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LORNOXICAM SUPPOSITORIES: *IN-VITRO* FORMULATION AND *IN-VIVO* EVALUATION

Hesham M. Tawfeek

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, 71526, Egypt

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Correspondence to Author:

Dr. Hesham Mohamed Tawfeek

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

E-mail: hesham_ipd@yahoo.com

ABSTRACT: The aim of the present study was to formulate lornoxicam into rectal suppositories as a new dosage form, to avoid its reported gastric irritation and to provide a rapid onset of action for children. Suppositories were prepared using fatty bases namely; witepsol H-15, suppocire AML, CM, witepsol E-75 and water soluble bases; mixtures of poly(ethylene glycol), PEGs, with different molecular weights. The prepared suppositories were investigated for their weight variation, drug content, melting point, fracture point, disintegration time and *in-vitro* release pattern. Moreover, aging study was performed both at room temperature and in refrigerator for 6 month. *In-vivo* study was also carried out in rabbits and the pharmacokinetic parameters were estimated. The prepared suppositories complied with the USP 34 pharmacopoeial requirements and PEGs-based suppositories released significantly higher amounts of lornoxicam compared with fatty bases (p<0.05, ANOVA/Dunnett). Furthermore, lornixocam in selected formulations was found to be stable in both fatty and PEGs bases after the aging study. Formulation No. 5 showed a higher C_{max} of 1.832±0.35 µg/ml, short t_{max} of 1 hr and absolute bioavailability of 80.1%. These findings suggest that lornoxicam was successfully formulated into rectal suppositories with a higher bioavailability.

INTRODUCTION: Lornoxicam (LOR) is considered one of the potent non-steroidal anti-inflammatory drugs, NSAIDs, with analgesic and anti-pyretic properties [1]. LOR is structurally related to piroxicam and tenoxicam; however, it is ten times more potent than both of them [2]. Lornoxicam inhibits both cyclooxygenase iso enzymes cox-I and cox-II, hence the gastrointestinal adverse effects still an issue especially with oral administration [3].

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Because it is used as a potent postoperative analgesic, the rapid onset of action is a desired attribute especially for infants and elderly patients.

The drug is available in the Egyptian market in the forms of oral tablets and parenteral formulations only. At the same time, there was no data in the literature regarding lornoxicam rectal formulation. Rectal route of NSAIDs is one of the alternative routes to avoid gastro-intestinal problems.

In addition, absorption of the drugs from rectal mucosa directly into venous circulation may bring about faster action than that observed after oral administration [4] and this is very important especially with drugs used to reduce post-operative pain. Recently, lornoxicam was formulated in the form of sustained release buccal patches for

treatment of patients suffering from post-operative pain and edema following maxillofacial operations [3]. However, the inconvenient nature associated with these patches administration, especially with elderly people and children, is considered a problem. Moreover, the patients cannot eat, drink or even speak when using these patches for prolonged period of time. Swallowing of saliva may also lead to the loss of dissolved and suspended drugs, as well as the low permeability of buccal membrane when compared with sublingual membrane [5].

The aim of this work was to formulate LOR in a rectal dosage form, suppositories, to fulfill many aspects e.g., rapid onset of action, avoiding GIT problems, as well as enhancing patients compliance especially for elderly people and children. Different formulations were prepared using fatty and water soluble, PEG, bases and investigated for their weight variation, drug content, hardness, disintegration time, melting range, *in-vitro* release. Furthermore, *in-vivo* study in rabbits was performed and the absolute bioavailability was determined. Pharmacokinetic parameters were also calculated through residual method. In addition aging study was performed for the best formulation having the highest *in-vitro* LOR release.

MATERIALS AND METHODS: LOR was kindly provided by (E.I.P.I. Co., Cairo, Egypt), polyethylene glycol of molecular weights 1500, 4000 and 6000 were purchased from Merck-Schuchardt, Germany. Suppocire AML, BM were purchased from Gattefosse establishments, France, witepsol E-75 and H-15 were obtained as a gift from Hüls America, INC. Xefo® ampoule (LOR for injection) were obtained from Boehringer Ingelheim International GmbH, Germany. Acetonitrile was purchased from Sigma Chem. Co. USA. Other solvents and chemicals were of analytical grades.

Preparation of LOR suppositories: Suppositories weighing 1 gram (each containing 8.0 mg of LOR) were prepared using fatty bases which are suppocire AML, suppocire BM, witepsol E-75 and witepsol H-15 and mixture of water soluble bases such as (PEG1000: PEG4000; 25:75%w/w) , (PEG1000: 6000; 25:75%w/w) and (PEG1000: PEG1500;25:75%w/w).

The composition of each suppository is illustrated in the **Table 1**.

TABLE 1: COMPOSITION OF THE PREPARED LOR SUPPOSITORIES

Formula No.	Suppository base	
	Type	Name & Composition
1	Fatty bases	Witepsol E-75
2		Witepsol H-15
3		Suppocire-BM
4		Suppocire-AML
5	Water soluble bases	PEG1000:PEG1500 (25:75%w/w)
6		PEG1000:PEG4000 (25:75%w/w)
7		PEG1000:PEG6000 (25:75%w/w)

The suppositories are prepared by using melting technique [6] where the used bases were melted over a water bath. LOR was added subsequently with stirring after each addition until homogenous mixture was produced. Then poured into 1 gram metal mould and allowed to cool. The displacement values of the prepared suppositories were calculated [7] and used for preparation of medicated suppositories.

Evaluation of LOR suppositories: The prepared LOR suppositories were evaluated by the following tests.

1. **Uniformity of drug content:** The test was performed according to the US Pharmacopeia 34 (USP 34) [8]. Six randomly selected LOR suppositories from each batch were evaluated individually. Each suppository was placed in 100 ml volumetric flask, dissolved in minimal amounts of acetone, and the flasks were shaken for 15 min. The volume was completed to 100 ml with a phosphate buffer of pH 7.4 and sonicated for 10 minutes followed by filtration using Whatman filter paper. The LOR content in each suppository was determined spectro-photometrically at λ_{max} of 372nm using Jenway UV/Vis. Spectrophotometer, UK. The average drug content is shown in **Table 2**.

2. **Weight variation:** The average weight was calculated by weighting twenty suppositories individually. The percent deviation from the means was subsequently calculated as shown in **Table 2**.

3. **Hardness test:** LOR suppositories were tested for hardness using Erweka hardness tester (type TAB, G.m.b.H., Germany) at at room temperature. The results are listed in **Table 2**.

4. **Disintegration time:** Disintegration time of the prepared suppositories was determined by using USP tablet disintegration apparatus (G.M.B.H., Germany) in distilled water at 37°C±1.0. The results are listed in **Table 2**.

5. **Melting range determination:** Melting range of the prepared suppositories was determined by using open capillary tubes and melting point SMP1 apparatus Stuart Scientific (U.K). The results are listed in **Table 2**.

TABLE 2: PHYSICAL CHARACTERISTICS OF THE PREPARED LOR SUPPOSITORIES

Formula No.	Suppository properties				
	Mean weight (g±SD)	Drug content (% of labeled amount ± SD)	FP (kg)	MR (°C)	DT (min)
1	1.15±0.08	100.01±2.50	4.25	37-39	10
2	1.17±0.11	100.23±3.10	4.75	33.5-35.5	6.0
3	1.11±0.09	101.01±1.60	4.50	36.0-37.5	5.0
4	1.16±0.24	99.98±2.31	4.50	35.0-36.5	5.0
5	1.15±0.14	100.05±3.22	3.75	44.5-53.5	11
6	1.14±0.06	99.23±2.65	3.75	46.2-54.5	15
7	1.15±0.13	98.50±1.45	3.50	46.5-55.5	18

FP: fracture point; MR: Melting range; DT: disintegration time

***In-vitro* release study:** The drug release from LOR suppositories (n=4) was accessed using the USP dissolution apparatus (i.e. non-membrane method) [4, 9, 10] Type II apparatus, SR6 dissolution test station (Hanson Researches Corporation, California, USA.).The dissolution medium was 500 ml phosphate buffer of pH 6.8 and it was maintained at 37°C±0.5 throughout the experiment and the stirring rate was kept at 100 rpm. At specified time interval, aliquots of 5ml were withdrawn, filtered and assayed spectrophtometrically at λ_{max} equal to 372nm for LOR content. The volume withdrawn was replaced by the same volume of the dissolution medium kept at the same temperature.

Effect of aging: Suppocire AML (Formulation No. 4) and PEGs (Formulation No. 5) were stored in amber colored glass jars and kept at both room temperature and in a refrigerator at 5.0°C±0.5 for six months. The physical properties were investigated after six month as well as the *in-vitro* release. Moreover, the LOR content was tested after 30, 60, 90, 120, 150 and 180 days. Briefly; suppository was dissolved in minimal amounts of acetone and the volume was completed to 100 ml by phosphate buffered saline followed by sonication for 15 minute. The resultant solutions were filtered using filter paper and 1 ml of the filtrate was transferred to a 10 ml volumetric flask then the volume was completed with a mobile phase (Phosphate buffer, pH 6.0: Acetonitril 60:40). The obtained clear solutions were filtered through 0.45 µm membrane filter, degassed and 20 µl were injected onto HPLC column. LOR content in each sample was determined from the constructed standard calibration curve in mobile phase.

***In-vivo* Absorption study:** The study was carried out to compare the pharmacokinetics of LOR suppository from the best achieved formulations in terms of dissolution and stability, Formulation No. 5, to LOR aqueous intravenous injection. This was performed through administration of single equal doses, 0.75mg/kg, of F5 and I.V. product in rabbits (2.0-2.5 Kg) using non-blind, two treatment design. The protocol of the study was approved by the research Ethics Committee in the Faculty of Medicine, Assiut University, Egypt.

Study design and Chromatographic conditions: Six rabbits were randomly distributed into two groups of equal numbers. The animals were kept in individual cages under well-defined and standardized conditions (humidity and temperature controlled room) and fed with standard food and water access. Prior to study day, the rabbits were cannulated in the right jugular vein, allowed to recover and fast overnight (12 hr) [11]. On the study day, each rabbit in the first group received LOR suppository Formulation No. 5 (Treatment A). Rabbits of the second group received equal doses of LOR through intravenous injection of Xefo® vial, October Pharm, Egypt (Treatment B).

Blood samples (200 µL) were collected just after administration of LOR injection in the second group and at scheduled time intervals (1, 2, 3, 4, 6 and 8 hr) from both treatments and treated with heparin to prevent blood clotting. The plasma were obtained via centrifugation (3500g) for 10 min (Centurion Scientific Ltd, UK), kept in glass tubes and then deep frozen at -25°C±2.0. Prior to HPLC analysis, aliquots of plasma (100 µL) or the calibration standards, 100 µL of an internal standard solution (piroxicam, 5 µg/ml) and 100 µL of 5M HCL were added to a glass tube. After brief vortex mixing (Maxi Mix, Thermolyne, USA) 5 ml of diethyl ether was added and the mixture was vortex mixed for 30s.

Each sample was centrifuged (2500 rpm for 10 min), and the organic layer was transferred to a new glass tube and evaporated to dryness under a gentle stream of nitrogen at 40°C. The residue was reconstituted with 500 µL of the mobile phase, (mixture of 20mM potassium monophosphate-acetonitrile 60:40, v/v, and was adjusted to pH 3.5 with ortho-phosphoric acid, at a flow rate of 1.2 ml/min), filtered and a 20 µL aliquot was injected into the HPLC system. The HPLC system, Knauer, Germany consisted of HPLC pump (Knauer D – 14163), UV- detector (Knauer, D – 14163), and integration interface box (Knauer, D – 14163).

Chromatographic separation was carried out using Kromasil C-18 column (250 x 4.60 mm, particle size: 20 µm). The detection wave length, 377 nm, was determined by scanning the maximum absorbance wavelength of lornoxicam and piroxicam in the mobile phase using an UV spectrophotometer (Jenway, Model 6305, UK).

Pharmacokinetic analysis: The pharmacokinetic parameters of the two treatments were estimated for each subject through the residual method. The maximum drug concentration (C_{max}, µg/ml), the time to reach C_{max} (T_{max}, hr), the absorption half-life ($t_{1/2a}$, hr), the elimination half-life ($t_{1/2e}$, hr) as well as the mean residence time ($MRT_{(0-\alpha)}$, hr) were obtained from the LOR plasma concentration time curves. The trapezoidal rule method was employed to calculate the area under curve from zero to 24 hr ($AUC_{(0-24)}$, µg.h/ml) [12]. Moreover, the area under curve from zero to infinity ($AUC_{(0-\alpha)}$, µg.h/ml) was calculated using equation (Eq. 1).

$$AUC_{(0-\alpha)} = AUC_{(0-t)} + C_t / K_e \quad \text{(Eq.1)}$$

Where C_t is the drug plasma concentration observed at time t, K_e is the apparent elimination rate constant. The absolute bioavailability (%) was calculated using equation (Eq. 2).

$$\text{Absolute bioavailability (\%)} = \frac{AUC_{(0-\alpha)} \text{ of formula F5}}{AUC_{(0-\alpha)} \text{ for i.v. injection}} \times 100 \quad \text{(Eq. 2)}$$

Statistical analysis: The results are expressed as mean values ± S.D. A two way analysis of variance (ANOVA) with Dunnett multiple comparison test was performed for the data derived from the of *in-vitro* release and *in-vivo* study (SPSS 14.0, SPSS Inc., Chicago, USA). Difference of $p<0.05$ are considered significantly different.

RESULTS AND DISCUSSION:

Physical characteristics of LOR Suppositories: The prepared LOR suppositories with PEGs or fatty bases were yellow or creamy yellow in color with a smooth, shiny surface. Furthermore, they were well formed and homogenous in shape. It is worth noting that after slicing the suppositories longitudinally they did not show any fissures, cracks or concentration holes. The weight variation and the LOR content were carried out according to the USP 34 and it was found that all the prepared LOR suppositories were within the pharmacopoeial limits for the uniformity of weight and drug content as shown in Table 2.

The hardness of the prepared LOR suppositories ranged from 3.50 to 5.0 kg. These results showed the good mechanical properties for the LOR suppositories and a higher resistance to fracture during the handling, packaging, transport and insertion. Additionally, it was found that the values of the melting range and disintegration time for the water soluble bases of LOR suppositories were higher than those from fatty base of LOR suppositories as depicted in Table 2.

***In-vitro* release study:** The release of the drug from suppositories is known to be influenced by various factors such as drug-vehicle interactions, type of vehicle and the chemical composition of the additives [13].

The release of LOR from fatty and PEGs bases are presented in **Figs. 1 and 2** respectively.

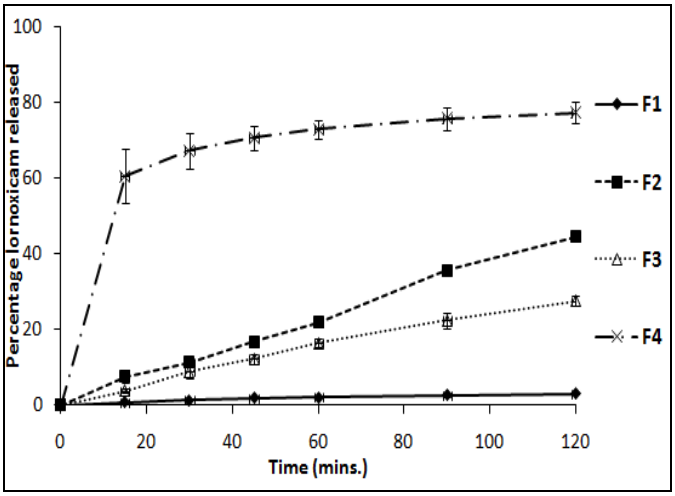

Fig. 1: THE PERCENTAGE OF LORNOXICAM RELEASED FROM FATTY SUPPOSITORY BASES. F1; witepsol E-75, F2; witepsol H-15, F3; suppocire BM and F4; suppocire AML.

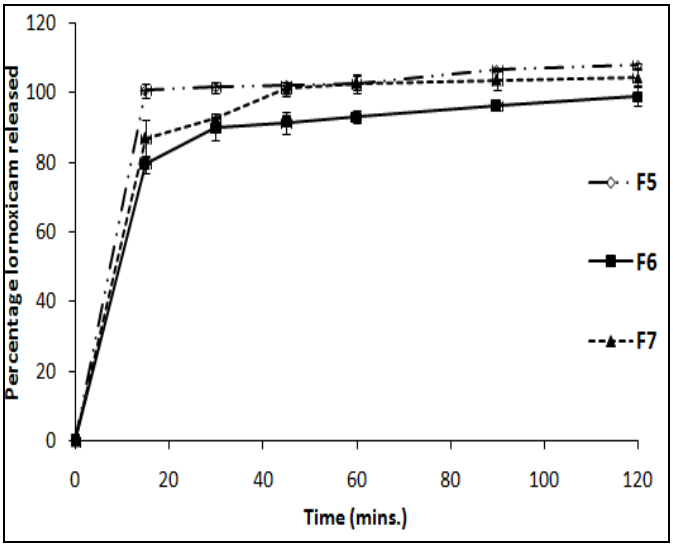

FIG. 2: THE PERCENTAGE OF LORNOXICAM RELEASED FROM PEGS SUPPOSITORY BASES. F5; (PEG1000: PEG4000; 25: 75%w/w), F6; (PEG1000: 6000; 25:75%w/w), F7; (PEG1000: PEG1500; 25:75%w/w).

Generally, PEGs bases showed significantly higher LOR release compared to fatty based bases. Moreover, there is no significant difference between Formulations 5, 6 and 7 containing different ratios of PEG after 45 min (p>0.05, ANOVA/Dunnett). Whilst, suppocire AML suppository (Formulation No. 4) showed significantly higher amounts of LOR release 60.58±7.09 % compared with 0.87 ± 0.28 %, 7.55 ± 1.65 and 3.93 ± 0.63 for witepsol E-75, witepsol H-15 and suppocire BM after 45 min. respectively (p<0.05, ANOVA/ Dunnett).

In the same time, PEG 1000:PEG1500 (25:75%w/w), Formulation No. 5, gave significantly the highest LOR release 100.85±2.0% compared to 79.57±2.5% and 86.96±5.51% for Formulations 6 and 7, respectively after 15 min (p<0.05, ANOVA/ Dunnett). The higher release of LOR from water soluble, PEGs, bases could be attributed to the hydrophilicity and the solubilizing effects of PEGs [14].

Furthermore, the fact that, LOR being water insoluble drug [15, 16] has high affinity towards the fatty bases than PEGs base [14]. This result also agrees with Abou-Taleb et al., 2006 who found that the release of rofecoxib, selective cox-II inhibitor, from PEGs bases was higher than those of fatty bases e.g., witepsol E-75 and suppocire AM and CM [4]. Also, it was found that the release of verapamil hydrochloride from PEG suppositories was greater than the release from witepsols and suppocire AM based bases [17].

The higher release of LOR from both suppocire AML and witepsol H-15 could be attributed to the low melting of these lipophilic bases and short softening time compared with witepsol E-75 and suppocire BM having higher melting point and long softening times (Table 2) and those two parameters are considered the rate limiting steps in the release of the drugs from fatty bases. Such results are in accordance with those reported by Thomas and Mccormack who stated that melting characteristics of the fatty suppository bases influence the drug release rate at 37°C [18].

However, the significantly faster and higher release of LOR from suppocire AML was due to the nature of the base. Suppocire AML is a triglycrides (C8-C18) containing a phospolipid (lecithin) which may add in the solubilisation process compared with suppocire BM (triglycrides C8-C18) and witepsol H-15 (triglycerides C10-C18 of saturated fatty acids) [19].

Effect of aging: It was then necessary to study the effect of storage on selected LOR suppositories. Suppocire AML (Formulation No.4) and PEG suppository (Formulation No.5) were chosen as the best formulae, which gave the highest drug release. It was found that the melting points and the softening time of the selected suppositories were not significantly affected by aging.

Furthermore, there is no significant difference in the *in-vitro* release upon aging. Suppocire AML seemed to be unaffected during the first three months (99.56±2.9%) then it started to decrease till (93.75±3.55%) after six months. However; Formulation No.5 had drug content of (98.97±2.45%) after the same time interval. Therefore, this formula was chosen for further investigation, *in-vivo* study.

***In-vivo* study and Pharmacokinetic analysis:** The pharmacokinetic parameters of LOR following rectal and intravenous administration of single doses of 0.75 mg/kg of;

(i) Formulation No. 5 and

(ii) LOR intravenous (Xefo® vial) into rabbits are shown in **Table 3**.

TABLE 3: PHARMACOKINETIC PARAMETERS OF LORNOXICAM AFTER RECTAL ADMINISTRATION OF THE BEST ACHIEVED SUPPOSITORY (FORMULATION NO. 5) AND LORNOXICAM AQUEOUS INTRA-VENOUS INJECTION TO RABBITS (mean ± S.D., n=3 for each group).

Treatment	C_{max}	T_{max}	MRT	Ka	$t_{1/2a}$	Ke	$t_{1/2e}$	$AUC_{(0-24)}$	$AUC_{(0-\alpha)}$
Formulation No. 5	1.832±0.35	1.0±0.1	9.43±0.98*	0.8261±0.05	0.839±0.12	0.08158±0.009	8.494±1.25	16.402±2.25	18.961±2.65
I.V. injection Xefo®	3.7±0.25**	0.00	7.68±0.85	-	-	0.11235±0.087	6.168±1.55	21.654±2.86**	23.683±1.75**

C_{max}: Maximum concentration in plasma (µg/ml); T_{max}: Time to reach the maximum concentration after administration (hr); MRT: Mean residence time (hr); Ka: absorption rate constant (hr^{-1}); $t_{1/2a}$: absorption half-life (hr); Ke: Elimination rate constant (hr^{-1}); $t_{1/2e}$: Elimination half-life (hr); $AUC_{(0-24)}$: The area under LOR plasma concentration time curve from (0-24, µg.hr/ml); $AUC_{(0-\alpha)}$: The area under LOR plasma concentration time curve from (0-α, µg.hr/ml). * Significantly different at $p<0.05$, ANOVA/Dunnett compared to I.V. product; ** compared to formulation No. 5.

The aim of this study was to investigate the pharmacokinetic parameters of LOR suppository as a new dosage form and estimate the absolute bioavailability percentage. The LOR plasma – concentration time profiles of both treatments are depicted in **Fig. 3** and could be best described by a one-compartment model with a first order absorption and elimination.

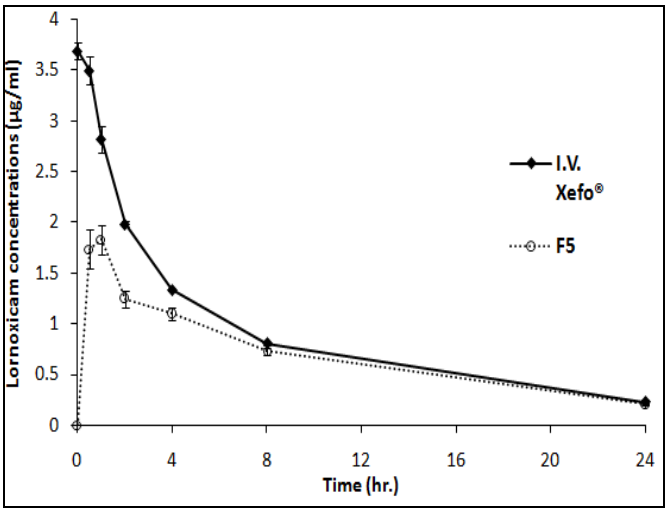

FIG. 3: PLASMA CONCENTRATION– TIME PROFILES OF LORNOXICAM FOLLOWING INTRAVENOUS ADMINISTRATION OF LORNOXICAM INJECTION XEFO® (I.V.) and Lornoxicam Suppository (Formulation No.5) (mean± SD, n = 3).

The data was fit in a one – compartment model of the formats [20].

$C = A (e^{-kelt} – e^{-Kat})$ (Eq. 3) and;

$C = A (e^{-kelt})$ (Eq. 4)

Where; C is the concentration of LOR in plasma at time t; A is a constant co-efficient or the intercept and K_{el} and K_a are the rate constants of elimination and absorption, respectively for suppository formulation F5 (Eq. 3) and I.V. injection (Eq. 4). The mean values of the pharmacokinetic parameters are given in Table 3. It is clear that remarkable difference between the two treatments was found and this is true when comparing rectal formulation with the I.V. product Xefo® having no absorption phase.

Significantly higher peak plasma concentration (C_{max}) was found with treatment (B; I.V. product) 3.691±0.25 µg/ml compared with treatment (A; Formulation No. 5) 1.832±0.35 µg/ml ($p<0.05$, ANOVA/Dunnett). The peak plasma concentration was achieved after 1hr for Formulation No. 5 with an absorption rate constant (ka) and absorption half-life ($t_{1/2a}$) of 0.8261±0.05 hr^{-1} and 0.839±0.12 hr, respectively. The $t_{1/2e}$ for elimination and $AUC_{(0-\alpha)}$ were found to be 8.494±1.25, 6.168±1.55 hr and 18.961±2.65, 23.638±1.75 µg.hr/ml for Formulation No.5 and I.V. product, respectively.

Furthermore a significantly higher $MRT_{(0-\alpha)}$ was found with rectal formulation compared with I.V. product 9.432±0.98 hr versus 7.679±0.85 hr, respectively (p<0.05, ANOVA/Dunnett). It is worth noting that the produced C_{max} from Formulation No.5 was higher than those obtained previously from Habiba *et al*., 2011 who found that the C_{max} from LOR oral batches produced from different formulations ranged from 0.899±0.05 to 1.248± 0.158 µg/ml [21].

Additionally, the lower T_{max} (1hr), higher MRT (9.43±0.98 hr) and the relatively long $t_{1/2e}$ (8.494±1.25 hr) suggesting the success of the rectal formulation in achieving rapid action extended for long duration and this is beneficial for postoperative patients.

Furthermore, the absolute bioavailability was found to be 80.06% and thus indicated that LOR formulation into rectal suppository was delivered into the systemic circulation with reasonable plasma concentration and high absolute bioavailability value.

CONCLUSION: LOR was efficiently formulated into rectal suppositories using fatty and PEGs suppository bases. Furthermore, the produced suppositories complied with the USP Pharmacopoeial requirements. *In-vitro* release study showed that PEGs based suppositories released significantly (p<0.05, ANOVA/Dunnett) higher amounts of LOR compared with fatty bases and there was no significant difference between different PEGs formulations. Additionally, LOR was stable after storage in both room temperature and in refrigerator after 6 months.

Formulation No. 5 had the highest *in-vitro* release, short onset (1 hr), long MRT (9.432±1.2 hr) and absolute bioavailability of 80.06%. These findings suggest that LOR administered as rectal suppositories may present a new dosage form with potential therapeutic use as a strong anti-inflmmatory and analgesic agent.

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