Research Article

PREPARATION AND EVALUATION OF MELOXICAM SOLID DISPERSIONS BY SOLVENT EVAPORATION METHOD

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ABSTRACT

Meloxicam (Class II drug according to Biopharmaceutical Classification System) is a highly potent non-steroidal anti-inflammatory drug of the enolic acid class of oxamic derivatives. The low solubility of Meloxicam in water and biological fluids results into its poor bioavailability. The aim of this study is to improve the solubility of Meloxicam, and hence bioavailability, by using solid dispersion technique. Nine physical mixtures of Meloxicam (PMMs) were prepared in three different proportions of MEL-to-carrier (PEG 4000, PEG 6000, and poloxamer 407). Solid dispersions of MEL (SDMs) were prepared by solvent evaporation method using the polymers mentioned above. Solubility studies for both PMMs and SDMs were conducted in a phosphate buffer (pH 6.8). The prepared SDM formulations were subjected for percentage of practical yield and drug content analysis. Fourier Transform Infra-Red (FT-IR) spectrophotometric and Differential Scanning Calorimetric (DSC) studies were also conducted to evaluate both PMMs and SDMs. Among all the prepared formulas the ratio of 1:5 MEL-to- poloxamer 407 was considered the best, which showed significant enhancement ($p < 0.05$) of the drug solubility for both PMM-9 and SDM-9. Good results were also observed concerning the drug content analysis and percent of practical yield for SDM-9. FT-IR studies confirmed the compatibility between MEL and poloxamer 407 for both PMM-9 and SDM-9. Moreover, according to DSC studies, there was a perfect change of MEL crystallinity to the amorphous state. Overall, results suggest that SDM-9 containing poloxamer 407 (Pluronic®F-127) as a carrier in a proportion of 1:5 drug: carrier was a successful resolution for the limited solubility of MEL.

Keywords: meloxicam, solid dispersion, poor water soluble, poloxamer 407.

INTRODUCTION

Meloxicam, an oxamic derivative, is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide). The molecular weight is 351.4. Meloxicam has pKa values of 1.1 and 4.2. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$ and it has a chemical structure as shown in Figure 1.

Figure 1: Chemical Structure of meloxicam²

Meloxicam is a potent non-steroidal anti-inflammatory drug (NSAID) and a selective cyclooxygenase-2 (COX-2) inhibitor. It is used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases^{1,2}. It has a wider spectrum of anti-inflammatory activity, combined with less gastric and local tissue irritation than NSAIDs available prior to its discovery². Moreover, meloxicam can reduce fever by decreasing plasma cortisol and interleukin-63. It is practically insoluble in water and is only slightly soluble in acetone.⁴ Its solubility increases significantly with an increase in pH^{4,5}. An enhancement of the dissolution rates of water-insoluble drugs

remains one of the most challenging tasks of drug development, because the enhanced dissolution rates can increase drug oral bioavailability^{6, 7}. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface active agents. Solid dispersion techniques have been widely used to improve the dissolution properties and bioavailability of poorly water soluble drugs⁸. In the early 1960s, Sekiguchi *et al.* reported that formulation of eutectic mixtures could lead to an improvement in the release rate and thereby the bioavailability of poorly soluble drugs, the explanation given for this behavior was that, after dissolution of the drug, a fine suspension of drug particles was exposed to the dissolution medium (saliva or GIT fluids) and that both the smaller particle size and better wettability of the drug particles in this suspension resulted in a faster dissolution rate⁹. There are several methods to produce solid dispersions: melt method, solvent melt method, and solvent evaporation method¹⁰. In 1970, Tachibani and Nakumara were the first to produce solid dispersion by solvent evaporation method⁸. Several water soluble carriers can be used to produce solid dispersion by solvent method such as polyethylene glycols (PEGs), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), hydroxypropylmethylcellulose (HPMC) and poloxamers⁹. Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight usually falling in the range 200 to 300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500 to 20 000 are usually employed. PEG 4000 and PEG 6000 were used as carriers for preparation of solid dispersion with meloxicam due to their properties i.e. easily soluble in water, physiologically inert, non-toxic, lack of absorption, thermally stable at melting temperature and improved compound wettability¹¹. The poloxamer series cover a range

of copolymers with different molecular weights. They are used in pharmaceutical formulations as surfactants, emulsifying agents, solubilizing agent and dispersing agents. Poloxamers are often considered as “functional excipients” because they are very essential components and play an important role in the formulation^{10,16}. In this study, PEG 4000, PEG 6000 and Pluronic®F-127 were selected to produce solid dispersions with meloxicam by solvent evaporation method.

MATERIALS AND METHODS

Materials

Pure Meloxicam (Apex pharma, Egypt), PEG 4000 and PEG 6000 (BDH Laboratory Supplies, UK), pluronic®F-127 (Sigma Aldrich Co, U.S.A.), acetone (Tedia Co, U.S.A.) and methanol (ANALYT, GCC, UK).

Methods

Preparation of Meloxicam physical mixtures

The PMMs were prepared by mixing MEL and the carrier in a mortar in proportions of 1:1, 1:3 and 1:5 (drug: carrier) for each carrier, as shown in Table 1, for 5 minutes and then sifted through a 0.25 mm sieve (# 60)22.

Preparation of Meloxicam Solid Dispersions

The SDMs were prepared by using several carriers (i.e. PEG 4000, PEG 6000 and Pluronic®F-127) in proportions of 1:1, 1:3 and 1:5 (drug: carrier) as shown in Table 1. The drug and carrier were triturated in dry mortar for 5 minutes and then the mixtures were dissolved in 100-500 ml acetone (depending on the total weight of the drug and carrier) with continuous stirring in a 500 ml-beaker using a magnetic stirrer until a clear solution of drug and carrier was obtained. The resultant solution was evaporated until a solid cake was obtained. The solid dispersion was scraped out with a spatula. Dispersions were pulverized using a mortar and pestle and passed through a 0.25 mm sieve (# 60) before packed in an airtight container and placed in a desiccator¹¹.

Solubility study of Meloxicam Physical mixtures

An excess amount of MEL (10 mg) and PMM (theoretically equivalent to 10 mg MEL) were added to a 25-mL conical flask containing 10 mL phosphate buffer (pH 6.8), placed in a shaking water bath at 37 ± 0.5 °C for 72 h. At the end of 72 h., samples were filtered by a 0.45 µm membrane filter, suitably diluted with phosphate buffer (pH 6.8) and analyzed by UV-spectrophotometer at 362 nm for equilibrium solubility⁸.

Solubility Study of Meloxicam Solid Dispersions

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Evaluation of Prepared Meloxicam Physical mixtures

Fourier Transform Infrared (FT-IR) Spectroscopy studies

The IR spectra of the prepared PMMs were recorded on FTIR spectrophotometer Samples of 2–3 mg were put onto a

platinum disk; pressure of 10.000–15.000 psi was applied. The IR spectra were recorded at scanning range from 4000–500 cm⁻¹ and resolution of 4 cm⁻¹ 6.

Differential Scanning Calorimetric (DSC) studies

Thermal analysis was conducted through DSC In order to detect the compatibility between the drug and the polymers PEG 4000, PEG 6000, and Poloxamer 407. Samples of 10 mg PMM-1, PMM-4, and PMM-7 were sealed in flat bottomed aluminium pans and heated in the DSC instrument at nitrogen flow rate of 100 ml/min, The heating rate was 10°C/min in a temperature range of 20–300 °C¹². The DSC thermo grams were recorded.

Evaluation of Prepared Meloxicam Solid Dispersions

Percentage of Practical Yield

Percentage of practical yield was calculated to know about the percentage of yield or efficiency of any method, thus it is help in selection of an appropriate method of production¹⁴. Solid Dispersions were collected and weighed to determine practical yield (PY) from the following equation:

$$PY\% = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug+carrier)}} \times 100$$

Drug Content Analysis

Accurately weighed quantity of solid dispersion (theoretically equivalent to 5 mg of MEL) was dissolved in small amount of methanol and volume was made up to 5 ml with phosphate buffer (pH 6.8). The solution was sonicated for 5 minutes then the solution was filtered through membrane filter 0.45 µm. The sample was diluted suitably and assayed by UV-spectrophotometer at 362 nm¹³. The actual drug content was calculated using the following:

$$\text{Drug Content}\% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Fourier Transform Infrared (FT-IR) Spectroscopy studies

The IR spectra of the pure drug and SDMs were recorded on FTIR spectrophotometer Samples of 2–3 mg were mixed with about 400 mg of dry potassium bromide then compressed into transparent disks under pressure of 10.000–15.000 psi. The IR spectra were recorded at scanning range from 4000–500 cm⁻¹ and resolution of 4 cm⁻¹ 6.

Differential Scanning Calorimetric (DSC) studies

Samples of 10 mg pure meloxicam and its solid dispersions with different polymers were sealed in flat bottomed aluminium pans and heated in the DSC instrument at nitrogen flow rate of 100 ml/min, to detect possible polymorphic transitions during crystallization process. The heating rate was 10°C/min in a temperature range of 20–300 °C^{1,12}. The DSC thermo grams were recorded.

Statistical Analysis

The results were statistically analyzed using t-test and given as mean $\pm$ SD. P values < 0.05 were considered as significant.

Table 1: Composition of the prepared meloxicam physical mixtures and solid dispersions with their assigned batch codes

PMM Batch code	SDM Batch code	(Meloxicam: carrier) ratio	Carrier
PMM-1	SDM-1	1:1	PEG 4000
PMM-2	SDM-2	1:3	PEG 4000
PMM-3	SDM-3	1:5	PEG 4000
PMM-4	SDM-4	1:1	PEG 6000
PMM-5	SDM-5	1:3	PEG 6000
PMM-6	SDM-6	1:5	PEG 6000
PMM-7	SDM-7	1:1	Pluronic®F-127
PMM-8	SDM-8	1:3	Pluronic®F-127
PMM-9	SDM-9	1:5	Pluronic®F-127

SDM₁₋₉-Solid dispersion of Meloxicam prepared using different carriers; PMM₁₋₉-Physical mixture of MEL prepared using different carriers

Table 2: Composition of the prepared meloxicam solid dispersions with their % practical yield (PY %), % drug content (values are expressed as mean $\pm$ SD, n = 3)

Batch codes	Carrier	MEL: Carrier	PY %	% drug content
SDM-1	PEG 4000	1:1	41.6 $\pm$ 2.4	53.3 $\pm$ 2.4
SDM-2	PEG 4000	1:3	44.5 $\pm$ 1.87	63.66 $\pm$ 3.3
SDM-3	PEG 4000	1:5	67.5 $\pm$ 1.5	94 $\pm$ 2.9
SDM-4	PEG 6000	1:1	54 $\pm$ 6.8	78 $\pm$ 2.16
SDM-5	PEG 6000	1:3	60 $\pm$ 2.16	72.3 $\pm$ 8.8
SDM-6	PEG 6000	1:5	49 $\pm$ 9.2	80 $\pm$ 4.1
SDM-7	Pluronic®F-127	1:1	40 $\pm$ 6.5	92.66 $\pm$ 5.2
SDM-8	Pluronic®F-127	1:3	44.5 $\pm$ 6.7	95.5 $\pm$ 4.1
SDM-9	Pluronic®F-127	1:5	47 $\pm$ 6.66	101.6 $\pm$ 1.2

Figure 2: Solubility of pure Meloxicam and physical mixture of Meloxicam and different proportion of different polymers

All values are expressed as mean $\pm$ SD, n = 3

Figure 3: Fourier Transform Infrared (FT-IR) Spectra of the prepared meloxicam physical mixtures

Figure 4: DSC thermo grams of pure meloxicam and meloxicam physical mixtures (PMM-1, PMM-4, and PMM-7) containing the drug-to-polymer ratio 1:1 for each polymer (PEG 4000, PEG 6000, and Poloxamer 407) respectively

Figure 5: Solubility of pure Meloxicam and Meloxicam solid dispersions using different proportions of polymers

All values are expressed as mean $\pm$ SD, n = 3

Figure 6: Fourier Transform Infrared (FT-IR) Spectra of pure MEL, PEG 4000, PEG 6000, Poloxamer 407, and the different prepared meloxicam solid dispersions

Figure 7: DSC thermo grams of pure meloxicam, poloxamer 407, and meloxicam solid dispersions

RESULTS AND DISCUSSION

The SDMs were prepared by using several carriers (PEG 4000, PEG 6000, and Pluronic®F-127). In the present work, nine PMM formulas and nine SDM formulas were prepared and their complete composition was shown in Table 1. During SDM preparation, acetone used was between 100 ml (as in 1:1 ratios) and 500 ml (as in 1: 5 ratios) with the aid of a water bath to raise the temperature of acetone to 35-40°C for the dissolution of both the drug and the carrier. Then evaporation of acetone was carried out until a dried mass was obtained.

Solubility study of Meloxicam physical mixtures

As demonstrated in Figure 2, the solubility of pure MEL in phosphate buffer (pH 6.8) at 37°C was found to be (4.5 ± 1.5) µg/ml while the solubility of PMM-1 (1:1 ratio) was (13.7 ± 4.07) µg/ml. Further increase in the ratio of PEG 4000 to 1:3 (PMM-2) results in significant increase of solubility ($p < 0.05$). However, increasing the ratio of PEG 4000 to 1:5 (PMM-3) results in no further significant increment of solubility ($p > 0.05$). Using of different grade of PEG, i.e. PEG 6000 result in no significant difference in comparing to PEG 4000. However, increasing the ratio of PEG 6000 from 1:1 (PMM-4) to 1:5 (PMM-6) results in significant enhancement in solubility ($p < 0.05$). Using of different polymer, Pluronic®F-127, showed significant enhancement in solubility ($p < 0.05$) in comparing to the solubility of meloxicam alone. Increasing the drug: polymer ratio of Pluronic®F-127 to 1:3 and then to 1:5 result in further enhancement of solubility. For all PMMs formulas, the highest significant increment of solubility (67.4 ± 1.092) µg/ml was found with the use (PMM-9), which consisted of drug and Pluronic®F-127 in 1:5 ratio. This result is in

agreement with M. Umesh *et al*¹⁷, who found that the solubility of MEL was increased with increased poloxamer188 concentration in solid dispersion formula.

Fourier Transform Infrared (FT-IR) Spectroscopy studies

FT-IR studies were performed to aid the evaluation of any important chemical interaction between MEL and the polymers (PEG 4000, PEG 6000, and Pluronic®F-127) in the physical mixtures. The two rings in MEL structure (Figure 1) are strong enough that could not be degraded easily by trituration and sieving during physical mixture preparation. The IR spectra of PMMs (Figure 3) showed no changes in the location or width of the characteristic infrared peaks of MEL (amide peak at $(1620-1660)$ cm⁻¹ and C-S-C peak at $(650-670)$ cm⁻¹), which indicated that there was no chemical interaction between MEL and the different carriers.

Differential Scanning Calorimetric (DSC) studies

The DSC curves obtained for pure drug and its PMMs were displayed in Figure 4. For physical mixtures, DSC studies were used to investigate compatibility between MEL and carriers used (PEG 4000, PEG 6000, and Poloxamer 407), the plots in Figure 4 showed that MEL endothermic peak was sharp at 259.61 °C corresponding to its melting point, while in PMM-1, PMM-4, and PMM-7 which contain 1:1 MEL-to-carrier ratio, MEL endothermic peak appeared reduction in intensity but still near the range of its melting point i.e. 246.66°C, 248.32°C, and 247.33°C respectively. The carriers endothermic peaks appeared also within the range of their melting points (55-65) C°. This indicated that there was no well observed interaction between MEL and carriers in the physical mixtures.

Evaluation of Meloxicam Solid Dispersions

Percentage of Practical Yield (PY %)

The results of PY % studies were shown in Table 2 below. Percent practical yields for all formulations of solid dispersions were found to be between 40-67.5 %. Maximum yield was found to be (67.5 ± 1.5) % in SDM-3. The PY % for SDM-1 (1:1 ratio) was found to be (41.6 ± 2.4) %. Increasing the ratio of MEL-to-PEG4000 to 1:5 (as in SDM-3) results in a very significant increase ($p < 0.05$) of the PY %. While if the ratio of MEL-to-PEG 6000 and poloxamer 407 increased to 1:5 as in SDM-6 and SDM-9 respectively, it results in no further significant enhancement of PY %

Drug Content Analysis

As explained in Table 2, the drug contents of the prepared SDMs were found to be in the range of (53.3- 101.6) %. The SDM-3, which consisted of an inexpensive and generally regarded as safe hydrophilic carrier PEG 4000, showed good drug content $(94 \pm 2.9)^{18}$. Regarding the influence of PEG on drug content analysis, results showed that PEG 4000 contained in SDM-3 in proportion of 1:5 (drug: polymer) had very significant influence on drug content analysis ($p < 0.05$) than that of PEG 6000 contained in SDM-6 which is (80 ± 4.1) % in same proportion; this may be due to the better solubility enhancement with PEG 4000 attributed to either solubilization of the drug or enhancement of the physical amorphism of MEL. In comparing SDM-3 with SDM-9, results showed that there is significant increase in % drug content with SDM-9 which composed of MEL and poloxamer407 in proportion of 1:5. Maximum result (101.6 ± 1.2) % was found in formula SDM-9, which may be due to the excellent solubilizing property of poloxamer 407.

Solubility Study

All solid dispersions of MEL prepared with PEG 4000, PEG 6000 and Pluronic®F-127 polymers showed enhanced drug solubility over the pure meloxicam ($p < 0.05$) (Figure 5). The maximum increment in solubility achieved by using Pluronic®F-127 especially at the ratio of 1:5 drug-to-carrier (SDM-9), where the solubility was (54 ± 6.66) µg/ml. Regarding the effect of the type of PEG, based on the results, PEG 4000 manifested better solubility enhancement which was between (30.7 ± 2.3) and (38.5 ± 2.06) µg/ml at all ratios of MEL: PEG 4000 than that of PEG 6000 which was between (20.8 ± 1.5) and (28 ± 1.014) µg/ml.

FT-IR Spectrophotometric studies

FT-IR studies were performed to aid the evaluation of any important chemical interaction between MEL and the dispersion polymers¹⁹ (PEG 4000, PEG 6000, and Pluronic®F-127). The FT-IR spectra of pure MEL, PEG 4000, PEG 6000, Pluronic®F-127 and the solid dispersions of MEL: PEG 4000, PEG 6000, and Pluronic®F-127 were shown in Figure 5. The two rings in MEL structure (Figure 1) are stable and could not be degraded easily by the usual method of solvent evaporation used in this study²⁰. The IR spectra (Figure 6) showed the absence of changes in the location or width of the characteristic infrared peaks of MEL (amide peak at $(1620-1660)$ cm^{-1} and C-S-C peak at $(650-670)$ cm^{-1}), which indicated that there was no well-defined chemical interaction between MEL and the different carriers.

Differential Scanning Calorimetric (DSC) studies

Thermal analysis were performed by using the DSC technique to observe any changes in crystallinity and also to

detect any possible interaction between MEL and dispersion polymers (PEG 4000, PEG 6000, and Poloxamer 407)^{19,23}. Polyethylene glycols are polymers of low melting points, they were used in the preparation of SDM -1 and SDM -2, after their melting; they dissolve drugs before reaching their own melting temperatures and which may be much higher²⁴. The DSC thermo grams of pure MEL and the SDM: PEG 4000, PEG 6000, and Poloxamer 407 were shown in Figure 7. The DSC profile for untreated drug showed a sharp endothermic peak at 259.61°C. This is corresponded to meloxicam melting point, which indicates the crystalline nature of the drug. The DSC profiles for MEL: PEG 4000, PEG 6000, or Pluronic®F-127 solid dispersions for the different drug: polymer ratios (1:1, 1:3, 1:5) showed a complete disappearance of MEL characteristic endothermic peak at 259.61°C. The disappearance of this peak indicates the homogenous dispersion of MEL. This is agree with the results of DSC studies of Gamal A. *et al*¹⁹, which showed that using of flufenamic acid solid dispersion with Pluronic®F-127 in different drug: polymer ratios resulted in a complete disappearance of the drug characteristic endothermic peak. Deeper analyzing of the DSC results showed a great shift of the endothermic peak as shown in SDM-6 (45.71 °C), SDM-7 (55.55 °C), SDM-8 (55.4 °C) and SDM-9 (55.84°C), this may be attributed to the presence of PEG 6000 in case of SDM-6 and Poloxamer 407 in case of SDM-7, 8 and 9 in the molten state. This result indicated that the presence of poloxamer 407 was sufficiently important to decrease the drug crystallinity to the amorphous state and at this ratio (1:5) most of the drug existed in amorphous form and the amount of polymers used was sufficient to solubilize most of the drug.

CONCLUSION

The present study demonstrated a successful and simple method to prepare meloxicam solid dispersions to enhance meloxicam solubility. The type and amount of the carrier used played an important role in solubility enhancement. Pluronic®F-127 in a ratio of 1:5 of drug-to-carrier showed a maximum solubility enhancement of both meloxicam physical mixtures and solid dispersions, with good compatibility between Meloxicam and polymer as shown by FT-IR study. The DSC studies proved a perfect reduction in crystallinity of the drug in solid dispersion formulations. To summarize, Solid dispersion of meloxicam by using Pluronic®F-127 is a successful remedy for the limited solubility of meloxicam and formula SDM-9 is a promising formula that can be selected for further study, most likely to be formulated as a fast dissolving dosage form.

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