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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF MELOXICAM

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ABSTRACT

Meloxicam is a newer preferantionalCOX-1 inhibitor, has been used to relieve the symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component. The present work aimed at preparing oral fast quick onset of action, which is very convenient for administration, without the problem of swallowing and using water. Oral fast dissolving films of Meloxicam were prepared using HPMC (E5, E15) polymers as film forming agents and PEG 400 as plasticizerby solvent casting method. FTIR showed that there is no interaction between drug and excipients. Dissolution of prepared fast dissolving oral films of Meloxicam was performed using USP type II apparatus in pH 6.8 phosphate buffer medium at 50 rpm with temperature being maintained at 37±0.5ºC. The films prepared were evaluated for various parameters like thickness, percent elongation, drug content uniformity, weight variation, disintegration time, folding endurance and *in vitro* drug release and were showed satisfactory results. In conclusion, development of fast dissolving oral films using HPMC E5 300 polymer gives rapid drug delivery and rapid onset of action.

KEYWORDS: Meloxicam, Oral fast dissolving films.

1. INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with

many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.

So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional or solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to water to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues exploredfor the rapid drug releasing products, oral strip technology is gaining much attention.Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simplyplaced on the patient's tongue or any oral mucosal tissue,instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for or mucosal and intragastric absorption.

Overview of oral cavity

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.

• Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).

• Oral cavity proper, which extends from teeth and gums back to the fauces(which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

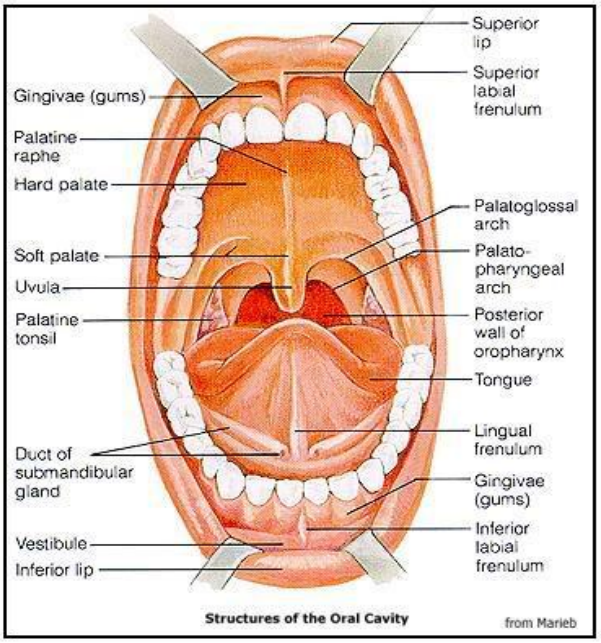


Figure1-1.Structure of Oral cavity.

The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein.

Classification of fast dissolving films

For ease of description, fast-dissolve technologies can be divided in to three broad groups

a) Lyophilized systems.

b) Compressed tablet-based systems.

c) Oral fast dissolving films.

a) The lyophilized systems

This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and through the use of a mould or blister pack, forming tablet shaped units. The units or tablets are then frozen and lyophilized in the pack or mould.

b) Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different

levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard blisters through to more specialist pack designs for product protection. CIMA Labs, PackSolv, for example. The speed of disintegration for fast dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients or super disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet.

c) Oral Fast Dissolving Films (OFDF)

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OFDF formats. Today, OFDFs are a proven and accepted technology for the systemic delivery of APIs for over the counter (OTC) medications and are in the early to mid development stages for prescription drugs.

Formulation considerations

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent
- Flavoring agent
- Coloring agent

Method of preparation

One or more of the following process can be used to manufacture the mouth dissolving films.

- Semisolid casting.
- Solvent casting.
- Hot melt extrusion.

- Solid dispersion extrusion.
- Rolling method.

Semisolid casting

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In Semisolid casting method gel mass is casted in to the films or ribbons using heat controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

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.

Water or suitable solvent

↓

Add polymer

↓

Viscous solution formed on stirring

↓

Add plasticizer

↓

Add other excipients

↓

Add API and keep for stirring

↓

Final film solution

↓

Degassed keeping in sonicator

↓

Casted into petriplate

↓

Dried in oven

↓

Film is cut into desired shape and size

Figure 2: Preparation process flow chart.

Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures should be 80ºC (zone 1), 115ºC(zone 2), 100ºC (zone 3)and 65ºC(zone 4). The extrudate (T = 65ºC) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion.

-Fewer operation units

-Better content uniformity

-An anhydrous process

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.

Rolling Method

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.

Packing

A variety of packaging options are available for fast dissolving films. In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the mouth dissolving films. The Rapid Card is exactly the same size as a credit card and holds three mouth dissolving films on each side.

The material selected must have the following characteristics

- They must protect the preparation from environment conditions.
- They must be FDA approved.
- They must be non-toxic.
- They must not be reactive with the product.

- They must not impart to product tasted or odors.
- They must meet applicable tamper-resistant requirement.

WAFERTAB™: is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth.

The WAFERTAB™ filmstrip can be flavored for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty swallowing.

FOAMBURST™: is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavors.

XGEL™: film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products it is non animal derived, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform.

General taste masking practices in oral pharmaceuticals

Various techniques available for masking bitter taste of drugs include taste masking with ingredients such as flavours, sweeteners, and amino acids; taste masking by polymer coating; taste masking by conventional granulation; taste masking with ion-exchange resins; taste masking by spray congealing with lipids; taste masking by formation of inclusion complexes with cyclo dextrins; taste masking by the freeze-drying process; taste masking by making

multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

2. PLAN OF WORK

The experimental work consist of,

1. Selection and collection of drug and excipients
2. Drug and polymer interaction studies by FTIR.
3. Construction of calibration curve of Meloxicam
4. Formulations of Meloxicam oral films with different polymers
5. Prepare a thin Meloxicam films
6. Physicochemical evaluation of films of Meloxicam

- Surface pH
- Swelling percentage.
- Thickness.
- Weight of films.
- Percentage elongation
- Tensile strength
- Folding endurance.
- Drug content estimation (assay).

7. *In-vitro* drug release studies by dissolution apparatus
8. *In-vitro* disintegration by disintegration apparatus.

3. LITERATURE REVIEW

Minako Nishigaki*et al.*, 2012, fast dissolving oral film were developed containing 4 mg dexamethasone and examined the clinical effect of the film as the antiemetic by a randomized controlled crossover study in breast cancer patients receiving a combination chemotherapy with anthracycline and cyclophosphamide, a highly emetogenic chemotherapy. The film was prepared using microcrystalline cellulose, polyethylene glycol, hypromellose, polysorbate 80 and 5% low substituted hydroxyl propylcellulose as base materials. The uniformity of the film was shown by the relative standard deviation of 2.7% and acceptance value of 5.9% by the Japanese Pharmacopoeia. Patients were administered with 8 mg dexamethasone as oral film or tablet on days 2–4 after chemotherapy in addition to the standard antiemetic medication. The rates of complete protection from vomiting during acute and delayed phases were not different between film-treated group and tablet-treated group. The time course of the

complete protection from nausea or vomiting during 0–120 h was also similar between the two groups. Patient's impressions on the oral acceptability in respect of the taste and ease in taking were significantly better for film than for tablet. Therefore, the present fast dissolving oral film containing dexamethasone seems to be potentially useful as an antiemetic agent in patients receiving highly emetogenic chemotherapy..

Bhupinder Bhyan*et al.*, 2011, Orally fast dissolving films (OFDFs) were developed which provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers, so OFDFs are gaining the interest of large number of pharmaceutical industries. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postagestamp in their shape, size and thickness. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of do singmedication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population.

Manish Kumar *et al.*, 2011,Ofloxacin films were developed to treat periodontitis infections. For local delivery, ofloxacin films were prepared by solvent casting technique using ethyl cellulose, hydroxy propyl methylcellulose and eudrag it RL-100 with dibutylphthalate and polyethylene glycol 400 as plasticizers. FTIR and UV spectroscopic methods revealed no interaction between ofloxacin and polymers. The films were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, tensile strength, and surface pH.

Sandeep Saini*et al.*, 2011, Fast dissolving films of levocetrizinedihydrochloride were developed by solvent casting method by using Maltodextrin& HPMC E15as the main film forming polymers. To decrease the disintegration time, concentration of maltodextrin & HPMC E15 were optimized using factorial design. Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Compatibility between drug and excipients were studied by means of DSC analysis.

Seema Saini*et al.*, 2011, were optimized the formulation of fast dissolving films made of pullulan polymer. The films formed from solvent casting method and subsequent evaporation of solvent resulted in pullulan forming a circular film. Pullulan was used as film forming agent due to excellent film forming property. PEG, propylene glycol, glycerin were used as plasticizers. Increasing pullulan concentration in formulation resulted in thick films as compared to lower. Thickness of the film was controlled by adjusting the concentration of polymer. Higher concentration of polymer and plasticizer results in increase in-vitro disintegration time and in-vitro dissolution time of films. PEG forms white colored films i.e. translucent films. Films containing glycerin takes longer time to dry than films containing propylene glycol. Lower concentration of pullulan and propylene glycol showed optimum performances.

Prasanthi N. L*et al.*, 2011, were developed a novel fast dissolving drug delivery system for an antiasthamtic drug such as Salbutamol suphate. The fast dissolving films were prepared by solvent evaporation technique using different water-soluble polymers (hydroxy propyl methylcellulose, hydroxy propyl cellulose and Sodium Alginate).In this study Tween 80 is used as a solubilizing agent and Aspartame is used as a sweetener. Concentration of water soluble polymers, Tween 80 and Aspartame were optimized during preliminary studies. The prepared films were evaluated for thickness, uniformity in drug content, folding endurance, disintegration time, swelling index, moisture loss, in-vitro drug release studies and drug-polymer compatibility studies. The results obtained showed no physical chemical incompatibility between the drug and the polymers. The prepared films were clear, transparent and smooth surface.

Sumitha Ch*et al.*, 2011, oral films of Seldinafil citratewere developed using Hydroxypropylmethylcellulose (HPMC E-5). Films of HPMC E-5 were prepared by film casting method. Polacriline potassium, an ion exchange resin was used to mask the bitter taste of the drug by forming a complex with the drug, although the exact mechanism is yet to be determined. Glycerol, menthol and sucralose were incorporated in the drug containing films as plasticizer, cooling agent and sweetener, respectively. The drug loading was 8mg Seldinafil citrate per 4×2.5 cm^2 of the film. The films were evaluated for hydration study, folding endurance and in-vitro drug dissolution in the distilled water. The films containing HPMC E-5 showed neutral surface pH when prepared using 0.1 N HCl as a solvent. Glycerol played a critical role in imparting flexibility to the film and improving the drug release from

film. The bitter taste of the drug was masked by using Polacriline potassium and menthol accompanied by the synergistic effect of glycerol.

Lucas Sievens-Figueroa*et al.*, 2011, developed a simple process of incorporating stable nanoparticles into edible polymer films is demonstrated with the goal of enhancing the dissolution rate of poorly water soluble drugs. Nano suspensions produced from wet stirred media milling (WSMM) were transformed into polymer films containing drug nanoparticles by mixing with a low molecular weight hydroxylpropyl methyl cellulose (HPMC E15LV) solution containing glycerin followed by film casting and drying. Three different BCS Class II drugs, naproxen (NPX), fenofibrate (FNB) and griseofulvin (GF) were studied. Differences in aggregation behavior of APIs in films were observed through SEM and NIR chemical imaging analysis. NPX exhibited the strongest aggregation compared to the other drugs. The aggregation had a direct effect on drug content uniformity in the film. Mechanical properties of the film were also affected depending on the drug–polymer interaction.

4. MATERIALS AND METHODS

Sl.No	List of Materials	Suppliers
1.	Meloxicam	SURA labs, AP, India.
2.	HPMC E15	Qualikems, Gujarath, India.
3.	HPMC E5	Qualikems, Gujarath, India.
4.	Methanol	S.d.fine chem. Ltd, Mumbai, India.
5.	PEG-400	S.d.fine chem. Ltd, Mumbai, India.
6.	Glycerin	S.d.fine chem. Ltd, Mumbai, India.
7.	Aspartame	S.d.fine chem. Ltd, Mumbai, India
8.	Ascorbic acid	Universal laboratories pvt ltd, Mumbai.

Drug profile

Meloxicam

Synonyms: Meloxicam.

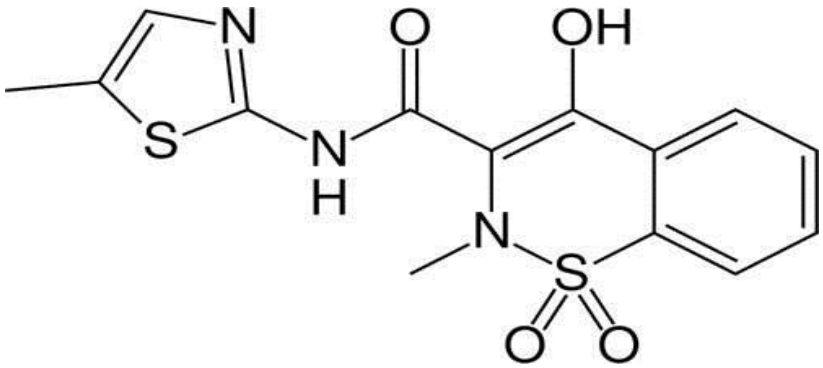
Proprietary names: Meloxicam.

Brand names: Mobic, Mobicox, Movalis, Novo-meloxicam, Movatec.

IUPAC name: 4-hydroxy, 2-methyl- N(5-methyl,1,3-thiazol-2yl) 2H-1,2- Benzothiazin, 3-Carboxamide,1,1-dioxide

Chemical Formula:$C_{14}H_{13}N_3O_4S_2$

Molecular structure



Structure of Meloxicam

Molecular Weight: 351.401

Drug category

- Anti-neoplastic agent
- Anti emetics
- Analgesics
- Growth Inhibitors
- Non-steroidal Anti-inflammatory Agents (NSAIAs)

Log P **:** 3.43

Solubility **:** water solublity- 7.15 mg/ml

Melting point **:** 254°C

Bio availability **:** 89%

Dose **:** 7.5mg, 15mg.

Protein binding **:** 99.4% bound, primarily to albumin

Half life **:** 15-20 hours

Volume of distribution **:** 10 L

Toxicity **:** LD_{50}, Acute: 84 mg/kg (Rat); Oral 470 mg/kg (Mouse); Oral 320 mg/kg (Rabbit)

Mechanism of action

Anti-inflammatory effects of meloxicam are believed to be due to inhibition of prostaglandin synthetase (cylooxygenase), leading to the inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis may be associated with the analgesic and antipyretic effects of meloxicam.

Excipients profile

Hydroxy propyl methyl cellulose

Nonproprietary Names

BP: Hypromellose

PhEur: Hypromellosum

USP: Hypromellose

Synonyms: Metolose, Hydroxy propyl methyl cellulose, HPMC, Methocel, methyl hydroxylpropyl cellulose, Metolose, Tylopur.

Chemical Name: Cellulose hydroxyl propyl methyl ether.

Molecular Weight: Approximately 10000-1500000.

METHODOLOGY

I. Preformulation studies for pure drug

1. Solubility
2. Determination of pH
3. Moisture content
4. Melting point
5. Drug polymer compatibility studies.

Preformulation studies

Solubility

The solubility of a drug may be expressed in number of ways. The U.S. pharmacopoeia and national formularies list the solubility of the drugs as the number of milliliters of solvent in which 1 gram of solute will dissolve, For substance whose solubility are not definitely known, the values are described in the pharmaceutical compendia by the use of certain general terms. One gm of Meloxicam was dispersed in the solvent and based on the following table solubility was determined. The solubility of the drug was determined in water, ethanol, methanol, chloroform and acetone.

Table No.1 Terms of approximate solubility.

Term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1 parts
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts

Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble or insoluble	More than 10,000 parts

Determination of pH

pH of the drug solution was tested by using previously calibrated pH meter. 4 % w/v solution of Meloxicamwas prepared using methanol as a solvent and sonicated for 30 minutes. The glass electrode of the pH meter was immersed in the prepared solution and the pH of the solution was recorded.

Moisture content

The moisture content was determined using sartorious moisture determining apparatus. Fivegm of the Meloxicamwas transferred to an aluminium plate and the moisture content was determined at 105^{0} C.

Melting point

Melting point of the drug was determined by using Scientek digital melting point apparatus.

Drug –Polymer compatibility studies by FT-IR

Drug polymer compatibility studies were performed by FT-IR(Fouriertransform infrared spectroscopy).In order to confirm that the entrapment of drug within the polymeric systemsinvolve only the physical process and no interaction between drug and polymer. FTIRabsorption spectra of pure drug and all the polymers used like HPMC, PVA andthe combination of drug and polymers were shows no significant interaction between drug and polymers.

Selection of the drug

- The Meloxicamwhich has significantly different pharmacokinetic profiles when compared with the same dose administered in a conventional dosage form.
- Meloxicamhas been used to relieve the symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component.
- Meloxicamwas insoluble in water but soluble in solvents.
- Meloxicam was stable at salivary pH.

Construction of calibration curvefor Meloxicam

Determinationofλmax

Meloxicamλmax was determined by spectrophotometer using pH 6.8 buffer medium.First dissolve 10mg of pure drug in 10ml of 6.8 buffer medium. From this 10µg/ml solution was prepared by using 6.8 buffer. 10µg/ml solution absorbance was measured at 200-400nm range by spectrophotometrically using 6.8 buffer as reference solution.

Preparation of calibration curve

1. **Primary stock solution:** Standard calibration curve of meloxicamin 6.8 buffer were prepared. First dissolve 10mg of pure drug in 10ml of 6.8 buffer this is primary stock solution.
2. **Second stock solution:**From the above primary stock solution pipette out 1ml of solution and again make up to 10ml this is secondary stock solution. From this secondary stock solution different concentrations of meloxicam (2, 4, 6, 8,10 and 12µg/ml) in 6.8 buffer were prepared and absorbance of these solutions measured at 359nm by spectrophotometricallyusing 6.8 buffer as reference solution.

Calculation of dose for meloxicam

The dose of meloxicam is 7.5mg. Therefore amount of meloxicamrequired in 1cm x 1cm square film is 7.5mg.

Area of petriplate=πr^2

=3.14 x 2.4 x 2.4 (petriplate diameter 4.8cm)

=18.08cm^2

Number of patches = Area of petriplate/size of the square film

= 18.08/2

= 9.04

Total amount of the drug = Number of patches x Dose

= 9.04 x 7.5

= 67.8mg

Therefore, 18.08cm^2 of petriplate should contain 67.8mg of drug. It is fixed for all formulations.

III. Preparation of mouth dissolving films

General method of formulation of oral dissolving films

Following processes are generally used to manufacture the mouth dissolving film.

1. Solvent casting[Bhupinderbhyan*et al.*, (2011)]
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

The current preferred manufacturing process for making this film is solvent casting method. In this method water soluble polymer is dissolved in suitable solvent to make homogenous viscous solution. In this other excipients (plasticizer and sweetner) including drug resinate complex were dissolved under stirring. Then the solution is degassed by keeping it in the sonicator. The resulting bubble free solution poured into petriplate and was kept in oven. Dried film is then cut into the desired shape and size for the intended application.

Preparation of blank films using different polymers

Procedure

- Accurately weighed quantity of polymer was dissolved in specific quantity of water.
- The dissolved polymer was made to a uniform dispersion using a homogenizer.
- During stirring other excipients (plasticizer and sweetner) were added.
- Then the solution is degassed by keeping it in the Sonicator.
- The bubble free solution poured into petriplate and was kept in oven.
- Then the dried films were used to select the best film forming polymers.

Selection of best film forming polymer

The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Film obtained should be tough enough to avoid the damage while handling or during transportation.

Different Polymers Used For Trails

- Hydroxy propyl methyl cellulose (HPMC) E5.
- Hydroxy propyl methyl cellulose (HPMC) E15.

Preparation of oral fast dissolving film

The fast dissolving films of meloxicam were prepared by solvent castingtechnique. The fast dissolving films were prepared using different polymers like HPMC(E5 and E15). Polyethelene glycol-400(PEG400) was used as plasticizer. The calculated amount of polymer was dispersed in the solvent with continuous stirring using magnetic stirrer and the homogenous solution is formed. Then add 6 drops of plasticizer. Then the sweetner and flavor was added to drug mixed polymeric solution. Then the solution was kept in sonicator for degassing. Then the bubble free solution was casted on to petriplate and was kept in hot air oven. Dried film is then cut into the desired shape and size (1cm x 1cm) for the intended application. By carrying out the trial and error method different quantity of film forming polymers were used for optimizing the formulation[Kulakarni A.S., Deokule H.A *et al.*,(2010)].

Formulation of Meloxicam oral fast dissolving films

Table No.2 Composition of Meloxicam oral dissolving films.

CODE	DRUG (mg)	HPMC E5 (mg)	HPMC E15 (mg)	PEG-400 (drops)	WATER (ml)	1N NAOH (ml)	METHANOL (ml)	ASPARTAME (mg)	ASCORBIC ACID (mg)
F1	67.8	-	250	6	5	1	2	25	5
F2	67.8	-	300	6	5	1	2	25	5
F3	67.8	-	400	6	5	1	2	25	5
F4	67.8	-	500	6	5	1	2	25	5
F5	67.8	-	600	6	5	1	2	25	5
F6	67.8	300	-	6	5	1	2	25	5
F7	67.8	400	-	6	5	1	2	25	5
F8	67.8	500	-	6	5	1	2	25	5
F9	67.8	600	-	6	5	1	2	25	5

Evaluation of fast dissolving films

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. The thickness was measured at three different spots of the films and average was taken[1].

Dryness/Tack test

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films, most of the

studies can be adapted intricately to evaluate pharmaceutical orally fast dissolving film. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are available for this study.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.

Tensile strength = Load at breakage/ Strip thickness × Strip Width

The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula.

Tensile stress = applied force/ cross sectional area =m × g/ b × t

Where, S = tensile stress in 980 dynes/cm2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm2)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

The strain is change resulting in size of strip after the force was applied to its original size. Therefore, the strain can be given as,

Strain (E) = total elongation / original length = $L-L_o/ L_o$

Where, L = length after force was applied

L0 = original length

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.

% Elongation = Increase in length ×100 / Original length

The percent elongation at break was measured by formula given below.

Strain (E) = total elongation / original length × 100

= L-Lo/ Lo × 100

Where, L = length after force was applied,

Lo = original length

Young's Modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the "**s".**Hard and brittle strips demonstrate a high tensile strength and young's modulus with small elongation.

Tearresistance Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51mm (2 in)/min is employed and is designed to measure the force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in ewton‟s (or pounds-force).

Folding endurance

Folding endurance is determined by repeated folding ofthe strip at the same place till the strip breaks. Thenumber of times the film is folded without breaking iscomputed as the folding endurance value.

Weight uniformity of films

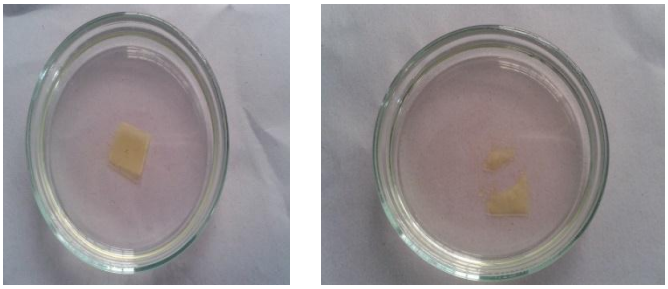
Film (size of 1 cm^2) was taken from different areas of film. The weight variation of each film is calculated.

Drug Content uniformity or Assay of film

The films were tested for drug content uniformity by UV Spectrophotometrical method. Films of 1cm x 1cm square size were cut from three different places from the casted films. Each patch was placed in 10 ml volumetric flask and dissolved in 6.8 phosphate buffer.The absorbance of the solution was measured at 359nm using UV/visible spectrophotometer.The percentage drug content was determined using the standard graph and the same procedure was repeated for all the formulations.

***Invitro*Disintegration time**

The *invitro*disintegration time of fast dissolving films was determined visually in a glass dish of 8 ml 6.8 pH phosphate buffer with swirling action.The disintegration time is the time when a film starts to break or disintegrate. The *invitro*disintegration time was calculated for different patches of the same film and average value was taken.



Initial Time **Disintegrated Film**

Figure 3: Disintegration of the film.

***Invitro* Dissolution Study**

*Invitro*dissolution of meloxicam oral dissolving films wasstudied in paddle type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used asdissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature ofdissolution medium was maintained at 37±0.5ºC throughout the experiment.Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analysed for drug release by measuring the absorbance at 359nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage drug release was calculated and plotted against time.

5. RESULTS AND DISCUSSION

I) Preformulation studies

The following are the results for preformulation studies performed for Meloxicam.

a) Solubility

Meloxicam is insoluble in water. Slightly soluble in methanol but Freely soluble in mixed solvents 1N Sodium hydroxide(1N NAOH) solution and methanol.

b) Determination of pH

Meloxicam 4% W/V solution in methanol showed pH of 4.68.

c) Moisture content

Moisture content of Meloxicam was found to be 0 .39 %.

d) Melting point

Melting point of the Meloxicam was found to be 254°c.

II) Analytical method development for Meloxicam

a) Construction of calibration curve

λmax determination

Meloxicam λ max was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 10mg of pure drug in 10ml of 6.8 buffer medium. From this 10µg/ml solution was prepared by using 6.8 buffer. 10µg/ml solution absorbance was scanned at 200 to 400nm range by spectrophotometrically using 6.8 buffer as reference solution and λ max was observed at 359nm.A standard graph of pure drug in suitable medium was prepared by plotting the concentration (µg/ml)on X-axis and absorbance on Y-axis. An excellent correlationco-efficient (R2=0.9976) was observed.

Table No.3 Calibration curve values of meloxicam in phosphate buffer pH 6.8 at λ max =359nm.

Concentration (µg/ml)	Absorbance (A.M ±S.D) λ max =359nm (n= 3)
0	0
2	0.156±0.154
4	0.290±0.239
6	0.454±0.122
8	0.611±0.187
10	0.740±0.234
12	0.854±0.176

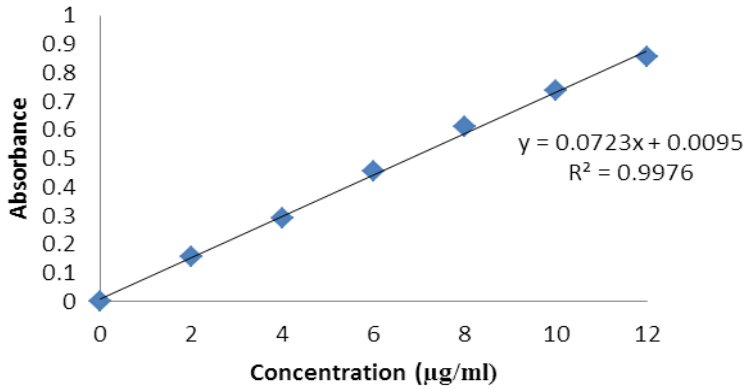


Figure 4: Calibration curve of Meloxicam in pH 6.8 phosphate buffer at λ max =359nm.

III) Drug-excipient compatibility (FTIR studies)

IR spectral analysis was carried out using FT-IR by the KBr disc method and the results showed that there were no interactions between drug and excipients.

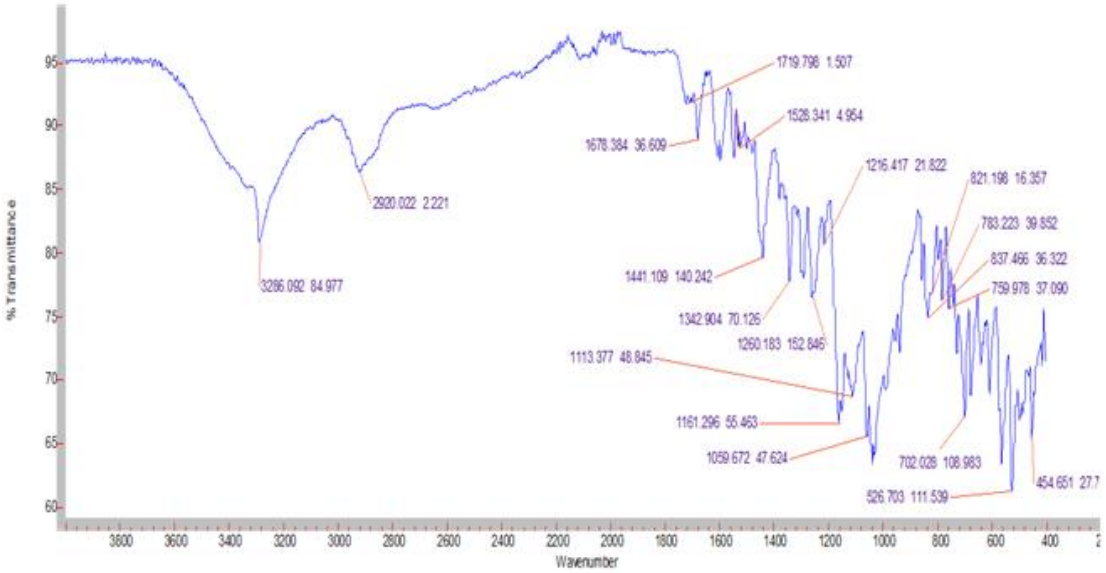


Figure 5: Ftir spectra of Meloxicam.

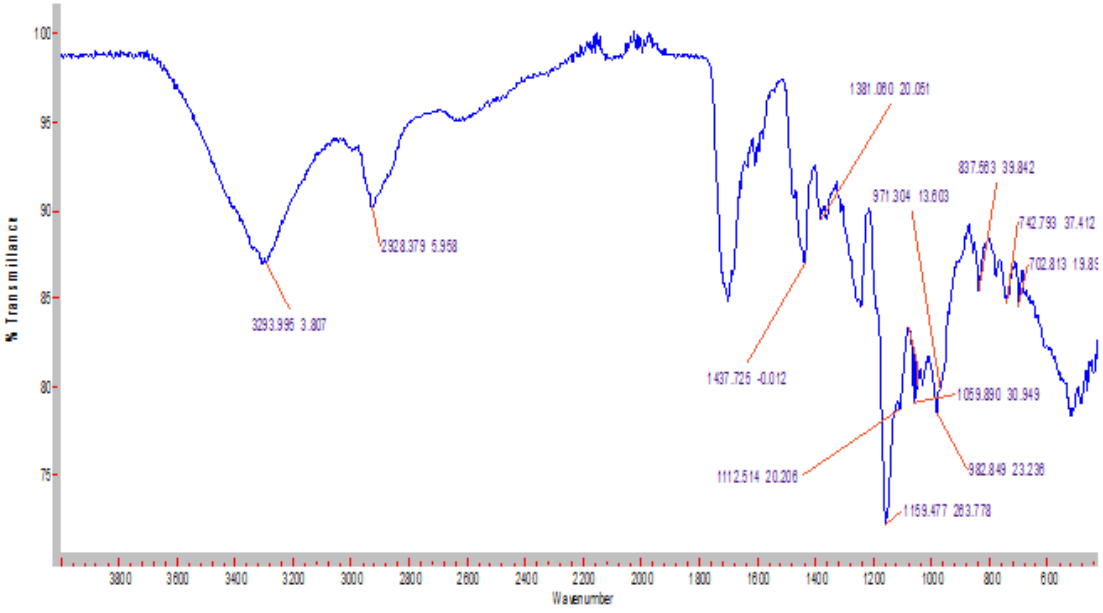


Figure 6 FTIR Spectra of HPMC E5

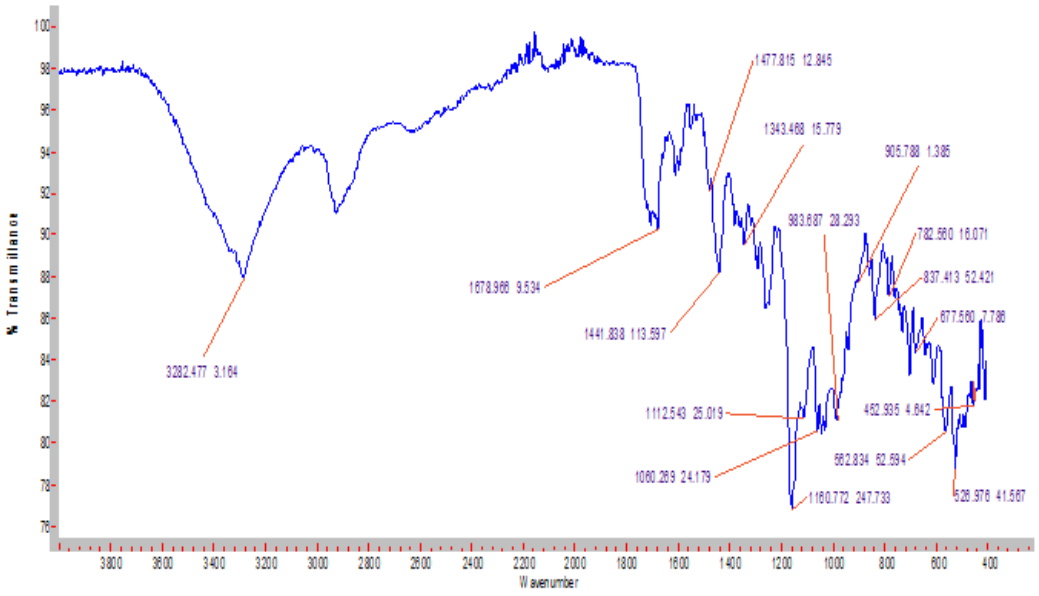


Figure 7: FTIR Spectra of MELOXICAM +HPMC E5.

FT-IR spectroscopy was employed to ascertain the compatibility of Meloxicam with polymers. The individual drug and drug with polymers were separately scanned. Both the spectra were compared for confirmation of common peaks. Meloxicam with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. Hence, it can be concluded that the drug is in free state and can release easily from the formulation the spectra are reported.

IV) Evaluation of fast dissolving films

Oral fast dissolving films were evaluated for the following parameters.

Meloxicam oral fast dissolving films were evaluated for

1) Weight Variation
2) Thickness
3) Tensile strength
4) Percent elongation
5) Folding endurance
6) Disintegration time
7) Content uniformity
8) *Invitro*dissolution studies

Weight Variation

Five films of meloxicameach of 2x2 cm^2 size were cut at five different places from casted films and weight variation was measured. Weight variation varies according to official limits. The results of weight variation are shown in the table 6-2.

Thickness

The thickness of the drug loaded films was measured with screwguage. The results of thickness are shown in the table 6-2.

Tensile strength& Percent elongation

Tensile strength of the film was determined with digital tensile tester. The film of specific size 3 inch x 10 mm was taken for the test. From the results it is clear that as the concentration of polymer increases the tensile strength of the film also increases. The formulation f6 showsthe maximum tensile strength, percent elongation and folding endurance. This might be formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. The results of Tensile strength & Percent elongation of the film was mentioned in the table 6-3.

Folding endurance

Folding endurance was measured manually. A strip of 2cm^2 was cut and subjected for this study. As the concentration of polymer increases folding endurance of the film also increases. The results of folding endurance of the film was mentioned in the table 6-3

Disintegration Time

Disintegration test was performed in the USP disintegration testing apparatus. Phosphate buffer of pH 6.8 was used as medium. The films were placed in the tubes of the container and the disks were placed over it. Disintegration time of the films was found to be increased with increase in the concentration of the polymer. The results are reported in the table 6-2.

Drug Content Uniformity

The prepared formulations were analyzed for drug content and it was observed that all the formulations found to contain almost uniform quantity of drug. The results are reported in the table 6-2.

***In- Vitro*-dissolution studies**

Dissolution profiles from films of meloxicam were carried out in USP dissolution apparatus-II. The results are reported in the table.

Table No.4 Physical evaluation parameters of all formulations.

Formulation Code	Thickness (mm)	Weight variation (mg)	Disintegration time (sec)	Drug content (%)
F1	0.137±0.12	29.21±0.56	18±0.93	99.66±0.92
F2	0.139±0.24	29.40±0.67	20±1.26	98.34±0.82
F3	0.142±0.17	30.33±1.60	21±1.29	100.66±0.43
F4	0.143±0.21	31.07±0.49	24±0.78	98.33±0.32
F5	0.150±0.22	32.86±0.59	31±0.98	97.80±0.87
F6	0.127±0.14	29.43±0.51	14±1.98	99.97±1.23
F7	0.131±0.19	30.33±0.44	18±2.12	98.09±1.78
F8	0.136±0.14	32.80±0.59	20±0.87	97.93±0.94
F9	0.142±0.19	33.41±0.62	28±0.98	99.76±0.76

Data represents Mean ±S.D, n =3

Table No.5: Mechanical properties of all formulations.

Formulation Code	Tensile strength(kg)	% Elongation	Folding Endurance
F1	1.159±0.05	22.56±0.12	95.3±9.87
F2	1.396±0.07	22.76±0.32	106.0±4.56
F3	1.436±0.10	23.63±0.21	133.2±6.45
F4	1.466±0.12	24.05±1.02	131.0±5.29
F5	1.595±0.22	25.46±0.93	134.6±5.37
F6	1.465±0.02	23.45±0.32	123.0±7.67
F7	1.495±0.08	26.63±1.34	128.3±6.45
F8	1.519±0.43	27.54±0.45	130.5±5.29
F9	1.565±0.87	29.65±0.23	132.6±8.12

Data represents Mean ±S.D, n =3

***Invitro* Dissolution Studies**

*Invitro*dissolution of Meloxicam oral dissolving films wasstudied in paddle type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used asdissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature ofdissolution medium was maintained at 37±0.5ºC throughout the experimentSamples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre filter at known intervals of time and analyzed for drug release by measuring the absorbance at 359nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.Cumulative percent of Meloxicam release was calculated and plotted against time.

Table 6: *In vitro*drug releases for F1 to F5 formulations.

Time (min)	(%) Cumulative drug release				
	F1	F2	F3	F4	F5
2	76.59±1.45	73.07±2.32	72.05±1.76	70.99±2.29	68.70±1.44
4	81.27±0.67	79.41±0.46	77.82±1.41	77.69±2.66	72.02±1.76
6	86.02±1.36	88.34±1.66	83.25±1.25	82.90±0.43	78.81±2.24
8	93.21±0.66	92.10±0.76	90.60±2.61	87.21±0.71	85.46±2.18
10	98.12±2.2	96.36±.1.12	97.13±2.17	95.55±1.99	94.97±1.38

Data represents Mean ±S.D, n =3

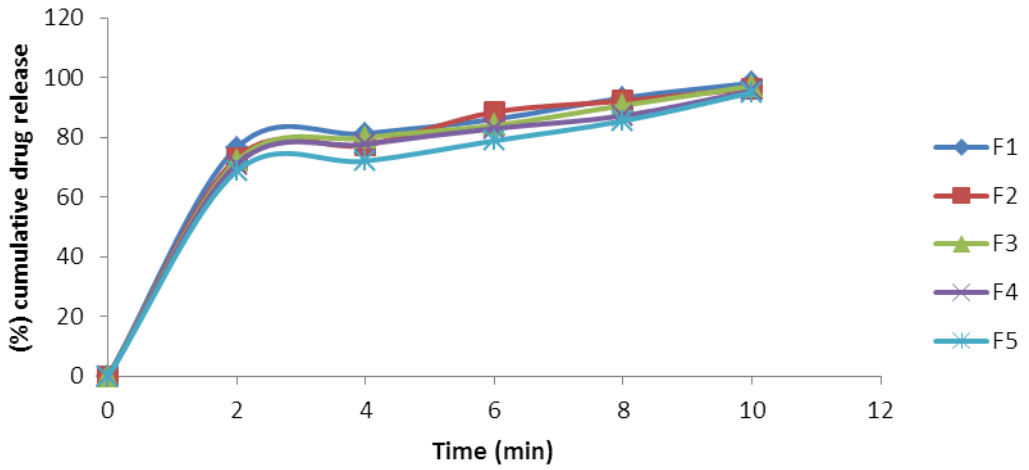


Figure 7: Comparission curve of *invitro* drug release for F1- F5 formulations.

*Invitro*dissolution study of formulations F1-F5 shown drug release of 98.12±2.2%, 96.36±1.12%, 97.13±2.17%, 95.55±1.99% and 94.97±1.38% respectively within 10min. Among the formulations F1 showed good dissolution property. F1 batch contain 250mg of HPMCE15 as film forming polymer.

Table No.7: *In vitro* drug releases for F6 to F9 formulations.

Time (min)	(%) Cumulative Drug Release			
	F6	F7	F8	F9
2	82.75±0.76	79.03±2.23	78.32±0.88	72.10±2.32
4	87.09±2.34	81.90±1.86	79.13±1.87	74.95±1.46
6	91.99±2.13	85.66±2.31	81.06±2.21	77.35±0.65
8	94.66±2.77	88.41±0.95	86.47±0.54	84.09±1.27
10	99.42±1.77	96.65±1.12	94.82±1.26	91.29±2.09

Data represents Mean ± S.D, n =3

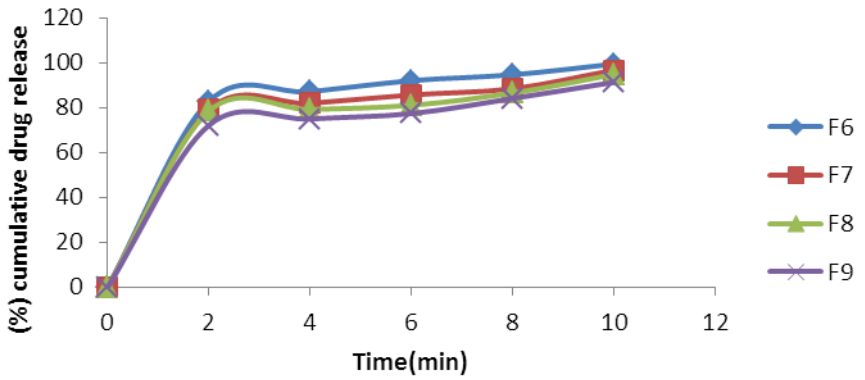


Figure 8: Comparission curve of *invitro* drug release for F6 to F9formulations.

In vitro dissolution study of formulation F6-F9 showed drug release of 99.42±1.77%, 96.65±1.12%, 94.82±1.26% and 91.29±2.09% within 10min respectively. Among formulations F6 showed good dissolution property. F6 batch contain300mg of HPMCE5 as film forming polymer.

Table No.8: *In vitro* drug release for F1, F3, F6 and F7 formulations.

Time (min)	(%) Cumulative Drug Release			
	F1	F3	F6	F7
2	76.59±1.45	72.05±1.76	82.75±0.76	79.03±2.23
4	81.27±0.67	77.82±1.41	87.09±2.34	81.90±1.86
6	86.02±1.36	83.25±1.25	91.99±2.13	85.66±2.31
8	93.21±0.66	90.60±2.61	94.66±2.77	88.41±0.95
10	98.12±2.2	97.13±2.17	99.42±1.77	96.65±1.12

Data represents Mean ± S.D, n =3

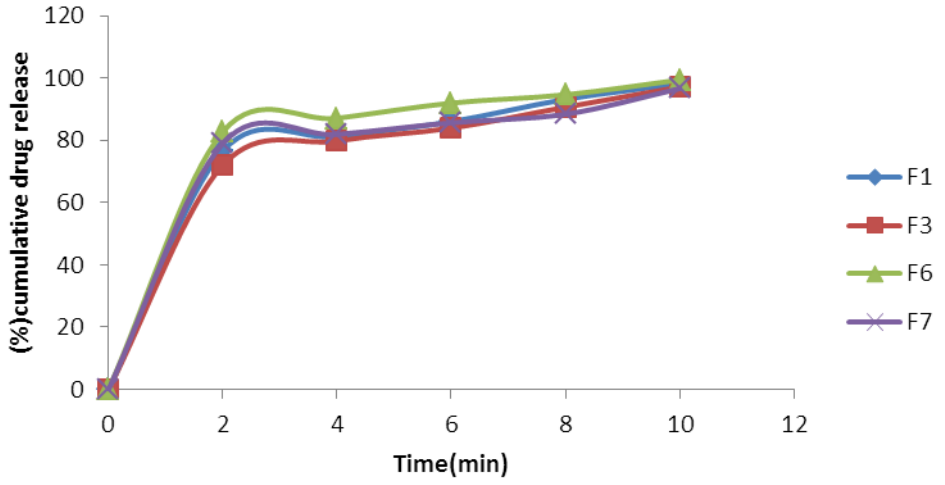


Figure 9: Comparission curve of*invitro*drug release for F1, F3, F6 and F7 formulations.

In vitro dissolution study of formulations F1, F3, F6 and F7 showed drug release of 98.12±2.2%, 97.13±2.17%, 99.42±1.77% and 96.65±1.12% respectively within 10 min. Among the formulations F6 showed good dissolution property.

DISCUSSION

Analytical method development for Meloxicam

λ max determination

λ max determination of Meloxicamin pH 6.8 phosphate buffer was determined by using UV Spectrophotometer at 359 nm.

Development of standard graph

Standard plot of Meloxicamin pH 6.8 phosphate buffer were plotted to concentration vs absorbance at 359nm and the slope value and R^2 value were found to be 0.0723 and 0.9976.

Evaluation properties

The different meloxicam film formulations were evaluated for mechanical properties like thickness, drug content uniformity, folding endurance, tensile strength, weight uniformity, disintegration time, in-vitro dissolution studies.

Thickness

The thickness of the films from F1-F5 formulations were ranged from 0.137± 0.12 to 0.150± 0.22mm. The thickness of the films from F6-F9formulations were ranged from 0.127± 0.14 to 0.142± 0.19mm. F5 formulation had the maximum thickness and F6formulation had the lowest thickness values in all the formulations. From the thickness values it is concluded that as the polymer concentration increases, thickness also increased.

Tensile strength& Percentage elongation

The tensile strength of the films from F1-F5 formulations were ranged from 1.159± 0.05 to 1.595± 0.22kg. The tensile strength of the filmsfrom F6-F9 formulations were ranged from 1.465± 0.02 to 1.565± 0.87kg. F5 formulation had the maximum tensile strength and F6 formulation had the lowest tensile strength values in all the formulations. From the tensile strength values it is concluded that as the polymer concentration increases, tensile strengthand percentage elongation also increased.

Drug content uniformity

The drug content uniformity of the filmsfrom F1-F5 formulations were ranged from 100.66±0.43% to 97.80±0.87%. The drug content uniformity of the films from F6-F9 formulations were ranged from 99.97±1.23% to98.09±1.78%. F6 formulation had the maximum drug content uniformity and F9 formulation had the lowest values in all the formulations.

Folding endurance

The folding endurance value of the films from F1-F5 formulations were ranged from 95.3±9.87 to 134.6±5.37. The folding endurance value of the films from F6-F9 formulations were ranged from 123.5±7.67 to 132.6±8.12. In HPMC containing formulations as polymer concentration increases folding endurance values were also increased.

Weight uniformity

Weight uniformity of films werecarried out for all the formulations and weight variation varies from 29.21 ± 0.56 to 33.41 ± 0.62mg.

Disintegration time

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro*disintegration time was calculated for all the formulations and it ranges from 14±1.98sec to 31±0.98sec. Disintegration time of the films was increased with increase in concentration of the polymer, as more fluid is required to wet the film in the mouth. F6 formulation was quickly disintegrated that is in 14±1.98sec.

Finally selection of the best formulation from all the formulations was carried by using *in vitro* dissolution studies.

***Invitro* dissolution studies**

In vitro dissolution study of F1-F5 formulations were showed different drug release of 98.12 ±2.2%, 96.36 ±1.12%, 97.13 ±2.17%, 95.55 ±1.99% and 94.97 ±1.38% respectively within 10min. Among the formulations F1 showed good dissolution property hence it is optimized and it contain 250mg of HPMC E15 as film forming polymer.

*In vitro*dissolution study of F6-F9 formulations were showed different drug release of 99.42 ±1.77%, 96.65 ±1.12%, 94.82±1.26% and 91.29 ±2.09% respectively within 10min. Among

the formulations F6 showed good dissolution property hence it is optimized and it contain300mg of HPMC E5 as film forming polymer.

Small differences were observed in dissolution of drug from the different formulations of the film. Present study reveals that maximum all formulated films showed satisfactory film parameters. From all formulations F1, F3, F6 and F7 were optimized. Among the optimized formulations F6 formulation showed better drug release of 99.42±1.77% within 10 min. F6 formulation contains 300mg of HPMC E5 polymer as film forming agent. Compared with among HPMCE15 and E5 formulations, HPMC E5(300mg) has good disintegration property which enable good dissolution of the formulations.

6. CONCLUSION

The Meloxicam oral films could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improve patient compliance and also meloxicam might be a right and suitable candidate for oral delivery.Low dose of drug can be suitable for oral films with low density of polymers. ODF are the thin film with more surface area they get wet quickly and disintegrate then dissolve faster than other formulations.From the present investigation it can be concluded that mouth dissolving film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

The meloxicamoral films (7.5mg) were prepared by solvent casting technique using Methanol and 1N NaoH as a mixed solvent and by using different polymers like Hydroxy Propyl Methyl Cellulose E5& E15 and the polymeric solutions are levitated with PEG-400 which served the purpose of plasticizer as well as penetration enhancer. The bitter taste was masked by aspartame as a sweetener. The standard graph was plotted in pH 6.8 phosphate buffer. Drug excipient compatibility studies were carried for pure drug and polymers, it was evident from the results that there were no interactions between drug and polymers.

The prepared meloxicam oral films were characterized based upon their physiochemical charecterstics like tensile strength, Disintegration time, thickness, weight uniformity, folding endurance, drug content uniformity, dissolution studies. all the results were found to be were found to be within the pharmacoepial limits.

Based on the results F6was the best one when compared to other. Based on disintegration and drug releases faster of the ODF formulation F6 has less disintegration time and compare to

F1, F3 and F7. F6 film exhibited required tensile strength, folding endurance and Assay. At HPMC concentration level it showed the least dispersion time of 14±1.98 sec and the highest release of more than 99% of the drug in 10min.So ODF formulated with HPMC E5 F6 is best formulation.