RESEARCH ARTICLE

Preparation and Evaluation of Meloxicam Nanoparticles as Oral Thin Film

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ABSTRACT

The principal objectives of this research were to prepare and evaluate Meloxicam nanoparticles loaded fast dissolving film, and nanoparticles were used to permit for enhancing dissolution of the drug, while the films were used to fasten the onset of action Meloxicam nanoparticles were fabricated by solvent/antisolvent method and then formulated as the oral thin films by casting method. The Meloxicam nanoparticles were prepared at selective polymer: drug ratios of 1:1, 2:1, and 3:1 using various polymers and specific grades of polyvinyl pyrrolidone and hydroxy-propyl methyl cellulose as stabilizers. The effect of polymer, ratio, and stirring rate on the size of the particulate, were studied, and found to have a significant ($p \leq 0.05$) effect. The best formula (FMx1) was obtained with a minimum average particle diameter of 59.5 nm and surface area 37.34 m^2/g contained 1:1 of HPMCE-50LV: Meloxicam. This formula was freeze-dried and studied for surface morphology by Field Emission Scanning Electron Microscope (FESEM), crystalline state by XRPD, and compatibility by FTIR and DSC. Then Meloxicam nanoparticles were formulated into an oral thin film. The obtained film Meloxicam content of 7.4 ± 0.02 mg per 4 cm^2 of film and disintegrated in 29 seconds. The Meloxicam nanoparticles film was illustrated a faster in vitro dissolution rate than the film prepared from pure Meloxicam, and the FESEM images indicated that Meloxicam nanoparticles were greatly distributed into the films. These results indicated that the oral film prepared from Meloxicam nanoparticles could be a favorable system to improve the dissolution and fasten the action.

Keywords: Dissolution rate, Meloxicam nanoparticles, Oral thin film, Solvent/antisolvent precipitation.

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INTRODUCTION

The bioavailability of peri oral administrated drugs depends on their dissolution rate and diffusion through the digestive tract.[1] Through this route of administration, drugs that are poor water soluble have low bioavailability as their low solubility in gastrointestinal media. The controlling step in the absorption of these drugs is the dissolution rate in the gastrointestinal liquids rather than diffusion through the gastrointestinal membrane.[2] The dissolution of drug and amount absorbed is affected by physicochemical properties of API, pharmaceutical dosage form, and physiological characteristics of the absorption site.[3] Therefore, developing of novel dosage forms to attain acceptable bioavailability has become a serious and challenging problem. Water insoluble drugs are formulated with aid of specific excipients whose aim is to improve dissolution and storing stability. Nanonization of drug proposals an excellent opportunity to overcome solubility problems to enhance bioavailability and then good therapeutic effect of drug and has numerous advantages in drug delivery.[4] Fast thin films is a peri oral dosage form that proposed some advantages over conventional ones which are: the ease of administration, as well as swallowing with no requirement for water thus successful elderly and pediatric patients. A larger surface area leads to fast disintegration and within seconds release of the active ingredient and hence a fast onset of action could be accomplished.[5] A confirmation of the polymeric oral films flexibility had established as suitable platforms for extension and adjustment for various delivery routes and encouraging markets. Meloxicam has been efficiently used as anti-inflammatory and analgesic. In addition to its emergent promising action in treatment of cancer. Meloxicam is a class II drug; with. Low water dissolution and high diffusion.[6] Chemically Meloxicam ($C_{14}H_{13}N_3O_4S_2$) is 4-Hydroxy–2–methyl-N- (5– methyl–2–thiazolyl)- 2H-1,2–benzothiazine–3–carboxamide–1,1–dioxide It has dissociation constant pKa (1.1, 4.2) and Molecular weight 351.41. It is yellow in colour powder with practical insolubility in water of 0.012 mg/mL, soluble in dimethylformamide (DMF), slightly soluble in acetone, very slightly soluble in methanol (96%) and in ethanol.[7-9]

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MATERIAL AND METHOD

Materials

Meloxicam (Mx) was purchase from Shenzhen Iodi chemical Co. Ltd India. HPMCE-15 LV, HPMCE-50LV (Gromax Chemicals–USA), PVP-K15 and PVP-K30 (ALPHA Chemika-India). Disodium hydrogen orthophosphate, sodium Chloride, and Hydrochloric acid 37% (BDH Laboratory England), potassium dihydrogen orthophosphate (Fine Chem-India), DMF (Thomas Baker Chemical-India), Glycerin (Fluka Chemi AG-Switzerland), Crosecarmelose (Sigma Chemical CO.-USA).

METHOD

Preparation of Meloxicam Nanoparticles

The Meloxicam nanoparticles were prepared using solvent/antisolvent of precipitation technique.[10] A specific amount of pure Meloxicam was completely dissolved in 5mL dimethylformamide (DMF). The drug solution was injected at 1mL/min using syringe into water solution containing specific concentration of stabilizer of each (HPMCE-50LV, PVP-K15, and PVP-K30) with continuous stirring. Nanoparticle precipitated regularly upon mixing. The nanoparticles were then dry with lyophilizer to get the nanoparticles powder. The composition and variable conditions of preparation of different formulas are listed below in Table 1.

Measurement the Particle Size, Poly Dispersity Index and SSA

The ABT-9000 dynamic light scattering Nano laser (Angstrom Advanced Inc. USA), was used to measure the average particle size, the specific surface area (SSA) and poly dispersity index which is measurement for the range of the size distribution, for all prepared meloxicam nanoparticles formulas.

Study of Variables Affecting on Size of Meloxicam N Anoparticles

Effect of Type and Concentration of Polymer

Different stabilizer at 3 ratios of drug to polymer concentration of 1:1, 1:2 and 1:3 were applied in the preparation of Mx nanoparticles. Formulas FMx1-FMx9, were prepared and utilized to illustrate the polymer type and concentration effects on the size of Mx nanoparticles.

The Effect of Stirring Rate

Was studied using 700 and 1100rpm at constant ratio of drug: polymer (1:1), this effect was examined in formulas (FM×1-FMx3 and FM×10-FMx12).

Characterization of Lyophilized Meloxicam Nanoparticles Powder

Determination Saturated Solubility

The saturated solubility was determined of Meloxicam raw powder and Meloxicam nanoparticle of selected formula was carried out using the shaking flask method. An excess amount of each the Meloxicam pure and nanoparticle powder placed in 10ml of simulated saliva solution (pH 6.75) with constant stirring on a water bath shaker at 37 ± 2°C for 48 hours. Drug concentration in clarified sample was determined spectrophotometric ally at λ max of Meloxicam.[11] The solubility of each sample was determined in triplicates and the mean value and standard deviation were reported.

Determination of Drug Content and Loading Efficiency.

The test was carried out by taking 15 mg powder of lyophilized nanoparticles and dissolved in 30 mL simulated saliva pH 6.75 in dry volumetric flask and sonicated for 20 minutes, and then volume was completed to 100 mL with same solvent and filtered on 0.22 µm filter. Then absorbance of filtrate was then determined using UV-visible spectrophotometer and the drug content was calculated accordingly. The loading efficiency of Mx nanoparticles was quantified from the theoretical and actual contents. This experiment was done in triplicate.

Field Emission Scanning Electron Microscope

Field emission scanning electron microscope (FESEM) (Zeiss-Germany) of pure Meloxicam powder, Meloxicam nanoparticles of selected formula and oral film made from it were confirmed by direct dusting of powder on carbon tape.

Table 1: Composition of meloxicam nanoparticles prepared with different polymers and different ratio of drug: polymer (1:1, 1:2 and 1:3) of (FMx1-FMx9) and, and effect of different stirring rate with constant drug: polymer ratio (1:1) of (FMx1-FMx3 and FMx10-FMx12).

Formula	*Meloxicam (mg)*	*HPMC-E50*	*PVPk-15 (mg)*	*PVPk-30 (mg)*	*1100*
FMx1	25	25			1100
FMx2	25		25		1100
FMx3	25			25	1100
FMx4	25	50			1100
FMx5	25		50		1100
FMx6	25			50	1100
FMx7	25	75			1100
FMx8	25		75		1100
FMx9	25			75	1100
FMx10	25	25			700
FMx11	25		25		700
FMx12	25			25	700

Images were taken by secondary electrons using 10kV and different magnification powers.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of samples were achieved using FTIR spectroscope at 4000–400 cm^{-1}. These samples were pure Meloxicam, HPMCE-50 LV, and Meloxicam nanoparticle of selected formula. Each sample was pulverized with KBr and pressed into a disc of 13 mm diameter.

Differential Scanning Calorimetry (DSC)

DSC (PerkinElmer) was used to specify the crystalline state of Meloxicam pure and nanoparticles. Thermal characteristics of samples were obtained by an automatic thermal analyzer system. Precisely weighed of 6.02 mg was placed in non-hermetically aluminum pan and heated at the rate of 20ºC/minute at temperature range of 40 to 600º C.

X-ray Powder diffraction (XRPD)

X-ray powder diffraction was operated to study crystalline structure of pure drug, and the prepared nanoparticles of Mx. The X-ray diffraction have the operating voltage and current were 30 kV and 30 mA, respectively.

Preparation of Oral Film

Meloxicam nanoparticles were formulated into oral thin film by solvent casting method.[12] A film of about 4 cm^2 area must have 15 mg of Meloxicam nanoparticles from selected formula that equal to 7.5 mg of raw Meloxicam was prepared. This film was prepared by gradual addition and dissolving of 420 mg of HPMC-E15 in 12 mL distilled water with stirring for 1-hour to ensure the complete dissolve all polymer, and then 0.5 mL of glycerin as plasticizer was to this solution with continuous stirring for additional half hour. Then the weighted nanoparticles powder was also added gradually with stirring for 1-hour, and to remove the entrapped air bubbles, gel was kept for 2 hours. The resulted gel was casted on to a petri dish of of 56 cm^2 and left to dry at room temperature for 36 hours. The required weight of Meloxicam nanoparticles in the preparation was calculated by dividing petri dish area of 56 cm^2 on dosing area of 4 cm^2 which gave 14 films each contained 15 mg of Meloxicam nanoparticles so that total petri dish will required 210 mg of Meloxicam nanoparticles powder.

Evaluation of Oral Thin Film of Meloxicam Nanoparticles

Visual Examination

The visual examination of film was involved in the physical appearance of films such as consistency, color and homogeneity films. These parameters were tested by visual examination of films and evaluation of quality by touch,[13] and also done by FESEM for this film.

Weight Variation

Ten films had been selected each of 4 cm^2 and were weighed separately and the average weight was calculated.[14] The weight variation test had confirmed the uniformity of the prepared oral thin film.

Thickness

This test is required to check the uniformity of the film thickness. A digital vernier caliper (Mitutoyo, Japan) was operated to determine thickness of the film using five different sites at center and four corners. The average and standard deviation were calculated for five films.

Folding Endurance

The folding endurance of oral film was stated by repetitively folding of oral film at a fixed point until broken. The recorded folding number before the film is broken indicates the value of folding endurance.[15]

The Surface pH of Oral Film

The oral film was put in 5 mL of distilled water and the pH of the solution was determined using pH-meter. A three trials was performed for this test and the average value were calculated.[16]

Drug Content

A 4 cm^2 film was transferred into 100 mL simulated saliva solution and stirring for 30 minutes for a complete dissolve of Mx nanoparticles. Sample of 1 mL was drawn and diluted to 10 mL with the simulated saliva solution and then analyzed by UV at λ max of this media. A three trials was performed for this experiment and the average value and standard deviation was calculated.[17]

Disintegration Test

The time of disintegration was specified by putting a film into the small container of distal water, and the time was accounted until it disintegrates.[18] The experiment was executed in triplicate and the mean value was calculated.

Swelling Index of Oral Film

Take Meloxicam films 4$cm^2$and weighed (W0) and placed into a pre-weighed stainless steel basket (basket of tablet dissolution apparatus). The basket containing oral film was dipped into petri dish of containing 35 mL simulated saliva solution. The increment in weight of oral film was measured at frequent time until a constant weight was detected.[19] The degree of swelling was determine using the equation number (1). The degree of swelling = $(W_t\text{-}W_0)/W_0$….Eq (1). Where Wt and W0 are the weight of film sample at time t and time zero respectively the experiment was achieved in triplicate and the mean value was calculated.

In Vitro Dissolution Study of Mx Nanoparticles Loaded Oral Film

The prepared oral film's in-vitro dissolution of Meloxicam nanoparticles was determined using USP type II dissolution apparatus (paddle type). Oral film containing 15 mg of Meloxicam nanoparticles of FMx1 and oral film containing 7.5 mg of raw Meloxicam was allowed to dissolve in 500 mL of simulated saliva (using special sinker), the paddle was modified to rotate at 50 rpm and 37 ± 0.5°C.[20] Samples of 5 mL were drawn by a syringe frequently at intervals of 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 minutes, filtered through 0.22 µm membrane filter and diluted with dissolution media (simulated saliva containing 0.05% DMF) then analyzed using

UV-spectrophotometry at recorded λ max. An equal volume of fresh simulated saliva was replaced after each sample. The dissolution profile of the drug was constructed by plotting the percentage of accumulative drug release against time. The test was performed in triplicate, and the mean value was calculated.

Statistical Analysis

The resultant values of the achieved test are given as mean samples ± standard deviation (SD) and were statically analyzed for differences using one-way analysis of variance (ANOVA) at $p \leq 0.05$.

RESULT AND DISCUSSION

Evaluations of Prepared Meloxicam Nanoparticles

Particle Size and Polydispersity Index Analysis

The particle diameter of all formulas was characterized and found within a range of nanometer sizes (667.5 nm–59.5 nm), as shown in Table 2. ABT-9000 Nano laser is a particle size analyzer working based on dynamic light scattering theory (DLS), was used to measure the size of Meloxicam nanoparticles and PDI; all formulas were showed monodisperse PDI except FMx4, and FMx6 which showed a mid-range polydispersity. This study revealed a decrease in particle size and accordingly high surface area of Meloxicam nanoparticles compared with pure drugs.[21]

Effect of Type and Concentration of Polymer on Meloxicam Nanoparticles:

Particle size of formulas FMx1-FMx3 of different polymer used at constant ratio of polymer: drug 1:1 gave different particle size range of 59.5–375 nm, this indicates that, polymers have different affinity to Meloxicam particle, although at same ratio as shown in Figure 1. The smallest particle size was achieved with HPMCE-50 LV polymer in F1 significantly ($p \leq 0.05$) decrease in particle size (59.5 nm) than other polymers, this due to high affinity of this polymer to Meloxicam particles than the other polymer used. The measured particle size of formula FMx4-FMx9 at polymer: drug ratio of 2:1and 3:1 was show increase in range from 105–667.5 nm, it is found that the increase in the polymer concentration lead to an increase in the prepared particle size of Meloxicam nanoparticles, aggregation of particles might appears as result of the higher thickness of layer around each particle and/or the high number of polymer chains that associated in the diffusion process that lead to increases in polymer-polymer interaction,[22] therefore, FMx1 which have smallest size was selected and subjected for further studies. The polymers used in this study were anionic and cationic, which influence the stability of the system by steric effect; this could be accomplished by adsorbing of polymer onto the surface of particle by an anchor part that is firmly detached with the dispersed particles, while the solvated tail part outspreads into the bulk medium.[23]

Table 2: Meloxicam nanoparticles particle size, specific surface area (SSA), and polydispersity index (PDI)

Formula no.	*Average particle size (nm)*	*Specific surface area SSA (m^2/g)*	*PDI*
FMx1	59.5	37.34	0.03
FMx2	298	7.17	0.003
FMx3	375	6.11	0.01
FMx4	105	20.66	0.19
FMx5	334	6.82	0.011
FMx6	426	5.44	0.2
FMx7	167.5	12.96	0.034
FMx8	530	4.02	0.008
FMx9	667.5	3.35	0.009
FMx10	165	13	0.007
FMx11	421	5.10	0.008
FMx12	561	3.9	0.007

The Effect of Stirring Rate on Meloxicam Nanoparticles

It was found that the increase in stirring rate led to a significant ($p \leq 0.05$) decrease in the size of the prepared Meloxicam nanoparticles as shown in Figure 2, two stirring rates of 1100 and 700 rpm with polymers of HPMC-E50, PVP-K15, PVP-K30 at constant polymer: drug ratios of 1:1, for formula FMx1, FMx2, FMx3 and F10Mx, FMx11, FMx12 respectively, high stirring rate will induce the fast nucleation produced very small drug particles.[24]

Saturated Solubility of Meloxicam Nanoparticles

The result of saturation solubility of Meloxicam raw powder and nanoparticles FMx1were 0.4 mg/mL and 2 mg/mL, respectively. Meloxicam is assigned as practical water-insoluble. It was categorized in class II of the biopharmaceutical classification system.[25] Saturated solubility of Meloxicam nanoparticles of FMX1 increased significantly ($p \leq 0.05$) five times in simulated saliva than raw meloxicam due to reduced particle size.

Drug Content Loading Efficiency

The measured drug content result from formula F1 was 7.4 ± 0.02 mg and the loading efficiency of it was 98.6 ± 0.05%, so that the solvent: antisolvent method was effective in preparing Meloxicam nanoparticles.

Field Emission Scanning Electron Microscope (FESEM)

FESEM imaging of Raw Meloxicam particles present with large and irregular shape, as shown in Figure 3, the FESEM

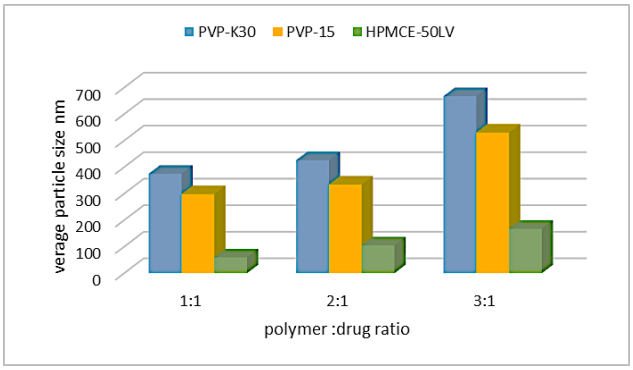

Figure 1: Effect of type and concentration of polymers in on average size (n=3) of Meloxicam nanoparticles

image with 15Kx magnification power while FESEM of FMX1 as in Figure 4 image at 60 Kx of magnification, elucidated uniform and reduced particles size less than 100 nm and this result might be caused by adsorption or capping effect of the stabilizer on the drug surface.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR is a potent technique and one of the most widely reported drugs–excipients compatibility studies for solid-state characterization. The pure Meloxicam showed a spectrum with characteristic peaks at 3288.63cm^{-1} (N-H stretching vibrations of secondary amide), 1620.21 cm^{-1} (C=N stretching vibrations of thiazole), 1548.84 cm^{-1}, 1525.69 cm^{-1} (N-H bending vibration of secondary amide), 1452.4 cm^{-1} (C=C stretching vibration of the ring), 1159.22 cm^{-1} (symmetric S(=O)$_2$ stretching vibrations of organic sulfoxide), and 1043.49 cm^{-1} (C-C-O stretching of secondary alcohol). These are the main characteristic absorption band of Meloxicam, as shown in Figure 5.[26] The results from FTIR of HPMCE50, and FMX1 as in Figures 6 and 7, showed the existence of prominent peaks of Meloxicam which indicates there is no interaction occur between Meloxicam and polymer during the preparation of nanoparticles.

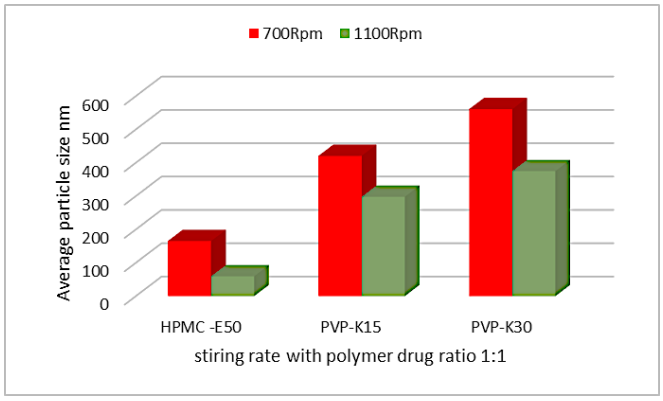

Figure 2: Effect of stirring rate on the average size (n=3) of Meloxicam nanoparticles

Differential Scanning Calorimetry (DSC)

DSC thermogram studies were done for raw Meloxicam powder of as shown in Figure 8. The results obtained that single sharp endothermic peak at 262°C, these result near the result by study.[27] While DSC of F1 in Figure 9 showed a remarkable decrease in peak sharpness in comparison with raw Meloxicam, this indicates a reduction of the crystalline state of Meloxicam and conversion of it to an amorphous state, this result agree with X-ray of formula FMX1.

X-ray Powder Diffraction Analysis

The attained spectrum of X-ray diffraction test of raw meloxicam showed several firm characteristic peaks at 2θ =25.674°, 19.07°,18.434°, and 14.771° as shown in Figure 10, which indicates the crystalline state of the raw drug. Meloxicam nanoparticles of FMX1, as shown in Figure 11, showed less number and low intense of diffraction peaks in comparison to that of pure Meloxicam, which indicates that the crystalline structure of Meloxicam was reduced and it converted into an amorphous state, a similar result was also found.[28]

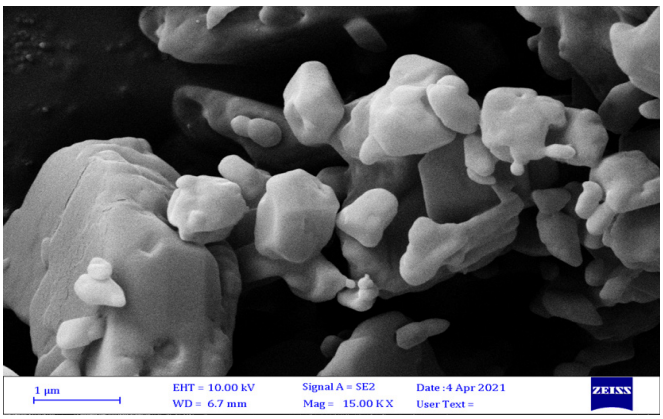

Figure 3: FESEM of Meloxicam with magnification power (15 kx)

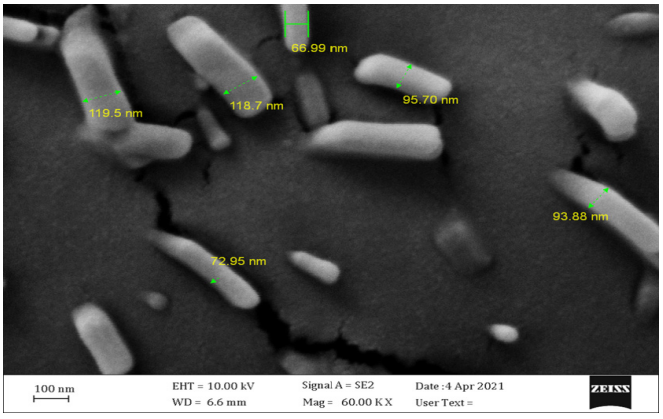

Figure 4: FESEM of FMX1 with magnification power (60 kx)

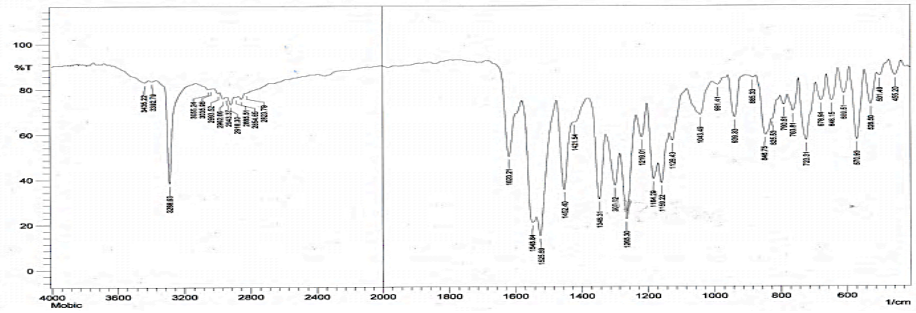

Figure. 5: FTIR spectrum of raw Meloxicam

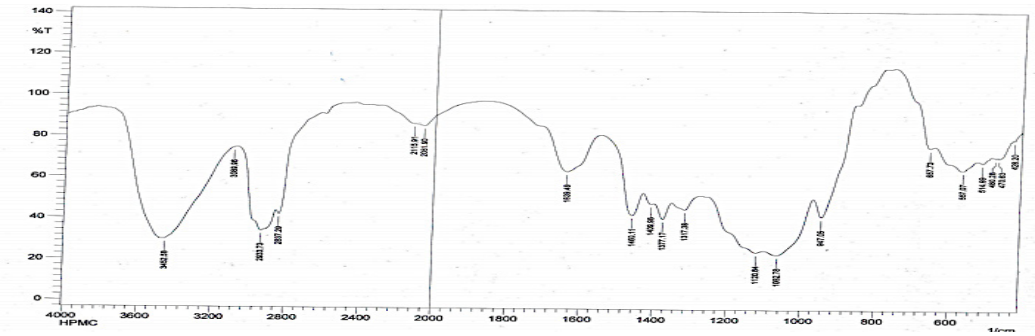

Figure 6: FTIR spectrum of HPMCE-50LV

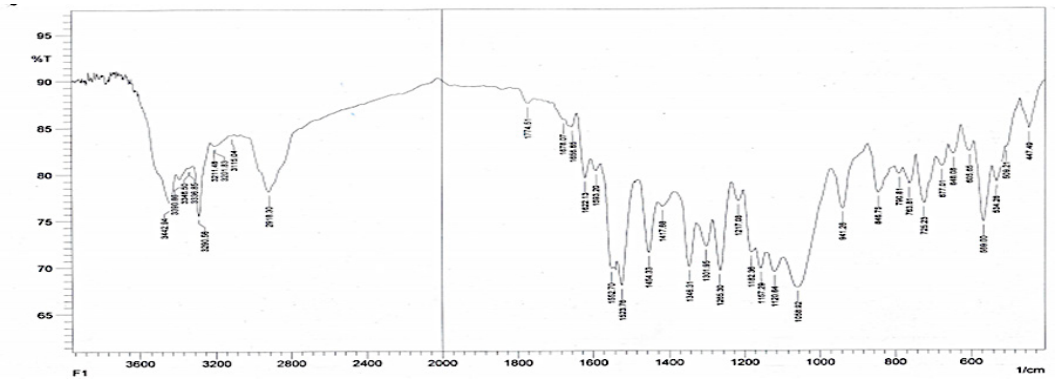

Figure 7: FTIR spectrum of F1

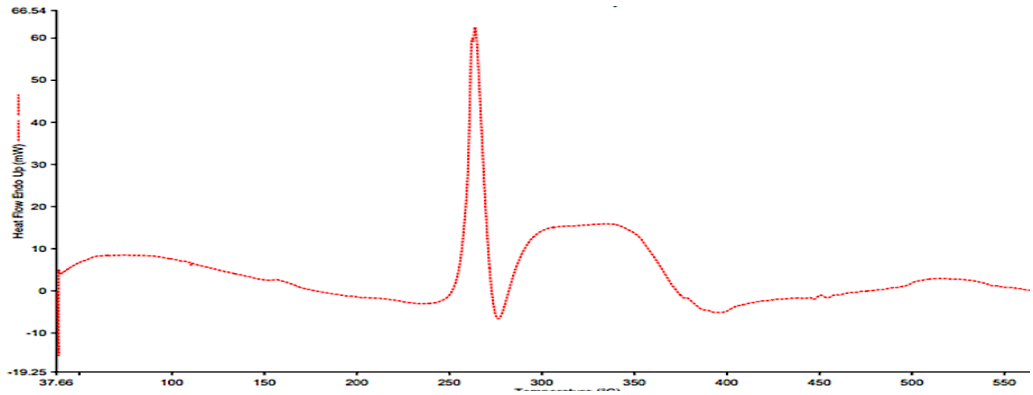

Figure 8: DSC of raw Meloxicam

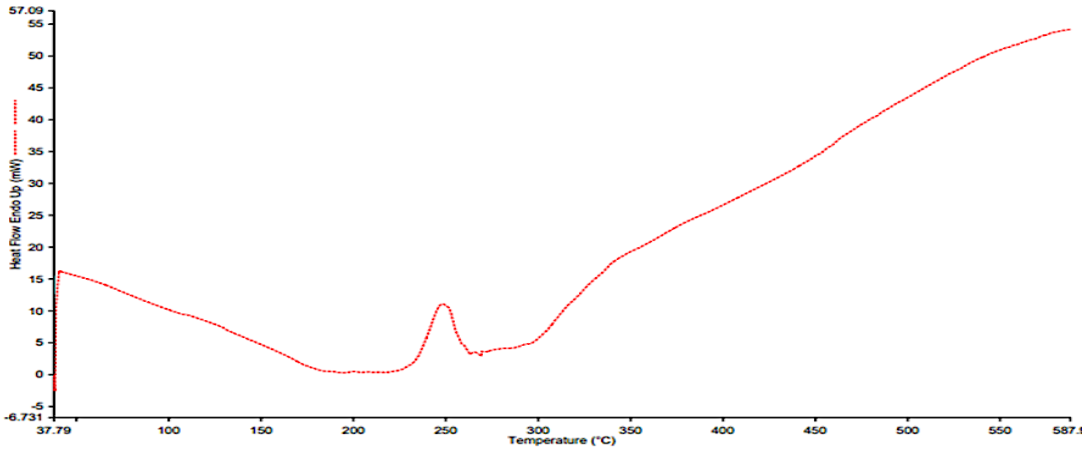

Figure (9): DSC of FMX1

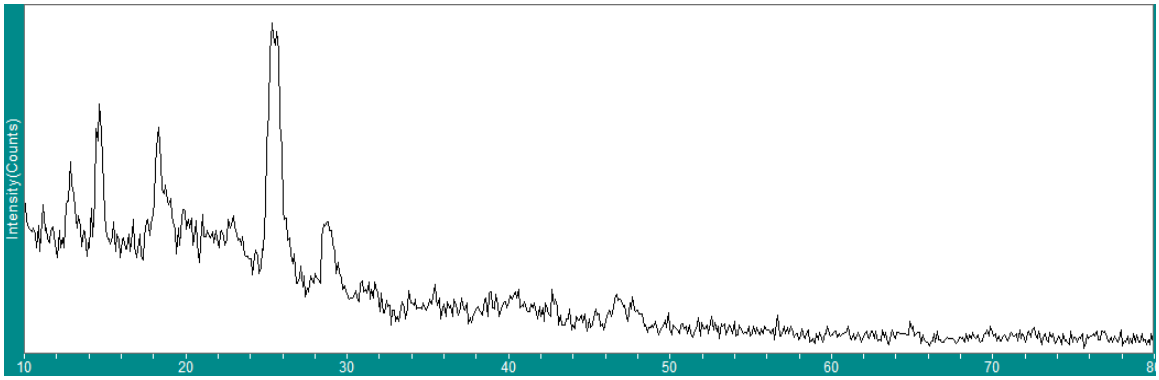

Figure 10: PXRD of Raw Meloxicam

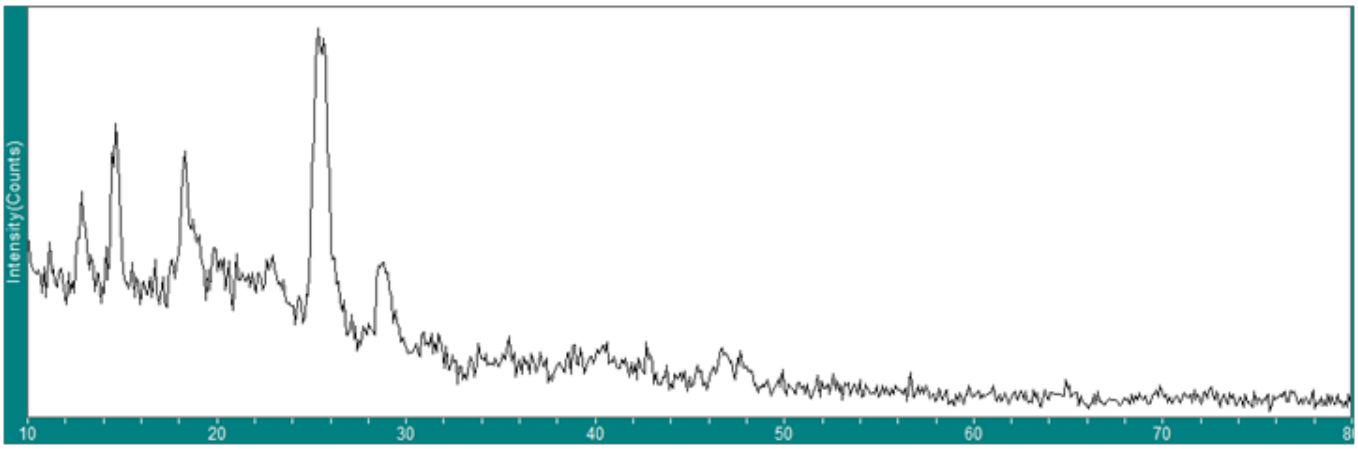

Figure 11: PXRD of (FMX1)

Visual Examination and FESEM of Oral Film

The film of Meloxicam nanoparticles (FMX1) prepared from HPMC-E15 was yellow, thin, and soft film, as shown in Figure 12. A good distribution of Meloxicam nanoparticles through the 4 cm^2 film as shown with FESEM of FMX1 in Figure 13.

Weight Variation of Oral Film

The average weight of ten films was equal to 48.86 mg ± 0.7, and lower stander deviation indicates that the oral films had a uniform weight.

Thickness of Oral Film

The thickness of the prepared five films was found to be (0.136 ± 0.015), (0.13 ± 0.017), (0.12 ± 0.026), (0.12 ± 0.01), and (0.11 ± 0.016) mm. The film thickness uniformity was revealed by shallow standard deviation values that approve the accuracy of the dose and constant thickness and so the success of solvent casting method in preparation of oral film.

Folding Endurance

The folding endurance of meloxicam nanoparticles film formulated by solvent casting method was found to be in range of 120–145 times.

The Surface pH of Oral Film

The pH of meloxicam nanoparticle films is (6.4 ± 0.23 - 6.9 ± 0.16). These pH values within accepted rang of oral mucosa pH do not cause oral mucosal irritation.

Drug Content of Oral Film

The accepted range of content uniformity is ranged from 85 to 115%,[29] the Meloxicam nanoparticles film gave good drug content of 98.4 ± 1.3 %, which indicates that the use of solvent casting method in preparing oral film was very effective.

Disintegration Time

The disintegration time of oral film prepared from FMx1was found to be within a range of 29 seconds within the assigned limit for the peri-oral disintegrating tablet of ≤30 sec. This recommendation is helpful for the development of oral thin film formulation.[30]

Swelling Index of Oral Film

The swelling index of the prepared oral film containing FMX1 shows complete hydration of film was occur at 4 minutes**,** as shown in Figure 14.

In-vitro Dissolution Study of Mx Nanoparticles Loaded Oral Film

Dissolution profiles of Meloxicam oral films were done for oral film formulated from Meloxicam nanoparticles (FMX1) and for oral film prepared from Meloxicam raw material using 500 mL simulated saliva solution PH 6.75 at 50 rpm and 37°C show in Figure 15. In this test used the time to reach 100% of release and % of release in 3 minutes to compare between film containing Meloxicam nanoparticles F1 and others containing

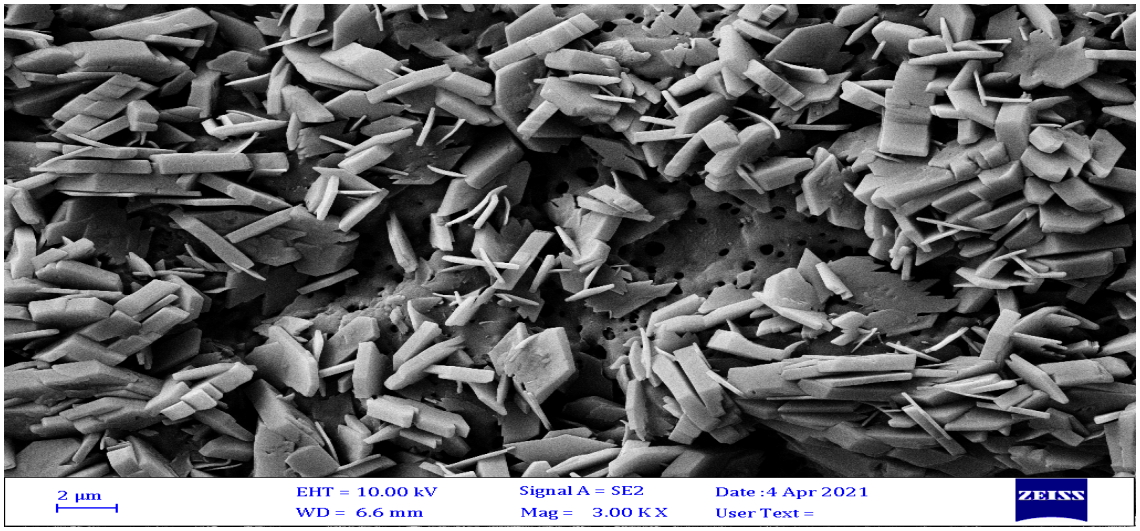

Figure.13: FESEM of oral film prepared from FMX1 with magnification power (3kx)

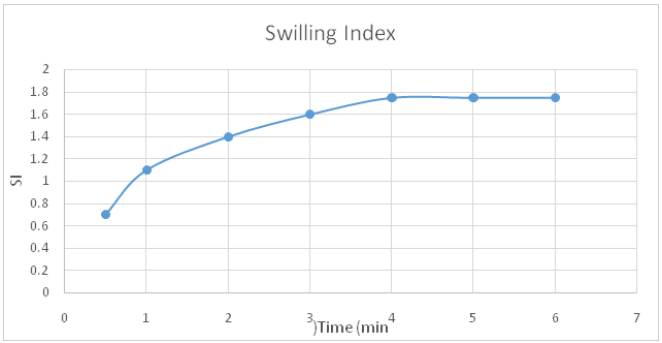

Figure.14: Swelling index of oral film containing FMX1with use HPMC-E15, mean (n=3)

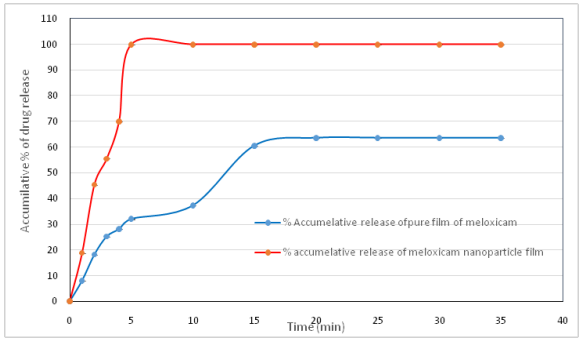

Figure.15: *In vitro* release profile of oral film in simulated saliva mean ± SEM (n = 3)

raw Meloxicam. The accumulative percentage of the release of Meloxicam from film containing FMX1 in three minutes was 55.5% and reached 100% at the time of 5 minutes. While, accumulative percentage of the release of raw Meloxicam film in three minutes was 25.2%, and did not reach 100% of release due to poor solubility of Meloxicam in simulated saliva, While oral film prepared with Meloxicam nanoparticles (FMX1) gave the best dissolution profile and quick release of Meloxicam nanoparticles, this can be attributed to its nanoparticles profile, as well known, decreasing particle size to the nanometer range could increase the solubility of poorly soluble drugs.

CONCLUSIONS

In this study, Meloxicam nanoparticles were made using the solvent antisolvent method. Then, the solvent casting method was applied for loading them into the oral film. The prepared Meloxicam nanoparticles and oral film revealed film thickness and drug content uniformity, fast disintegration, and desirable dissolution profile. The FESEM images and PXRD implied that Meloxicam nanoparticles were uniformly distributed into the films. Therefore, Meloxicam nanoparticles prepared as the oral thin film could be a sound delivery system to fasten the onset of action and to enhance the dissolution and bioavailability.

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