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Original Article

Formulation, development and evaluation of an osmotic drug delivery system for lornoxicam

Shoaeb Mohammad Syed[1], Iftequar Ahmed Syed[2], Rajendra Panditrao Marathe[3]

[1]Dayanand College of Pharmacy Department of Pharmaceutics, Latur, India
[2]Y B Chavan College of Pharmacy, Aurangabad, India
[3]Government College of Pharmacy, Ratnagiri-India

ORCID IDs of the authors: S.M.S. 0000-0002-1239-9990; I.A.S. 0000-0003-3380-6003; R.P.M. 0000-0001-9675-8446

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ABSTRACT

Background and Aims: The current study aimed to develop an osmotic drug delivery system for Lornoxicam to prolong its release.

Methods: Two different approaches were used for development of the osmotic drug delivery system; the first one was to formulate a controlled porosity osmotic tablet and the other was to design an elementary osmotic tablet. The controlled porosity osmotic tablets were coated with different concentrations of osmogents, a pore former, and varying coating thicknesses, and the effects were observed on the release. In the elementary osmotic pump, the tablets were drilled to make an orifice that creates pressure to release the drug by osmosis, and drug release was studied.

Results: The formulations were evaluated for different parameters namely 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 the different concentrations of pore-forming sorbitol were studied. A comparison was made between the controlled porosity osmotic tablet in which the membrane coating contains water-soluble pore-forming polymers that leach when the membrane comes in contact with water thereby permitting water inside the wall and creating the osmotic pressure to release the drug, and the elementary osmotic tablet containing the osmotic agent sodium chloride coated with the rate-controlling semipermeable membrane, cellulose acetate, which contains an orifice of a critical size through which the drug is delivered.

Conclusion: From the results, it was found that the developed formulation of the controlled porosity osmotic tablet was able to release Lornoxicam (CPOP) over 12 hours at zero-order kinetics and, the concentration of the osmotic agent, level of pore former, and thickness of the membrane coating are responsible for controlling the release of lornoxicam. The membrane coating was subjected to SEM analysis, which showed the formation of pores in the membrane. The developed controlled porosity osmotic pump tablet of lornoxicam was found to control the drug release for 12 hours.

Keywords: Lornoxicam, Controlled porosity osmotic tablet, elementary osmotic tablet, drug release, osmotic agent, pore former & scanning electron microscopy

Address for Correspondence:
Shoaeb Mohammad SYED, e-mail: ybccpsh@gmail.com

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INTRODUCTION

Oral administration is one of the ancient and widely used routes for effective and convenient drug delivery with both local and systemic effects (Theeuwes, 1975). Conventional preparations are usually administered twice or three times a day, which leads to a large fluctuation in drug plasma concentration and side effects on the human body. Constant plasma levels can offer a therapeutic advantage for many drugs in terms of both efficacy and tolerance of the treatment (Theeuwes, 1975). Once-daily controlled-release formulations are often desirable. Osmotic drug delivery is a reliable and convenient controlled drug delivery system (CDDS). Osmotic pressure acts as a driving force for these systems to release the drug in a controlled manner. The osmotic pump tablet (OPT) generally consists of a core including the drug(s), an osmotic agent, other excipients, and a semipermeable membrane coat. Osmosis is a phenomenon that tends to achieve a zero-order drug release. It acts as a driving force for the release of drugs from the dosage form. The osmotic tablet works on the principle of osmosis i.e., water moving through a permeable membrane driven through the difference in osmotic pressure across the membrane. It is driven by a difference in solute concentration across the membrane that allows the passage of water but rejects most solute molecules or ions. Based on this principle, osmotic drug delivery results in better drug release independent of the concentration of the drug. The aim of controlled release drug delivery is to sustain the action of the drug at a determined rate by maintaining a constant and effective drug level in the body with minimum side effects (Zenter, McClelland, & Sutton, 1991; Santus & Baker, 1995; Herbig, Cardinal, Korsmeyer, & Smith, 1995; Patel et al., 2010).

The osmotic pump tablet is preferred among the controlled release systems and has many advantages, such as reducing the risk of adverse reaction, improving the compliance of patients, and exhibiting comparable *in vitro/in vivo* drug release. Drug substances can be delivered in a controlled pattern over a long period by osmotic pressure with the increased interest in the development of osmotic devices over the past two decades. Delivery of drug substances from osmotic systems is not affected by the varying physiological factors within the gut lumen and the drug release patterns can be easily predicted from the known properties of the drug substance and the dosage form (Pritam, Braj, Ambikanadan, Prakash, & Rajesh, 2007; Kumar, Singh, & Mishra, 2009; Syed, Farooqui, Mohammed, Dureshahwar, & Farooqui, 2015). Lornoxicam, from the class of oxicam cluster of non-steroidal anti-inflammatory drugs, is used as an analgesic and anti-inflammatory. Its commercially available dosage forms 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 has a half-life of 3-5 hours, a 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 (Santus et al., 1995; Govt. of India 1996; Syed, et al., 2015).

In 1974, Theeuwes invented an elementary osmotic pump (Theeuwes, 1975). The elementary osmotic pump delivers the drug by the osmotic process at a controlled rate. The control rests in: *a)* water permeation characteristics of a semi-permeable membrane surrounding the formulating agent *b)* osmotic properties of the formulation. This system contains an osmotically active agent surrounded by the rate-controlling semi-permeable membrane. The device is created by a drug having appropriate osmotic pressure into a tablet using a tableting machine followed by coating the tablet with a semi-permeable membrane and drilling of small hole through the membrane (size varies from 0.5 to 1.5 mm).The drilling may be done by mechanical drilling or laser drilling (CO_2 laser beam with a wavelength of 10.6μ) (Herbig et al., 1995; Patel et al., 2010). On exposure of the dosage form to the aqueous environment, the imbibition of water occurs by the core osmotically at a controlled rate and is determined by the permeability of the membrane and osmotic pressure of the core formulation. The volume of saturated drug solution delivered is equal to the volume of solvent uptake (Chai, Xu, & Liu, 2008). The advantages of this system include being easy to develop, suitable for the drug having moderate solubility, and economical. The disadvantages are that the size of the hole is critical, and blockage of the orifice is possible (Pritam et al., 2007; Chai et al., 2008; Kumar et al., 2009; Edavalath, Shivanand, Kalyani, Prakash, & Goli, 2011 Syed, et al., 2015).

For design of controlled porosity osmotic pump; the pump can be made with a single or multi-compartment dosage form. In either form, the delivery system comprises a core with the drug surrounded by a membrane that has an asymmetric structure, i.e., it comprises a skinny layer with a supporting porous substructure. The membrane is formed by a phase inversion process in which controlled by the evaporation of a mixed solvent system. The membrane is porous to water, however, rubberizes to solutes and is insensitive to pore-forming additives dispersed throughout the wall. When exposed to water, low levels of water-soluble additives are leached from the polymer materials that were permeable to water yet remained insoluble. The resulting sponge-like structure forms the controlled porosity walls of interest and is substantially permeable to both water and the dissolved drug agents (Liu et al., 2007; Chai et al., 2008; Kumar et al., 2009; Edavalath et al., 2011; Syed et al., 2015).

The current study aimed to develop an osmotic drug delivery system for Lornoxicam. Two different approaches were used for the formulation. The first one was to formulate a controlled porosity osmotic tablet and the other was to design an elementary osmotic tablet. The formulations were evaluated for different parameters namely appearance, uniformity of weight, drug content, hardness, and drug release pattern. In addition, the effect of different osmotic agents responsible for developing the osmotic pressure such as sodium chloride and mannitol along with the different concentrations of pore-forming sorbitol were studied. The controlled porosity osmotic tablet

in which the membrane coating contains water-soluble pore-forming polymers that leach when the membrane comes in contact with water thereby permitting water inside the wall, and creating the osmotic pressure to release the drug were compared with the elementary osmotic tablet containing the osmotic agent coated with the rate-controlling semi-permeable membrane which contains an orifice of a critical size through which the drug is delivered.

MATERIALS AND METHODS

Materials

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

Analytical method

Preparation of standard stock solution: The standard drug solution of lornoxicam was prepared by dissolving 10 mg in phosphate buffer pH 7.2 and the volume was made up to 100 ml to obtain a stock solution concentration of 100 µg/ml. Ultrasonication procedure was applied to obtain a clear solution (Liu et al., 2007; Edavalath et al., 2011; Syed, & Mohammed, 2014)

Determination of measurement wavelength: From the standard stock solution, 1 ml was pipetted out into a 10 ml volumetric flask. The volume was made up to 10 ml with a phosphate buffer solution of pH 7.2. The resulting solution containing 10 µg/ml was scanned between 200 and 400 nm. (Liu et al., 2007; Edavalath et al., 2011; Syed, & Mohammed 2014).

Preparation of calibration curve of Lornoxicam in phosphate buffer pH 7.2: Aliquots of 0.2 to 1.4 ml portions of stock solutions were transferred to a series of 10 ml volumetric flasks, and the volume was made up to the mark with phosphate buffer pH 7.2. Serial dilutions of the range of 2, 4, 6, 8, 10, 12, and 14 µg/ml were prepared. The absorbance was measured at λ_{max} 376 nm (Liuet al., 2007; Edavalathet al., 2011; Syed**,** & Mohammed, 2014).

IR spectroscopic analysis: The identification of Lornoxicam was done by FTIR spectroscopy. The IR absorbance spectrum of Lornoxicam was recorded using a Jasco-4100 spectrometer over a range of 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}. KBr powder was dried at 60 °C for one hour. The dried KBr powder was mixed uniformly with the drug and IR spectra were taken for this mixture (Liuet al., 2007; Edavalathet al., 2011; Syed**,** & Mohammed, 2014).

Solubility study

The solubility of the compound was carried out in water, 0.1 N HCl, and phosphate buffer pH 6.8, pH 7, pH 7.2, and pH 7.4. An excess amount of drug was dissolved in 5 ml of solvent. The solution was then subjected to ultrasonication for 30 minutes. It was then allowed to stand for 24 hours at room temperature in tightly closed vials to attain a saturation equilibrium. After 24 hours, the solution was filtered through Whatman filter paper No 41. It was then diluted appropriately with the solvent and was analyzed at 376 nm by UV Spectrophotometry (Liuet al., 2007; Edavalathet al., 2011; Syed**,** & Mohammed, 2014).

Excipients compatibility study

It is very important to perform a physicochemical evaluation of all excipients which are probably used in the formulations. While most excipients have no direct pharmacological action, they do perform either useful tasks or damaging actions (such as speeding up the degradation of the drug). Interactions in the solid state between the active ingredient and the excipients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs. The IR study was performed between drug and the excipients (Liuet al., 2007; Edavalathet al., 2011; Syed**,** & Mohammed, 2014).

Preparation of osmotic core tablet

The osmotic core tablets were prepared by the wet granulation method. The granules were prepared by the non- aqueous (IPA) granulation technique. Lornoxicam and all the excipients previously passed through ano. #60sieve. Then, Lornoxicam was mixed with all the excipients except the binding and solubilizing agents as per the formulas given in Table 1-2 The blend was mixed for 10 minutes in a polybag and later, the mixture was granulated with a PVP K-30 (binder) in isopropyl alcohol (IPA) (solvent for wet granulation) and wetting/solubilizing agents. The resulting wet mass was passed through a no. #25 sieve and the granules were dried at 50 °C for 15 minutes to obtain a loss on drying (LOD) value between 1% and 1.2%, after which they were passed through a no #30 sieve and compressed using tablet machine (Rimek mini press-II, Gujrat, India) .

The core tablets containing 8 mg of lornoxicam for primary batches were formulated using NaCl (16, 24, 32 mg) as an os-cellulte bat (o

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Elementary osmotic pump (EOP) tablets of Lornoxicam were prepared which contained the osmogent (NaCl) in the 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 a mechanical driller with manual rotation (PCP driller) of orifice size 0.8 mm. Figure 4 represents the mechanical driller for the orifice in the EOP tablet and coated with 4% w/w cellulose acetate without pore former. The coating weight gain was maintained at 4% for each tablet, as per Table 1-2.

Table 1. Primary Batches of an osmotic tablet with sodium chloride.

Ingredients (mg)	LOX01	LOX02	LOX03	LOX04	LOX05	LOX06	LOX07	LOX08	LOX09	LOX10	LOX11	LOX12	LOX13	LOX14	LOX15
Core Tablet Lornoxicam	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Sod. Chloride	--	16	24	32	16	24	32	16	24	32	16	24	32	16	24
MCC	162	146	138	130	146	138	130	146	138	130	146	138	130	146	138
Lactose	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
SLS	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
PVP K-30	12	12	12	12	12	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.	q.s.	q.s.	q.s.	q.s.	q.s.
Mag. Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Coating Wt gain %	3%	3%	3%	3%	4%	4%	4%	5%	5%	5%	3%	3%	3%	4%	4%
Pore former (Sorbitol%)	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	30%	30%	30%	30%	30%

Table 2. Primary Batches of an osmotic tablet with sodium chloride/mannitol.

Ingredients (mg)	LOX16	LOX17	LOX18	LOX19	LOX20	LOX21	LOX22	LOX23	LOX24	LOX25	LOX26	LOX27	LOX28
Core Tablet Lornoxicam	8	8	8	8	8	8	8	8	8	8	8	8	8
Sod. Chloride/ Mannitol LOX20 onwards	--	16	24	32	16	24	32	16	24	32	16	24	32
MCC	162	146	138	130	146	138	130	146	138	130	146	138	130
Lactose	50	50	50	50	50	50	50	50	50	50	50	50	50
SLS	12	12	12	12	12	12	12	12	12	12	12	12	12
PVP K-30	12	12	12	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.	q.s.	q.s.	q.s.
Mag. Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Coating Wt gain %	3%	3%	3%	3%	4%	4%	4%	5%	5%	5%	3%	3%	3%
Pore former (Sorbitol%)	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	30%	30%	30%

Table 3. 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%

Table 4. Formulations of core tablets with Sodium chloride (Osmogent).

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 5. Formulation of the 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 v/v	90:10 v/v

The polymers and their concentrations were chosen based on the literature as well as results obtained from primary batches.

Table 6. Formulations of core tablets with Mannitol (Osmogent).

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

Evaluation of uncoated osmotic tablets

Measurement of thickness and diameter

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

Hardness

The Monsanto hardness tester model VMT-239 manual (VinSyst) manufactured by VinSyst 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 are placed under tension by a 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.

Friability

Twenty tablets, as prescribed in the 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 re-weighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula,

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

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 the 20 tablets. The individual weights were compared with the average weight. Since the average weight of the tablet was250 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 test requirements are met if not more than 2 tablets of individual weight deviate from the percentage, i.e., 5%.

Drug content uniformity

Ten tablets were weighed and the average weight was calculated. All tablets were crushed, powder equivalent to 8 mg drug was dissolved in 8 ml of 0.1 N NaOH and the volume was made up to 100 ml with pH 7.2 phosphate buffer. The solution was shaken for 1 hour and kept at room temperature for 24 hour. From the stock solution, a 1 ml aliquot was transferred to a 10 ml empty volumetric flask and the volume was made with pH 7.2 phosphate buffer. The solution was filtered and the absorbance was measured spectrophotometrically at 376 nm against a pH 7.2 phosphate buffer as a blank. The amount of drugs contained in one tablet was calculated.

Preparation of coating solution

The coating solution containing cellulose acetate and sorbitol (pore-forming agent) was prepared as per the formula given in Table 5. An accurately weighed quantity of cellulose acetate was added to acetone (90%). The mixture was stirred until a clear solution was formed. The weighed quantity of sorbitol was dissolved in 2 to 4 ml of distilled water, then this solution was added to IPA (10%) and the solution was added slowly to the cellulose acetate solution. The mixture was stirred continuously for 30 minutes. Then the solution was filtered through a muslin cloth.

Coating of lornoxicam osmotic core tablet

The solution of cellulose acetate in acetone: IPA (90:10, v/v) 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 India), 4 inches with 3 baffled stainless-steel pans by a spray coating process. The coating parameters were optimized on placebo tablets made of lactose monohydrates and 0.5% magnesium stearate. Initially, the tablets were kept at 40 °C for 10 minutes while the pan rotated at 15 rpm.

The rotating speed was then increased to 15 to 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 the blower. The coating process parameters were optimized concerning coating pan speed, coating pan inlet air temperature, atomizing air pressure, and spray rate.

Evaluation of lornoxicam osmotic coated tablet

Percentage weight gain

From the batch of lornoxicam tablets, 30 core tablets were randomly selected and subjected to coating. The initial weight of 30 uncoated tablets was recorded. After a period of coating, the spraying of the coating solution was stopped and the tablets were allowed to dry for 10–15 min in the coating pan at 45 °C to remove the majority of the solvent moisture. The weight of the 30 coated tablets was recorded. The percent weight gain was calculated.

The thickness of film

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

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 the coating membrane was taken out. This membrane was cleaned with a dried cloth to remove any adherent particles and was used for SEM. Similarly, the 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 to 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 desiccator 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 the coating membrane was in front of an electronic beam and was examined under a scanning electron microscope.

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 for the first 2 hours in 900 ml dissolution medium of 0.1 N HCl, then the remaining 10 hours in 900 ml dissolution medium of phosphate buffer pH 7.2 using a USP type II (Paddle) dissolution apparatus with 100 rpm at 37±0.5 °C. The samples (5 ml) were withdrawn at an interval of 1, 2, 3, 4, 6, 8, and 12 hours with the addition of fresh buffer solution (5 ml) maintaining the sink condition. The withdrawn samples

were replaced with a fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed spectrophotometrically at 376 nm.

Drug release kinetics

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

Statistical analysis

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

RESULTS

Solubility study

The solubility of Lornoxicam was determined in various mediums. Thus, from the results, the drug shows pH-dependent solubility. The solubility data is given in Table 7.

Compatibility of the drug with excipients

To check the interaction between the drug and polymers used in the formulations, IR studies were performed. In the IR study, it was found that all the prominent peaks which were present in the individual graphs of lornoxicam and polymers were also present in the IR of the physical mixture of the drug and polymers. These peaks were not affected and were prominently observed in FT-IR spectra (Figures 1, 2, and 3).Thus, we can say that no significant interaction between the drug and polymers were observed (Table 8).

Table 7. Solubility study of Lornoxicam.

Sr. no.	Medium	Solubility (mg/ml)
1.	Water	0.257
2.	0.1 N HCl	0.464
3.	Phosphate buffer pH 4	0.396
4.	Phosphate buffer pH 6.8	0.621
5.	Phosphate buffer pH 7.2	1.862
6.	Phosphate buffer pH 7.4	4.120

Evaluation of core osmotic pump tablet

All formulated osmotic core tablet batches were shiny yellow with a smooth surface, circular curved face and with good texture. The thickness of the tablet was found to be 4.3 to 4.5mm, due to the constant tablet press setting across all batches irrespective of weight variation. Thickness depended on punch size (8.5mm) and tablet weight (250mg); the coefficient of variation (based on 20 tablets/ batch) for each batch was less than ± 5 %, which indicates good thickness uniformity. The diameter of the core of the 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 9.

Evaluation of coated osmotic pump tablet

Percentage weight gain

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

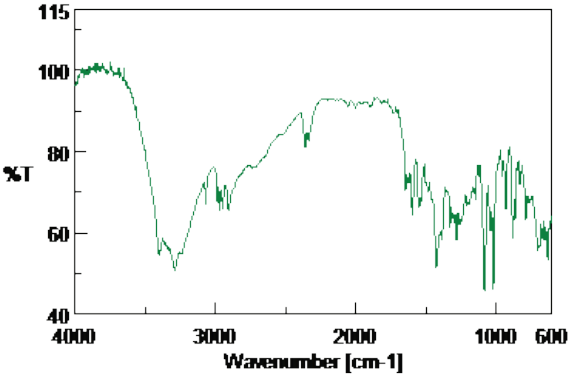

Figure 2. IR of Spectrum of mixture of Lornoxicam and Sodium chloride.

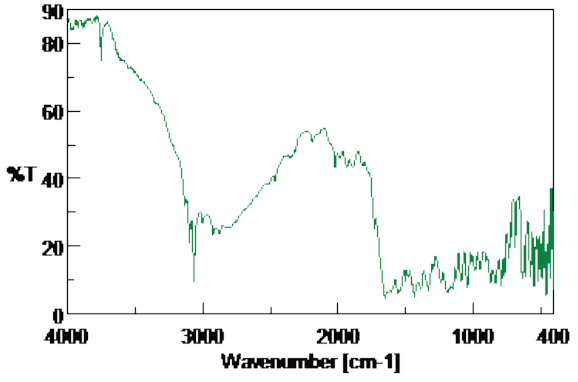

Figure 1. IR Spectrum of Lornoxicam).

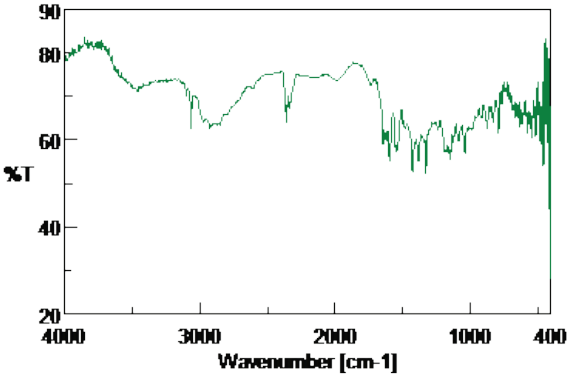

Figure 3. IR Spectrum of mixture of Lornoxicam and Mannitol.

Table 8. IR Study of Lornoxicam with excipients.

Groups	Range	Lornoxicam	Lornoxicam +Sodium chloride	Lornoxicam +Mannitol
-NH (Stretch)	3000-3500	3101.94	3100.19	3100.17
-CONH amide	1630-1680	1651.73	1645.95	1645.95
-NH (bend) sec amide	1550-1640	1555.31	1550.49	1549.52
S=O	1050	1043.3	1146.47	1043.89
C-Cl	540-785	766.56	765.601	768.707
C-H (bend) aromatic ring	690-900	831.16	831.169	830.205

Table 9. Evaluation of Lornoxicam core tablet.

Batch Code	Thickness, Diameter	Friability (%)	Hardness (Kg/ cm^2)	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

The thickness of the tablet

The thickness of each primary batch was found to be in the range of 4.46 to 4.59 mm.

The thickness of the film

The thickness of the coating film of the primary batches was measured with electronic digital calipers and the mean thickness was calculated. It was 0.067-0.094 mm for each tablet as provided in Table 9.

Hardness

The hardness of the coated osmotic tablets of the primary batches LOX01 to LOX28 was maintained between4.6 -5.8 kg/ cm^2 as provided in Table 9.

Uniformity of weight

The uniformity weight for all batches was found to be between 254 -267 mg as provided in Table 9.

Scanning electron microscopy (SEM)

Cellulose acetate (CA) membranes of the primary formulation of coating solution (F1), obtained before and after dissolution, were studied by SEM. Membranes obtained before dissolution clearly showed a nonporous region (Figure 2). After 12 hours of dissolution, the exhausted membrane containing a plasticizer (PEG 400, 12.5 %) and a pore former (sorbitol, 22 %) clearly showed a microporous region (pores) in the range of 1 to 15 µm (Figure 5). Because sorbitol is present in the coating membrane, the leaching of it from the membrane leads to the formation of pores, and thus the release of the drug takes place.

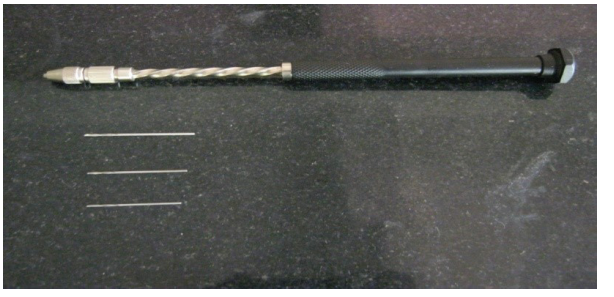

Figure 4. Mechanical driller for drill the orifice in the EOP Tablet.

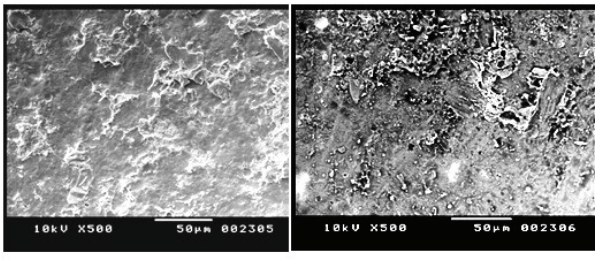

Figure 5. SEM micrograph of coating membranes of primary formulation, before and after dissolution.

Dissolution study

Osmotic tablets were subjected to *invitro* drug release studies in simulated gastric and intestinal fluid. A dissolution study was performed in 0.1 N HCl for the first 2hr and the remaining 10 hr in Phosphate buffer pH 7.2. The results are summarized in Figures 6-8.

Hence, it was evident that when an increase in the concentration of osmogent occurred, the drug release from the system was found to be increased but again reduced the drug release after an increase in the external coat thickness (wt. gain) occurred. The Pore former (sorbitol) produced a significant effect on the release profile. A decrease in the Pore former concentration system failed to release 100% of the drug.

Two types of osmogent (sodium chloride and mannitol) were used in the formulation of CPOP tablets. Both osmogents have different osmotic pressure and to study the effect of the 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 a coating composition, F1 and F2 containing 22% and 30% wt/wt of sorbitol respectively. The release profile from these formulations is shown in Figures 6-8.

DISCUSSION

The results revealed that the formulation LOX01 was devoid of any osmogent in the core and showed less drug release in 12 hours. In the formulation containing a greater amount of osmogent, i.e., sodium chloride, with 22% pore former (sorbitol), LOX04 showed an increase in drug release with 3% weight gain compared to 4% and 5% weight gain in 12 hours. In the formulation containing sodium chloride with 30% pore former (sorbitol), LOX13 showed an increase in drug release with 3% weight gain compared to 4% and 5% weight gainin 12 hours. In another formulation set containing mannitol as the osmogent with 22% pore former (sorbitol), LOX22 showed an increase in drug release with 3% weight gain compared to 4% and 5% weight gain in 12 hours.

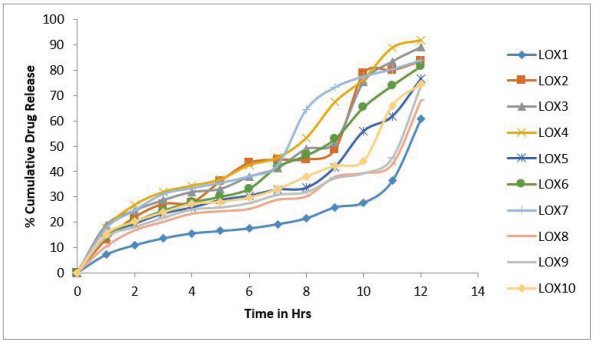

Figure 6. Comparison of *in vitro* release of batches LOX01 to LOX10.

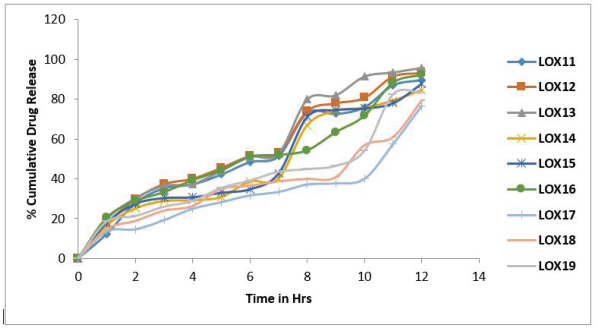

Figure 7. Comparison of *in vitro* release of batches LOX11 to LOX19.

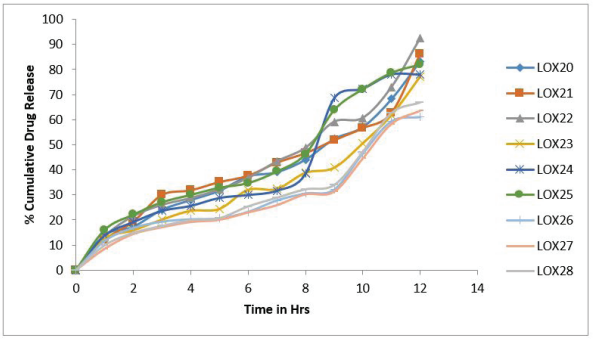

Figure 8. Comparison of *in vitro* release of batches LOX20 to LOX28.

Effect of drug to osmogent (osmotic agents) ratio

The comparative dissolution profile of all the formulations containing different ratios of drug to osmogent, i.e., sodium chloride in the ratio of 1:4 and mannitol in the ratio of 1:20, gave a better release of the drug from the osmotic tablet. From these release profiles, itis clear that an increase in the concentration of the osmotic agent, the greater the driving force, and this enhanced the release of the drug and thus had a direct effect on drug release. When the coated tablet was exposed to an aqueous environment, water diffused through the film coating (due to the active gradient of water), hydrating the core. The solvation of the osmotic agents created an osmotic pressure difference between the core contents and the external environment, which resulted in greater Lornoxicam release. The CPOP formulation containing sodium chloride as an osmogent showed a better release profile as compared to mannitol because sodium chloride has a higher osmotic pressure than mannitol.

Effect of pore forming level

To study the effect of the pore-forming agents, core formulations of lornoxicam were coated with varying coating compositions of sorbitol as a pore former. Sorbitol was added at 22% and 30% w/w of the coating polymer. The release profile from these formulations is shown in Figures 6-8. The release profile showed that the formulation LOX13 containing 30% w/w of sorbitol released 95.81% of the drug whereas the formulation LOX04 containing 20% w/w of pore former released only 91.82% of the drug as shown in Figure 6-7. The level of sorbitol had a direct effect on drug release. As the level of pore former increased, the membrane became 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.

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). The release profile of Lornoxicam from these formulations is shown in comparison for LOX13 and LOX19. The release profile showed that formulations LOX04, LOX13, and LOX22 with 3% weight gain increased drug release more than other formulations, which were coated with 4% and 5% weight gain. Drug release from the 5% weight gain showed much less drug release than 3% and 4% because the cellulose acetate film thickness inhibited the release rate of the drug. Drug release decreased with an increase in the weight gain of the membrane.

Drug release kinetics

The majority of the formulations showed the diffusional exponent, "n", in between 0.5 and 1.0 which indicates the anomalous transport or kinetics which means the drug is released by the combined mechanism of pure non-Fickian diffusion-controlled and swelling-controlled drug release. For some formulations, the "n" value was approximately 0.5 which indicated that the drug was released by a 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 occurred by the usual molecular diffusion of the drug due to a chemical potential gradient and is provided in Table 10.

Comparative study of CPOP and EOP

EOP Lornoxicam tablet was drilled with a mechanical driller having an orifice size of 0.8 mm and delivered the drug up to 12 hours. It was observed that with an orifice size of 0.8mm Lornoxicam released 84.5% of the drug within 12 hours. Based on this release, it was observed that formulations containing no osmogent showed a decreased release of the drug than formulations containing an osmogent. Amongst all the EOP formulations,

Table 10. 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

EOP04 showed the highest release rate, i.e., 84.5% of the drug in 12 hr as compared to other formulations (Figure 9).

An elementary osmotic pump Lornoxicam tablet (EOP) was taken for comparison with the controlled porosity osmotic pump Lornoxicam tablet (CPOP) and dissolution studies were observed. In the comparative study of the CPOP tablet and EOP tablet containing the same proportion of osmogent (sodium chloride) and when the release profile of CPOP formulation was compared with EOP formulation it was found that the CPOP formulation showed significantly higher release as compare to the EOP formulation. The comparison of CPOP and EOP tablets is shown in Figure 10.

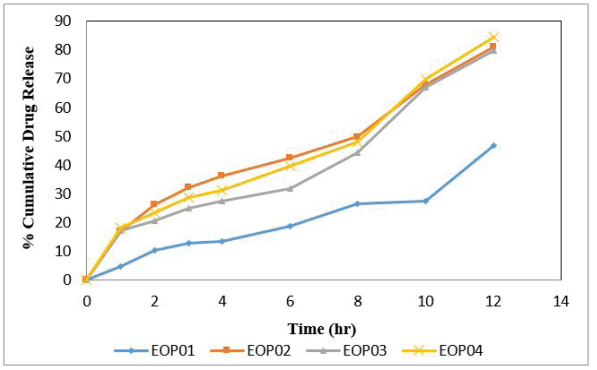

Figure 9. Comparison of *in vitro* release of batches EOP 01 to 04.

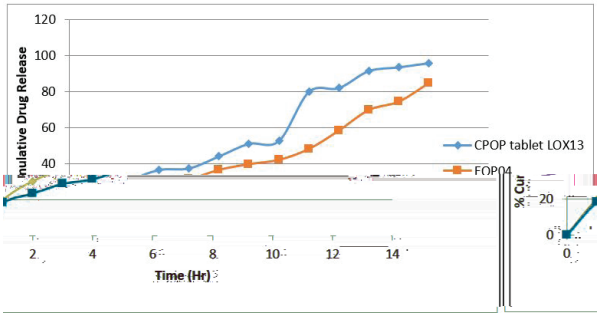

Figure 10. Comparison of *in vitro* release of batches EOP04 to CPOPLOX13.

In the EOP tablet, there is a chance of orifice blockage, which requires an extra formulation stage to increase the amount of drilling (for creating the orifice), which is time-consuming. Hence, CPOP is easier and more cost-effective to formulate. Based on the above, it is concluded that CPOP is superior to conventional EOP.

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 all the formulations were statistically significant $P<0.01$.

CONCLUSION

An osmotically regulated oral drug system (OODS) is suitable for the controlled release of drugs throughout the GI tract. A controlled porosity osmotic tablet is a novel concept in OODS, which is cost-effective and easy to formulate. In the present study, a controlled porosity osmotic (CPOP) tablet and an Elementary osmotic pump (EOP) tablet of Lornoxicam were formulated. The study involved the formulation and development of the CPOP and EOP and evaluation for various parameters like concentration of osmogent (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 an increase in the release of the drug. The increase in lornoxicam release is due to the formation of more pores after coming in contact with an aqueous environment. The conclusions arrived at in this study indicated that the controlled porosity osmotic pump and Elementary osmotic pump tablet of Lornoxicam developed in this investigation were found to be a better-controlled.

Finally, it can be concluded that an osmotically controlled drug delivery system can control the release of Lornoxicam for 12 hours with a zero-order release kinetics, which can reduce dosing frequency and increase patient compliance and it will be a promising tool for better oral administration.

Abbreviations

OODS: Osmotically regulated oral drug system;
SPSS: Statistical Package for Social Science;
OPT: Osmotic pump tablet;
CDDS: controlled drug delivery systems
DOE: Design of experiment;
ANOVA: Analysis of variance;
DSC: Differential scanning colorimetry;
FTIR: Fourier transform infrared;
EOP: Elementary osmotic pump lornoxicam tablet;
CPOP: Controlled porosity osmotic pump lornoxicam tablet;
SEM: Scanning Electron Microscopy
CA: Cellulose acetate

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.M.S., I.A.S., R.P.M.; Data Acquisition- S.M.S., I.A.S., R.P.M.; Data Analysis/Interpretation- S.M.S., I.A.S., R.P.M.; Drafting Manuscript- S.M.S., I.A.S.; Critical Revision of Manuscript- R.P.M.; Final Approval and Accountability- S.M.S., I.A.S., R.P.M.

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