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# Formulation and Evaluation of Coated Lornoxicam Tablets for Colon Delivery

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## ABSTRACT

Lornoxicam is a non steroidal anti-inflammatory drug of oxicam class and it has the same side effects of this group when taken orally and has a relatively short plasma half-life (3 to 4 h) which makes it a good candidate for colon targeting. It could avoid the systemic side effects, enhance its low oral bioavailability due to hepatic first pass metabolism and delay drug release to target the colon. Eighteen tablet formulations of lornoxicam were prepared by wet granulation and coated with different polymers (pectin, chitosan, ethyl cellulose, cellulose acetate phthalate, eudragit L-100 and eudragit L-100-55), each at three concentration. The tablets were evaluated for their physical characters, in–vitro dissolution in gradient pH, as well as, mathematical modeling using DDSolver software package. The dissolution data best fitted to first order with $T_{lag}$ model with Krosmyer Pepas (n) values around unity suggesting erosion mechanism for all tablets except pectin coated ones which showed Fickian diffusion mechanism. Fitting the release data to the different erosion models suggested heterogeneous erosion mechanism. Lornoxicam tablets coated with 6% Eudragit L-100 were successfully delivered to the colon with a relative bioavailability of 531.96% compared to the conventional commercial tablets in rabbits.

**Keywords:** Lornoxicam, Colon targeting, Tablet, Eudragit L-100.

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## INTRODUCTION

Lornoxicam has strong analgesic and anti-inflammatory effects. It is used in the treatment of pain and inflammation in patients suffering from osteoarthritis and rheumatoid arthritis. Lornoxicam is also recommended in the therapy of colorectal cancer[1]. It has high potency compared to other oxicams probably due to its relatively short half-life[2]. Lornoxicam shows hepatotoxicity and nephrotoxicity. These are prominent with long term use where potential toxic effects are very high [(1)] Development of new drug molecule is expensive and time consuming. Safety efficacy ratio of old drugs can be improved by formulating them in novel drug delivery system. Colon targeting of lornoxicam was studied before as matrix tablets of lornoxicam using natural polymers such as Tamarind seed polysaccharide, Guar gum, Xanthan gum as carriers[3], as matrix-mini-tablets filled in capsule in the treat of early morning peak symptoms of rheumatoid arthritis[4] and as microspheres using guar gum and glutaraldehyde used as a cross-linking agent[5]. The present study focused on the development of colon specific delivery of lornoxicam for the chemoprevention action of colon cancer. This could increase its bioavailability, decrease dosing frequency and side effects. The study will investigate different coating polymers at different concentrations. The prepared formulations will be evaluated in-vitro and in experimental animals.

## MATERIALS AND METHOD

Lornoxicam was kindly provided by Global Napi Company, Cairo, Egypt, potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium hydroxide, Lactose, Chitosan and Pectin were purchased from Himedia Laboratories pvt LTD, Mumbai, India, glacial acetic acid, hydrochloric acid were received from Adwic, El Nasr pharmaceutical chemical co., Saudi Arabia. Acetone, Isopropyl alcohol, Eudragit L100, Eudragit L100-55, Rohm, Loba chemie pvt LTD, Mumbai, India. Polyvinylpyrolidine K30, (Zhejiang Ouhua Chemical Imp, China), Hydroxypropyl methylcellulose, Aqualon ACROS organics, New jersy, USA, Xefo™ marketed tablet, Nycomed company batch number 16943520, Maize starch, Talc, Magnesium Stearate, Glycerol, Cellulose acetate phthalate Polyethylene glycol 400, Ethyl alcohol, Ethyl cellulose, Sigma Aldrich® chemicals (Gillingham, UK).

### Preparation of granules

Tablet blends were wet granulated using 10% polyvinylpyrolidine K30. Maize starch (10%) was used as disintegrating agent and lactose as a diluent. Lornoxicam was added as 8 mg/tablet. The wet mass was immediately passed through 2500 µm sieve and the prepared granules were dried in

hot oven at 55°-60°C till loss on drying values around 4%. A total amount of granules for 2000 tablets were prepared.

**Evaluation of Granules**

The Angle of Repose was calculated using the funnel method and the average of five trials was calculated. The granules were allowed to flow smoothly through the funnel orifice under gravity. Height of the formed pile was measured. Angle of repose (θ) was calculated as follows:

$\theta = \tan^{-1} (h/r)$

Carr's compressibility index was calculated as follows:

Carr's index (%) = (TBD - LBD)/ TBD x100

Where, loose bulk density (LBD) and tapped bulk density (TBD) are defined as:

LBD =Weight of the Powder /Volume of the packing

TBD =Weight of the powder /Tapped volume of the packing

**Preparation of core tablet**

The dried granules were passed through 900 µm sieve and lubricated with 2% talc, 0.3% magnesium stearate for 5 min. The granules were compressed using single punch compression machine, Erweka GmbH, (Heusenstamn, Germany) fitted with a plain standard concave oblong punches for a tablet weight of 325 mg.

**Evaluation of core Tablets**

Uncoated tablets were visually examined for shape, color, overall elegance and surface texture. Odour and taste were evaluated by four human volunteers using a scale graded from 1-3, where 1 indicates acceptable, 2 moderate and 3 is unacceptable odour and taste. Ten tablets were used for thickness and diameter measurements using a dial-caliper. Twenty tablets were selected randomly and weighed individually to check for weight variation. Based on tablet weight of 325mg, a 5% maximum difference is allowed (USP 34). The hardness of the tablets in $kg/cm^2$ was determined using Monsanto Hardness Tester, Copley, Nohingham, United Kingdom. Ten tablets were randomly picked and the mean and standard deviation values were calculated. The friability of tablets was determined using Copley Friabilator, TAR200, (Heusenstamn, Germany). It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again ($W_{final}$). The % friability was then calculated by:

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

Tablets were ground after weighing and dissolved in 0.1 N sodium hydroxide with sonication. Absorbance of the diluted samples was measured at 374 nm, and concentration of drug in sample

was calculated using standard calibration curve. Disintegration time was measured using copley disintegration tester, Nohingham, United kingdom in 0.1N HCl at 37° ±1°C.

**Coating of tablets**

Pectin, chitosan, ethyl cellulose, cellulose acetate phthalate, eudragit L-100 and eudragit L-100-55) were used for coating each at three concentrations; composition of the coated tablet is shown in table 1. Coating solutions were prepared using suitable solvents and plasticizers. For pectin mixture of isopropyl alcohol and acetone (60:40), HPMC 0.5% was used as a solvent. A mixture of ethyl alcohol and 1% acetic acid (75:25) was used for chitosan solution. In case of Eudragit L100 and Eudragit L100-55, isopropyl alcohol was the solvent. Ethyl alcohol and acetone (50:50) was used for dissolving cellulose acetate phthalate. Ethyl alcohol was used for ethyl cellulose solution. 0.25% glycerol used as a plasticizer for pectin and chitosan solutions, 3% polyethylene glycol 400 for Eudragit L100, Eudragit L100-55 and cellulose acetate phthalate solutions, while a Propylene glycol was used for ethyl cellulose. Coloring agent, Allura Red AC, CI 16035 was added to all the coating solutions. Coating was done using Erweka coating pan (GNBH AR 402, Heusenstamm, Germany) at tablet bed temperature of 42°C and pan rotating speed of 20 rpm. The coating level was fixed at 6 % per tablet core.

**Evaluation of coated Tablets**

Coated tablets were revaluated after coating for color and shape, odour and taste, dimensions, weight variation, friability, hardness and drug content. Disintegration test was done in 0.1N HCl for 2 h followed medium change to pH 6.8 for 1h at 37° ±1°C. *In vitro* dissolution was tested in 450 ml 0.1 N HCl for 2h at 100 rpm and 37°C ±0.5 using USP dissolution apparatus Type II. The pH was changed to 4.5 by adding 1.7 g of $KH_2PO_4$ and 2.225 g of $Na_2HPO_4.2H_2O$ and suitable quantity of 1.0 M NaOH[6] for another 2 h. Another pH change was achieved to 6.8 by adding 1.0 M NaOH for the end of the experiment (24h). Two milliliter samples were withdrawn at certain time intervals and replaced with fresh medium. The samples were diluted properly and the drug content was determined using UV analysis. All experiments were performed in triplicate. Dissolution efficiency after 8h ($DE_{8h}$) was calculated according to Khan and Rodhes, 1975[7] as follows:

$$\% DE = \frac{\int_0^t Y dt}{Y_{100}t}$$

Where Y is the percent drug dissolved at time t.

**Release profile optimization**

The desirability function was used for optimization of the coated tablets according to Derringer and Suich, 1980. The targeted release profile should have high $RE_{8h}$ and lowest release at 2 hours and 6 hours. It was calculated for the maximized response using equations group (1) and those for the minimized responses using equations group (2):

$$d_1 = \frac{Y_i - Y_{min}}{Y_{target} - Y_{min}} \; for \; Y_i < Y_{target} \qquad d_1 = 1 \; for \; Y_i > Y_{target} \qquad (1)$$

$$d_2 or \; d_3 = \frac{Y_{max} - Y_i}{Y_{max} - Y_{target}} \; for \; Y_i > Y_{target} \qquad d_2 or \; d_3 = 1 \; for \; Y_i < Y_{target} \qquad (2)$$

Where $d_{1\text{-}3}$ is the individual desirability factors of each response and $Y_i$ is the experimental result. The overall desirability values were calculated from the individual values using the following equation: $D = (d_1 d_2 d_3)^{1/3}$ (3)

The dissolution data were analyzed by DDSolver software package according to zero order, first order, first order with $T_{lag}$, Higuchi, Peppas, Hixson Crowell, Hopfenberg and Baker-Lonsdale models[8-15].

***In- Vivo* study**

*In- vivo* study was done by randomized parallel design for the selected colon targeted Lornoxicam tablet after protocol approval by research ethics committee, Faculty of Pharmacy, Cairo University (PI 610). Twelve healthy male rabbit, weighing 2.5-3 kg, were assigned randomly into two groups. Formulas (2.6mg/kg body weight) were received via polyethylene tubing under light ether anesthesia. The two groups were: (1) reference group (n=6), receiving marketed conventional lornoxicam tablet (Xefo™) (2) test group (n=6), receiving lornoxicam coated tablet. Rabbits were fasted for 16 h before the experiment and allowed for water. Blood samples of 1 ml were collected, in heparinzed covets, from the ear vein or from orbital sinus at time intervals of 1, 2, 3, 4, 6, 8 and 24h. The samples were centrifuged for 10 min at 3000 rpm and the collected plasma samples were stored at -20$^{o}$C till analysis. Lornoxicam was analyzed in plasma using the method adapted by S. Radhofer-Welte, P. Dittrich, (1998)[(16)] with slight modifications. A High-performance liquid chromatography (HPLC, L-7100) with a Rheodyne injector valve with 20µL loop and L-7400 UV detector, Merck Hitachi limited, Tokyo, Japan, was used. Acetonitrile was used for precipitation of the plasma protein. Separation was done on a Nucleosil 100-5 (C18) column (150 × 4.6 mm). The mobile phase was acetonitrile-0.01 M potassium dihydrogen phosphate (pH 6.3) in a ratio of 35:65 (v/v), and the flow rate was 1mL/min. A wavelength of 374 nm was used. The pharmacokinetic parameters were calculated

using the Kinetica 2000, (Adept scientific, Herts, UK) program extravascular model. Namely, time to $Cp_{max}$ ($T_{max}$, h), the peak plasma concentration ($Cp_{max}$, ng/ml), area under the plasma concentration–time curve extrapolated to infinity ($AUC_{(0–24)}$, ng.h/ml). The obtained data were statistically analyzed by applying ANOVA test, where differences were considered significant at $p<0.05$. The percentage relative bioavailability of the colon targeted formulations compared to reference product (the marketed lornoxicam tablet Xefo™) was calculated as follows:

$F_{rel}$ = $AUC_{(0-24)}$ (tested formula)/$AUC_{(0-24)}$ (reference formula) x 100

## RESULTS AND DISCUSSION

Results for evaluation of granules showed excellent flow property with average angle of repose value of $23.19^0$± 1.09. LBD and TBD were 0.47±0.22 % and 0.55±0.24% respectively and compressibility index values ranging around 14.83±0.05 %. Visual examination showed uniform yellow colour tablets due to drug color, without any markable manufacturing defects. Surface was elegant, smooth, shiny and uniform. Odour and taste were graded 2.75±0.5 which is considered as unacceptable. Tablet mean thickness (n=10) were almost uniform in all the formulations and values ranged from 3.34 to 3.7 mm. The mean length value was 1.2±0.02 cm and the width was 0.6±0.03 cm. The standard deviation values indicated that all the formulations were within the range. The weight of all the tablets was found to be uniform with low standard deviation values 325 ±1.98 mg\tablet. The mean hardness values (n=10) were 5.6±0.36 kg/cm$^2$, the values of friability test were 0% indicating good mechanical strength. A percent drug content value of Lornoxicam is within 99.16% to 100.1%. The results within range indicate uniformity of mixing. The disintegration time ranged from 2-5 min. Evaluation of the coated tablet showed no significant change in shape, surface and texture while the color changed to red due to addition of coloring agent Allura Red. There were little or no defects in the tablets after coating. Odour and taste were graded 1.25±0.5 which is considered acceptable. Coated tablet mean thickness (n=10) were almost uniform in all the formulations and values ranged from 3.4±0.021 to 3.9±0.025 mm. The length was determined to be 1.25±0.03 cm long and the width was 0.65±0.02 cm. The weight of all the tablets was found to be uniform with low standard deviation values. The percent friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. Hardness values were 6.7±0.46 kg/cm$^2$, the percentage drug content of the drugs in all the formulated tablets was found to be within 99.16% to 100.17%. The coated tablets didn't disintegrate in 0.1N HCL for two hours while it disintegrated in pH 6.8 in 10 min, Table 1.

**Table 1: Composition and evaluation parameters for coated tablet**

| Formulation code | Coating polymer | Concentration of the coating solution | Hardness in kg | Drug Content (mg/tab) | Disintegration time in pH 6.8 (min) | Dissolution efficiency % ($DE_{8h}$) | Desirability factor |
|---|---|---|---|---|---|---|---|
| F1 | Pectin | 0.5% | 6.7±0.12 | 7.99±0.01 | 2.2±0.98 | 56±0.34 | 0 |
| F2 | | 1% | 6.6±0.2 | 7.98±0.02 | 2.4±1.1 | 55.9±0.22 | 0.11 |
| F3 | | 2% | 6.7±0.15 | 7.97±0.02 | 2.3±1.08 | 51±0.19 | 0.35 |
| F4 | Chitosan | 0.5% | 6.7±0.13 | 8±0.01 | 2.5±0.87 | 53.8±0.52 | 0.179 |
| F5 | | 1% | 6.6±0.11 | 7.99±0.02 | 2.4±0.92 | 51±0.48 | 0.27 |
| F6 | | 2% | 6.7±0.12 | 7.98±0.03 | 2.6±0.95 | 49.3±0.62 | 0.28 |
| F7 | Ethyl cellulose | 5% | 6.8±0.09 | 7.97±0.01 | ---- | 5.89±0.18 | 0.080 |
| F8 | | 7.5% | 6.8±0.08 | 8±0.01 | ---- | 5.6±0.15 | 0 |
| F9 | | 10% | 6.8±0.09 | 7.99±0.02 | ---- | 6.1±0.58 | 0.068 |
| F10 | Cellulose acetate phthalate | 3% | 6.6±0.12 | 7.98±0.03 | 3.1±0.69 | 29.6±0.83 | 0.60 |
| F11 | | 4% | 6.7±0.13 | 7.97±0.02 | 3.3±0.78 | 31.5±0.63 | 0.63 |
| F12 | | 5% | 6.6±0.15 | 8±0.01 | 3.2±0.1.06 | 35.2±0.52 | 0.53 |
| F13 | Eudragit L100 | 3% | 6.8±0.16 | 7.99±0.02 | 5±0.85 | 44.5±0.47 | 0.26 |
| F14 | | 6% | 6.7±0.15 | 7.98±0.03 | 4.9±0.56 | 58±0.46 | 0.85 |
| F15 | | 9% | 6.8±0.07 | 7.97±0.03 | 5±0.69 | 42.1±0.52 | 0.36 |
| F16 | Eudragit L100-55 | 3% | 6.7±0.08 | 8±0.02 | 4.8±0.92 | 33.9±0.32 | 0.57 |
| F17 | | 6% | 6.6±0.11 | 7.99±0.02 | 4.5±0.83 | 33.8±0.26 | 0.63 |
| F18 | | 9% | 6.8±0.09 | 7.98±0.03 | 4.7±0.49 | 32.2±0.35 | 0.64 |

***In vitro* dissolution study**

In vitro dissolution data are shown in figure1 (a, b, c, d, e and f). All the formulations resisted dissolution in the first 2 h at pH 1.2 except for the formulations coated with pectin and chitosan. For the next 4 h, only tablets coated with Eudragit L100 and ethyl cellulose showed very small or negligible release. All formulations dissolved when the dissolution medium was changed to pH 6.8 except for tablets coated with ethyl cellulose. Formulation coated with 6% Eudragit L100 was found to be optimum for further investigation according to the dissolution efficiency and desirability factor as shown in table 1. The result of the mathematical modeling of the *In -vitro* dissolution data are shown in table 2 For pectin based tablet formula from 1-3 the data best fitted in Higuchi model. This result was supported by the exponent n values obtained from Krosmyer Pepas equation (≤0.5). For the rest of the formulation the release were best fitted to first order $T_{lag}$ model. The n values were around the unity suggesting erosion mechanism. by fitting the release data to the different erosion model (Hopfenberg, Hixson-Crowell and Baker-Lonsdale) the highest $R^2$ adjusted suggested heterogeneous erosion which start by wetting the outer surface of the tablet and drug in the swollen area will be released then it proceed to the second layer till complete erosion of the tablet.

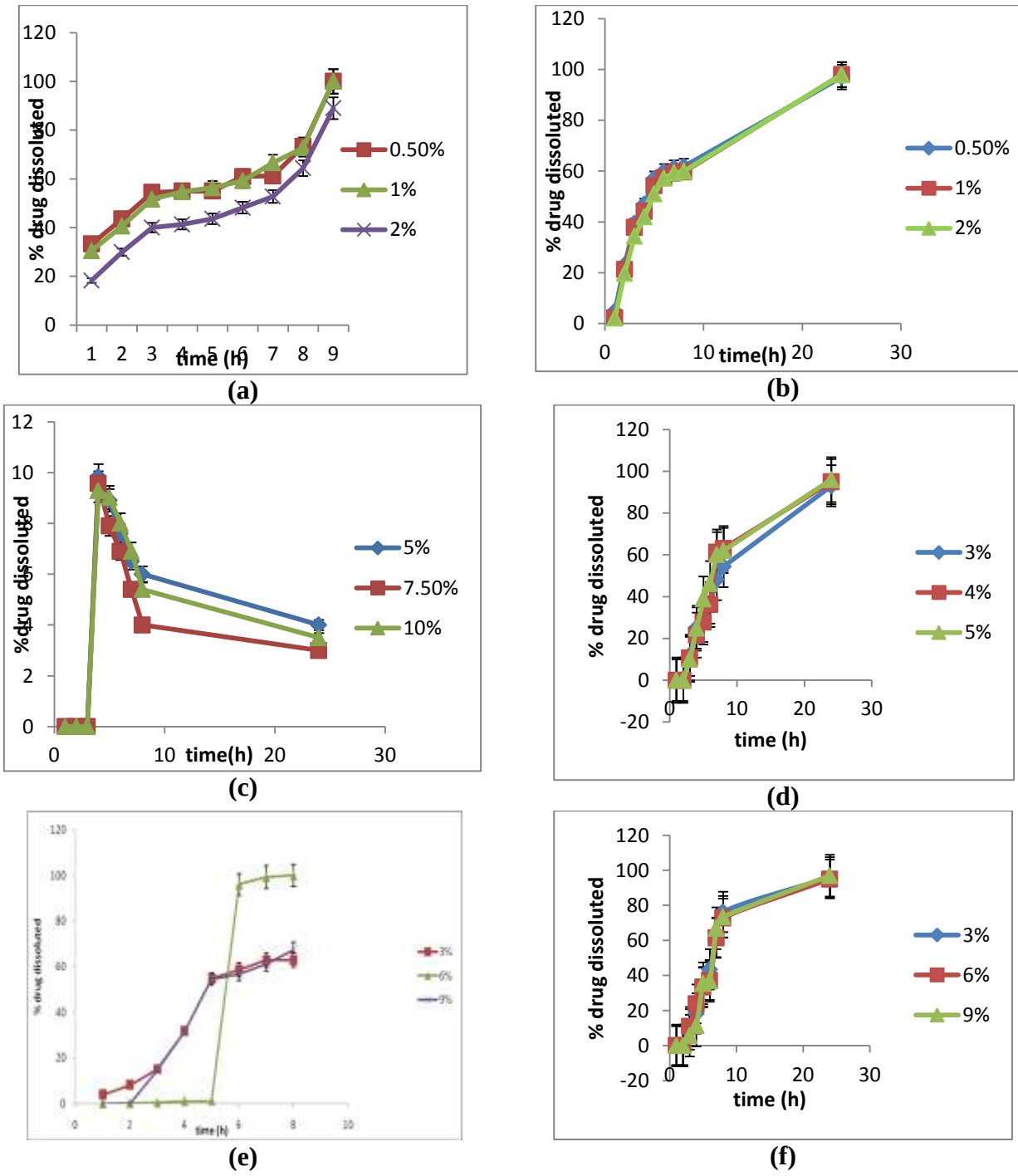


**Figure 1: *In-vitro* release of lornoxicam from tablet coated with a) Pectin, b) chitosan, c) ethyl cellulose, d) cellulose acetate phthalate, e) Eudragit L-100 and f) Eudragit L-100-55 at different concentrations in gradient pH**

**Table 2: Mathematical modeling for dissolution data using DD Solver**

| Formulation code | First order with $T_{lag}$ | Higuchi | Korsmeyer-Peppas | Hixson-Crowell | | Hopfenberg | Baker-Lonsdale |
|---|---|---|---|---|---|---|---|
| | $R^2$adj | $T_{lag}$ | $R^2$adj | N | $R^2$adj | $R^2$adj | $R^2$adj |
| F1 | 0.6529 | -3.787 | 0.741 | 0.33 | 0.617 | 0.685 | 0.949 |
| F2 | 0.6777 | -2.551 | 0.816 | 0.39 | 0.761 | 0.818 | 0.983 |
| F3 | 0.6666 | -1.379 | 0.947 | 0.49 | 0.865 | 0.903 | 0.966 |
| F4 | 0.9611 | 0.408 | 0.896 | 0.88 | 0.954 | 0.96 | 0.884 |
| F5 | 0.9597 | 0.484 | 0.905 | 1.06 | 0.956 | 0.957 | 0.871 |
| F6 | 0.9772 | 0.582 | 0.91 | 1.09 | 0.97 | 0.969 | 0.867 |
| F7 | -0.285 | 23.865 | -0.0942 | -0.45 | -0.22 | -0.39 | -0.63 |
| F8 | -0.283 | 23.778 | -0.0944 | -0.86 | -0.22 | -0.39 | -0.62 |
| F9 | -0.283 | 23.842 | -0.0937 | -0.13 | -0.22 | -0.39 | -0.43 |
| F10 | 0.9799 | 1.522 | 0.7917 | 0.917 | 0.942 | 0.937 | 0.723 |
| F11 | 0.9338 | 1.676 | 0.745 | 1.01 | 0.891 | 0.954 | 0.679 |
| F12 | 0.9625 | 1.607 | 0.773 | 0.963 | 0.91 | 0.948 | 0.708 |
| F13 | 0.9439 | 1.191 | 0.807 | 1.12 | 0.92 | 0.927 | 0.758 |
| F14 | 0.9873 | 2.303 | 0.412 | 4.58 | 0.53 | 0.999 | 0.369 |
| F15 | 0.9516 | 1.494 | 0.774 | 0.789 | 0.899 | 0.919 | 0.716 |
| F16 | 0.9108 | 1.746 | 0.716 | 1.07 | 0.859 | 0.963 | 0.653 |
| F17 | 0.9213 | 1.671 | 0.735 | 0.975 | 0.876 | 0.963 | 0.673 |
| F18 | 0.8745 | 1.848 | 0.681 | 1.3 | 0.828 | 0.929 | 0.619 |

***In- Vivo* absorption study**

Figure 2 shows the comparative drug plasma concentration levels after oral administration of lornoxicam coated tablet and marketed tablet Xefo™. For rabbits receiving marketed tablet Xefo™, the maximum drug plasma concentration was 264.42ng/ml in three hours then fell to 43.19 ng/ml after 6 h. The release of the prepared coated tablet showed a lag time of 5h. The maximum $Cp_{max}$ was 319ng/ml after 8 hours. The data confirms that lornoxicam was delivered as colon targeted and was absorbed through the colon; the pharmacokinetic parameters calculated for the two administered lornoxicam formulations were shown in table 3.

**Table 3: Summary of pharmacokinetic parameters of lornoxicam following administration of the reference and test formulations**

| Pharmacokinetic parameter | Test | Reference |
|---|---|---|
| $Cp_{max}$ | 319.87 ±6.1 | 264.61±18.2 |
| $T_{max}$ | 8 | 3 |
| $AUC_{(0-24)}$ | 5043.12±17.2 | 948.05±13.6 |
| F relative | 531.96 | ---------- |

The calculated pharmacokinetic parameters were analyzed using ANOVA procedure. For the $AUC_{(0-24)}$ mean values, a significant difference was observed between the two formulations at $p<0.05$. Colon targeted tablets showed higher $AUC_{(0-24)}$ value. Similarly the coated colon targeted

tablet recorded higher $Cp_{max}$ than marketed tablet. The percentage relative bioavailability of lornoxicam tablet was 531.96. Thus the prepared coated tablet products were more bioavailable and colon targeted compared to reference conventional product with regard to the maximum drug plasma concentration and the extent of the drug absorbed.

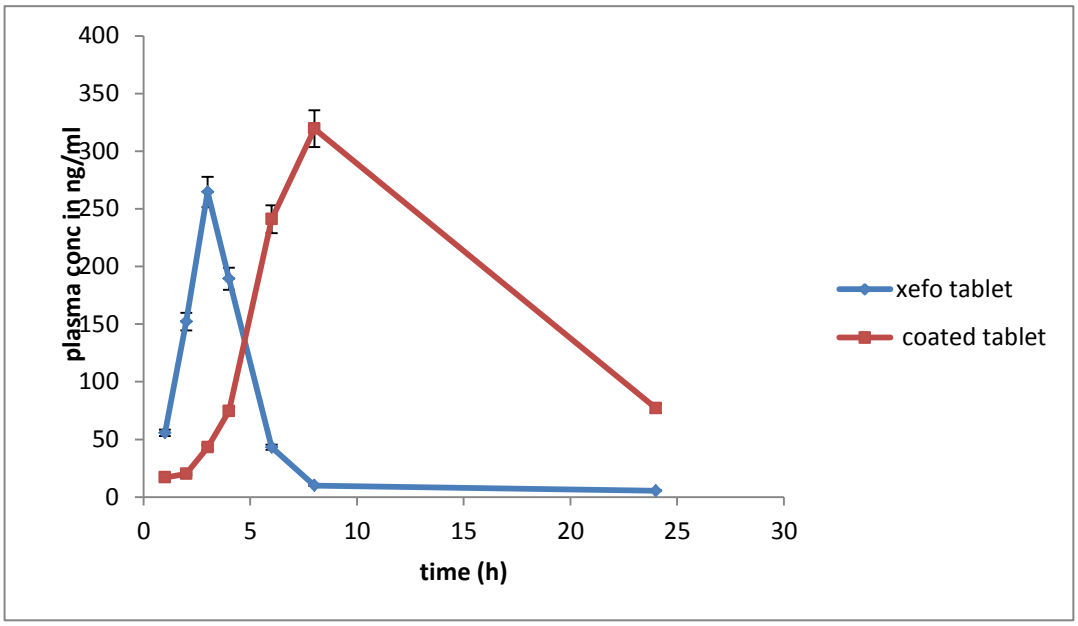


**Figure 2: The average drug plasma concentration level after oral administration of lornoxicam coated tablet as compared with marketed tablet Xefo™**

## CONCLUSION

The lornoxicam tablets coated with 6% Eudragit L100 showed optimum colon targeting release. This result was confirmed by conducting *In-vivo* test. So our goal of colon targeting lornoxicam were achieved.

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