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Development of a Self-Microemulsifying Solid Dosage Formulation for Enhanced Solubility and Stability of Meloxicam: A Comprehensive Study

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Abstract

Meloxicam (MLX), a nonsteroidal anti-inflammatory drug belonging to the oxicam family, is commonly used to alleviate inflammation and pain. However, MLX's limited solubility and subsequent low bioavailability necessitate the development of innovative formulations. This study aimed to improve the dispersibility and stability of MLX by incorporating it into a self-microemulsifying liquid drug delivery system (SMLDDS) and subsequently converting it into a solid dosage form, specifically capsules. The liquid formulation, consisting of oleic acid oil (10%), Tween 80 (38.57%), propylene glycol (25.72%), and Transcutol P (25.72%), was transformed into a solid powder using an adsorbent mixture of Avicel PH 101, Avicel PH 102, and Aerosil 200. Among the self-microemulsifying capsules (SSMEDDS) developed, SSMEDDS-1 exhibited excellent flow properties, the highest drug content (99.96%), and rapid cumulative drug release (100% within 20 minutes). Characterization studies confirmed the absence of any drug-component interactions, as evidenced by characteristic peaks of meloxicam in Fourier-transform infrared spectroscopy (FTIR). X-ray powder diffraction (XPRD) and differential scanning calorimetry (DSC) analyses revealed the conversion of MLX from its crystalline to amorphous form, enhancing solubility and dissolution rate. A three-month stability test conducted at various temperatures demonstrated the formulation's stability in terms of appearance, with minimal changes in drug content and consistent in vitro drug release profiles. This study presents a successful approach to enhance the solubility and stability of meloxicam through a self-microemulsifying solid dosage formulation. The optimized formulation offers potential benefits for improving the therapeutic efficacy and patient compliance of MLX, thereby advancing the field of drug delivery systems for poorly soluble drugs.

Meloxicam (MLX), chemically known as "4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide," belongs to the oxicam class of NSAIDs, the chemical structure is shown in figure 1. MLX has a molecular weight of 351.4 g/mol and an empirical formula of C14H13N3O4S2. It exhibits anti-inflammatory, analgesic, and antipyretic effects. However, its poor aqueous solubility, classified as Class II in biopharmaceutical classification systems, and erratic bioavailability(1) restricts its efficient absorption and distribution within the body, leading to suboptimal therapeutic outcomes(2)

To address the solubility challenge and enhance the bioavailability of MLX, various formulation strategies have been explored like solid dispersion (4), Vesicles-based methods such as bilosomes (5) ,microemulsions and nanoemulgel (6) etc... Among these strategies, self-microemulsifying drug delivery systems (SMEDDS) have emerged as a promising approach. SMEDDS are lipid-based formulations capable of solubilizing

lipophilic drugs, such as MLX, by forming transparent microemulsions with droplet sizes typically less than 100 nm. These microemulsion droplets, composed of oil, surfactants, and co-surfactants, serve as carriers for the drug, increasing its surface area and facilitating dissolution upon administration. The use of SMEDDS enables improved drug release kinetics, leading to enhanced absorption and more consistent blood-time profiles In addition to their solubilizing effect, SMEDDS offer several advantages over conventional drug delivery systems. First, they exhibit physical stability, maintaining a dispersed state without phase separation or precipitation, ensuring consistent drug delivery and avoiding formulation-related issues. Second, SMEDDS can be easily formulated into solid dosage forms, providing convenience and flexibility in dosing regimens. The lipid-based nature of SMEDDS also allows for compatibility with both hydrophobic and hydrophilic drugs, expanding their applicability.

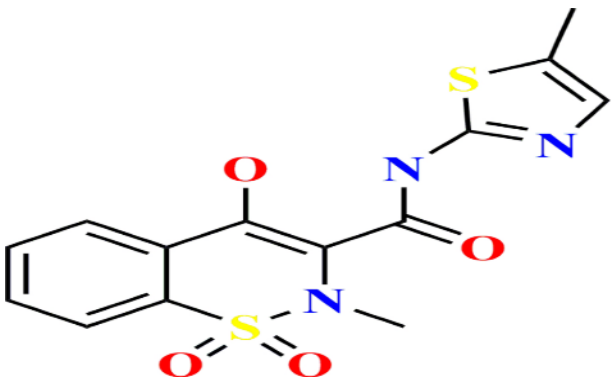


Figure 1:Chemical structure of Meloxicam(3)

The success of a SMEDDS formulation lies in the selection of an appropriate oil-surfactant combination that can effectively solubilize the drug at the desired therapeutic concentration. This selection process takes into consideration the drug's physicochemical properties, such as lipophilicity, and evaluates the compatibility and stability of various excipients. Co-surfactants and co-solvents may be incorporated to further optimize formulation properties and enhance drug solubility.

In recent years, efforts have been made to develop solid self-microemulsifying drug delivery systems (SSMEDDS) as an alternative to liquid SMEDDS. SSMEDDS offer advantages in terms of improved stability, ease of handling, and increased patient compliance. Various techniques have been employed to solidify the SMEDDS formulation, including capsule filling with a liquid, adsorption to solid carriers, spray drying, spray cooling, melt granulation, and melt extrusion.

Adsorption onto solid carriers is a particularly useful technique, transforming liquid self-microemulsion formulations into easily dispersed powders. This process involves blending the liquid mixture with suitable carriers, such as microporous materials, colloidal inorganic adsorbents, cross-linked polymers, or nanoparticle adsorbents. The resulting powder can be directly used to fill capsules or combined with appropriate excipients before being compressed into tablets. Adsorption offers advantages in terms of ensuring consistency in the material's composition and enhancing the stability of the formulation.

In this comprehensive study, we aim to develop a self-microemulsifying solid dosage form of MLX to overcome its solubility limitation and improve its therapeutic efficacy. The study will involve evaluating different oil-surfactant combinations, co-surfactants, and solid carriers to optimize the formulation. Physicochemical characterization, such as droplet size analysis, dissolution studies, and stability assessments, will be conducted to assess the performance of the developed formulation. Furthermore, in vitro and in vivo studies will be carried out to evaluate the enhanced solubility, stability, and bioavailability of MLX in its self-microemulsifying solid dosage form.

Materials

MLX was obtained from Hyperchem (China), Transcutol p from Gattefosse Sas (France), Tween 80 and propylene glycol from Chemical Point (Germany), oleic acid oil from Central Drug House (P) Ltd. (India), methanol from Sigma-Aldrich (Bljika), and hydrochloric acid from ReAgent Chemicals (UK), fumed silica gel (Aerosil 200) from Central Drug House (P) Ltd. (India), microcrystalline cellulose (Avicel PH102), microcrystalline cellulose (Avicel PH101) from Changsha Goomooooo Chemical Technology Co. (China), and Mobic 7.5 mg from Boehringer Ingelheim (Germany).

Methods

Preparation of meloxicam liquid SMEDDS

Surfactants and oils in SMEDDS do not dissolve

MLX well. To provide a suitable basic environment for solubilizing MLX, a concentrated basic solution of salts, such as tris (hydroxymethyl) aminomethane (trizma) can be added to the SEDDS. In a solution, the weight ratio of base to water is 1:2. The solution has a pH of 11.1 when measured by pH-meter. The SMEDDS of oleic acid were generated by adding the following components in the following order to the trizma buffer (20%): oleic acid (10%), Tween 80 (38.57%), propylene glycol (25.72%), and Transcutol p (25.72%). The Smix ratio is 3:4 and the oil:Smix ratio is 1:9. The materials were combined in a beaker placed on a magnetic stirrer and heated for thirty minutes in a water bath at 60°C to produce a clear solution. The combination was then loaded with 7.5 milligrams of MLX and mixed for an stirrer for an additional hour yielding a clear yellow liquid (7). After 48 hours, the formulations were visually assessed for turbidity and phase separation (8).

Preparation of MLX solid SMEDDS

The liquid formula was thoroughly mixed with a variety of adsorbents at a 1:1 ratio. Table 1 shows the adsorbent mixtures used which are consisting of Avicel PH101 with Aerosil 200 and Avicel PH102 with Aerosil 200. Physical mixing was used to adsorb the liquid SMEDDS of MLX (0.4g) onto the carrier. To guarantee that the formulation was distributed evenly and to generate a freely flowing, non-sticky solid powder, the combination of components was triturated with a mortar and pestle after each addition. Each of the resulting mixtures was dried at 40°C in an oven for 48 hours. Then, the resultant powder was sieved with the use of a mesh screen with a pore size of 150 µm to remove all the remaining clumps(9). A specific amount of powdered SMEDDS which containing 7.5 mg of MLX was filled in hard gelatin capsules for further characterizations (10).

Table (1): Compositions of MLX Solid Self-Micro Emulsion Formulations

Formula – code	Smix ratio	Oil:Smix ratio	Avicel PH 101 (mg)	Avicel PH 102 (mg)	Aerosil 200 (mg)
SSMEDDS-1	3:4	1: 9	225	-	225
SSMEDDS-2	3:4	1: 9	-	225	225

height was designed such that the tip of the funnel barely touches the top of the powder heap. The sample, which had been precisely weighed, was allowed to flow freely through the funnel and onto the surface. The powder cone's diameter was measured, and the angle of repose was calculated using the following equation (12):

$$\tan \theta = h/r$$

Where **θ** is the angle of repose, **h** is the height, and **r** is the radius.

The flowability of the powder was assessed based on the angle of repose and according to the angle values shown in Table 2.

Evaluation of MLX solid self-microemulsion

Powder flow properties

I. Angle of repose

Powder cohesiveness is evaluated by determining the moisture, particle size, and shape at which the interparticulate attraction becomes stronger than the gravitational force (11).The funnel technique was used to calculate the angle of repose of SSMEDDS. The funnel

Table (2): Powder Flowing Properties Based on Angle of Repose (11).

The angle of repose (degrees)	Type of flow
(25-30)	Excellent
(31-35)	Good
(36-40)	fair (flow aid not needed)
(41-45)	passable (a flow aid might be needed)
(46-55)	poor (agitation or vibration needed)
(56-65)	very poor
over 66	very, very poor

II. Bulk density (BD)

The bulk density is calculated by dividing the

powder's total weight in grams by its entire volume in cubic centimeter. The volume of 3 grams of SSMEDDS powder was measured in a 10 mL measuring cylinder. A bulk density calculation was performed according to the following equation(13):

Bulk density (BD) = weight of the blended powder/volume of the poured blended powder

III. Tapped density (TD)

It is the ratio of the total weight of powder in grams to the tapped volume in cubic centimeter. Tapping the weighted powder (3g) of SSMEDDS to constant volume yielded the tapped volume. The following equation was used to compute tapped density (13):

Tapped density (TD) = amount of the blended powder/volume of the tapped blended powder

IV. Carr's index and Hausner ratio

Carr's index and Hausner ratio are excellent predictors of powder flowability. The Carr's index: The Carr's compressibility index is a measure of powder flow properties that may be determined using the following equation (13):

$$\text{Carr's index} = TD - BD / TD * 100$$

While Hausner ratio, a similar index to the compressibility index, is the ratio of tapped density to bulk density and can be measured by using the following equation (14):

$$\text{Hausner ratio} = TD/BD$$

The properties of powder flow based on Carr's index and Hausner ratio were assessed according to values shown in Table (3).

Table (3): Powder Flowing Properties Based on Carr's Index and Hausner Ratio (11).

Carr's index	Hausner ratio	Type of flow
1 – 10	1.00 - 1.11	excellent
11 – 15	1.12 - 1.18	good
16 – 20	1.19 - 1.25	fair
21 – 25	1.26 - 1.34	passable
26 – 31	1.35 - 1.45	poor
32 – 37	1.46 - 1.59	very poor
> 38	> 1.60	very, very poor

Drug content

Powdered SSMEDDS, equivalent to 7.5 mg of MLX, was dissolved in methanol at a concentration of 1% in a volume of 100 mL. In order to extract MLX from methanol, the solution was put in a sonicater for 10 minutes before being filtered. The absorbance of filtrate in methanol was measured using a UV-visible spectrophotometer (15).

In vitro drug release study

The in vitro drug release of the produced MLX SSMEDDS formulations (capsules) and Mobic 7.5 mg tablet was carried out in 900 ml of 0.1 N HCl media using the USP dissolution apparatus type II (16). A capsule containing the equivalent of one dosage of MLX was used. Throughout the course of 40 minutes, five mL of the dissolution medium were withdrawn at predetermined time intervals (0, 2, 5, 10, 20, 30, and 40 minutes). Following each drawing, the volume of the dissolution medium removed was substituted with fresh media of equal volume. A UV/visible spectrophotometer was used to determine the amount of drug released (17).

The comparison in the release of the optimum formula to that of the Mobic 7.5 mg tablet in the buffer is done due to MLX monograph recommendation which used 900 ml of phosphate buffer (PH 7.5)for MLX in vitro drug release. Throughout the course of 60 minutes, five milliliters of dissolution media were withdrawn at regular time intervals (0, 10, 20, 30, 40, 50, and 60 min). Following each drawing, the volume of the dissolution medium removed was substituted with fresh equal volume of it. A UV/visible spectrophotometer was then used to quantify the drug that was released (18).

Selection of optimum MLX solid self-micro emulsion

The optimal MLX SSMEDDS formula was chosen based on the results of the assessment tests, which included drug content, angle of repose, Hausner ratio, Carr's index, and an in vitro drug release study.

Evaluation of selected optimum MLX solid self-microemulsion

Fourier transform infrared spectroscopy (FTIR)

The potassium bromide (KBr) disc method was used to record the infrared spectra of MLX, Avicel PH101, Aerosil 200, physical mixture at a 1: ratio, and selected MLX SSMEDDS formula. The powder sample was mixed with KBr before being ground into fine powder and compressed into a KBr disc. Each KBr disc was then scanned over a wave number region of 400–4000 cm^{-1}(19)

X-Ray diffraction study

The study was conducted by using an X-ray diffractometer at a continuous scan range of 5°–80°C of 2θ. The operating voltage was 40 kV, employing a CuKα source, and the current was 30 mA(20,21).

Differential scanning calorimetry (DSC)

Two to three milligrams of the MLX SSMEDDS formula were weighed, sealed in an aluminum pan, and then put into the DSC equipment. A rate of 10 °C/min was used to get the sample up to 300 °C(22).

Stability study

The study was performed to assess the MLX SSMEDDS formula stability. The capsule was stored at different temperatures of 25, 40, 50ºC for three months. The samples were withdrawn at regular intervals on weeks (0, 2, 4, 6, 8, 10 and 12) checked for physical appearance and drug content(23). While the in vitro drug release test performed at the end of the storage duration.

Statistical analysis

The results of the experiments were shown as the standard deviation of the mean of three replicate samples. The results were analyzed according to the one-way analysis of variance (ANOVA) at the level of ($P < 0.05$) to determine if the changes in the applied factors are statistically significant at the level of ($P \leqslant 0.05$) and non-significant at the level of ($p > 0.05$) using SPSS software version 21.

Result and discussion

Prepared meloxicam liquid SMEDDS

There is no visible phase separation or drug precipitation in the observed liquid MLX SMEDDS formulations, and the mixtures are uniform, clear, and yellow to brown in color, as shown in Figure (2). This formula was optimized based on our previous work(24).

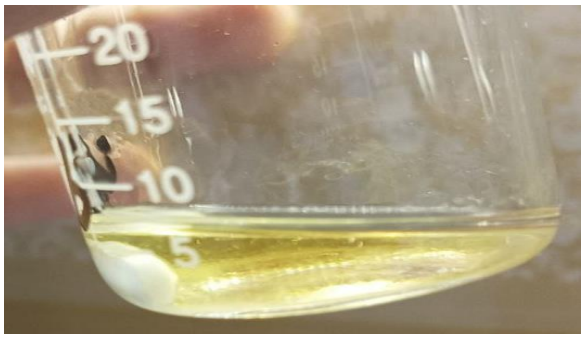


Figure (2):The prepared liquid formula

Preparation of MLX solid self-micro emulsion

By subjecting the MLX liquid formula to adsorption onto various solid adsorbent carriers, we successfully generated white powders, transforming the formulation into a solid dosage form. This conversion eliminates stability issues associated with liquid formulations and improves patient compliance.The adsorption technique provides a practical solution for overcoming stability challenges in liquid dosage forms. By obtaining MLX in a solid SME form, the risks of leakage, evaporation, and degradation are eliminated, ensuring long-term integrity and potency. Furthermore, the solid SME formulation enhances patient compliance by offering a convenient administration method. Solid dosage forms, such as tablets or capsules, are more familiar and easier to handle for patients compared to liquid formulations. Overall, the successful generation of white powders from the MLX liquid formula demonstrates the effectiveness of the adsorption technique in producing a stable and patient-friendly MLX solid SME formulation. This approach shows promise in improving pharmaceutical stability and patient compliance(25).

Evaluation of MLX solid self-microemulsion

Powder flow properties

The flow properties of powders evaluated using three tests with different techniques. MLX-SSMEDDS are shown in Table (4) along with their angle of repose, Hausner ratio, and Carr's index. The results reveal that every powder produced has excellent flow properties.

Table (4): Angle of Repose, Hausner Ratio and Carr's Index of MLX Solid Self-Micro Emulsion (mean ±SD) n=3.

F – code	The angle of repose(Θ)	Hausner ratio	Carr's index	Result
SSMEDDS-1	27.536 ± 0.061	1.046 ± 0.045	8.426 ± 0.166	Excellent
SSMEDDS-2	28.843 ± 0.059	1.07 ± 0.04	9.734±0.062	Excellent

Drug content

Both of the produced MLX-SSMEDDS, F1 (99.96% ± 0.06) and F2 (99.856% ± 0.124), had drug contents over 99%, falling within the permissible range (90–110%) as specified by the USP(26). The results indicating that there was no precipitation of drug in any of the prepared formulations.

In vitro drug release study

Figure 3 depicts the profiles of MLX brand tablet (Mobic 7.5 mg), MLX SSMEDDS-1 capsule, and MLX SSMEDDS-2 capsule in 0.1N HCl. The development of the two MLX SSMEDDS formulations resulted in faster dissolution rates and the formation of spontaneous microemulsions. The MLX SSMEDDS-1 capsule achieved complete release (100%) within 20 minutes. On the other hand, the release rate from the MLX SSMEDDS-2 capsule reached 94.6% within 40 minutes. The release characteristics of the two SSMEDDS capsules were significantly different, with a similarity below 50. In other words, the dissolution release profile of the MLX-SSMEDDS-1 capsule ($f2 < 50$) was markedly different from that of the Mobic tablet, which exhibited slower release and only reached 64% release after 60 minutes. Several factors contributed to the increased rate of disintegration and release. These included the use of different adsorbent mixes with a wide surface area, resulting in an amorphous nature, small particle size, improved wettability, and rapid dispersibility in the dissolution media. This facilitated a faster rate of drug release into the aqueous phase (27).

The disintegrant Avicel played a role in enhancing MLX wetting and dissolving by acting as a lubricant due to the presence of moisture within its structure. Aerosil 200, a non-porous hydrophilic silica, significantly improved the drug dissolution rate in SSMEDDS by enabling spontaneous emulsification and enhancing MLX dissolution (28).

The smaller particle size of Avicel PH101 compared to Avicel PH102 was found to be the most crucial factor influencing drug release from different SSMEDDS systems (29). The SSMEDDS formula with Avicel PH102 resulted in a slower rate of MLX dissolution compared to the formula with Avicel PH101. This suggests that the desorption process involving the larger particle size of the adsorbent slows down the initial phase of drug dissolution (30). The tiny particle size, wide surface area, and porous structure of the adsorbent contribute to faster MLX dissolution by promoting better wetting of the drug and increased interaction with the dissolving liquid (31). Researchers observed that MLX SSMEDDS-1 capsules exhibited quicker and more effective dissolution compared to Mobic tablets. Both the optimal formula and Mobic were tested using phosphate buffer 7.5 as the release medium. Figure 4 demonstrates that SSMEDDS-1 achieved a release of 83% after 60 minutes, whereas Mobic only reached 75%. Additionally, the release profiles of the two formulations were significantly different ($f2 < 50$)

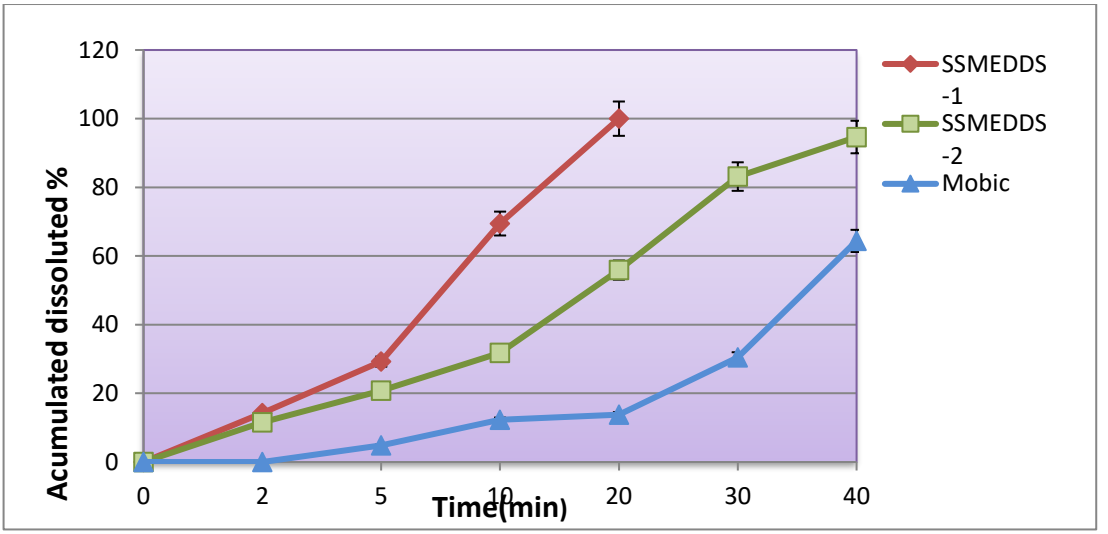


Figure (3): Release profile of MLX in SSMEDDS -1 capsule, SSMEDDS-2 capsule and Mobic tablet in 0.1N HCl.

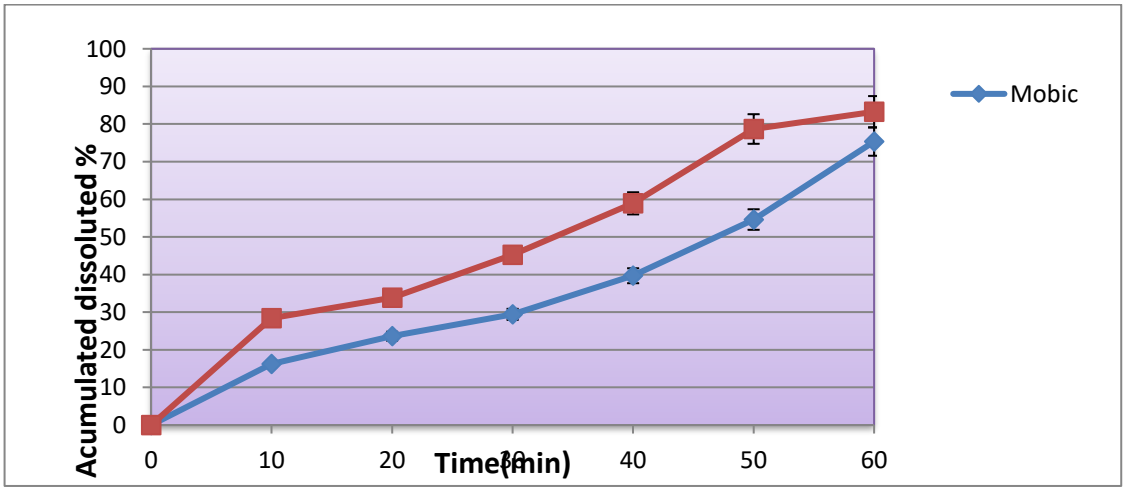


Figure (4): Release profile of MLX in SSMEDDS -1 capsule and Mobic tablet in phosphate buffer 7.5.

Selection of optimum MLX solid self-microemulsion

The findings of the assessment tests, which include the angle of repose, Hausner ratio, Carr's index, drug content, and in vitro drug release research, were used to determine the best MLX SSMEDDS formula. The best self-micro emulsifying capsule, SSMEDDS-1, contains 10% oleic acid oil, 38.57% Tween 80, 25.72% propylene glycol, 25.72% transcutol P, 225 mg Avicel PH101, and 225 mg Aerosil 200. Excellent flow characteristics, maximum drug content (99.96%), and a rapid cumulative drug release (100% in 20 min) are all features of this formula.

Evaluation of the selected optimum MLX solid self- micro emulsion

Fourier transform infrared spectroscopy (FTIR)

FTIR is a very effective method for finding and assessing any chemical interaction between the medicine and its excipients. Figure (5) depicts the FTIR spectra of the MLX, Avicel PH101, and Aerosil 200, as well as the physical mixture (1:1:1) and the chosen formula (SSMEDDS - 1). The spectrum of pure MLX revealed notable peaks at 3286 cm^{-1} (N-H stretching of secondary amine vibrations), 1620 cm^{-1} (NH2 scissoring vibrations), and 1041,1153 cm^{-1} (S=O stretching vibrations) , 3091 cm^{-1} (C-H stretch, aromatic), 2911 cm^{-1} (C-H stretch, aliphatic CH3 sym), 1536 cm^{-1} (C = N stretch), 1454 cm^{-1} (C = C stretching), and prominent bands such as 844-567 cm^{-1} (-CH aromatic ring bending and heteroaromatic), and the findings were consistent with previous research (19,32). According to the FTIR

results, in the spectrum of the selected formula SSMEDDS-1, the peaks corresponding to the NH vibrations (3286 and 1620 cm^{-1}) decreased significantly along with the broadening of S=O and C=N, suggesting hydrogen bonding between MLX and the liquid vehicles used in the preparation, which are the reasons behind dissolution enhancement. Some groups in MLX were preserved. These results indicate that no chemical interaction occurred between MLX and the excipients used in the preparation. While the spectrum of the physical mixture (PM) was similar to some of the characteristic aerosol 200 bands and some of the MLX bands indicated the absence of interactions that increase the solubility as compared to the best formula(33).

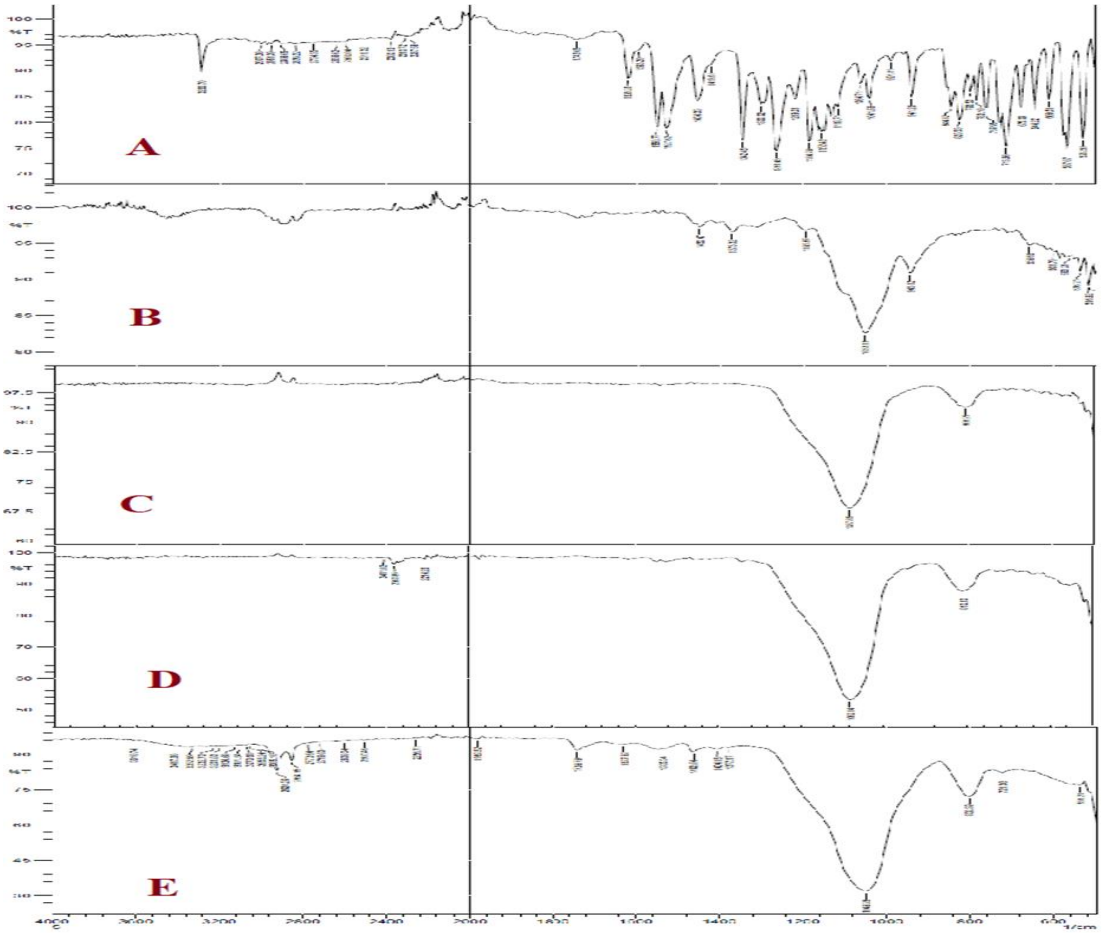


Figure (5): FTIR spectra of: (A) MLX (B) Avecil PH 101(C) Aerosil 200 (D) physical mixture (MLX: Avicel PH101: Aerosil 200) (E) selected MLX SSMEDDS-1 formula

X-Ray powder diffraction study

As can be seen in Figure 6-A, the diffraction spectrum of MLX alone reveals that the medicine is a highly crystalline powder with a sharp, intense peak. Figure 6-B depicts the chosen MLX SSMEDDS-1 diffraction pattern, which exhibits a broadening as a result of the disappearance of the drug's sharp peak. These results indicate that the drug is most likely found in its amorphous or messy crystalline phase in the oily interior core.

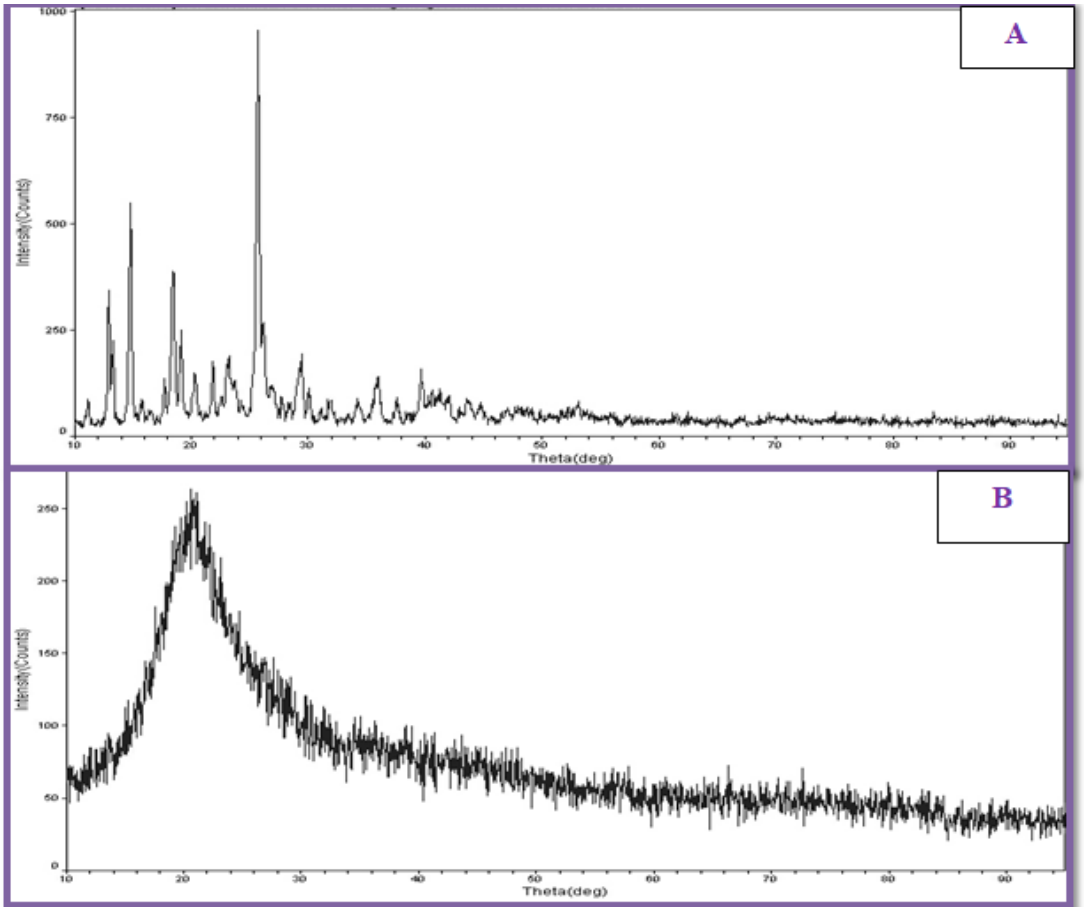
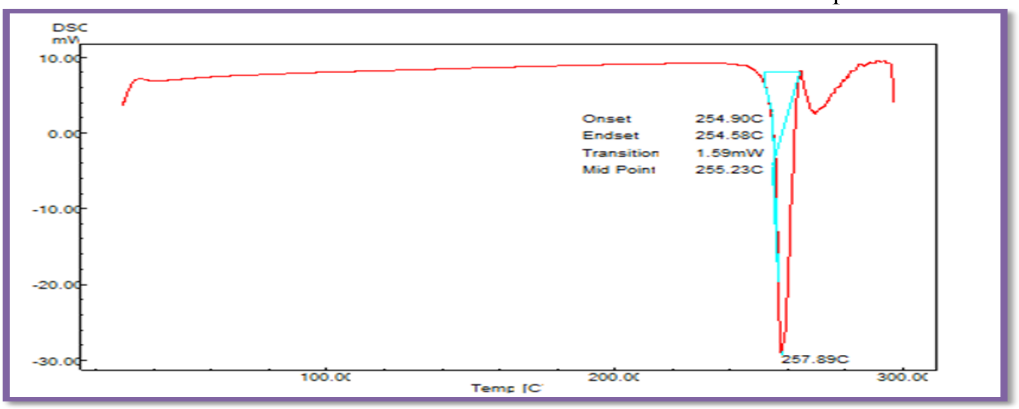


Figure (6): X-ray diffraction: (A) pure MLX, (B) selected MLX SSMEDDS-1 formula.

to the drug's melting point in its crystalline form, which is close to the reported value(34).The absence of the endothermic beak of MLX in figure(7-B) means the conversion of MLX from crystalline to amorphous form, which leads to an increase in the solubility of MLX.

Differential scanning calorimetry (DSC)

The DSC test used to find out if the drug is crystalline or amorphous (9). Figure (7-A) depicts the DSC thermogram of MLX, which shows a sharp characteristic endothermic peak at 257°C corresponding



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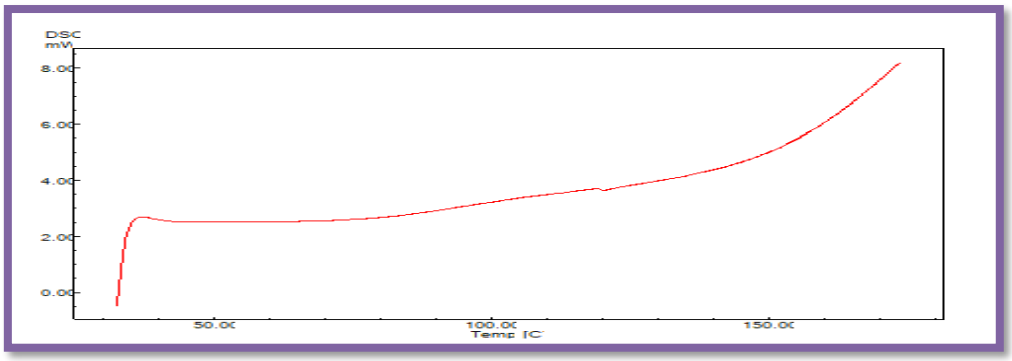

B

Figure (7): DSC thermogram: (A) MLX, (B) selected MLX SSMEDDS – 1 formula

Stability Studies

For 12 weeks, the stability of the chosen optimal MLX SSMEDDS-1 was evaluated at three distinct temperatures: 25 ºC, 40 ºC, and 50 ºC. The accelerated stability testing revealed that there were no apparent or physical changes in the MLX SSMEDDS-1 capsules with a black and white background and that there was a little drop in drug content after storage(35), without any changings in the drug release at the end of storage.

Conclusion

The SSMEDDS of MLX has been successfully developed and tested in vitro. When compared to brand MLX, the chosen formula SSMEDDS-1 of MLX produces greater and faster in vitro release profiles . As a result of the SSMEDDS formulation's increased solubility, absorption and oral bioavailability may improve. The SSMEDDS is an excellent approach to increasing poorly soluble drugs and enhancing their absorption, targeting drugs through their nanoscale, and reducing drug side effects with stable formulations. The current work might be used to formulate and develop different hydrophobic medicines as self-micro emulsifying drug delivery systems

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