Preparation and Evaluation of Meloxicam Microsponges as Transdermal Delivery System

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Abstract

The aim of present study was to develop gel formulation of microsponges of poorly soluble drug meloxicam (MLX) in order to enhance the release and dissolution of MLX which is the limitation for preparation in topical forms. Also skin delivery is an alternative administration for MLX that can minimize gastrointestinal (GI) side effects and improve patient compliance. The microsponges of MLX were prepared by quasi-emulsion solvent diffusion method. The effects of drug:polymer ratio, stirring time and Eudragit polymer type on the physical characteristics of microsponges were investigated and characterized for production yield, loading efficiency, particle size, surface morphology, and in vitro drug release from microsponges. The selected microsponge formula was incorporated into gel. The prepared microsponge gel was evaluated as visual inspection, pH, spreadability, viscosity, in addition to *in vitro* drug release. The results showed that the microsponge formula with Eudragit L100 polymer had optimum physical properties and enhanced the dissolution and release of MLX when compared with other formulas and pure drug. MLX microsponge carbopol gel produced a significant ($p<0.05$) improvement of the in vitro release than pure MLX gel. Hence quasi emulsion solvent diffusion method was a promising method to produce MLX microsponges with markedly enhanced dissolution rate.

Keywords: Meloxicam, Microsponges, Gel.

تحضير وتقييم لدواء الميلوكسيكام كأسفنجيات مايكرويه كنظام تسليم عبر الجلد

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الخلاصة

الهدف من الدراسه المقدمة هو تطويرصياغة هلام من اسفنجيات مايكروية من دواء الميلوكسيكام قليل الذوبان لتعزيز ذوبانيه و تحريره باشكال موضعيه واستخدامه عن طريق الجلد كوسيلة بديلة للتقليل من اثاره الجانبية على الجهاز الهضمي فضلا عن زيادة امتثال المريض .حضرت الاسفنجيات بطريقة انتشار المذيبات من شبه مستحلب ثم اختبرت ال تأثيرات على الخصائص الفيزياويه للاسفنجيات مثل نسبة الدواء الى البوليمر , مدة الخلط و نوع البوليمر . كما تم تقيم الاسفجيات بالنسبه الى عائد الانتاج , لكفاءة التحميل, حجم الجسيمات, شكل السطح, وتحرر الدواءخارج الجسم . بعدها اضيفت الاسفنجيات المختاره في الهلام وتم تقييم الهلام من حيث الفحص البصري, ودرجة الحموضة, الانتشار, اللزوجة, بالإضافة إلى تحرر الدواء من الهلام مختبريا . وأظهرت النتائج أن الصيغة المثلى للاسفنجيات هي التي تحتوي على ايودراجت ل 100 بوليمر زيادتها الخصائص الفيزيائية المثلى وتعزيز تحرير وإطلاق دواء الميلوكسيكام بالمقارنة مع الصيغ الأخرى والدواء النقي كذلك هلام الكاربوبول المحتوي على الاسفنجيات للميلوكسيكام اظهر زيادة في تحرر الدواء مختبريا مقارنة م ع هلام الميلوكسيكام النقي. وبذلك اثبتت طريقة انتشار المذيبات من شبه مستحلب وسيلة واعدة لإنتاج الميلوكسريكام كأسفنجيات مايكروية مع تعزيز ملحوظ في معدل تحرر الدواء.

الكلمات المفتاحية: الميلوكسيكام, الاسفنجيات المايكروية, هلام.

Introduction

Solubility of the drug is the factor that controls its formulation, as well as its therapeutic efficacy, and therefore, considered as the most critical factor in formulation development. The major problem associated with transdermal delivery system (TDS) is most of the drugs are poorly water soluble which pose many problems while formulating them in conventional dosage forms. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability . These approaches include micronization, solubilization using co-solvents, use of permeation enhancer, salt formation, liposomes, emulsions, microemulsions, solid-dispersions and inclusion complexes using cyclodextrin show reasonable success but they lack in universal applicability to all drugs. Hence there is need of some different and simple approach which can resolve these problems [(1)].

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The microsponge delivery system (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. Microsponge delivery system enhances the rate of dissolution of poorly water soluble drugs by entrapping such drugs in microsponge pores. Dissolution rates of the sparingly soluble drugs are related to the shape as well as the particle size. Therefore decrease in particle size by micronization of such drugs result in an increase in dissolution rate [(2)].

Meloxicam is a highly potent, non-steroidal anti-inflammatory drug (NSAID), which is used for the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases. However, adverse effects on the gastrointestinal (GI) tract, such as stomachache and indigestion, and patient compliance are weakened of the oral and injectable MLX administrations. Chemically MLX ($C_{14}H_{13}N_3O_4S_2$) is 4-Hydroxy–2–methyl-*N*-(5–methyl–2–thiazolyl)-2*H*-1,2–benzothiazine–3–carboxamide–1,1–dioxide as shown in figure (1). It has dissociation constant pK_a (1.1, 4.2) and partition coefficient Log P (octanol/water) 3.43 and its practically insoluble in water (0.012 mg/ml) [(3)].

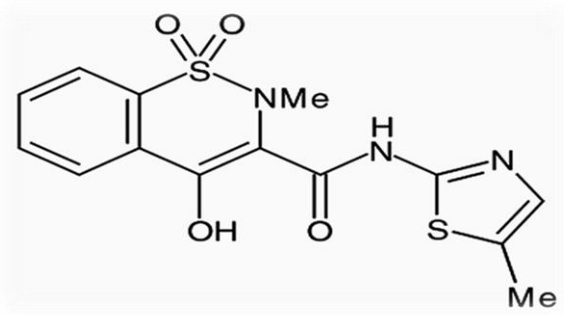


Figure 1: Chemical structure of meloxicam

The aim of present study was to design microsponges as new carrier for poorly water soluble drug MLX in order to enhance the release and the dissolution of MLX. This investigation consisted of preparation, optimization, and evaluation of MLX microsponges and incorporation of optimized microsponges in a gel to obtain acceptable product.

Materials and Methods

Materials

Meloxicam powder was supplied by Alsafa drug industry-Iraq, Eudragit polymers (RS, S100) powder were obtained from Barlocher-GMBH-Germany ,Eudragit (E100 granules, L100 powder) were supplied from Samara drug industry-Iraq, polyvinyl alcohol(PVA) from Barcelona Espana, and carbopol 934 from HiMedia (Mumbai, India). All other materials used in this study were of analytical grade.

Methods

Preparation of meloxicam microsponge

MLX microsponges were prepared by quasi-emulsion solvent diffusion method. The organic internal phase was consisted of Eudragit RS PM , Eudragit S100 , Eudragit L100 or Eudragit E100 and glycerol (1ml) dissolved in dichloromethane. Glycerol was used as plasticizer. Then, MLX was added to solution and dissolved under ultrasonication at 35°C for 15 minutes. The resulting solution was then poured into 0.05 g of PVA solution in water (external phase of 200 ml volume). The mixture was stirred at 500 rpm for 1hr, 2hr or 4hr at room temperature to remove dichloromethane from the reaction flask. The formed microsponges were filtered and dried at 40^0C for 12 hr and stored for further investigations [(4)]. The composition of various microsponge formulations is given in table (1).

Characterization and evaluation of microsponges formulation

Determination of the production yield

The production yield of the microsponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained [(5)].

$$\text{Production yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + drug)}} \times 100 \quad \text{..... equation (1)}$$

Determination of loading efficiency

A sample of MLX microsponges (10 mg) was dissolved in 100 ml of phosphate buffer, freshly prepared (pH 7.4). The solutions were subsequently diluted suitably with the phosphate buffer pH 7.4 and spectrophotometric absorbance was taken at the maximum wave length of MLX. The drug content was calculated from the calibration curve and expressed as the loading efficiency [(5)].

$$\text{Drug loading} = \frac{\text{Mass of drug present in microsponges}}{\text{Theoretical mass of MLX}} \times 100 \quad \text{..... equation (2)}$$

Table (1): The composition of microsponges formulas

Formulas	Internal phase composition					External phase		Stirring rate (rpm)	Stirring time (hr)
	Drug:polymer ratio	Drug (g)	Type of Eudragit polymer	Polymer (g)	Dichloromethane (ml)	Water (ml)	PVA (g)		
F1	3:1	0.6	RS PM	0.2	5	200	0.05	500	1
F2	6:1	1.2	RS PM	0.2	5	200	0.05	500	1
F3	9:1	1.8	RS PM	0.2	5	200	0.05	500	1
F4	12:1	2.4	RS PM	0.2	5	200	0.05	500	1
F5	9:1	1.8	RS PM	0.2	5	200	0.05	500	2
F6	12:1	2.4	RS PM	0.2	5	200	0.05	500	2
F7	9:1	1.8	RS PM	0.2	5	200	0.05	500	4
F8	12:1	2.4	RS PM	0.2	5	200	0.05	500	4
F9	12:1	2.4	S 100	0.2	5	200	0.05	500	1
F10	12:1	2.4	L 100	0.2	5	200	0.05	500	1
F11	12:1	2.4	E 100	0.2	5	200	0.05	500	1

Particle size analysis

Determination of the average particle size of MLX loaded microsponges was determined with an optical microscope using a calibrated ocular and stage micrometer under a regular polarized light. A minute quantity of microsponges was spread on a clean glass slide and the average particle size was calculated by measuring 100 particles of each batch [6].

$$d_{av} = \sum nd / \sum n \quad \text{..... equation (3)}$$

Where: d_{av} is the average diameter of particles (μm), n is number of particles per group, and d is the middle value (μm).

Scanning electron microscope (SEM) study

For morphology and surface topography, the prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscope (VEGA3 Tescan Czech republic) [7].

In-vitro drug release studies of microsponge formulations

In vitro dissolution study was performed using USP dissolution test apparatus-II (paddle assembly) (Copley dissolution 8000, Copley scientific, UK). The dissolution was performed in 900 ml of phosphate buffer solution (pH 7.4) as a dissolution medium and maintained at 32 ± 0.5°C and 100 rpm for optimum MLX microsponge formulas. A sample of microsponges equivalent to 20 mg of MLX was used in each test. Samples of dissolution fluid (10 ml) were withdrawn at different time intervals and immediately replaced with 10 ml of the fresh dissolution medium to maintain a sink condition. The samples were filtered through a filter (0.45 μm, Millipore), suitably diluted and analyzed at λ max of MLX using a UV-visible spectrophotometer (Cary 100, Varian, Australia) [8]. In addition, the dissolution study was performed for the above mentioned microsponge formulas in comparison with pure MLX powder.

Fourier transform infrared (FTIR) analysis

FTIR spectra of the pure MLX, physical mixture of MLX and polymer at ratio (1:1), and selected microsponge formula were recorded in potassium bromide disc using a Shimadzu Model 8300 FTIR spectrometer to ascertain compatibility [(9)].

Differential scanning calorimetric (DSC) analysis

DSC can be used to determine the compatibility between the drug and excipients and can also use to evaluate the crystalline state of drug. Thermal analysis using DSC was carried out on the same samples used in FTIR by using (Shimadzu DSC-60 Thermal Analyzer). Accurately weighed samples (5mg) were loaded into aluminum pans and sealed. All samples were run at a heating rate of 10 ^{0}C/min. over a temperature rang 0-350 ^{0}C in atmosphere of nitrogen [(10)].

Powder x-ray diffraction analysis (PXRD)

X-rays diffraction patterns (diffractograms) can be used to confirm the crystalline nature of a sample. The study was confirmed by powder X-ray diffractometer at continuous scan range of 2θ = 5 - 50^o; the operating voltage and current were 40 (kV) and 30 (mA) respectively [(11)]. Samples studied by using XRD are the same used in FTIR study.

Kinetic modeling of drug release from microsponge

To analyze the mechanism of MLX release from the formulas, the in- vitro release data were fitted into various release kinetic models. The models used are: zero order, first order, Higuchi model, Hixon- Crowell model and Korsmeyer - Peppas [(12)]. The model with the highest correlation coefficient was considered to be the best fitted model.

Preparation of meloxicam microsponge carbopol gel

0.5% w/w carbopol 934 gel was prepared. The preservative (methyl paraben) was dissolved in a sufficient quantity of water pre-warmed to 40°C. The carbopol 934 was then added in small amount with vigorous stirring. The dispersion was homogenized using a magnetic stirrer for 1hr and then left for 24 hr for complete swelling. After that, the triethanolamine was added drop by drop with continuous mixing and the final weight was completed to 100 g with water. Weighted amounts of MLX microsponge formula was incorporated, so that the final concentration of MLX is 1% w/w in the final gel formula [(13)]. A control formula was prepared by the same procedure using pure MLX powder only in a concentration of 1% w/w in the prepared gel.

Physical properties of the prepared gel

The visual examination

The examination considered a series of visual characteristics (consistency, color, and homogeneity).

pH determination

The pH of the prepared gel was measured using pH – meter by putting the tip of the electrode into the gel and after 2 minutes the result was recorded [(14)].

Spreadability

A sample of 0.1g of gel was pressed between 2 slides with 500g weights and left for about 5 min where no more spreading was expected. Diameters of spread circles were measured in cm and were taken as comparative values for spreadability (diameter of the spread circle – initial diameter [(15)].

Viscosity

Rheology includes the measurement of viscosity, which indicates resistance of a fluid to flow. The viscosity of gel was determined by using Myr Rotational (cup and bop) digital Viscometer with spindle no. R7 with an optimum speeds 2.5, 3, 4, 5, 6, 10, 12 rpm at room temperature.

Determination of meloxicam content in the gel formula

MLX content in the gel was determined by taking required quantity of the prepared gel which is equivalent to 10 mg of meloxicam and transferred to 100 ml volumetric flask containing phosphate buffer (pH 7.4), it allowed to sonicate and filtered. Then, suitably diluted and analyzed at λ max of MLX [(16)].

In-vitro dissolution test of meloxicam microsponge gel

The *in vitro* release of MLX from gel formula was performed by using dissolution apparatus-II (paddle type). A weighing quantity of a gel (2 g that contain 20 mg MLX) was uniformly spread on a disk 4.5cm in diameter, and this was immersed in dissolution jar filled with 900 ml dissolution media (phosphate buffer pH 7.4) at 32 ± 0.5°C . The paddle was about 2cm above the disk and rotated at speed of 100 rpm, samples of 10 ml were withdrawn at intervals of 30, 60, 90, 120, 150, 180 minutes and were replaced with equal volume of the fresh buffer solution each time to maintain constant volume. The samples were filtered through a filter (0.45 μm, Millipore), suitably diluted and analyzed at maximum wave length of MLX [**(17)**].

Kinetic modeling of drug release from the gel

The *in vitro* release data were fitted into kinetic model to analyze the mechanism of drug release.

Statistical analysis

The results of the experiments are given as a mean of three samples ± standard deviation and were analyzed according to the one-way analysis of variance (ANOVA) test using Microsoft Excel Program 2010. Differences were considered to be statistically significant at $p < 0.05$.

Result and Discussion

Quasi-emulsion solvent diffusion method was used because of its simplicity and reproducibility. Also this method seen to be promising for the preparation of MLX microsponges with being easy, rapid, and cost effective method and has an advantage of avoiding solvent toxicity [(18)].

In quasi-emulsion solvent diffusion method, the formation of the microsponges could be by the rapid diffusion of dichloromethane into the aqueous medium, might reduce the solubility of the polymer in the droplets, since the polymer was insoluble in water. The instant mixing of the dichloromethane and water at the interface of the droplets induced precipitation of the polymer, thus forming a shell enclosing the dichloromethane and the dissolved drug. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of the solvent [(18)].

The production yield (PY) was between 56–100% for all formulas. The loading efficiency (LE) varied between 30–90% for all formulas. The mean particle size of the formulas was between 22-66 µm. There was a significant difference between formulas ($p < 0.05$) in the PY, LE, and mean particle size.

Effect of drug to polymer ratio on meloxicam microsponges formulation

The drug-polymer ratio has considerable effect on the nature of microsponges as shown in table (2). It was indicated that increasing the drug: polymer ratio increased the production yield and loading efficiency . At higher drug: polymer ratios, the available polymer can encapsulate more amount of drug. The highest loading efficiency, greater the amount of drug was encapsulated. It was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratios, the amount of polymer available per microsponge was comparatively lower. Probably in high drug polymer ratios less polymer amount surrounds the drug and microsponges with smaller size were obtained [(19)]. This provides an extensive surface area for high entrapment.

Table (2): Effect of drug to polymer ratio on meloxicam microsponges formulation (Mean±SD)

Formulas	Drug: polymer	PY %	LE %	Particle size (µm)
F1	3:1	59	41.51 ±0.06	66.4
F2	6:1	70	54.74 ±0.08	51.6
F3	9:1	99	70 ±0.05	44.2
F4	12:1	100	85 ±0.06	40.5

Effect of stirring time on microsponges

The stirring time had significant effect on the formation of microsponges [Table 3]. It was observed when increasing the stirring time from 1 to 2 hr (in F5 and F6) and from 1 to 4 hr (in F7 and F8). One hour stirring was appropriate for the preparation and additional stirring time has no significant effect on the formation of microsponges. In this respect, the optimum stirring time was selected as 1 h. These findings are similar to the results reported previously [(20)].

Effect of polymer types of internal phase on microsponges

Table (4) shows that the polymer types have significant effect on loading efficiency and particle size of microsponges. Eudragit S100 and Eudragit L100 polymers increased the drug loading in microspoges formula F9 (92.42% MMS 100) and F10 (88% MML 100) respectively when compared to Eudragit RS PM polymer in formula F4 (85% MMRS), while the lowest loading observed among them in F11 (71.19% MME 100) when Eudragit E100 polymer is used. This may be attributed to the increasing viscosity of the internal phase containing the Eudrgit S100 and L 100 polymers, reducing the drug mobility outside the formed droplets, and hence entrapping larger amount of MLX [(21)].

The appearant viscosities of Eudragit polymer are [(22)]:

50-200 mpa.s for Eudragit S 100 and Eudragit L 100

1-15 mpa.s for Eudragit RS PO and RS 100

3-6 mpa.s for Eudragit E 100

Particle size also had an impact on the entrapment efficiency. The observations suggested that entrapment efficiency of the microsponges increased with the decrease in the particle size.

Consequently F9 of 22.47 µm had 92.41% entrapment efficiency while the F11 with the particle size of 56.25 µm entrapped 71.19% of MLX. As a well-known fact, lower the particle size more will be the availability of surface containing active sites for adsorption of drug, resulting in the better drug loading [23].

Table (3): Effect of stirring time on the production yield and loading efficiency of MLX microsponges (Mean±SD)

Formulas	Stirring time (hr)	PY%	LE%
F3	1	99	70±0.05
F4	1	100	85±0.06
F5	2	91.7	73.77±0.07
F6	2	97.69	81.7±0.05
F7	4	92.5	77.3±0.05
F8	4	97.3	81.6±0.09

Table (4): Effect of polymer types on loading efficiency and particle size of MLX microsponge (Mean±SD)

Formulas	Eudragit polymer types	Appearant viscosity (mpa.s)	LE%	Particle size(µm)
F4	RS	1-15	85±0.06	40.5
F9	S 100	50-200	92.42±0.08	22.47
F10	L 100	50-200	88±0.06	22.5
F11	E 100	3-6	71.19±0.09	56.25

In-vitro release studies of MLX microsponges

The dissolution profile was done for MLX microsponge formulas (F4,F9, and F10) because they provide the optimum microsponges production parameters (higher loading efficiency and smaller mean particles size). From the *in vitro* release data, it can be concluded that F10 that contain Eudragit L100 polymer gave the best release in comparison with other formulas (F9 that contain Eudragit S100 and F4 that contain Eudragit RS) and the formula shows a cumulative percentage drug release of 95.52% at the first 60 minutes.

This higher dissolution rate of microsponge F10 in comparison with other formulas and with pure drug figure (2) may be attributed to the fact that the reduction of drug particle size caused an increase in the surface area and consequently enhances the contact between particles and dissolution medium. The obtained results are in good accordance with Noyes–Whitney equation which states that the decrease in particle size lead to an increased dissolution rate [24]. Microsponge system enhance the solubilization of drug which are poorly soluble by entrapping these drug inside theirs pores. As these pores are very small, the drug is effectively reduced to microscopic particle and increase surface area lead to increase rate of solubilization [25].

The release of drug from the polymer matrix takes place after complete swelling of the polymer, and then degradation of the polymer lead to release of drug. F10 and F9 microsponges consist of Eudragit L100 and S100 which are the most commonly used pH-dependent coating polymers. Eudragit L dissolve above pH 6 and Eudragit S above pH 7 with the formation of polymeric salts while Eudragit RS are pH independent [26].

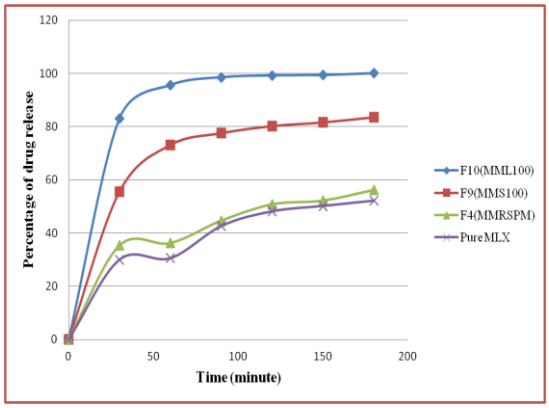


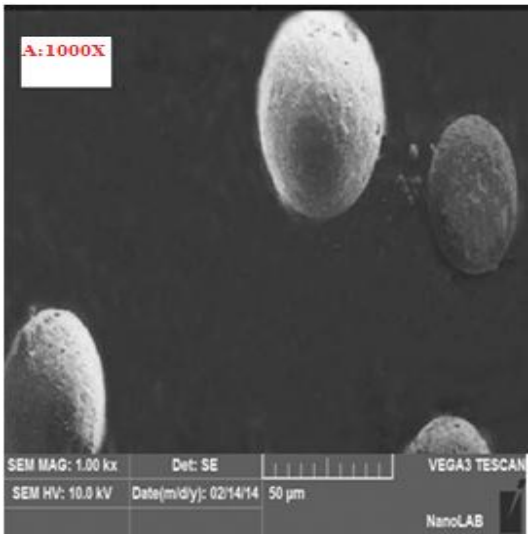
Figure 2: Dissolution profile of MLX from microsponge formulas (F10, F9, F4) and pure MLX drug in buffer solution (pH 7.4)

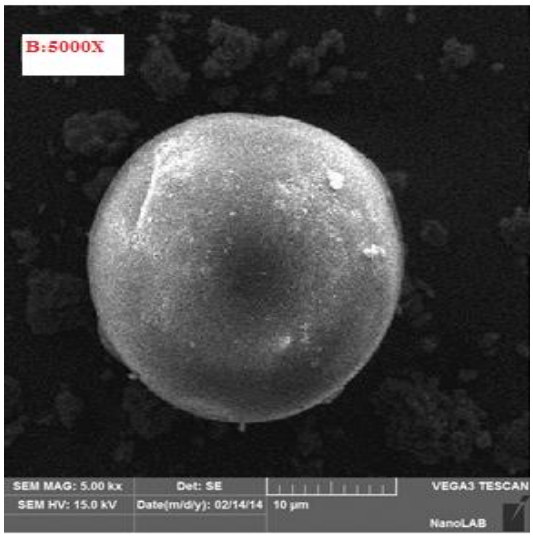
Evaluation of the shape and surface morphology by scanning electron microscope (SEM)

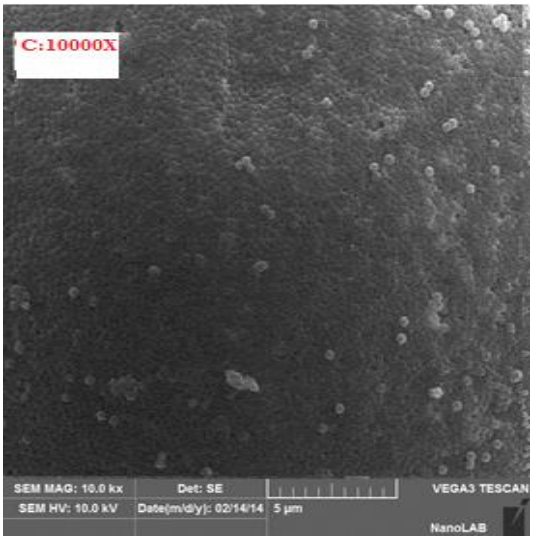
SEM picture of the selected formula F10 is presented in figure (3) at 1000X, 5000X, 10000X, and 25Kx magnification. It was observed by SEM analysis that the microsponges were finely spherical, smooth, porous. The surface topography reveals that MLX microsponges contained tiny pores. The

pores were induced by the diffusion of the volatile solvent (dichloromethane) from the surface of the microparticles. The appearance of the particles was such that they were termed microsponges. These findings are similar to the results reported in literature [27].

Electron micrographs also showed the formation of drug crystals over particle surfaces because the optimum microsponge formula prepared with higher drug/polymer ratio (12:1). It is easily deducible from the earlier hypothesis that at higher drug/polymer ratios, more drugs will reach the surface of the nascent microsponges being dissolved in the solvents during diffusion. Moreover, as the diffusion of solvents becomes slower with the increase in drug/polymer ratio, there is more time for the formation of drug crystals. Orlu et al. [20], reported similar findings with flurbiprofen microsponges.







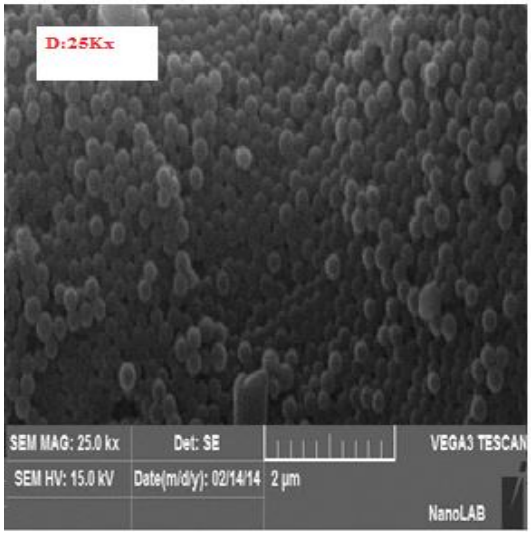
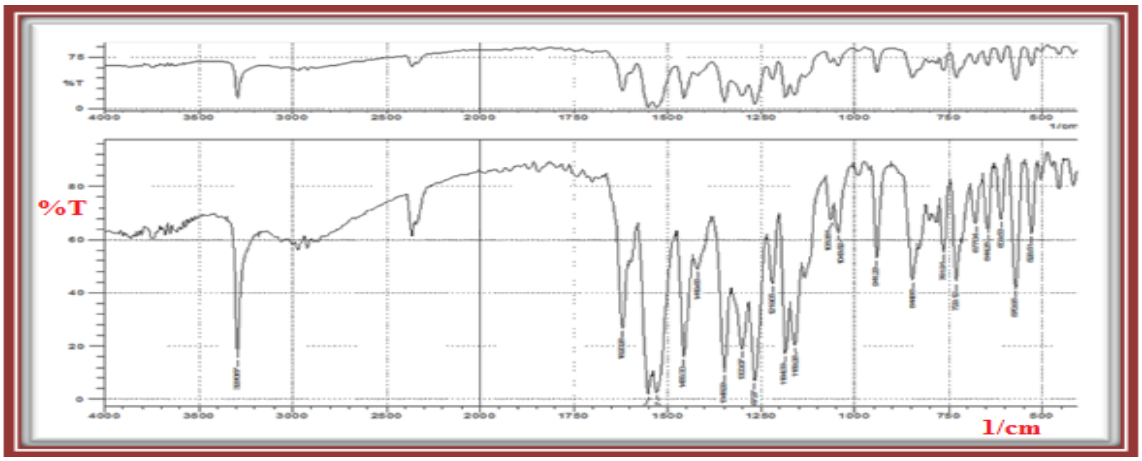


Figure 3: SEM of F10 (A, B, C, D)at 1000X,5000X,10000X and 25Kx magnification. Photograph A represents whole image; photographs B, C, D represents surface topography.

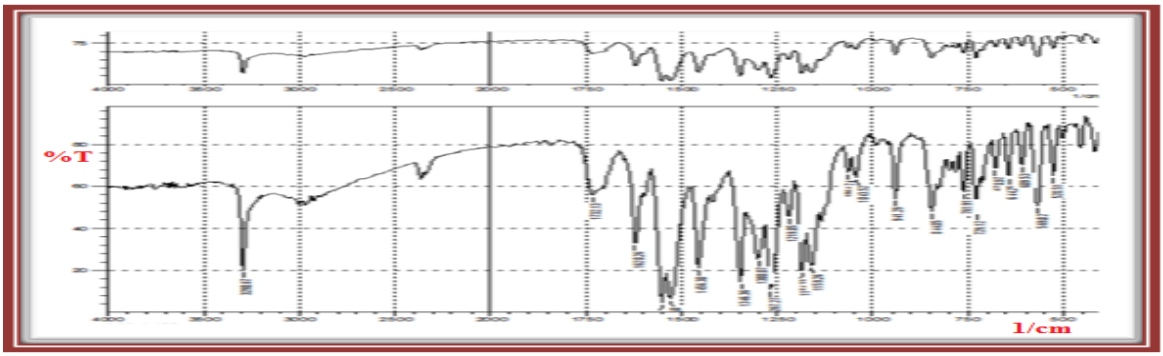
Fourier transform infrared spectroscopy

The FT-IR spectrum of pure MLX, physical mixtures, and selected microsponge formula (F10) are given in figure (4:A-C).The spectrum of pure MLX showed characteristic peaks at 3290 .67cm-1 (N-H stretching vibrations of secondary amide), 1620.26 cm-1 (C=N stretching vibrations of thiazole), and 1159.26 cm-1 (symmetric S(=O)2 stretching vibrations of organic sulfoxide). The spectrums of physical mixtures were equivalent to the spectrum of the drug and polymer, indicating no chemical interaction or complexation occur. The spectrum of the selected formula (F10) exhibited very slight decrease in intensity of N-H stretching vibrations and C=N stretching vibrations, but there is no appearance or disappearance of peaks and/or shift of their positions, only a

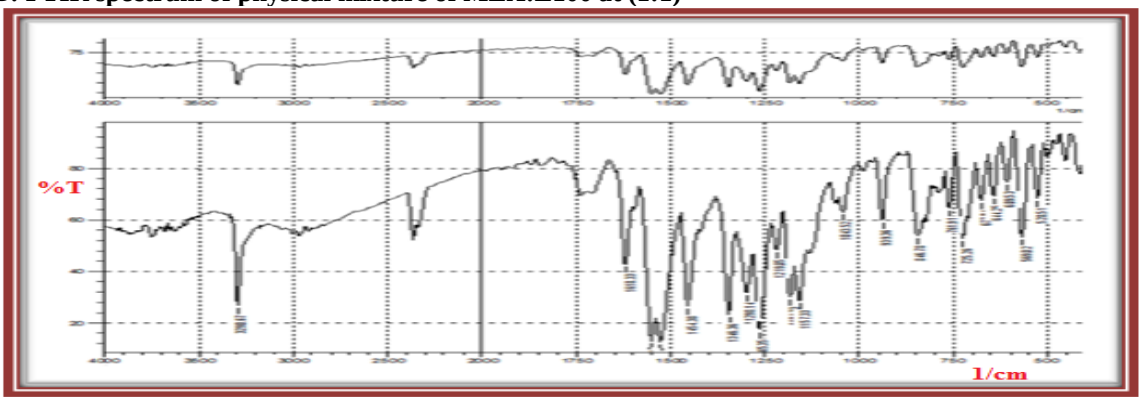
very slight shift in C=N vibration peak, this indicates lack the possibility of interaction between MLX and excipients used in the preparation of microsponge [28] and MLX was apparently stable in the microsponges.



A: FTIR spectrum of pure MLX



B: FTIR spectrum of physical mixture of MLX:L100 at (1:1)

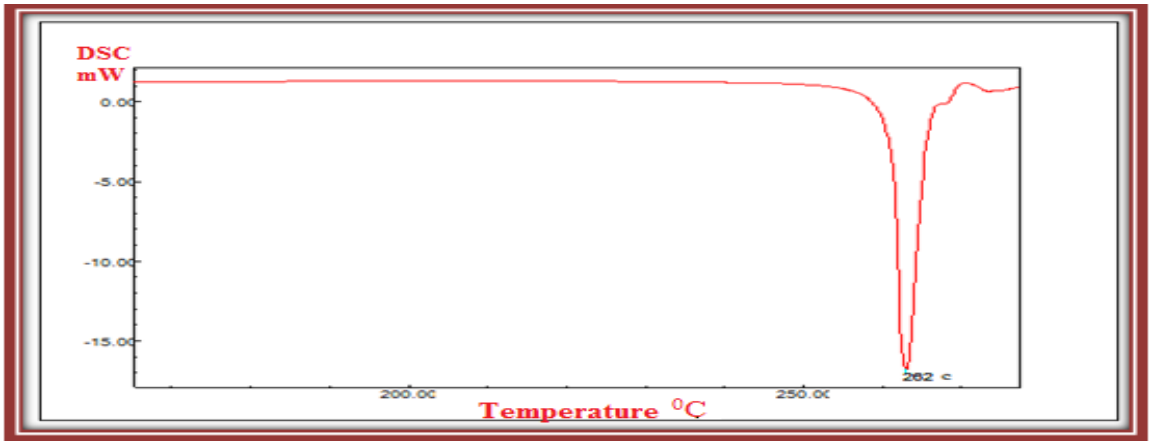


C: FTIR spectrum of MLX microsponge F10 (MML100)

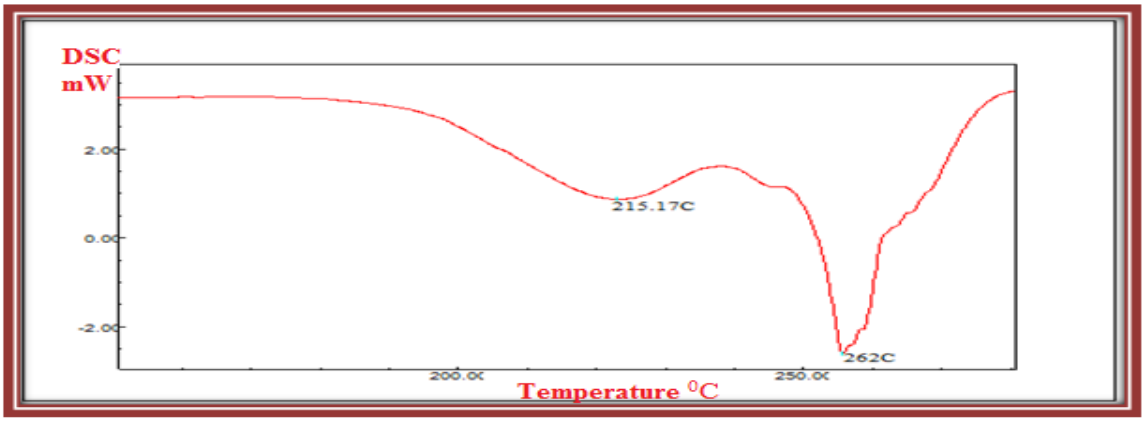
Figure 4: FTIR spectrum (A-C)

Differential scanning electron microscopy (DSC)

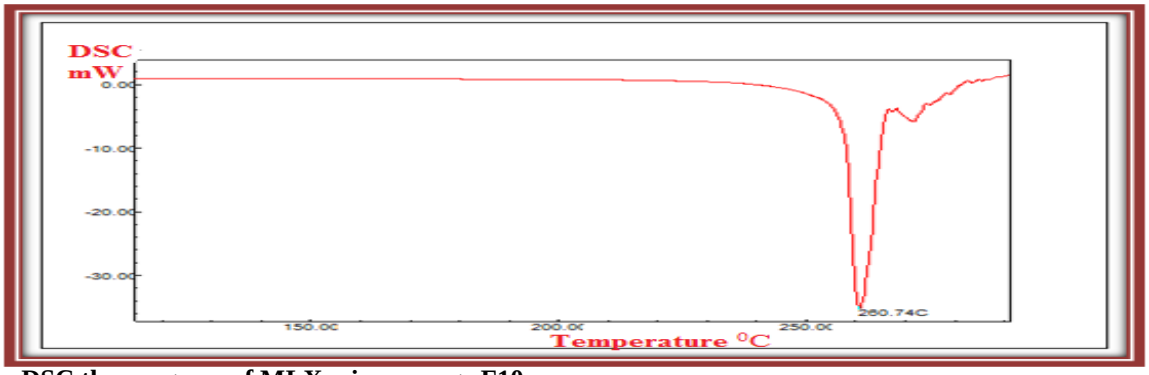
The DSC curves figure(5) of MLX presented a sharp characteristic endothermic peak at 262˚C corresponding to the melting point of the drug in the crystalline form. The thermograms of physical mixture showed that the drug was in its crystalline form and also there was no interaction between them. The DSC curve of F10 showed only typical signals for the drug crystals. Disappearance of polymer peaks mainly due to the lower amount of polymer used in the preparation of F10 in comparison to the amount of the drug [29], in addition to the amorphous nature of the polymer. Such results showed no interaction between MLX and polymers, indicating that microsponge production process used for preparation of MLX microsponges did not change the nature of the drug in microsponges.



a. DSC thermogram of MLX



b. DSC thermogram of physical mixture of MLX:L100 at (1:1)

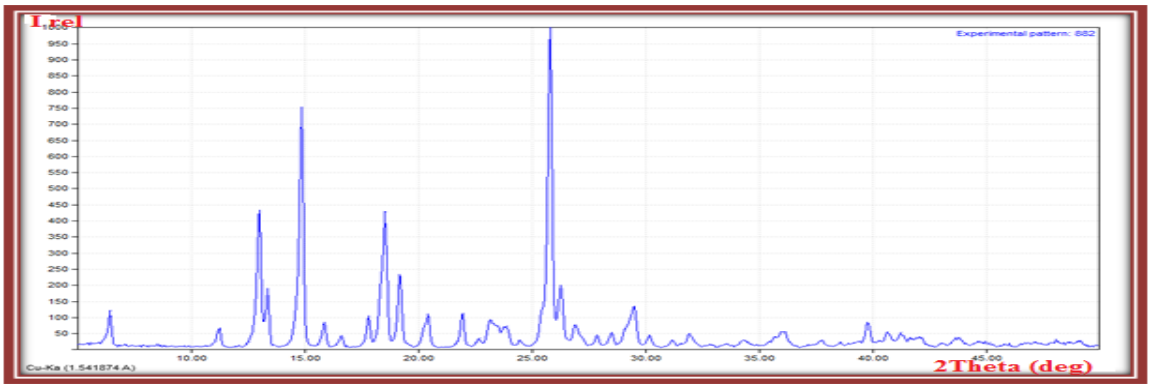


c. DSC thermogram of MLX microsponge F10

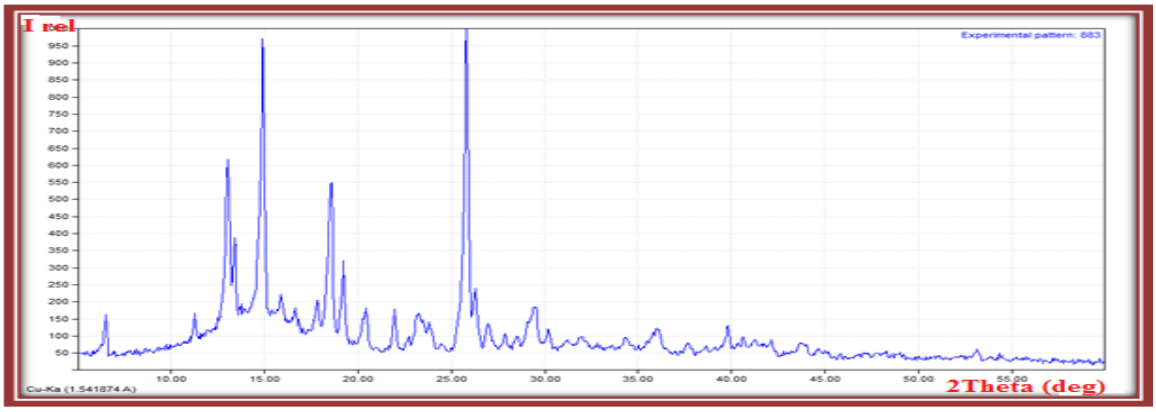
Figure 5: DSC of (a-c)

Powder X-ray diffraction

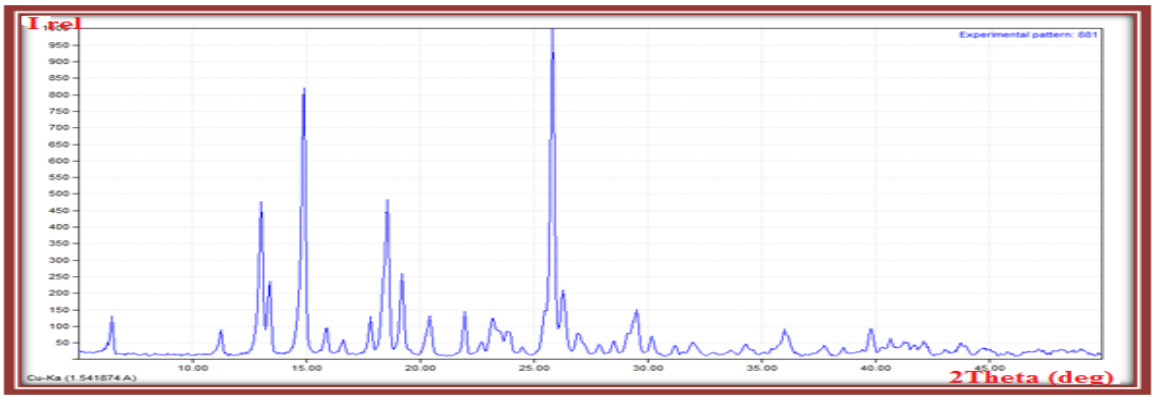
The PXRD patterns of MLX as a pure drug showed sharp and numerous distinctive diffraction peaks as shown in figure (6 A) indicating the crystalline nature of the drug. The strongest three peaks of MLX at 2θ were 25.8359°, 14.9422° and 18.5839°.While the physical mixture of MLX and Eudragit L100 at ratio 1:1 also showed the characteristic crystalline diffraction peaks of MLX, so no interaction could be detected as seen in figure (6 B).The diffraction patterns of MLX microsponge F10 demonstrated in figures (6 C). A PXRD analysis of F10 still showed clearly the typical signals but with lower intensity for drug crystals only because the systems prepared using lower amounts of polymer and these results agreed with the results of DSC study. No appearance of new diffraction peaks which rules out any chemical interaction between the components [30]. A decrease in the intensity of the strongest peak which indicates reduction in crystallinity and these results are consistent with those from the DSC and the FTIR.



A: XRD of pure MLX



B: XRD of physical mixture of MLX and Eudragit L100 (1:1)



C: XRD of MLX microsponge F10

Figure 6: XRD of pure MLX (A), physical mixture of MLX and Eudragit L100 (1:1) (B), and microsponge F10(C)

Kinetic modeling of drug release from microsponge

The release of MLX from microsponge F10 mainly obeys Hixon- Crowell release kinetic as their (R^2) values gave higher results. The results showed that the release exponent "n" value of F10 microsponges is >0. 5 and <1 indicating non Fickian (anomalous) transport. Thus, it was proposed that this formula delivered their active ingredient by coupled diffusion and erosion [31].

Characteristics of MLX microsponge gel

Macroscopic feature (organoleptic)

Visual inspection of prepared gel indicated the homogeneity of formula, no phase separation, non-transparent, with pale-yellow gel.

The pH determination

The result of pH for F10 carbopol gel is 5.68±0.02 due to neutralization of formula by TEA [32].

Spreadability measurement

The efficacy of a topical therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose. Spreadability is therefore an important characteristic of these formulations and is responsible for correct dosage transfer to the target site and ease of application on the substrate. F10 carbopol 934 forms a gel with 2 cm spreadability. Spreadability of prepared gels was decreased as the polymer concentration increased [33].

Determination of MLX content in the gel formula

The MLX content of the gel formula is 98.3% ± 0.1. The drug content of the formulations showed that the drug was uniformly distributed in the gels.

Viscosity of microsponge gel

Viscosity holds a major contribution in deciding the drug content and its release from prepared gel formulation. F10 carbopol gel showed approximate viscosity between 31,000 CP-105,000 CP. It was found that as the shear rate increased the viscosity of gel decreased [34] as shown in figure (7).

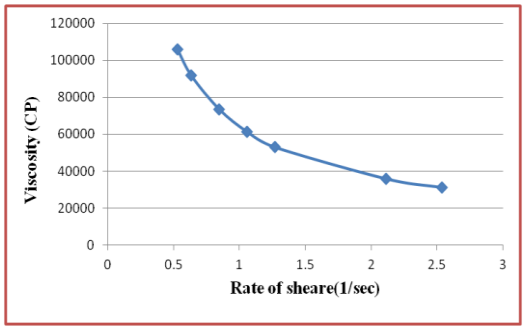


Figure 7: Viscosity versus shear rate for microsponge gel formula.

In vitro drug release study from microsponge gel

It is showed from the release profile Figure (8) that F10 carbopol 934 gel has produced a great improvement in the dissolution rate which is significantly higher ($p<0.05$) than that of pure MLX gel .

The manufacturer stated that the carbopol 934 gel has the lowest cross–linking density, while that of C 981 is the intermediate and that of C 940 is the highest. Also increasing the polymer concentration in the gel increases viscosity which prolonged drug diffusion through the gel matrix. The same effect was obtained by Attia et al [35] who studied the diffusion of piroxicam from different polymer gel at different concentrations of sodium alginate(7% ,10% w/v) hydroxypropylmethylcellulose (2.5%, 5% w/v) and methyl cellulose (3% , 5% w/v).

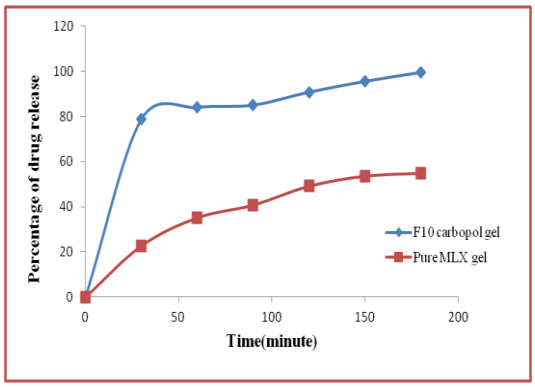


Figure 8: Dissolution profile of MLX from microsponge gel formula and pure MLX gel in phosphate buffer solution (pH 7.4)

Kinetic modeling of drug release from the gel

The kinetic data of the in vitro release of MLX from gel was found to follow first order release kinetic as their (R^2) values gave higher results. The mechanism of drug release is non fickian diffusion where release is controlled by a combination of diffusion and polymer relaxation [36].

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