



Oral Osmotic System for Delivery of Lornoxicam: Development and *In Vitro* Characterization

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ABSTRACT

An oral osmotic system which can deliver Lornoxicam for an extended period of time is developed and characterized in a view to reduce the problems associated with the side effect of Non steroidal anti inflammatory drugs. However, a lot of controlled and sustain release matrix based systems were developed previously still they not overcome the problems like effect of food and other GI factors on release of drug from the delivery system, such drawbacks are overcome by the oral osmotic drug delivery system (tablet). Osmotic drug delivery has become the benchmark to deliver the drugs in controlled-release fashion for long term therapy. In diseases like the arthritis patient put on long-term therapy of NSAIDs, which results in a lot of GI side effects and poor drug release. In present study osmotic core tablet was prepared and coated with cellulose acetate; pore was drilled with the help of mechanical microdrill and efforts are taken to improve release of NSAIDs in controlled fashion without effect of food and other gastrointestinal factors. Different batches of Lornoxicam were developed and evaluated *In vitro*, in which batch 6b release (65.29%) the drug in controlled fashion.

Keywords: oral osmotic system, osmogen, Lornoxicam, cellulose acetate, osmotic tablet.

1. INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). Among various NDDS available in the market, per oral controlled release (CR) systems hold the major market share because of their advantages over others. Conventional drug delivery systems have little or no control over the drug release, and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipient, physiological factor such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on. [1]

These systems are capable of delivering the drug in a predetermined time and rate thus maintaining the peak plasma level in therapeutic level for a long time period. These dosage forms increase the patient compliance by reducing the dosage frequency (Hamza *et al.*, 2010). However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of

food in the GI tract. To overcome these drawbacks osmotically controlled oral drug delivery systems (OCODDS) is developed. Which utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system. [2,4]

2. EXPERIMENTAL

Lornoxicam was obtained from Glenmark pharmaceuticals, Mumbai, Cellulose acetate (D.S. 39.8%) from Lupin Pharmaceuticals Pune, microcrystalline cellulose, castor oil, Potassium chloride, sodium bicarbonate and Isopropyl alcohol from Samar chemicals Nagpur, Sodium chloride from ACME Chemicals Mumbai, Magnesium stearate, talc and acetone was obtained from Research lab and fine chemical industries, Mumbai.

2.1. Preparation of core tablet [5]

Core tablet of Lornoxicam was prepared by wet granulation method. The different batches were prepared, and their composition formula is mentioned in the table 1.

Accurately weighed quantities of ingredients mentioned in formula were passed through the sieve No. 85 (aperture size 180 micron, British standard). The entire ingredient, except lubricant (magnesium stearate, glidant talc and binder polyvinylpyrrolidone (PVP)), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution of 10% (m/v) PVP, and granulated through sieve No.18 (aperture size 1003 micron, US standard) and dried in a hot air oven at 60°C for sufficient time (3 to 4 hr) so that the moisture of the granules reached 2-4 %. The dried granules were passed through the sieve. No.25 (aperture size 710 micron, US standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (100 mg) using 10mm diameter, deep concave punch. The compression was adjusted to giving the tablet with approximately 7-8 kg cm² hardness on a Monsanto tablet hardness tester.

2.2. Coating of core tablet:

Accurately weighed quantities of ingredients mentioned in formula of table 2 were passed through the sieve. The coating operation was performed on 40 tablet batch in a conventional laboratory model stainless steel, 20 cm diameter pear shaped, baffled coating pan. Baffles were three in a number to allow free tumbling of tablets. The pan speed was adjusted 30 rpm and the coating solution was sprayed on tumbling bed of tablets with the help of the spray gun manually. The inlet air temperature was 40-45°C and the manually coating procedure used was intermittent spraying and drying technique. The coat weight and coating thickness was controlled by the volume of coating solution consumed in the coating process. Coated tablets were allowed to dry completely in a hot air oven at 60°C and finished by standard polishing procedure. An appropriate orifice was drilled on one face of the tablet through the membrane by mechanical microdrill.

2.3. Evaluation of tablet

2.3.1. In-vitro release:

In-Vitro releases of Lornoxicam OPTs were investigated as mentioned in table 3 using the standard USP dissolution apparatus II at 50 rpm. One tablet was placed in 900ml of dissolution media equilibrated to 37 ± 0.1°C. Then 5-ml samples were withdrawn, from the point halfway between the surface of the dissolution medium and the top of the paddle, with pipette at the different time intervals, replacing with an equal volume of pre-warmed (37±0.1°C) fresh dissolution medium and analyzed spectrophotometrically at 275nm after suitable dilution. Each study was done in triplicate, and the mean values are reported.

2.3.2. Drug release as a function of agitation intensity:

To study the effect of agitation intensity, drug release studies were performed at a relatively high (100 rpm) and low (50 rpm) agitation intensity and at static condition using the USP dissolution apparatus in pH 1.2, similarly as described above in figure 3. Under static conditions, samples at different times were taken after uniform mixing of the medium to preclude any possible sampling error.

2.3.3. Effect of pH of the dissolution medium on release rate:

Release rates of Lornoxicam from OPTs in the phosphate buffer of pH 1.2 and 7.4 were compared as mentioned in figure 6 using the USP dissolution apparatus II at 50 rpm, similarly as described above.

2.3.4. Drug release kinetics(6)

To explain the kinetics of drug release more clearly, release data were fitted to the Korsmeyer equation(1) which described the general behavior of solute release from controlled release polymeric tablets.

$$Q = Kt^n \text{-----}[1]$$

Where,

Q-is the percent of drug released

t - is the release time.

K - is the constant that incorporated structure and geometric.

Characteristics of the release device and n - is the release exponent that indicates the mechanism of release.

When n - is equal to 1, the release mechanism approaches zero order.

2.4. Drug and Excipient interaction:

To detect any incompatibility of drug with the excipient the IR spectroscopic analysis was carried out; the potassium bromide disc-containing drug and physical mixture of drug and excipient was prepared to record the spectrum in the range of 400 to 4000 cm⁻¹ by using FTIR Spectrophotometer.

3. RESULT AND DISCUSSION:

3.1. Drug release:

In-vitro cumulative percent drug release of different EOP's batches of Lornoxicam in Saline phosphate buffer pH 7.2 was shown in table 3.

3.1. Kinetics of drug release:

For comparison of *In-vitro* drug release profile of Lornoxicam from osmotic tablets of different membrane

Sr. No.	Ingredients (mg/tablet)	Batch code									
		1a	2a	3a	4a	5b	6b	7b	8c	9c	10d
01	Lornoxicam	08	08	08	08	08	08	08	08	08	08
02	MCC	119	119	187	119	119	89	79	69	79	44
03	NaCl	-----	-----	-----	-----	30	40	50	-----	-----	50
04	KCl	-----	-----	-----	-----	-----	-----	-----	30	40	-----
05	NaHCO ₃	-----	-----	-----	-----	-----	-----	-----	-----	-----	25
06	SLS	12	12	12	12	12	12	12	12	12	12
07	Talc	03	03	03	03	03	03	03	03	03	03
08	Mg Stearate	03	03	03	03	03	03	03	03	03	03
09	PVP	05	05	05	05	05	05	05	05	05	05

MCC - microcrystalline cellulose, NaCl - Sodium chloride, NaHCO₃ - Sodium bicarbonate, SLS - Sodium lauryl sulphate, PVP - polyvinylpyrrolidone.

Table 01- Composition of designed batches of lornoxicam

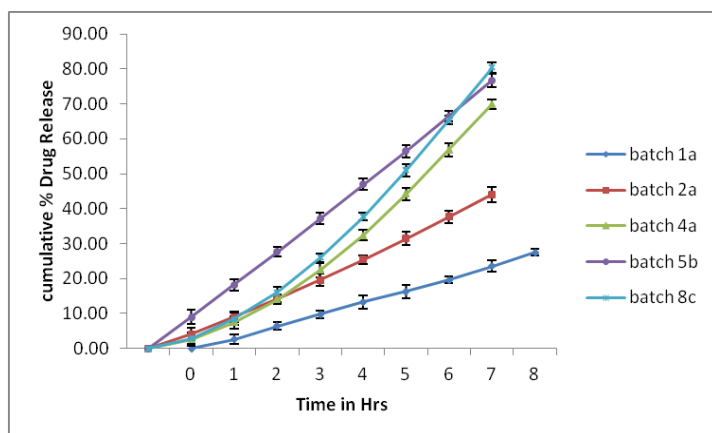


Figure 1: Release profile of Lornoxicam from EOPs coated with different membranes in phosphate buffer 7.4, Bars represent SD (n=3)

To explain the kinetics of drug release, release data were fitted to the modified Korsmeyer equation (1)

When the logarithm of the cumulative percent released (CPR) is plotted against the logarithm of the time in minutes, the slope of the graph will give the value of the time exponent n . The category of batches for which the release kinetic was compared is semipermeable and microporous membrane coated batches as mentioned in figure 1. The semipermeable membrane was formed by using water in soluble plasticizer, castor oil, and microporous membrane was formed when the water-soluble plasticizer, polyethylene glycol (400) was used. The microporous membrane was formed by water soluble plasticizer. As it gets in contact with water get soluble and forms porous, sponge like membrane, which is evident from the release profile of 4a, and 8c, coded batches. The drug release is almost diffusion controlled as can be observed by following their curve and can also be confirmed by the value of the time exponent. The

observance of nonsignificant zero lag time is attributed to the same reason of nature of membrane, i.e. microporous. On the other hand, the semipermeable membrane coated EOP batches such as 6b, and 7b, formed by using castor oil as a plasticizer exhibited zero order release pattern. The release was mainly through the delivery orifice and has shown a lag time of short duration. Thus the drug release from the microporous coated EOPs is diffusion controlled while the drug release from semipermeable coated EOPs is controlled by convection resulting in consistent linear release. The release rate of drug from the oral osmotic pump depends on factors, which can summarize from the formula as below in equation (2)

$$(dM/dt)_z = S/h K p C_s \text{-----}[2]$$

Where,

$(dM/dt)_z$ - is the rate of delivery of the solute (drug) under zero-order condition, S - is the semipermeable membrane area; h is the membrane thickness; K - is a permeability coefficient, and p is the osmotic pressure of the formulation under zero-order condition. For a solute (drug) having insufficient inherent osmotic pressure, to have a required therapeutically effective release rate needs more osmotic pressure. The increase in osmotic pressure can be obtained by incorporating additional osmotic agent in core tablet

Effect of agitation intensity:

Osmotic pump drug delivery system is such a delivery system which is unaffected by environmental condition as agitation intensity. To characterize this feature of osmotic pump the batches coded with 2a and 5b were stirred at 50 and 100 rpm and their release profile was observed. The release profile has not shown any significant changes even on the increase of stirring rate, which can be observed from the graph plotted in Figure 2.

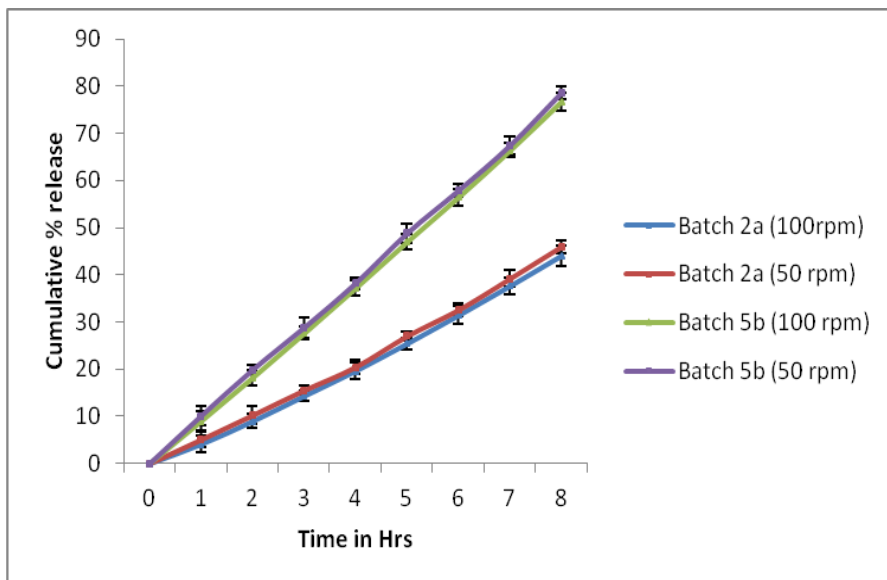


Figure 2: Effect of agitation intensity on release of Lornoxicam from EOPs in Phosphate buffer 7.4. Bars represent SD (n=3).

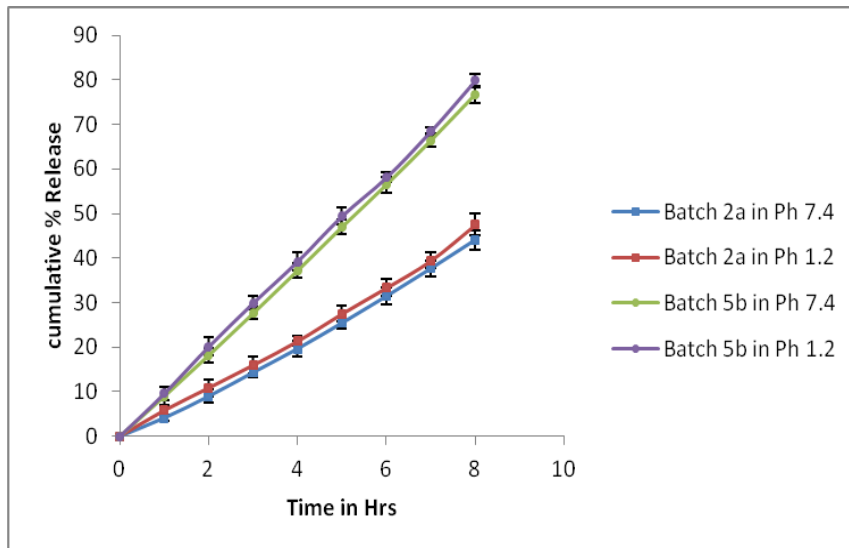


Fig 03: Effect of pH of the dissolution medium on release rate of Lornoxicam (S.D. n=3)

Coating formula

Cellulose acetate	2% w/v
Castor oil or	20% of total solid polymer
PEG 400	10%v/v
Isopropyl alcohol	10% v/v
Acetone	q.s. to 100% v/v

Table 02- Coating composition

HRS	BATCH CODE									
	1a	2a	3a	4a	5b	6b	7b	8c	9c	10d
01	2.58 (1.41)	4.12 (1.811)	4.89 (1.39)	2.58 (1.91)	8.99 (2)	7.20 (1.1)	6.94 (1.63)	2.84 (1.71)	7.20 (1.15)	6.68 (1.91)
02	6.42 (1.04)	8.98 (1.42)	10.26 (1.34)	7.44 (1.76)	18.19 (1.69)	18.44 (1.49)	14.35 (1.12)	8.47 (1.76)	12.57 (1.68)	13.58 (1.15)
03	9.73 (1.032)	14.32 (1.20)	16.11 (1.95)	14.05 (1.26)	27.59 (1.35)	29.87 (1.01)	21.47 (1.64)	16.09 (1.42)	18.93 (1.49)	20.7 (2.04)
04	13.28 (1.89)	19.63 (1.65)	21.93 (1.24)	22.39 (2.14)	37.19 (1.64)	41.49 (1.95)	29.3 (1.15)	25.94 (1.3)	24.49 (3.56)	28.03 (2.58)
05	16.3 (1.85)	25.41 (1.20)	28.21 (2)	32.44 (1.53)	46.99 (1.70)	53.54 (1.78)	36.84 (1.02)	37.74 (1.11)	29.77 (5.25)	35.82 (1.40)
06	19.56 (1.001)	31.41 (1.89)	34.96 (1.93)	44.18 (1.74)	56.48 (1.78)	66.03 (1.40)	44.59 (1.23)	50.97 (1.84)	36.02 (3.4)	44.31 (1.45)
07	23.54 (1.55)	37.62 (1.75)	41.92 (1.75)	56.84 (1.90)	66.41 (1.45)	78.2 (1.36)	53.04 (1.7)	65.37 (1.30)	41.74 (1.814)	53.5 (1)
08	27.5 (1.01)	44.04 (2.14)	49.08 (2.73)	69.92 (1.35)	76.78 (1.95)	91.04 (1.51)	61.68 (1.28)	80.47 (1.52)	47.67 (1.47)	63.13 (1.16)

Table 03: Percentage release per hour of Lornoxicam in mg(Mean. (S.D.)(n=3))

Effect of pH of the dissolution medium:

To verify that the drug-delivery profile from osmotically driven delivery system is independent of the other environmental factor as pH of the dissolution mediums, the dissolution test was carried out in pH 1.2 and in pH 7.4. This is one of the important tests to mark the distinguishing characteristic of osmotic pump and advantage over other delivery systems. The semi permeable membrane was truly ion selective. Ions are not allowed to diffuse through the membrane while solvent molecules are allowed to pass through it. The release profiles are plotted in Figure 5 & 6 of the batches was tested in different pH of the dissolution mediums. The average release rate in different pH media was tested for a statistically significant difference and has resulted in no consequential difference.

An important feature of any osmotic drug delivery system is that to maintain its mechanical stability and resistance of the film coating to rupture during passage through the gastrointestinal tract. None of the tablets ruptured during the dissolution studies. Empty polymeric shell retained their original shape and floated on the dissolution medium after completion of drug release. Release rate of

semipermeable membrane coated osmotic pump tablet was unaffected by hydrodynamic condition as well by the pH of the dissolution mediums, which confirmed the nature of membrane was a semipermeable which in addition confirmed by release rate as it was inversely proportional to the membrane thickness. The semipermeable membrane coated batches as 2a, 3a, 5b, and as well as 6b, behaved as a true semipermeable. The semipermeable nature of the membrane was believed to involve the passage of solvent through the membrane by a diffusion process or by dissolving the material of the membrane in which the solute was insoluble. [8] The kinetics of drug release remains linear as long as the transport mechanism was unidirectional. [9]

Conclusion:

From the results obtained, it can be inferred that the release of drug from elementary osmotic pump can be controlled efficiently by the addition of osmotic agent in to the core formulations. The oral osmotic pumps possess many advantages over the simple matrix type of SR/CR oral dosage forms. The pumps gave better controlled release and time duration for the release can be extended up to 24 hour. This can lead to the development of these

formulations as potential candidate for once a day dosage form. The kinetics of drug release from formulations follow Hixson–Crowell cube root model and mechanism of release would follow non-Fickian diffusion process. It can be concluded from the study that tablet coating and osmotic agent play a considerable role in controlling the release of Eterocoxib from elementary osmotic pumps.

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Conflict of Interest: None Declared