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New Multi-Particle Systems for Colon-Targeted Meloxicam

Eva Navarro Ruiz[1*], Covadonga Álvarez Álvarez[2], Juan J García Rodriguez[1,3], Santiago Torrado Durán[1,3], Susana Torrado Durán[1,3] and de la Torre Iglesias PM[1,3]

[1]*Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Complutense University of Madrid, Madrid 28040, Spain*

[2]*Department of Parasitology, Faculty of Pharmacy, Complutense University of Madrid, Madrid 28040, Spain*

[3]*Institute of Industrial Pharmacy, Complutense University of Madrid, Madrid 28040, Spain*

[*]**Corresponding author:** Eva Navarro Ruiz, Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Complutense University of Madrid, Madrid 28040, Spain, Tel: +346557564196; E-mail: eva.navarro.ruiz@gmail.com

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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-inflamatory (AINE) from the Oxicam family [1-11]. This group of AINEs is frequently used in the treatment of rheumatic arthritis and post operatory inflammations; besides it is known as a good antioxidant. Recently, it has been found to have utility in chemoprevention, chemosupression 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.

FORMULATIONS	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 8h, resulting the most balanced release profile. Granulate FS was the slowest, releasing only the 24.52% of the MLX at t=8 h.

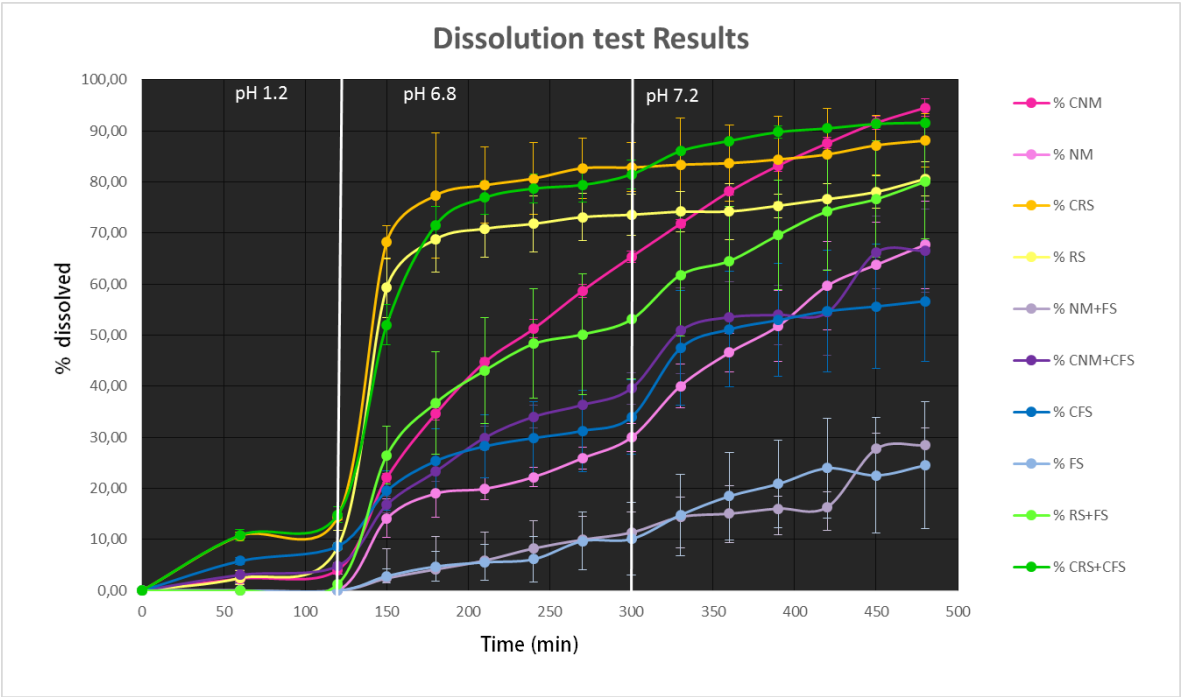

Figure 1: Release profiles at 37°C of several products in SCF: CNM (-•-); NM (-•-); CRS (-•-); RS (-•-); NM+ FS (-•-); CNM+CFS (-•-); FS (-•-); CFS (-•-); RS+FS (-•-) and CRS+CFS (-•-).

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.

References

1. Srivastava R, Kumar D, Pathak K (2012) Colonic luminal surface retention of meloxicam microsponges delivered by erosion based colon-targeted matrix tablet. International Journal of Pharmaceutics 427: 153-162.
2. Kumar Shukla R, Tiwari A (2012) Carbohydrate Polymers: Applications and recent advances in delivering drugs to the colon. Carbohydrate Polymers 88: 399-416.
3. Patel MM, Amin AF (2011) Formulation and development of release modulated colon targeted system of meloxicam for potential application in the prophylaxis of colorectal cancer. Drug Deliv 18: 281-293.
4. Tsujii M (2001) COX-2 inhibitor and colon cancer. Gan to Kagaku Ryoho 28: 1799-1805.
5. Gao C, Huang J, Jiao Y, Shang L, Liu Y, et al. (2006) In vitro release an in vivo absorption in Beagle dogs of Meloxicam from Eudragit FS 30 D-coated pellets. Int J Pharm 322: 104-112.
6. Mishra DN, Vijaya Kumar SG (2006) Preparation, characterization and in vitro dissolution studies of solid dispersion of meloxicam with PEG 6000. Yakugazu Zasski 127: 495-498.
7. Bauer C, Frost P, Kirschner S (2014) Pharmacokinetics of 3 formulations of meloxicam in cynomolgus macaques (*Macaca fascicularis*). J Am Assoc Lab Anim Sci 53: 502-511.
8. Vijaya Kumar SG, Mishra DN (2006) Analgesic, antiinflamatory and ulcerogenic studies of meloxicam solid dispersion prepared with polyethylene glycol 6000. Methods Find Exp Clin Pharmacol 28: 419-422.
9. Ingrao JC, Johnson R, Tor E, Gu Y, Litman M, et al. (2013) Aqueous stability and oral pharmacokinetics of meloxicam and carptofen in male C57BL/6 mice. J Am Assoc Lab Anim Sci 52: 553-559.
10. Kendall LV, Hansen RJ, Dorsey K, Kang S, Lunghofer PJ, et al. (2014) Pharmacokinetics of sustained-release analgesics in mice. J Am Assoc Lab Anim Sci 53: 478-484.
11. Gruen ME, Griffith E, Thomson A, Simpson W, Lascelles BDX (2014) Detection of clinical relevant pain relief in cats with degenerative joint disease associated pain. J Vet Inter Med 28: 346-350.

12. Sengel Türk CT, Hasçiçek C, Dogan AL, Esendagli, Guc D, et al. (2012) Preparation and *in vitro* evaluation of meloxicam-loaded PLGA nanoparticles on HT-29 human colon adenocarcinoma cells. Drug Dev Ind Pharm 38: 1107-1116.
13. Goldman AP, Williams CS, Sheng H, Lamps LW, Williams VP, et al. (1998) Meloxicam inhibits the growth of colorectal cancer cells. Carcinogenesis 19: 2195-2199.
14. Tsubouchi Y, Mukai S, Kawahito Y, Yamada R, Kohno M, et al. (2000) Meloxicam inhibits the growth of non-small cell lung cancer. Anticancer Res 20: 2867-2872.
15. Jain V, Singh R (2010) Development and characterization of Eudragit RS100 loaded microsponges and its colonic delivery using natural polysaccharides. Acta Pol Pharm: Drug Res 67: 407-415.
16. Woraphatphadung T, Sajomsang W, Gonil P, Treetong A, Akkaramongkolporn P, et al. (2016) pH-Responsive polymeric micelles based on amphiphilic chitosan derivatives: Effect of hydrophobic cores on oral meloxicam delivery. Int J Pharm 497: 150-160.
17. Palugan L, Cerea M, Zema L, Gazzaniga A, Maroni A (2015) Coated pellets for oral colon delivery. J Drug Del Sci Tech 25: 1-15.