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EFFECTIVE DEVELOPMENT AND EVALUATION OF ORAL THIN FILM OF ETORICOXIB

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ABSTRACT

The aim of the present investigation was to develop oral thin films of etoricoxib, an analgesic agent and to investigate the effect of the formulation variables like concentration of film forming polymer, emulsifying agent and plasticizer on the physico chemical properties and in vitro dissolution studies. Hydroxylpropyl methylcellulose was used as a film former, Tween 80 as an emulsifying agent and polyethylene glycol (PEG) 6000 as a plasticizer. These three variables were studied at two levels thus, a 2^3 full factorial design was applied and six different formulations were developed by solvent casting method and evaluated. The role of HPMC in deciding the film properties was significant. It affected thickness, weight variation, folding endurance, surface PH, swelling propertics, disintegration time and in vitro dissolution rate significantly. PEG 6000 also found to play a role in deciding the properties of films. The film that contained HPMC (15 mg /film i.e. 2x3 cm^2) in low levels and Tween 80 (30 mg/film i.e. 2x3 cm^2) and PEG 6000 (8 mg/film i.e. 2x3 cm^2) in high levels was found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum in vitro release.

KEYWORDS: Etoricoxib, oral films, solvent casting method, formulation variables.

1. INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsions etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using super-disintegrates and hydrophilic ingredients. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin.[1] FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

OTFs also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture.[2] Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near futureaccording to Technology Catalysts.[3]

The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets/capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients.

Eventually, film formulations having drug/s will be commercially launched using the OTF technology.[4]

In North America more than 80 oral thin film brands launched since 2003, the market remains limited when compared to ODTs. However, for future growth point of view the OTF sector is well-positioned. In US market the OTC films of pain management and motion sickness are commercialized. More importantly, prescription OTFs have now been approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly.[5]

Fast dissolving film combines all the advantages of tablets (accurate dose, self administeration) with those of liquid dosage forms (easy swallowing, quick bioavailability). The administration of drugs by the oral route has several advantages over other route of administration such as no special set up required for the industry**,** Availability of larger surface area that leads to rapid**,** disintegrating and dissolution in the oral cavity and promote the systemic absorption of APIs**,** No need of water or a spoon for administration and without chewing**,** Dose accuracy in comparison to syrups**,** Rapid onset of action**,** The drug enters the systemic circulation with reduced hepatic first pass effect**,** Lower doses**,** Minimal side effects**,** Destructive acidic environment of stomach can be avoided**,** Delivery can also be terminated relatively easily if required, Site specific action and local action**,** Noninvasive, Patent life extension etc.[6] The disadvantage of OTF is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip 7 Expensive packaging of oral film.[7]

Drugs with larger doses are difficult to formulate into FDT e.g. rifampin (600 mg), ethambutol (1000mg) etc. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.[8]

The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin.[9] There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.[10]

For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer.

Several classes of drugs can be formulated as oral dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paracetamol, meloxicam, valdecoxib). Less bitter, potent and highly lipophilic drug should be preferred for OTF as in case of fast dissolving tablets. Most advanced research has proven that the concentration level of API per dose can extend up to 50% per dose weight. Novartis Consumer Health's Gas-X thin film has proven this by loading 62.5 mg of simethicone per thin film.[11]

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases Some of the water soluble polymers used as film former are HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrin and Eudragit RD108,9,10,11,12 Eudragit RL100. Polymerized rosin is a novel film forming polymer.[12, 13]

By addition of plasticizers, the mechanical properties of formulation (tensile strength and elongation) can be improved. Mechanical property is plasticizers concentration dependent property. The commonly used plasticizers are glycerol, di-butylpthallate polyethylene glycols etc.[14]

Poorly aqueous soluble drugs are usually characterized by a low bioavailability due to less absorption, which is a major concern of pharmaceutical industries worldwide. Attempts to improve the solubility of these drug candidates have been performed by various approaches.[15] Among them, solid dispersion technique has attracted considerable interest as an efficient means of improving the dissolution rate, which increases the bioavailability of a range of poorly aqueous soluble drugs. Fast and immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug

particles, and existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles using various hydrophilic carriers.[15-18] Etoricoxib, 5-chloro-6_-methyl-3 [4-(methyl sulfonyl) phenyl]-2, 3_–bypyridine, is a highly selective second generation

cyclooxygenage-2 (COX-2) inhibitor administered orally as an analgesic and nonsteroidal anti-inflammatory analgesic drug that has shown some improved efficacy versus traditional NSAIDs.[19] It is used in the treatment of rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic back pain, and acute gout.[20, 21] Moreover, recent studies evidenced its efficacy in patients with ankylosing spondylitis.[19] But it's very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action.[20, 22] Therefore, improvements in solubility and/or dissolution rate of etoricoxib may be achieved through the preparation of solid dispersions. In the literature, various solid dispersions of etoricoxib are reported for improving the dissolution of etoricoxib using various carriers like polyvinyl pyrrolidone K 30 (PVP K 30),[23] polyethylene glycol 4000 (PEG 4000) and polyvinyl pyrrolidone K 30 (PVP K 30) combination,[24] Poloxamer 188,[25] and Gelucire 50/13, Compritol, and Sterotex K NF.[26]

So, the aim of the present investigation is to prepare and characterize etoricoxib oral thin films using various excipients like HPMC, PEG, Citric acid, Teew 80 and mannitol as carriers for improvements of solubility and/or dissolution of poor aqueous soluble drug, etoricoxib.

3. MATERIALS AND METHODS

3.1. Solvent casting method

In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.[27,28]

3.2. Materials

Etoricoxib (Kindly supplied by Beximco pharmaceutical Ltd, Bangladesh), $HPMCK_{15}$ cps, PEG 6000, Tween 80, citric acid, manitol, (Kindly supplied by Sigma corporation, Germany). All other chemicals and reagents were of analytical grade.

3.3. Formulation design of oral fast dissolving strips

Different polymers were used in different combination for the formulation of fast dissolving strip. Preparations of strips were done by solvent-casting method.

Oral thin films of etoricoxib were prepared using solvent casting method (Dixit et al., 2009). The Formulation codes and their respective compositions are given in Table 1. An aqueous solution of HPMC was prepared by dissolving in a fixed quantity of distilled water. To this polymeric solution measured quantities of Etoricoxib, HPMC K_{15}, HPMC(ISPC), Tween 80, PEG $_{6000}$, citric acid, manitol were added. The suspension was stirred for 30 min. The thick viscous suspension was degassed to remove air entrapment by using ultrasonicator. Measured quantity of suspension was cast on a 10 × 12 cm2 glass plate The film was carefully removed from the glass plate, checked for any imperfections and cut to the required size to deliver the dose equivalent to 30 mg (2 × 3 cm2) per strip. The films were stored in airtight containers for further studies. The film samples were also stored for accelerated stability studies as per International Conference on Harmonization (ICH) guidelines.[29]

3.4. Thickness

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

3.5. Weight Variation

Weight variation is studied by individually weighing 10 randomly selected ET films and calculating the average weight. The average weight should not deviate significantly from the average weight.

3.6. Folding endurance

The folding endurance along with tensile strength of a film is related to the flexibility of a film and hence represents its physical stability during manufacturing, packing and use. It was measured manually by firmly folding a film repeatedly through the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of folding endurance.[30]

3.7. Surface pH

The surface pH of Etoricoxib fast dissolving oral thin films was determined in order to investigate the possibility of any side effects in vivo. Oral strip was slightly wet with the help

of water. The pH was measured by bringing the electrode in contact with the surface of the film (by using portable PH meter).

3.8. Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed.[31, 32]

The degree of swelling was calculated using parameters

$\alpha = wt - wo/wo$

wt is weight of film at time t, and wo is weight of film at time zero.

3.9. Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of films at 284 nm. The transparency of the films was calculated as follows:

Transparency = (logT600)/b = - €c

Where T284 is the transmittance at 284 nm and b is the film thickness (mm) and c is concentration.[33, 34]

3.10. *In vivo* Disintegration test

Disintegration test was performed among 6 healthy men volunteer. Each oral thin film of etoricoxib was placed on tongue individual volunteer. A disintegration time was performed by stop watch. Disintegration times are shown in the table 2.

3.11. *In vitro* dissolution studies

The dissolution rate of ET films was studied in 900 ml of pH 6.8 buffer using USP dissolution test apparatus with basket stirrer at 50 rpm. A temperature of $37^{o}C + 1^{o}C$ was maintained throughout the study. One film containing 30 mg of ETS oral thin film was used in each test. Samples of dissolution media (5 ml) were withdrawn at predetermined intervals suitably diluted and assayed for ETS at 284 nm respectively. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. The dissolution experiments were conducted in triplicate. Drug percent dissolved at 10 min (DP10), values were calculated from the dissolution data given table 1.

3.12. Uniformity of drug content

Drug content of all batches of ETS thin films was determined by UV- spectrophotometric method. For this one strip of 4 cm2 was dissolved in 100ml of pH 6.8 buffer. Then the solution was suitably diluted and the absorbance was recorded at 240nm.

Five films from each formulation batch were picked randomly and were weighed individually. Each film was agitated in methanol for 24 hours and the mixture was suitably diluted to measure absorbance spectrophotometrically at 284 nm. The average drug content was calculated.

The uniformity of dosage units of the oral film preparation was tested using 10 preparations, and the content of Etoricoxib was determined by UV-spectrophotometry. The acceptance value (AV) of the preparation is less than 15%, according to the JP15.

While in USP27, the contents of preparations are between 85% and 115% and the relative standard deviation is less than or equal to
6.0%. AV for JP15 was calculated according to the following equation:

$AV = |M - X| + ks$

Where, *M* is label claim (100%), *X* the average (%) of individual contents, *k* the acceptability constant (2.2), and *s* is the standard deviation.

Table 1: different formulations of oral thin films of Etoricoxib.

INGREDIENTS	MF1	MF2	MF3	MF4	MF5	MF6
Etoricoxib (mg)	30	30	30	30	30	30
HPMC K_{15} (gm)	0.5	1	0.5	-	-	-
HPMC(ISCP) K_{15} (gm)	-	-	-	0.75	0.25	0.5
$Tween_{80}$ (ml)	0.5	0.5	0.5	0.5	0.5	0.5
PEG $_{6000}$ (gm)	0.1	0.15	0.15	0.1	0.1	0.1
Citric acids (gm)	0.1	-	0.1	0.1	0.1	0.1
Manitol (gm)	2	2	2	2	2	2
H_2O	q.s	q.s	q.s	q.s	q.s	q.s

3.13. Microscopic View

All Etoricoxib oral thin formulations are evaluated in the fluorescence microscope. In this study we can evaluate the particle size in the formulation. The fluorescence microscope was set on 30×10. Particles are arranged in the formulation are shown in the fig 6.

RESULT AND DISSCUSSION

Table 2: Evaluation for thickness, folding endurance, disintegration time, surface ph, % drug content, weight variation of Etoricoxib oral thin films formulation

FORMULATION	THICKNESS (MM)	Weight variation	Folding endurance	SURFACE pH	Swelling property	DISINTEGRATION TIME in vivo(SEC)	% DRUG CONTENT
MF1	0.59±0.012	0.13±0.03	57.67±2.52	3.67±0.15	1.41±0.02	24.67±0.58	98.33 ±0.15
MF2	0.96±0.01	0.14 ±0.01	71.67±2.89	4.14±0.15	1.44±0.05	14.67±0.58	96.80 ±0.10
MF3	0.59±0.01	0.11±0.04	67.67±2.52	3.84±0.31	1.45±0.02	10.34±0.58	98.16 ±0.25
MF4	0.86±0.01	0.14±0.02	52.34±2.52	3.7±0.20	0.69±0.51	12.34±0.58	99.16±0.11
MF5	0.73±0.01	0.16±0.02	39.67±1.52	4.27±0.21	0.96±0.01	18.34±0.58	98.33 ±0.15
MF6	1.09±0.01	0.14±0.01	105.34±2.52	4.07±0.15	1.17±0.02	29.67±0.58	99.46 ±0.15

Thickness

Table 5 gives the average thickness values of films of all the formulation. The thickness was found to vary between 0.59 to 1.09 mm. A very low standard deviation value is indicating that the method used for the formulation of films is reproducible and give films of uniform thickness and hence dosage accuracy in each film can be ensured. Average thicknesses of all films are shown in the Fig 1.

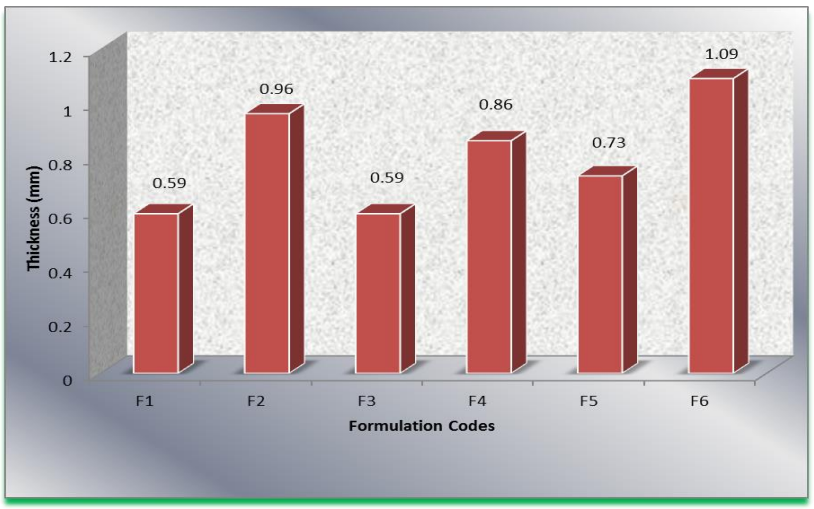

Figure 1: Comparative thickness of all the formulations.

Weight Variation

Table 5 gives the average weight variation values of films of all the formulations. The weight variation was found to vary between 0.11 to 0.16 gm. As per USP requirements, the formulations were found to meet the criteria for weight variation. Weight variation of the

product with low standard deviation indicates the reproducibility of the products. Average weight variations of all films are shown in the Fig 2.

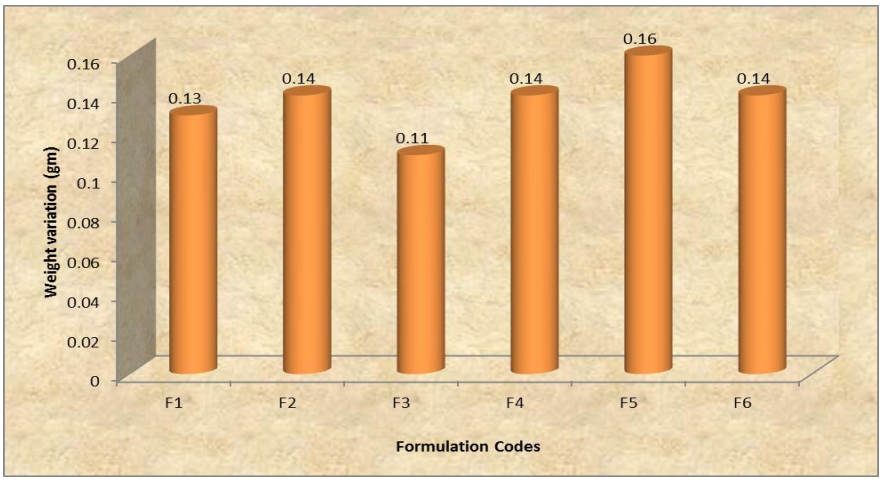

Figure 2: Comparative Weight Variation of all the formulations.

Folding endurance

Table 5 gives the folding endurance values of films of all the formulation. The folding endurance was found to vary between 39.67 to 105.34. Folding endurance indicate packaging conditions of the product. These allow the product safely transport without breakage of the product and also indicate the plasticity of the products. Average folding endurance of all films is shown in the Fig 3.

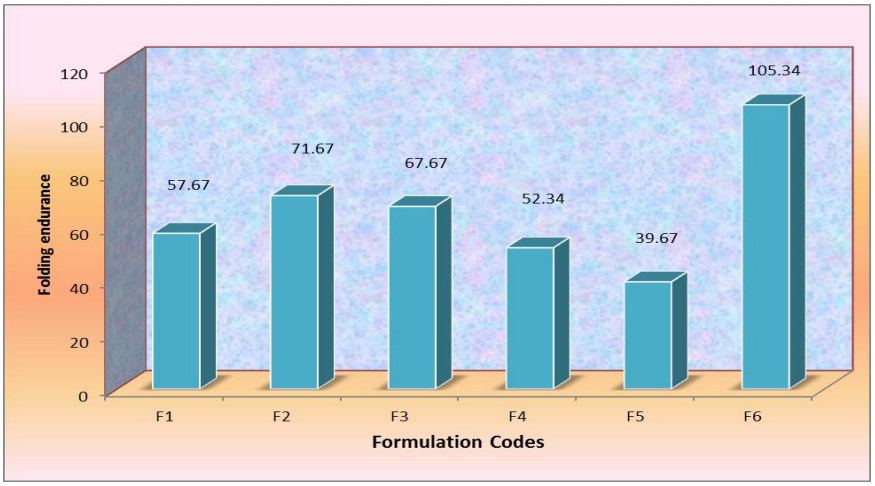

Figure 3: Comparative Folding endurance of all the formulations.

Surface PH

The surface pH of Etoricoxib fast dissolving oral thin films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause

irritation to 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 strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the film. Average surfaces PH ranging from 3.70 to 4.26. Average surfaces PH of all films are shown in the Fig 4.

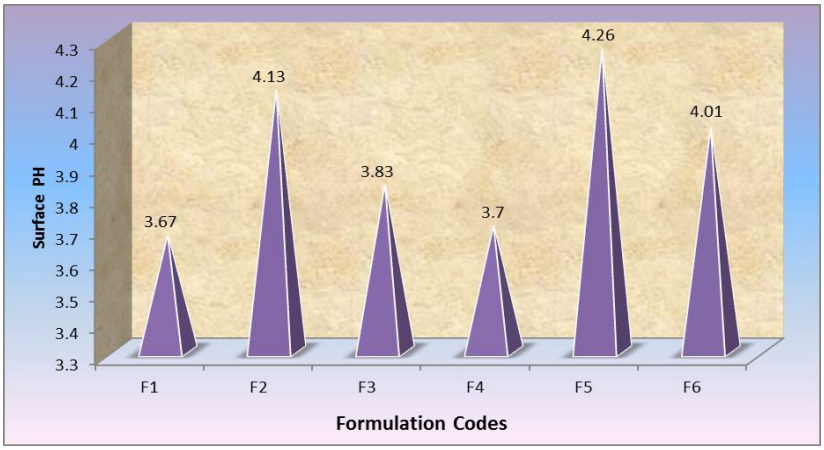

Figure 4: Comparative Surface PH of all the formulations.

Swelling property: Table 5 gives the average swelling property of films of all the formulation. The swelling property was found to vary ranging from 0.69 to 1.45. Swelling property of the formulations indicates how much moisture gain by the films. A very low standard deviation value is indicating that the method used for the formulation of films is reproducible.

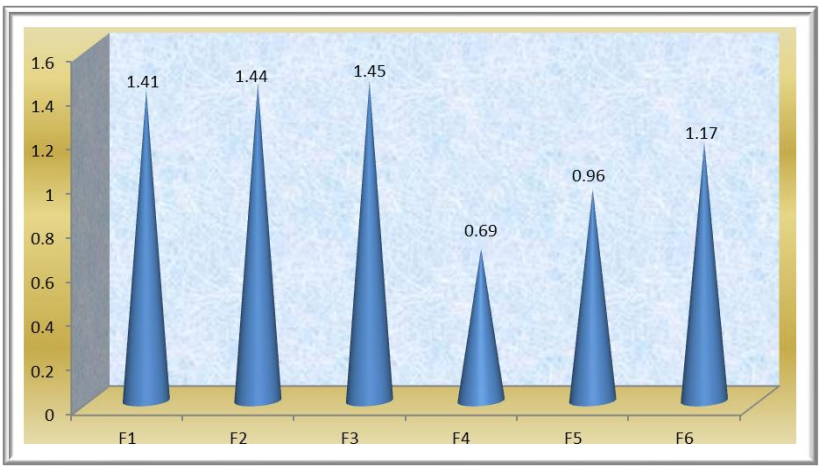

Figure 5: Comparative swelling property of all the formulations.

Microscopic View: All Etoricoxib oral thin formulations are evaluated in the fluorescence microscope. In this study we can evaluate the particle size in the formulation. The

fluorescence microscope was set on 30×10.Particles are arranged in the formulation are shown in the fig 6**.**

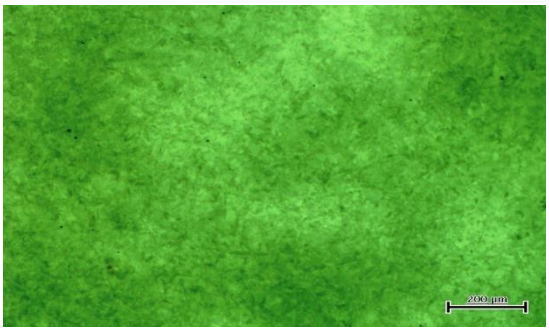

Fig: F-1

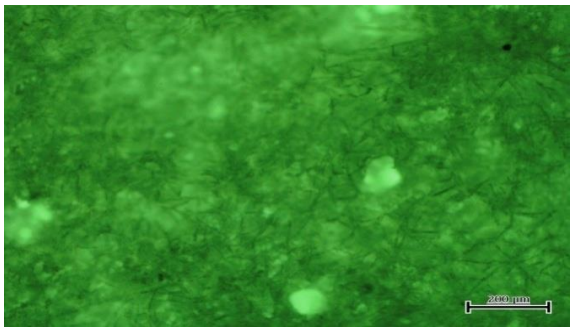

Fig: F-2

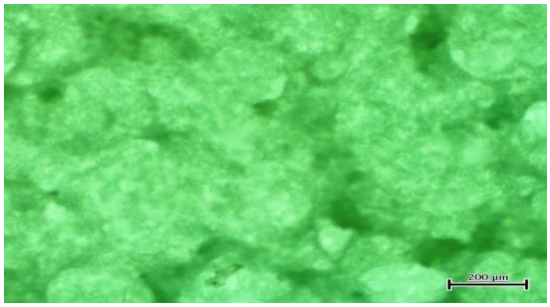

Fig: F-3

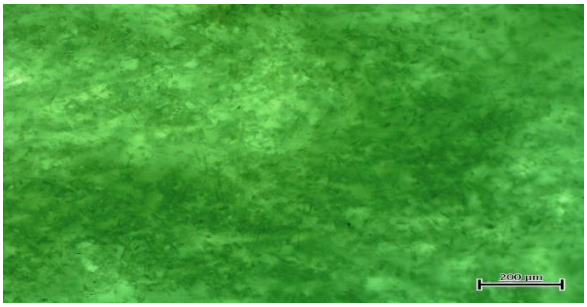

Fig: F-4

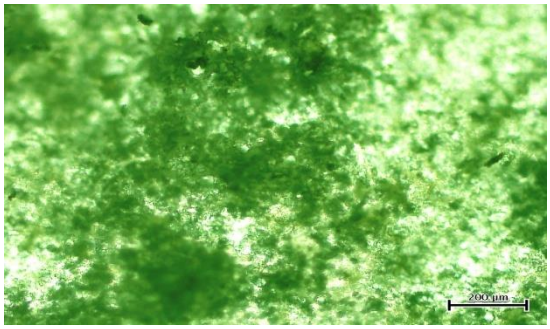

Fig: F-5

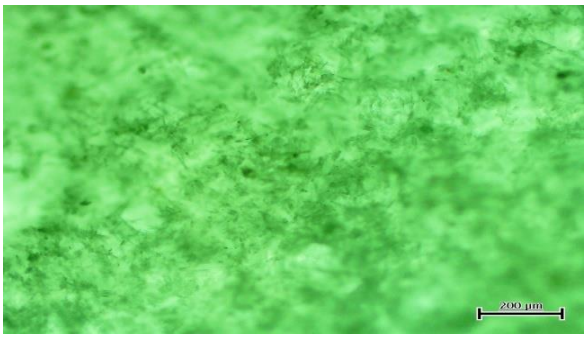

Fig: F-6

Figure 6: Comparative microscopic view of all the formulations.

Disintegration test in vivo

Table 5 gives the average Disintegration test in vivo of films of all the formulation. The Disintegration test in vivo was found to vary ranging from 10.34 to 29.67. Disintegration test in vivo of the formulations indicates how quickly particles are separated by the films into the solution. A very low standard deviation value is indicating that the method used for the formulation of films is reproducible.

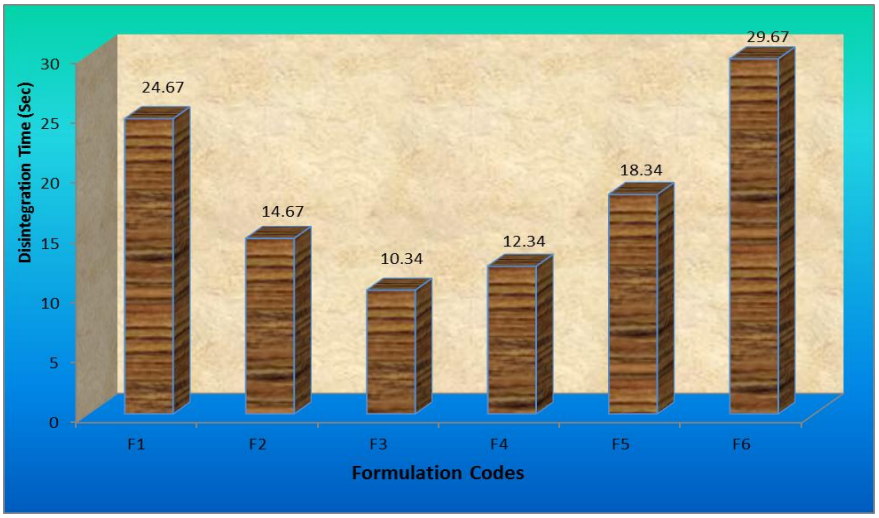

Figure 7: Comparative disintegration times of all the formulations.

% drugs Content

All formulations are meet USP requirements among them F3, F4, F5 shows significant results. These formulations releases maximum drug within 10-24 sec. Shows fig-8.

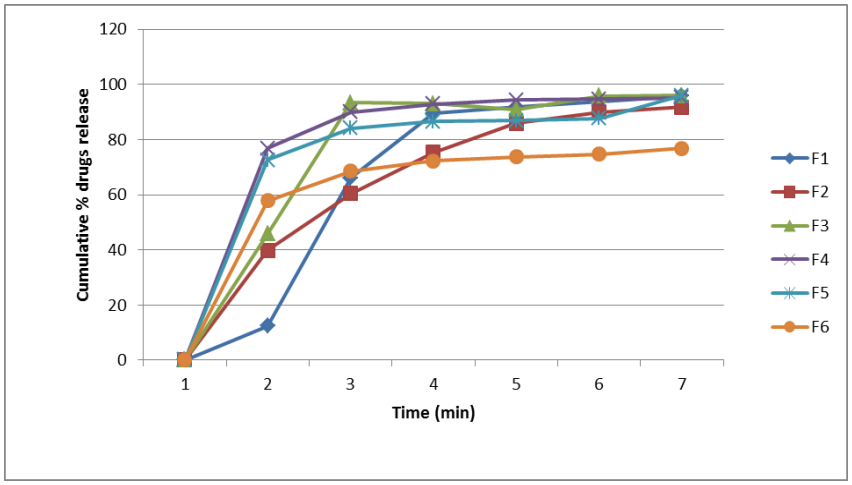

Figure 8: Comparative % drugs release of all the formulations.

CONCLUSIONS

It can be concluded that oral fast disintegrating thin films of Etoricoxib, an analgesic agent can be formulated using HPMC as a film forming material such as Tween 80 as an emulsifier and PEG 6000 as a plasticizer. Formulation variables like amount of HPMC, amount of plasticizer and amount of emulsifier were found to influence thickness, folding endurance, disintegration time and in vitro dissolution of the films. Prepared films were found to be thin and fast. These formulations are meets all requirements according to USP.

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