CHAPTER 6

FORMULATION DEVELOPMENT (LORNOXICAM)

6.0 Formulation Development Lornoxicam (LXM):

The main objective of the present work is to develop extended release solid oral formulation of Lornoxicam with sufficient burst release for maintaining therapeutic blood levels of the drug for initial and extended period of time which can reduce dosing frequency and improve patient compliance by minimizing local and systemic adverse effect. Table 1-6 lists the equipment used for development.

Equipments

Sr. No.	Instruments	Make
1.	Compression	8-station compression machine, KMP-8, Cadmach Engg, Ahmedabad, India.
2.	Digital weighing balance	AG-64, Mettler Toledo, Switzerland
3.	Tap density tester	ETD-1020, Electrolab, Mumbai, India.
4.	Hardness tester	6-D, Dr Schleuniger Pharmatron, Manchester, NH, USA
5.	pH meter	Mettler Toledo, Switzerland
6.	Tray dryer	Bombay Eng. Works, Mumbai, India
7.	Friability tester	EF-2, Electrolab, Mumbai, India
8.	Thickness gauge	Digimatic Caliper, Mitutoyo, Japan
9.	Bath sonicator	DTC 503, Ultra Sonics, Vetra, Italy
10.	Stability chamber	Thermolab, Mumbai, India
11.	Differential Scanning Calorimeter (DSC)	Mettler DSC 20, Mettler Toledo, Switzerland
12.	Dissolution apparatus	Electrolab, Mumbai, India
13.	Stability oven	Shree Kailash Industries, Vadodara
14.	HPLC system	LC 20-AT prominence, Shimadzu Corp., Japan
15.	UV-Visible Spectrophotometer	Shimadzu UV-1601, Japan
16.	Nuclepore Polycarbonate membrane 2 µm 25mm	Whatman, USA

Table 1 - 6 Equipment Used

6.1 Drug Substances:

Lornoxicam

The drug substance attribute, affects the drug product development, manufacturing, performance and stability. The following aspects were considered during the product development:

Physiochemical properties of Drug

As physicochemical drug properties plays an important role in the manufacturing of a dosage form and its therapeutic activity, the characterization of the powder properties of Lornoxicam among all the physicochemical properties was found to be important.

Particle size & size distribution of drug substance : Lornoxicam is poorly soluble in water drug (Bramhane D. M., 2011) , particle size can affect the formulation properties and subsequently bioavailability but because the drug is used in soluble form in the formulation it is not critical parameter for this development. Bulk density and tapped density:

Bulk Density: 0.36 gm/ml; Tap Density : 0.48 gm/ml

Partition coefficient: Partition Coefficient of lornoxicam is 1.8 in n-octanol and phosphate buffer (pH 7.4) (Ahmed M. O et al., 2011)

Physical Description

Orange to yellow crystalline powder

Melting Point: 225°C to 230°C (Ahmed M. O et al., 2011).

Solubility

Since lornoxicam is a weak acid (pKa of 4.7), the aqueous solubility of lornoxicam is pH dependent. Increasing pH leads to decrease in the ratio of non-ionized to ionized drug, and in solubility-pH profiles, the solubility of lornoxicam decreases exponentially with the increase of pH from alkaline pH 9.0 to acidic pH 3.0.

Stability

Lornoxicam is very stable compound no individual degradation products were identified during forced degradation studies.

Biopharmaceutical Classification System (BCS) category: BCS has categorized Lornoxicam in Class II, i.e. Low solubility High permeability.

6.2 Pharmacokinetics

Lornoxicam is dissolves slowly, absorbed rapidly and completely from the GIT. C_{max} is within 2 to 2.5 hrs considered as BCS Class II drug. On repeated administration, peak

plasma concentration is increased in dose related manner. No drug accumulation occurs if repeated drug administration. Food related reduction in absorption of the drug is observed. Almost 99% is protein bound exclusively to albumin. No first-pass effect has been observed. Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity. CYP2C9 (CYP450) has been shown to be the primary enzyme responsible for the biotransformation of the lornoxicam to its major metabolite, 5'-hydroxy lornoxicam unlike other oxicams, the plasma half-life of lornoxicam is about 3 to 5 hours.. Approximately 2/3 of drug is eliminated via the liver and 1/3 of drug via the kidneys as inactive substance. It does not undergo enterohepatic recirculation. Glucuroconjugated metabolites are excreted in urine and faeces with a half-life of about 11 hours. It readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies. Lornoxicam synovial fluid: plasma AUC ratio is 0.5, after administration of 4 mg twice daily. (Byrav D S Prasad, 2009)

Absolute oral bioavailability of LOR is more than 90%. Lornoxicam is found in the plasma in hydroxylated and unchanged form. It readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies. In elderly patients the clearance of lornoxicam is reduced by about 30% to 40%; thus the half-life is somewhat higher. Even in the presence of impaired kidney and liver function, no major differences in pharmacokinetics have been observed. On account of its short half-life, no accumulation happens on repeated administration. The maximum plasma concentration of lornoxicam that produce therapeutic analgesic activity is 1μg/ml. After administration of lornoxicam 4 mg tablets to healthy volunteers, mean peak serum concentrations of 300 to 360 ng/mL were reported at 1.6 to 3 hours

Food protracts the average time to maximum concentration and can reduce the area under the curve (AUC) by up to 20% (Ahmed M. O et al., 2011)

The absolute bioavailability of Lornoxicam is 90–100%. No first-pass effect was observed (Pruss T.P.at al, 1999)

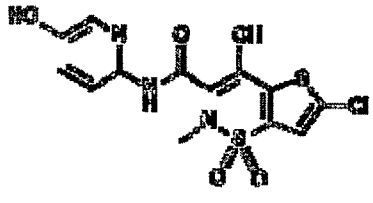


Figure 1 - 6 Lornoxicam Structure

6.3 Pharmacodynamic Properties

Lornoxicam is an active substance from the group of acidic anti-pyretic analgesics. The accumulation of acidic analgesics in the inflamed tissue is considered to be a significant aspect of their anti-inflammatory effect. In cases of painful inflammatory reactions, the capillaries in the inflamed tissue are damaged and plasma proteins along with bound pharmaceutical substances are discharged into the extravascular space. On account of the reduced pH value in inflamed tissue, analgesic acids are able to move from the extracellular space and enter the cells more easily. This also explains why the duration of action of acidic substances is generally longer than one would expect in consideration of their plasma half-life. The inflamed tissue probably behaves like a deep compartment whose filling and depletion adjust to the plasma concentrations with substantial delay.

Mechanism of Action

Lornoxicam is a non steroidal anti-inflammatory drug, analgesic in nature and it fit in to the class of oxicams. Same as that of other NSAIDs, lornoxicam acts by biosynthesis inhibition of prostaglandin through blocking the cyclooxygenase enzyme. Lornoxicam inhibits both COX-1 and COX-2 enzymes. It exerts analgesic action by inhibiting cyclooxygenase, which suppresses the production of thromboxanes & prostaglandins leading to reduction of pain and inflammation. The analgesic activity shows almost equal inhibition of COX- 1 and COX-2 and release endogenous dynorphin and β endorphin with reported central analgesic activity. Unlike some NSAIDs, the inhibition of cyclooxygenase by lornoxicam does not result in an increase in leukotriene formation and not allow unexpected shunting of arachidonic acid to the 5-lipoxygenase cascade, which reduces some potential adverse events, e.g. allergic reactions.

6.4 Excipients:

6.4.1 Excipient used in drug product:

Following table describes the list of excipients. Table 2-6 includes all raw materials used in the manufacture of the drug product, whether they appear in the finished product or not. All excipients used in fabrication of drug product matches with specifications commonly used in design of oral products.

Ingredients	Functional Category	Source
Lornoxicam HCl	Active	Cadila Healthcare Ltd., Moraiya, Gujarat, India
Lactose Monohydrate	Filler	Granulac 200, Meggle.
Microcrystalline cellulose	Filler	Celphere CP-102, AsahiKASEI, Japan
Purified Talc	Antiadherant	Luzenac
Magnesium stearate	Lubricant	Mallinckrodt, USA
Colloidal silicon dioxide	Glidant	Aerosil 200, Degussa, Frankfurt, Germany
HPMC K4M	Matrix forming agent	Methocel K4M, Colorcon Asia Pvt. Ltd, Goa, India
HPMC K15M	Matrix forming agent	Methocel K15M, Colorcon Asia Pvt. Ltd, Goa, India
HPMC K100M	Matrix forming agent	Methocel K100M, Colorcon Asia Pvt. Ltd, Goa, India
HPMC K100LV	Matrix forming agent	Methocel K100LV, Colorcon Asia Pvt. Ltd, Goa, India
Polyvinyl Pyrrolidone	Binder	Kollidon, BASF, Germany
Polyethylene oxide (Polyox WSR Series)	Matrix forming Agent	Polyox WSR N750 and WSR N10, The Dow Chemical Company, MI, USA
Sodium Hydroxide	Buffering agent	S.D. Fine Chemicals Ltd, Mumbai, India
Meglumine	Buffering agent/Stabilizer	S.D. Fine Chemicals Ltd, Mumbai, India
Distilled Water *	Processing solvent	Prepared in laboratory by distillation

Table 2 - 6 List of excipients

*Used as processing agent, does not remain in the final product.

6.4.2 Supplier specifications of the excipients

Microcrystalline cellulose

Specifications	
Loss on drying	% 3.0 - 5.0
Bulk density	0.26 - 0.31 g/cc
Identification	A, B Passes
Degree of polymerization, units	NMT 350
pH	5.5 - 7.0
Conductivity,	NMT 75 µS/cm
Residue on ignition,	% NMT 0.05
Water soluble substances,	mg/5g NMT 12.5
Water soluble substances,	% NMT 0.25
Ether soluble substances,	NMT 5.0 mg/10g
Heavy metals,	NMT 0.001 %
Solubility in Copper Tetrammine Hydroxide	Soluble
Microbial limits:	
Total aerobic microbial count	NMT 100 cfu/g
Total yeast and mold count, cfu/g *	NMT 20 cfu/g
Pseudomonas aeruginosa in a 10g sample	Absent
Escherichia coli in a 10g sample	Absent
Staphylococcus aureus in a 10g sample	Absent
Salmonella species in a 10g sample	Absent
Coliform species in a 10g sample	Absent
Additional FMC Specifications	
Particle size (Air Jet):	
wt. % + 60 mesh (250 microns)	NMT 1.0
wt. % + 200 mesh (75 microns)	NMT 30

Lactose Monohydrate

Specifications USP NF 23	
Identification	Pass
Appearance/color of solution	Pass
Optical rotation	+54.4 to +55.9°
Acidity or alkalinity	Pass
Heavy metals	≤5 µg/g
Absorbance 210–220 nm	≤0.25
Absorbance 270–300 nm	≤0.07
Loss on drying	≤0.5%
Water	≤1.0%
Residue on ignition	≤0.1%
Heavy metals,	NMT 0.001 %
Solubility in Copper Tetrammine Hydroxide	Soluble

Microbial limits:	
Total aerobic microbial count	NMT 100 cfu/g
Total yeast and mold count, cfu/g *	NMT 50 cfu/g
Escherichia coli in a 10g sample	Absent
Isomer ratio	Pass
Salmonella species in a 10g sample	Absent

Polyox WSR 303	
Specifications USP NF 23	
Identification	Pass
Loss on drying	≤1.0%
Silicon dioxide and nonsilicon dioxide residue on ignition	≤2.0%
Silicon dioxide	≤3.0%
Heavy metals	≤0.001%
Free ethylene oxide	≤0.001%
Organic volatile impurities	Pass
Viscosity	Pass

Methocel	
Specifications USP 28	
Identification	Pass
Apparent viscosity	Pass
Loss on drying	≤5.0%
For viscosity grade >50 mPa s	≤1.5%
For viscosity grade ≤50 mPa s	≤3.0%
For type 1828 of all viscosities	≤5.0%
Heavy metals	≤0.001%
Organic volatile impurities	Pass
Methoxy content	
Type 1828	16.5–20.0%
Type 2208	19.0–24.0%
Type 2906	27.0–30.0%
Type 2910	28.0–30.0%
Hydroxypropoxy content	
Type 1828	23.0–32.0%
Type 2208	4.0–12.0%
Type 2906	4.0–7.5%
Type 2910	7.0–12.0%

Purified Talc	
Specifications USP NF	
Identification	Complies with EP/BP tests
Acidity or alkalinity	
Change colour to pink	NMT 0.3 ml of 0.01 M NaOH
Water-soluble substances	Max 0.2%
Aluminium	Max 2.0%
Calcium	Max 0.90%
Iron	Max 0.25%
Lead	Max 10.0 ppm
Magnesium	17.0% to 19.5%
Loss on ignition	Max 7.0%
Microbial contamination	
Total viable aerobic count	NMT total of 10^2 bacteria and fungi per gram.

Aerosil 200	
Specifications USP NF 23	
Identification	Pass
pH (4% w/v dispersion)	3.5–5.5
Arsenic	8 µg/g
Loss on drying	2.50%
Loss on ignition	2.00%
Organic volatile impurities	Pass
Assay (on ignited sample)	99.0–100.5%
Specific Surface Area	200 ± 25 m^2/g
Tapped Density	0.05 g/cm^3

Magnesium Stearate	
Specifications USP NF 23	
Identification	Pass
Microbial limits	
Aerobic microbeal Count	$10^3/g$
Fungi and yeasts	500/g
Acidity or alkalinity	Pass
Specific surface area	Pass
Loss on drying	6.00%
Chloride	0.10%
Sulfate	1.00%
Lead	0.001%
Relative stearic/palmitic content	Pass
Organic volatile impurities	Pass
Assay (dried, as Mg)	4.0–5.0%

Meglumin	
Specifications USP NF 28	
Identification	Pass
Loss on drying	1.00%
Melting Range	128–132°C
Specific Optical rotation	5.7 to 7.3°
Residue on ignition	0.100%
Absence of reducing substances	Pass
Heavy metals	0.002%
Assay	99.0–100.5%

Sodium Hydroxide	
Specifications USP NF	
Identification	Pass
Insoluble substances and organic matter	Pass
Potassium	Pass
Heavy metals	0.003%
Assay (total alkali calculated as NaOH)	95.0–100.5%

Ingredients	Approval Status (USFDA)	Qty (mg)
Cellulose, microcrystalline	Oral; table	1385.30
Lactose monohydrate	Oral; tablet, film coated	587.44
Talc	Oral; tablet, extended release	80.00
Silicon dioxide, colloidal	Oral; tablet	99.00
Meglumine	Oral; tablet	24.00
Sodium hydroxide	Oral; tablet	6.72
Hydroxypropyl Methyl cellulose	Oral; tablet	100.4
Sodium Hydroxide	Oral; tablet	6.72
Polye ethylene oxide	Oral; tablet	Not Approved
Meglumine	Oral; tablet	24.0 mg

Table 3 - 6 Approval Status of ingredients used

6.4.3 Drug excipients compatibility study:

At an early stage of proposed drug product development, drug-excipient compatibility study was performed, to identify the potential incompatibilities of drug with the excipients intended to be used for product development. The pre-formulation study was based on the

excipients to be used in the finished product. All the inactive ingredient guide (USFDA) approved ingredients were selected for the study as mentioned in table 3-6.

Lornoxicam was mixed with Lactose and Microcrystalline cellulose in ratio of 1:5 w/w, with water in 1:5 w/v proportion with distilled water and other excipients in drug to Excipient ratio of 5:1 proportion of binary mixture and the blend were exposed to 40°C /75%RH temperatures for 4 weeks to accelerate drug degradation and interaction with excipients in USP type I amber glass vials with LDPE (low density polyethylene) stopper for evaluation of their compatibility at stress condition. The blend exposed to stress conditions and then compared with their respective initial blend stored at controlled condition by physical observation. The samples are then characterized for the drug content, which were determined quantitatively using developed analytical method after dissolving the drug in equal proportion mixture of PBS 7.5 : Methanol and percentage drug content verified initially and after 4 weeks and compared.

Results of drug-excipient compatibility study are described below in table 4-6.

Drug : Excipients	Initial		4 Week 40°C /75%RH	
	Observation	% Drug Content	Observation	% Drug Content
Lornoxicam	Orange to yellow crystalline powder.	101.72	Orange to yellow crystalline powder. No change in physical appearance observed	102.67
Lornoxicam & PVP k 30	Orange to yellow crystalline powder.	102.14	Orange to yellow crystalline powder. No change in physical appearance observed	101.24
Lornoxicam & Magnesium Stearate	Orange to yellow crystalline powder.	101.78	Orange to yellow crystalline powder. No change in physical appearance observed	101.41
Lornoxicam & Lactose Monohydrate	Orange to yellow crystalline powder.	102.52	Orange to yellow crystalline powder. No change in physical appearance observed	100.61
Lornoxicam & Purified Talc	Orange to yellow crystalline powder.	102.59	Orange to yellow crystalline powder. No change in physical appearance observed	99.40
Lornoxicam & Colloidal Silica	Orange to yellow crystalline	100.38	Orange to yellow crystalline powder. No change in physical appearance observed	99.56

Drug :	Initial		4 Week 40°C /75%RH	
	powder.			
Lornoxicam & MCC 101	Orange to yellow crystalline powder.	101.33	Orange to yellow crystalline powder. No change in physical appearance observed	99.49
Lornoxicam & HPMC	Orange to yellow crystalline powder.	100.21	Orange to yellow crystalline powder. No change in physical appearance observed	100.94
Lornoxicam & Polyethylene Oxide	Orange to yellow crystalline powder.	96.53	Orange to yellow crystalline powder. No change in physical appearance observed	94.52
Lornoxicam & Meglumin	Orange to yellow crystalline suspension.	101.39	Orange to yellow crystalline powder. No change in physical appearance observed	100.41
Lornoxicam & Purified water	Orange to yellow crystalline suspension.	99.67	Orange to yellow crystalline suspension. Probable degradation of Lornoxicam may be there.	77.36
Lornoxicam & Sodium Hydroxide 1M Solution	Yellowish solution.	98.65	Yellowish solution. No change in physical appearance observed	93.51

Table 4 - 6 Drug excipients compatibility study results

Conclusion : Under 40°C /75%RH for 4 weeks, lornoxicam did not reveal show sharp fall in content so it can be concluded that it do not show any incompatibilities with the proposed excipients as summarized in table 4 -6. It seems not stable in aqueous vehicle for after one week of time. Preformulation studies show that the selected excipients are compatible with Lornoxicam.

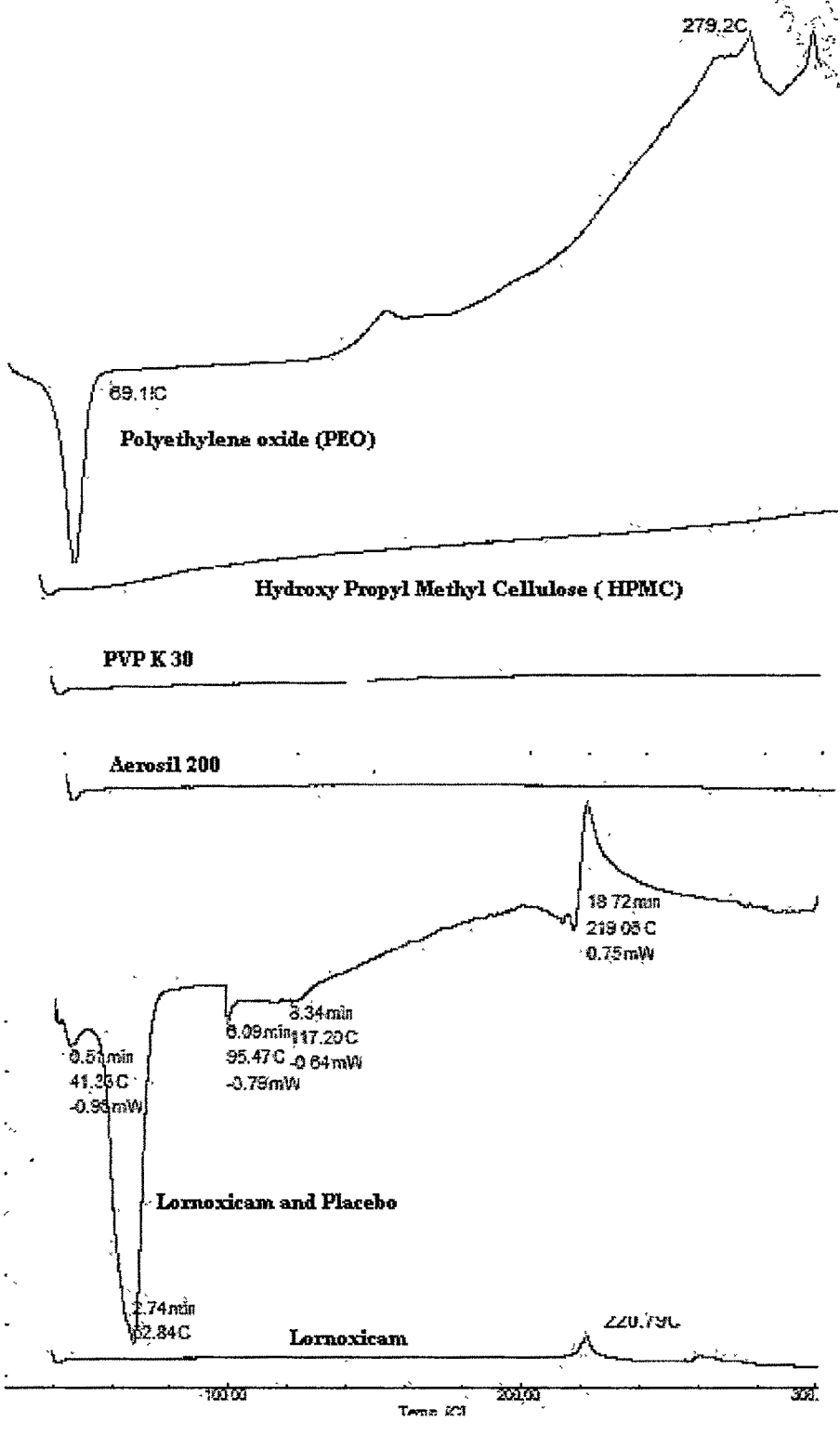


Figure 2 - 6 DSC Study

Differential scanning Calorimetry

The DSC of samples was carried out by scanning the samples using differential scanning colorimeter (Mettler). Thermograms were analyzed using Mettler Toledo star SW 7.01. An empty aluminium pan was used as the reference for all measurements. During each scan, 2 to 3 mg of sample was heated, in a hermetically sealed aluminium pan. DSC studies were performed under nitrogen flush at heating rate of 10 °C from 35 °C to 300 °C to investigate the any incompatibility between drug and excipients.

DSC curve of lornoxicam exhibited sharp endothermic peak at 220.79° C, which is due to melting of lornoxicam with decomposition.

For that DSC of plain drug was done followed by DSC study of individual excipients to be used in dry form. i.e. aerosil 200, PVP K 30, HPMC and PEO and then DSC of drug mixed with placebo was done. NaOH and Meglumine are to be used in solution form so DSC study was not performed.

Conclusion:

It is evident from figure 2 - 6 (DSC study graph) that no changes observed in the DSC of drug mixed with placebo and the original melting endotherm of the crystalline form of drug which exhibited melting endotherm at (220°C). Hence it is clear that there is no specific interaction between the drug and excipients found used in the formulation.

6.5 Drug Product Formulation Development:

The proposed target for formulation development must be easy to manufacture, chemically and physically stable throughout the manufacturing process, product shelf life and bio-available in predicted manner. During design of the formulation, critical formulation and manufacturing variables were identified and adjusted to yield quality product. Design of experiments was used to improve and establish the robustness of the formulation around target formulation.

The proposed drug product (Lornoxicam Extended release formulation16 mg) is intended to have following primary attributes:

- Product to be formulated as coated tablet or matrix tablet.
- Product to be developed as an coated dosage form where coating shall be nonfunctional and must comply with predicted release specifications.

6.5.1 Predicted Plasma concentration of Lornoxicam

From data of oral immediate release formulation's plasma drug concentration of available in literature total amount of drug required to achieve steady state level in particular time frame is found out. The target release profile was decided from the AUC of the oral immediate release blood concentration data by Wagner nelson de-convolution process and is shown in figure 3-6. The target drug release profile is depicted in table 5 -6 & 6 - 6

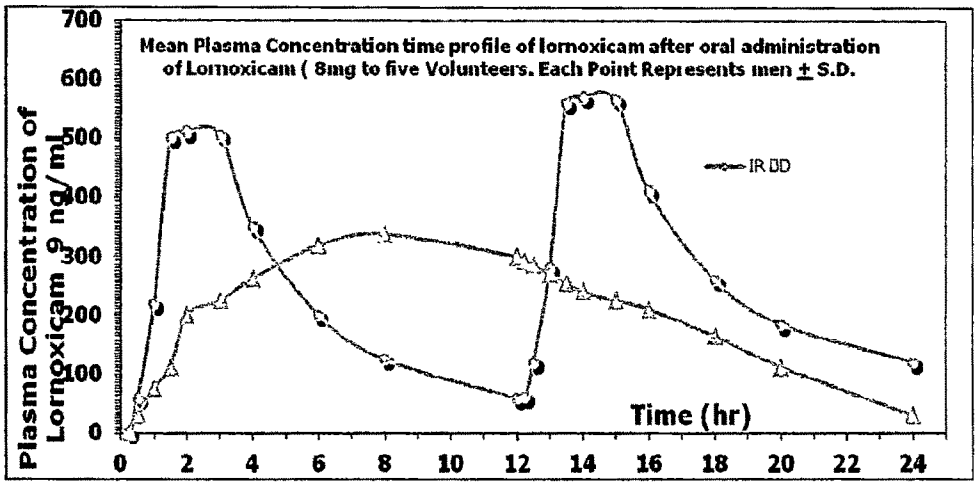


Figure 3 - 6 Predicted plasma concentration of Lornoxicam

Above mentioned graph (Figure 3-6) shows actual plasma concentration time profile after administration of two IR formulation administration at the interval of 12 hours (Young Hoon Kim et al., 2007) and from the plasma concentration of the IR formulation plasma concentration time profile of ER formulation predicted considering pharmacokinetic data. From the data of ER plasma drug concentration profile In-vitro target release profile was calculated through deconvolution using Microsoft excel. The method is discussed in detail in literature (F. Langenbucher., 1985).

Time (Hr)	Target Profile (Dose 16mg)	Actual IR Plasma Profile ng/ml	Predicted XR Plasma Profile ng/ml
0.50	4.42	60	60
1.00	11.64	220	150
2.00	27.86	510	330
3.00	37.31	505	390

4.00	47.63	350	450
6.00	63.08	200	480
8.00	76.80	125	480
12.00	96.21	60	400
13.00	97.12		340
14.00	98.82		300
15.00	101.52		280
16.00	100.79		220
18.00	101.91		160
20.00	101.31		100
24.00	100.00		30

Table 5 - 6 Final Target release profile (Detail)

Time (hr)	Target Range Cumulative % release profile
0	0
2	NMT 40
4	40 to 60
8	70 to 80
12	NLT 85

Table 6 - 6 Final Target release profile (Brief)

The release studies for Lornoxicam formulation in different release media. One tablet containing 16 mg drug was placed in dissolution vessel containing 900 ml of release medium using paddle (USP Type II) at 50 RPM maintained at 37 $\pm$2°C. Aliquots were taken out at different time interval and replaced with equal quantity of release media. The dissolved drug in release medium analyzed as per the method discussed analytical method section. The amount of the drug released and cumulative percentage release was determined.

Drug Name : Lornoxicam			Dosage Form : Extended Release		
Stage	**USP Apparatus**	**Speed (RPM)**	**Medium**	**Volume (ml)**	**Recommended Sampling Time points**
Stomach	II (Paddle)	50	PBS pH 7.5	900	up to 12 Hrs in buffer stage

Table 7 - 6 Dissolution Conditions

6.5.2 Quality of target product profile (QTTP) :

As a target for the development of a manufacturing process, the following attributes were identified that will ensure the desired product quality to match all aspects of Quality target product profile:

1. Correct amount (Assay) of drug substance in the drug product.
2. Content Uniformity (represents compression uniformity)
3. Dissolution (Conditions mentioned in table 7 – 6) of drug substance in the drug product (Target release profile table 5 - 6 & 6 – 6).
4. Weight variation of the drug product.
5. Type and concentration of excipients that directly influences the quality and performance of the drug product.
6. Container closure system to provide intended protection to drug product.
7. Overages requirement if product loss during process.
8. Hardness : 2 – 5 kg/cm^2
9. Friability NMT 1 %
10. Bulk density and tapped density

6.5.3 Selection of Manufacturing Process:

Lornoxicam is poorly soluble in water and slightly soluble in simulated gastric fluid. Its poor aqueous solubility can lead to absorption rate limiting step and thus delay in onset of action. Solubility being an important parameter for absorption of water insoluble drugs it is a key rate-limiting step. An enhancement in the solubility and the dissolution rate may result in the higher bioavailability and it lead to improved therapeutic efficacy. Various efforts have been made to enhance the solubility of poorly water soluble drugs including the use of surfactants, amorphous form of drug, micronisation and incorporation of alkalizing agents in formulation (US patent : 6599529 and US patent application US 2006/0024365 A1) are some of the options available micronisation do not provide sufficient fast release, excess of surfactants may be damaging to body and amorphous form may not be stable enough to give stability to formulation so further trials were initiated incorporating an alkylating agent Meglumine in the formulation, in addition of dissolution another objective is to have drug release over extended period of time so matrix forming polymers i.e. HPMC K15 M CR were used in the initial formulation.

Drug substance sourced as USP grade and evaluated for physio-chemical and analytical parameters as per IH method of analysis.

Preparation method of tablets

Core tablets were prepared by wet granulation method and the composition is given in table 8-6. For preparation of core tablets, the batch size was kept as 750 tablets. The drug (Sieved through 40 #) was added to the mixture of lactose (Sieved through 40 #), MCC (Sieved through 40 #) and meglumine (Sieved through 40 #) through geometric dilution method and sifting three times. The blend was mixed with 10 % W/V PVP K 30 solution in isopropyl alcohol for binding and granulated by passing through 22 # sieve. The granules were dried at 50°C (approximately 1 h) after which they were passed through 40 # sieve. These sized granules were then blended with extra granular matrix forming agent (HPMC K15 M CR) (40 # passed) for 5 minutes followed by talc (Sieved through 100 #), aerosol 200 (Sieved through 60 #) and magnesium stearate (Sieved through 100 #) and blending for 3 min after addition of each. The blend was compressed to tablets using a rotary tablet compression machine (General Machinary Company, India) fitted with 7 mm standard concave punches. Initial development composition made with formula mentioned in table 8-6 and subjected to dissolution studies as mentioned in table 7 -6, the results are summarized in table 9-6 and plotted as graph in figure 4-6.

6.5.3.1 Initial Development composition

	A	B	C
Material	**mg**	**mg**	**mg**
Lornoxicam	16.00	16.00	16.00
Lactose Monohydrate	55.75	60.00	51.50
Micro crystalline Cellulose	55.75	60.00	51.50
Meglumin	25.50	17.00	34.00
Binding			
PVP k 30	5.00	5.00	5.00
Extra-granular			
HPMC K15M CR	17.00	17.00	17.00
Mg. Stearate	2.00	2.00	2.00
Purified Talc	2.00	2.00	2.00
Aerosil 200	1.00	1.00	1.00
Total	180.00	180.00	180.00

Table 8 - 6 Initial Development composition

Bulk uniformity for above mentioned composition was within 90 to 110 % but the RSD of 10 results was 10.23 %, 9.59 5 and 11.46 % with mean 102%, 98% and 103.71 % for composition a, B and C respectively. RSD for blend uniformity was targeted less than 5%. Drug uniformity in the powder blend using above mentioned procedure was not achieved and desired initial release was not observed additionally tablets were showing mottling because drug being insoluble. Many other formulation developers have tried to solve the issue by micronisation of drug but that could not completely solve the issue. Further trials were taken using drug in binder solution made by addition of sodium hydroxide and meglumine which was expected to solve the mottling, uniformity issue and initial fast release profile requirement.

Dissolution Studies

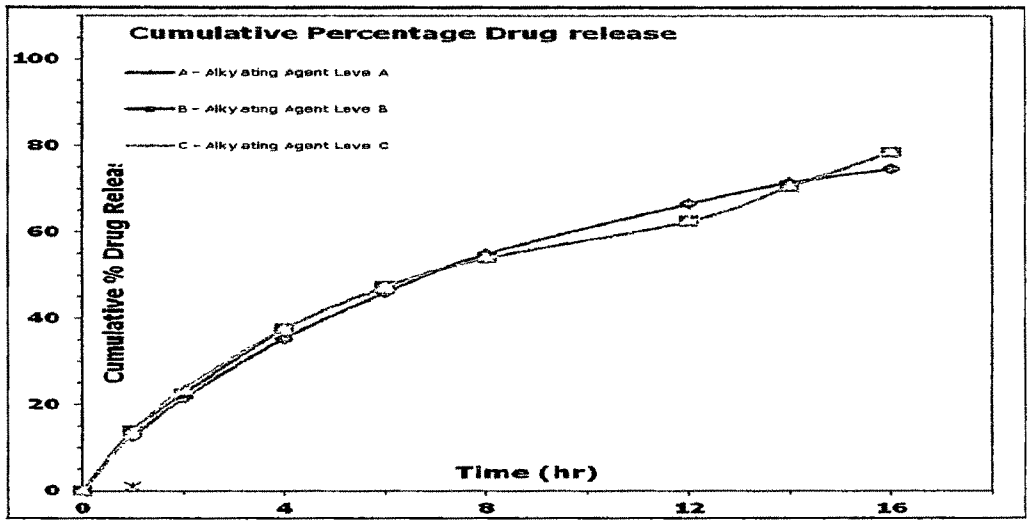


Figure 4 - 6 Dissolution Studies graph of initial development composition

Time (hr)	Cumulative % Drug release		
	A	B	C
0	0	0	0
1	12.52	14	13.6
2	21.45	22.5	23.6
4	35.28	37.5	37.5
6	45.92	47.3	47.3

8	54.87	53.9	53.9
12	66.49	62.4	62.4
14	71.41	70.5	70.5
16	74.59	78.4	78.4

Table 9 - 6 Dissolution Studies results initial development composition

6.5.3.2 Optimisation of core for achieving initial release

Best possible answer to this issue of uniformity and initial release requirement was to use the drug in solution form, drug being soluble at basic pH further trail was conducted by using the dissolved form of drug containing Sodium Hydroxide and meglumine for binding of granules. For that 12 g of drug was dissolved in 80 ml aqueous solution of 2.25 g of sodium hydroxide & 25.5 g of meglumin and using it for binding of 81 gm of dry mix of Lactose Monihydrate & MCC using wruster coater. The above granules further mixed with extra granular matrix forming agent different grades of HPMC (40 # passed) for 5 minutes followed by talc (Sieved through 100 #), aerosol 200 (Sieved through 60 #) and magnesium stearate (Sieved through 100 #) and blending for 3 min after addition of each. The blend was compressed to tablets using a rotary tablet compression machine (General Machinary Company, India) fitted with 7 mm standard concave punches.

	N	D	E	F	G
Lornoxicam	16.00	16.00	16.00	16.00	16.00
HPMC K15M CR	17.00				
HPMC K100M CR		17.00			
HPMC K100LV			17.00		
HPMC E50LV				17.00	
Polyox WSR 303					17.00
PVP k 30	5.00	5.00	5.00	5.00	5.00
Lactose Monohydrate	54.25	54.25	54.25	54.25	54.25
Micro crystalline Cellulose	54.25	54.25	54.25	54.25	54.25
Meglumin	25.50	25.50	25.50	25.50	25.50
NaOH	3.00	3.00	3.00	3.00	3.00
Mg. Stearate	2.00	2.00	2.00	2.00	2.00
Purified Talc	2.00	2.00	2.00	2.00	2.00
Aerosil 200	1.00	1.00	1.00	1.00	1.00
	180.0	180.0	180.0	180.0	180.0

Table 10 - 6 Initial release optimisation trial dissolution studies Composition

Further trials were made to optimize the viscosity of matrix forming agent once initial burst effect was achieved mentioned in table 10-6 and subjected to dissolution studies as mentioned in table 7 -6, the results are summarized in table 11-6 and plotted as graph in figure 5-6.

Bulk uniformity for above mentioned composition was within 90 to 110 % and the RSD of 10 results was 3.45 %, 2.19, 2.74, 3.12 and 2.41 % with mean 102%, 101%, 100%, 99% and 102 % for composition N, D, E, F and G respectively. RSD for blend uniformity was targeted less than 5% was achieved. Drug uniformity in the powder blend using above mentioned procedure was achieved and desired initial release was observed and tablets were not showing mottling

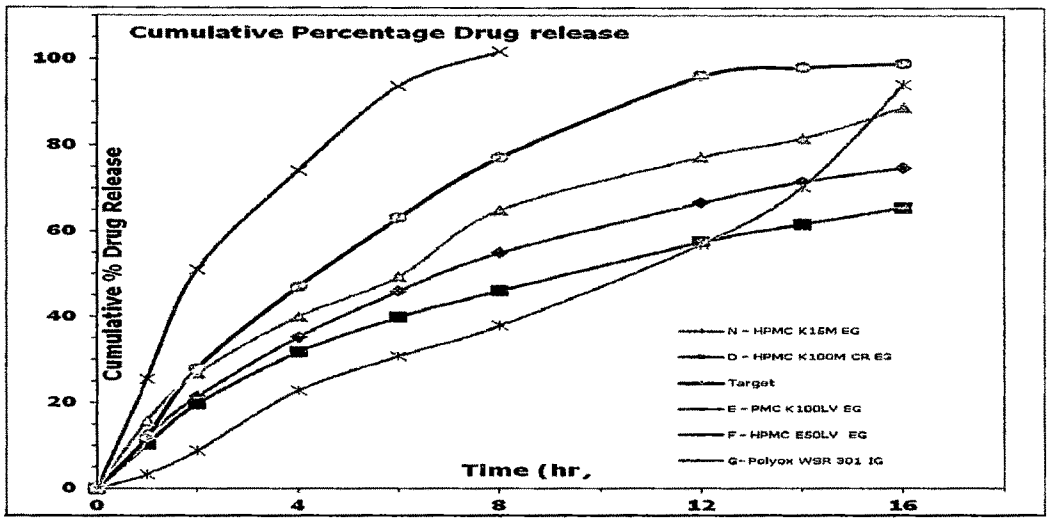


Figure 5 - 6 Fast release part release optimisation trial dissolution studies graph

Time (hr)	Cumulative % Drug release				
	N	D	E	F	G
0	0	0	0	0	0
1	12.52	10.2	15.7	25.45	3.33
2	21.45	19.7	26.8	51	8.83
4	35.28	31.7	40	74	22.8
6	45.92	39.9	49.3	93.72	30.8
8	54.87	46	64.7	101.6	37.9
12	66.49	57.4	77		56.9
14	71.41	61.6	81.4		70.3
16	74.59	65.4	88.6		94

Table 11 - 6 Dissolution studies results fast release part optimisation trials

6.5.3.3 Optimisation of extended release part

Trials were conducted to optimize the ratio of viscosity of matrix forming agent to optimize extended release effect once initial release profile was achieved composition is mentioned in table 12-6.

Formulation were subjected to dissolution studies as mentioned in table 7 -6, the results are summarized in table 13-6 and plotted as graph in figure 6-6.

	H	I	J	K	L	M
Lornoxicam	16.00	16.00	16.00	16.00	16.00	16.00
HPMC K15M CR	8.50			8.50	8.50	
HPMC K100M CR	8.50	8.50				8.50
HPMC K100LV		8.50	8.50		8.50	
HPMC E50LV			8.50	8.50		8.50
PVP k 30	5.00	5.00	5.00	5.00	5.00	5.00
Lactose Monohydrate	54.25	54.25	54.25	54.25	54.25	54.25
Micro crystalline Cellulose	54.25	54.25	54.25	54.25	54.25	54.25
Meglumin	25.50	25.50	25.50	25.50	25.50	25.50
NaOH	3.00	3.00	3.00	3.00	3.00	3.00
Mg. Stearate	2.00	2.00	2.00	2.00	2.00	2.00
Purified Talc	2.00	2.00	2.00	2.00	2.00	2.00
Aerosil 200	1.00	1.00	1.00	1.00	1.00	1.00
	180.0	180.0	180.0	180.0	180.0	180.0

Table 12 - 6 Extended release optimisation trial composition

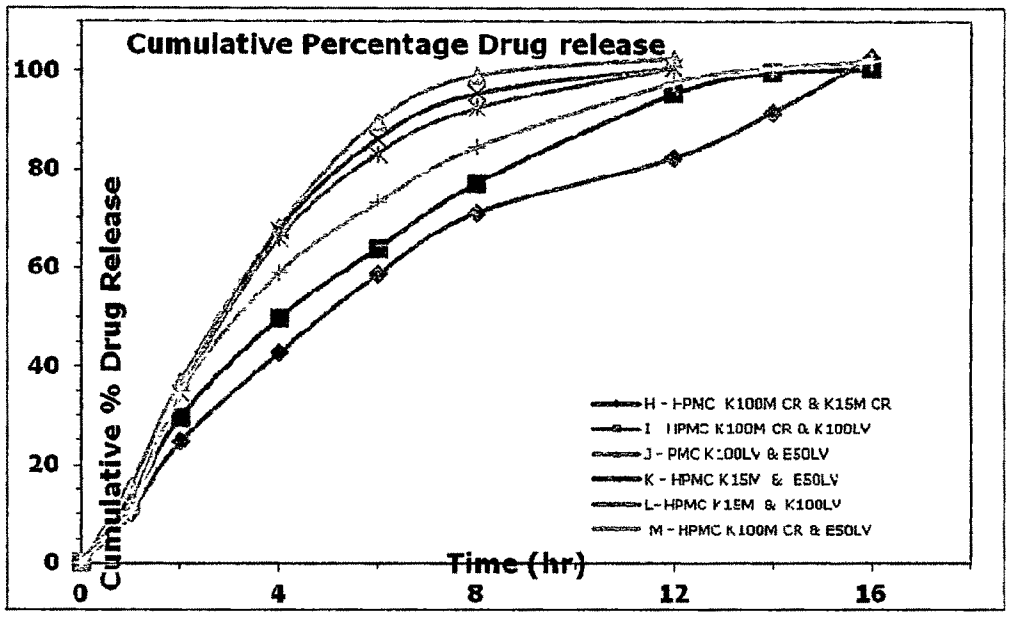


Figure 6 - 6 Extended release optimisation trial dissolution studies graph

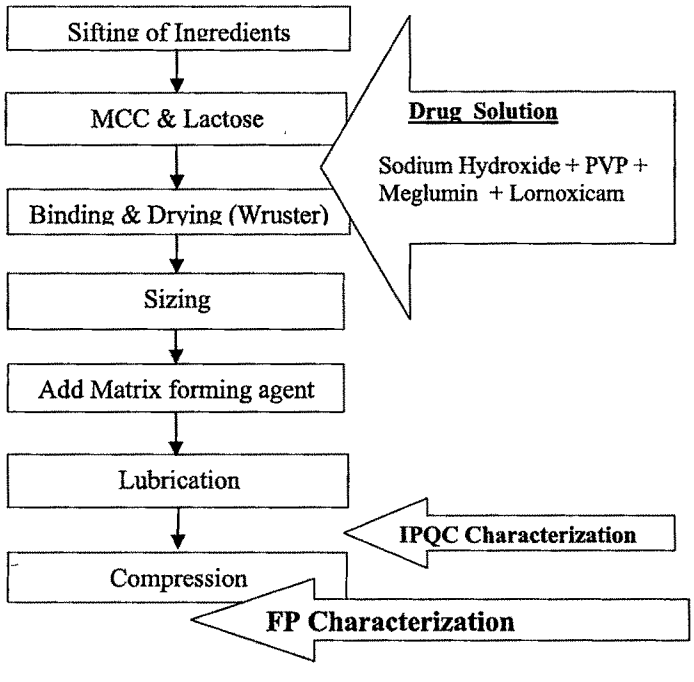
Bulk uniformity for above mentioned composition was within 90 to 110 % and the RSD of 10 results was 2.35 %, 3.16, 3.54, 2.42 and 3.13 %, 2.12 with mean 100%, 102%, 101%, 99%,102% and 103 % for composition H, I, J, K, L and M respectively. RSD for blend uniformity was targeted less than 5% was achieved. Drug uniformity in the powder blend using above mentioned procedure was achieved and desired initial release was observed and tablets were not showing mottling.

Time (hr)	Cumulative % Drug release					
	H	I	J	K	L	M
0	0	0	0	0	0	0
1	10.214	12.2	15.7	12.21	12.2	10.21
2	24.65	29.7	36.8	34.65	34.7	34.65
4	42.732	49.7	68.3	67.52	65.9	58.87
6	58.675	63.9	89.7	86.16	83.2	73.16
8	71.16	77.2	99	95.38	92.4	84.38
12	82.38	95.4	102	100.6	101	97.6
14	91.6	99.6				100.5
16	102.69	100				102

Table 13 - 6 Extended release optimisation trial dissolution studies results

Discussion & Conclusion: Lornoxicam is poor solubility in aqueous solution drug optimisation trails were aimed at initial drug release profile and then extended release profile. The target release profile was achieved in optimised formulation 'I". During initial trial only meglumine was added to the formulation but that was not proven suffice for providing sufficient basic microenvironment so combination sodium hydroxide and meglumine were added with dissolved drug in binder solution. Quantity of extra-granular hydrophilic matrix forming agent was optimised to get release up to extended period of time. Formulation "I" containing equal amount of HPMC K100M CR and HPMC K100LV was showing optimum drug release consistently hence, that was considered for further characterisation studies. With good blend uniformity, initial release profile and extended release profile was achieved and tablets were not showing any motteling.

6.5.4 Process Flow Chart of the optimised process



6.5.5 Unit Operations of the Preparation process

Sieving : All the excipients were sieved before use to break the agglomerates sieve sizes used for sieving are mentioned in table 14 - 4.

Following sieve was used for the same.

Excipients	Sieve Size
HPMC	40 #
Lactose Monohydrate	40 #
MCC 101	40 #
Polyethylene Oxide	40 #
Mg. Stearate	100 #
Talc	100 #
Aerosil 200	60 #

Table 14 - 6 Sieving details of ingredients

Sieving : Dry granules were again passed through 40# to break the agglomerates.

Matrix forming agent: HPMC was added to the granules and blended for 5 min poly bag for uniform distribution of HPMC.

Lubrication : Glident, lubricant and anti adherent were added in sequence respectively and blended for 3 min in poly bag to get uniform coating on the granules.

Top spray granulation process (Fluid bed processor)

Binding, granulation and drying process varies with type of system, binding solution was added through top spray granulation process. Henceforth, palmglatt autocoater was used for granulation. For top spray granulation palmglatt requires minimum load of approx 100 gm.

Coating process: Coating process optimised on equal proportion powder mixture of Lactose Monohydrate and Microcrystalline cellulose.

Solvent Selection

Considering solubility of drug 0.62 M Sodium Hydroxide solution was used PVP k 30, meglumine and lornoxicam was added in it.

Solid content

Binding Composition 389.50 gm (Total)	
Ratio within Solid content	
Sodium Hidroxide	32.32 % w/w
PVP K 30	10.10 % w/w
Meglumin	51.51 % w/w

Lornoxicam	6.06 % w/w
Ratio of Water : Solid	
Water	82.90 % w/w
Solid	17.10 % w/w

Table 15 - 6 Composition of the binder solution

Binder solution preparations:

Step 1: Dissolved sodium hydroxide in water.

Step 2: PVP k 30 dissolved in step – 1 Solution.

Step 3: Meglumin dissolved in step – 2 Solution.

Step 4: Drug dissolved in step – 3 Solution

Table 15-6 summaries composition of binder solution used in palm glatt wurster process the critical process parameters for the process are given in table 16-6, figure 7-6 shows schematic diagram of wurster coating process.

Characterization of Granules : Assay, Blend uniformity, Loss On drying, Bulk Density, Tapped Density, compressibility index.

Compression : Compression was done on 8 Station rotary tablet compression machine from general machinery company.

Compression Parameters :

Turret Speed : 9 RPM

Compaction Force: 4 – 5 kg

Thickness Adjustment Lever: Optimised to 3.1 to 3.3 mm thickness.

Parameter	Value	Justification
Fluid nozzle (mm)	0.7	Fixed Machine Parameter
Inlet air temperature (°C)	65 - 70 °C	Selected considering solvent to be evaporated
Out let air temperature (°C)	50-55 °C	Output

Product Temp (°C)	55 - 60 °C	Curing
Atomizing air pressure (kg/cm^2)	0.6 - 0.8 kg/cm^2	Studied on dummy
Inlet Opening	50 - 70	Studied on dummy
Spray rate (g/min)	2.0 ± 0.5	Observed optimum rate
Peristaltic Pump RPM	9 ± 1 RPM	Observed optimum speed
Purging Time	2 Sec	Observed optimum

Table 16 - 6 Fluid Bed processor critical process parameters (CPP)

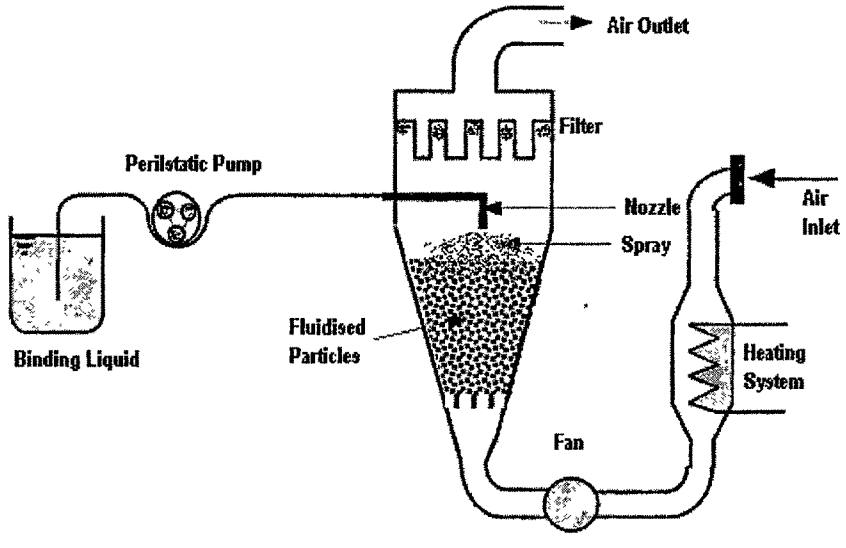


Figure 7 - 6 Schematic top spray fluid bed processor

Spray Rate / Paristaltic Pump RPM: Least achievable peristaltic pump speed was 6 RPM at which the spray was pulsative and Very high speed i.e. 16 RPM was resulting in very high spray rate which may result in non uniform distribution. On 8 to 10 RPM peristaltic pump speed was optimum to have continuous flow with minimum speed.

Spray rate

Spray rate is critical process parameter. Spray rate range 1.5 to 2.5 g/min was studied for it's impact on drug release, coaitng with consistent quality was produced at the 100 gm scale. Spray rate is a scale dependent parameter. The spray rate per nozzle shall be kept the same. The total spray rate can be increased to any fold by multiplying spray guns. However, a processing equipment can be change from a 6″ palm glatt.

Product Temperature:

An acceptable product temperature range was identified 55 - 60 °C. In the studied range, drug-layered granules with consistent quality were produced at the 100 gm scale. Spray drying and agglomeration were minimized. Product temperature is a scale-independent parameter and can be applied to other scales. The risk of product temperature to impact the assay of the drug-layered beads is low.

Air volume

Air volume range was identified and an optimal fluidization pattern was achieved. In the studied range, drug-layered beads with consistent quality were produced at the 100 gm scale. Air volume is a scale-dependent parameter.

Atomization air pressure

Atomization air pressure 0.6 - 0.8 kg/cm^2 was identified as critical process parameter affecting coating quality and so drug release critical quality attribute. The range of Atomization air pressure studied for consistent coating quality at the 100 gm scale. Atomization air pressure is an equipment-dependent parameter.

6.6 Results:

The results of characterization at pre-compression (granules) stage for Assay, Bulk Uniformity (BU), Water content(WC), Loss On Drying (LOD), Bulk Density (BD) & Tap Density(TD) are summarized in table 17-6.

The results of characterization after compression (Core Tablet) for Description, Average Weight (mg), Assay (%), Water Content, Hardness (kg/cm2), Friability (%), Thickness (mm), Diameter (mm), Uniformity of content are mentioned in table 18-6.

6.6.1 Pre-compression characterisation

Bulk powder of the optimsed formulation before compression was subjected to characterization studies and results are mentioned in the table 17-6

Parameter	Limits	Result
Assay	90.00 to 110.00 %	99.51
Bulk Uniformity	Minimum 90 %	Minimum 97 %
	Maximum 110 %	Maximum 107 %
	Mean 95 % to 105 %	Mean 102.97 %
	RSD 5 %	RSD 3.16 %
LOD	NMT 3%	2.4 %
Initial Bulk Density of powder before binding	0.30 - 0.40 gm/ml	0.34 gm/ml
Final Bulk Density of granules after wuruster coating	0.40 - 0.50 gm/ml	0.46 gm/ml
Tapped Density	0.50 - 0.60 gm/ml	0.54 gm/ml
Water Content	NMT 5 %	2.8
Hausner ratio	NMT 1.25	0.85
Carr's Index	NMT 20	17.39

Table 17 - 6 Characterization of optimised batch "I" bulk powder:

Optimised formulation was subjected to characterization studies and results are tabulated in the table 18-6.

6.6.2 Compressed Formulation

Parameters	Limit	Result
Description	Yellow colored, circular, biconvex, uncoated tablet. plain on both side	Complies

Uniformity of Weight (mg)	Target - 180 mg (180 ± 3%)	181.83 mg/ tablet
Hardness (kg/cm^2)	5-8	7 kg/cm^2
Friability (% wt loss)	NMT 0.10	0.01 %
Thickness (mm)	3.1 – 3.3	3.03 mm
Diameter (mm)	7	7 mm
Dissolution (%)	2 Hr – NMT 40 %	29.7
	4 Hr – 40 to 60 %	49.7
	8 Hr – 70 to 80 %	77.2
	12 Hr – NLT 85	95.4
Assay (%)	95 to 105 %	100.20 %
Water Content	NMT 5%	2.4
Content Uniformity (%)	Minimum : 90.00 %	Minimum : 100.51
	Maximum : 110.00 %	Maximum : 102.18
	Average : 95 to 105 %	Average : 101.37
	% RSD : (RSD NMT 5%)	% RSD : 3.86

Table 18 - 6 Characterization of optimised batch "I" Tablet:

6.6.3 Effect of agitation intensity (RPM)

Optimised formulation was verified for impact of agitation intensity (RPM) on drug release in USP type II (Paddle) dissolution test apparatus 900 ml PBS pH 7.5 as release media, impact of dissolution media volume on drug release was verified using USP type II (Paddle) dissolution test apparatus PBS pH 7.5 as media at 50 RPM, figure 8 - 6 and figure 9 – 6 represents graphical representation of the results obtained and results are tabulated in table 19 - 6 and table 20 - 6.

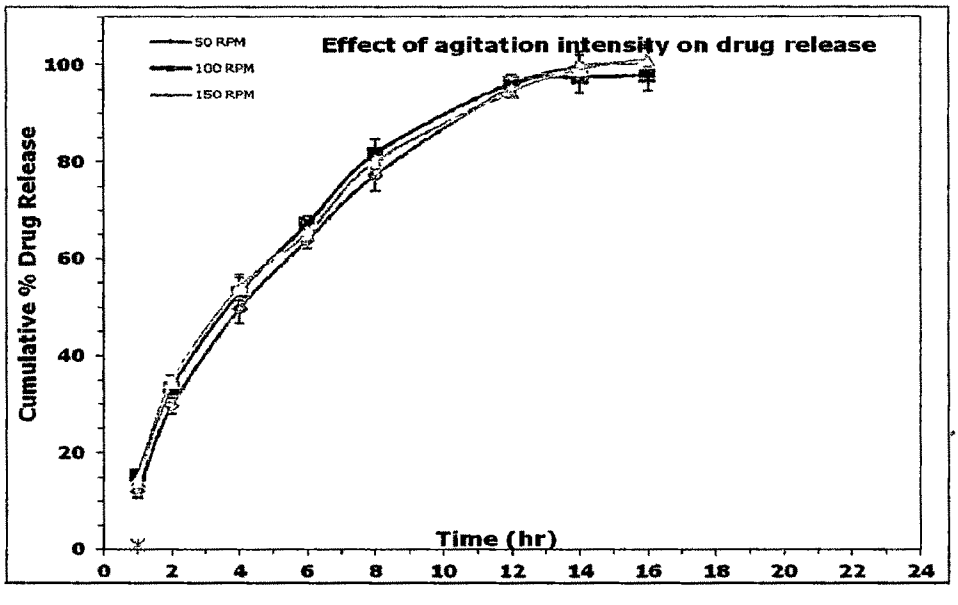


Figure 8 - 6 Effect of Agitation intensity graph

Time (hr)	50 RPM	SD	100 RPM	SD	150 RPM	SD
1	12.21	1.38	15.37	1.27	14.21	1.67
2	29.65	1.47	33.41	1.34	34.65	1.27
4	49.73	3.07	53.05	3.03	54.05	2.70
6	63.87	1.79	67.14	1.55	65.25	1.19
8	77.16	3.16	81.63	3.11	79.99	2.03
12	95.38	1.96	96.18	1.74	94.38	1.19
14	99.60	3.17	97.39	3.10	99.13	2.93
16	100.39	3.17	97.74	3.00	101.14	2.93

Table 19 - 6 Effect of agitation intensity results

Discussion : It needs to be verified that if developed hydrophilic matrix formulation gives constant drug release irrespective of agitation intensity. The drug release from optimised formulation was confirmed at various agitation speed i.e. 50, 100, and 150 RPM.

It is clearly evident from (table 19-6) that the release from hydrophilic matrix formulation is independent of the agitation intensity. The $f1$ and $f2$ values were found to be $f1$ 4.36 and $f2$ 74.17 (between 50 RPM and 100 RPM), $f1$ 2.55 and $f2$ 83.69 (between 100 RPM and 150 RPM) for $f1$ 3.27 and $f2$ 76.87 (between 50 RPM and 150 RPM).

Hence, it can be expected that the release from the developed hydrophilic matrix formulation will not have much impact of agitation conditions at the absorption site.

6.6.4 Effect of dissolution volume

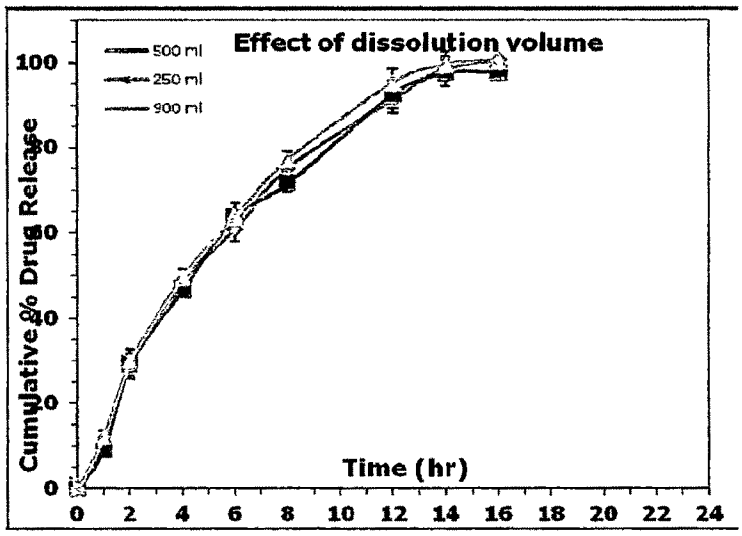


Figure 9 - 6 Effect of Dissolution Volume Graph

Time (hr)	500 ml	SD	250 ml	SD	900 ml	SD
0	0.00		0.00		0.00	
1	10.21	1.30	9.14	1.38	12.21	1.38
2	28.65	1.43	29.18	1.60	29.65	1.47
4	48.73	2.97	46.73	3.35	49.73	3.07
6	60.87	1.77	63.87	1.79	63.87	1.79
8	75.16	2.80	71.63	3.16	77.16	3.16
12	91.38	1.50	92.62	1.96	95.38	1.96
14	98.60	3.08	97.60	3.17	99.60	3.17
16	100.63	2.85	97.82	3.17	100.39	3.17

Table 20 - 6 Effect of dissolution volume results

Discussion: It needs to be verified that if developed hydrophilic matrix formulation gives constant drug release irrespective of volume if sink conditions are maintained. The drug release from optimised formulation was confirmed at different release volume i.e. 250, 500, and 900 ml.

It is clearly evident from (table 20-6) that the release of LOR from hydrophilic matrix formulation is independent of the dissolution volume. The $f1$ and $f2$ values were found to be $f1$ 2.99 and 81.16 (between 500 ml and 250 ml), $f1$ 2.70 and 81.48 (between 900 ml and 500 ml) and $f1$ 3.82 and $f2$ 75.63 (between 900 ml and 250 ml).

Hence, it can be expected that the release from the developed formulation will not have drastic impact of the volume available if sink conditions are maintained at the absorption site.

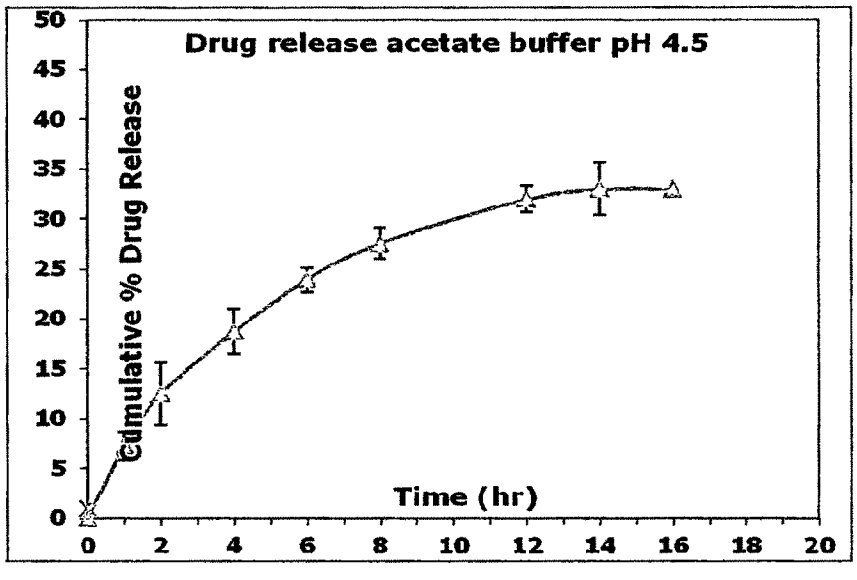


Figure 10 - 6 Drug release acetate buffer

Effect of pH on drug release : Drug shows pH dependent solubility having no solubility in water and acidic pH, good solubility at basic pH which was known fact since beginning of the development and affected the manufacturing process so the dissolution studies are done in PBS pH 7.5 an attempt was made to perform dissolution studies at different pH i.e acetate buffer pH 4.5, figure 10-6. Limited drug release up to 30% due to non sink condition observed.

Lornoxicam (pKa 4.7) shows pH dependent solubility having poor solubility in the acidic pH henceforth, multimedia testing at pH 1.2 was not verified, limited drug release up to 30% due to non sink condition observed at pH 4.5 and to maintain the sink condition dissolution was carried out in PBS 7.5 pH.

6.6.5 Dose Dumping Study

Discussion : Dose dumping is most commonly seen in drugs taken orally and digested in the gastrointestinal tract. Around the same time patients take their medication, they may also ingest other substances like fatty meals or alcohol that increase drug delivery. The substances may act on the drug product to speed up drug release, or they may stimulate

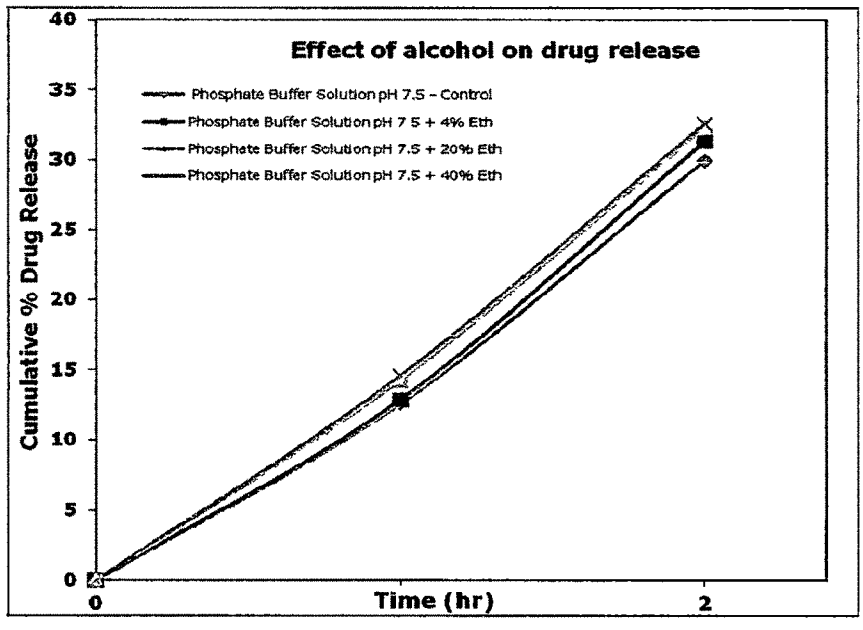


Table 21 - 6 Drug release in presence of various concentration alcohol

the body's absorptive surfaces to increase the rate of drug uptake. Developed formulation was subjected to ethanol induced dose dumping study to emulate a "worst case" scenario. Figure 21-6 the graph showing drug release under various concentration of ethanol. It was observed that no major impact of alcohol on drug release. Hence, it is expected that accidental co-administration of alcohol will not lead to any dose dumping.

Curve fitting analysis

In order to describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed in past. Release data obtained was applied to different release models in order to establish the drug release mechanism and kinetics. Best goodness of fit test (R2) was taken as criteria for selecting the most appropriate model. For calculation of best model Microsoft excel was used. The values are tabulated in table 22-6.

Model	Zero Order	First Order	Higuchi Model	Peppas.
Calculated R2	0.9838	0.7863	0.9405	0.9676

Table 22 - 6 Calculated R2 Values for Developed formulation for different models

Discussion: Calculated R2 for Zero order of drug release is nearest to 1, It can be concluded that the drug release from developed formulation gives constant drug release.

6.7 Result of Development studies

Optimised Dosages Form:

Hydrophilic matrix formulation is developed as Yellow colored matrix, circular, biconvex uncoated tablet plain on both sides containing 16mg of Lornoxicam for oral administration.

Formulation Details:

Yellow colored matrix , circular, biconvex uncoated tablet plain on both sides containing 16mg of Lornoxicam and following are inactive ingredients Lactose Monohydrate, Microcrystalline Polyvinyl Pyrrolidone, Magnesium Stearate, Silicon Dioxide, HPMC, Polyethylene Oxide, Sodium Hydroxide and Meglumine and water as solvent which shall not be part of final product.

Packing Profile:

Dosage form to be packed in HDPE Bottle pack of 100s.

6.7.1 Components of the Developed Drug Product:

The quantitative composition (per tablet and % W/W), compandial status and function of each component used in the developed drug product is provided in table 23-6.

Formula ingredients	Specification	Function(s)	Quantity (mg/tablet)	Quantity (% w/w)
Binding Stage :				
Lornoxicam	USP	API	16.00	8.89
PVP K 30	NF	Binder	5.00	2.78
Lactose Monohydrate	USP NF	Filler	54.25	30.14
Micro crystalline Cellulose *	USP NF	Filler	54.25	30.14
Meglumin	USP NF	pH modifier - Alkalizing agent	25.50	14.17
NaOH	USP NF	pH modifier - Alkalizing agent	3.00	1.67
Distilled Water**	IH	Processing Solvent	Q.s.	Processing Solvent
			158.00	87.78
Addition of extra-granular Hydrophilic Matrix forming agent				
HPMC K100M CR	USP NF	Matrix Forming agent	8.50	4.72
HPMC K100LV	USP NF	Matrix Forming agent	8.50	4.72

Formula ingredients	Specification	Function(s)	Quantity (mg/tablet)	Quantity (% w/w)
Total weight of core tablet			175.00	97.22
Lubrication Stage :				
Mg. Stearate	USP NF	Glidant	2.00	1.11
Talc/Purified Talc	USP NF	Antiadherent	2.00	1.11
Colloidal silicon dioxide	USP NF	Lubricant	1.00	0.56
Total weight of core tablet			**180.00**	**100.00**

Table 23 - 6 Optimised Composition of Lornoxicam tablet (mg/tablet)

* Quantity is compensated depending on the potency of Lornoxicam to maintain tablet weight constant.** Used as processing solvent, does not remain in the final product.

6.7.2 Coating process

Ratio of solids used in coating solution is Critical Process parameter and it has direct impact on drug release table 24-6 mentions binding /coating solution composition.

Binding Composition 389.50 gm (Total)	
Ratio within Solid content	
Sodium Hidroxide	32.32 % w/w
PVP K 30	10.10 % w/w
Meglumin	51.51 % w/w
Lornoxicam	6.06 % w/w
Ratio of Water : Solid	
Water	82.90 % w/w
Solid	17.10 % w/w

Table 24 - 6 Optimised Coating/Binding Solution composition

6.7.3 Critical Quality Attributes: (CQAs)

1. Blend Uniformity
2. Uniformity of weight
3. Assay
4. Dissolution
5. Uniformity of Dosage unit
6. Stability

6.7.4 Critical Process Parameters (CPPs)

1. Spray Rate / Paristaltic Pump RPM
2. Product Temperature:
3. Air volume
4. Spray rate
5. Atomization air pressure
6. Compression (Speed, Compression force)

6.8 Conclusion:

Robust, 16 mg of Lornoxicam formulation is developed which gives drug release independent of agitation intensity and dissolution volume, retarding the drug release through hydrophilic matrix formulation. The optimised formulation will subjected to stability studies and *in-vivo* studies.

6.9 References:

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