Utilization of spray drying technique for improvement of dissolution and anti-inflammatory effect of Meloxicam

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Abstract: Meloxicam (MLX) is a poorly water-soluble non steroidal anti-inflammatory drug (NSAID). The main objective of the present work was to enhance the dissolution of MLX and thus its bioavailability by the aid of additives. The novelty of this work rises from the utilization of spray drying technology to produce micro particulates solid dispersion systems containing MLX in the presence of small amount of additives. Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), and Scan Electron Microscope (SEM) were used for studying the physico-chemical and morphological properties of MLX samples. The dissolution of MLX samples was investigated in two different pH media. The morphology of MLX solid dispersion micro-particles was spherical in shape according to SEM. FT-IR profiles indicated that a complex was formed between MLX and the additives. DSC patterns of the MLX micro-particles suggested a reduction in the crystallinity of MLX and probability of presence of an interaction between MLX and the additives. The rate of dissolution of the spray-dried MLX enhanced as compared with the unprocessed MLX in both acidic and neutral media. It was found that 100% of the added MLX released within 5 min in phosphate buffer dissolution medium (pH 7.4) compared to that of the unprocessed MLX (15% in 60 min). Such increase rate in the dissolution of the spray dried MLX could be attributed to the increase in wettability of MLX particles and the hydrophilic nature of the additives. The anti-inflammatory effect of the spray dried MLX was explored using formalin induced rat paw edema model. The spray-dried samples showed an increase in the anti-inflammatory activity of MLX as compared to the unprocessed MLX. This work reveals that the spray drying technique is suitable for preparation of micro-particles with improved dissolution and anti-inflammatory effect of MLX.

Keywords: Meloxicam; spray drying; dissolution; anti-inflammatory effect.

INTRODUCTION

The bioavailability of a drug is mainly affected by its dissolution rate and its permeability through gastrointestinal wall (Stegemann *et al.*, 2007). Low bioavailability and an inadequate therapeutic effect are mainly due to incomplete wettability, sparing water-solubility, low dissolution rate and/or poor permeability (Rainsford, 1999).

Meloxicam (MLX) is 4-hydroxy-2-methyl-N- (5-methyl-3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] (fig. 1). It belongs to cyclooxygenase (COX)-II inhibitor non-steroidal anti-inflammatory drug (NSAIDs). MLX has an anti-inflammatory and analgesic effects. It is frequently used for rheumatoid arthritis, osteoarthritis and other joint diseases (Tsubouchi *et al.*, 2000). MLX showed a number of advantages include absence of aspirin-like hypersensitivity reaction (Bavbek *et al.*, 2007), and acceptable gastro-intestinal tolerance profile compared with other NSAIDs (Sameer *et al.*, 2005). However, it is a lipophilic compound, its log *P* varied according to the pH of the aqueous phase, recording log *P* of 1.9 at pH 5. MLX is practically insoluble in water at low pH values and its solubility increases with increasing pH of the aqueous media (Luger *et al.*, 1996). MLX was classified as Class II according to the Biopharmaceutical Classification System (BCS) (Yazdanian *et al.*, 2004). Therefore, increasing its dissolution rate in the GIT is important to reduce the dose-dependent side-effects and enhance its therapeutic efficacy.

For lipophilic drugs, one of the strategically important actions is to solve problems associated with their solubility in the gastrointestinal tract (GIT) content and bioavailability. Such action helps in decreasing the amount of the drug dose and unwanted side-effects and improves drug bioavailability (Hassan *et al.*, 2004). A number of advanced technological methods are available to modify the physico-chemical properties and increase the dissolution rate of the lipophilic drugs. The most common technologies are particle size reduction (Dinesh and Gleb, 2004), cyclodextrin inclusion complexation (Brewster and Loftsson, 2007), the use of inert water soluble drug carriers in solid solutions or dispersions (Blagden *et al.*, 2007; Shou-Cang *et al.*, 2010) and the

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preparation of nanocrystalline or amorphous forms of Active Pharmaceutical Ingredients (APIs) (Kocbek *et al.*, 2006). Among these techniques, solid dispersion is considered the common and easiest method applied for enhancing the dissolution of poorly water-soluble drugs (Dhirendra *et al.*, 2009). The preparation of solid dispersion system is based on solubilizing or dispersing of lipophilic drug on a water-soluble polymer (s). Co-evaporation, co-fusion, co-precipitation, lyophilization and spry drying are examples of technologies that were used to prepare solid dispersion systems. Polyethylene glycol and pluronic 68 were extensively used as dissolution enhancement additives. However, a high ratio of these additives to drug was used to achieve the desired drug dissolution in a GIT simulation media (Pathak *et al.*, 2008). Gelucier 50/13 is a saturated polyglycolized glyceride contains mixture of glycerides and fatty acid esters of polyethylene glycol. It is an amphiphilic molecule with hydrophilic-lipophilic balance value of 13. Geluciers are recently used as dissolution enhancers for several poorly water-soluble drugs (Fukushima *et al.*, 2007).

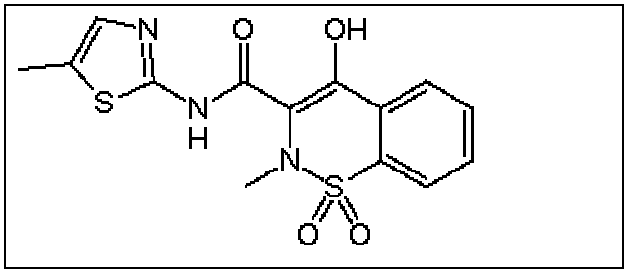

Fig. 1: Structure of MLX.

Several endeavors have been performed to enhance the dissolution rate of MLX utilizing different techniques include complexation (Lenuța *et al.*, 2010) solid dispersion (Pathak *et al.*, 2008), spray congealing (Zaky and Abdel-Raheem, 2011). These studies showed that more than 90% of MLX have been dissolved after using high weight ratio of excipient to MLX. For instance, study showed that PEG 4000: MLX at ratio of (9: 1) is needed for MLX to get 90% of MLX released within 45 min of the *in vitro* dissolution test. Zaky and Abdel-Raheem, 2011, have concluded that excipient (s)-MLX in a ratio of 9:1 enhanced the dissolution rate of MLX in pH 7.4. Another study showed that a high amount of mannitol to MLX (10:1) was used to improve the dissolution of MLX (Nassab *et al.*, 2006).

The main objective of this study is to investigate the impact of binary and quaternary dispersion systems in reducing the amount of excipient (s) needed to enhance dissolution, hence the anti-inflammatory effect of MLX. Reducing the amount of excipients used in a pharmaceutical dosage form frequently results in reducing cost and excipient-related side effects. Spray drying technology which is extensively used in the pharmaceutical industry (Vehring, 2008) was utilized to prepare these dispersion systems.

Additives such as polyethylene glycol 6000 (PEG 6000), Gelucire® 50/13 (GL), and Pluronic® 68 (PL) were used alone or in combination at different ratios with MLX. This work was further extended to compare the dissolution and the anti-inflammatory effect of the spray dried MLX with that of unprocessed MLX. The solid state properties of the spray dried MLX particles were characterized using scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR).

MATERIALS AND METHODS

Materials

Meloxicam was kindly supplied by Riyadh Pharma Medical & Cosmetic Products Co. Ltd. (Riyadh, Saudi Arabia), Polyethylene glycol 6000 (PEG 6000) was obtained from Winlab Laboratory Chemicals, Leicestershire, UK. Gelucire 50/13 (GL) was provided by Gattefosse (Cedex, France). Pluronic F68 (PL) was obtained from Sigma Chemical Co. (St. Louis, MO, USA). Formalin 1% and Urethan 25% were obtained from Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.Methanol (HPLC grade), acetonitrile (HPLC grade), were purchased from BDH, England. Isopropanol (HPLC grade) was obtained from central drug house, CDH®, New Delhi, India. Other chemicals and reagents were of analytical grade.

Preparation of spray dried MLX microparticles with polymers (SD)

Binary and quaternary solid dispersion systems of MLX were prepared. These solid dispersions of MLX containing excipients according to the composition showed in table 1. Binary systems were prepared by dissolving MLX and an excipient (GL, PEG 6000, or PL) in a weight ratio of 1g:0.25g in dichloromethane/methanol binary solvent system (200mL). Solid dispersions of MLX-excipient binary systems (Formula III (MLX-GL), Formula IV (MLX-PEG 6000, and Formula V (MLX-PL) were achieved by removing the organic solvent utilizing a Büchi mini spray dryer model B-191 (Büchi Laboratoriums-Technik AG, Flawil, Switzerland). Quaternary systems were achieved when all of the three excipients (GL, PEG 6000, and PL) and MLX were dissolved in a solvent system similar to that mentioned above (200mL of dichloromethane/methanol binary solvent system) and spray dried together using different weight ratios to produce Formula VI (MLX: GL: PEG 6000:PL at weight ratio of 1: 0.25: 0.25: 0.25) and Formula VII (MLX: GL: PEG 6000: PL at weight ratio of 1:0.5:0.5:0.5). The spray drying parameters were set as follows: liquid feed 4.5-5.0 ml/min, inlet temperature 50 °C and outlet temperature 40°C, the aspirator capacity was 75%, pressure as −25 mbar and air flow rate 4 psi.

Fourier transform infrared spectroscopy (FT-IR)

The FTIR spectra of formulae I-VII was recorded using an FTIR spectrophotometer (Thermo Scientific Nicolet 380, USA). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm^{-1}.

Differential scanning calorimetry (DSC)

Thermal profile of the spray dried MLX in the presence and absence of excipient (s) was investigated utilizing a differential scanning calorimetry (DSC-60, Shimadzu, Japan). Samples of the spray dried solid dispersions containing amount of 3-4 mg of MLX were loaded in an aluminum pan and sealed with aluminum lids by a crimper. Each solid dispersion sample was then thermally scanned against an empty aluminum pan with lid covering range of 25-300^{o}C at heating rate of 10^{o}C/min under nitrogen purging at a rate of 40 ml/min. The thermal parameters of the scanned samples were obtained by using the TA-60WS thermal analysis software.

X-ray diffraction

The crystalline state of the unprocessed MLX and the spray dried form in the presence and absence of excipients was investigated utilizing automated Rigaku Ultima IV, X-ray Diffractometer. The X-ray profiles of the investigated samples were collected using 2theta scan axis at scan speed of 0.5 deg. per min and covering scan range of 3.0-60.0 deg. All scanning processes were performed at room temperature.

Scanning electron microscopy (SEM)

The surface morphology of the raw drug and formulated powder was visualized by scanning electron microscopy (SEM) (Joel JSM 5400LV SEM, Japan) operated at 15kV. The samples were sputter coated with gold (SPI, sputter, USA) and images were then acquired using a scanning electron microscope.

In vitro dissolution studies

The *in vitro* dissolution studies of all formulas were carried out using the USP type II (paddle) method using Electrolab dissolution tester (TDT-06N, India) was adopted. Samples equivalent to 15 mg of pure drug were dispersed in 900mL of 0.1N HCl and 0.2M phosphate buffer (pH 7.4). The dissolution media were maintained at 37°C±0.5°C and stirred at 75 rpm. Samples were collected periodically and replaced by fresh dissolution medium. After filtration through a microfilter (0.45 µm), the concentration of MLX was determined spectro-photometrically (Jenway 6305 spectrophotometer, UK) at 361 nm. All experiments were carried out in triplicate.

Anti-inflammatory study

In vivo anti-inflammatory activity was evaluated on the basis of the inhibition of the volume of the hind paw edema induced by injecting an irritant (formalin 1% w/v in 0.9% w/v saline) into rat's paw (Wheeler-Aceto *et al.*, 1990).

Selection of animals

Adult male Wistar Albino rats aging approximately 3 months ranging in weight from 150 + 10g, were obtained from the Animal Care Center, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The animals were housed in metabolic cages under controlled environmental conditions (25^{o}C and a 12 h light/dark cycle). Animals had free access to pulverized standard rat Pellet food and tap water. The protocol of this study has been followed the instruction of the Research Ethics Committee of College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The animals were divided into five groups, each consisting of three rats. The first group was considered as control without taking any medicament. The other groups II, III, IV and V were taken 1 ml of a suspension of samples I, II, VI and VII respectively at a dose of 2 mg/kg (Hakan *et al.*, 2011). After half an hour, the animals were generally anesthetized by intraperitoneal injection of 1 ml of urethane (25%). After one hour, 0.1 ml formalin (10%) was injected subcutaneously into the plantar region of the right hind paw for all groups. At time intervals 1.5, 2.5, 3.5 and 4.5 hours, the inflammation was measured using 37140-Plethysmometer (UgoBasileSrl., Comerio VA, Italy). The anti-inflammatory (% response) was calculated according to the following equation:

Response % = (C-T) / C *100

C = inflammation of right paw-inflammation of left paw for control rat

T = inflammation of right paw-inflammation of left paw for treated rat

STATISTICAL ANALYSIS

The data from each treatment groups have been subjected to analysis using ANOVA test to determine the P-value for the different used variables. The Fisher's least significant difference (LSD) test was used to find the significant differences between each two variables.

RESULTS

The powder yield of the spray dried samples of MLX in the presence and absence of excipients was nearly 60% of the starting amount. This percentage of solid recovery is in agreement with other studies utilizing spray drying as a solvent removal technology (Maa and Prestrelski, 2000; Maury*et al.*, 2005). The 40% loss of the powder was attributed to the aspiration effect of the system in which submicron particles are not able to settle down on the collector vessel and are removed a way by the aspirator.

Solid state characterization

FT-IR study was performed to explore any interaction that may take place between MLX and the additives. Fig. 2 Showed the FT-IR spectra of the investigated samples. FT-IR spectra of the unprocessed MLX and the spray dried one showed a distinct peaks at 3291 cm^{-1} (secondary -NH or –OH), 1620 cm^{-1} (C=O stretching), 1340 cm^{-1}

(S=O stretching), and 846 to 567 cm^{-1} (-CH aromatic ring bending and heteroaromatics) (Pomázi *et al.*, 2011; Organic Chemistry, 2011). The characteristic peak for -NH or -OH was disappeared in the spray-dried samples containing additives (formulas III-VII). This could be attributed to the physical interaction (complexation) between MLX and the additives. Moreover, a slight shift and broadening in characteristic peaks at 3384cm^{-1}, 1631cm^{-1} (NH), and 1582 cm^{-1} (CO) was observed in formulas (III-VII). These finding were accompanied with changes in the DSC and XRD profiles of MLX samples. The shift in the FR-IR bands may result from the formation of hydrogen bond between MLX and the additives (Hassan, 2006). Dhumal *et al.*, 2009, have explained the broadness of cefuroxime axetil characterized peaks at 3480-3210 cm^{-1} (NH, NH2 complex) to the interaction between the amide of cefuroxime with carbonyl and hydroxyl of Gelucire (Dhumal *et al.*, 2009).

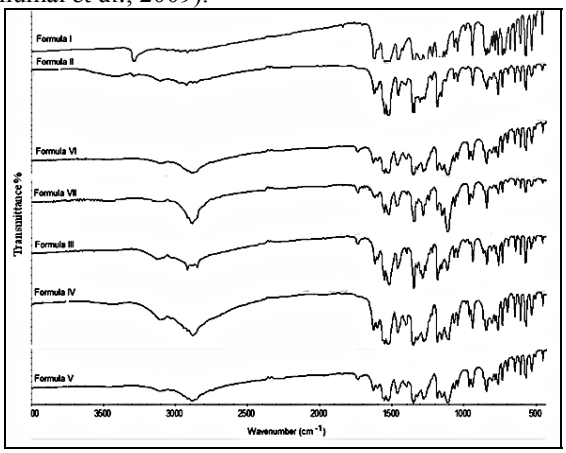

Fig. 2: FT-IR spectrum of unprocessed MLX (Formula I), Formula II (MLX SD), Formula III (MLX co-spray dried with GL, 1:0.25w/w), Formula IV (MLX co-spray dried with PE, 1:0.25w/w), Formula V (MLX co-spray dried with PL, 1:0.25w/w), Formula VI (MLX co-spray dried with GL, PE and PL, 1:0.25:0.25:0.25w/w) and Formula VII (MLX co-spray dried with GL, PE and PL, 1:0.5:0.5:0.5w/w).

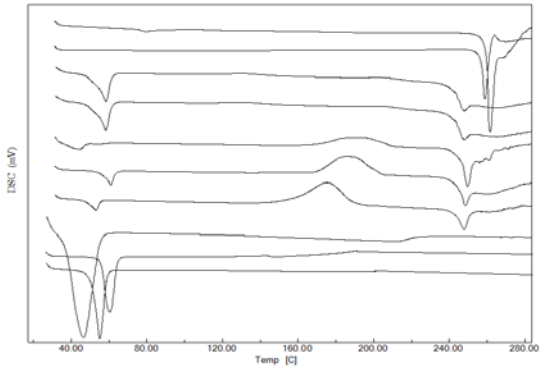

Fig. 3: DSC Thermograms of unprocessed MLX (A), Formula II(B), Formula VI (C), Formula VII (D), Formula III(E), Formula IV (F), Formula V (G),GL (H), PE (I) and PL (J).

The thermal analysis of a compound, utilizing DSC, usually offers information about several physicochemical properties such as crystalline nature and thermal stability of the investigated compound. The thermograms of MLX in the presence and absence of different additives are presented in fig. 3. The thermogram of the unprocessed MLX exhibited a sharp endothermic peak at 262^{o}C, which is attributed to the melting point of MLX (EL-Badryand Fathy, 2006), followed by and an exothermic peak, which has been attributed to the decomposition of MLX after melting (Pomázi *et al.*, 2011).

The thermogram of spray dried form of MLX, (formula II) showed reduction in the melting point recording 258°C. Such slight change in the melting point may indicate changes in the crystallinity state of MLX after spray drying process. Such assumption is supported by the X-ray data (fig. 4). The X-ray profile of the spray dried MLX revealed that MLX is still in crystalline state, however, significant changes in the crystalline nature were observed compared to unprocessed MLX (arrows depicted in the diagram point to peaks that either formed or disappeared). Reduction of the peak intensity with slightly shifting at peaks of 13° and 15° and forming a new peaks such as that at 16°, 16.6° and 17.7° are examples of these changes. Further reduction in MLX melting point with change in its peak intensity and broadness was observed in spray dried MLX samples containing additives (GL, PEG 6000, and PL). MLX melting point of formula III, IV and V has decreased by more than 14^{o}C (recording melting point around 248^{o}C) for these formulas (fig. 3). The reduction in the melting point of MLX was accompanied with broadening and decreasing in the intensity of the melting point peak. Such changes in MLX melting point in the presence of additives could be attributed to the partial transformation of MLX molecular arrangement in particles from crystalline state to amorphous one. Furthermore, these changes may be attributed to the formation of complex between MLX and the additives used. The X-ray data support these suggestions (fig. 4). A significant reduction and shifting in a distinguish X-ray peak of unprocessed MLX at 26° was observed for spray dried MLX formulas III, IV and V containing GL, PEG 6000, and PL, respectively. The thermogram of formulations III, IV and V showed significant exothermic peaks at 192, 190 and 175ºC, respectively (fig. 3). Several studies refer such peaks to the crystallization of a substance before melting (Bandyopadhyay *et al.*, 2007; Supaphol *et al.*, 2004). The relaxation of the molecules of the solid dispersion due to the elevated temperature facilitates the crystallization process of MLX which appears as an endothermic peak. Formulas VI and VII that formed by spray drying of MLX in the presence of the three additives together (GL, PEG 6000 and PL) showed a significant reduction and broadening in the endothermic peak of MLX (fig. 3). These alterations in the DSC profiles of these formulas

were accompanied of changing in the intensity and position of XRD profiles of these formulas (arrows in fig. 4 point to these peaks; 12º 17º, 19º, 23.5º and 25.5º-27.5º).

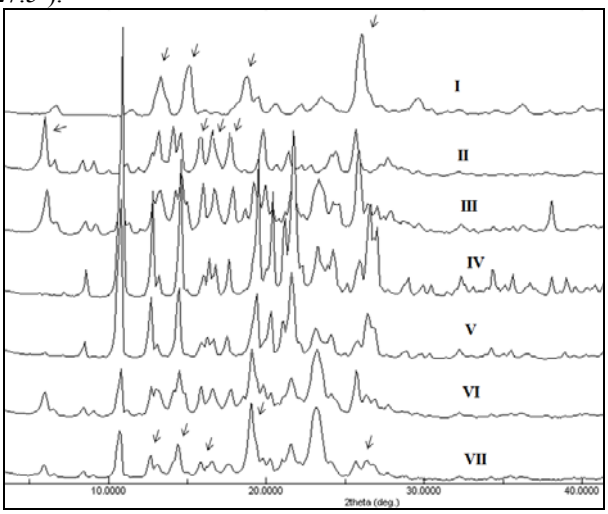

Fig. 4: X-ray diffraction patterns of meloxicam samples. Thepatterns from top to bottom are: I (unprocessed meloxicam), II (spray dried meloxicam), III (MLX co-spray dried with PE, 1:0.25w/w (IV) (MLX co-spray dried with GL, 1:0.25w/w), V (MLX co-spray dried with PL, 1:0.25w/w), VI (MLX co-spray dried with GL, PE and PL, 1:0.25:0.25:0.25w/w), and VII (MLX co-spray dried with GL, PE and PL, 1:0.5:0.5:0.5w/w)

Scanning Electron Microscope (SEM)

The impact of the spray drying process in the presence and absence of additives on the morphology of MLX particles was inspected. The morphology of the unprocessed MLX sample was characterized by irregular shaped crystals (fig. 5A). Such characteristic shape of MLX particles was changed after spray drying. In case of spray dried MLX (Formula II), it was difficult to distinguish the presence of MLX crystals (fig. 5B). The spray dried micro-particles prepared from binary phase of MLX-GL (formula III) exhibited mixture of spherical and irregular particles with slightly rough surfaces (fig. 5C), while the micro-particles of spray dried MLX containing PEG 6000 and PL showed spherical particles with slightly smooth surfaces (fig. 5D and 5E). For quaternary system, micro-particles with regular spherical shape were observed (fig. 5F and 5G). The improvement of the surface of micro-particles could be attributed to the presence of the three additives GL, PEG 6000 and PL. Such changes in the morphology of the investigated MLX samples correlate with the results obtained from DSC and X-ray data. The changes in the morphology of the particles due to the presence of additives have been considered as an evidence of the formation of a solid dispersion (Vilhelmsen *et al.*, 2005).

In vitro dissolution studies

Fig. 6 presents the *in vitro* dissolution profile of different MLX samples comprise unprocessed MLX and MLX spray dried in the presence and absence of additives using 0.1 N HCl dissolution medium at 37±0.5°C. Table 2 shows the dissolution efficiency (DE %) as a percentage of total theoretical dissolution profile for MLX. According the results presented in fig. 6 and table 2, MLX either unprocessed or in the spray dried form exhibited poor and very slow dissolution profile. The unprocessed MLX observed very low dissolution rate in acidic medium with about 2.2% of MLX dissolved after 60 min of the dissolution time, represented 1.7% of DE%. The *in vitro* release rate of the spray dried MLX was slightly increased recording 7.7% during 60 min of the dissolution time which represents 5.0% of DE%. These low values of the rate of MLX dissolution are in agreement with other studies (Pathak *et al.*, 2008; El-Badry, 2011).

Co-spray drying of MLX with the additives, e.g. GL, PEG 6000 and PL (as single or in combination) has significantly improved the dissolution rate of MLX.

The dissolution rate and DE% of MLX was considerably increased by more than 3 times when single additive, GL, PEG 6000, or PL, was co-spray dried with MLX in comparison with control. During the first 15 min of the dissolution test PL and GL showed faster dissolution rate than that observed with PEG 6000 (fig. 6). Such behavior has also been noticed in a previous study on binary solid dispersion systems of gliclazide with PEG 6000 and PL (El-Maghraby and Alomrani, 2011). Binary systems of MLX with PL, PEG 6000, or GL showed increase in MLX dissolution by 12 to 14 times more than that of the unprocessed MLX, recording 24 to 28% of DE%. Such enhancement of MLX dissolution by these additives could be attributed to several factors include the following; 1- improvement of the wettability of MLX particles due to the presence of highly hydrophilic polymers as in case of PEG 6000 and/or 2- the reduction of the surface tension of the dissolution media by surfactants as in case of GL and PL, 3- reduction of the particle size of MLX particles by spray drying technique, as it is revealed by SEM pictures (fig. 5) (Tantishaiyakul *et al.*, 1999; Vippagunta *et al.*, 2002; Ahuja *et al.*, 2007).

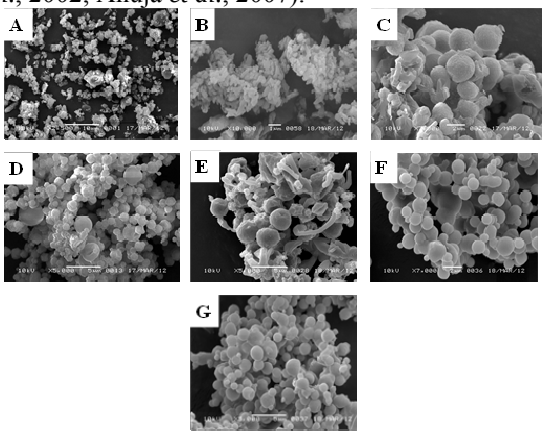

Fig. 5: SEM Photographs of Formulae I (A), II (B), III (C), IV (D), V (E), VI (F) and VII (G).

Further increase in the dissolution of MLX was observed when MLX, PEG 6000, GL, and PL at weight ratio of (1.0:0.25:0.25:0.25) and (1.0:0.5:0.5:0.5) were co-spray dried. These combinations showed a significant enhancement in the dissolution rate and DE% of MLX by more than 24 and 40 times, respectively compared to unprocessed MLX. This could be attributed to the synergistic effect of these additives.

On the other hand, the dissolution rate of MLX in a media mimic to intestinal pH (pH 7.4) exhibited different mode. It was reported that MLX solubility increases by elevating pH of the media (Seedher and Bhatia, 2003). Fig. 7 represents the *in vitro* dissolution of unprocessed MLX and spray dried MLX in the presence and absence of additives using phosphate buffer pH 7.4 at 37±0.5°C. It was observed that at pH 7.4 almost 8% of the unprocessed MLX released during the first 60 min of the dissolution test compared to 2.2% in acidic pH. The dissolution test of the spray dried MLX reported 80% of MLX released within the first 60 min compared with 7.7% in acidic media. Such result reflected the impact of spray drying technique on the dissolution of MLX (Sarkar *et al.*, 2011). The presence of additives in single or combined form imparted a significant enhancement in MLX dissolution reporting 100% of MLX released within the first 10 min compared with 22% of the spray dried MLX in the absence of additives.

In vivo anti-inflammatory study

The anti-inflammatory effect of MLX in the presence and absence of additives was conducted using Paw edema inflammation study. The unprocessed MLX and MLX samples that spray dried in the absence and in the presence of additives at ratios of (1: 0.25: 0.25: 0.25) and (1: 0.5: 0.5: 0.5) of (MLX: PEG 6000: PL: GL) were selected for this test. Each sample was dispersed in water immediately before given to the rats.

Fig. 8 demonstrated the percent of the edema inhibition due to MLX. It is obvious that the presence of additives significantly reduced the inflammation. The magnitude of edema inhibition by the investigated MLX samples was reflected the impact of additives on the bioavailability of MLX. The anti-inflammatory effect of the samples ranked as Formula VII ≥ Formula VI > Formula II > Formula I. Rapid onset of action (edema inhibition) was observed with formulae VII followed by VI. The percent response of formula VII was higher as compared with that of formula VI. For formula VII, the magnitude of inhibition was more than 50% at 1.5 and 2.5 hour after formalin injection, respectively. However, the present of response for formulae I and II was insignificant. Thus the spray dried MLX in the presence of additives (formula VI and VII) showed superiority in suppression of edema through the first two hours over unprocessed (formula I) and spray dried (formula II) MLX.

The significant increase in an anti-inflammatory effect of MLX in the presence of additives could be attributed to the enhancement of the dissolution of MLX as it was reflected from the dissolution test (figs. 6 and 7).

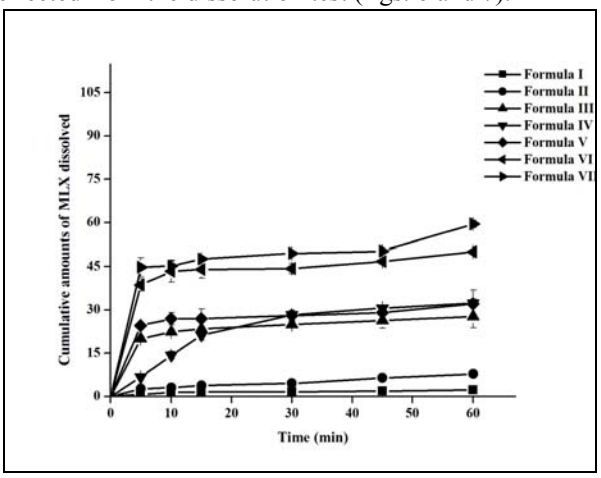

Fig. 6: *In vitro* release of Formulae I, II, III, IV, V, VI and VII in 0.1 N HCl at 37±0.5°C.

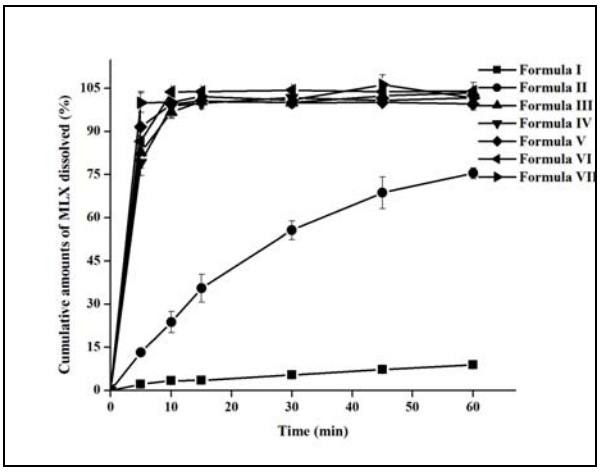

Fig. 7: *In vitro* release of Formulae I, II, III, IV, V, VI and VII in phosphate buffer pH 7.4 at 37±0.5°C.

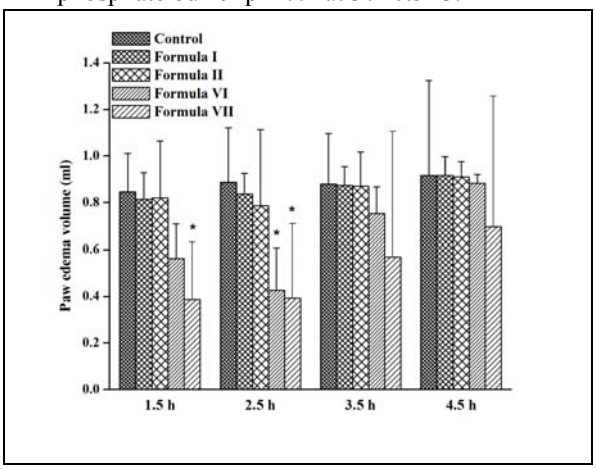

Fig. 8: The Anti-inflammatory activity of orally delivered formulae I, II, VI and VII.
Data expressed as mean ± SD (n=3).
*Significant difference (p>0.05).

Table 1: Composition of spray dried MLX –excipient (s) solid dispersion systems.

Formula No.	MLX (g)	GL (g)	PEG 6000 (g)	PL (g)
I*	1			
II**	1			
III	1	0.25		
IV	1		0.25	
V	1			0.25
VI	1	0.25	0.25	0.25
VII	1	0.5	0.5	0.5

*Pure MLX; ** MLX spray dried (MLX SD). GL: Gelucire 50/13; PEG 6000: polyethylene glycol 6000; PL: pluronic F 168

Table 2: Dissolution efficiency (DE%)

Sample	DE% in 0.1N HCl dissolution medium	DE% in 0.1M Phosphate buffer dissolution medium
Formula I	1.7	5.5
Formula II	5.0	51.7
Formula III	24.7	99.4
Formula IV	25.1	98.9
Formula V	28.3	99.3
Formula VI	45.1	102.5
Formula VII	49.9	102.5

DISCUSSION

The DSC, XRD, FTIR, and SEM data of MLX spray dried samples in the presence and absence of additives reflect the presence of partial transformation of MLX molecular arrangement in particles from crystalline state to amorphous one. Such transformation took place a result of spray drying process and increased due to the presence of additives, which could be attributed to the formation of solid dispersion system (Vilhelmsen *et al.*, 2005). *In vitro* dissolution results observed that MLX has low dissolution profile which is in agreement with other studies (Pathak *et al.*, 2008; El-Badry, 2011) which found that less than 20% of MLX was released during the first 60 min of the dissolution test. Such extremely low dissolution rate of MLX may be attributed to the poor wettability of MLX particles and to their agglomeration. Particles wettability was considered among factors affecting dissolution rate of poorly soluble drugs (Craig, 2002). Spray drying process has significantly affected the dissolution profile of MLX. *In vitro* dissolution findings reflected the impact of spray drying technique on the dissolution of MLX which are correlated with others (Sarkar *et al.*, 2011). Moreover, MLX dissolution profile enhanced by additives and elevating pH of the media (Seedher and Bhatia, 2003). Such findings reflect the importance of dissolution enhancer additives in increasing the dissolution of low aqueous soluble drugs (Chaudhary *et al.*, 2012).

It was suggested that the enhancement of the dissolution of the spray dried drugs was attributed to the good properties of the yielded solid particles. These properties include the uniform, less aggregates and small particles of the spray dried drug particles (Guterres *et al.*, 2009).

Different literatures proposed a number of mechanisms that verify the reasons behind the enhancement of the dissolution rate of a spray-dried drug in the presence of additives. These mechanisms include reduction of the particle size of a drug, solubilisation and wetting effect of the additives, conversion of a drug to its amorphous form, dissolution of the drug in the hydrophilic excipient and/or deaggregation of the drug particles by the aid of additive (Tantishaiyakul *et al.*, 1999; Vippagunta *et al.*, 2002; Sengodam and Mishrs, 2006; Dhumal *et al.*, 2009; Ahuja *et al.*, 2007). Such mechanisms could be extended to explain the finding of the current study; the enhancement of the dissolution of the spray dried MLX in the presence of PEG 6000, GL, and PL. In many literatures, PEG 6000 showed an increase in the dissolution rate of a number of drugs such as piroxicam (Pan, 2000) and naproxen (Vélaz, 1998). However, the dissolution enhancement effect of PEG 6000 observed at high weight ratio of additives to drug. The current work provided an alternative strategy to enhance the dissolution of low aqueous soluble compound by utilizing spray drying technology and using low weight ratio of additives to drug.

For quaternary systems, the synergistic effect of combined additives could illustrated the remarkable enhancement in the dissolution rate of MLX in which the hydrophilic polymer, PEG 6000, may enhance the wettability and the surfactants, GL and PL, could reduce the surface tension of the dissolution media and increase MLX by micellar effect (Chauhan *et al.*, 2005). The results of anti-inflammatory effect of MLX were in correlation with the findings of other tests. In addition to the enhancement of the dissolution rate of MLX, the enhancement of MLX absorption by these additives

should not be excluded. For instance several studies showed that the presence of Gelucire improved the bioavailability of drugs such as glibenclamide (Chauhan *et al.*, 2005) and Cefuroxime axetil (Dhumal, *et al.*, 2009). It was suggested that Gelucires may play as an absorption enhancer (Fukushima, *et al*., 2007). The results showed in this study support such suggestion.

CONCLUSIONS

This study has succeeded to enhance the dissolution of MLX by using low amount of excipients. Spray drying of MLX with additives in single or combined form showed not only a significant enhancement in MLX dissolution but also enhance the anti-inflammatory effect of MLX compared with pure MLX.

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REFERENCES

Ahuja N, Katare OP and Singh B (2007). Studies on dissolution enhancement and mathematical modelling of drug release of a poorly water-soluble drug using water soluble carriers. *Eur. J. Pharm. Biopharm.*, **65**: 26-38.

Bandyopadhyay J, Ray SS and Bousmina M (2007). Thermal and Thermo-mechanical Properties of Poly (ethylene terephthalate) Nanocomposites, *J. Ind. Eng. Chem.,* **13**(4): 614-623.

Bavbek S, Dursun AB, Dursun E, Eryılmaz A and Mısırhgil Z (2007). Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or Nasal Polyps. *Int. Arch. Aller. Imm.,* **142**: 64-69.

Blagden N, de Matas M, Gavan PT and York P (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv. Drug Deliver Rev.*, **59**: 617-630.

Brewster ME and Loftsson T (2007). Cyclodextrins as pharmaceutical solubilizers. *Adv. Drug Deliver Rev.*, **59**: 645-666.

Chaudhary A, Nagaich U, Gulati N, Sharma VK and Khosa RL (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. *J. Adv. Pharm. Ed. Res.*, **2**(1): 32-67.

Chauhan B, Shimpi S and Paradkar A (2005). Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur. J. Pharm. Sci.*, **26**: 219-230.

Craig D (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.*, **231**: 131-144.

Dhirendrak, Lewiss, Udupa N and Atin K (2009). Solid dispersions: A review-*Pakistan J. Pharm. Sci.*, **22**(2): 234-246.

Dhumal RS, Biradar SV, Aher S and Paradkarb AR (2009). Cefuroxime axetil solid dispersion with polyglycolized glycerides for improved stability and bioavailability. *J. Pharm. Pharmacol.*, **61**: 743-751.

Dinesh BS and Gleb BS (2004). Engineered microcrystals for direct surface modification with layer-by-layer technique for optimized dissolution. *Eur. J. Pharm. Biopharm.*, **58**: 521-527.

El-Badry M (2011). Physicochemical characterization and dissolution properties of meloxicam-gLucire 50/13 Binary Systems. *Sci. Pharmaceut.*, **79**(2): 375-386.

EL-Badry M and Fathy M (2006). Enhancement of the dissolution and Permeation rates of meloxicam by formation of its freeze-dried solid dispersion in polyvinylpyrrolidone K-30. *Drug Dev. Ind. Pharm.*, **32**: 141-150.

El-Maghraby GM and Alomrani AH (2011). Effect of binary and ternary solid dispersions on the *in vitro* dissolution and in-situ rabbit intestinal absorption of gliclazide. *Pakistan J. Pharm. Sci.*, **24**(4): 459-468.

Fukushima K, Terasaka S, Haraya K, Kodera S, Seki Y, Wada A, Ito Y, Shibata N, Sugioka N and Takada K (2007). Pharmaceutical approach to HIV protease inhibitor atazanavir for bioavailability enhancement based on solid dispersion System. *Biol. Pharm. Bull.*, **30**: 733-738.

Fukushima K, Terasaka S, Haraya K, Kodera S, Seki Y, Wada A, Ito Y, Shibata N, Sugioka N and Takada K (2007). Pharmaceutical approach to HIV protease Inhibitor atazanavir for bioavailability enhancement based on solid dispersion System. *Biol. Pharm. Bull.*, **30**(4): 733-738.

Guterres SS, Beck RCR and Pohlmann AR (2009). Spray-drying technique to prepare innovative nanoparticulated formulations for drug administration: A brief overview. *Braz. J. Phys.*, **39**(1A): 205-209.

Hakan T, Toklu HZ, Biber N, Celik H, Erzik C, Oğünç AV, Çetinel S and Sener G (2011). Meloxicam exerts neuroprotection on spinal cord trauma in rats. *Int. J. Neurosci.*, **121**(3): 142-148.

Hassan HB, Kata M, Eros I and Aigner Z (2004). Preparation and investigation of inclusion complexes containing gemfibrozil and DIMEB. *J. Inclusion Phenom.*, **50**: 219-226.

Hassan M, Dehghan G and Jafar M (2006). Improving dissolution of meloxicam using solid dispersions. *Aranian J. Pharm. Res.*, **4**: 231-238.

Kocbek P, Baumgartner S and Kristl J (2006). Preparation and evaluation of Nano suspensions for enhancing the

dissolution of poorly soluble drugs. *Int. J. Pharm.,* **312**: 179-186.

Lenuța M. Maria, Lavinia V, Vlaia V, Hădărugă D and Mircioiu C (2010). Preparation and characterisation of inclusion complexes of eloxicam and α-Cyclodextrin and β-Cyclodextrin. *Farmacia*, **58**(5): 583-593.

Luger P, Daneck K, Engel W, Trummlitz G and Wagner K (1996). Structure and physicochemical properties of meloxicam, anew NSAID. *Eur. J. Pharm. Sci.*, **4**: 175-187.

Maa Y and Prestrelski SJ (2000). Biopharmaceutical powders: Particle formulation and formulation considerations. *Curr. Pharm. Biotech.*, **1**: 283-302.

Maury M, Murphy K, Kumar S, Mauerer A and Lee G (2005). Spray-drying of proteins: Effects of sorbitol and trehalose on aggregation and FT-IR amide I spectrum of an immunoglobulin G. *Eur. J. Pharm. Biopharm.*, **59**: 251-261.

Nassab P, Rajk R, Szab P, Parya R, Robert R and Piroska SR (2006). Physicochemical characterization of meloxicam-mannitol binary systems. *J. Pharm. Biomed.*, **41**:1191-1197.

Organic Chemistry, TWG Solomons C (2011). Fryhle, 10th edition upgrade Wiley, New York, p/86

Pan RN, Chen JH and Chen RR (2000). Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. *Drug Dev. Ind. Pharm.*, **26**(9): 989-994.

Pathak D, Dahiya S and Pathak K (2008). Solid dispersion of meloxicam: Factorially designed dosage form for geriatric population. *Acta. Pharmaceut.*, **58**: 99-110.

Pomázi A, Ambrus R, Sipos P and Szabó-Révész P (2011). Analysis of co-spray-dried meloxicam-mannitol systems containing crystalline micro-composites. *J. Pharmaceut. Biomed.*, **56**(2): 183-190.

Rainsford KD (1999). Profile and mechanisms of gastrointestinal and other side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). *AJM*, **107**(6): 27-35.

Sameer S, Praveen S, Shraddha B and Atmaram P (2005). Adsorption of meloxicam on porous calcium silicate: Characterization and tablet formulation. *AAPS. Pharm. Sci. Tech.*, **6**: 618-625.

Sarkar B, Tiwari S, Shankar S and Kaushal A (2011). Use of spray dried micro-spheres technique to enhance solubility of poorly soluble drug. *Asian J. Pharm. Life Sci.*, **1**(2): 118-123.

Seedher N and Bhatia S (2003). Solubility enhancement of Cox-2 Inhibitors using various solvent systems. *AAPS Pharm. Sci. Tech.*, **4**(3): 33.

Sengodam K and Mishrs D (2006). Preparation, characterization and *in vitro* dissolution studies of solid dispersion of meloxicam with PEG 6000. *Pharm. Society of Japan*, **126**(8): 657-664.

Shou-Cang S, Kiong NG, Chia WL and Dong YC (2010). Stabilized amorphous state of ibuprofen by co-spray drying with mesoporous SBA-15 to enhance dissolution properties. *J. Pharm. Sci.*, **4**: 1997-2007.

Stegemann S, Leveiller F, Franchi D, de Jong H and Linden H (2007). When poor solubility becomes an issue: from early stage to proof of concept. *Eur. J. Pharm. Sci.*, **31**: 249-261.

Supaphol P, Dangseeyun N, Thanomkiat P and Nithitanakul M (2004). Thermal, Crystallization, Mechanical and Rheological Characteristics of Poly (trimethylene terephthalate)/Poly(ethylene terephthalate) Blends. *J. Polym. Sci. Part B.*, **42**: 676-686.

Tantishaiyakul V, Kaewnopparat N and Ingkata-wornwong S (1999). Properties of solid dispersions of piroxicam in polyvinylpyrrolidne. *Int. J. Pharm. Sci.*, **181**: 143-151.

Tsubouchi Y, Sano H, Yamada R, Hashiramoto A, Kohno H, Kusaka Y and Kondo H (2000). Preferential inhibition of cyclooxygenase-2 by meloxicam in human rheumatoid synoviocytes. *Eur. J. Pharmacol.*, **395**: 255-263.

Vehring R (2008). Pharmaceutical particle engineering via spray drying. *Pharm. Res.*, **25**(5): 999-1022.

Vélaz I, Sánchez M, Martín C and Martínez-Ohárriz MC (1998). Effect of PEG 4000 on the dissolution rate of naproxen. *Eur. J. Drug Metab. Ph.*, **23**: 103-108.

Vilhelmsen T, Eliasen H and Schaefer T (2005). Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharm.*, **303**: 132-142.

Vippagunta SR, Maul KA, Tallavajhala S and Grant DJ (2002). Solid-state characterization of nifedipine solid dispersions. *Int. J. Pharm.*, **236**(1-2): 111-123.

Wheeler-Aceto H, Porrec F and Cowan A (1990). The rat paw formalin test: Comparison of noxious agents. *Pain*, **40**(2): 229-23.

Yazdanian M, Briggs K, Jankovsky C and Hawi A (2004). The high solubility definition of the current FDA Guidance on Biopharmaceutical classification system may be too strict for Acidic Drugs. *Pharm. Res.*, **21**(2) 293-299.

Zaky AA and Abdel-Raheem IT (2011). Solubility enhancement of Meloxicam prepared via Binary and Ternary Phases Using Spray Congealing. *Asian J. Pharm. Health Sci.*, **1**(4): 196-203.