

Analgesic, Anti-Inflammatory and Ulcerogenic Studies of Meloxicam Solid Dispersion in Rodents

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Received December 20, 2005; Revised July 29, 2006; Accepted July 31, 2006

This paper is available online at <http://ijpt.iuims.ac.ir>

ABSTRACT

Meloxicam is a non steroidal anti-inflammatory drug, used in the treatment of rheumatoid arthritis and oosteoarthritis. It is practically insoluble in water leading to poor dissolution, variations in bioavailability and gastric irritation on oral administration. In order to modulate its gastric side effect and to increase aqueous solubility, physical mixture and solid dispersion of the drug were prepared with polyethylene glycol 6000 and polyvinyl pyrrolidine. The analgesic, anti-inflammatory and ulcerogenic effects were assessed for physical mixture and solid dispersion in comparison with meloxicam alone. The results indicate that both physical mixture and solid dispersion possess better analgesic and anti-inflammatory properties with less ulcerogenic potential as compared to pure meloxicam.

Keywords: Meloxicam, Solid dispersion, Analgesic, Anti-inflammatory, Ulcerogenic study

Meloxicam (MLX) is a non steroidal anti inflammatory, analgesic and antipyretic agent, used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases [1]. Like other non steroidal anti inflammatory drugs (NSAIDs), MLX is also practically insoluble in water leading to poor dissolution, variations in bioavailability and gastric irritation on oral administration [2-5]. Solid dispersion (SD) in water-soluble carriers had attracted considerable interest as a mean of improving the dissolution rate and bioavailability [2, 3, 6]. These SDs provide possibility of reducing the particle size of such drugs to nearly molecular level, due to transformation of the drug from the crystalline to the (partial) amorphous state, and/or to increase the saturation solubility [7] In this study, physical mixtures (PM) and SD of MLX were prepared using polyethylene glycol 6000 (PEG 6000) and poly vinyl pyrrolidine (PVP) with 10% drug concentration in order to enhance aqueous solubility, while maintaining the original pharmacological activity of the drug. We assume that this method could result in the increased and more predictable dissolution rate benefiting the therapeutic response. The SD may be considered as potential dosage form modifications for the MLX and other poor water soluble or insoluble drugs that are commonly administered orally, where an increase in the bioavailability, enhancement of therapeutic effects and lowering of side effects are desirable. Therefore, the PM and SD were subjected to analgesic, anti inflammatory and ulcero-

genic studies using rodents in comparison to the pure MLX.

MATERIALS AND METHODS

Drugs

Meloxicam was obtained as gift sample from Sun Pharmaceuticals Ltd. India. Polyethylene glycol 6000, poly vinyl pyrrolidine and acetic acid were purchased from S.D Fine Chemicals, India, Carrageenan type 4 was procured from Sigma Co. USA and all other chemicals/solvents used were of analytical grade.

Animals

Swiss Albino mice (20-30 g) and Wistar Albino rats (180-200 g) of either sex were used for pharmacological studies. The animals were housed under standard laboratory conditions in polypropylene cages, provided with food and water *ad libitum*. The animals were acclimatized to the laboratory environment for at least one week before the experimental session. The experimental protocol was approved by Institutional Animal Ethical Committee.

Preparation of Physical Mixtures and Solid Dispersion

The PM of MLX was prepared by mixing MLX, PEG 6000 and PVP (10% drug concentration) that were

Table 1. Analgesic effect of MLX, PM and SD

Treatment	Number of abdominal writhing	% Inhibition
Control	39.2 ± 1.2	-
MLX	26.6 ± 1.6 *	32.14
MLX-PEG 6000-PVP(PM)	23.6 ± 1.50 *	40.81
MLX-PEG 6000-PVP (SD)	20.2 ± 1.98 *†	48.72

Data were expressed as mean ± SEM, n=5.

* $p < 0.001$ compared with control.

† $p < 0.05$ compared with same does of MLX.

previously sieved (75-150 μ m). SD of MLX was prepared by solvent evaporation method [8] using a specified amount of PM dissolved in dichloromethane. The mixture was stirred and evaporated at 40°C in vacuum oven until dry. The dried mass was pulverized and sieved (75-150 μ m). All the samples were stored in a desiccator over silica gel till further use.

Analgesic Study

Acetic acid induced abdominal writhing. Mice were divided randomly into four groups of five animals each. The first three groups were administered orally, MLX, PM or SD in a dose of 4 mg/kg of MLX (40 mg/kg of PM and SD equivalent to 4 mg/kg of MLX). The fourth group was given 1% (w/v) sodium carboxyl methyl cellulose suspension, as vehicle control. The abdominal writhing syndrome was elicited by an inter-peritoneal injection of 1% (v/v) acetic acid at a dose of 10 mg/kg body weight. The analgesic response was assessed by counting the number of abdominal writhings in 20 mm [9] after 5 mm of acetic acid injection.

Anti-inflammatory Study

Carrageenan induced paw oedema. The rats were fasted for 18 h and water was provided *ad libitum*. The animals were divided randomly into four groups of five animals each. MLX, PM or SD were administered orally at a dose of 4 mg/kg of MLX (40 mg/kg of PM and SD equivalent to 4 mg/kg of MLX) to the first three groups. The fourth group received 1% (w/v) sodium carboxyl methyl cellulose suspension, serving as vehicle control. After 1 h the oedema was induced by sub plantar injection of 0.1 mL of 1% (w/v) freshly prepared suspension of carrageenan type 4 (Sigma, USA) into the right hind paw of each rat after 1 h of the drug treatment and the paw volume was measured at 0, 1, 3, and 5 h after the injection of carrageenan using a plethysmometer [10].

Ulcerogenic Study

The ulcerogenic potential of PM and SD was studied in rats by the method reported by Nagarsenker et al., [11] and compared with MLX. The animals were randomly divided into four groups comprising four animals each. The first three groups were chronically treated with MLX, PM or SD at a dose of 4 mg/kg of MLX (40 mg/kg of PM and SD equivalent to 4 mg/kg of MLX) for seven consecutive days. Similarly, the fourth group

(control) was administered with 1% (w/v) sodium carboxyl methyl cellulose suspension for seven consecutive days. On the seventh day, the rats were starved for 24 h but water was provided *ad libitum*. On day eight, the rats were killed and the abdomen was opened. The stomach was removed, incised along the greater curvature and gently washed with water. Hemorrhagic lesions, produced in the glandular portion were observed under a dissection microscope ($\times 20$ magnification) and evaluated by the following score:

- 0.0 Normal (no injury, bleeding and latent injury).
- 0.5 Latent injury or widespread bleeding.
- 1.0 Slight injury (2 to 3 dotted lines).
- 2.0 Severe injury (continuous lined injury or 5-6 dotted injuries).
- 3.0 Very severe injury (several continuous lined injury).
- 4.0 Widespread lined injury or widened injury.

Statistical analysis. The data are presented as mean \pm SEM and were subjected to one way analysis of variance (ANOVA), followed by students 't' test. $p < 0.05$ was considered significant.

RESULTS AND DISCUSSIONS

The present study was aimed to enhance aqueous solubility of the drug by the use of PM and SD using PEG 6000 and PVP as to get formulations with similar or better analgesic and anti-inflammatory activity and lower side effects than the pure drug.

The results (Table 1) demonstrated that the MLX, PM and SD significantly reduced the number of abdominal writhing after 1% (v/v) acetic acid injection (10 mL/kg, i.p) as compared to the control. Both the PM and SD considerably improved the analgesic activity (40.81 and 48.72 % respectively) in comparison to the MLX (32.14%). The increase in analgesic activity was significant with SD in comparison to the same dose of MLX. The results are in accordance with analgesic effects of poorly water soluble NSAID in PM and SD [6, 12].

Table 2. Ulcerogenic potential of MLX, PM and SD.

Treatment	Ulcer index
Control	0.00 ± 0.00
MLX	1.75 ± 0.14*
MLX-PEG 6000-PVP(PM)	1.3 ± 0.30*
MLX-PEG 6000-PVP (SD)	0.7 ± 0.12**

Data were expressed as mean \pm SEM, n=5, * $p < 0.001$ compared with control, † $p < 0.05$ Compared with same does of MLX

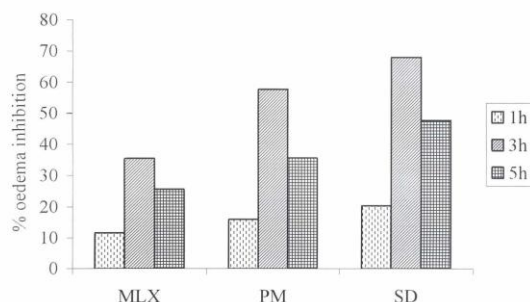


Fig 1. Comparisons of percent oedema inhibition of MLX, PM and SD, n=5.

Fig 1 illustrates the anti-inflammatory effect of MLX, PM and SD. Both PM and SD showed significant increase in anti-inflammatory effect, in the carrageenan induced paw oedema compared to X at 1, 3 and 5 h after carrageenan injection. The SD showed maximum anti-inflammatory activity (67.85 ± 1.2) at 3 h, which is consistent with reported results [11, 13-15].

In the ulcerogenic studies, MLX, PM and SD showed significant ulcerogenic potential compared to the control in rats treated chronically for seven consecutive days (4 mg/kg MLX, 4 mg/kg of MLX in PM or SD, p.o). The PM and SD showed less ulcerogenic potential with the ulcer score of 1.3 ± 0.30 and 0.7 ± 0.12 , respectively as compared to MLX (1.75 ± 0.14). Further, SD possessed significantly less ulcerogenic potential as compared with pure MLX and PM. The results (Table 2) indicate that SD and PM protect the gastric mucosa from injury, which is in accordance with analgesic effects of poorly water soluble NSATD in PM and SD [6, 16].

It has been reported that crystals of non-steroidal anti-inflammatory agents are poorly soluble in gastric acid and remain in contact with the stomach wall for a longer period, thus producing a highly dangerous local concentration. This leads to local irritation of the stomach wall followed by ulceration [11, 17]. It is expected that in the complexed form, the drug dissolves fast and shows an accelerated absorption. Moreover, it will not come in direct contact with the stomach wall in crystalline state, as it remains encapsulated by the polymer, until its dissolution.

It was concluded that SD and PM formulations of MLX with PEG 6000 and PVP showed better analgesic and anti-inflammatory properties with less ulcerogenic potential as compared to pure drug (MLX).

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