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Formulation development and evaluation of osmotic drug delivery system for lornoxicam

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Abstract

Osmotic systems are the most reliable controlled drug delivery systems and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug(s), an osmotic agent, other excipients and semipermeable membrane coat. The aim of current study was to develop osmotic drug delivery system for Lornoxicam. Two different approaches were used for formulation, one was controlled porosity osmotic tablet and other was elementary osmotic tablet. The formulations were evaluated for different parameters like appearance, uniformity of weight, drug content, hardness and drug release also the effect of different osmotic agents responsible for developing the osmotic pressure such as sodium chloride and mannitol along with different concentration of pore former sorbitol were studied and comparison was made between first controlled porosity osmotic tablet which include the osmotic tablet in which coating membrane contains water soluble pore forming polymers when the membrane comes in contact with water the leaching of polymers occur thereby permitting the water inside the wall and creating the osmotic pressure to release the drug and second the elementary osmotic tablet containing osmotic agent sodium chloride coated with the rate controlling semipermeable membrane of cellulose acetate, this membrane contains an orifice of a critical size through which the drug is delivered. From the results it was found that the developed formulation the controlled porosity osmotic tablet of Lornoxicam (CPOP) was able to release the drug over 12 hrs at zero order and also the concentration of osmotic agent, level of pore former and thickness of coating membrane are responsible for controlling the release of Lornoxicam. The coating membrane was subjected to SEM analysis which showed formation of pores in the membrane. The developed controlled porosity osmotic pump tablet of lornoxicam was found to control the release for 12 hrs.

Keywords: Lornoxicam; Controlled porosity osmotic tablet; Elementary osmotic tablet; Drug Release; Osmotic agents; Pore former & Scanning Electron Microscopy

1 Introduction

Oral ingestion is one of the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects. [1]Conventional preparation is usually administered two or three times a day, which will lead to large fluctuation in drug plasma concentration and side effects on human body. Constant plasma levels can offer a therapeutic advantage for many drugs in terms of both efficacy and tolerance of the treatment [1]. Once-daily controlled release formulations are often desirable. Osmotic systems are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure

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is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug(s), an osmotic agent, other excipients and semipermeable membrane coat. Osmosis is an aristocratic phenomenon that seizes the attention for its exploitation in zero-order drug delivery systems. It acts as driven force for release of drug from dosage form. Osmotic tablet worked on the principle Osmosis i.e. movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. It is driven by a difference in solute concentration across the membrane that allows passage of water, but rejects most solute molecules or ions. On the basis of this principle osmotic drug delivery results in better drug release independent on concentration of drug. Controlled drug release systems attempt to sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects [2-5].

The osmotic pump tablet that holds a prominent place among controlled release systems has many advantages, such as reducing risk of adverse reaction, improving compliance of patients and exhibiting comparable *in vitro/in vivo* drug release. Pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure; there has been increasing interest in the development of osmotic devices over the past two decades. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form [6-8].

Lornoxicam, belonging to the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs), is found to possess potent anti-inflammatory and analgesic activities. A commercially available dosage form includes conventional immediate release tablets 4 mg/8 mg, rapid release 8 mg tablets, and parenteral formulations of 4 mg/ ml for intravenous and intramuscular use. Lornoxicam has been widely used for the treatment of pain and inflammation in patients with osteoarthritis and rheumatoid arthritis, pre-operative and post-operative pain associated with gynecological, orthopedic, abdominal and dental surgeries. As Lornoxicam shows half life of 3-5 hrs, dosing frequency of twice or thrice a day and intermediate solubility in water it was selected for the development of osmotic drug delivery system dosage forms [3, 6 & 13].

1.1 Elementary Osmotic Pump

In 1974 Theuwes invented elementary osmotic pump. The elementary osmotic pump is a new delivery system for drugs which delivers the drug by an osmotic process at a controlled rate. Control resides in the: a) Water permeation characteristics of a semi permeable membrane surrounding the formulating agent b) Osmotic properties of the formulation. This system contains osmotically active agent surrounded by the rate controlling semipermeable membrane. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet using a tableting machine. The tablet is then coated with a semi permeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating (size varies from 0.5 to 1.5 mm).The drilling may be done by mechanical drilling, laser drilling (CO_2 laser beam with wavelength of 10.6μ) [4-5]. When the dosage form exposed to the aqueous environment, the core imbibes water osmotically at a controlled rate, which is determined by the water permeability of the semipermeable membrane and by the osmotic pressure of core formulation. The volume of saturated drug solution delivered is equal to the volume of solvent uptake [9].

1.2 Advantages of EOP

Easy to develop Suitable for drug having moderate solubility Economical [6-10]

1.3 Disadvantages of EOP

Size of hole is critical Blockade of orifice is possible [6-10]

1.4 Controlled Porosity Osmotic Pump

The pump can be made with single or multicompartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents [6, 9-11].

1.5 Advantages of CPOP

The release of drugs from controlled porosity osmotic pump tablets follows zero order kinetics after an initial lag.

The delivery of drug may be delayed or pulsatile.

The drug release is independent of physiological conditions of the body, gastric pH, and drug and of hydrodynamic condition [10-11].

1.6 Disadvantages of CPOP

The method of preparation is very costly. Retrieval therapy is not controllable in case of unexpected adverse effects. There is a chance of dose dumping if the coating process is not well controlled [10-11].

The aim of current study was to develop osmotic drug delivery system for Lornoxicam. Two different approaches were used for formulation, one was controlled porosity osmotic tablet and other was elementary osmotic tablet. The formulations were evaluated for different parameters like appearance, uniformity of weight, drug content, hardness and drug release also the effect of different osmotic agents responsible for developing the osmotic pressure such as sodium chloride and mannitol along with different concentration of pore former sorbitol were studied and comparison was made between first controlled porosity osmotic tablet which include the osmotic tablet in which coating membrane contains water soluble pore forming polymers when the membrane comes in contact with water the leaching of polymers occur thereby permitting the water inside the wall and creating the osmotic pressure to release the drug and second the elementary osmotic tablet containing osmotic agent coated with the rate controlling semipermeable membrane, this membrane contains an orifice of a critical size through which the drug is delivered.

2 Methodology

2.1 Materials

Lornoxicam was obtained as a gift sample from Piramal Healthcare, Mumbai, sodium chloride and mannitol (Universal Laboratories Pvt. Ltd, Mumbai). Cellulose acetate was obtained from Shreya Life Sciences, Aurangabad. PVP k-30 & Sodium Lauryl sulphate were obtained from Merck Specialities Pvt. Ltd, Mumbai.

2.2 Analytical Method

2.2.1 Preparation of standard stock solution

Standard drug solution of Lornoxicam was prepared by dissolving 10mg in phosphate buffer pH 6 and the volume was made up to 100ml to obtain stock solution of 100µg/ml concentration. Ultrasonication was done to obtain a clear solution. [10-12]

2.2.2 Determination of analytical wavelength

From the standard stock solution, 1 ml was pipette out into 10 ml volumetric flask. The volume was made up to 10 ml with phosphate buffer solution of pH 7.2. The resulting solution containing 10µg/ml was scanned between 200 and 400 nm. [10-12]

2.2.3 Preparation of Calibration curve of Lornoxicam in phosphate buffer pH 7.2

Aliquots of 0.2 to 1.4 ml portion of stock solutions were transferred to a series of 10 ml volumetric flasks, and volume made up to the mark with phosphate buffer pH 7.2. The serial dilution of the range of 2, 4, 6, 8, 10, 12 and 14 µg/ml was prepared. The absorbance was measured at λmax 376nm [10-12].

2.3 Preparation of Osmotic core tablet:

The core tablets containing 8 mg of lornoxicam for primary batches were formulated using NaCl (16, 24, 32 mg) as an osmogen in 1:2, 1:3, 1:4 proportions respectively with drug to study the consistency of coat (excess amount of osmogen may cause bursting of external coat or membrane), Sodium lauryl sulphate (SLS) was added as a solubilizer (5%) to increase the dissolution of lornoxicam. Lactose and microcrystalline cellulose were used as diluents to ajust the bulk, magnesium stearate was added as a lubricant to prevent sticking and talc as glidant to promote the uniform flow of powder as per Table 01 & 02.

Table 1 Formulations of core tablets with Sodium chloride (Osmogen)

Ingredients (mg)	LOX A0	LOX A	LOX B	LOX C
Lornoxicam	8	8	8	8
Sodium chloride	--	16	24	32
Microcrystalline cellulose	162	146	138	130
Lactose	50	50	50	50
SLS	12	12	12	12
PVPK-30	12	12	12	12
IPA	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3
Talc	3	3	3	3
Tablet weight	250	250	250	250

Table 2 Formulations of core tablets with Mannitol (Osmogen)

Ingredients (mg)	LOX D	LOX E	LOX F
Lornoxicam	8	8	8
Mannitol	40	80	160
Microcrystalline cellulose	132	92	52
Lactose	40	40	40
SLS	12	12	12
PVPK-30	12	12	12
IPA	q.s	q.s	q.s
Magnesium stearate	3	3	3
Talc	3	3	3
Tablet weight	250	250	250

The core tablets were coated with coating solution as per table 3 containing 4% w/v of cellulose acetate (4 gm/100 ml) with 22% and 30% w/w sorbitol equivalent to weight of cellulose acetate such as 0.88gm (22%) and 1.2 gm (30%) as pore former or channeling agent in solvent system acetone: IPA in the ratio 90:10 (90 ml acetone and 10 ml isopropyl alcohol) and maintained the weight gain 3%, 4% and 5% of tablet for each formulation respectively as provided in Table 04 & 05.

Table 3 Formulation of coating solution for lornoxicam core tablets

Ingredients	F1	F2
Cellulose acetate	4 % w/v	4 % w/v
PEG 400	12.5 % w/w	12.5 % w/w
Sorbitol	22 % w/w	30 % w/w
Acetone :IPA	90:10	90:10

Table 4 Primary Batches of osmotic tablet with sodium chloride

Ingredients (mg)	LOX01	LOX02	LOX03	LOX04	LOX05	LOX06	LOX07	LOX08	LOX09	LOX10
Core Tablet Lornoxicam	8	8	8	8	8	8	8	8	8	8
Sodium Chloride	--	16	24	32	16	24	32	16	24	32
Microcrystalline cellulose	162	146	138	130	146	138	130	146	138	130
Lactose	50	50	50	50	50	50	50	50	50	50
SLS	12	12	12	12	12	12	12	12	12	12
PVPK-30	12	12	12	12	12	12	12	12	12	12
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3
Coating ingredients Wt gain (%)	3%	3%	3%	3%	4%	4%	4%	5%	5%	5%
Pore Former (sorbitol %)	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%

q.s means quantity sufficient in ml, weight in mg, and % in w/w.

Table 5 Primary Batches of osmotic tablet with sodium chloride

Ingredients (mg)	LOX11	LOX12	LOX13	LOX14	LOX15	LOX16	LOX17	LOX18	LOX19
Core Tablet Lornoxicam	8	8	8	8	8	8	8	8	8
Sodium Chloride	16	24	32	16	24	32	16	24	32
Microcrystalline cellulose	146	138	130	146	138	130	146	138	130
Lactose	50	50	50	50	50	50	50	50	50
SLS	12	12	12	12	12	12	12	12	12
PVPK-30	12	12	12	12	12	12	12	12	12
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Coating ingredients Wt gain (%)	3%	3%	3%	4%	4%	4%	5%	5%	5%
Pore Former (sorbitol %)	30%	30%	30%	30%	30%	30%	30%	30%	30%

q.s means quantity sufficient in ml, weight in mg and % in w/w.

Table 6 Primary Batches of osmotic tablet with mannitol

Ingredient (mg)	LOX20	LOX21	LOX22	LOX23	LOX24	LOX25	LOX26	LOX27	LOX28
Core tablet Lornoxicam	8	8	8	8	8	8	8	8	8
Mannitol	40	80	160	40	80	160	40	80	160
Microcrystalline cellulose	132	92	52	132	92	52	132	92	52
Lactose	40	40	40	40	40	40	40	40	40
SLS	12	12	12	12	12	12	12	12	12
PVPK-30	12	12	12	12	12	12	12	12	12
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Coating ingredients Wt gain (%)	3%	3%	3%	4%	4%	4%	5%	5%	5%
Pore Former (sorbitol %)	22%	22%	22%	22%	22%	22%	22%	22%	22%

q.s means quantity sufficient in ml, weight in mg and % in w/w.

In another formulation mannitol was used instead of sodium chloride as an osmotic agent in the proportion of 1:5, 1:10 and 1:20 with drug. Excipients like solubility modifier, diluents, lubricant was added and coated with 4% w/w cellulose acetate and 22% w/w pore former (sorbitol) and maintained the weight gain 3%, 4% and 5% of tablet with for each formulation respectively in Table 06.

Elementary osmotic pump tablets of lornoxicam were prepared which contains osmogen (NaCl) in ratio 1:2 (16 mg), 1:3 (24 mg) and 1:4 (32 mg) with 4% weight gain without pore forming agent (sorbitol). The elementary osmotic tablets were drilled with mechanical driller with manual rotation (PCP driller) of orifice size 0.8 mm was selected. The Figure 01 represents the mechanical driller for drill the orifice in the EOP tablet and coated with 4% w/w cellulose acetate without pore former. Coating weight gain maintained was 4% for each tablet as per table 07.

Table 7 Primary batches of EOP osmotic tablet (with Sodium chloride)

Ingredient (mg)	EOP 01	EOP 02	EOP 03	EOP 04
Core tablet Lornoxicam	8	8	8	8
Sodium chloride	--	16	24	32
Microcrystalline cellulose	162	146	138	130
Lactose	50	50	50	50
SLS	12	12	12	12
PVPK-30	12	12	12	12
IPA	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3
Talc	3	3	3	3
Coating ingredient Wt gain (%)	4%	4%	4%	4%

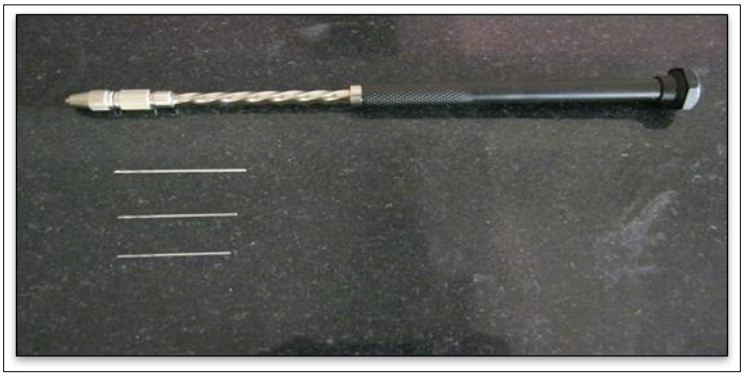

Figure 1 Mechanical driller for drill the orifice in the EOP Tablet

2.4 Evaluation of uncoated Osmotic tablet

2.4.1 Appearance and Shape

The general appearance of the tablet includes the morphological characteristics like size, shape, color etc. also tablets may have lines, break-marks and may bear a symbol or other markings. These values were checked and used to adjust the initial stages of compression. As in current study no any symbol or marking was used so the appearance was set as plain surface.

2.4.2 Measurement of thickness and diameter:

The uniformity of the diameter and thickness was measured using vernier caliper. The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average

2.4.3 Hardness

Monsanto hardness tester model VMT-239 manual (vinsyst) manufactured by vincyst technologies Mumbai was used to check the hardness of the tablet. The tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load was increased and at collapse the applied pressure from the spring was measured in kg/cm^2. The mean ± SD was calculated.

2.4.4 Friability

Twenty tablets as prescribed in Indian Pharmacopoeia were weighed and placed in a Roche friabilator (Electrolab, India). Twenty reweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula,

$$\% \text{ loss } = \frac{\text{Initial wt. of tablets } - \text{ Final wt. of tablets}}{\text{nitial wt. of tablets}} \text{x } 100$$

2.4.5 Uniformity of dosage form

To study weight variation, 20 tablets were weighed individually using an electronic balance and the test was performed according to the official method. The average weight was calculated from the total weight of 20 tablets. The individual weights were compared with the average weight. Since the average weight of tablet is 250 mg, the percentage difference in the weight variation should be within the permissible limits according to the Indian Pharmacopoeia the limit for weight variation for tablets weighing 250 mg or more is ± 5 %. The tests requirements are met if not more than 2 tablet of individual weights deviates from the percentage ie.5%.

2.4.6 Drug Content Uniformity

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 8 mg drug and dissolved in 8 ml of 0.1N NaOH and the volume was made upto 100 ml with pH 6.8 phosphate buffer. The solution was shaken for 1 hr and kept for 24 hr. From the stock solution, 1 ml solution was taken in 10 ml empty volumetric flask and the volume was made with pH 6.8 phosphate buffer. Solution was filtered and absorbance was

measured spectrophotometrically at 376 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

2.5 Preparation of Coating Solution

The coating solution containing cellulose acetate and sorbitol (pore forming agent) was prepared as per the formula given in the Table 03. Accurately weighed quantity of cellulose acetate was added to acetone (90%). The mixture was heated at 40^0C and stirred until the formation of clear solution. The weighed quantity of sorbitol was dissolved in 2-4ml of distilled water, then this solution was added in IPA (10%) and the solution was added slowly to the cellulose acetate solution. The mixture was stirred continuously for 30 min. Then solution was filtered through muslin cloth.

2.6 Coating of Lornoxicam osmotic core tablet

The solution of cellulose acetate in acetone: IPA (90:10) was used to achieve a weight gain of approximately 3-5% per tablet. The core tablets were film coated in a conventional pharma R & D coater (mfg by- Ideal cures Pvt. Ltd), 4 inches with 3 baffled stainless steel pan by spray coating process. The coating parameters were optimized on placebo tablets made by lactose monohydrates and 0.5% magnesium stearate. Initially the tablets were kept at 40°C for 10 min while the pan rotated at 15 rpm.

The rotating speed was then increased to 15-30 rpm and the coating solution was sprayed at a rate of approximately 1-2 ml/min. The atomizing pressure was adjusted to 1-2 kg/cm^2, and the inlet and outlet temperatures were varied from 35-55°C. The process was continued until the whole solution was sprayed onto the tablets. The coated tablets were rotated for a further 15 min under blower. The coating process parameters were optimized with respect to coating pan speed, coating pan inlet air temperature, atomizing air pressure and spray rate.

2.7 Evaluation of Lornoxicam osmotic coated tablet

2.7.1 Percentage Weight gain

From the batch of Lornoxicam tablets, 30 core tablets were randomly selected subjected to coating. The initial weight of 30 uncoated tablets was recorded. After period of coating, spraying of coating solution was stopped an allowed to drying for 10–15 min, in the coating pan at 45°C to remove the majority of solvent moisture. The weight of 30 coated tablets was recorded. The percent weight gain was calculated. Samples were collected for predetermined weight gain (approximately).

2.7.2 Thickness of film

Three tablet of each batch were evaluated for thickness of film. After dissolution, tablet shell is cut with help of cutter and washed with water to obtain a clear film. The thickness of the film was measured using screw gauze.

2.8 Scanning Electron Microscopy (SEM)

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope (SEM). Before dissolution, the tablets were cut with a sharp blade and coating membrane was taken out. This membrane was cleaned with dried cloth to remove any adherent particles and was used for SEM. Similarly, coating membrane was taken out from the tablets after 12 hr of dissolution study and was used for SEM. The coating membrane was carefully washed 3-4 times with water to remove any adherent solid particles. Coating membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination.

The small pieces of coating membranes were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape in such a way that the outer portion of coating membrane comes in front of electronic beam and was examined under scanning electron microscope.

2.8.1 Dissolution Studies

The release rate of lornoxicam from CPOP and EOP (n=3) was determined from all the batches. Batches were evaluated by studying the release study for first 2 hr in 900 ml dissolution medium of 0.1 N HCl ,then remaining 10 hrs in 900 ml dissolution medium of phosphate buffer pH 7.2 using USP type II (Paddle) dissolution apparatus with 100 rpm at 37°C ± 0.5°C. The samples (5 ml) were withdrawn at an interval of 1, 2, 3, 4, 6, 8 and 12hr. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed spectrophotometrically at 376 nm.

2.8.2 Kinetics of drug release

The dissolution profile of all the batches were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model. In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated.

2.9 Comparison of release profiles for CPOP and EOP

From the comparison study it was found that the release of drug from CPOP tablet was better and greater showing to the maximum 95.81% with maximum formulation following zero order kinetics as compared to EOP tablet which showed the maximum release of 84.50% with zero and first order kinetics. The CPOP system as compared to EOP system was easy to formulate and avoid the risk of blockade. The CPOP system is cost effective, saves time and manpower required for the drilling operation. Release kinetic between CPOP and EOP was compared.

2.9.1 Statistical analysis

The release rate of different formulations were compared using one-way ANOVA at $p<0.5$. The statistical analysis was performed using Graph Pad InStat version 3.10 (10-17).

3 Results and discussion

3.1 Evaluation of core osmotic pump tablet

All formulated osmotic core tablet batches were shiny yellow with smooth surface, circular curved faced with good texture. The thickness of the tablet was found to be 4.3 to 4.5mm, due to constant tablet press setting across all batches irrespective of weight variation. Thickness depended on punch size (8.5mm) and tablet weight (250mg); coefficient of variation (based on 20 tablets/ batch) for each batch was less than ± 5 %, which indicates good thickness uniformity. Diameter of core tablet was 8.5 mm for each formulation. The hardness of the tablet was found to be in the range of 4.0 to 5.2 kg/cm^2. This ensured good mechanical strength. Drug content was uniform within each batch and ranged from 85 – 115 % of the theoretical value as per Table 08.

3.2 Evaluation of coated osmotic pump tablet

3.2.1 Percentage weight gain

To study the effect of weight gain of the coating on drug release, core tablets of lornoxicam were coated to obtain tablets with different weight gains (3%, 4%, and 5% wt/wt) for entire primary batches of individual tablet.

3.2.2 Thickness of tablet

Thickness of each primary batches were found to be in the range 4.46 to 4.59 mm.

3.2.3 Thickness of film

The thickness of coating film of primary batches was measured with electronic digital calipers and mean thickness was calculated. It was 0.067-0.094 mm for each tablet as provided in Table 08.

3.2.4 Hardness

The hardness of coated osmotic tablet of primary baches LOX01 to LOX28 are maintained from 4.6 -5.8 kg/cm^2 as provided in Table 08.

3.2.5 Uniformity of Weight

Uniformity weight for all batched was found to be between 254 -267 mg as provided in Table 08.

Table 8 Evaluation of Lornoxicam core tablet

Batch Code	Thickness, Diameter	Friability (%)	Hardness (Kg/ cm²)	Uniformity of weight (mg)	Drug content
LOX A	4.48± 0.01 mm thickness,8.5 mm diameter	0.43 ± 0.03	4.2 ± 0.57	245 ± 2.09	99.01±1.10
LOX B	4.51 ± 0.04 mm thickness , 8.5 mm diameter,	0.55 ± 0.02	5.1 ± 0.76	248 ± 1.48	101.25±1.12
LOX C	4.48 ± 0.03 mm thickness ,8.5 mm diameter	0.27 ± 0.01	4.6 ± 0.88	253 ± 2.47	101.91±0.64
LOX D	4.47 ± 0.05 mm thickness, 8.5 mm diameter,	0.74 ± 0.04	4.9 ± 0.54	251 ± 1.98	103.23±1.08
LOX E	4.47 ± 0.08 mm thickness, 8.5 mm diameter	0.65 ± 0.02	4.8 ± 0.58	247 ± 2.86	99.45±2.12
LOX F	4.50 ± 0.02 mm thickness, 8.5 mm diameter	0.13 ± 0.50	5.3 ± 0.43	258 ± 2.06	102.78±1.54

3.3 Scanning Electron Microscopy (SEM)

Cellulose acetate (CA) membranes of primary formulation of coating solution (F1), obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region (Figure 02). After 12-hour dissolution, the exhausted membrane contained plasticizer (PEG 400, 12.5 %) and pore former (sorbitol, 22 %) clearly showed a microporous region (pores) in range of 1 to 15 µm (Figure 03). Because of sorbitol is present in coating membrane, the leaching of it from the membrane leads to formation of pores, and thus the release of drug takes place.

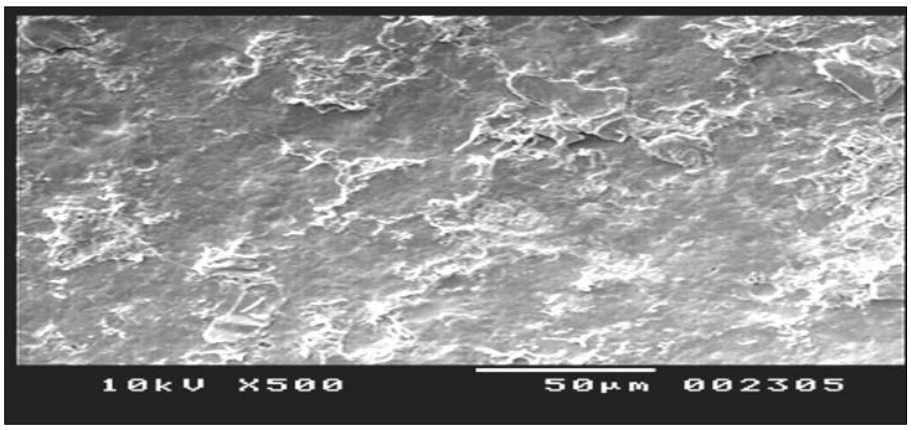

Figure 2 SEM micrograph of coating membranes of primary formulation, before dissolution

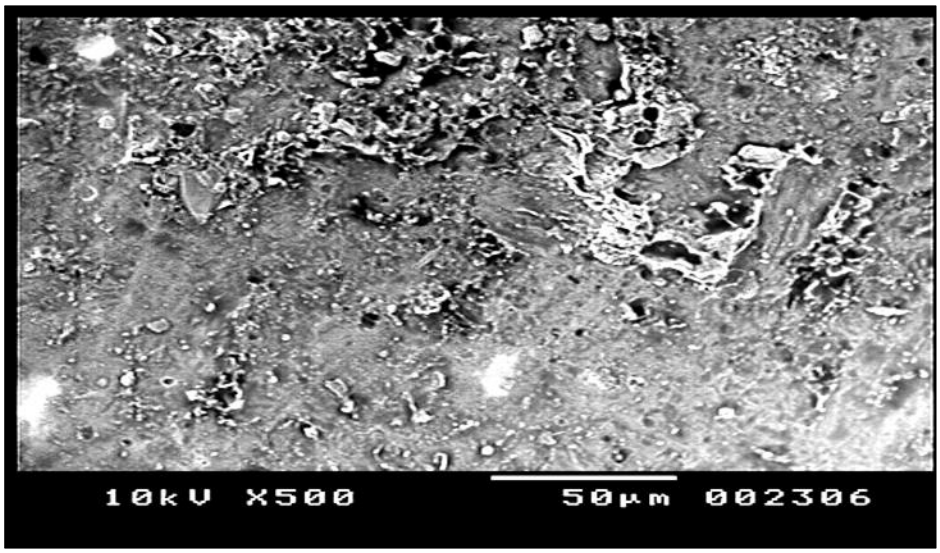

Figure 3 SEM micrograph of coating membranes primary formulation after dissolution

4 Dissolution study

Osmotic tablet were subjected to *Invitro* drug release studies in simulated gastric and intestinal fluid. Dissolution study was performed in 0.1 N HCl for first 2hr and for remaining 10 hr in Phosphate buffer pH 7.2. Result summarized in Figure 04 to 12.

Hence, it was evidence that increase in concentration of osmogen the drug release from the system found to be increased, but again reduces the drug release after increase in the external coat thickness (wt. gain). Pore former (sorbitol) produces a significant effect on release profile. Decrease in Pore former concentration system fail to release 100% drug.

Two types of osmogent (sodium chloride and mannitol) are used in the formulation of CPOP tablet. Both osmogen has different osmotic pressure and to study the effect of osmogent ratio, core formulations were prepared. The ratios of drug to osmogent i.e. sodium chloride were 1:2, 1:3, and 1:5 and with other osmogent i.e mannitol were 1:5,1:10 and 1:20. All the core formulations were coated with coating composition, F1 and F2 containing 22% and 30 % wt/wt of sorbitol respectively. Release profile from these formulations is shown in figure 04-12.

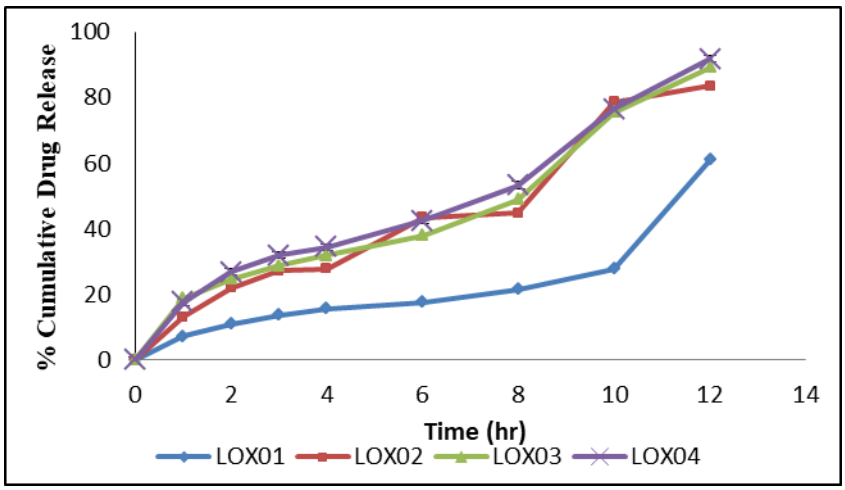

Figure 4 Comparison of *in vitro* release of batches LOX01 to LOX04

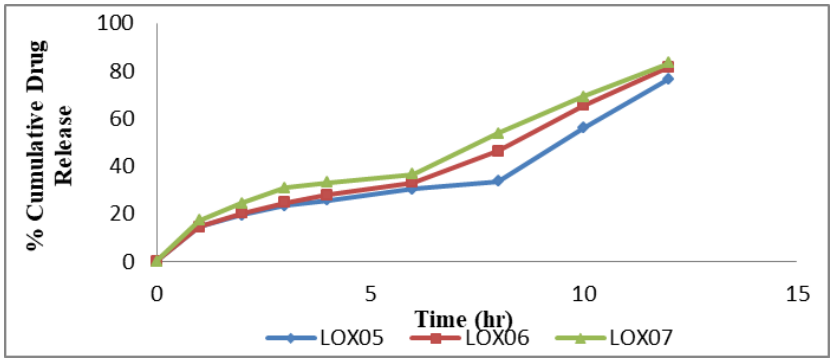

Figure 5 Comparison of *in vitro* release of batches LOX05 to LOX07

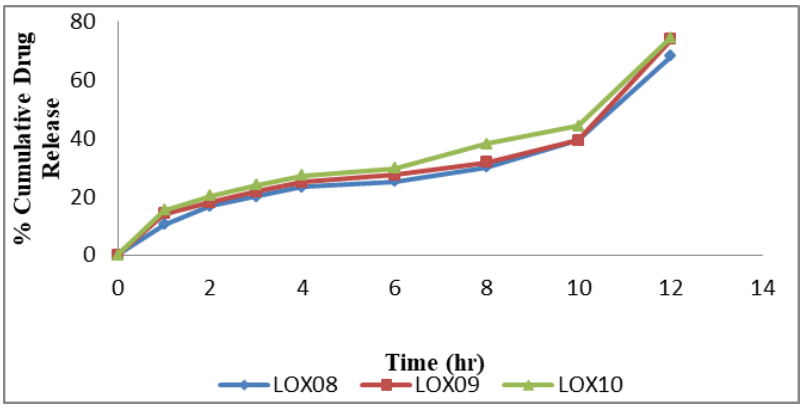

Figure 6 Comparison of *in vitro* release of batches LOX09 to LOX10

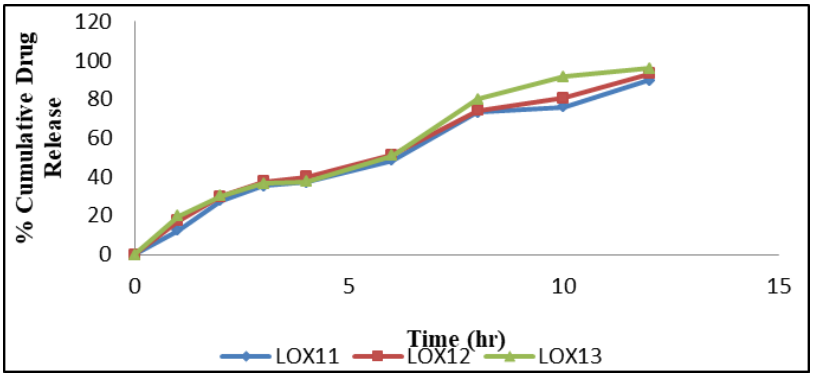

Figure 7 Comparison of *in vitro* release of batches LOX11 to LOX13

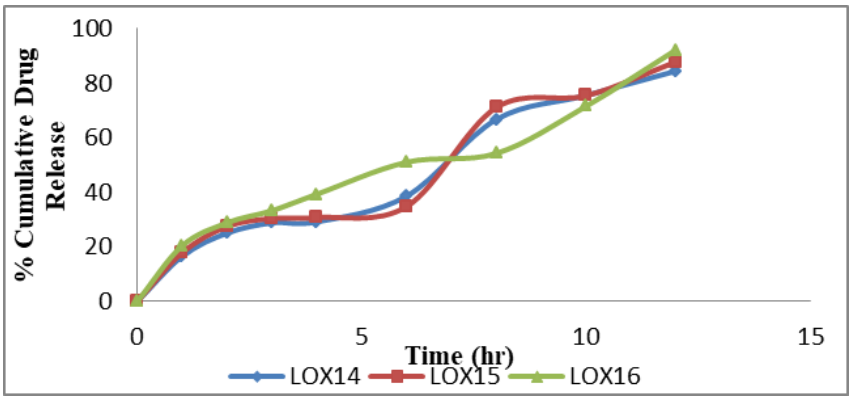

Figure 8 Comparison of *in vitro* release of batches LOX14 to LOX16

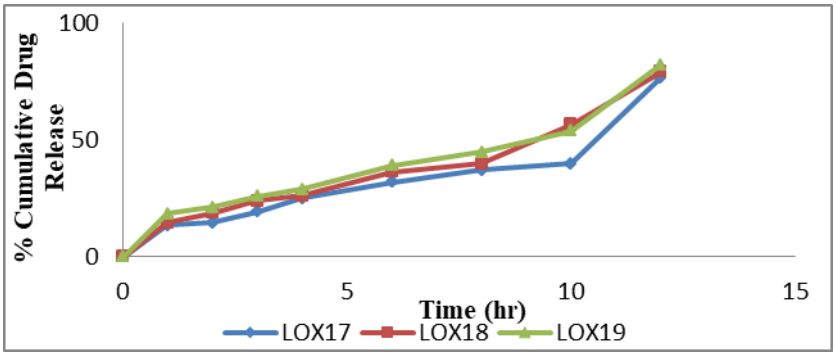

Figure 9 Comparison of *in vitro* release of batches LOX17 to LOX19

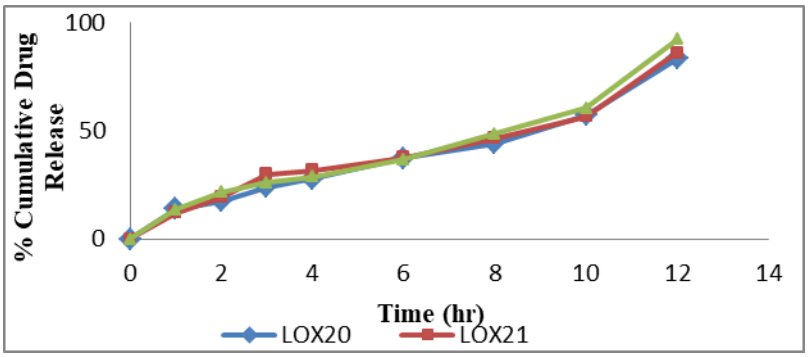

Figure 10 Comparison of *in vitro* release of batches LOX20 to LOX22

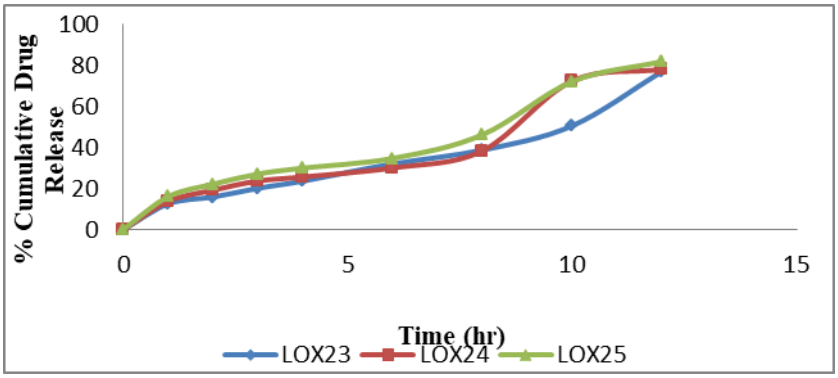

Figure 11 Comparison of *in vitro* release of batches LOX23 to LOX25

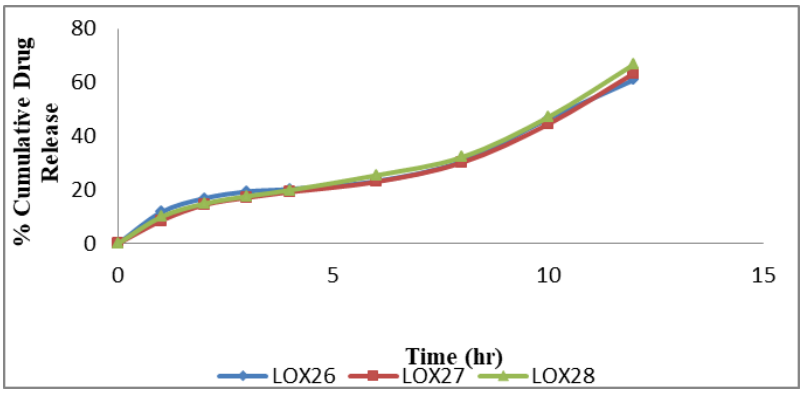

Figure 12 Comparison of *in vitro* release of batches LOX26 to LOX28

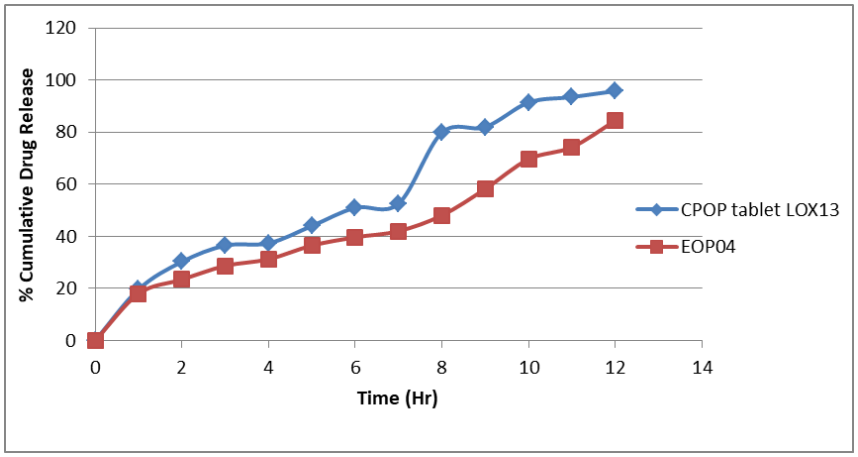

Figure 13 Comparison of *in vitro* release of batches EOP04 to CPOPLOX13

Table 9 Drug release kinetics of the formulated batches

Batch code	R^2					n	k
	Zero order	1st order	Matrix	Peppas	Hixson Crowell		
LOX01	0.8905	0.8153	0.8069	0.9216	0.8436	0.6827	6.2915
LOX02	0.9731	0.8997	0.9099	0.9660	0.9305	0.7142	12.1489
LOX03	0.9570	0.8755	0.9053	0.9319	0.9171	0.6070	15.3291
LOX04	0.9722	0.8894	0.9285	0.9596	0.9365	0.9365	15.6322
LOX05	0.9463	0.8889	0.8961	0.9324	0.9174	0.6006	12.2260
LOX06	0.9799	0.9233	0.9195	0.9631	0.9525	0.6853	12.0217
LOX07	0.9670	0.9371	0.9419	0.9598	0.9610	0.6066	15.3437
LOX08	0.9240	0.8664	0.8911	0.9500	0.8932	0.6109	9.9547
LOX09	0.8963	0.8215	0.8741	0.9204	0.8565	0.5127	12.2218
LOX10	0.9340	0.8838	0.8981	0.9285	0.9096	0.5644	13.0470
LOX11	0.9746	0.9503	0.9582	0.9844	0.9768	0.7490	13.7751
LOX12	0.9692	0.9361	0.9641	0.9860	0.9727	0.6634	17.1903
LOX13	0.9797	0.9222	0.9480	0.9604	0.9616	0.6613	17.6939
LOX14	0.9672	0.9416	0.9179	0.9401	0.9587	0.6785	13.9232
LOX15	0.9582	0.9291	0.9169	0.9276	0.9506	0.6453	15.2203
LOX16	0.9555	0.8923	0.9575	0.9761	0.9412	0.5809	18.5326
LOX17	0.9353	0.8527	0.8852	0.9417	0.8901	0.6358	10.6651
LOX18	0.9513	0.8928	0.9208	0.9597	0.9249	0.6197	12.5847
LOX19	0.9425	0.8612	0.9059	0.9374	0.9016	0.5895	14.7264
LOX20	0.9746	0.8308	0.9138	0.9715	0.9033	0.7076	12.0618
LOX21	0.9586	0.8676	0.9340	0.9811	0.9180	0.6881	12.0935
LOX22	0.9769	0.8998	0.9233	0.9732	0.9394	0.6922	11.5430
LOX23	0.9634	0.8881	0.8932	0.9531	0.9221	0.6859	10.0106
LOX24	0.9483	0.8970	0.8694	0.9209	0.9186	0.7175	10.9664

LOX25	0.9720	0.9274	0.9170	0.9508	0.9516	0.6609	13.3600
LOX26	0.9541	0.8995	0.8697	0.9438	0.9218	0.7179	8.2398
LOX27	0.9501	0.9010	0.8658	0.9452	0.9209	0.7283	7.5699
LOX28	0.9431	0.9089	0.8792	0.9150	0.9242	0.6151	9.7895

5 Discussion

The result revealed that formulation LOX01 that was devoid of any osmogent in the core and showed less drug release in 12 hours. A greater amount of osmogen i.e sodium chloride with 22% pore former (sorbitol) containing formulation LOX04 showed increase drug released with 3% weight gain than 4% and 5% weight gain in 12 hours Formulation which containing sodium chloride with 30% pore former (sorbitol), LOX13 showed increase drug released with 3% weight gain than 4% and 5% weight gain in 12 hours.

In another set of formulation containing mannitol as an osmogen with 22% pore former (sorbitol), LOX22 showed increase drug released with 3% weight gain, 4% and 5% weight gain in 12 hours.

5.1 Effect of Ratio of Drug to Osmogent (Osmogent/osmotic agents)

The comparative dissolution profile of all the formulation containing different ratios of drug to osmogen i.e sodium chloride 1:4 and mannitol in the ratio 1:20 gives better release of drug from osmotic tablet. From these release profile, it is clear that increase in the concentration of osmotic agent, greater the driving force and enhances the release of drug and thus had a direct effect on drug release. When the coated tablet is exposed to an aqueous environment, water diffuses through the film coating (due to the active gradient of water), hydrating the core. The solvation of the osmotic agents creates osmotic pressure difference between the core contents and external environment results in greater lornoxicam release.

The CPOP formulation containing sodium chloride as an osmogen showed better release profile as compare to mannitol; because of sodium chloride has high osmotic pressure than mannitol.

5.2 Effect of Pore Forming Level

To study the effect of pore forming agent, core formulations of lornoxicam were coated with varying coating compositions of sorbitol as a pore former. Sorbitol was added 22%, and 30% wt/wt of coating polymer. Release profile from these formulations is shown in figure 07-15. The release profile showed that the formulation LOX13 containing 30% wt/wt of sorbitol increased 95.81% of drug where as the formulation LOX04 containing 20% wt/wt of pore former release only 91.82% of drug as shown in figure 18. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. The level of pore former also affects the burst strength of exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in the level of sorbitol, the membrane became more porous after exposure to water, leading to a decrease in its strength.

5.3 Effect of Weight Gain

To study the effect of weight gain of the coating on drug release, core tablets of lornoxicam were coated to obtain tablets with different weight gains (3%, 4%, and 5% wt/wt). Release profile of lornoxicam from these formulations is shown in comparison for LOX13 & LOX19 as per figure 19. The release profile showed that formulation LOX04, LOX13 and LOX22 with 3% weight gain increased drug release than other formulation which coated with 4% and 5% weight gain. Drug release from 5% weight gain show very less than 3% & 4% because of cellulose acetate film thickness inhibit the release rate of drug. It is clearly evident that drug release decreases with an increase in weight gain of the membrane.

5.4 Drug release kinetics

Majority of the formulations showed the diffusional exponent; “n” in between 0.5 and 1.0 which indicate the anomalous transport or kinetics that means the drug is released by the combined mechanism of pure non-fickian diffusion controlled and swelling controlled drug release. For some formulations “n” value was approximately 0.5 which indicated that drug was released by pure diffusion controlled mechanism (fickian diffusion). The n ($0.5<n<1$) value also revealed the drug release mechanism via diffusion coupled with erosion. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient as provided in table 10.

5.5 Comparative study of CPOP and EOP

EOP lornoxicam tablet was drilled with mechanical driller having orifice size 0.8 mm and deliver the drug upto 12 hr. It was observe that, with orifice size 0.8mm lornoxicam released 84.5% within 12 hr. On the basis of these release, it is observed that formulation containing without osmogen shown decreased in release of drug than formulation containing osmogen. Amongest all the EOP formulation, EOP04 showed highest release rate i.e. 84.5% of drug in 12 hr as compare to other formulation.

Elementary osmotic pump lornoxicam tablet (EOP) was taken for comparison with controlled porosity osmotic pump lornoxicam tablet (CPOP) and dissolution studies was observed. Comparative study reveals that, CPOP tablet and EOP tablet containing same proportion of osmogen (sodium chloride) and when the release profile of CPOP formulation were compared with EOP formulation it is found that CPOP formulation showed significantly higher release as compare to EOP formulation. Release kinetics data are shown in the table, showed that elementary osmotic pump formulation follow zero order and peppas release model but R^2 for zero order is less than CPOP the comparison of CPOP and EOP tablet has been shown in figure 20.

In the EOP tablet, it is chance of orifice blockage, and extra formulation stage increase for drilling, which is time consuming. Hence, CPOP is easier and cost effective to formulate.

On the basis of above, it is concluded that CPOP is superior to conventional EOP.

5.6 Statistical analysis

The release rate of different formulations was compared using one-way ANOVA. The statistical analysis was performed using Statistical Package for Social Science (SPSS) version 11. It was found that there is significant difference in primary batch, except, some batches like LOX12, LOX15, LOX18, LOX18, LOX24 and LOX28.

6 Conclusion

Osmotically regulated oral drug system (OODS) is suitable for the controlled release of the drugs throughout the GI tract. Controlled porosity osmotic tablet is novel concept in OODS, which is cost effective and easy to formulate. In present study on Controlled porosity osmotic tablet and Elementory osmotic pump tablet of Lornoxicam was formulated. The study involved the formulation and evaluation of the CPOP & EOP and evaluation for various parameters like concentration of osmogen (NaCl, Mannitol), weight gain (percentage coating) and concentration of pore former (sorbitol). Drug release was directly proportional to the initial level of pore former (sorbitol) i.e pore former increases with increase in release of drug. The increase in lornoxicam release is due to formation of more pores after coming in contact with aqueous environment. The conclusions arrived in this study indicated that the controlled porosity osmotic pump and Elementary osmotic pump tablet of lornoxicam developed in this investigation was found to be better controlled release osmotic system. Thus the objectives envisaged in this study were observed. Finally, it can be concluded that osmotically controlled drug delivery system can control the release of lornoxicam for 12 hr with zero order release kinetics, which can reduce dosing frequency and patient compliance and it will be a promising tool to better oral administration.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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