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Original Article

Preparation and Evaluation of Oral Thin films of Ketorolac Tromethamine using mucilage from *Abelmuchus Esculentus* and *Plantago Ovata*

Shristi Shrestha, Uttam Budhathoki and Rajan Shrestha

Drug Delivery Research lab, Department of Pharmacy, Kathmandu University, GPO box 6250 (Kathmandu), Nepal

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ABSTRACT

This study aim to formulation and characterization of *Abelmoschus Esculentus* and *Plantago Ovata* mucilage based oral thin film of ketorolac tromethamine by solvent casting method. The films were prepared using film forming polymer, HPMC E15, natural polysaccharide *Abelmoschus Esculentus* and *Plantago Ovata* mucilage as disintegrants, and plasticizer, pprropylene glycol 400. Ketorolac tromethamine is used as a peripheral analgesic for short term therapy, also exhibits anti-inflammatory and antipyretic activity. It undergoes rapid and complete first pass metabolism following oral administration upto 80%, resulting in reduced systemic bioavailability. Hence to overcome first pass metabolism and to have quick onset of action for better therapeutic efficacy, ketorolac tromethamine is an ideal drug candidate to formulate into oral thin films that might improve the therapeutic profile.. The disintegration time of optimized formulation was found to be 16 ± 1.25 seconds and dissolution studies of optimized formulation showed cumulative percentage drug released of 98.33±1.28 (n=6) at 8 minutes which is just half time than fast dissolving tablets. Disintegration time of natural disintegrants in combination was found to be better than natural disintegrant alone, synthetic disintegrant and combination of natural and synthetic disintregent.

Keywords: Fast dissolving films; Ketorolac tromethamine; *Plantago Ovata*; *Abelmoschus Esculentus*; Solvent casting method

INTRODUCTION

Oral films are gaining popularity due to high patient compliance and therapeutic advantages[1]. Oral administration of tablet dosage forms is the most commonly used method due to greater flexibility in dosage form and high patient acceptance, but it shows problem in case of poorly water soluble drugs (BCS Class II drugs) for which dissolution rate is slow[2]. Many pharmaceutical companies are switching their products from tablets to fast dissolving oral thin films (OTFs). The films

Address for Correspondence: Dr. Uttam Budhathoki, Drug Delivery Research lab, Department of Pharmacy, Kathmandu University, GPO box 6250 (Kathmandu), Nepal; E-mail: uttam@ku.edu.np

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have advantages of tablets such as precise dose, ease of administration and those of liquid dosage forms including ease of swallowing and rapid bioavailability. Statistics have shown that four out of five patients prefer orally disintegrating dosage forms over conventional solid oral dosages forms. Pediatric, geriatric, bedridden, emetic patients and those with Central Nervous System disorders have difficulty in swallowing or chewing solid dosage forms[3]. Many of these patients are non-compliant in administering solid dosage forms due to fear of choking[4]. The oral cavity has been investigated as a site for drug delivery for many years. Drug delivery through the oral cavity offers many advantages. Among all the routes of administration, the oral route is most preferred route [5]. OTFs offer superior properties over those of oral tablets or capsules such as no need of water to intake. Thus, special patients, pediatrics and geriatrics prefer films since the elderly patients population is ever increasing, companies are shifting from oral capsules and tablets to OTFs.

Ketorolac tromethamine is non-steroid anti-inflamatory agent (NSAID) that is continually available in the market as a tablet. Generally tablets are available in the strength of 10 mg and are usually used after intravenous (IV) or intramuscular (IM) supply and is not used for more than five days and not more than 40mg/day due to severe adverse effect such as peptic ulcer, gastric perforation which may be fatal. OTFs may decrease the incidence of adverse reaction of this drug such as GI perforation and peptic ulcers as it is dissolved in oral cavity Natural mucilage extracts have been studied as potential disintegrants in the formulations of tablets[6a, 6b, 6c, 6d].The objective of the present research is to examine *Abelmoschus Esculentus* (okra) and *Plantago Ovata* husk (psyllium) mucilage in the formulation of fast releasing OTFs of Ketorolac Tromethamine.

MATERIALS AND METHODS

The two factors two level (2^2) Central composite design (CCD) was done to design experiment (Table 8) for optimization of dependent factors (mucilages) from the two natural sources.

Extraction of mucilage from *Abelmoschus Esculentus* mucilage powder: Collected okra was carefully washed and dried under shade for 24 h. and further dried at 30-40℃ until a constant weight was obtained. Size was reduced using grinder and the resultant powder stored in an air tight container until further use [7].

Characterization of *Abelmuscus Esculentus* mucilage powder

1. **Solubility test:** solubility of the extracted mucilage was evaluated qualitatively by stirring 10 mg of Abelmuscus Esculentus mucilage powder in 10 ml of each water, acetone, chloroform and ethanol. Solubility was determined by visual observation of the solute.
2. **pH determination:** A 1% w/v dispersion of the sample in water was stirred consistently for 5 min and pH was determined using a pH meter (Hanna, Germany).
3. **Loss on drying (L.O.D): A** 1 g of sample was dried at 105℃ and kept in hot air oven and checked at 10 min interval until it gives constant weight.
4. **Total ash value:** Powder (1 g) was dried in a crucible. Dry at 100-105℃ for 1h and then ignited at 600±25℃.
5. **Acid insoluble ash:** In total ash value crucible, 15 ml water was added then boiled for 10 min. After cooling, it was filtered. Then filtrate in paper was washed further with hot water until its neutral pH ignited to dull redness cooled and weighed.
6. **Total microbiological count:** This was carried out as per Indian Pharmacopoeia [11]

Extraction of *Plantago Ovata* mucilage: Husks of *Plantago Ovata* were soaked in distilled water for 48 h. and then boiled for 20 minutes for complete release of mucilage. The material was squeezed through muslin cloth for filtering and separating out the marc. Then filtrate was treated with acetone and precipitate was filtered through muslin cloth and dried in hot air oven at temperature less than 40^oC over night. A hard mucilage cake was obtained which was ground, sieved through sieve # 60, stored in a dessicator until further use [8a, 8b]. Characterization of *Plantago Ovata* mucilage was carried out as described above for *Abelmuscus Esculentus* mucilage powder.

Compatibility study of drug with natural mucilage: The Fourier Transform Infra-Red (FTIR, Shimadzu) spectra of pure drug and drug combined with polymers and natural disintegrants were measured using FTIR. Pure drug and drug combined with polymers and disintegrants were separately mixed and scanned over a range of 4000 to 400 cm^{-1}.

Preparation of Ketorolac tromethamine fast dissolving film using solvent casting method: Ketorolac tromethamine films were prepared by a solvent casting method (Figure 1 A). Water soluble polymers were dissolved in water along with plasticizers, then drug along with other excipients were dissolved in water, then both solution were mixed and stirred. After adjusting the pH to neutral, the solution were cast in a glass mould having aluminum foil as backing layer (Figure 5), and kept for drying at room temperature. The resultant films were cut into dimension of 2×2 cm^2

in size. The amount of drug added was calculated based on area of prepared film so that each dosage form (2×2 cm^2) contained 10 mg of Ketorolac tromethamine.

EVALUATION

Physical appearance and surface texture: This parameter was checked simply with visual inspection of films and evaluation of texture by touch.

Thickness: It is measured by a calibrated digital Vernier caliper (Mitutoyo, japan) at the four corners and the center of each square. Mean value of five readings was calculated and reported in Table 9.

Weight variation: Twenty films of each formulation were selected. The weight of each film was measured using a digital electronic balance (Ohaus). The mean weight and standard deviation for optimized film were calculated and reported in Table 11.

Folding endurance: Three films of each formulation were selected randomly and subjected to this test by using latex gloved hands folding the film at the same place repeatedly several times until a visible crack was observed. Mean and the standard deviation were calculated and reported in Table 9.

Surface pH measurement: The fim to be tested was placed in a Petri dish and was moistened with 1 ml of distilled water and kept for 30 sec..The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1min [9].

In-vitro disintegration time: In - vitro disintegration time was determined in a Petri dish with10ml pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The mean and standard deviation of the times were calculated for each type of film and are reported in a Table 10.

Content uniformity and Assay: The films were tested for drug content uniformity by UV visible spectrophotometric method. 10 films of each formulation were placed in separate 100ml volumetric flask and was dissolved using the distilled water with sonication and made up to the volume and the resultant solution was filtered. A 5ml sample of filtered solution was transferred into a 50ml volumetric flask and the volume was made up to mark. The absorbance of resulting solution was measured at 322 nm against a blank in a UV spectrophotometer (Shimadzu, 1800, Japan). The percentage drug content was determined using the equation of a standard calibration curve (Figure 4).

Dissolution Test: Dissolution test for optimized batch was conducted at 37±0.5C using USP Dissolution Type I at 50rpm. Dissolution medium of 900 ml of phosphate buffer (pH 6.8), 5ml sample was taken out from medium at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 minutes and equal volume of medium was replaced into dissolution vessel after each sampling. Absorbance of each filtrate obtained using sintered glass filter was measured in UV spectrophotometer at wave length 322 nm and the cumulative percentage drug release determined by validated method is shown in Figure 3.

RESULT AND DISCUSSION

Mettu and Veerareddy designed an oral fast dissolving tablets of Ketorolac tromethamine and found that the cumulative percent drug release in 15 min (Q15) was 94.34±1.68 where as the conventional tablets, in the same study, showed 28.78±0.82 in 15 min [2]. We found cumulative percentage drug release 98.33±1.28 with in 8 min in oral film which is better in terms of cumulative percentage drug release and time. Thus, aforementioned data showed that for Ketorolac tromethamine following orders of dosage forms in terms of drug release rate oral films> fast dissolving tablets> conventional tablets. Ketorolac tromethamine is available in market as tablets and intramuscular (IM) injection. Therapeutic objective is one of biopharmaceutical consideration of dosage form design[10]. Rapid relief of pain can be achieved by releasing drug from dosage form as quickly as possible. Oral thin films can release this drug quicker, within 8 minutes, moreover oral films are having advantages of tablets, capsules and even oral liquids such as dose accuracy within one dosage form and ease of swallowing.

Thus this dosage form can be a promising dosage form in the future for quick relief of pain in coming days. Moreover it can overcome disadvantages of tablets and capsules such as Ulcers, GI perforation. Results of FTIR (Figure 1, B) showed that these mucilages are showing no interaction with drug. Weight and Thickness uniformity (Table 4 and 11) and folding endurance (Table 9) showed that these are strong enough to prepare and market as a dosage form in coming days. Characterization and preformulation tests of Ketorolac tromethamine was done as per Indian Pharmacopoeia [11] or as indicated and shown in Table 1. Characterization of *Abelmoschus Esculentus* mucilage was as per IP (2014) and articles. Then following results were seen (Table 2). Preformulation studies of *Plantago Ovata* mucilage were carried out as per IP (2014) and references described. Results are shown in Table 3.

Table 1: Result for preformulation studies of Ketorolac tromethamine

Test	Observation	Complies as per
Solubility	Freely soluble in water and phosphate buffer, soluble in ethanol	[11]
Identification	I.R was done Stretching at 3350 cm^{-1}, 2895 cm^{-1}, 1550 cm^{-1}, 1350 cm^{-1}, 1250 cm^{-1}, 1015 cm^{-1}, 700 cm^{-1}	[12]
Appearance of solution	Clear solution was obtained in water	[11]
pH	6.5 (Limit: 5.7-6.7)	[11]
Sulphated ash	0.077% (Limit: NMT 0.1%)	[11]
Loss on drying (L.O.D)	0.31% (Limit: NMT0.5%)	[11]
Assay	100.51% (Limit: 98.5%-101.5%)	[11]

Table 2: Preformulation studies for *Abelmoschus Esculentus* mucilage

Tests	Observation	Complies as per
Solubility	Soluble in water insoluble in chloroform, ethanol and acetone	[11]
I.R	Stretching near to 3250 cm^{-1}, 2900 cm^{-1}, 1650 cm^{-1}, 1450 cm^{-1}, 1050 cm^{-1}	[13]
pH	6.8	
Loss on drying (L.O.D)	8.89%, Limit (NMT 12 %)	[11]
Total ash	2.64%, Limit (NMT 4.5%)	[11]
Acid insoluble ash	0.40%, Limit (NMT 0.45%)	[11]

Table 3: Preformulation studies for *Plantago Ovata*

Test	Observation	Complies as per
Solubility	Soluble in water insoluble in acetone, chloroform and ethanol	
I.R	Stretching seen near to3350 cm^{-1}, 2900 cm^{-1}, 1650 cm^{-1}, 1350 cm^{-1}, 1050 cm^{-1} as	[14]
pH	7.11	
L.O.D	10.91%, Limit NMT 12 %	[11]
Total ash	2.63%, Limit NMT 4.5%	[11]
Acid insoluble ash	0.165%, Limit NMT 0.45%	[11]
Total microbial count	Bacterial: 28 CFUs/g Fungal: 78 CFUs/g	[11]

FTIR spectra showed that there was no interaction between drug and excipients used in film forming (Figure 1B).The FTIR spectrum exhibits peaks near to 3350 [1], 2895 , 1550 , 1350, 1250 , 1015 , 700 for N-H stretching,--- C=C aromatic and aliphatic stretching, C-N stretching, -OH bending, C-H bending respectively. Nearly same peak of drug was observed for the drug with excipients physical mixture. The spectra (Figure 1B) showed no incompatibility between drug and excipients. Three factors (*Abelmoschus Esculentus*, *Plantago Ovata* mucilages and disintegration time, two factors two level Central composite design (2^2 CCD) was done using Minitab 17 (Table 8) version which gave 13 formulation in combination. 13 batch of oral films were prepared and their disintegration time was noted. Based on the Contour plot (Figure 2) was obtained using the same software. Based on the contour plot (Figure 2) optimized formulation (Table 7) was chosen as *Plantago Ovata* mucilage 5 mg and *Abelmoschus Esculentus* mucilage 5.6 mg gives best result i.e, 16 ±1 seconds as disintegration time which was as per objective below 30 seconds for oral films by definition. The thickness of the films was measured by using digitial Vernier caliper. Optimized Formulation was measured for thickness and calculated standard deviation values are given in table 4.

Table 4: Data for thickness of optimized film

S.no	Corner 1	Corner 2	Corner 3	Corner 4	center	Average
1	0.08mm	0.07mm	0.08mm	0.08mm	0.07mm	0.076±0.0049
2	0.07mm	0.08mm	0.07mm	0.08mm	0.08mm	0.076±0.0049
3	0.08mm	0.08mm	0.07mm	0.08mm	0.08mm	0.078±0.004

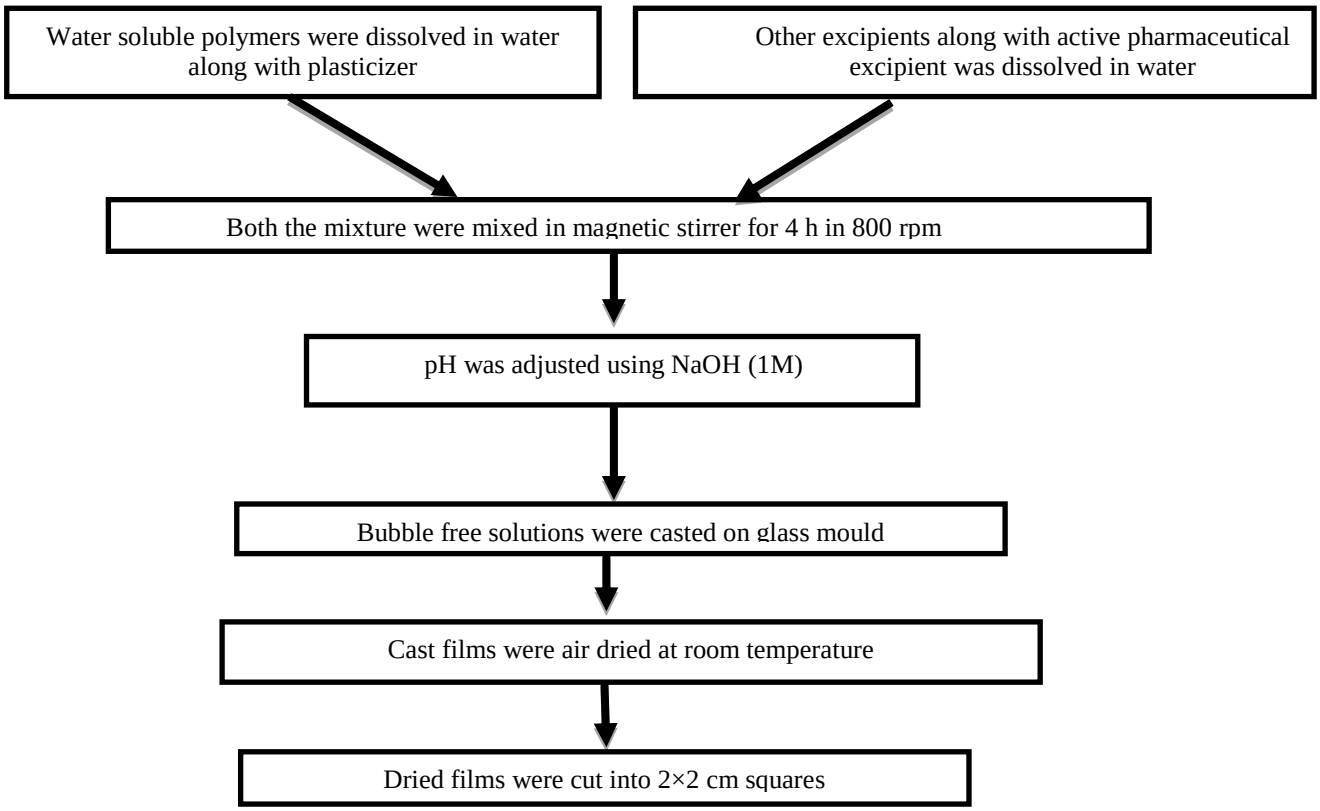

Figure 1A. Solvent Casting Method for Oral Thin Film

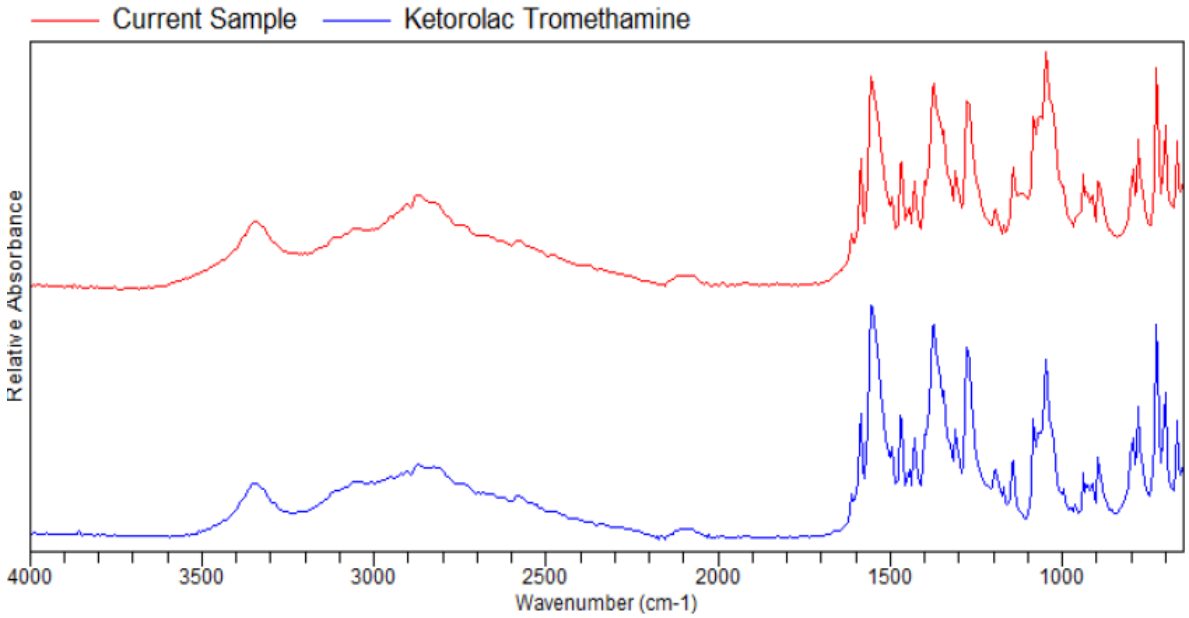

Figure 1B: IR spectra of physical mixture of Ketorolac tromethamine with all excipient compared with pure drug

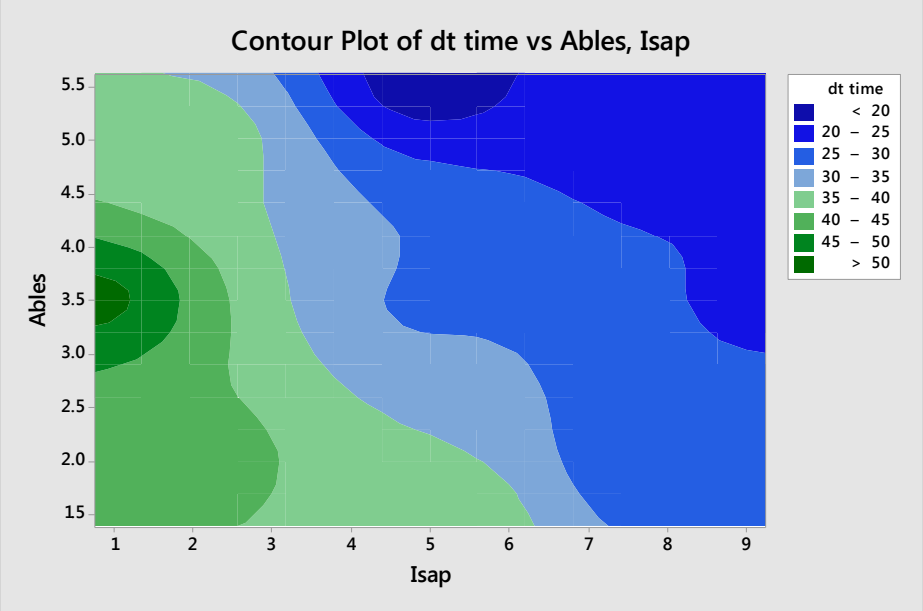

Figure 2: Contour plot for the response Disintegration Time versus *Plantago Ovata* mucilage (Isap) and *Abelmoschus Esculentus* mucilage (Ables)

Average weight oral films (n=20) of optimized formulation is 56.515±2.063559mg. The average surface pH of optimized film (n=20) was found to be 6.9 ±0.01.The calculated assay and content uniformity is tabulated in Tables 5 and 6.

Table 5: Data for assay of optimized film

	N=1	**N=2**	**N=3**	**Average**
S1	100.79	99.82	99.86	
S2	99.81	101.77	99.63	
Average	100.31	100.80	99.75	100.29
S.D	0.48772	0.973	0.113	0.525

Table 6: Data for content uniformity of optimized film

Film no.	**N=1**	**N=2**	**N=3**
1	101.75	98.86	99.6
2	105.08	98.86	98.86
3	99.16	98.67	101.45
4	100.82	98.67	99.41
5	101.75	98.30	98.67
6	104.52	98.86	97.75
7	98.97	98.30	100.70
8	98.97	98.67	100.52
9	99.71	97.75	100.52
10	100.08	97.38	99.05
Average	101.08	98.44	99.65
S.D	2.10316	0.48	1.071
Avg. S.D	1.22		

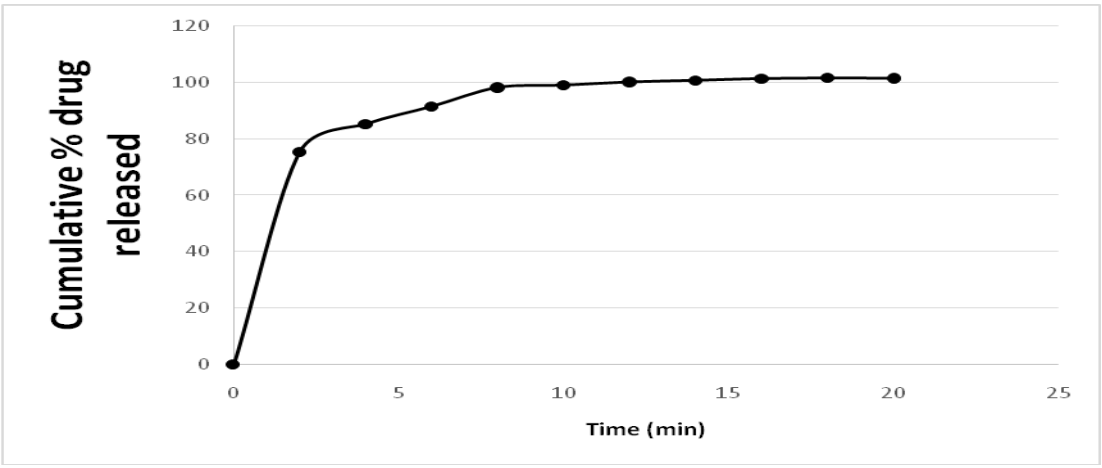

Figure 3: Cumulative percentage drug release from optimized film.

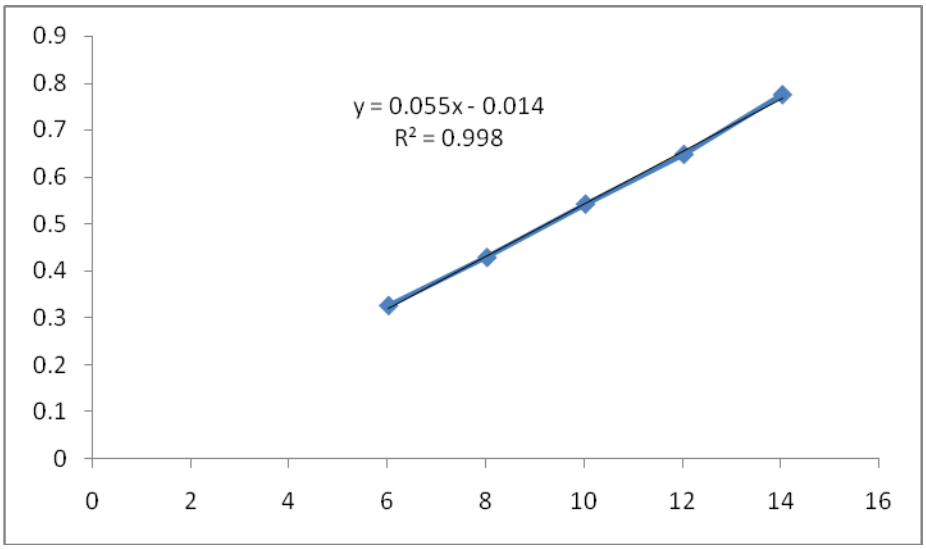

Figure 4: Standard calibration curve of Ketorolac tromethamine in water

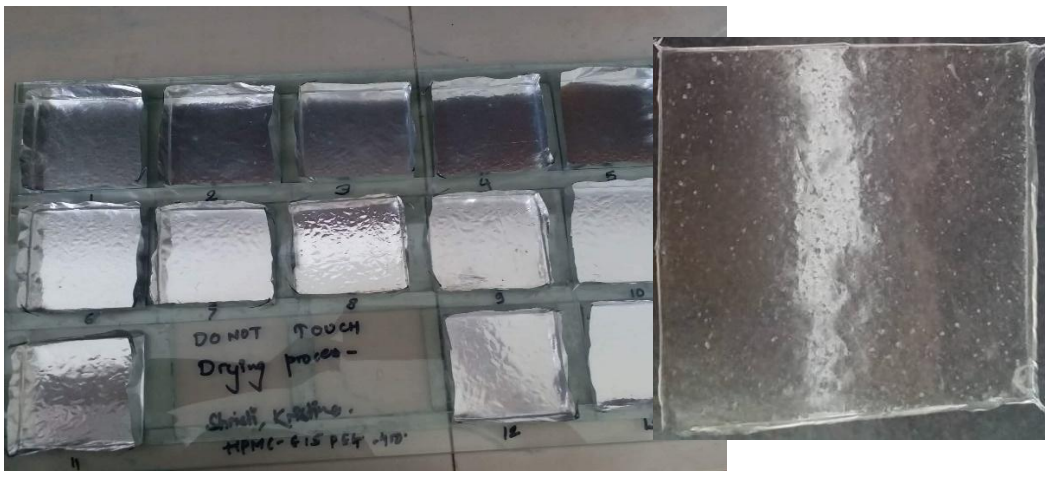

Figure 5: Oral film prepared by solvent casting method in mold.

Table 7: Optimized formulation based on disintegration time

S. no	Materials	Quantity
1	HPMC E15	295 mg
2	PEG-400	0.19 ml(≈228 mg)
3	Ketorolac tromethamine	151 mg
4	AbelmoschusEsculentus mucilage powder	5.6 mg
5	Plantagoovata mucilage powder	5 mg
6	Sodium saccharin	28 mg
7	Orange flavor	1ml
8	Water	Q.S

Table 8: Formulation design using CCD for HPMC E5 & PEG 400 with *Plantago Ovata* mucilage and *Abelmoschus Esculentus* mucilage

Formulation	HPMC (mg)	PEG-400 (ml)	*PlantagoOvata* mucilage (mg)	*AbelmoschusEsculentus* mucilage (mg)
F01	295.00	1.89	9.24	3.5
F02			2.	5.
F03			5.	3.5
F04			2.	2.
F05			5.	3.5
F06			8.	5.
F07			0.76	3.5
F08			5.	3.5
F09			5.	5.62
F10			8.	2.
F11			5.	3.5
F12			5.	3.5
F13			5.	1.38

Table 9: Data for Thickness and Folding Endurance

Formulation	HPMC E5 +PEG 400		HPMC E5 + PEG 6000		HPMC E15 + PEG 6000		HPMC E15 + PEG 400	
	Thickness (mm)	**F.E**	**Thickness (mm)**	**F.E**	**Thickness (mm)**	**F.E**	**Thickness (mm)**	**F.E**
1	0.38±0.02	14±3.6	0.11±0.01	16±1	¤ 0.09±0.01	¤ 27±1	0.11±0.01	>300
2	0.44±0.14	1±0	0.11±0.03	12±2	0.09±0.01	24±1.7	0.21±0.03	>300
3	0.44±0.08	2±1	0.12±0.06	15±2	0.11±0.01	26±4	0.26±0.01	>300
4	0.35±0.01	2±1	0.16±0.06	43±1.73	¤ 0.11±0.01	¤ 64±2.7	0.21±0.03	>300
5	0.24±0.06	213±3.6	¤ 0.08±0.05	¤ 57±1.73	0.03±0.01	81±1	0.07±0.01	>300
6	#0.26±0.04	# 2±0	0.07±0.01	104±2	0.07±0.01	205±2	0.2±0.01	>300
7	0.37±0.04	0	#0.04±0.01	#91±1	0.07±0.01	113±1	0.22±0.01	>300
8	0.36±0.03	2±0	0.08±0.04	73±1	0.09±0.01	96±1	0.2±0.02	>300

9	# 0.38±0.03	# 1±0	* 0	* 0	¤ 0	¤ 0	0.39±0.01	>300
10	*0	*0	0.1±0.03	80±1	0.11±0.01	102±1.7	0.41±0.01	>300
11	0.19±0.02	13±1.7	0.05±0.01	137±2	0.43±0.04	154±2	0.1±0.01	>300
12	0.32±0.02	3±1	0.05±0.004	273±4.36	0.05±0.01	>300	0.22±0.01	>300
13	*0	*0	0.07±0.01	36±1	¤ 0.08±0.01	¤ 56±2	0.34±0.03	>300

NOTE: *---Gelly #---Sticky ¤---Broken ±--- Standard deviation

Table 10: Data for Disintegration Time (D.T)

Formulation	D.T of *Plantago Ovata* mucilage and crospovidon as disintegrant in secs± S.D	D.T of Plantago ovata and *Abelmoschus Esculentus* mucilage as disintegrant in secs± S.D
1	72±2	23±0.5
2	53±2	37±0.9
3	84±1.6	31.67±2.5
4	36.67±1.2	42.33±2.05
5	63.67±1.2	36.67±0.94
6	83.33±0.9	21±0.94
7	50.67±0.9	51±0.94
8	71±0.47	27±1.4
9	47±1.6	16±0.8
10	56±2	25.67±0.47
11	65±2	25±1.4
12	53±0.9	26.67±1.24
13	66±1.6	39.67±1.24

±--- Standard deviation

Table 11: Data for weight variation of optimized film

52.6 mg	57.8mg	54.7mg	59.8mg	61.3mg	54 mg	57.1mg	56.4mg	56.8mg	57.4mg
55.6mg	58.4mg	56.5mg	56.8mg	55.2mg	53.9mg	58.4mg	56.9mg	53.9mg	56.8mg
Average= 56.515									
Standard deviation= 2.063559									

CONCLUSION

Most of the pharmaceutical companies are shifting their oral solid dosage products into oral thin films as it has advantages of both oral solid dosage forms as well as oral liquid dosage forms. Moreover, it has advantages of no need of water for intake, suitable for pediatric and geriatric patients and patients with swallowing problems, dysphagia. Cumulative percentage drug released showed that almost all drug released within 8 mins an improvement over fast dissolving tablets of same drug (15mins) and conventional tablets. Disintegration time was also less than 30 seconds (16sec) that is also using natural mucilage in combination (mucilage of *Abelmoschus Esculentus* (5mg) and *Plantago Ovata* (5.5mg). Thus oral thin films of this drug is a promising dosage form for quick relief of acute pain in the patients which had been proved in this study with the biopharmaceutical consideration of dosage form design (reducing disintegration and dissolution time), though its bioavailability has to be studied further in the healthy volunteers.

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