

PREPARATION AND EVALUATION OF MELOXICAM SOLID DISPERSION BY MELTING METHOD

ANMAR ADHAM ISSA^{1,2*}, DANIELA MARCHIDAN², VICTOR COJOCARU², VALENTINA ANUȚA²

¹ Department of Pharmacy, Ministry of Health, Iraq

² University of Medicine and Pharmacy „Carol Davila“, Faculty of Pharmacy, 6 Traian Vuia, 020956, Bucharest, Romania

*corresponding author: anmaar77@yahoo.com

Abstract

Drug formulation as solid dispersion (SD) represents a good method for the enhancement in solubility of poorly water soluble drugs, as well as for the reduction of ulcerogenicity of non-steroidal anti-inflammatory drugs (NSAID). The poorly water soluble Meloxicam (MLX) was used as model drug to prepare solid dispersion. Solid dispersion of MLX was prepared by melting method, using Poloxamer 188 as hydrophilic carrier. A 3² factorial design was used to study the influence of individual and combined effects of 2 factors (drug:polymer ratio and cooling temperature) on the responses. Using the polynomial equation describing the effect estimates on the dependent variables and the surface response methodology, an optimal formulation was developed. A drug:polymer ratio of 1:4.69 and a cooling temperature of 5°C were found to be the optimum values for the independent variables. The optimized solid dispersion was further characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR) and X-ray powder diffraction (XRD) analysis, whereas the dissolution behavior was studied in 900 ml of 0.25% w/v sodium lauryl sulphate solution by means of USP Apparatus 2 (50 rpm). The results confirmed obtaining of a solid dispersion of low crystallinity with a complete *in vitro* release of the active substance within 60 minutes.

Rezumat

Formularea medicamentelor ca dispersie solidă (DS) reprezintă modalitate eficientă de îmbunătățire a solubilității substanțelor greu solubile în apă, permițând totodată reducerea caracterului ulcerogenic al medicamentelor antiinflamatoare nesteroidiene (AINS). Ca model de substanță activă cu solubilitate redusă în apă a fost folosit meloxicamul (MLX). Dispersia solidă cu meloxicam a fost preparată prin metoda topirii, folosind Poloxamer 188 drept vehicul hidrofil.

Pentru studiul efectelor individuale și combinate a celor mai importante variabile de formulare asupra proprietăților dispersiei solide a fost utilizat un plan factorial de tip 3², cu două variabile (raportul substanță activă:polimer și respectiv temperatura de răcire) la trei nivele. Utilizând ecuația polinomială care descrie efectele acestora asupra variabilelor dependente, precum și metodologia suprafețelor de răspuns au fost determinate valorile optime ale variabilelor independente (respectiv raportul MLX:polimer 1:4.69 și temperatura de răcire de 5°C), fiind dezvoltată și preparată formularea optimizată. Această formulare a fost caracterizată utilizând microscopia electronică de baleiaj (SEM), calorimetria dinamică diferențială (DSC), spectroscopia în IR cu transformată Fourier (FTIR) și difracția de raze X (XRD). Cinetica de cedare *in vitro* a substanței active a fost studiată în 900 ml soluție

lauril sulfat de sodiu 0.25% (w/v), utilizând aparatul 2 USP, la 50 rpm. Rezultatele au confirmat obținerea unei dispersii solide cu un grad scăzut de cristalinitate, și cu o cedare completă a substanței active în 60 de minute.

Keywords: Meloxicam, Solid dispersion, Melting method.

Introduction

Oral drug delivery is the simplest and most desirable way of administering therapeutic agents. Because of the greater stability, smaller bulk, accurate dosage and ease of manufacturing, solid oral dosage form is preferred over other types of oral dosage forms, therefore, most of the new chemical entities under development these days are intended to be used as a solid dosage form [31, 18, 40]. For any orally administered drug product the fundamental parameters controlling the drug absorption rate and extent are its aqueous solubility and gastrointestinal permeability [5, 21, 22]. Various physical or chemical approaches are available in order to improve the solubility of poorly soluble drugs, one of the most popular being drug dispersion in carriers (eutectic mixtures, solid solutions, solid dispersions) [2, 26]. Drug formulation as solid dispersion is one of the most promising strategies to improve the oral bioavailability of poorly water-soluble drugs. The term “solid dispersion” (SD) refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state [4, 9]. Recently, it has been shown that the release rate and extent of the active ingredient can be substantially improved if the carrier has surface activity or self-emulsifying properties (third generation carriers) [1, 4].

The objectives of present study are to optimize a preparation technique of solid dispersions of NSAID intended for once daily chronic use in arthritis and osteoarthritis by using melting method. Meloxicam (MLX) was selected as model drug. Meloxicam (MLX) is BCS class II compound, an oxycam derivative non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities [24]. MLX chemical structure is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazoly)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide with the following structural formula (Figure 1) and its physicochemical characteristics shown in Table I [35].

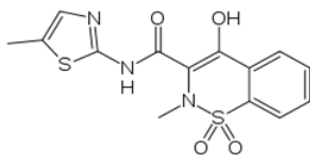


Figure 1

The chemical structure of meloxicam

Table I
Physicochemical properties of meloxicam

Chemical formula	C ₁₄ H ₁₃ N ₃ O ₄ S ₂
H ₂ O solubility	12 ug/ml
Melting point	257°C

Among the important methods that have been used to characterize SDs are thermo-analytical analysis, X-ray diffraction, infrared spectroscopy and measurement of release rate of drug [20, 33]. Thermo-analytical methods include all the examination of a characteristic of the system as a function of temperature. Of these assays, the differential scanning calorimetry (DSC) is the most highly regarded method. On the other hand, the principle behind X-ray diffraction is that when X-ray beam is applied to the sample, interference bands can be detected. Crystallinity in the sample can be identified from number and intensity of the peaks in the diffraction pattern. Structural changes and lack of the crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy [39].

Materials and Methods

Materials

Meloxicam as gift sample was supplied by Changzhou Longcheng pharmaceutical Co., Ltd., China. Poloxamer 188 was supplied by BDH, England. Anhydrous methanol was supplied by Merck, Germany. All other chemicals were of analytical grade. The following instruments were used: DSC 6 Differential scanning calorimeter (DSC) (Perkin Elmer., USA), DT6 Dissolution system (Erweka GMBH, Germany), 1720 FTIR spectrometer (Perkin Elmer., USA), D8 Advance X-ray Diffractometer (Burker AXS, Germany), UV-1601 Spectrophotometer (Shimadzu, Japan), Universal 320R centrifuge (Hettich, Germany), Vibramax 100 shaker (Heindolph, Germany).

Methods

A 3² factorial design was used in development of the dosage form. In this design, 2 factors were evaluated, each at 3 levels, in order to study the influence their individual and combined effects on the responses (dependent variables) [6, 12]. Response surface and contour plots were generated to understand the interaction between different variables.

A mathematical quadratic regression model was developed for predicting system responses within selected experimental conditions.

Experimental data were fitted according to the following second-order polynomial equation calculated by multiple regression analysis:

$$Y = b_0 + \sum_{i=0}^n b_i X_i + \sum_{i=0}^n b_{ii} X_i^2 + \sum_{i < j}^n b_{ij} X_i X_j + \varepsilon \quad (1)$$

where Y represents the measured response, b are coefficients calculated by multiple regression analysis, X_i represent the main effects of the independent variables, $X_i X_j$ the interaction terms between variables, X_i^2 quadratic expressions of the independent variables (included into the model in order to assess nonlinearity) and ε is the random error.

The optimum experimental conditions were determined by using desirability functions.

The experimental design, data analysis and quadratic model building were computed by means of Statistica™ Statsoft 8.0 software (StatSoft, Tulsa, OK, USA).

Preparation of Meloxicam solid dispersion

Physical mixtures (PM) were prepared by mixing MLX with Poloxamer 188 (PXM) in (drug:polymer) ratios of 1:2, 1:5 and 1:8 (factor 1, X_1) for 5 min using glass mortar and pestle. The PM was heated while stirring at 65°C, in thermostatic water bath, to achieve a homogenous dispersion. It was subsequently cooled to one of the three cooling temperatures (5, 15 and 25°C), according to the design of the experiment. The cooling temperature represents factor 2 (X_2) of the experimental plan. The freeze-dried mass was pulverized, passed through a 30-mesh sieve, stored in a vacuum desiccator for 48 hours and finally passed through a 60-mesh sieve before packaging in an amber colored, airtight container. The yield was determined using the following formula [9]:

$$\text{Yield \%} = \frac{\text{Practical weight of the solid dispersion}}{\text{Theoretical weight (drug+carrier)}} \cdot 100 \quad (2)$$

Meloxicam phase solubility study

The phase-solubility technique allows evaluation of the affinity between MLX and the carrier (PMX) in water. The experiments were carried out according to the method described by Higuchi and Connors [15]. Excess amounts of MLX were placed into stoppered conical flasks containing 20 ml aqueous solutions of PMX at different concentrations in the range 0.1- 1%.

The resulting suspensions were shaken at ambient temperature until equilibrium was reached, i.e. for 48 h, on a Heidolph Vibramax 100 shaker.

The samples were filtered through a 0.22 μm membrane filter. The filtrate was suitably diluted and spectrophotometrically analyzed for MLX at $\lambda=362$ nm. Each sample was analyzed in triplicate.

Aliquots of 5 ml were withdrawn and filtered immediately using 0.22 μm cellulose nitrate disc filter. The filtered samples were diluted suitably and assayed for MLX by measuring absorbance at $\lambda= 358\text{nm}$ against blanks by means of a UV-1601 spectrophotometer (Shimadzu, Japan).

Each sample was analyzed in triplicate.

Characterization of the prepared solid dispersion containing Meloxicam

Determination of drug content in the prepared solid dispersions

A SD mass equivalent to 10 mg of MLX was weighed and placed in beaker containing a suitable quantity of methanol. The sample was mixed for 1 hour by using a Heidolph Vibramax 100 shaker, and centrifuged for 10 minutes at 4000 rpm.

The resulting solution was suitably diluted with methanol and spectrophotometrically assayed for drug content at 362 nm. The drug content was determined by using a standard plot of absorbance versus concentration.

Determination of MLX solubility

Saturation solubility measurements were conducted for both pure MLX and MLX solid dispersions, in order to assess the increase in solubility of MLX when formulated as SD.

For solubility study, excess amounts of MLX powder and SD (equivalent to approximately 15 mg active substance) were dispersed in 20 ml water in an appropriate screw capped vial and vigorously mixed for 2 seconds at 5000 rpm. The suspensions formed were equilibrated under continuous agitation for 24 hours at room temperature, centrifuged for 5 minutes at 10000 rpm and then filtered through a 0.22 μm cellulose nitrate membrane filter to obtain a clear solution.

The filtrate was appropriately diluted with distilled water and analyzed for MLX content by means of a spectrophotometric method, with detection at 362 nm.

In vitro dissolution studies

In vitro dissolution studies of MLX, PM and SD were carried out using the United State Pharmacopeia (USP) Apparatus II (paddle), by

dispersed powder technique [8]. Briefly, samples of the MLX solid dispersions equivalent to 15 mg of pure drug were added to 900 ml distilled water containing 0.25% w/v sodium lauryl sulphate, maintained at 37 ± 0.5 °C. An agitation speed of 50 rpm was used for all dissolution studies. Experiments were run in triplicate for each of the experimental and optimized SD formulations. Aliquots of 5 ml were withdrawn at predefined time intervals up to 120 minutes by using a syringe filter. The withdrawn volume was immediately replaced with an equivalent volume of pre-warmed (37°C) dissolution medium, in order to maintain the total volume constant. The filtered samples were suitable assayed for MLX by measuring absorbance at $\lambda = 358\text{nm}$ against blank dissolution medium.

Experimental concentrations were corrected for losses of drug and dissolution volume during sampling by means of the following equation [34]:

$$C_i = A_i + \sum_{k=1}^{n-1} A_k \frac{V_k}{V_k - V_s} \quad (3)$$

where C_i is the corrected absorbance of the observation, A_i is the observed specific absorbance, V_s is the sample volume and V_k is the total volume of the dissolution medium.

Dissolution profiles were compared by using Moore and Flanner model independent mathematical approach to calculate similarity factor (f_2) and difference factor (f_1). [29]

$$f_2 = 50 \cdot \log \frac{100}{\sqrt{1 + \frac{\sum_{t=1}^n (R_t - T_t)^2}{n}}} \quad (4)$$

$$f_1 = \frac{\sum_{t=1}^n |R_t - T_t|}{\sum R_t} \cdot 100 \quad (5)$$

where R_t and T_t are the cumulative percentage of drug dissolved at each of the selected n time points of the reference and test product.

Generally, a f_2 value greater than 50 in accordance with f_1 value up to 15 signify somewhat “a less than 10 % difference” between profiles and is accepted as similarity between dissolution profiles [29].

Angle of repose determination

Static angle of repose of the SD and PM were determined by the funnel method. The angle of repose was measured by passing the accurately

weighed solid dispersions through a sintered glass funnel of 27 mm internal diameter, on a horizontal surface. The angle of repose (ϕ) was calculated as follows:

$$\tan \phi = \frac{h}{r} \quad (6)$$

where h and r are the height and radius of the powder cone.

Differential Scanning Calorimetry (DSC)

The DSC study was performed in order to detect possible polymorphic transition during the crystallization process. The analyses were carried out by means of a DSC 6 Differential scanning calorimeter (Perkin Elmer., USA). Briefly, accurately weighted samples (2-4 mg) of each drug, carrier and drug solid dispersions were heated in hermetically sealed aluminium pans over a temperature range of 30°C to 300°C at a constant rate of 10°C/min under nitrogen purge (20ml/min) [37].

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectral measurements were performed at ambient temperature using a 1720 FTIR spectrometer (Perkin-Elmer, USA). FTIR spectra of the drug, carrier and solid dispersions were obtained in the range 500- 4000cm⁻¹ at a resolution of 2 cm, by using the KBr disc method [36, 38]. KBr pellets were prepared by gently mixing the sample with KBr (1:100 ratio).

Powder X-ray diffraction analysis (XRD)

Powder X ray diffraction study was carried out for all MLX, PXM and SD in order to assess their degree of crystallinity. X ray diffraction patterns for all samples were determined by means of a previously described protocol [13], using a D8 Advance X-ray Diffractometer (Burker AXS, Germany), employing a CuK α source. The diffractometer was operated at 40 kV, 40 mA in a 2 θ range from 5° to 50° with a step size of 0.01°, and a count time of 1 s/step. The positions and intensities of diffraction peaks were used in the identification and comparison of crystallinity degree of the samples.

Results and Discussion

Phase solubility study of Meloxicam-Poloxamer mixture

The phase solubility results indicated a linear increase of MLX solubility as a function of polymer (PXM) concentration (r=0.996,

slope=0.0145) with 3, indicative of a A_L type solubility diagram [15]. In general, if the slope of the phase solubility diagram is less than 1, the complex stoichiometry will be assumed to be 1:1 and such profiles according to Higuchi and Connors [15] are of A_L type. In the case of a 1:1 complex, the apparent stability constant ($K_{1:1} = 1181.7$ ml/g), calculated using equation (6), represents the intrinsic solubility of the drug (S^0). Similar results have been reported for many drugs using hydrophilic polymers, due to formation of soluble complex and/or co-solvent effect of carrier [10, 30 and 16].

$$K_{1:1} = \frac{Slope}{S^0(1 - Slope)} \quad (7)$$

Characterization of prepared solid dispersion of Meloxicam

Full factorial design analysis of solid dispersions

The use of a factorial design experiment is an efficient method of indicating the relative significance of a number of variables in the formulation. Also it offers the advantage to provide a way of analyzing the results to decide on the most significant variables. Analysis of variance (ANOVA) is generally used, but with factorial design a maximum outcome can be drawn out of this model, with the use of a small number of experiments. In addition, they allow a mean of assessing interaction which exists between variables over the response [3].

For all SD factorial design batches (A1-A9) study of % yield of the in vitro release kinetics was performed. The mean in vitro dissolution curves for the experimental batches are plotted in Figure 2:

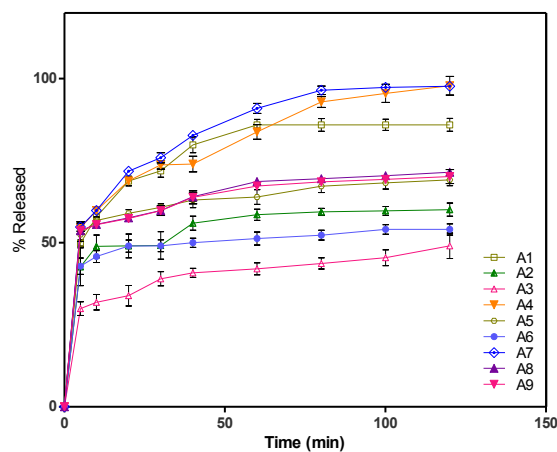


Figure 2
Release profiles of MLX from the experimental formulations

Results of SD factorial design batches (A1-A9) are listed in Table II below, which includes Y1 (% MLX released at 30 min), Y2 (% MLX released at 60 min), Y3 (% MLX released at 120 min), Y4 (% yield of the SD preparation method). The % yield and % released (Figure 2) for all 9 batches showed wide variation (Table II) and the data clearly indicated that the % released (Y1-Y3) is significantly dependent on X_1 (polymer to drug ratio) and X_2 (cooling temperature), while the % yield depends only on X_1 (Table II). The fitted equation relating the response % yield and % released to X_1 and X_2 was generated by replacing the estimated values of coefficient (Table III) in equation (1).

The values for the correlation coefficient shown in Table III indicate a good fitting for the suggested model to represent the relation between factors and responses.

Table II
Results of factorial design batches of SDs prepared using melting method

Results of factorial design batches of SDBs prepared using melting method						
	Variables Levels		Response			
Batch Code	X ₁	X ₂	Y1	Y2	Y3	Y4
A1	-1	-1	71.92	85.92	85.94	86.86
A2	-1	0	49.17	58.54	60.09	87.00
A3	-1	+1	39.02	42.07	49.08	89.00
A4	0	-1	73.71	83.78	97.83	96.36
A5	0	0	60.77	63.94	69.16	90.10
A6	0	+1	49.08	51.30	54.07	84.60
A7	+1	-1	75.90	90.93	97.69	82.00
A8	+1	0	59.81	68.66	71.49	69.00
A9	+1	+1	59.78	67.27	70.17	71.00
	Actual values		X ₁ : polymer to drug ratio; X ₂ : cooling temperature; Y1: % MLX released at 30 min; Y2: % MLX released at 60 min; Y3: % MLX released at 120 min; Y4: % yield			
Coded terms	X ₁	X ₂				
-1	2	5				
0	5	15				
+1	8	25				

Table III
Results of regression analysis of SDs prepared using melting method

Response	Coefficients estimates						R^2
	b_0	b_1	b_{11}	b_2	b_{22}	b_{12}	
Y1	59.91	5.90	0.96	-12.27	-2.49	4.19	0.9841
P value	0.000	0.011	0.371	0.001	0.072	0.048	
Y2	68.05	6.72	-1.28	-16.67	-3.25	5.05	0.992
P value	0.000	0.006	0.229	0.000	0.031	0.024	
Y3	72.84	7.37	0.64	-18.02	-4.44	2.34	0.9772
P value	0.000	0.026	0.707	0.002	0.064	0.364	
Y4	83.99	-6.81	4.77	-3.44	-1.47	-3.29	0.9384
P value	0.000	0.019	0.033	0.101	0.332	0.165	

Table IV
The ANOVA results of SDs prepared using melting method

Response		.df(1,3)	SS	MS	F
Y1	Regression	5	1239.87	218.37	32.75
	Error	3	20.00	6.67	
Y2	Regression	5	1310.21	144.36	21.65
	Error	3	17.22	5.74	
Y3	Regression	5	2570.09	123.13	27.20
	Error	3	57.47	19.16	
Y4	Regression	5	3897.52	91.07	24.43
	Error	3	38.83	12.94	

The data demonstrate that both X_1 and X_2 affect the drug solubility (Y1-Y3 responses), while only X_1 affects the % yield (Y4). In terms of drug release, the most significant terms ($p < 0.05$) for the suggested model are b_1 , b_2 and b_{12} . It may be concluded that the high level of X_1 and low level of X_2 favor higher drug solubility/release. It was observed that while the temperature decreases, the amount of drug dissolved increases. A similar finding has been observed by Kapsi and Ayers [19] for enhancement in dissolution of itraconazole from its SD with polyethylene glycol and by Chutimaworapanet al [9] for enhancement in dissolution of nifedipine from its SD with different water soluble carriers like PEG, hydroxyl propyl β -cyclodextrin (HP- β -CD) and PXM.

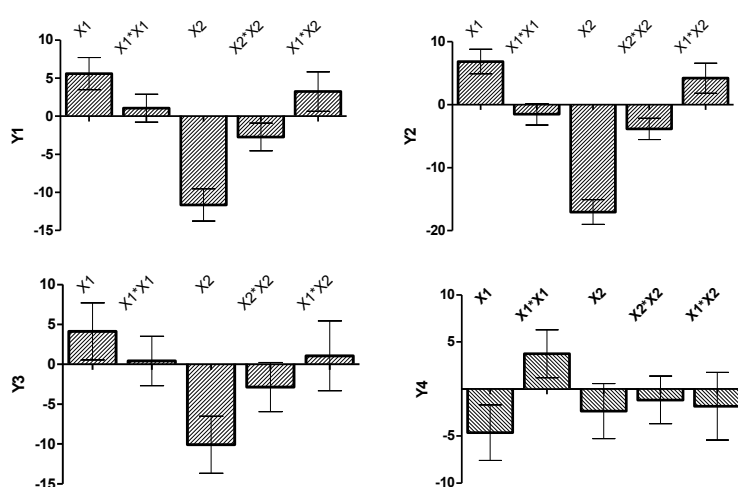


Figure 3

Influence of the formulation factors on the release (Y1-Y3) and yield (Y4) of the meloxicam solid dispersion prepared by melting method

For the response % yield, the significant terms ($p < 0.05$) in the model suggested by the statistical software are b_1 and b_{11} , meaning that the % yield is significantly affected by polymer to drug ratio (X_1), with no significant effect of cooling temperature (X_2). This finding is in agreement with rofecoxib SD study which may be due to difficulty of sieving when higher polymer ration is used [28] (Figure 3).

The relationship between the dependent and independent variables is further illustrated using the response surfaces, which enable the visual checking of the effects in the three dimensional space (Figure 4).

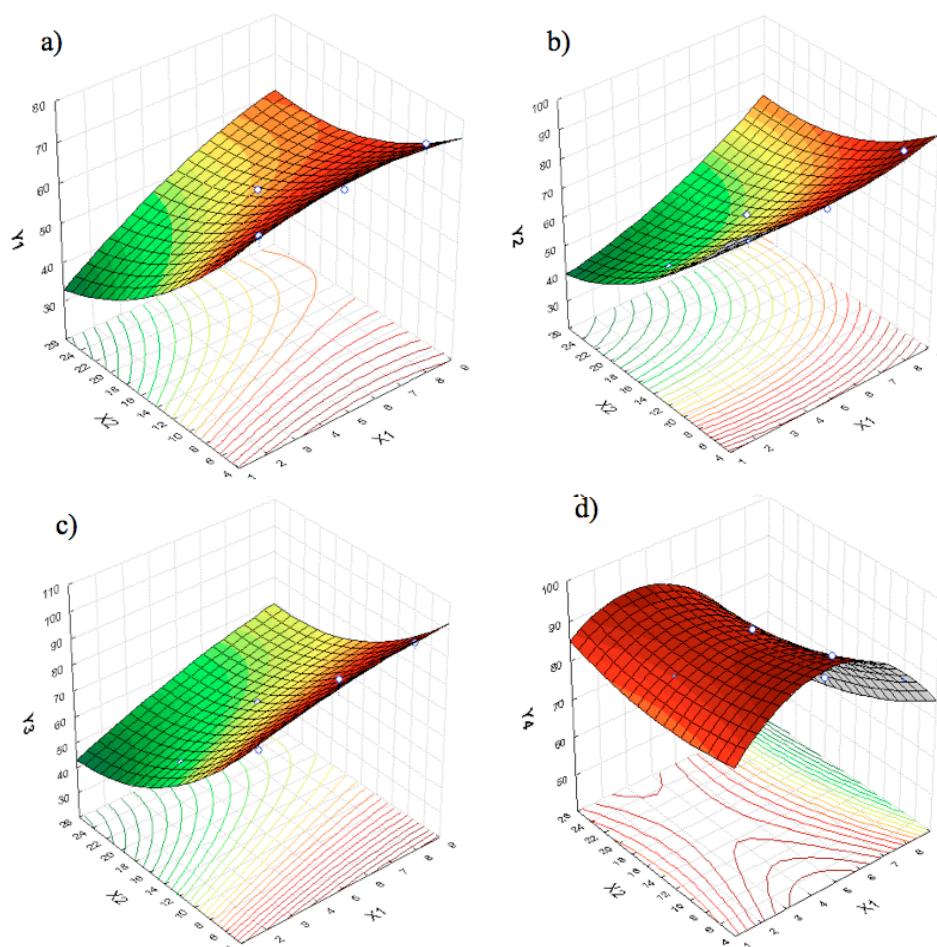


Figure 4

Response surface plot for effect of variables X_1 and X_2 on a) Y_1 ; b) Y_2 ; c) Y_3 ; d) Y_4 for the meloxicam solid dispersion prepared by melting method

Selection and characterization of the optimum formulation

Using the polynomial equation describing the effect estimates on the dependent variables and the surface response methodology, an optimal formulation was developed. A drug:polymer ratio of 1:4.69 and a cooling temperature of 5°C were found to be the optimum values for the independent variables (Figure 5).

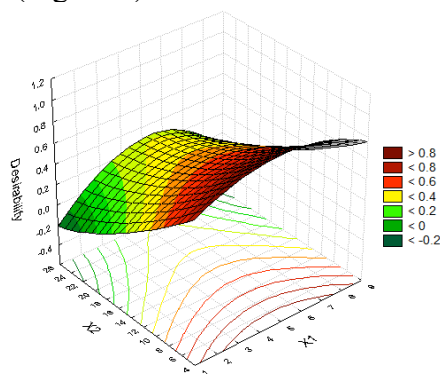


Figure 5

Desirability contour plot for selecting the optimum formulation parameters.

Maximum desirability (0.9344) corresponds to $X_1=4.69$ and $X_2=5$

The mean dissolution profile of the optimized formula prepared using the melting method was compared to both pure MLX and with MLX: poloxamer physical mixture. The results indicate that a significant increase in the release rate of MLX could be obtained by its formulation as SD (Figure 6).

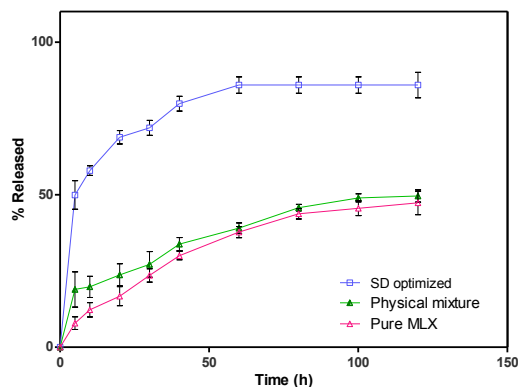


Figure 6

Comparison of dissolution profiles in 0.25% sodium lauryl sulphate for the optimized SD formula of MLX prepared by melting method, MLX and poloxamer physical mixture, and pure MLX (mean for three replicates)

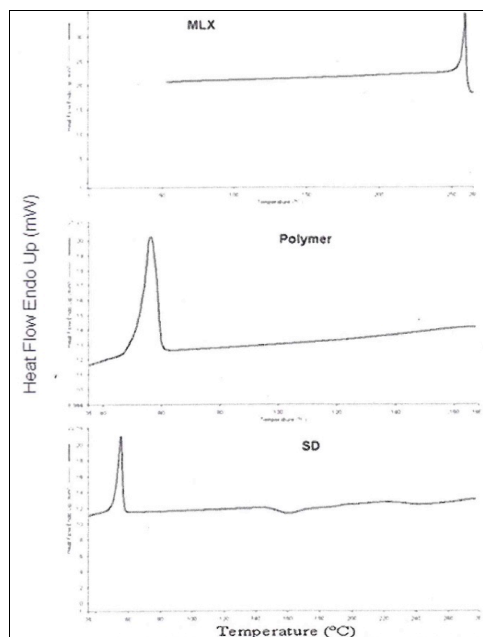
On the other hand, the solubility of MLX at 28°C from optimized SD formula increased from 12.45 µg/ml for pure MLX to 273.9 µg/ml for solid dispersion, respectively (Figure 8)., whereas when preparing the SD by kneading method, MLX solubility was found to be 214.4 µg/ml [13]. In addition, the data from contact angle measurement indicate that the wettability was improved for the SD compared with pure drug, as the contact angle was 39° for SD, 35° for pure PXM compared to 78° for pure MLX. Thus, the wettability is better in SD than in pure drug. The general conclusion from the characterization work of SDs is that the difference in improvement of dissolution for SDs prepared by different drug: polymer ratio may be reflected on the difference in degree of particle size reduction of dispersed drug and in degree of drug crystallinity reduction [25].

Angle of repose

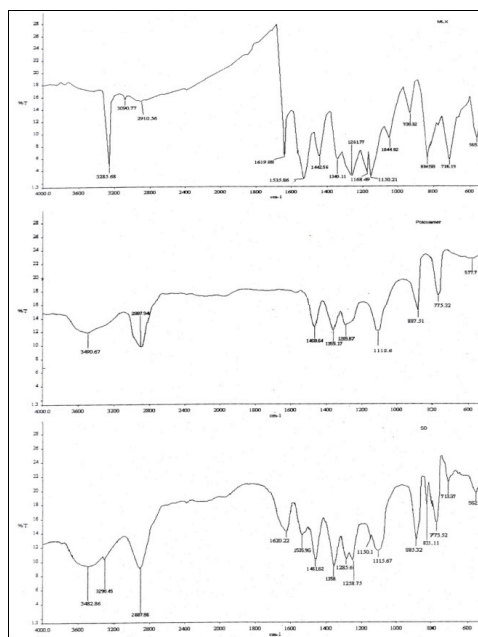
To get an idea about the flowability properties of the SD, the angle of repose for the prepared optimized formula was determined. In general, if the angle of repose exceeds 50°, the material will not flow satisfactory, whereas materials having value below 50° near the minimum, the material will flow easily. The rougher and more irregular the surface of the particles, the higher is the angle of repose [32]. The angle of repose for the prepared optimized formula of SD was found to be of mean of 29.7°±0.96 which indicates acceptable free flowability.

Differential scanning calorimetry

Representative thermograms for pure MLX, PXM and optimized formula of SD are presented in Figure 7. The DSC curve for the pure MLX exhibited a sharp endothermic peak at about 260°C corresponding to its melting point, indicating crystalline nature of the substance. The thermal behaviour of PXM showed melting endotherms at 56°C, while the DCS of solid dispersion exhibited melting point for the PXM around 53°C, with no endothermic peak corresponding to MLX. The absence of a MLX peak indicates that the drug is amorphous or is present as a solid solution inside the PXM matrix.

**Figure 7**

DSC thermograms of pure MLX, PXM and optimized formula of solid dispersion prepared by melting method.

**Figure 8**

FTIR images of pure MLX, PXM and optimized formula of solid dispersion prepared by melting method.

Fourier transform infrared spectroscopy

The FTIR spectra of pure MLX, PXM and optimized formula of SD are presented in Figure 8.

FTIR Spectra of meloxicam was characterized by principal absorption peaks at 3286 cm^{-1} , (secondary amine stretch), 3091 cm^{-1} (C-H stretch, aromatic), 2911 cm^{-1} (C-H stretch, aliphatic CH_3 sym), 1620 cm^{-1} (NH_2 scissoring vibrations), 1536 cm^{-1} (C = N stretch) and 1150 cm^{-1} (S=O stretch).

The IR spectrum of PXM is characterized by principal absorption peaks at 2888 cm^{-1} (C-H stretch aliphatic), 1355 cm^{-1} (in-plane O-H bend) and 1113 cm^{-1} (C-O stretch), which were consistent in all binary systems with the drug. A very broad band was also visible at 3491 cm^{-1} , which can be attributed to the presence of water.

Analysis of the spectra for the solid dispersion revealed that the peaks corresponding to the NH vibrations (3286 and 1620 cm^{-1}) decreased significantly, suggesting hydrogen bonding. However, no additional peak

was observed in any binary system indicating absence of any chemical interaction between MLX and carrier.

X-ray powder diffraction analysis

Powder X-ray analysis put in evidence the crystalline structure of meloxicam. Some of the peaks of MLX appeared also in SD but with smaller intensities, suggesting the presence of a little amount of MLX in crystalline form SD.

As the amorphous forms are generally more soluble than the crystalline ones, decrease in crystallinity of both drug and carrier leads to a enhancement in drug solubility and release rate, with improved bioavailability of the drug [14].

Conclusions

MLX-SDs were prepared using the melting method using a optimized formula determined by means of experimental design. The SD showed an increase in the release rate of the active drug in comparison to pure substance. Solubility of MLX from optimized SD was also significantly increased. The release kinetics of the prepared solid dispersion was significantly dependent on both polymer to drug ratio and on cooling temperature. Data of contact angle measurement indicated that wettability was significantly improved for SD compared with the pure drug. The investigation of the selected SD formula using FTIR, SEM, DSC and XRD revealed that the crystallinity of the product is lower than that of pure drug.

References

1. AftabModi and Pralhad Tayade. Enhancement of dissolution profile by solid dispersion (Kneading) technique. *AAPS PharmSciTech* 2006; 7 (3): Article 68 E1-E6.
2. Ahjel SW, Lupuleasa D. Enhancement of solubility and dissolution rate of different forms of atorvastatin calcium in direct compression tablet formulas. *Farmacia*, 2009, 57(3): 290-300.
3. Alkhesheh As, Badawi SS, Badawi AA. Optimization of reconstitutable suspension of rifampicine using 2^4 factorial designs. *Drug Dev. Ind. Pharm* 1996; 22(7):623-630.
4. Ambike AA, Mahadik KR, Paradkar A. Stability study of amorphous valecoxibe. *Int J Pharm.* 2004; 282: 151-162.
5. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995; 12:413-420.
6. Bolton S, Charles S. *Pharmaceutical Statistics*. New York, NY: Marcel Dekker Inc. 2004.
7. British Pharmacopoeia (B.P.). London, UK: Stationary Office London; 2008.
8. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci.* 1971; 60:1281-302.

9. Chutimaworapan S, Ritthidej GC, Yonemochi E, Oguchi T, Yamamoto K. Effect of water soluble carriers on dissolution characteristics of nifedipine solid dispersions. *Drug Dev Ind. Pharm* 2000; 26: 1141-1150.
10. Andreea Cernat, Mihaela Tertis, Sophie Griveau. New modified electrodes with HRP immobilized in polymeric films for paracetamol analysis. *Farmacia* 2012, 60, 1: 1-12.
11. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *Eur J Pharm Sc.* 2001; 13: 123-133.
12. Franz RM, Brown JE, Lewis AR. Experimental design, Modeling and optimization strategies for product and process development, In: Libermann HA, Reiger MM, Banker GS, eds. *Pharmaceutical dosage form: disperse systems*. New York, NY: Marcel Dekker Inc 1988; 1:427-519.
13. Ghareeb M.M., Abdulrasool A.A., Hussein A.A, Noordin M.I. Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188, *AAPS PharmSciTech*. 2009, 10(4): 1206–1215
14. Heo MY, Piao ZZ, Kim TW, Cao QR, Kim A, Lee BJ. Effect of solubilizing and microemulsifying excipients in polyethylene Glycol 6000 solid dispersetocanazole. *Arch Pharm Res.* 2005; 28(5):604-11.
15. Higuchi T, Connors KA. Phase-solubility techniques. In: Rilly CN, ed. *Advances in Analytical Chemistry and Instrumentation*. New York, NY: Wiley-Interscience; 1965:117-212.
16. Hitoshi S, Masahiro N, Takaichi A. Inhibitory effects of polyvinylpyrrolidone on the crystallization of drugs. *Chem. Pharm Bull.* 1978; 26: 118-126.
17. Imai T, Nishiyama T, Ueno M, Otagiri M. Enhancement of the dissolution rates of poorly water-soluble drugs by water-soluble gelatin. *Chem. Pharm Bull.* 1989 Aug; 37(8):2251-2.
18. Kagan L, Hoffman A. Selection of drug candidates for gastroretentive dosage forms; pharmacokinetics following continuous intragastric mode of administration in a rat model. *Eur. J Pharm Biopharma.* 2008; 69(1): 238-246
19. Eleonora Mircia, Emese Sipos, Silvia Imre, Veronica Avrigeanu, Gabriel Hancu, Barna Iantovics, Teodora Balaci. New modified release tablets with pentoxifylline based on lipophilic matrix. Note 1. Formulation, physical study and determination of dissolution profiles of the active substance from the proposed formulations. *Farmacia* 2012, 60, 2: 218-226.
20. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersion. *Eur J Pharm Biopharm.* 2000; 50: 47-60.
21. Mircioiu C, Mircioiu I, Voicu V, et al. Dissolution – Bioequivalence non-correlations. *Basic ClinPharmacolToxicol*, 2005, 96(3): 262-264.
22. Mircioiu C, Prasacu I, Sandulovici R, et al. Release of metoprolol from solid dosage forms. Choice and validation of theoretical model. *Farmacia* 2009, 57(1): 89-98.
23. Moore J, Flanner H. Mathematical comparison of dissolution profiles. *Pharm Tech.* 1996; 20:64-74.
24. Pairet M, Van Ryn J, Schierok H, Hauz A, Trummlitz G, Engelhardt G. Differential inhibition of cyclooxygenase-1 and -2 by meloxicam ant its 4- isomer. *Inflamm Res.* 1998; 47(6):270-276.
25. Patel RP, Patel MM. Physiochemical characterization and dissolution study of solid dispersion of lovastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. *Pharm Dev. Technol.* 2007; 12(1):21-33.
26. Pinnamaneni S, Das NG, DAS SK. Formulation approaches for orally administered poorly soluble drugs. *Pharmazie.* 2002; 57:291-300.
27. Ruan LP, Yu BY, Fu GM, Zhu D. Improving the solubility of ampelisin by solid dispersions and inclusion complexes. *J Pharm Biomed Anal.* 2005; 38: 457-464.
28. Shah TJ, Amin AF, Parikh JR, Parikh RH. Process optimization and characterization of poloxamer solid dispersions of a poor water-soluble drug. *AAPS PharmSciTech.* 2007; 8(2): Article 29.

29. Shah VP, Tsong Y, Sathe P, Liu JP. In vitro dissolution profile comparison –statistic and analysis of the similarity factor, f_2 ., Pharm Res, 1998, 15(6):889-896
30. Shahjahan M, Enever RP. Investigation of the nature of the interaction of nitrofurazone with urea. Int. J Pharm. 1992; 82:229-232.
31. Shaji J, Patole V. Protein and peptide drug delivery: Oral approaches Indian Journal of pharmaceutical science 2008; 70(3):269-277
32. Shibataa Y, Fujii M, Sugamura Y, et al. The preparation of solid dispersion powder of indomethacin with crospovidone using a twin-screw extruder or kneader. Int J Pharm. 2009; 365: 53-60.
33. Shin SC Kim J. Physiochemical characterization of solid dispersion of furosemide with TPGS. Int. J Pharm. 2003; 251:79-84.
34. Singh B, Kaur T, Singh S. Correction of raw dissolution data for loss of drug and volume during sampling. Indian J Pharm Sci. 1997; 59:196-199.
35. Starek M, Krzek J. A review of analytical techniques for determination of oxicam, nimesulide and nabumetone. Talanta2008: 1-18.
36. Tomuță I, Iovanov R, Bodoki E, Leucuța SE. Quantification of meloxicam and excipients on intact tablets by near infrared spectrometry and chemometry. Farmacia 2010, 58(5): 559-571.
37. Vijaya Kumar SG, Mishra DN. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. YakugakuZasshi. 2006; 126(2):93-97.
38. Vijaya Kumar SG, Mishra DN. Preparation, characterization and in vitro dissolution of solid dispersion of meloxicam with PEG6000. YakugakuZasshi. 2006; 126(8): 657-664.
39. Xie Y, Xie P, Song X, et al. Preparation of esomoprazole zinc solid dispersion and study on its pharmacokinetics, Int. J Pharm. 2008;360:53-57
40. Yuksel N, Karatas A, Ozkan Y, et al. Enhancement bioavailability of piroxicam using Gelucire 44/14 and labrasol: in vitro and in vivo evaluation. Eur. J Pharm Biopharm. 2003; 56:453-459.

Manuscript received: June 14th 2012