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Research Article

PREPARATION AND CHARACTERIZATION OF MELOXICAM COLON TARGETED COATED TABLETS

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ABSTRACT

Meloxicam (MLX) is an oxicam derivative nonsteroidal anti-inflammatory drug (NSAID) with analgesic and fever reducer effects. Recently has been reported that MLX play important role in cholorectal carcinogenisis therapy.

Objective: The objective of this study was to prepare MLX as a colon targeted tablet. Methods: Meloxicam matrix tablets containing several retarding agents (carnauba wax, ethyl cellulose and Eudragit RS) separately were used in order to extend the release of drug over the desired period of time from the core tablet. The drug release profile for uncoated tablet was evaluated in phosphate buffer pH 6.8 and 7.5.

Results: Although the prolongation of drug release was obtained with the retarding agent, but carnauba wax and ethyl cellulose show higher release in the first few hours while Eudragit RS shows reasonable release profile for long time. The uncoated tablet contains 5% w/w Eudragit RS as a retardant with lactose as a diluent was found to be suitable for targeting. The selected formula coating trials involves shellac (5&10% w/v) and different percentage of Eudragit mixture (L: S at ratio 1:1).

Shellac 5% w/v or Eudragit L: S mixture (1:1) 1% w/v shows the best enteric properties and ability to protect the tablet cores from premature drug release in stomach for enough time. The selected formula was further evaluated by stability study. The results of stability study of two types of coatings (1%Eudragit mixture or 5% shellac) shows expired date around two years with no significant changes ($p>0.05$) in physical properties of prepared tablets after storage.

Conclusion: It can be concluded the prepared tablets consider a good potential for colon targeting of meloxicam.

Keywords: Meloxicam, colon targeted drug delivery system, Eudragit

INTRODUCTION

The colon targeting approaches can be used for both local and systemic action of drugs. Local delivery is required in cases such as inflammatory bowel disease and colorectal cancer [1]. Colon-specific systems could also be used in diseases that have diurnal rhythms [2].

Numerous approaches have been tried to obtain colon delivery such as pH-dependant drug release, time-dependant drug release, microbially triggered system, pressure controlled system, pulsatile drug delivery system and osmotically controlled system [3-8].

Commercially available polymers with pH-sensitive properties like Eudragit® L100 (EL100) and Eudragit® S100 (ES100) have been conventionally employed for coating oral solid dosage forms intended for colonic delivery. EL100 dissolves at pH 6 while ES100 dissolves at pH 7. The pH-dependent solubility of these polymers is on account of the difference in the carboxylic acid group substitution on the methyl methacrylate backbone [9].

Meloxicam is yellow powder practically insoluble in water (0.012 mg/ml) It is a relatively well-permeable drug [10].

The antitumor effect of NSAIDs is mediated through cyclooxygenase-2 (COX-2)-dependent and -independent regulation of oncogenic and tumor-suppressive pathways. Recent discoveries have shed new light on the regulation of COX-2 at the molecular level in these cancers [11].

Meloxicam has been reported to play an important role in cholorectal carcinogenisis, ovarian cancer, renal, and prostate cancer [12-15].

The major objective of the present study is to develop tablet specifically delivered to the colon for potential use for cancer therapy.

MATERIALS AND METHODS

Meloxicam powder was supplied by Alsafa drug industry-Iraq. Acetone, ethanol, hydrochloric acid, and phosphoric acid were purchased from Fluka-Switzerland. Carnauba wax, lactose, and polyvinylpyrrolidine were purchased from Riedel-De Haen AG Hannover –Germany. Eudragit (RS, S100, L100) and methanol were purchased from Barlocher-GMBH-Germany. All other materials used in this study were of analytical grade.

Formulation the core of the tablets

Different formulas were prepared by granulation method using different retardant compound include carnauba wax, Eudragit and ethyl cellulose.

In formulas (F1-F3) carnauba wax was used as a waxy retardant by fusion method ,In brief the procedure involves dispersing of MLX in melted carnauba wax in a beaker using water bath then sieving the solidified mass through sieve 18 mesh, a known weight of the granules were mixed with specified amount of talc 2% and magnesium stearate 1% in well closed container and compressed into tablets using single punches machine at a constant load (7Kn) to form flat tablet of 9mm diameter, 2mm thickness and 200mg weight. In case of using ethyl cellulose as retarding agent, 10%PVP as granulating agent was used in F4-F7,while when Eudragit RS used (F8-F12), ethanol utilized as granulating liquid. Table 1 shows the formulas composition of MLX colon targeting tablet.

Table 1: Formulas composition of core Meloxicam colon targeting tablets

Composition (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Meloxicam	15	15	15	15	15	15	15	15	15	15	15	15
Carnauba wax	15	7.5	0.75									
Ethylcellulose				15	10	7.5	3.75					
Eudragit RS								15	11.25	10	7.5	3.75
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
PVP 10% in ethanol				Q.S	Q.S	Q.S	Q.S					
Lactose up to	200	200	200	200	200	200	200	200	200	200	200	200

Preparation of coating solution

Eudragit coating mixture

Eudragit L and S were prepared as a mixture in ratio 1:1 and 1:2 and coated with two concentrations 1% and 3% of each ratio.

The coating solution was prepared according to the Rohm pharma recommendations as shown in table (2) [16].

Table 2: Composition of enteric coating solution

Material	Amount (gm)
Eudragit L100 or S100	6
Isopropranol	115.7
Acetone	77.1
Dibutylphthalate	1.2
Semithicone	Few drops

Shellac coating solution

Shellac 5 and 10% w/v was prepared in equal volume of acetone and isopropranol

Tablets coating

The core tablets of the selected formula were coated by dipping method. Each tablet was held by forcipes and dipped in the coating lacquer in and out 15-20 times, the coat dried by steam of warm air between each dip [17].

Characterization of prepared tablets

Weight Variation Test

The test was done for the 20 prepared tablets before and after coating for all formulas.

Hardness Test

The hardness of three tablets of the prepared formulas was determined individually using Monsanto hardness tester

Friability Test

This test was done by subjecting 10 tablets utilizing Roche friabilator that revolves at 25 rpm. Compressed tablets that lose a maximum of not more than 1% of their weight are generally considered acceptable according to pharmacopeia [18].

Drug Content

Assay was done by grinding 10 tablet in mortar and transfer the powder to a 1000-mL volumetric flask, 100 ml of 1 N sodium hydroxide was added , shake to disperse the powder and add 800 ml of methanol. The solution was sonicated for 15 min and stirred for 30 min, finally diluted with methanol to volume. Fifteen ml of the filtered solution transferred to a 25-mL volumetric flask, and diluted with water up to the volume, then 25 µL was injected to the HPLC system.

The chromatographic condition includes column L1 (4-mm ×10-cm), flow rate 0.8 ml/min, temperature 40°C and UV 254 nm as a detector [18]. Mobile phase was prepared by mixing two Solutions (**A** 63ml: **B** 37ml)

Solution A: 2.0 g/L of dibasic ammonium phosphate solution. Adjust with phosphoric acid to a pH of 7.0 ± 0.1.

Solution B: Methanol and isopropyl alcohol (13:2)

In vitro drug release study

Drug release was studied for all tablet formulations pre and post coating tablets by USP apparatus II (paddle) and 900 ml was filled with the medium at 37±0.5°C and the rotation was 100 rpm. The first two hours of dissolution was in 0.1N HCl (only for coated tablet), followed in phosphate buffer pH 6.8 for one hour and then complete the dissolution using phosphate buffer pH 7.5 At the end of the third hour (phosphate buffer pH 6.8) 20 ml of the medium was taken and replaced by 20 ml 2N NaOH and adjusted pH to 7.5[18].

Fourier Transform Infrared Spectroscopy (FTIR*)*

Samples of MLX powder, MLX uncoated tablet and coated tablet was grinded, mixed with potassium bromide) then analyzed by FTIR spectroscopy from 4000-400 cm^{-1}

Stability Study

The stability of the selected coated formulas FLS3 and FSh1 was studied at three different temperatures; 40, 50, and 60 ºC for 16 weeks.

After an interval of four months, samples were withdrawn and tested for various physical tests (hardness, friability, uniformity of dosage unit and drug release study)[19].

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one-way analysis of variance (ANOVA) to determine if the differences are statistically significant at ($P < 0.05$).

RESULTS AND DISCUSSION

Effect of carnauba wax concentration on MLX release

Fig. (1) shows the effect of carnauba wax concentration on the release of MLX from formulas (F1-F3) which utilizes (7.5, 3.75 and 0.375%) of carnauba wax.

The results indicate that there is a significant differences ($p < 0.05$) in the release of MLX when the carnauba wax concentration was changed. Although the release of drug was prolonged, but high percentage of drug was released in the first few hours.

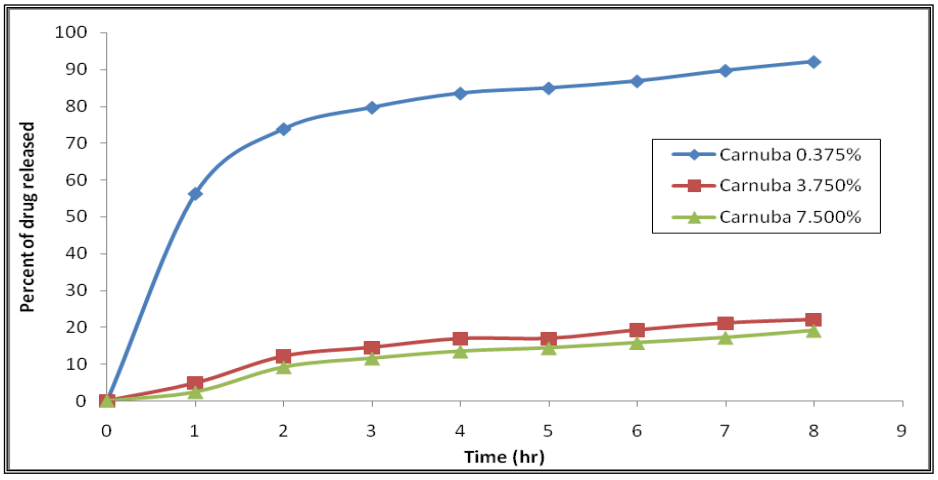

Fig. 1: Effect of carnauba wax concentration on release of MLX from CT tablets in phosphate buffer (pH6.8 and 7.5) at 37°C

Effect of ethylcellulose concentration on MLX release

Formulas (F4-F7) were used to study the effect of ethyl cellulose concentrations (7.5, 5, 3.75, and 1.875%) on release of MLX from tablet.

The dissolution profiles shown in Fig. (2) indicate that increasing the concentrations of ethyl cellulose tend to decreases the drug release significant differences ($p < 0.05$). Same behavior of drug release from carnauba matrix was observed in these formulas recording burst release of drug.

Effect of Eudragit RS concentration on MLX release

The release of MLX from formulas F8-F12 which were formulated using Eudragit RS and lactose (diluents) in different concentrations (7.5, 5.625,5, 3.75 and 1.875%) is shown in Fig. (3).

The results indicated that increasing the concentration of polymer tend to decrease the drug release significantly ($p < 0.05$) this is due to decrease in the porosity with a concomitant increase in the tortuosity of matrix and this is in agreement with the results found in formulation of nicotine matrix[20]. Reasonable release profile for long time was obtained with 5%w/w Eudragit RS, thus this formula was selected as the best one and subjected to coating.

Effect of Eudragit coating solutions constituent on MLX release

The tablets (F10) with no signs of cracking or splitting or peeling was coated to prevent the release of drug in 0.1 N HCl and to target the drug to the colon.

Fig. (4) shows the effect of different concentrations 1% FLS1 and 3% FLS2 of Eudragit mixture L: S in ratio (1:1) in three pH medium (acidic 0.1NHCl, phosphate buffer 6.8, and 7.5).

Effect of Shellac coating solutions constituent on MLX release

Shellac is a natural polymer commonly used as an enteric coating material, Shellac coating solution was used to coat the selective formula 10 using two concentrations; 5% FSh1 and 10%.

Fig. (5) shows that there is no significant difference ($P > 0.05$) between these two concentration which means that both concentrations provide the enteric properties for 2 hours, thus 5% concentration was preferred due to lower cost of formulation. This result is in agreement with the coating of theophylline pellets with shellac [21].

Evaluation of prepared MLX Tablets

The weight variation, drug content, hardness, and friability of the prepared tablets were within the accepted values.

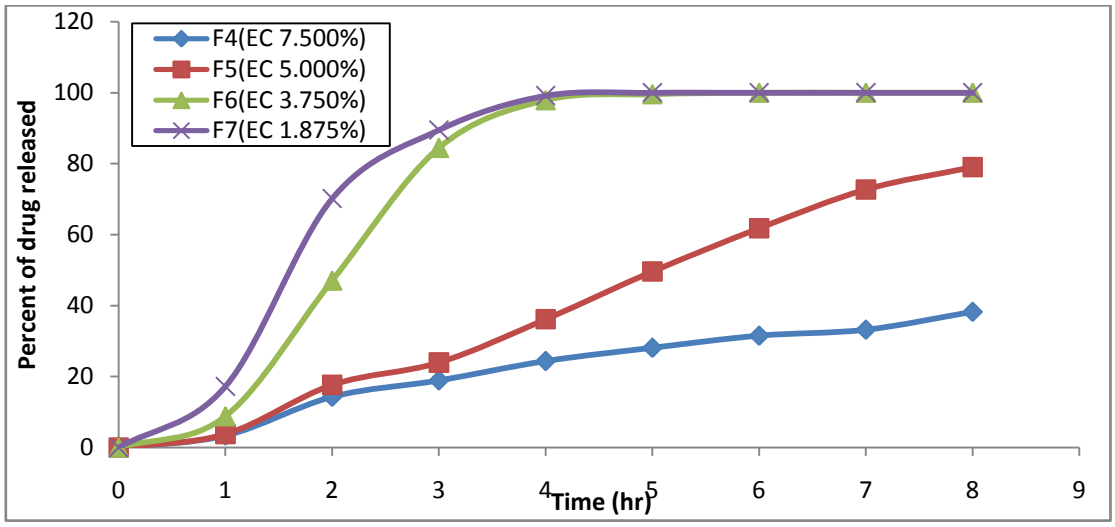

Fig. 2: Effect of ethylcellulose concentration on release of MLX from CT tablets in phosphate buffer (pH6.8 and 7.5) at 37°C

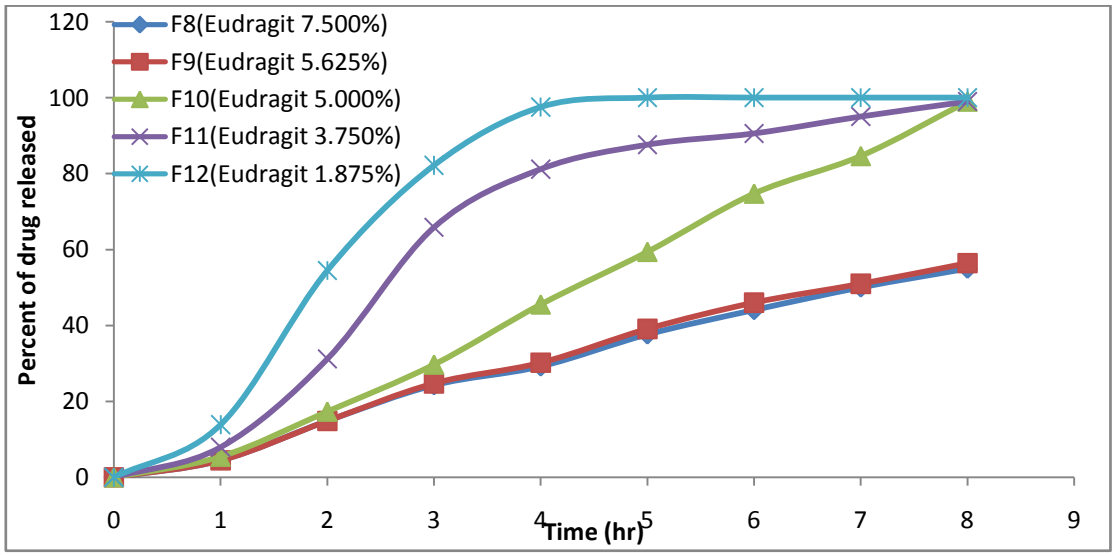

Fig. 3: Effect of Eudragit RS concentration on release of MLX from CT tablets in phosphate buffer (pH6.8 and 7.5) at 37°C

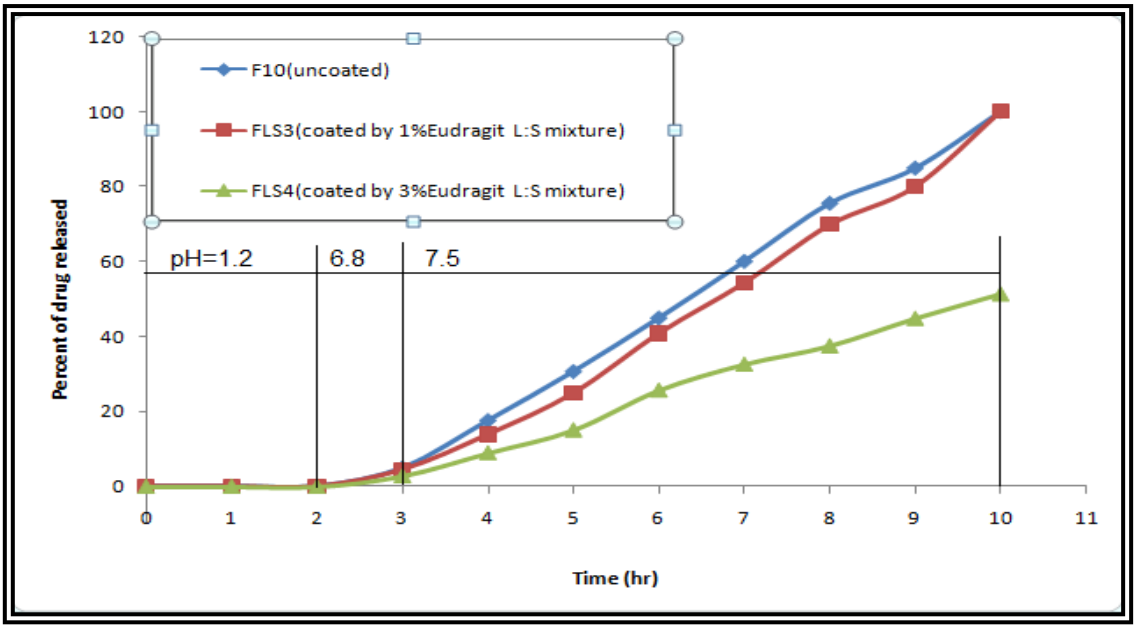

Fig. 4. Effect of Eudragit L: S (1:1) coating mixture concentration on release of MLX from C.T. tablet in 0.1NHCl, phosphate buffer (pH6.8 and 7.5) at 37°C.

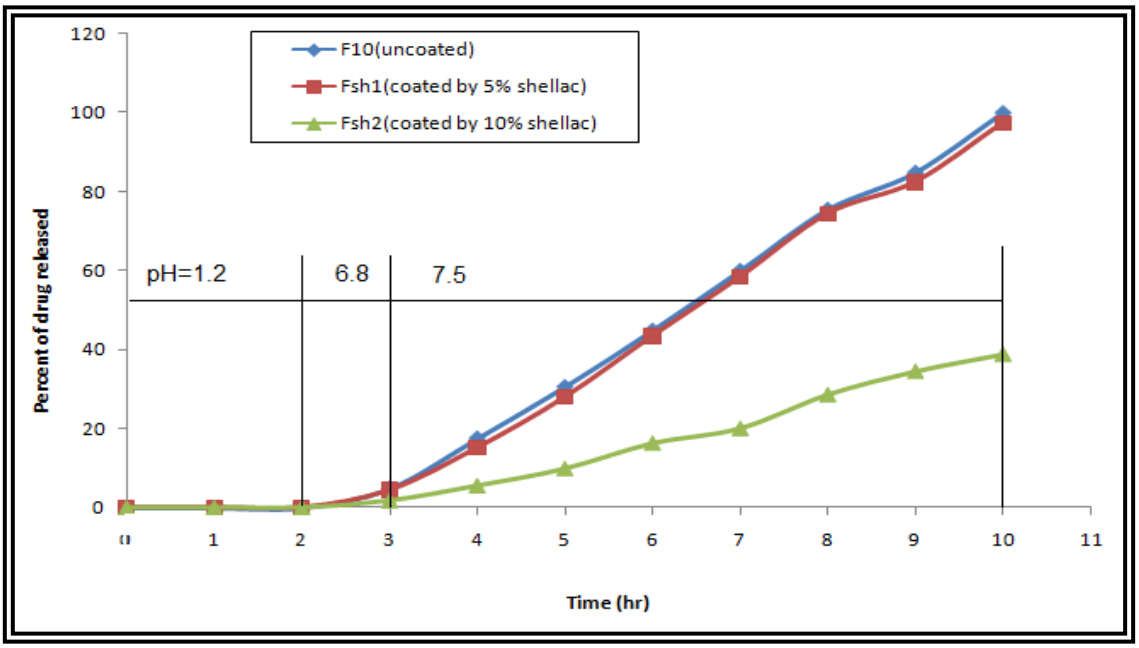

Fig. 5: Effect of shellac coating solution concentration on release of MLX from C.T. tablet in 0.1NHCl, phosphate buffer (pH6.8 and 7.5) at 37°C.

Fourier Transform Infrared Spectroscopy (FTIR*)*

The MLX coated and uncoated tablet exhibited similarity in the spectrum which indicated that the coating with Eudragit and shellac not affect the core tablet.

Stability Study

The degradation rate constants (*K*) at three temperatures were determined from the slope of each line, and these are summarized in table (3). Arrhenius plot was constructed to estimate the degradation rate constant (K_{25}) at 25ºC, the value of which was found to be 1×10^{-3} $week^{-1}$. This value was used to calculate the shelf life of the product by using the following equation;

$T_{90\%} = 0.105/K_{25}$

where $t_{90\%}$ is the time required for a drug to lose 10% of its potency. The estimated shelf life of the selected formula was found to be 105 weeks or about 2years. Tablets inspected at the end of stability study exhibited no change in their appearance FLS3 and FSh1.

Table 3: Degradation rate constants (*K*) for coated MLX CT tablets at different temperatures

Temperature (°C)	*K* ($week^{-1}$)
40	2×10^{-3}
50	4×10^{-3}
60	5×10^{-3}

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