

New Multi-Particle Systems for Colon-Targeted Meloxicam

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Abstract

Meloxicam (MLX) is a non-steroidal anti-inflammatory drug (NSAIDs) from the Oxicam family. This group of NSAIDs has been highly used in the treatment of rheumatoid arthritis and post-operative inflammation and is known as good antioxidants. Recently, their activity in chemoprevention, chemo-suppression, UV-sensitization and UV-protection was also identified. MLX has been described as a COX-2 selective inhibitor. Its use has some advantages regarding to its selectivity, namely, less adverse effects as gastrointestinal aggression and anticlotting activity. As MLX is better absorbed in colon and its properties against colon cancer and colonic inflammatory diseases are being studied, it is interesting to investigate a new MLX formulation for colonic delivery.

We are studying the solubility and the dissolution of different combined formulations at pH 1.2, 6.8 and 7.4 to mimic their absorbance in the colon. These formulations are composed by different excipients that provide pH and time-dependent deliveries such as cellulose (Metolose[®]) and methacrylic acid esters with quaternary ammonium groups (EUDRAGIT[®] RS 30D, EUDRAGIT[®] FS 30D and EUDRAGIT[®] NM 30D).

Keywords: Meloxicam; Colon targeting; Granulated

Introduction

Meloxicam (MLX) is a non esteroidic anti-inflammatory (AINE) from the Oxicam family [1-11]. This group of AINEs is frequently used in the treatment of rheumatic arthritis and post operative inflammations; besides it is known as a good antioxidant. Recently, it has been found to have utility in chemoprevention, chemosuppression and UV protection. The MLX is a selective inhibitor for COX-2 [3,4,7,11-14], with high selectivity and fewer gastrointestinal side effects. Because this drug is well absorbed in the colonic region, they are studying their properties against colon cancer and diseases of this area, so it is interesting to investigate new formulations of colonic delivery of this active substance [1,3,4,13-17].

Materials and Methods

Materials

Meloxicam (MLX, Fagron, Barcelona, Spain); Methylcellulose (MC, Metolose[®] 90 SH 100, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan); aqueous dispersion of a copolymer of ethyl acrylate and methyl methacrylate (EUDRAGIT[®] FS 30D and Eudragit[®] NM 30D, Evonik Röhm gift, D); alpha-lactose monohydrate (L, Fagron, Barcelona, Spain). All products of pharmaceutical grade or higher.

Preparation of formulations

The studied MLX was granulated with lactose and three types of Eudragit[®]: RS, FS and NM; some granules containing 5% of cellulose

(Metolose[®] 90 SH 100). Different granulates (Table 1) were prepared with different proportions of these components and those granules with diameters between 0.350 and 0.355 mm selected.

FORMULATION S	MLX (%)	L (%)	MC (%)	EUDRAGIT [®] RS	EUDRAGIT [®] FS	EUDRAGIT [®] NM
RS	17.5	53.0	5.0	30.0	0	0
FS	17.5	53.0	5.0	0	30.0	0
NM	17.5	53.0	5.0	0	0	30.0
RS+FS	17.5	53.0	5.0	15.0	15.0	0
NM+FS	17.5	53.0	5.0	0	15.0	15.0
CRS	17.5	48.0	5.0	30.0	0	0
CFS	17.5	48.0	5.0	0	30.0	0
CNM	17.5	48.0	5.0	0	0	30.0
CRS+CFS	17.5	48.0	5.0	15.0	15.0	0
CNM+CFS	17.5	48.0	5.0	0	15.0	15.0

Table 1: Composition of formulations.

In vitro release

The granules were subjected to test dissolution rate in dissolution apparatus containing in their buckets 10 mg or equivalent MLX granulated with 500 ml of pH 1.2, 37°C and 50 rpm, for 2 h, after that the medium was completed with 167 ml from buffer to reach pH 6.8,

37°C and 50 rpm for 3 h, then 5 ml of NaOH 2 M was added to obtain pH 7.4, 37°C and 50 rpm. The experiment lasted 24 h. Aliquots were taken every hour the first two hours and then every half hour until 8 h, taking one last aliquot at 24 h. The samples were measured undiluted on the spectrophotometer at 364 nm wavelength. Each determination at each time point was performed in triplicate and the error bars on the graphs represented the standard deviation.

Results and Discussion

The rate of dissolution test noted that the best results (Figure 1) obtained was the CNM granulate containing Eudragit[®] NM and 5% cellulose, which releases the 94.52% if the active ingredient at 8 h, resulting the most balanced release profile. Granulate FS was the slowest, releasing only the 24.52% of the MLX at t=8 h.

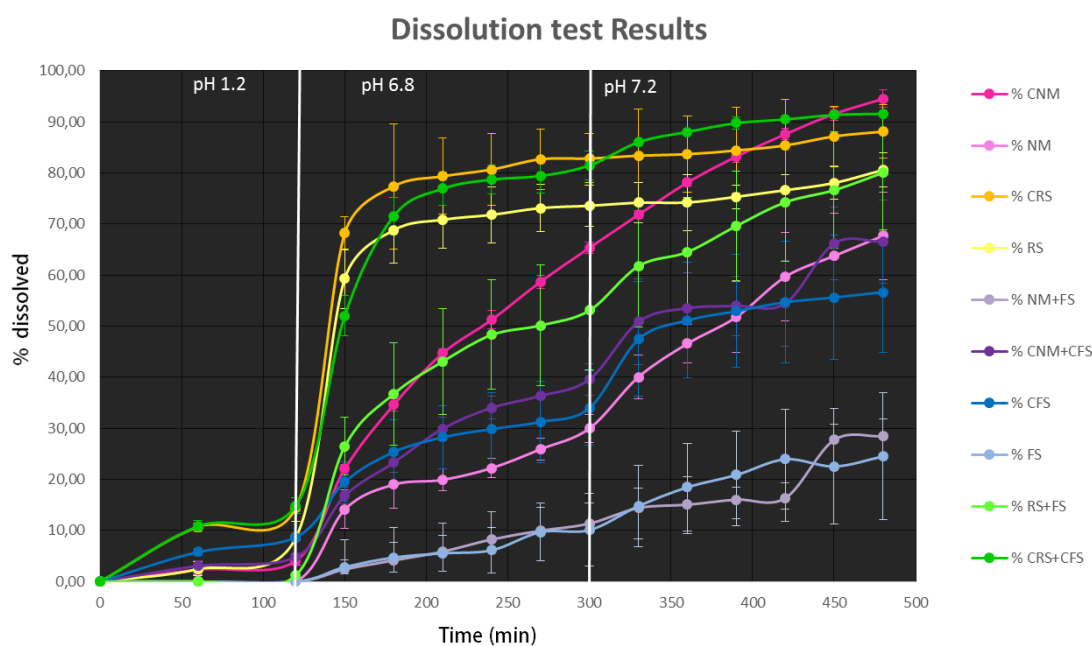


Figure 1: Release profiles at 37°C of several products in SCF: CNM (-.-); NM (-.-); CRS (-.-); RS (-.-); NM+ FS (-.-); CNM+CFS (-.-); FS (-.-); CFS (-.-); RS+FS (-.-) and CRS+CFS (-.-).

As an intermediate granulate we chose CFS, which gives a 56.69% after 8 h.

It was observed that, by adding cellulose (Metolose[®] 90 SH 100) the solubility coefficient is increased because it facilitates the disintegration of the formulation.

Conclusion

We have developed a new colonic formulation of multiparticulate MLX, easy and economical to produce industrially. For subsequent studies, we will select the granule with higher percentage of release (CNM) after 8h, the one with lower percentage (FS) and the one that was intermediate (CFS) to perform *in vivo* assays in mice and other analytical studies to corroborate the results.

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