMC E15LVwas prepared in the ratio of 1:1:1 and IR spectrum was recorded in the range from 4,000 to 400 cm^{-1}.3^2 factorial design shall be used to prepare 9 different batches for assessing the influence of critical variables: PVP (X_1) and HPMC E15LV (X_2).Fast dissolving films were prepared by solvent casting method Aqueous solution I was prepared by dissolving polymer HPMC E15LV and PVP in 5 ml distilled water with stirring to produce a clear solution. The thickness of each film was measured at three different locations the thickness of the film was measured by micrometre screw gauge. The *in-vitro* disintegration time of film strips was determined by the visual method. The film strip was placed in a glass Petri dish containing 25 ml of distilled water at37°C. ketorolac tromethamine was carried out by USP type II Dissolution apparatus i.e. paddle type 100 containing 500 ml of the simulated salivary fluid (pH 6.5) as a dissolution medium, maintained at 37 ± 0.5°C.The stability study of prepared fast dissolving film of ketorolac tromethamine was carried out at 40/75(°C/RH) and for one month.

KEY WORDS: ketorolac tromethamine, fast dissolving tablet, HPMC E15LV, PVP.

1. INTRODUCTION: Polymers are the most important ingredient of the oral fast dissolving film. Robustness of the film depends on the amount of polymer added in the oral strip. These polymers are mostly attracted considerable attention by medical and neutraceuticals industry. Generally 45% w/w of polymer is used which is based on total weight of dry film. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva. Currently, both natural & synthetic polymers are used for the preparation of fast dissolving film. Now a day's various natural & synthetic polymers are available in preparation of fast dissolving film. Polymers frequently used as film formers are water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K-90, polyethylene glycols, pullulan, gelatin, carboxymethylcellulosecekol 30, hydroxy propyl methyl cellulose E-3 and K-3, methyl cellulose A-3, A-6 and A-15, pectin, sodium alginate hydroxyl propylcellulose, maltodextrins and eudragit RD10[1]

2. EXPERIMENTAL WORK:

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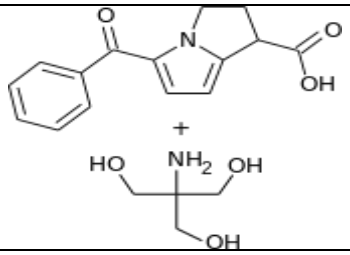
Table 2.1: Profile of Ketorolac Tromethamine[2-4]

Parameters	Description
A. Analytical profile	
CAS number	74103-07-4
Chemical structure	
Chemical formula	$C_{19}H_{24}N2O_6$
Chemical name	5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid - 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
Molecular weight	Average: 285.303 g/mol
Λ max	245nm (100mm hydrochloric acid)
B. Pharmaceutical profile	
Appearance	A whitish, crystalline powder
Melting point	165-167°C
Solubility	200 g/l in water
Log p	3.385
Storage	Air tight container
C. Pharmacodynamic profile:	
Therapeutic category	Anti-Inflammatory agent, Non-Steroidal, Cyclooxygenase inhibitors
Mechanism of action	The anti-inflammatory effect of KT is due to inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) pathways.

The aim of this section was to investigate a robust prototype formulation of rapid dispersible tablets. The Pre-formulation of formulation is investigated by using characterization of active, and drug excipients compatibility study.

Table: 2.2: Details of API used:

Name of Item	Manufacturer
Ketorolac Tromethamine	Perkin laboratories, kukatpally, Hyderabad

Table: 2.3: Chemicals / Reagent Used

Name of Item	Manufacturer
PVP	S.D. Fine Chem. Limited Mumbai
HPMC E15LV	LOBA Chemicals, Mumbai
Citric Acid	LOBA Chemie. Pvt. Ltd. Mumbai INDIA
Menthol	LOBA Chemicals, Mumbai
Tween 80	LOBA Chemicals, Mumbai
Ethanol	Jay Chemicals and Pharma Works
Purified water	In house Laboratory

Table: 2.4: List of glassware used

Name of Item	Specification(grade)
Beaker	Borosil
Conical flask	JSGW borosilicate,
Volumetric flask	Borosil
Measuring cylinder	Borosil
Pipette	Borosil
Funnel	Borosil
Spatula	Stainless steel
Test tubes	Borosil

Table: 2.5: Equipment/Instrument used

Name of Equipment	Maker and Model
IR Spectrophotometer	Bruker, ALPHA-E/T
UV Spectrophotometer	Elico, UV-1800
Digital pH meter	Hanna, PHep®
Magnetic Stirrer	Remi, 1MLH
Analytical Weighing balance	AdirDutt-FX 200
Electronic weighing balance	Adair Dutt, AD-200E
Dissolution apparatus	Electrolab TDT-06L
Hot air oven	Swastika lab. Equipment

2.1 PREFORMULATIONSTUDY OF KETOROLAC TROMETHAMINE, HPMC E15LV AND PVP:

2.1.1 Identification of Ketorolac Tromethamine by IR Spectroscopy: IR spectrum of ketorolac tromethamine was recorded using Bruker spectrophotometer equipped with a temperature controlled circle cell accessory.[5]

2.1.2 Melting Point Determination by Capillary Method: Melting point of ketorolac tromethamine was determined by capillary method using melting point apparatus.capilary.[6]

2.1.3 Analytical Studies by UV Spectrophotometry: UV-Visible spectral analysis of ketorolac tromethamine was done by using Elico double beam UV-Visible spectrophotometer 1800 model with a matched pair of quartz cell (Optiglass U.K Limited).[7]

2.2PREPARATION OF STOCK SOLUTION:

Accurately weighed 100 mg of ketorolac tromethamine was taken in 100 ml volumetric flask and dissolved in q.s. 100 ml of citrophosphate pH 6.5 to prepare a stock solution of 1000 ppm. Further, 1 mL of solution was pipette out from 1000 ppm stock solution and diluted to 10 mL with citrophosphate pH 6.5 to make 10 ppm solution.[8]

2.3 PREPARATION OF STANDARD SOLUTION:

From the above stock solution aliquots of 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4 1.6 and 1.8 were transferred separately into 10 ml volumetric flasks and volume was made up to 10 ml with citrophosphate pH 6.5 to get the standard solutions of 2 to 18µg/ml respectively.[9]

2.4 SOLUBILITY DETERMINATION BY SHAKE FLASK METHOD:

An excess quantity of ketorolac tromethamine was dissolved in 20 ml of citrophosphate pH 6.5 and stirred magnetically at 100 rpm, then allowed to equilibrate for 24 hrs at room temperature.[10]

2.5 DRUG-EXCIPIENT COMPATIBILITY STUDY:

2.5.1 Ketorolac Tromethamine, PVP and HPMC E15LV: Physical mixture of ketorolac tromethamine, PVP and HPMC E15LVwas prepared in the ratio of 1:1:1 and IR spectrum was recorded in the range from 4,000 to 400 cm^{-1}. This mixture was kept for 14 days at 37 ^{0}C and IR spectrum was again recorded. The respective IR spectra are shown in Figure 7 at day 0 and day 14.[11]

3. FORMULATION DESIGN:

In the present research work full 3^2 factorial design shall be used to prepare 9 different batches for assessing the influence of critical variables: PVP (X_1) and HPMC E15LV (X_2). The full factorial design of preparation of fast dissolving film.[12]

Table 3.1: Variables and their levels with actual values for preparation of ketorolac tromethamine fast dissolving film

Level / Factor	Low	Medium	High
PVP (mg) (X_1)	50	75	100
HPMC (mg) (X_2)	350	400	450

3.1 PREPARATION OF FAST DISSOLVING FILM:

Fast dissolving films were prepared by solvent casting method Aqueous solution I was prepared by dissolving polymer HPMC E15LV and PVP in 5 ml distilled water with stirring to produce a clear solution. Aqueous solution II was prepared by dissolving flavor plasticizer and drug in 2ml distilled water. The aqueous solutions I and II were mixed and stirred for 1 h. The solutions were cast on to 9-cm diameter Petri dish and were dried at 45°C for 24 h. The films was carefully removed from the Petri dish and checked for any imperfection and cut according to size required for testing (square film 2 cm length, 2 cm width) so that each film contained 10 mg of the drug.[13]

Table3.2: Full3^2 factorial design for preparation of ketorolac tromethamine fast dissolving film (2x2 cm)

Batch Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
KT(mg)	160	160	160	160	160	160	160	160	160
PVP (mg)	50	50	50	75	75	75	100	100	100
HPMC E15 LV (mg)	350	400	450	350	400	450	350	400	450
Propylene glycol 400 (ml)	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Citric Acid (mg)	15	15	15	15	15	15	15	15	15
Menthol (mg)	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020
Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water (ml)	10	10	10	10	10	10	10	10	10
Ethanol (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
2x2 cm film contains 10 mg ketorolac tromethamine									

3.2 EVALUATION OF THE PREPARED FORMULATIONS FOR ASSESSMENT OF EFFECTS AND INTERACTION OF INDEPENDENT PROCESS VARIABLES OF KETOROLAC TROMETHAMINEFAST DISSOLVING FILM:

3.2.1 Thickness: The thickness of each film was measured at threedifferent locationsthe thickness of the film was measured by micrometre screw gauge at different 3 strategic locations.[14]

3.2.2 Surface pH: The film to be tested was placed in a Petri dish and was moistenedwith 5 ml of distilled water and kept for 30 s. The pH was notedafter bringing the electrode of the pH meter in contact with thesurface of the formulation and allowing equilibration for 1 min. Theaverage of three determinations for each formulation was done.[15]

3.2.3 Folding Endurance: The folding endurance is expressed as the number of folds(number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also givesan indication of brittleness of the film. A strip of 2 cm × 2 cm (4 cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crackwas observed, and the values were reported.[16]

3.2.4 Disintegration Test: The *in-vitro* disintegration time of film strips wasdetermined by the visual method. The film strip was placed in a glass Petri dish containing 25 ml of distilled water at37°C, with swirling every 10 s. The disintegration time wasrecorded as the time at which the film starts to break ordisintegrate. Disintegration time was measured.[17]

3.2.5 Weight Variation:

The film 2 x 2cm ($4cm^2$) was cut at three different places in the cast film. The weight of each filmstrip was taken and the weight variation was calculated.[18]

3.2.6 Uniformity of Drug Content

The drug content uniformity of each film was tested by dissolving film 2 x 2 cm containing 10 mg of ketorolac tromethamine dissolving in 100 ml of simulated saliva of pH 6.5 for 30 minute with continuous shaking. Then the solution was filtered by membrane filter and further diluted with simulated salivary fluid 10 ml, the absorbance was measured at 321nm using a spectrophotometer and the drug content was calculated.[19]

3.3 *IN-VITRO*DISSOLUTION STUDIES:

The simulated salivary fluid was taken as the dissolution mediumto determine the drug release.The dissolution profile of quick release films of ketorolac tromethamine was carried out by USP type II Dissolution apparatus i.e. paddle type 100 containing 500 ml ofthe simulated salivary fluid (pH 6.5) as a dissolution medium,maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm.Aliquots (5 ml) of the dissolution medium were withdrawn at30, 60, 90, 120, and 150 sec. time intervals and the sameamount was replaced with the fresh medium.Sampleswereassayedspectrophotometeric ally at 321 nm. Three trials werecarried out for all the samples and the average value was taken.The percentage of the drug dissolved at various time intervalswas calculated and plotted against time.[20]

4. STABILITY STUDY FOR SELECTED OPTIMIZED FORMULATION AS PER ICH Q1 STABILITY TESTING GUIDELINE:

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resist detoriation.[21]

5. RESULT & DISCUSSION:

5.1 ANALYTICAL STUDIES BY UV SPECTROPHOTO-METRY:

UV-Visible spectral analysis of ketorolac tromethamine was done by using Elico double beam UV-Visible spectrophotometer 1800 model with a matched pair of quartz cell (Optiglass U.K Limited). Accurately weighed 100 mg ketorolac tromethamine was transferred to 100 ml volumetric flask and dissolved in citrophosphate buffer pH 6.5. Volume was made up to mark with citrophosphate buffer pH 6.5 to make a 1000 ppm solution. 1 ml of this solution was diluted to 100 ml with citrophosphate buffer pH 6.5 to make 10 ppm solution. Further, different solution of 2,4,6,8,12,14,16,18, ppm were made and the absorbance was measured between the wave-length of 200-400 nm UV spectrum is presented in Figure 5.1

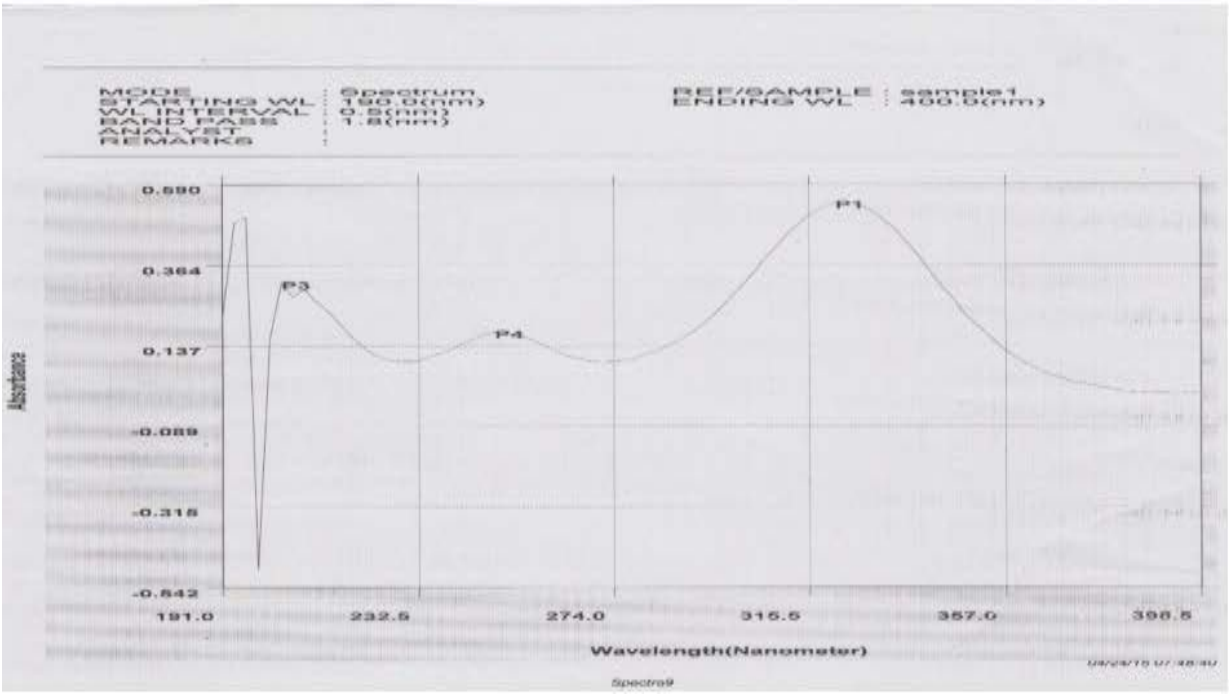


Fig. 5.1 UV spectrum of ketorolac tromethamine in citrophosphate pH 6.5

Table 5.1: Calibration curve data of ketorolac tromethamine

Concentration (µg/ml)	Absorbance				
	1	2	3	Average	±SD
2	0.208	0.205	0.207	0.207	0.002
4	0.281	0.288	0.282	0.284	0.004
6	0.341	0.345	0.348	0.345	0.004
8	0.429	0.429	0.426	0.428	0.002
10	0.541	0.543	0.545	0.543	0.002
12	0.643	0.641	0.647	0.644	0.003
14	0.737	0.734	0.738	0.736	0.002
16	0.873	0.872	0.875	0.873	0.002
18	0.971	0.973	0.972	0.972	0.001

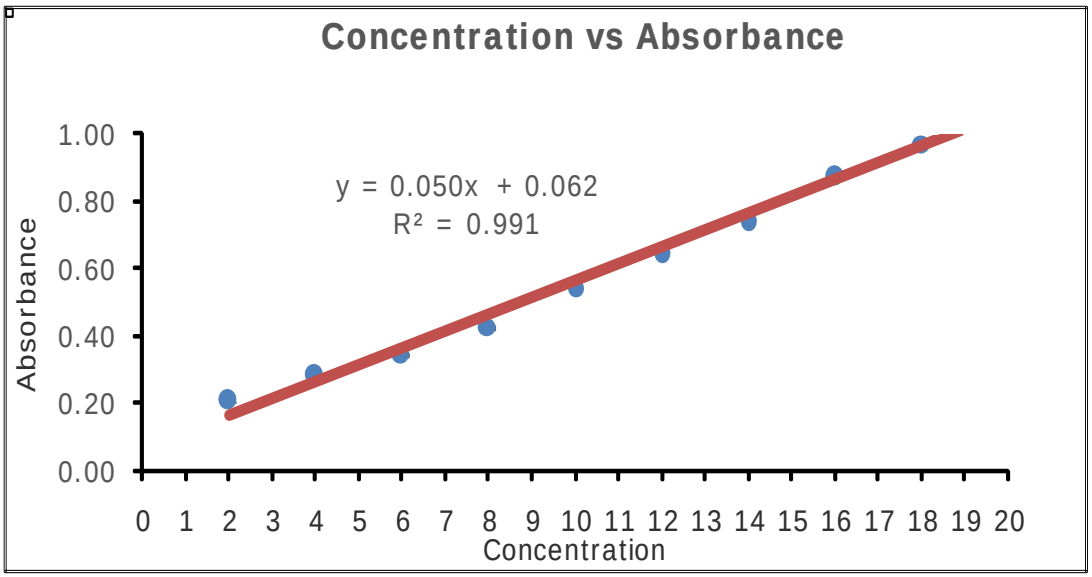


Fig. 5.2 Calibration curve for ketorolac tromethamine in pH 6.5 at 321 nm

It was observed that the method was linear and the Beer's law was obeyed in concentration range of 2-18µg/ml at 321 nm. The slope and intercept were found to be 0.0501 and 0.0620 respectively with correlation coefficient of r is 0.9916.

5.2 DISINTEGRATION TEST

Table 5.2: Disintegration time of prepared fast dissolving film of ketorolac tromethamine

Formulation	Disintegration time (Sec.)
F1	37.0±1.73
F2	49.3±2.08
F3	57.7±2.52
F4	36.3±3.51
F5	52.3±2.52
F6	52.7±2.52
F7	49.0±5.29
F8	49.0±3.61
F9	54.3±1.15

The disintegration time of various formulations was found to in the range between 36.3±3.51 to 57.7±2.52. The result were found in the range i.e. <60 sec.

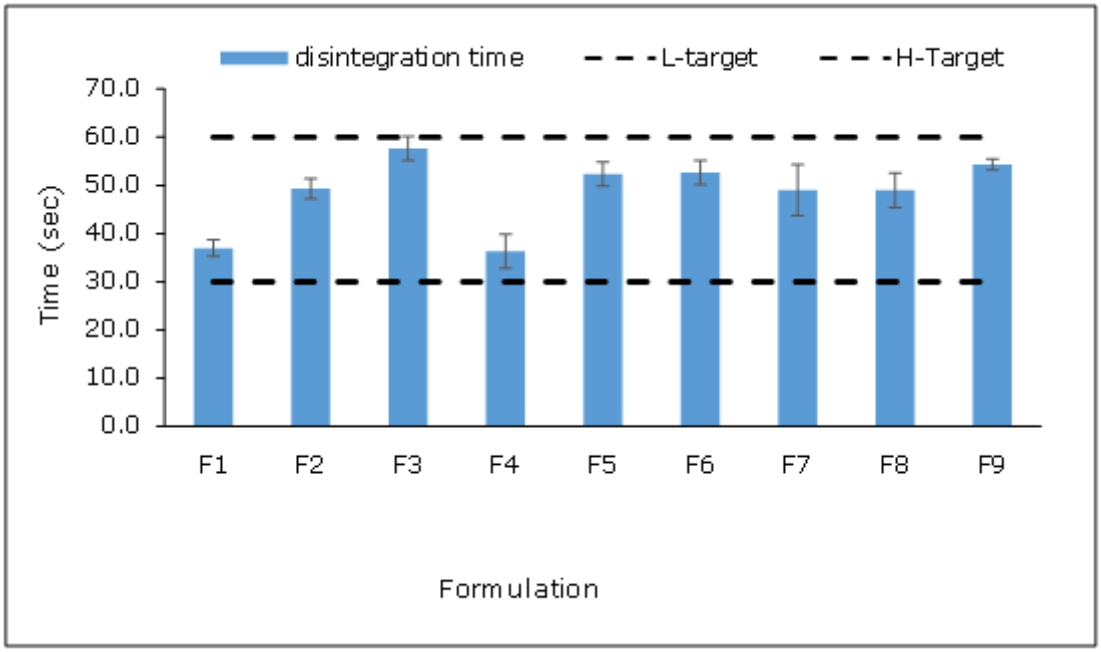


Fig. 5.3 Disintegration time of different formulation

5.3 *IN-VITRO* DISSOLUTION STUDIES:

Table 5.3: *In-vitro*release of ketorolac tromethamine film prepared formulations, plain ketorolac tromethamine and theoretical profile

Cumulative drug release (%)	Time (Sec.)	30	60	90	120	150	300	Similarity Factor f2
	F1	7.41 ±0.1	13.65 ±0.0	39.45 ±0.4	73.32 ±1.4	84.49 ±1.0	90.88 ±1.1	40.808
	F2	7.06 ±0.1	13.31 ±0.1	37.59 ±0.83	67.73 ±0.1	92.54 ±1.0	99.20 ±0.2	42.654
	F3	6.34 ±0.1	12.41 ±0.0	33.26 ±0.3	54.29 ±2.3	86.09 ±0.9	91.88 ±1.0	53.235
	F4	7.12 ±0.1	12.01 ±0.2	35.26 ±0.9	66.60 ±0.6	89.48 ±0.3	94.67 ±1.0	45.170
	F5	6.60 ±0.1	12.28 ±0.0	40.65 ±2.3	62.14 ±0.9	81.96 ±0.7	89.49 ±1.9	46.838
	F6	6.86 ±0.0	12.48 ±0.1	28.67 ±0.4	51.23 ±0.5	85.36 ±0.4	94.49 ±1.0	60.474
	F7	6.66 ±0.7	12.16 ±0.4	44.64 ±0.6	63.67 ±0.8	82.58 ±0.9	90.88 ±1.0	43.993
	F8	7.41 ±0.1	13.65 ±0.8	44.64 ±0.6	51.23 ±0.5	86.09 ±0.9	92.49 ±1.0	45.211
	F9	6.80 ±0.1	13.89 ±0.5	43.04 ±0.5	51.56 ±0.1	86.69 ±1.0	92.09 ±1.0	48.22
	TP	6.25	12.50	25.00	50.00	75.00	100.00	

The percentage release of various formulations was found to in the range between 89.49±1.9 to 99.20±0.2%

Table 5.4: The release kinetics of various formulations

Release kinetics-Model Fitting							
Formulation Code	Co-relation Coefficient for the model					Korsemeyer-Peppas	
	0 - order R% vs T	1 - order log R% vs T	Highuchi R% vs $T^{1/2}$	Hixon-Crowell ($100^{1/3}$ - $R\%^{1/3}$) vs T	Korsemeyer-Peppas M_t/M_∞ vs T	K	N
F1	0.9781	0.9739	0.9601	-0.9781	0.9781	0.0002	1.6800
F2	0.9821	0.9844	0.9560	-0.9821	0.9821	0.0002	1.6800
F3	0.9761	0.9895	0.9456	-0.9761	0.9761	0.0002	1.6500
F4	0.9787	0.9836	0.9514	-0.9787	0.9787	0.0002	1.6600
F5	0.9867	0.9719	0.9676	-0.9867	0.9867	0.0002	1.6600
F6	0.9644	0.9966	0.9287	-0.9644	0.9644	0.0003	1.5700
F7	0.9849	0.9639	0.9694	-0.9849	0.9849	0.0002	1.6600
F8	0.9715	0.9699	0.9495	-0.9715	0.9715	0.0003	1.5700
F9	0.9744	0.9731	0.9515	-0.9744	0.9744	0.0003	1.6000

For formulations, F1, F5, F7, F8 and F9 the best fit model was zero order andfor formulation F2, F3, F4 and F6 the best fit model was 1-Order model.

5.4 ACCELERATED STABILITY TESTING:

The selected formulation F3 showed good physical stability, as there was no discoloration or any physical changes after storage. Formulation release profile at 4th week was compared to the profile at 0 week and theoretical reference profile.

Table 5.5: Physical stability data of the developed fast dissolving film formulation F3

Quality Attribute	Sampling interval				
	0 day	1st week	2nd week	3rd week	4th week
Thickness (µm)	105	105	107	108	110
PH	6.4	6.4	6.3	6.3	6.2
Folding endurance	>300	>300	>300	>300	>300
Disintegration time (sec.)	55	55	54	58	56
Uniformity of weight	110.30	110.75	112.33	112.87	114.65
Uniformity of drug content	100	99.44	98.61	98.02	95.95
***In-vitro* drug release (%) (150 sec.)**	83.60	83.42	82.06	81.89	81.71

6. CONCLUSION:

Fast dissolving film may be preferred over tablet in terms of flexibility and comfort. On the basis of above mention criteria it is wise to prepare fast dissolving film of ketorolac tromethamine. Therefore, it is proposed to prepare fast dissolving film of ketorolac tromethamine and to study the effect of concentration of polymer on drug release.The present study is undertaken with a view to prepare a fast dissolving film providing systemic delivery of ketorolac tromethamine, Plasticizer was usedPEG-400 and polymer were used PVP and HPMC LV15. The amount of drug: polymer was selected on the basis of optimum quantity required for fast dissolving film preparation, as reported in literature. It was found that prepared fast dissolving films prepared using solvent casting technique possessed desirable swelling index, surface pH, folding endurance, dissolution property and prepared films showed fast release profile. The proposed 9 formulations were prepared and evaluated.

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