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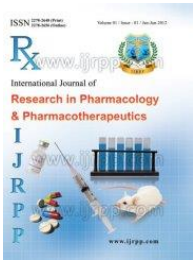

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Formulation and evaluation of fast dissolving film of meloxicam

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ABSTRACT

Fast dissolving dosage forms have acquired great importance in pharmaceutical industry. The aim of this study was to formulate and characterize fast dissolving film containing meloxicam (MLX) for oral use. In this study, as an approach to improve the solubility of MLX, solid dispersions (SD) of MLX were prepared by melting and solvent evaporation methods using Poloxamer 188 and Gelucire 44/14 alone as carrier and combination of both. The physicochemical characterizations were done by X-ray diffraction (XRD) and differential scanning calorimetry (DSC) for MLX-loaded SD and their corresponding physical mixtures as well as the individual components to investigate the drug polymer interaction. The solubility was enhanced 5-8 folds using the solid dispersion technique (F1, F4 and F9). All the prepared formulations showed about 65-100% MLX release after 60 min compared to a maximum of 23% release from the pure MLX sample. The obtained DSC and XRD results indicated that MLX was molecularly dispersed in the matrix of SD. Then, the promising formula (F9) that contained (15:42.5:42.5, drug: poloxamer: Gelucire, w/w) and prepared by melting was further incorporated into fast dissolving film (FDF) formulations. Films were prepared by solvent casting method using different quantity of film former HPMC E6. The prepared films were found to contain almost a uniform quantity of the drug. Film 2 (contained 400 mg polymer) showed the best property concerning drug release, fast disintegration time (46.3sec), mechanical strength and surface pH.

Keywords: Meloxicam, Poloxamer, Gelucire, Film, Oral, Evaluation, Solubility.

INTRODUCTION

Oral drug delivery is the most simple and desirable way for administration of therapeutic agents, which have many advantages, it is more stable, more accurate and easy to manufacture. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has

developed great potential in recent era [1]. Fast dissolving films (FDFs) are the most advanced form of oral solid dosage forms due to more flexibility and comfort. It improves the efficacy of active pharmaceutical ingredients (API) by dissolving within minutes, it gets hydrated in the oral cavity after the contact with saliva and then disintegrates to release the medication for oromucosal and intragastric absorption, without chewing and intake of water [2, 3, 4 and 5]. Also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug [6, 7]. This convenience provides both a marketing advantage and increased by patient compliance [8, 9].

Fast dissolving films come in the form of a thin strip and can be produced by solvent casting method, hot melt extrusion and rolling method [11, 12]. The disintegration time of FDF is usually short, due to their lower thickness, but the dose of the drug that can be incorporated into the film is strongly limited (usually not more than 60 mg). Moreover, they are more resistant to humidity and less brittle than the lyophilized dispersible tablet [13]. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form [14, 15]. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or systemic action [16]. It is specially designed for drugs which have extensive first pass metabolism for the enhancement of bioavailability [17].

Meloxicam (MLX) was selected as a model drug. Meloxicam (MLX) is Biopharmaceutics Classification system (BCS) class II compound, an oxicam derivative non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities [18]. MLX (Fig. 1) is used to treat pain or inflammation caused by osteoarthritis, rheumatoid arthritis and other joint diseases in adults and children who are at least 2 years old [19, 23]. Meloxicam is poorly soluble in Water and hence has poor bioavailability after oral administration [22]. Thus, increasing the aqueous solubility and dissolution of MLX is of therapeutic importance.

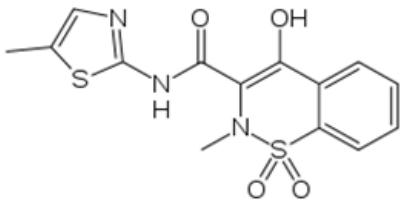

Figure 1: MLX chemical structure: is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazoly)- 2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Solid dispersion technique is one of the effective approaches to enhance the dissolution of poorly water soluble drugs. Several attempts have been made to increase the solubility of MLX via solid dispersion [24, 25], Co-solvency [26]. cyclodextrins [27, 28 and 29] and rapid disintegrating tablets [30].

AIMS AND OBJECTIVES

The aim of the study is to formulate a fast dissolving film of Meloxicam (MLX) by employing solid dispersion technique intended for once daily chronic use in arthritis and osteoarthritis.

Objectives

1. Prepare different solid dispersions of MLX as an approach to improve its solubility using Poloxamer and Gelucire in different drug/carrier ratios using different techniques (physical mixture, melting and solvent evaporation).
2. Characterize the prepared solid dispersions and physical mixtures for drug content, differential scanning calorimetery, x- ray diffraction, saturation solubility, and in vitro dissolution rate.
3. Select the optimized formulation for further incorporation in fast dissolving film (FDF) containing equivalent amount to 7.5 mg meloxicam.
4. Evaluate the prepared FDF for drug content, weight variation, in vitro drug release, surface pH, folding endurance, tensile strength, and disintegration in oral cavity.

MATERIALS AND METHODS

Materials

Meloxicam as gift sample was supplied by Changzhou Longcheng pharmaceutical Co., Ltd., China. Poloxamer 188 was purchased from BASF AG (Ludwigshafen, Germany). Gelucire 44/14® (Lauroyl polyoxyl-32 glycerides, m.p. 44 °C; HLB14) was obtained as gift samples from Gattefosse (Saint-Priest, France). Hydroxpropyl methyl cellulose (HPMC E6) was procured from Reddys labs, Hyderabad. Propylene glycol 400, sorbitol and citric acid are purchased from Himedia labs, Mumbai. All the other chemicals used were of analytical grade.

METHODS

Preparation of Physical Mixtures (PMs)

Physical mixtures were obtained by uniform mixing of drug and carrier (Table 1). The solid mass was then pulverized in glass mortar. The resultant product was passed through a sieve of 80 mesh size to get uniformly sized particles.

PREPARATION OF SOLID DISPERSIONS (SDS)

Melting method

About 1 g of each Formula F1-F6 and F9 was heated in porcelain plate until complete melting was achieved. The mixture was kept in a refrigerator at 4°C for 2 days to solidify, and then crushed, milled in a mortar [31]. The solid dispersions were then stored in glass vials and kept in the desiccator at 20±1°C until further analysis.

Solvent evaporation method

The effect of solvent evaporation method was investigated on two formulations (F7, F8). Minimal amount of methanol was used to dissolve MLX and carriers by continuous stirring with a magnetic stirrer for an hour at room temperature. The solvent was then completely evaporated at 40°C with constant stirring until a uniform solid mass was formed. The resultant mass was desiccated at 20±1°C until further analysis.

Table 1: Percent composition of solid dispersions.

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9
Method of preparation	Melting						solvent evaporation	solvent evaporation	Melting
Components % (w/w)									
Meloxicam	15	10	5	15	10	5	15	15	15
Poloxamer188	85	90	95	-	-	-	85	42.5	42.5
Gelucire44/14	-	-	-	85	90	95	-	42.5	42.5

CHARACTERIZATION OF SOLID DISPERSION

Drug content

The formulation equivalent to 7.5 mg of MLX was weighed and dissolved separately in suitable quantity of methanol. The sample was mixed for 1 hour using Heidolph Vibramax 100 shaker and centrifuged for 10 minutes at 4000 rpm. Drug content was assayed spectrophotometrically at 362 nm by UV spectrophotometer (UV-1601 Spectrophotometer, Shimadzu, Japan). The drug content was determined by using a standard plot of absorbance versus concentration. The blank formulation was treated in the same manner as the MLX formulations and used as a blank. Each sample was analyzed in triplicate.

Saturation solubility studies

Saturation solubility studies were conducted according to the method reported by Patel [16]. MLX and solid dispersions equivalent to 7.5 mg of MLX were added to 10 ml distilled water in screw-capped test tubes, vortexed for 5 min, and shaken (Heidolph Vibramax 100 shaker) at room temperature for 24 hrs until equilibrium was achieved. Undissolved solid dispersions suspended in distilled water were centrifuged at 8,000 rpm for 10 min and clear supernatants obtained were filtered through 0.22 µm membrane filter then diluted with distilled water, and analyzed spectrophotometrically at 362 nm. Each sample was analyzed in triplicate to calculate the solubility of MLX [23].

Dissolution studies

The in vitro dissolution studies of MLX, PMs, and SDs were carried out using USP Paddle dissolution apparatus (DT6 Dissolution system (Erweka GMBH, Germany). The dissolution medium is 900 ml phosphate buffer pH 6.5 at 37 ± 0.5 °C with a rotation rate of 50 rpm. Sample equivalent to 7.5 mg of MLX was filled in hard gelatin capsules (size 0) and placed in the dissolution flask. An aliquot of 5 ml was withdrawn at different time intervals with a syringe filter (0.22 µm) and replaced with the same volume of the prewarmed dissolution medium. The samples were estimated for dissolved MLX by measuring absorbance at 362 nm.

X-Ray Diffraction (XRD)

X-ray diffraction study was carried out for pure drug, carriers and some selected formulations in order to assess their degree of crystallinity using x-ray diffractometer (Burker AXS, Germany). Scanning interval: 5–50 °C 2θ range; using monochromatic copper Cu Kα radiation of wavelength λ = 1.78896 Å, under the following condition: voltage 40 kV, current 40 mA. Count time 1/step, with a step size of 0.02 ° [25].

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded using a differential scanning calorimeter (DSC-6-Perkin-Elmer, USA). An accurately weighted sample (2-4 mg) of pure drug, carriers and some selected formulations were heated in hermetically sealed aluminum pans under nitrogen purge (20 ml/min) over a temperature range of 30°C to 300°C at a constant rate of 10°C/min.

Preparation of Fast Dissolving Films

Fast dissolving films of MLX were prepared using solvent casting method (Table 2). The required amount of film forming polymer (HPMC E6) was accurately weighed, dispersed in distilled water and soaked aside for 1hour for swelling of polymer. Accurately weighed quantity of MLX solid dispersion (F9) was dissolved in polyethylene glycol400 (PEG400) which used as a plasticizer. Citric acid as saliva stimulating agent, menthol (flavoring agent), and sucrose (sweetener) were dissolved in distilled water in another beaker. After complete hydration of the polymer with water, drug-plasticizer solution and the other excipients solution were added to the polymer solution and mixed thoroughly with magnetic stirrer. The resulting solution was sonicated for 20 min for removal of air bubbles. The bubble free solution was casted on to a Petri dish of 9 cm diameter which was placed over a flat surface. Funnel was inverted over petri dish and kept for 24 hours at room temperature for drying. The film was removed from the Petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film of area 9 cm2 (3 X 3) was cut and wrapped in an aluminum foil and stored in desiccators [32].

Table 2: Formulation of fast disintegrating films of meloxicam

Film Code	MLX SD (mg) (equivalent to 7.5 mg drug)	HPMC E6 (mg)	PEG (mL)	Citric acid (mg)	Menthol (mg)	Sucrose (mg)	Water (mL)
F1	353	300	2	20	1	1	10
F2	353	400	2	20	1	1	10
F3	353	500	2	20	1	1	10

EVALUATION OF FAST DISSOLVING FILMS

Physical characterization

Physical characterization can be carried out by visual inspection for characteristics such as colour, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity [32].

Film thickness

The film thickness can be measured by micrometer screw gauge (Mitutoyo, Japan) at 5 different locations and the average value was calculated. This is essential to determine uniformity in the film thickness which is subsequently related to the accuracy of dose in the film [33].

Weight variation

For weight variation three films (3 x 3 cm) of every formulation were weighed individually using Analytical balance ((Mettler, AJ150, Greifensee, Switzerland), then average weight was calculated [34].

Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks [35]. Tensile strength of the films (3x3 cm) were measured using texture analyzer (Shimadzu EZ-SX, Japan). Tensile strength is calculated by the applied load at rupture divided by the cross-sectional area of the film as given by the equation below [36].

$$\text{Tensile strength} = \frac{\text{Load failure}}{\text{Film thickness x film width}}$$

Drug content uniformity

Three films (3×3cm) were transferred into separate graduated flasks containing 100 ml of phosphate buffer pH 6.5 and stirred for 2 hours. The contents were filtered, suitably diluted and analyzed spectrophotometerically at 362 nm [37].

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives the indication of brittleness of the film. A strip of 3x 3 cm was subjected to this test by folding the film repeatedly at the same plane for several times until a visible crack was observed, and the values were reported [38].

Disintegration time

One film (3x3 cm) of each formulation was introduced into one tube of disintegration apparatus (Electrolab, ED-21, Mumbai, India). A disc was added into the tube. The assembly was suspended in a beaker containing phosphate buffer pH 6.5 maintained at 37°C and the Time till complete film disintegration was calculated. Test was conducted in triplicates [39].

Saturation solubility studies

The primary goal of SD is to increase the solubility and dissolution rate of a poorly water soluble drug. Pure MLX was found to have a saturation solubility of 19.7 µg/mL. The solubility was enhanced by 5-8 folds using the solid dispersion technique (F1, F4 and F9, Table 3). Similarly, the solubility of drug increased by 2-3 folds in physical mixtures. Solubility studies showed that the highest solubility was obtained in SDs prepared by melting rather than those prepared by solvent evaporation.

Surface pH

One film (3x3 cm) of each formulation was transferred into a petri dish and moistened with 1 ml of distilled water and kept for 1 h. The surface pH was measured by bringing the electrode of the pH meter (Mettler Toledo, Greifensee, Switzerland) in contact with the surface of the film and allowing it to equilibrate for 1 min [40]. A mean of three readings and standard deviation was recorded.

In vitro dissolution studies

In vitro dissolution of meloxicam fast dissolving films was carried out in USP dissolution apparatus II using 900 mL phosphate buffer pH 6.5 adjusted at 37± 0.5ºC. Each square cut film sample (3x3 cm) was submerged into the dissolution medium and 5 mL aliquots were withdrawn at specific intervals for 60 min and replaced with equal volumes of phosphate buffer pH 6.5. The drug concentration of the dissolved meloxicam was determined using UV spectrophotometer at 362 nm [4]. The results were presented as an average of three such concentrations.

RESULTS AND DISCUSSION

Characterization of Meloxicam Solid Dispersions & Physical Mixtures

Drug content

MLX content of the prepared PM and SD formulations was in the range of 99.0% to 100.5% ± 5%, indicating uniform drug distribution within the prepared solid dispersions.

The enhanced aqueous solubility of MLX observed with SD was possibly due to micellar solubilization by carriers, reduction in particle size and formation of an amorphous state of the drug [16].

Dissolution studies

Dissolution data were evaluated on the basis of cumulative percentage drug release, which was plotted against time. Fig. 2-4 show the dissolution profile of MLX and MLX solid dispersions and physical mixtures. All the PMs and SDs prepared in

varying Poloxamer and Gelucire ratios showed an improved drug release compared to pure MLX sample. The prepared solid dispersions showed drug release of 65-100% after 60 min compared to only 23% drug released from pure MLX sample. For better comparison of the formulations, the dissolution data up to 10 and 30 min; Q10 and Q30 (i.e., percentage of drug release in 10 and 30 min, respectively) are calculated in Table 3. In addition, the release mechanisms from various formulations were studied. The data was found to best fit the Higuchi model (Table 3), indicating diffusion-restricted release [41].

Table 3: Solubility studies and in vitro dissolution data of MLX solid dispersions and physical mixtures.

Formula code	Solubility (µg/ml)	Q10	Q30	Correlation regression coefficient values (r)		
				First order	Higuchi	Zero order
Drug	19.0654	0.75	8.07	0.923	0.994	0.968
F1	108.2243	27.14	90.66	0.668	0.911	0.842
F2	84.11215	10.24	80.22	0.904	0.989	0.974
F3	58.8785	9.35	60.63	0.952	0.988	0.981
F4	153.0841	56.97	114.92	0.618	0.987	0.736
F5	45.42056	18.32	71.03	0.743	0.989	0.877
F6	52.14953	6.88	86.95	0.830	0.988	0.929
F7	62.80374	9.86	69.91	0.938	0.963	0.968
F8	35.3271	66.47	100	0.700	0.859	0.775
F9	155.8879	61.18	100	0.741	0.875	0.797
PM1	40.37383	8.59	49.27	0.916	0.986	0.973
PM2	42.05607	9.94	61.23	0.787	0.987	0.904
PM3	54.95327	6.28	39.71	0.895	0.989	0.977
PM4	43.73832	15.63	33.64	0.902	0.988	0.994
PM5	61.68224	20.34	54.43	0.923	0.988	0.988
PM6	89.15888	12.11	51.14	0.921	0.985	0.974

A ratio of 15:85 drug: carrier, w/w was selected to compare the effectiveness of the melting and solvent evaporation method. Figure 4 illustrates the dissolution profile of MLX from the solid dispersions prepared in Poloxamer in 15: 85 ratio. After 15 min, solid dispersions prepared by solvent evaporation method showed 12% MLX release compared to 68% MLX release by the melting method. However, after 30 min 97% drug release was obtained by the melting method against 99% release from the solvent method. On the other hand, the solid dispersion formulations (F8, F9) with equal combination of Poloxamer and Geluicre prepared by melting or solvent method showed similar release profiles (Fig. 4). Statistical analysis showed that there was no significant difference in the % MLX release from solid dispersions prepared by the melting and solvent method.

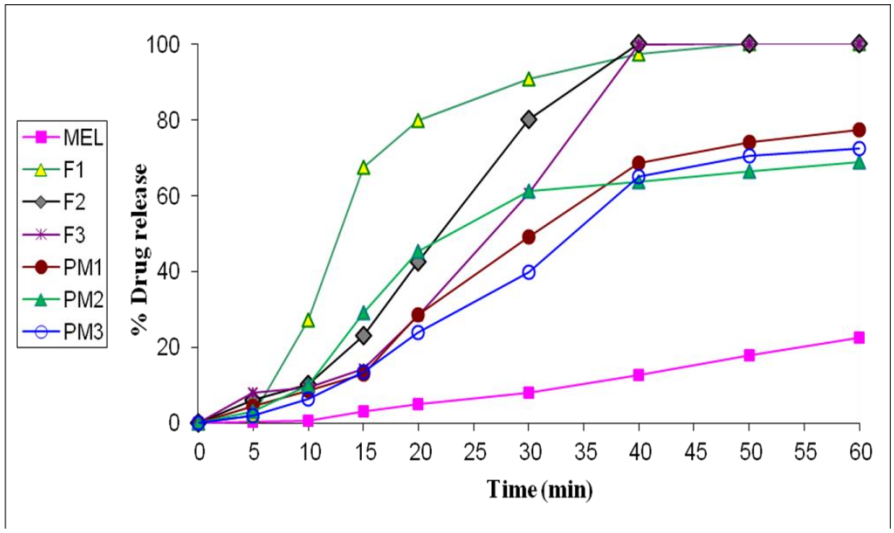

Figure 2. Dissolution profiles of MLX, PM 1-3 and SD 1-3 prepared by melting method

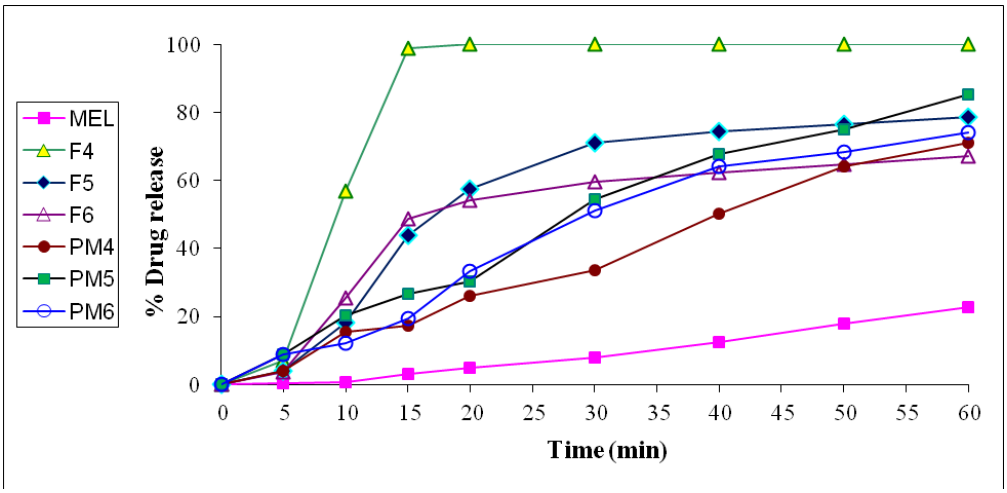

Figure 3. Dissolution profiles of MLX, PM 4-6 and SD4-6 prepared by melting method

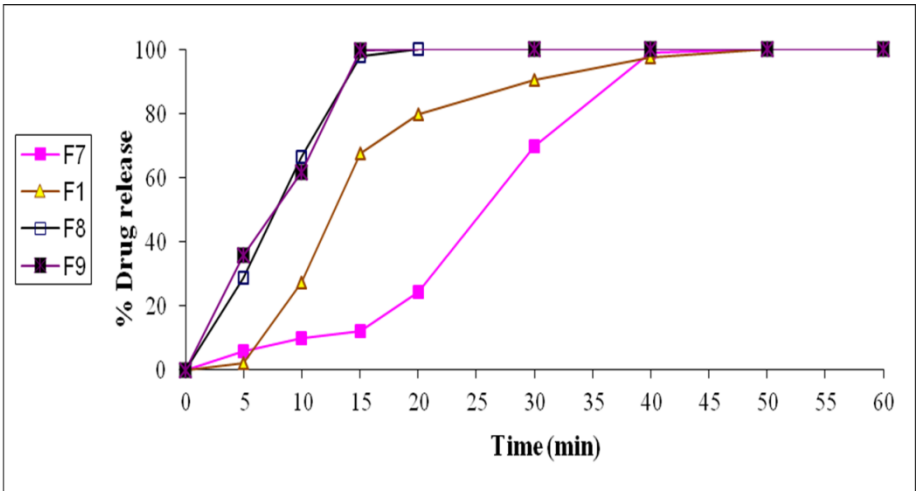

Figure 4. Dissolution profiles of MLX, SD F 1, F7-9 ; F 1 and F 9 prepared by melting compared with F 7, F 8 prepared by solvent method.

From the in vitro studies, it can be inferred that SD of F9 was the best of all formulations. The solubility and the dissolution rate exhibited by this formulation were maximal and higher than other formulations. Therefore F9 was selected for further studies.

Solid state studies of the MLX formulations

The thermograms for pure MLX, Poloxamer, Gelucire, SDs of F1, F4, F9 and PMs of F1, F4 are shown in Fig. 5. MLX exhibited a single, sharp endothermic peak corresponding to the melting of the drug at 263.68°C [25]. Poloxamer and Gelucire exhibited an endothermic peak at 49.19 °C and 44.56 °C, respectively. No differences were apparent between the DSC thermograms of PMs and SDs. The complete disappearance of the drug melting peak observed in both PMs and SDs was attributable to the drug dissolution in the melting carrier before reaching the fusion temperature. Similar results were reported by [42].

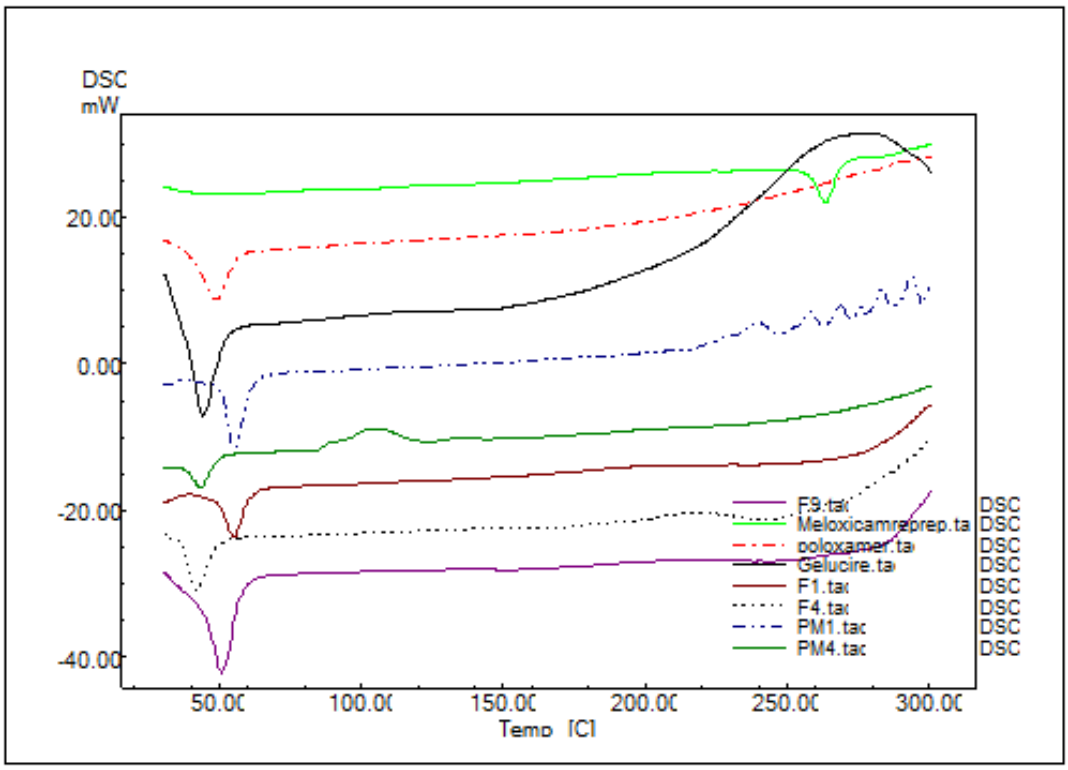

Figure 5. Differential scanning calorimetry thermograms of MLX, PM1, PM4, F1 SD, F4 SD and F9

Powder X-ray diffractograms of MLX, pure MLX, Poloxamer, Gelucire, SDs of F1, F4, F9 and PMs of F1, F4 are shown in Fig. 6 Major characteristic diffraction peaks of MLX observed at 2θ diffraction angle of 6.12, 2, 16.96, 19.26, 20.18, 21.30, and 24.96° whilst poloxamer188 and gelucire showed two peaks at 19° and 23° corresponding to the crystalline structure of the carriers. On comparison of the formulation patterns with that of pure drug, it was observed that the number and intensity of peaks are reduced in the PM and SD samples. Moreover, major diffraction peaks corresponding to MLX were absent and no new peaks were observed in the formulation F9. As it is reported that amorphous system is responsible for the enhancement in dissolution and bioavailability [43].

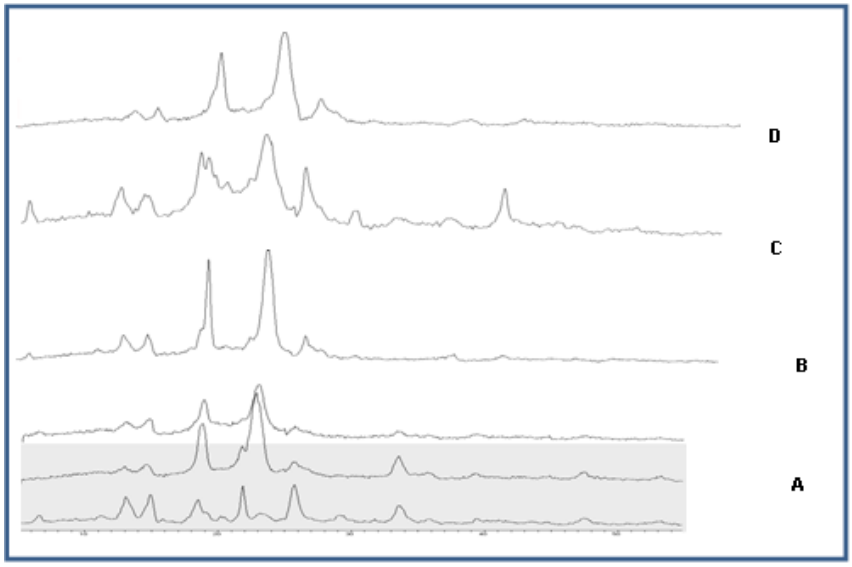

Figure 6. X ray powder diffraction of: (A) MLX and PM1, PM4; (B) F1; (C) F4; (D) F9

EVALUATION OF FAST DISSOLVING FILMS

Physicochemical evaluation of fast dissolving films

All films were evenly yellow colored, homogenous, thin, and non brittle, with no spot on the film surface. Formulation FDF1was soft and difficult to handle, so it was excluded from the other evaluations. The prepared FDF was evaluated according to the following parameters: weight variation, thickness, surface pH, % drug content, tensile strength and folding endurance as shown in Table 4. The weight variation of the formulations are in the range 330.1-343 mg which is acceptable. Thickness values are in the range of 1.1 - 1.5 mm. Both thickness and weight of the FDF were depend on the concentration of the polymer. Similar results were reported by Bhikshapathi [10]. No significant difference was found in surface pH of different films. The surface pH of films was found to be around neutral pH and hence, it will be more acceptable by the patients. Disintegration time ranges between 46.3-48 seconds which was short and desirable for quick onset of action. The prepared films were found to contain an almost uniform quantity of the drug, drug content in the films ranged from 95.8- 97.2 % indicating reproducibility of the technique. The results showed that the tensile strength of prepared films varies from 35.5 – 123.6 g /cm2. Folding endurance value of the prepared films ranged from 82-90. It was observed that as the concentration of polymer increases, folding endurance of the films increase.

In-vitro release of MLX from FDF

The results of in vitro release of MLX from the prepared films (FDF2 & FDF3) are demonstrated in Fig.7. The optimized formulation (FDF) showed faster and higher percentage of drug release. Drug release profile of the formulation FDF2, shows an initial phase of release of the drug 90.5% ±1.4 within 5mi mn compared to 72.5% release from FDF3 and this can be explained on the basis of lower polymer content. The influence of polymer levels are found to be vital in regulating the drug release [44].

Table 4: Evaluation parameters of meloxicam fast dissolving films.

*Values in parenthesis is SD

Film Code	Weight (mg)	Thickness (mm)	Surface pH	Disintegration time (sec)	% Drug content	Tensile strength (g/cm2)	Folding endurance (count)
FDF2	330.1± (23.5)	1.1 ± (0.58)	6.72 ± (0.01)	46.3 ± (4.0)	95.8± (0.58)	35.54 ± (8.03)	82 (2)
FDF3	343.2 ± (15.7)	1.5 ± (0.03)	6.76 ± (0.01)	48 ± (2.0)	97.2± (0.46)	123.60 ± (8.59)	90 (4)

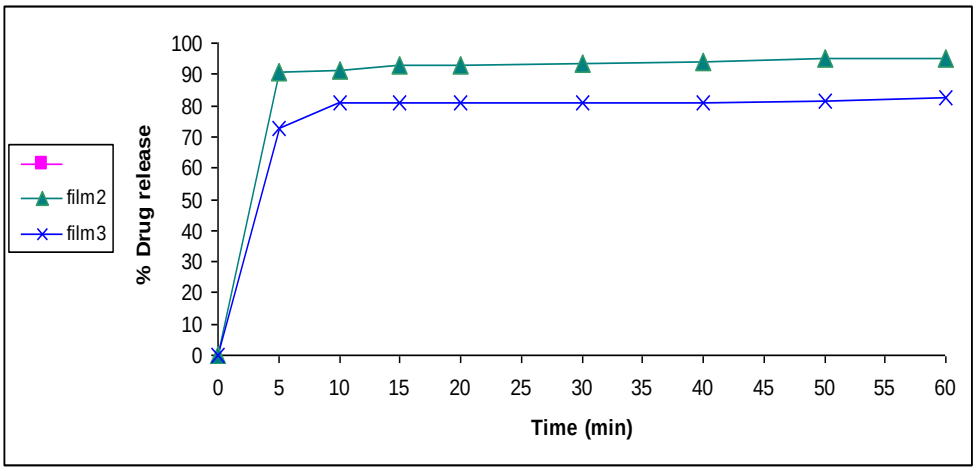

Figure 7. In vitro release of MLX from fast dissolving films

CONCLUSION

Fast dissolving oral films of meloxicam (MLX) were formulated with different concentrations of HPMC-E6 as film forming polymer using film casting method. Solid dispersion (SD) of MLX using combination of 1:1 w/w Poloxamer and Gelucire and prepared by melting technique was incorporated in film formulation as an approach to improve the release of drug from the film.

The in vitro drug release from optimized formulation FDF2 (400 mg HPMC-E6) was found to be 90.5% ±1.4 in 5min. The optimized formulation FDF2 also showed satisfactory pH (6.7), drug content (95.8 %), effective in vitro drug release (95% in 60 min) and disintegration time of 46.3 seconds. Fast dissolving film can be a potential novel drug dosage form for improved oral delivery of MLX in both pediatric and geriatric patients.

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