CHAPTER 8

IN-VIVO PHARMACOKINETIC STUDIES

8.0 IN-VIVO PHARMACOKINETIC STUDIES

8.1 Methods

8.1.1 Animals

All animal experiments conducted were approved by the Social Justice and Empowerment Committee for the purpose of control and supervision on animals and experiments, Ministry of Government of India. Wistar rat weighing between **250-300 gm** were selected for PK studies.

8.1.2 Dosing Procedure

Mini Tabs were dosed intact to the rat by the following procedure. Rats were partially anesthetised using chloroform. Rats were restrained by grasping the scruff of the neck with one hand and the rear with the other hand. Rat's tail was wrapped around small finger to secure the lower portion of the rat. The minitab was placed in the center of the mouth using the holder follow the roof of the mouth to the opening of the oesophagus. The rat's head was tilted back with the shaft of the sample holder. This straightens the oesophagus and makes insertion of the makes the insertion of easier. After dosing, rats were dose with a few ml of water as this further facilitate movement of the minitab into the stomach.

8.1.3 Blood Sampling Procedure

Collection Site: **Tail Vein**

The acceptable quantity and frequency of blood sampling was determined by the circulating blood volume and the red blood cell (RBC) turnover rate. Excessive blood collection may result in hypovolemic shock, physiological stress and even death of the animal.

Because it was necessary to take multiple samples, smaller blood volumes i.e. 300 µl were drawn 5 time. Without fluid replacement, the maximum blood volume which can be safely removed for a one time sample is 10% of the total blood volume or 5.5-7 ml/kg. For a 300 g rat, this was equivalent to 1.7-2.1 ml. For a 300 g rat if subcutaneous fluid replacement is done then collection volume can be increased equivalent to 2.5-3.2 ml.

Animal recovery : If sampling done every 2 weeks, up to 10% of the total blood volume may be drawn or 5.5-7 ml/kg (4). For a 300 g rat, this is equivalent to about 1.7-2.1 ml every 2 weeks. Approximate Blood Sample Volumes for Body Weights are tabulated in table 1-8.

Body weight (g)	**Circulating Blood Volume (ml) (CBV)**	**10% CBV (ml) every 2 wks†**
250	13.75 – 17.50	1.4 – 1.8
300	16.50 – 21.00	1.7 – 2.1

Table 1 - 8 Approximate Blood Sample Volumes for Body Weights

8.1.4 Sampling Procedure

- Tail vain sampling is recommended for collecting a large volume of blood sample (up to 2ml /withdrawal)
- Animal was restrained properly.
- The tail was not rubbed from the base to the tip as it may result in leukocytosis. If the vein was not visible, the tail is dipped into warm water (40°C).
- Local aesthetic cream was applied on the surface of the tail 30 min before the experiment.
- A 23G needle inserted into the blood vessel and blood is collected using a a syringe with a needle. In case of difficulties, 0.5 to 1 cm of surface of the skin is cut open and blood is collected with a syringe with a needle.
- Having completed blood collection, silver nitrate ointment was applied to stop the bleeding.
- Each sample was immediately placed in an apendrop tube containing potassium EDTA equivalent to 2 mg/ml and refrigerated.
- Blood sample were frozen 20 °C until analysed.
- Plasma Sample obtained by centrifugation of blood samples at 4000 RPM.
- Butorphanol Tartrate equivalent to 1 ng / µl of plasma was spiked to make the released drug quantifiable.

8.2 Study Design

Two treatments, four Periods, cross-over bioavailability study design. Blood sample were collected at 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing after giving 20 day washout same rats were dosed again and blood samples were collected at 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing. Same procedure was followed for BT extended release formulation and BT solution. And LOR extended release formulation and LOR IR formulation. In-vivo Study design for both formulation is tabulated in table 2-8.

Blood Sampling Time Points After 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing		**Blood Sampling Time Points After 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing**	
Cohort I	**Cohort II**	**Cohort I**	**Cohort II**
Rat 1 – T	Rat 7 – R	Rat 1 – T	Rat 7 – R
Rat 2 – T	Rat 8 – R	Rat 2 – T	Rat 8 – R
Rat 3 – T	Rat 9 – R	Rat 3 – T	Rat 9 – R
Rat 4 – T	Rat 10 – R	Rat 4 – T	Rat 10 – R
Rat 5 – T	Rat 11 – R	Rat 5 – T	Rat 11 – R
Rat 6 – T	Rat 12 – R	Rat 6 – T	Rat 12 – R
Blood Sampling Time Points After 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing		**Blood Sampling Time Points After 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing**	
Cohort I	**Cohort II**	**Cohort I**	**Cohort II**
Rat 1 – R	Rat 7 – T	Rat 1 – R	Rat 7 – T
Rat 2 – R	Rat 8 – T	Rat 2 – R	Rat 8 – T
Rat 3 – R	Rat 9 – T	Rat 3 – R	Rat 9 – T
Rat 4 – R	Rat 10 – T	Rat 4 – R	Rat 10 – T
Rat 5 – R	Rat 11 – T	Rat 5 – R	Rat 11 – T
Rat 6 – R	Rat 12 – T	Rat 6 – R	Rat 12 – T

Table 2 - 8 In-vivo Study design

8.3 Statistical Analysis

All data are reported as mean ± SD (standard deviation) and the difference between the groups were tested using Student's t-test at the level of $P<0.05$. Non-Compartmental analysis of plasma data after extravascular input was evaluated using PK Solver Software Ver. 2.0 with Linear Trapezoidal method. The pharmacokinetic parameters of Butorphanol tartrate in rat after oral administration of drug solution and ER formulation were recorded.

8.4 Preparation of Equivalent formulation for Rat Model

Rat LD 50 of Butorphanol Tartrate is 315 mg/kg dose proportional

Dose proportional formulation was prepared for ingestion in to rat model except thickness of the coating needed to increase from 6 % to 9% to have similar release profile as that of the original formulation. The whole process was similar to that of the original formulation.

Formula ingredients	**Quantity (mg/tablet)**	**Quantity (% W/W)**
Dry Mixing		
Butorphanol tartrate	0.51	3.99
Sodium Chloride	5.12	39.85
Lactose*	5.12	39.85
PVP K 30	0.61	4.78
Isopropyl Alcohol**	Processing Solvent	Processing Solvent
	11.38	88.48
Lubrication		
Mg. Stearate	0.15	1.20
Talc/Purified Talc	0.15	1.20
Colloidal silicon dioxide	0.10	0.80
Total weight of un coated core tablet	**11.79**	91.66
Coating 9 % Weight Gain		
Cellulose CA398-10	0.54	4.17
PEG 400	0.40	3.08
D – Sorbirol	0.14	1.08
Purifies Water **	Processing Solvent	Processing Solvent
Acetone**	Processing Solvent	Processing Solvent
Total weight of coated tablet after coating	**13**	**100.00**

Table 3 - 8 Composition of Butorphanol tartrate for In-vivo studies.

Tablet Size:

Diameter : 3 mm

Thickness : **1.8 mm**

Dissolution :

Volume: 250 ml

Dissolution medium : SGF for 2 Hrs followed by SIF

Time (hr)	SGF 2 Hrs + SIF
0	0.00
1	4.18
2	9.23
4	20.48
6	31.62
8	39.13
10	47.21
14	62.58
17	72.19
21	82.17
24	93.58

Comparison of rat and Human Extended release formulation:

Similarity Factor	F2	89.01

Similarity factor confirms the developed formulation and formulation for In-vivo studies have similar behaviour.

8.5 Pharmacokinetic Studies of Butorphanol tartrate formulation

The extended release formulation and immediate release solution of Butorphanol Tartrate were evaluated for pharmacokinetic studies in rat for 48 hrs after oral administration. The results of pharmacokinetic for formulations are tabulated.

The extended release 510 mcg formulation and immediate release solution 170 mcg triplicate at of 0 hr, 9 hr and 17 Hr administration of Butorphanol Tartrate were evaluated for similarity in pharmacokinetic studies in rat for 48 hrs after oral administration. The results of pharmacokinetic for formulations are tabulated.

Subject No	Test			Referance		
	(C_{max})	(AUC_{inf})	(AUC)	(C_{max})	(AUC_{inf})	(AUC)
1	1.81	30.12	29.12	1.56	31.32	31.32
2	1.67	28.72	28.72	1.67	32.56	32.3
3	1.73	28.52	28.32	1.52	31.92	31.92
4	1.68	30.19	30.05	1.63	30.87	30.87
5	1.67	29.22	29.52	1.43	31.39	31.3
6	1.71	28.62	28.02	1.69	32.98	32.08
7	1.69	27.42	27.6	1.54	31.99	31.79
8	1.64	29.23	29.03	1.65	31.02	31.02
9	1.63	27.39	28.94	1.52	30.9	30.9
10	1.79	28.21	27.14	1.79	31.32	31.32
11	1.64	27.03	28.43	1.5	31.42	31.42
12	1.63	30.12	29.12	1.54	31.64	31.64
N	12	12	12	12	12	12
Mean	1.69	28.73	28.67	1.59	31.61	31.49
SD	0.060	1.096	0.816	0.100	0.652	0.463
CV %	3.54	3.81	2.85	6.33	2.06	1.47
Geo. Mean	1.690	28.713	28.657	1.584	31.605	31.487

Table 4 - 8 Individual Cmax, AUC and AUC inf data for Test and reference formulation of Butorphanol tartrate

Individual C_{max}, AUC and AUC $_{inf}$ data for Test and reference formulation of Butorphanol tartrateare tabulated in table 4 – 8.

	Ratio (% Ref)	CI 90 Lower	CI 90 Higher
C_{max}	1.07	1.03	1.10
AUC	0.91	0.89	0.93
AUC_{Inf}	0.91	0.89	0.93

Table 5 - 8 Summary of Pharmacokinetic Parameters for butorphanol tartrate

Pharmacokinetic Parameter	BT (XR Formulation)	(Solution)
T_{max} (hr)	12	21
C_{max} (ng/ml)	1.69	1.59
$AUC_{(0\rightarrow t)}$ ng/ml*h	28.67	31.49
$AUC_{(0\rightarrow \infty)}$ ng/ml*h	28.73	31.61
$T_{1/2}$ (hrs)	4.62	4.23

Table 6 - 8 Pharmacokinetic parameters of Butorphanol tartrate formulations

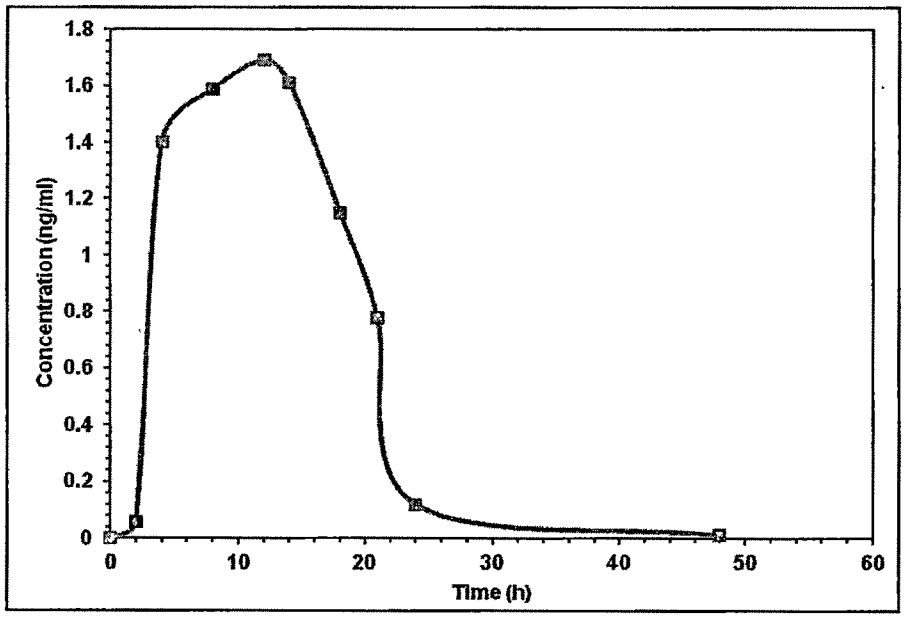

Figure 1 - 8 Plasma Concentration vs Time profile for Butorphanol Tartrate Extended release formulation

Figure 1-8 shows Plasma Concentration vs Time profile for Butorphanol Tartrate Extended release formulation. Figure 2 - 8 shows Plasma Concentration vs Time profile on log normal scale for Butorphanol Tartrate Extended release formulation

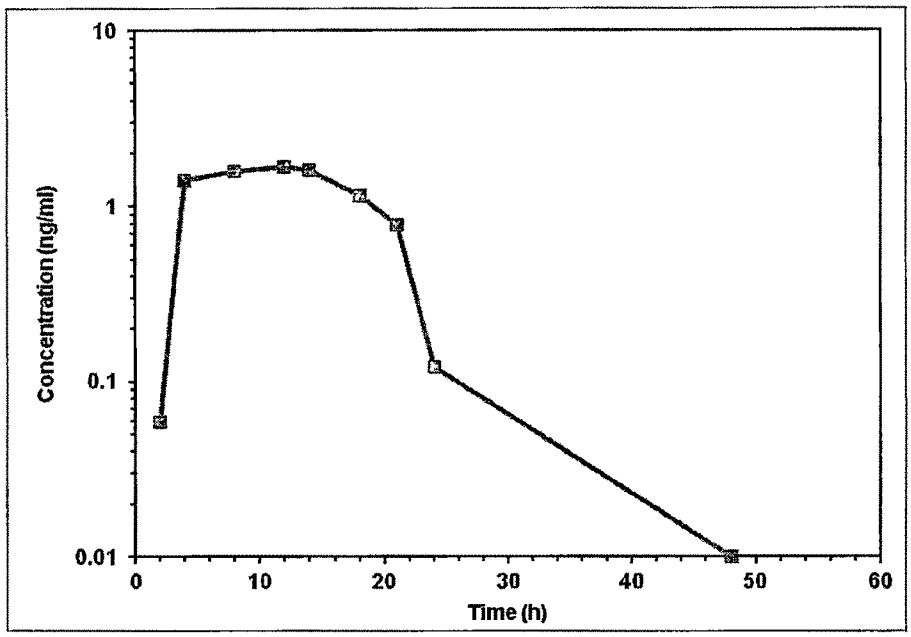

Figure 2 - 8 Plasma Concentration vs Time profile on log normal scale for Butorphanol Tartrate Extended release formulation

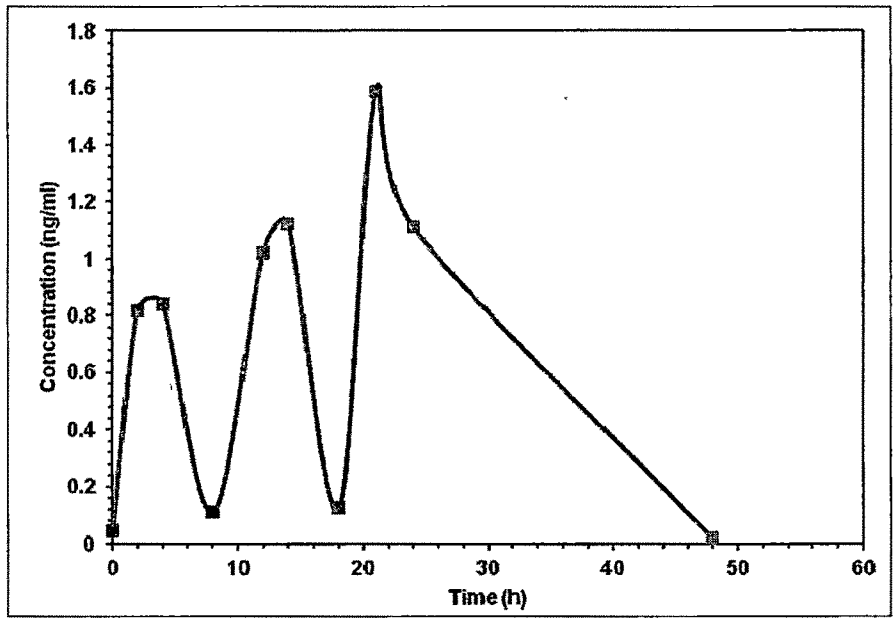

Figure 3 - 8 Plasma Concentration vs Time profile for Butorphanol Tartrate Immediate release solution formulation

Figure 3 - 8 shows plasma Concentration vs Time profile for Butorphanol Tartrate Immediate release solution formulation, Figure 4 - 8 Plasma Concentration vs Time profile log normal scale for Butorphanol Tartrate Immediate release solution formulation

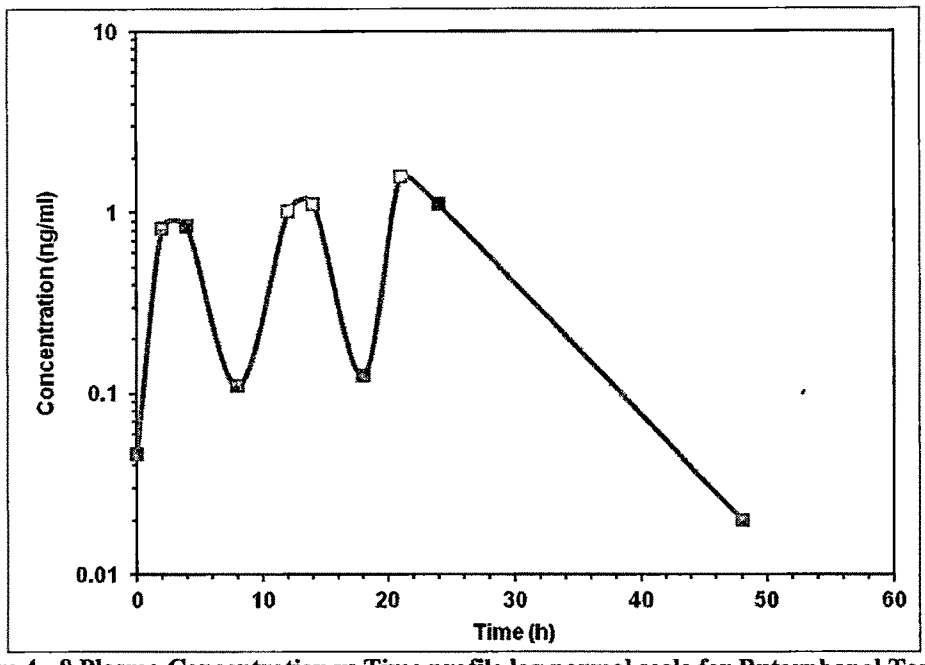

Figure 4 - 8 Plasma Concentration vs Time profile log normal scale for Butorphanol Tartrate Immediate release solution formulation

Constant blood level of Butorphanol tartrate was observed following administration of extended release formulation 510 mcg formulation and typical saw tooth pattern was observed following immediate release solution 170 mcg triplicate at of 0 hr, 9 hr and 17 Hr administration of Butorphanol Tartrate indicative of maintaining the therapeutic concentration after oral administration.

8.6 LORNOXICAM

8.7 Methods

8.7.1 Animals

All animal experiments conducted were approved by the Social Justice and Empowerment Committee for the purpose of control and supervision on animals and experiments, Ministry of Government of India. Wistar rat weighing between **250-300 gm** were selected for PK studies.

8.7.2 Dosing Procedure

Mini Tabs were dosed intact to the rat by the following procedure. Rat were partially anesthetised using chloroform. Rat were restrained by grasping the scruff of the neck with one hand and the rear with the other hand. Rat's tail was wraped around small finger to secure the lower portion of the rat. The minitab was placed in the center of the mouth using the holder follow the roof of the mouth to the opening of the esophagus. The rat's head was tilted back with the shaft of the sample holder. This straightens the esophagus and makes insertion of the makes the insertion of easier. After dosing, rat were dose with a few ml of water as this further facilitate movement of the minitab into the stomach.

8.7.3 Blood Sampling Procedure

Collection Site: **Tail Vein**

The acceptable quantity and frequency of blood sampling was determined by the circulating blood volume and the red blood cell (RBC) turnover rate. Excessive blood collection may result in hypovolemic shock, physiological stress and even death of the animal.

Because it was necessary to take multiple samples, smaller blood volumes i.e. 300 µl were drawn 5 time. Without fluid replacement, the maximum blood volume which can be safely removed for a one time sample is 10% of the total blood volume or 5.5-7 ml/kg. For a 300 g

rat, this was equivalent to 1.7-2.1 ml. For a 300 g rat if subcutaneous fluid replacement is done then collection volume can be increased equivalent to 2.5-3.2 ml.

Animal recovery : If sampling done every 2 weeks, up to 10% of the total blood volume may be drawn or 5.5-7 ml/kg (4). For a 300 g rat, this is equivalent to about 1.7-2.1 ml every 2 weeks.

Rat Body weight (g)	**Circulating Blood Volume (ml) (CBV)**	**10% CBV (ml) every 2 wks†**
250	13.75 – 17.50	1.4 – 1.8
300	16.50 – 21.00	1.7 – 2.1

Table 7- 8 approximate Blood sample volumes for rat body weight

Table 7 -8 shows approximate Blood Sample Volumes that for normal rat with normal body weights

8.7.4 Sampling Procedure:

- Tail vain sampling is recommended for collecting a large volume of blood sample (up to 2ml /withdrawal)
- Animal was restrained.
- The tail was not rubbed from the base to the tip as it may result in leukocytosis. If the vein was not visible, the tail is dipped into warm water (40°C).
- Local aesthetic cream was applied on the surface of the tail 30 min before the experiment.
- A 23G needle inserted into the blood vessel and blood is collected using a a syringe with a needle. In case of difficulties, 0.5 to 1 cm of surface of the skin is cut open and blood is collected with a syringe with a needle.
- Having completed blood collection, silver nitrate ointment was applied to stop the bleeding.
- Each sample was immediately placed in potassium EDTA and refrigerated.
- Plasma Sample obtained by centrifugation of blood samples.
- Blood sample were frozen 20 °C until analysed.

8.8 Study Design

Two treatment, four Period, cross-over bioavailability study design under fasting condition. Design as mentioned in table 8-8. Blood sample were collected at 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing after giving 20 day washout same rats were dosed again and blood samples were collected at 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing. Same procedure was followed for BT extended release formulation and BT solution. And LOR extended release formulation and LOR IR formulation.

Blood Sampling Time Points After 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing		**Blood Sampling Time Points After 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing**	
Cohort I	**Cohort II**	**Cohort I**	**Cohort II**
Rat 1 – T	Rat 7 – R	Rat 1 – T	Rat 7 – R
Rat 2 – T	Rat 8 – R	Rat 2 – T	Rat 8 – R
Rat 3 – T	Rat 9 – R	Rat 3 – T	Rat 9 – R
Rat 4 – T	Rat 10 – R	Rat 4 – T	Rat 10 – R
Rat 5 – T	Rat 11 – R	Rat 5 – T	Rat 11 – R
Rat 6 – T	Rat 12 – R	Rat 6 – T	Rat 12 – R
Blood Sampling Time Points After 0Hr, 2Hr, 4Hr, 8Hr, 12 Hr after dosing		**Blood Sampling Time Points After 14Hr, 18Hr, 21Hr, 24Hr, 48 Hr after dosing**	
Cohort I	**Cohort II**	**Cohort I**	**Cohort II**
Rat 1 – R	Rat 7 – T	Rat 1 – R	Rat 7 – T
Rat 2 – R	Rat 8 – T	Rat 2 – R	Rat 8 – T
Rat 3 – R	Rat 9 – T	Rat 3 – R	Rat 9 – T
Rat 4 – R	Rat 10 – T	Rat 4 – R	Rat 10 – T
Rat 5 – R	Rat 11 – T	Rat 5 – R	Rat 11 – T
Rat 6 – R	Rat 12 – T	Rat 6 – R	Rat 12 – T

Table 8 - 8 Study design for lornoxicam formulation

8.9 Statistical Analysis

All data are reported as mean ± SD (standard deviation) and the difference between the groups were tested using Student's t-test at the level of $P<0.05$. Non-Compartmental analysis of plasma data after extravascular input was evaluated using PK Solver Software Ver. 2.0 with Linear Trapezoidal method. The pharmacokinetic parameter of Lornoxicam in rat after oral administration of ER formulation were recorded and compared with that of the pharmacokinetic parameter after administration of Lornoxicam Immediate Release formulation.

8.10 Preparation of Equivalent formulation for Rat Model

Rat LD 50 of Butorphanol Tartrate is 315 mg/kg dose proportional

Extended release formulation	**Quantity (mg/tablet)**	**Quantity (% W/W)**
Lornoxicam	1.14	8.89
HPMC K100M CR	0.61	4.72
HPMC K100LV	0.61	4.72
PVP k 30	0.36	2.78
Lactose Monohydrate	3.88	30.14
Micro crystalline Cellulose	3.88	30.14
Meglumin	1.82	14.17
NaOH	0.21	1.67
Mg. Stearate	0.14	1.11
Purified Talc	0.14	1.11
Aerosil 200	0.07	0.56
	12.86	100

Table 9 -8 Lornoxicam formulation for In-vivo studies.

Immediate Release formulation of lornoxicam	**Quantity (mg/tablet)**	**Quantity(% W/W)**
Lornoxicam	0.57	4.38
Micro crystalline Cellulose	12.08	92.92

Mg. Stearate	0.14	1.08
Purified Talc	0.14	1.08
Aerosil 200	0.07	0.54
	13	100

Table 10 - 8 Lornoxicam IR formulation for In-vivo studies

Tablet 9-8 and 10-8 respectively show XR and IR formulation of lornoxicam for In-vivo studies.

Specifications of Core Tablet

Diameter : 3 mm

Thickness : **1.9 mm**

Dissolution :

Volume: 250 ml

Dissolution medium: SIF

Time (hr)	PBS 4.5
0	0.00
1	11.27
2	28.40
4	47.21
6	61.75
8	75.18
12	92.85
14	98.48
16	101.59

Table 11 - 8 Release profile of XR formulation for in-vivo studies.

Comparison of Extended release Lornoxicam rat and Human formulation:

Similarity Factor	F2	84.01

Similarity Factor: As the name specifies, it stresses on the comparison of closeness of two comparative formulations.

$f2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$

8.11 Pharmacokinetic Studies of Lornoxicam formulation

The extended release formulation and immediate release formulation of lornoxicam were compared & evaluated for pharmacokinetic studies in rat for 48 hrs after oral administration. The results of pharmacokinetic for formulations are tabulated.

The extended release 1.14 mg formulation and immediate release formulation 570 mcg duplicate at of 0 hr and 11 Hr administration of Lornoxicam were evaluated for similarity in pharmacokinetic studies in rat for 48 hrs after oral administration. The results of pharmacokinetic for formulations are tabulated.

Subject No	Test			Reference		
	(C_{max})	(AUC_{inf})	(AUC)	(C_{max})	(AUC_{inf})	(AUC)
1	513	7554	7023	570	7819	7539
2	465	7845	7836	583	7987	7877
3	475	7577	7309	594	7645	7613
4	456	7534	7535	538	7874	7873
5	502	7772	7723	561	7834	7834
6	476	7774	7751	579	7802	7712
7	487	7128	7034	593	7696	7396
8	462	7364	7390	556	7459	7459
9	493	7391	7356	586	7813	7813
10	461	7688	7369	553	7535	7535
11	472	7428	7123	579	7758	7648
12	498	7804	7783	548	7884	7834
N	12	12	12	12	12	12
Mean	480.00	7571.58	7436.00	570.00	7758.83	7677.75
SD	18.355	217.067	290.936	18.503	151.347	170.042
CV %	3.82	2.87	3.91	3.25	1.95	2.21
Geo. Mean	479.681	7568.703	7430.775	569.723	7757.469	7676.017

Table 12 - 8 Individual Cmax, AUC and AUC inf data for Test and reference formulation of Lornoxicam

Table 12-8 shows Individual C_{max}, AUC and AUC $_{inf}$ data for Test and referene Lornoxicam formulation

	Ratio (% Ref)	CI 90 Lower	CI 90 Higher
C_{max}	0.84	0.82	0.86
AUC	0.97	0.95	0.98
AUC $_{Inf}$	0.98	0.96	0.99

Table 13 - 8 Summary of Pharmacokinetic Parameters

Table 13-8 ND 14- 8 shows Summary of Pharmacokinetic Parameters obtained for lornoxicam after administration in rat model.

Pharmacokinetic Parameter	**LOR (XR Formulation)**	**LOR (IR Formulation)**
T_{max} (hr)	08	14
C_{max} (ng/ml)	480	570
$AUC_{(0\rightarrow t)}$ ng/ml*h	7436	7677
$AUC_{(0\rightarrow \infty)}$ ng/ml*h	7571	7758
$T_{1/2}$ (hrs)	7.22	6.24

Table 14 - 8 Summary of Pharmacokinetic Parameters

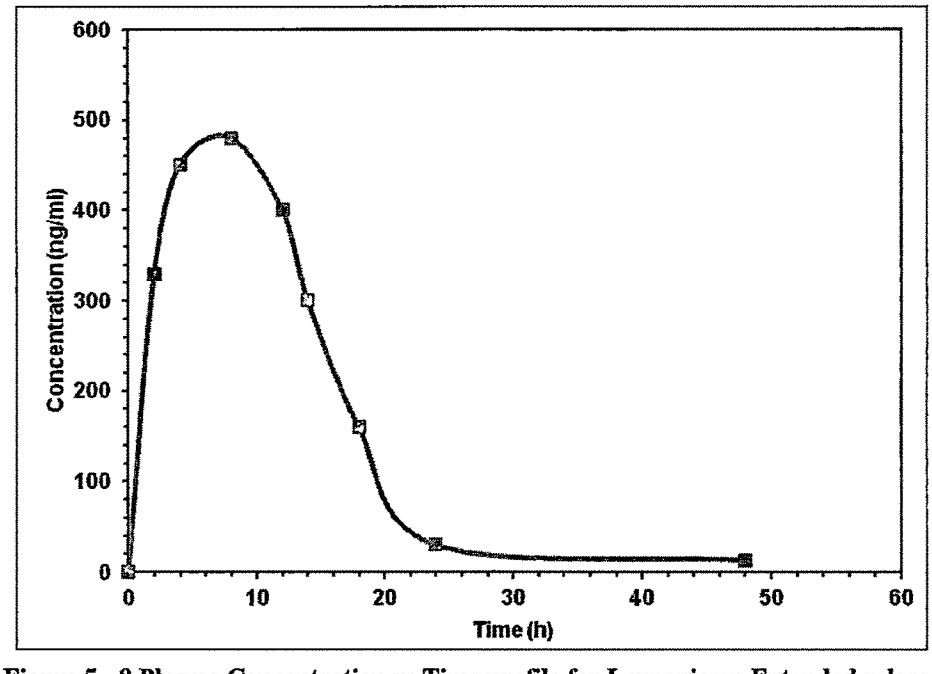

Figure 5 - 8 Plasma Concentration vs Time profile for Lornoxicam Extended release formulation

Figure 5 - 8 shows plasma Concentration vs Time profile for Lornoxicam Extended release formulation

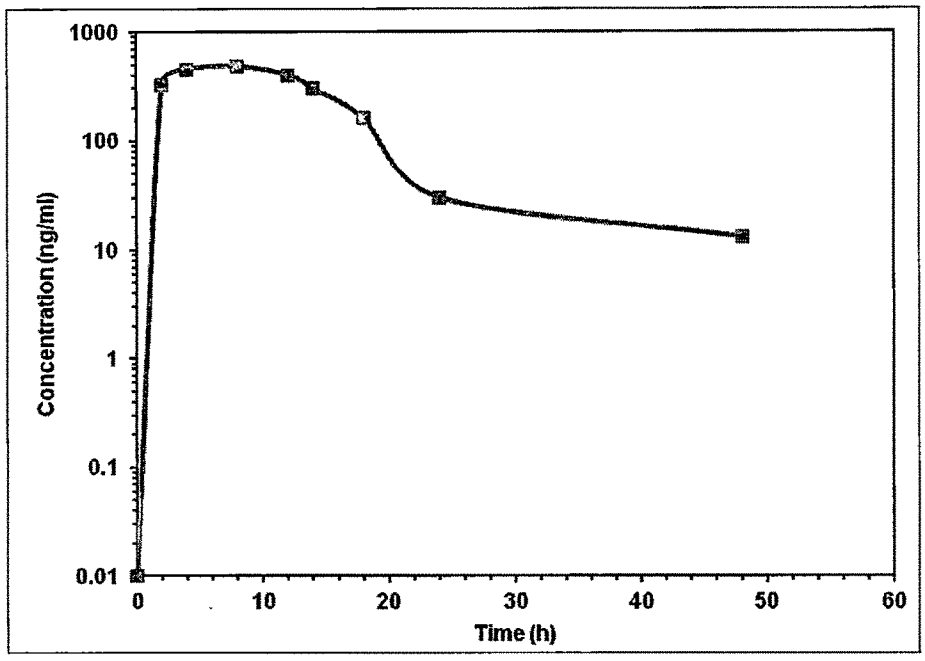

Figure 3 - 8 Plasma Concentration vs Time profile on log normal scale for Lornoxicam Extended release formulation

Figure 4 - 8 shows plasma Concentration vs Time profile on log normal scale for Lornoxicam Extended release formulation

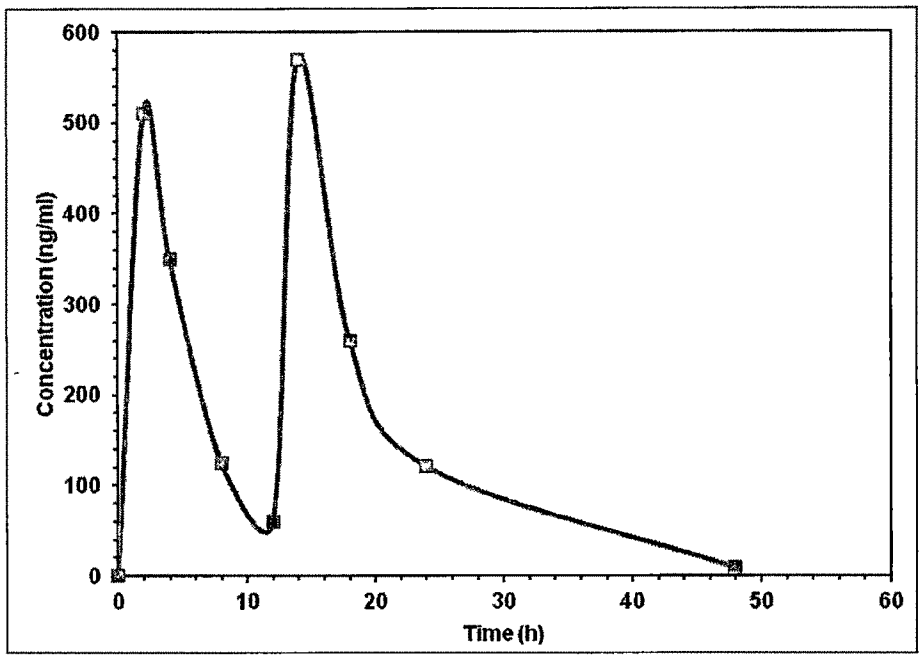

Figure 75 - 8 Plasma Concentration vs Time profile for Lornoxicam Immediate release solution formulation

Figure 7 - 8 shows plasma Concentration vs Time profile for Lornoxicam Immediate release solution formulation.

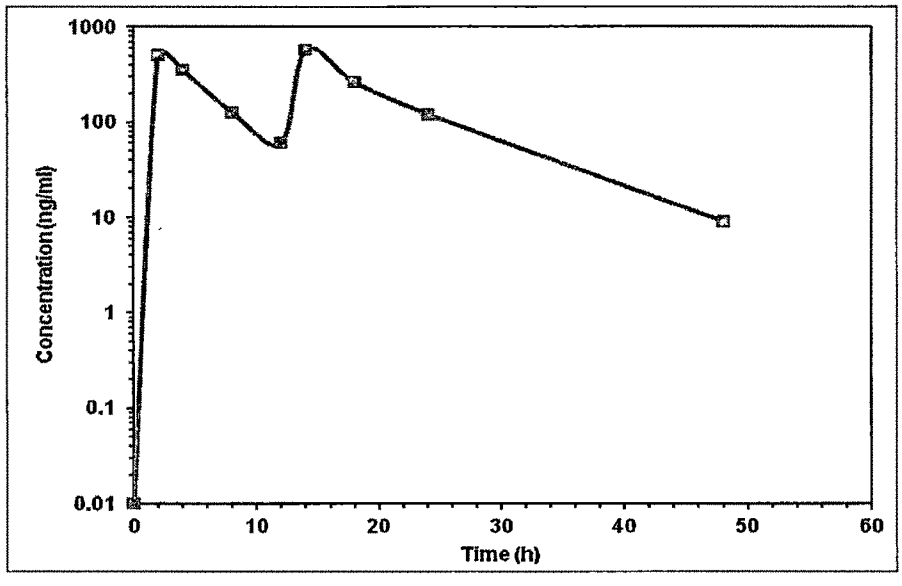

Figure 8 - 8 Plasma Concentration vs Time profile log normal scale for Lornoxicam Immediate release solution formulation

Figure 8 - 8Plasma Concentration vs Time profile log normal scale for Lornoxicam Immediate release solution formulation

8.12 Conclusions

To conclude, equivalent pharmacokinetic parameters of butorphanol tartrate observed following administration of extended release formulation 510 mcg formulations compared to immediate release 170 mcg triplicates. Additionally typical saw tooth pattern observed following immediate release 170 mcg triplicate at of 0 hr, 9 hr and 17 Hr administration of Butorphanol Tartrate.

Equivalent pharmacokinetic parameters of Lornoxicam observed following administration of extended release formulation 1.14 mg formulation compared to immediate release 570 mcg duplicate. Additionally typical saw tooth pattern observed following immediate release 570 mcg duplicate at of 0 hr and 10 Hr administration of Lornoxicam.

Extended released formulations of Butorphanol tartrate and Lornoxicam and are bio-available as compared to the immediate release dosage form. The ratios of AUC0-t, C_{max}, and $AUC0-_{inf}$ from Extended release formulation to Immediate release formulation both the drug at 90 % confidence interval fall within 80-125.

8.13 References

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