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Formulation Development of Lornoxicam Drug Implant

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ABSTRACT

The implants, which are to be implanted under the skin (usually of the thigh or abdomen) with a special injector or by surgical incisions. Implants, are considered as a useful drug delivery system especially in chronic disorders. Literature survey revealed that numerous studies have been conducted on subcutaneous Implants to investigate use of different polymers for controlling the drug release for prolonged therapy, the pharmacokinetics and pharmacodyanamics of subcutaneous Implants, the safety of the polymers. In this investigation, it was planned to prepare implants of Lornoxicam, the NSAID by using gelatin as polymer and glycerin as a plasticizer, under aseptic conditions. The implants weighing 10 mg were hardened with Formaldehyde. The formulated implants were evaluated for thickness, wt variation, drug content uniformity, free Formaldehyde, drug polymer interaction and sterility. In vitro drug release studies were conducted in phosphate buffer pH 7.4. The stability studies were carried out at ambient temperature for 3 months.

Keywords: Lornoxicam, gelatin, subcutaneous implants.

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INTRODUCTION

Implants are sterile, small, usually cylindrical shaped solid objects intended to be implanted subcutaneously for the purpose of providing the continuous release of medicaments over a prolonged period of time. The pellets, which are to be implanted under the skin (usually of the thigh or abdomen) with a special injector or by surgical incisions. The implantation provides the patient with an economical means of obtaining long-lasting effects of drugs (up to many months after a single implantation) and obviates the need for frequent parental or oral hormonal therapy. The implanted pellets, which might contain 100 times the amount of drug (e.g, deoxycorticosterone, estradiol, testosterone) given by other routes of administration, to release slowly into the general circulation. Pellets were formulated without any binders, diluents, to permit total dissolution and absorption of the pellet from the site of implantation[1]. The concept of implantable therapeutic systems for long-term, continuous drug administration with the development of a subcutaneously implantable drug pellet. The technique was then rediscovered in 1936 by Densely and Parkes[2] who administrated crystalline hormones in the form of solid steroid pellets to mimic the steady, continuous secretion of hormones from an active gland for hormone substitution therapy[3]. The subcutaneous release rate of steroids from the pellets implantation was found to be slowed and hormonal activities were prolonged by dispersing the steroids in cholesterol matrix during pellet fabrication[4] unfortunately, it was observed that the subcutaneous absorption of steroids from the cholesterol pellets varies greatly from one condition to another. The subcutaneous drug administration by pellet implantation method was then subjected to modification by several investigators[5, 6]. Radholfer-Welte S,(2000.) [7]studied that Lornoxicam has been shown to be at least as effective as comparative NSAIDs and more effective than 10 mg morphine when used at low dose 8 mg to control pain after oral surgery. In addition, oral doses of lornoxicam of 16-24 mg daily have been more effective than tramadol 300 mg daily in pain following knee surgery. The clinical trials published so far, mostly comparative, clearly do- cument the efficacy of lornoxicam as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and rheumatoid arthritis.

MATERIALS AND METHOD

Lornoxicam was obtained as a gift sample from Gift sample from Mark Drugs Ltd., Kompally, Hyderabad. Gelatin was purchased from S.D. Fine Chemicals Ltd; Mumbai. Glycerin and Formaldehyde were purchased from Ranbaxy Laboratories Ltd. Punjab. Formaldehyde was

purchased from Loba Chemicals Mumbai. All other chemicals used were of analytical grade.

Preparation of Implants[8]

Gelatin implantable discs containing Lornoxicam were prepared under aseptic conditions. Three formulations with different grades of gelatin are prepared. Weighed quantity of gelatin i.e. Grade –I, II, and Grade –III Were sprinkled on the surface of the water and stirred well to avoid formation of lumps and allowed to hydrate for 30 minutes. Glycerin (10% as a plasticizer, was added to each formulation. It was heated on a water bath at 60^0c with continuous stirring until gelatin was dissolved in water completely. Weighed quantity of Lornoxicam for each formula was taken and dissolved separately in a small quantity of Methanol and this solution was mixed with the above all three formulations FI, F2, & F3 respectively. This solution was poured in to a glass Petri dish to a 3 mm height and allowed to gel for 30 minutes by placing the glass moulds on ice and then dried at room temperature for 48 hours. After drying, the Implants were cut into spherical discs of 6 mm size by specially designed stainless steel cutter.

Hardening of Implants[9]

Formaldehyde solution (37% v/v) was transferred in a Petri dish and placed in an empty glass dessicator. A wire mesh containing the implantable discs was kept on the top of the Petri dish and immediately the dessicator was closed. The discs were made to react with Formaldehyde vapors for different time intervals i.e. 1, 3, 6, 12, 24 and 48 hours. Then they were removed and air-dried for 72 hours so that the reaction between Formaldehyde and gelatin was completed. Afterwards the discs were kept in an open atmosphere in aseptic conditions for a week, to make sure that the residual Formaldehyde gets evaporated.

Evaluation

Procedure for drug content uniformity test[10]

Drug content of Implants from every batch was estimated. From each batch of Implants, 3 samples of 6 mm in size and 3 mm thick were taken and analyzed for Lornoxicam. The implant was cut in to small pieces and were taken in 25 ml volumetric flask and methanol was added and heated at 60^0 C to dissolve the drug after cooling the

Method for measurement of Implants thickness and weight variation

Thickness measurement of Implants[10]

The thickness of Implants from every batch were measured with the help of screw gauge and were subjected to the previously mentioned statistical analysis, 3 samples were taken for study from each batch.

Weight Variation[11]

Samples of Implants from each batch (n=3) were taken and weighed individually. The average weight and % deviation was calculated.

Tests for sterility[12]

The sterility test was conducted by membrane filtration method on soyaben- casein digest medium and found to be Implants are sterile. The tests for sterility are intended for detecting the presence of viable forms of micro-organisms in or on pharmacopoeial preparations. The tests must be carried out under conditions designed to avoid accidental contamination of the product during the test. Precautions taken for this purpose should not adversely affect any micro-organisms which should be revealed in the test. The working conditions in which the tests are performed should be monitored regularly by sampling the air and surfaces of the working area and by carrying out control tests. The tests are based upon the principle that if micro-organisms are placed in a medium which provides nutritive material and water, and kept at a favorable temperature, the organisms will grow and their presence can be indicated by a turbidity in the originally clear medium.

Soyabean-casein digest medium

Pancreatic digest of casein	17.0 g
Peptic digest of soybean meal	3.0 g
Sodium chloride	5.0 g
Dibasic potassium phosphate (K_2HPO_4)	2.5 g
Dextrose ($C_6H_{12}O_6,H_2O$)	2.5 g
Distilled water to	1000 ml

Dissolve the solids in distilled water, warming slightly to effect solution. Cool to room temperature and add, if necessary, sufficient 0.1M sodium hydroxide to give a final pH of 7.1±0.2 after sterilization. Filter, if necessary, distribute into suitable containers and sterilize in an autoclave at 121^0C for 20 minutes.

Membrane Filtration

Apparatus

A suitable unit consists of a closed reservoir and a receptacle between which a properly supported membrane of appropriate porosity is placed. A membrane generally suitable for sterility testing has a normal pore size not greater than 0.45 μm and diameter of approximately 47mm, the effectiveness of which in retaining micro-organisms has been established. Preferably assemble and sterilize the entire unit with the membrane in place prior to use. Where the sample

to be tested is oil, sterilize the membrane separately and, after thorough drying, assemble the unit, using aseptic precautions.

Diluting Fluids

Dissolve 1 gm of peptic digest of animal tissue (such as bacteriological peptone) or its equivalent in water to make 1 liter, filter or centrifuge to clarify, adjust to pH 7.1 ± 0.2, dispense into flasks in 100-ml quantities and sterilize at 121^{0}C for 20 minutes.

Method of Test

For aqueous solutions: prepare each membrane by aseptically transferring a small quantity (sufficient to moisten the membrane) of fluid on to the membrane and filtering it. For each medium to be used, transfer aseptically into two separate membrane filter funnels or to separate sterile pooling vessels prior to transfer not less than the quantity of the preparation being examined that is prescribed in Table. Alternatively, transfer aseptically the combined quantities of the preparation being examined prescribed in the two media onto one membrane. Draw the liquid rapidly through the filter with the aid of vacuum. If the solution being examined has antimicrobial properties, wash the membrane(s) by filtering through it (them) not less than three successive quantities, each of approximately 100ml quantity, of sterile fluid. The quantities of fluid used should be sufficient to allow growth of a small innoculum of organisms (approximately 50) sensitive to the antimicrobial substance in the presence of the residual inhibitory material on the membrane. After filtration, aseptically remove the membrane (s) from the holder, cut the membrane in half, if only one is used, immerse the membrane, or one-half of the membrane, in 100 ml of soyabean-casein digest medium and incubate at 20^{0}C to 25^{0}C for not less than 7 days.

Quantity in each container of injectable preparation	Minimum quantity to be used for each culture medium
For Solids	
Less than 50 mg	Total contents of a container
50 mg or more but less than 200 mg	Half the contents of a container
200 mg or more	100 mg

Analytical instrument and method

For determination of drug content uniformity, the Implants were analyzed by using UV spectrophotometer 1700 Shimadzu at wavelength of 260 nm. The drug content was determined with the help of previously established standard curve.

Qualitative test for free Formaldehyde[13]

Formaldehyde was used to harden the Implants. Since formaldehyde is toxic in nature, it was important to ensure that the Implants did not contain any residual formaldehyde. To ascertain the absence of free formaldehyde, the Implants were subjected to pharmacopoeial test for free formaldehyde. Any color change was observed. The result for free formaldehyde with polymer is the bright yellow colored solution is the Standard Formaldehyde solution. The Implants, after being subjected to the pharmacopoeial test for free formaldehyde, were observed for color changes against the standard solution. The intense the yellow color of the solution of the samples, the greater the amount of free formaldehyde. The figure reflects that the color of the sample solutions were colorless. This indicates that these Implants did not retain any free formaldehyde.

Drug polymers interaction study[14]

The IR spectra of lornoxicam prepared with gelatin hardened with formaldehyde for 12Hrs.(F3FH-12Hrs)were obtained using FTIR series model SN/LE-735/00735spectrometer. The Sub dermal Implants of Lornoxicam prepared with Gelatin hardened with Formaldehyde were tested for compatibility of the drug with the excipients like, Gelatin, Glycerin hardening agents by I.R. Study. The I.R. Spectrum of the pure drug and the formulated discs are shown in the figure.

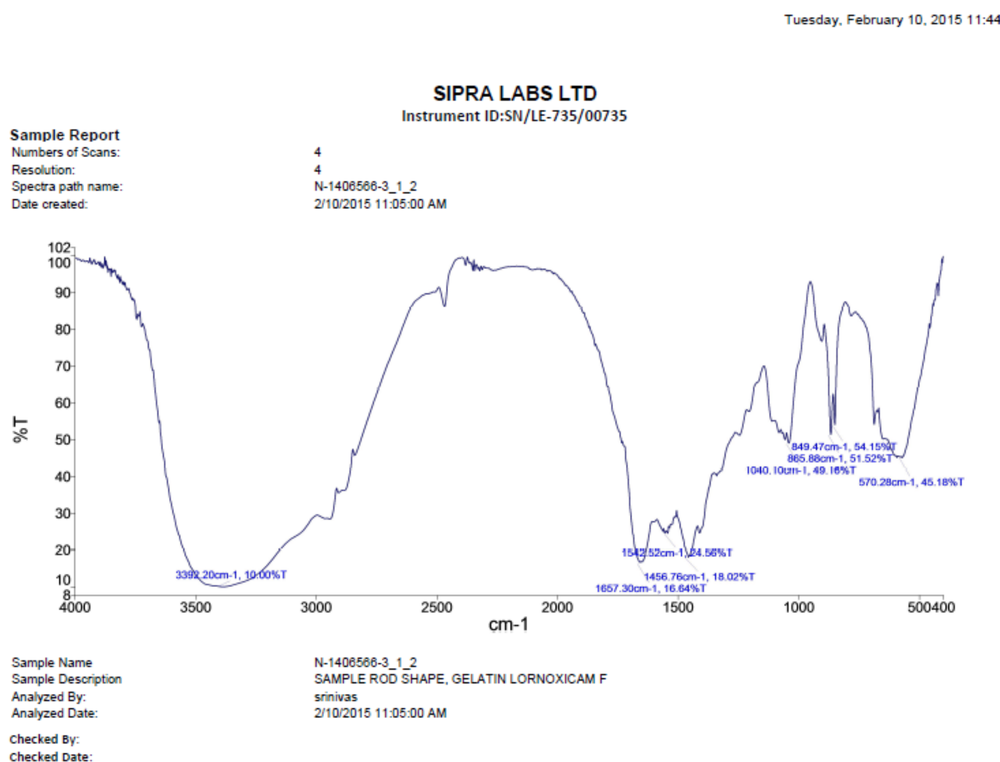
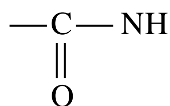


Figure:1 The IR spectra of Lornoxicam and its formulations

Implants hardened with formaldehyde

Broad peak at **3392.20** cm^{-1} is due to O–H stretching and peak at **1657.730**cm^{-1} and **1542..52** $\mathbf{cm^{-1}}$ are due to structure-1 functional group confirm the undisturbed drug in formulation.



Structure -1

The I.R. Spectrum of Lornoxicam with excipients Gelatin is similar to that spectra of pure drug (Lornoxicam). All the characteristics bands of drug are retained in the I.R. spectra gelatin formulation indicating that the drug has not reacted with the excipients present in it. Hence, from the I.R study it is confirmed that there is no interaction between the drug and excipients used.

Stability studies: (Effect of Temperature)[15]

The stability of the discs was studied at ambient temperature. The discs of size (6 mm) were weighed in a six sets (8 discs in each set). The discs were wrapped individually in butter paper and placed in Petri dishes. These dishes were stored at ambient temperature for a period of three month. The sample was analyzed for physical change like colors, texture and the drug content was determined at an interval of fifteen days.

Procedure for in-vitro drug release study[16, 17, 18]

Static dissolution studies

Implants were placed separately into a 10 ml vials containing 10 ml of phosphate buffer pH 7.4. The vials were sealed with rubber stoppers and kept in incubator thermostated at 37^0C $\pm 5^0$C. The dissolution fluid was changed for given time intervals and replaced with fresh 10 ml phosphate buffer pH 7.4. The drug concentration in every dissolution fluid was analyzed spectrophotometrically at 261 nm after suitable dilution with phosphate buffer pH 7.4

RESULTS AND DISCUSSION

The results indicated that all the prepared discs of three formulations were uniform in the shape i.e. circular and uniform in diameter i.e. 6 mm (Table 1)

Table 1: Formulae of Implants.

Ingredients	Formulations		
	F_1	F_2	F_3
Lornoxicam	1 gm	1 gm	1 gm
Gelatin	20 gm	20gm	20 gm
Glycerin	2ml	2.5 ml	5 ml
Water QS	100 ml	100ml	100 ml

F1 - Gelatin Grade-I

F_2 - Gelatin Grade-II

F_3 - Gelatin Grade-III

Figure 2: Pellets hardened with formaldehyde

The thickness measurement studies were conducted on plain discs i.e. without hardening and hardened with formaldehyde Implants. The results indicated that exposure to the hardening agent did not produce an appreciable shrinkage in the Implants. The results of weight uniformity test indicated that the wt of plain Implants and hardened Implants did not show appreciable variation in the weight of Implants. The drug content uniformity results revealed that there was no appreciable variation in drug present in each implantable disc and found to be uniform in all Lornoxicam Implants. (Table 2)

Table 2: Evaluation of drug implants

Formula	Thickness in mm			Weight of the discs in (mg)			Drug content in (mg)		
	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
F1	3.01	0.0014	0.0465	57.14	0.0030	0.0039	10.15	0.002	0.020
F2	2.99	0.0014	0.0468	55.61	0.0009	0.0012	10.20	0.001	0.009
F3	3.08	0.0004	0.0140	57.10	0.0026	0.0033	9.74	0.010	0.100
F3FH 1Hr.	3.03	0.0006	0.0208	53.13	0.0021	0.0016	9.73	0.001	0.010
F3FH 3 Hrs	2.99	0.0026	0.0650	52.17	0.0011	0.0013	10.15	0.002	0.020
F3FH 6 Hrs	3.04	0.0041	0.1359	54.18	0.0022	0.0028	10.15	0.002	0.020
F3FH 12 Hrs	2.98	0.0017	0.0581	58.19	0.0039	0.0039	9.98	0.013	0.014
F3FH 24 Hrs	3.03	0.0028	0.0924	56.14	0.0026	0.0036	9.76	0.010	0.017
F3FH 48 Hrs	3.10	0.0010	0.0322	55.19	0.0023	0.0036	10.32	0.036	0.034

*F3FH(Hardened with formaldehyde for different time intervals)

The IR spectral studies depicted three peaks at similar wavelengths in case of pure drug and in implantable discs hardened with Formaldehyde and Formaldehyde, indicating absence of interaction between Lornoxicam and the excipients used. The comparative R_f values of the pure drug Lornoxicam and its two formulations on the chromatogram indicated that there was no interaction between drug and the carriers in implantable discs. At intervals during the incubation period, and at its conclusion, when the media was examined for macroscopic evidence of microbial growth, no evidence of micro-organisms was found. Thus the Implants passed the test for sterility. The *In-vitro* dissolution studies indicated that the drug release was minimum and slow in case of F3, further the Implants from F3 hardened with Formaldehyde for 12 hours showed sustained release of the drug for 144hrs. The mechanism of drug release was found to be diffusion and it followed first order rate kinetics. In addition to diffusion, the gelatin Implants were found to erode slowly giving out the drug. It was also observed that the drug release was sustained as exposure time to the hardening agent increases. Gelatin based implantable discs hardened with Formaldehyde for 12hours was found to be optimum. (Table 3)

Table 3: *In Vitro* release of Lornoxicam in phosphate buffer of pH7.4 from discs prepared

-	**Hardened with formaldehyde for 12 Hrs**		**without hardening**	
Time in Hrs	**Cumulative percent drug released**	**Cumulative percent drug retained**	**Cumulative percent drug released**	**Cumulative percent drug retained**
0	0	0	0	0
12	14.35	85.65	15.66	84.34
24	27.80	72.20	27.00	73.00
36	41.76	58.24	43.56	56.44
48	52.31	47.69	73.00	27.00
72	63.82	36.18	83.52	16.48
96	76.37	23.63	94.00	6.00
120	87.43	12.57	-	-
144	96.12	3.88	-	-

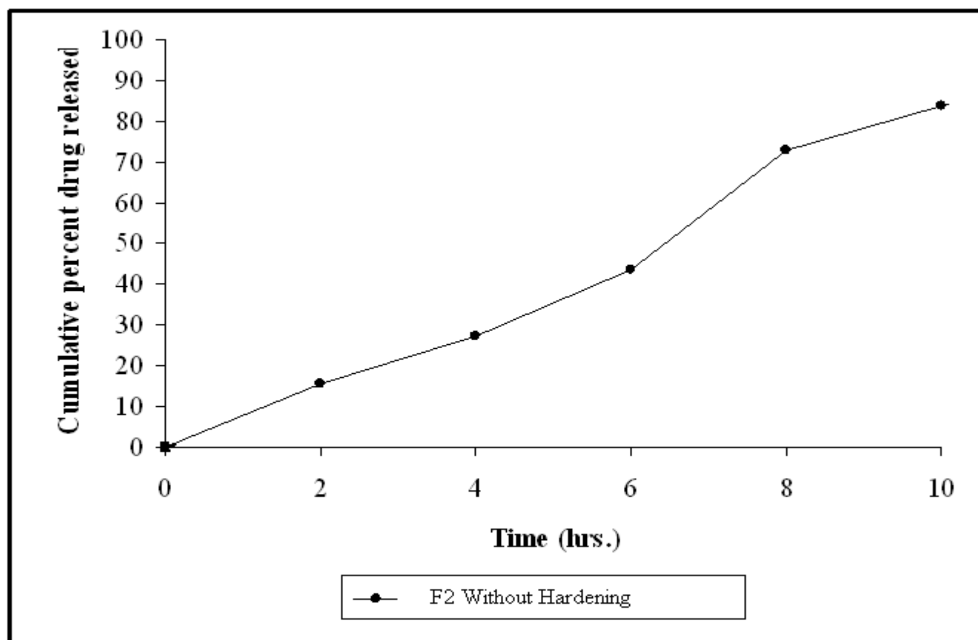


Figure 3: Comparative cumulative percent drug released versus time (zero order kinetic model) plots of Implants prepared using gelatin without hardened

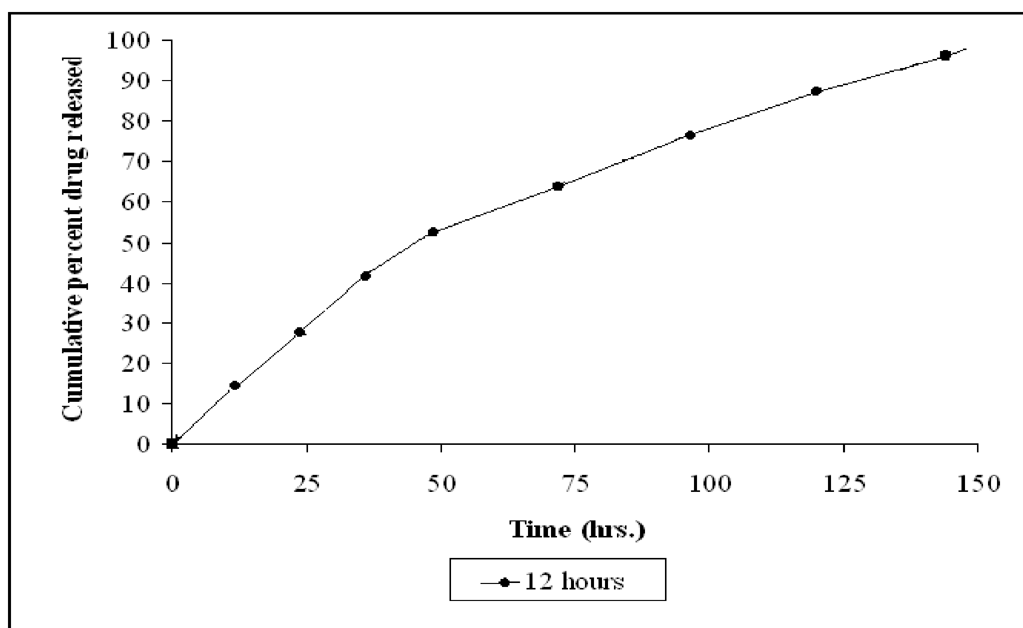


Figure 4: Comparative cumulative percent drug released versus time (zero order kinetic model) plots of Implants prepared using gelatin hardened for 12 hrs

Stability studies of the prepared drug Implants has clearly indicated that even after a period of three months; there was ho change in weight, color, size and drug content of the polymeric discs. It revealed that the prepared Implants were stable at ambient temperatures. (Table .4 and 5)

Table 4: Stability Study of Implants prepared with Gelatin without hardening

Time in Days	Implant without hardened		
	Ambient temperature		
	Concn. of drug remaining in (mg)	Percentage of drug remaining	Log percentage of drug remaining
0	8.88	100.00	2.0000
15	8.87	99.88	1.9994
30	8.82	99.32	1.9970
45	8.78	98.87	1.9950
60	8.74	98.42	1.9930
75	8.72	98.19	1.9920
90	8.70	97.97	1.9910
K= –0.00020 day^{-1}			

Table 5: Stability study of Implants prepared with gelatin and hardened with formaldehyde for 12 hrs.

Time in Days	Implant hardened for 12 hrs. Formaldehyde		
	Ambient temperature		
	Conc. of drug remaining in (mg)	Percentage of drug remaining	Log percentage of drug remaining
0	8.80	100.00	2.0000
15	8.78	99.77	1.9989
30	8.76	99.54	1.9979
45	8.74	99.31	1.9969
60	8.70	98.86	1.9950
75	8.69	98.75	1.9945
90	8.67	98.52	1.9935
K= –0.0002039 day^{-1}			

CONCLUSION

Gelatin based sub dermal Implants containing Lornoxicam can be prepared. The release of drug from the gelatin implantable discs can be modulated by varying the Concentration of the polymer (gelatin), the nature of cross linking /hardening agent and the time of exposure to hardening agent. The prepared sub dermal Implants of Lornoxicam provide sustained release of drug for 144 hrs. Thus they are more useful in pre/post operative Conditions and during the treatment of musculoskeletal disorders where drug action is required for prolonged period.

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