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Effect of various Membranes and their Thickness on Osmotic Tablet of Lornoxicam.

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ABSTRACT

Osmotic systems use the principle of osmosis as delivery force to deliver the drug from the system, and the release rate is unaffected by the body's pH and other physiological and gastrointestinal factors. Osmotic tablet of lornoxicam is prepared successfully to deliver drug in controlled release form for once day therapy in arthritis by overcoming all the side effect and enhancing bioavailability. The objective of the present work was to design osmotically driven oral drug delivery system containing Lornoxicam as an active ingredient and evaluate the effect of various membranes(microporous and semipermiable) on release of drug from osmotic tablet. Core tablet of lornoxicam is prepared, coated with cellulose acetate (39.8 D.S.) in which batch 6b (semipermiable) give the maximum of 91.04% release from osmotic tablet of lornoxicam in control passion as compare to other(microporous membrane coated batches.

Keywords: Osmotic tablet, Lornoxicam, NSAID's, oral osmotic table, cellulose acetate.

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INTRODUCTION

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. Therefore, 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[1] These system are capable of delivering the drug in a predetermined time and rate thus maintaining the peak plasma level in therapeutic level for a long period of time. These dosage forms increases the patient compliance by reducing the dosage frequency.

To overcome these drawback 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]

In present study, microporous and semipermiable membranes are formed by cellulose acetate (D.S.39.8) as a polymer and using polyethylene glycol and castor oil as plasticizer. Efforts are taken to compare rate of release from various membrane coated (e.g. semipermiable and microporous) batches of tablet. The batches having semipermiable membrane release the drug in controlled passion following zero order release while batches of microporous membrane follow first order release.[3]

MATERIAL & METHODS:

Lornoxicam is obtained from Glenmark pharmaceutical Mumbai, Potassium chloride, microcrystalline cellulose, isopropyl alcohol, castor oil and sodium bicarbonate from Samar chemicals Mumbai, sodium chloride ACME chemicals Mumbai, cellulose acetate (D.S. 39.8) from Lupin pharmaceutical Mumbai, Talc research lab fine chemical industry Mumbai, polyethylene glycol 400 from new modern chemical corporation Mumbai, and PVP from Dr. Reddy's laboratories, Hyderabad.

Preparation of core tablet[5]

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

Table 1: Designed composition details of different EOP tablet batches.

Sr. no	Ingredients (mg/tablet)	Batch code									
		1a	2a	3a	4a	5b	6b	7b	8c	9c	10d
1	Lornoxicam	8	8	8	8	8	8	8	8	8	8
2	MCC*	119	119	119	119	89	79	69	89	79	44
3	Sodium Chloride	----	-----	----	-----	30	40	50	--	---	50
4	Potassium Chloride	----	-----	----	-----	---	--	----	30	40	----
5	Sodium Bicarbonate	----	-----	----	-----	--	--	----	---	---	25
6	SLS**	12	12	12	12	12	12	12	12	12	12
7	Talc	3	3	3	3	3	3	3	3	3	3
8	Mag. Stearate	3	3	3	3	3	3	3	3	3	3
9	PVP	5	5	5	5	5	5	5	5	5	5

MCC*- microcrystalline cellulose, SLS**-Sodium lauryl sulphate

Accurately weighed quantities of ingredients mentioned in formula were passed through sieve No. 85 (aperture size 180 micron, British standard). The entire ingredient, except lubricant (magnesium stearate, glidant talc and binder polyvinyl pyrolidone (PVP)), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moisten 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 ^{0}C for sufficient time (3 to 4 hr) so that the moisture of the granules reached 2-4 %. The dried granules were passed through sieve No.25 aperture size 710 micron, US standard) and blended with talc and magnesium Stearate. The homogeneous blend is then compressed into tablets (150 mg) using 8 mm diameter, deep concave punch. The compression was adjusted to give tablet with approximately 7-8 kg cm^2 hardness on a Monsanto tablet hardness tester.

Coating of core tablet:

Coating polymer and Coating formulation

The coating operation is performed on 40 tablet batch in a conventional laboratory model in stainless steel, 20 cm diameter pear shaped, baffled coating pan by using the formula as shown in table 2.

Table 2: Formula used for coating purpose.

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

Baffles were three in number to allow free tumbling of tablets. The pan speed is adjusted 30 rpm and the coating solution was sprayed on tumbling bed of tablets with the help of spray gun

manually. The inlet air temperature was 40-45^{0}C and the manually coating procedure used was intermittent spraying and drying technique. The coat weight and coating thickness is 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^{0}C and finished by standard polishing procedure. An appropriate orifice is drilled on one face of the tablet through the membrane by mechanical microdrill.[5]

Evaluation of tablet

***In-vitro* release: [6]**

In-vitro releases of Lornoxicam from various OPTs were investigated using the standard USP dissolution apparatus II at 50 rpm. One tablet was placed in 900ml of dissolution media equilibrated to 37 ± 0.1^{0}C. Then 5-ml sample were withdrawn, from the point halfway between the surface of the dissolution medium and the top of the paddle, with pipette at different time interval, replacing with an equal volume of pre-warmed (37±0.1^{0}C) fresh dissolution medium and analyzed spectrophotometrically at 380nm after suitable dilution. Each study was done in triplicate and the mean values were reported.

Drug release kinetics[6]

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

$$Q = Ktn \quad \text{----------(1)}$$

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

n - is the release exponent that indicates the mechanism of release when n - is equal to 1, the release mechanism approaches zero order.[7]

RESULTS AND DISCUSSION:

Drug release:

In-vitro cumulative percent drug release of different EOP's batches of lornoxicam in7.4 pH was shown in table 3.

Kinetics of Drug release:

For comparison of In-vitro drug release profile of Lornoxicam from osmotic pump tablets of different membrane type i.e. semipermiable and microporous are shown in Fig:1.

Table 3. Percentage drug release per hour in mg (Mean (SD) (n=3))

Hours	Batch Code									
	1a	**2a**	**3a**	**4a**	**5b**	**6b**	**7b**	**8c**	**9c**	**10d**
01	2.58 (1.41)	4.12 (1.81)	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)

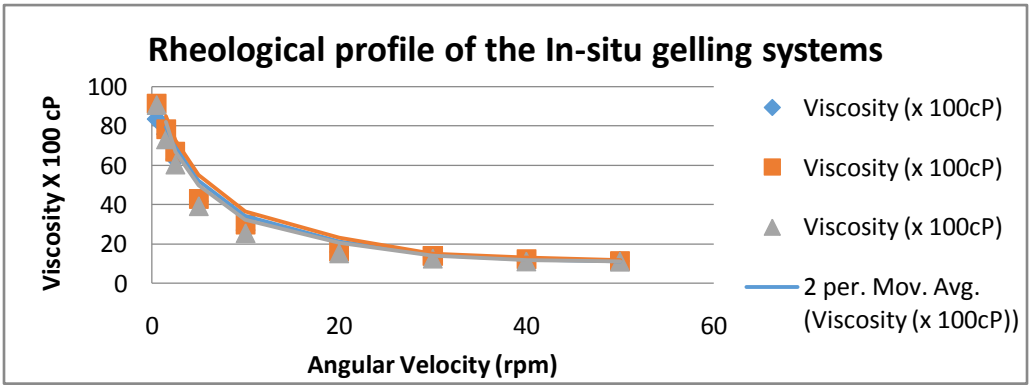

Figure 1: Release profile of Lornoxicam from EOPs coated with different membranes in phosphate buffer 7.4, Bars represent SD (n=3)

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

When the logarithm of the cumulative percentage 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. Calculated values of n, along with other release characteristics such as lag time, average release rate, and CPR at 8 hr, for various batches of EOPs are listed in table 4 for comparison.

The category of batches for which the release kinetics was compared is semipermiable and microporous membrane coated batches. The semipermiable membrane was formed by using water insoluble plasticizer, castor oil, and microporous membrane was formed when the water soluble plasticizer, polyethylene glycol (400) was used.

Table:4 Various drug release parameters of different batches

Batch code	Average lag time(Hrs)	Average release rate(mg/Hr)	CPR* at 8 Hrs
1a	1.01	0.27	27.5
2a	1.03	0.44	44.04
3a	0.99	0.49	49.08
4a	Zero	0.7	69.92
5b	1.02	0.76	76.78
6b	1.01	0.91	91.04
7b	1.01	0.61	61.68
8c	Zero	0.80	80.47
9c	1.03	0.47	47.67
10d	0.98	0.63	63.13

*CPR-Cumulative percentage release.

The microporous membrane is formed by water soluble plasticizer as it gets in contact with water get soluble and form 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 time exponent. The observance of non-significant zero lag time is attributed to the same reason of nature of membrane i.e. microporous.

On the other hand, the semipermiable membrane coated EOP batches such as 2a and 5b formed by using castor oil as a plasticizer exhibited zero order release pattern.[10] 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 drug release from semipermiable coated EOPs is controlled by convection resulting in consistent linear release.

The release rate of drug from oral osmotic pump depend on factors which can summarized from formula as below:

Table 5 Membrane characteristic of various EOPs Designed.(Mean (SD) (n=20))

S. No	Items	Batches of EOP's									
		1a	2a	3a	4a	5b	6b	7b	8c	9c	10d
01	Coat Nature	SP	SP	SP	MP	SP	SP	SP	MP	SP	SP
02	Coat weight(mg)(±SD)	4.4 (0.1)	4.36 (0.11)	4.4 (0.1)	7.2 (0.25)	4.5 (0.15)	5.8 (0.2)	6.3 (0.3)	7.3 (0.15)	4.5 (0.15)	4.4 (0.1)
03	Coat Thickness (µm)(±SD)	40 (0.2)	40 (0.2)	40(0.4)	75 (3)	40 (0.4)	50(0.4)	60 (0.3)	75 (1.5)	40 (0.2)	40 (0.2)
04	Orifice diameter (mm)(±SD)	---	0.3 (0.04)	0.5 (0.02)	----	0.3 (0.01)	0.3 (0.04)	0.3 (0.01)	----	0.3 (0.01)	0.3 (0.04)

MP- Microporous cellulose acetate coat with Polyethylene glycol plasticizer, SP- semipermeable membrane with castor oil as plasticizer

$$(dM/dt)z = S/h\ K\ \pi Cs \text{----------(2)}$$

Where, (dM/dt)z is the rate of delivery of the solute (drug) under zero-order condition,

S-is the semipermiable membrane area ;

h - is the membrane thickness;

K - is a permeability coefficient, and

π- is the osmotic pressure of the formulation under zero-order condition.

The core tablet was fabricated by using microcrystalline cellulose as a diluent, magnesium Stearate as a lubricant, and talc as a glidant. Different batches of osmotic pump tablets were fabricated by using different type and concentration of osmogen. The batches with different membrane thickness, delivery orifice size, and plasticizer were developed to evaluate their effect. The core tablet developed was coated with cellulose acetate polymer because of its high water vapor transmission rate and mechanical strength than other polymer. Two different category polymers of water soluble, polyethylene glycol (400) and water insoluble, castor oil, type was used. The core tablets were coated by using dilute polymer solution as it has advantage of resulting in more uniform coating and less sticking during coating operation.

A plasticizer was included in the coating formulation in order to improve the stability of the film by increasing the flexibility of the membrane. The plasticizer improve the membrane forming properties of polymer by improving its physical properties such as flexibility, hardness, tensile strength, and elasticity.[13,14,15]

Table 6: Determination of Uniformity of Coating

SR No	Batches Item		1a, 2a, 3a	4a	5b	6b	7b	8c	9c	10d
1	Coefficient of weight variation	Before coating	4.094	4.082	4.105	4.163	4.225	4.175	4.118	4.118
		After coating	4.14	4.211	4.185	4.242	4.590	4.329	4.367	4.210
2	Coefficient of Thickness variation	Before coating	0.577	0.577	0.577	0.578	0.576	0.577	0.578	0.575
		After coating	0.578	0.580	0.578	0.579	0.578	0.58	0.581	0.577
3	Coefficient of Diameter variation	Before coating	0.942	0.942	0.942	0.944	0.943	0.942	0.941	0.94
		After coating	0.943	0.944	0.943	0.948	0.945	0.944	0.944	0.942
4	Coefficient Of Coat weight variation		0.666	0.881	0.66	0.785	0.816	0.882	0.666	0.667
5	Coefficient of Coat thickness Variation		2.108 µm	3.19 µm	2.617 µm	2.82 µm	2.802 µm	3.2 µm	2.509 µm	3.44 µm

Table:7 Comparison of release characteristic and time exponents of different batches

Batch No.	R^2 Values					
	Zero Order	First Order	Hixon& Crowell	Korsmeyer & Peppas		Higuchi Model
				R^2	n	
1a	0.998	0.997	0.998	0.996	1.14	0.897
2a	0.997	0.991	0.994	0.999	1.13	0.882
3a	0.998	0.992	0.995	0.999	1.08	0.890
4a	0.960	0.938	0.945	0.999	1.5	0.777
5b	1	0.988	0.994	0.999	1.02	0.905
6b	0.995	0.972	0.982	0.998	1.2	0.869
7b	1	0.993	0.996	0.999	1.03	0.904
8c	0.957	0.929	0.939	0.999	1.6	0.772
9c	0.998	0.999	0.999	0.998	0.89	0.934
10d	0.999	0.992	0.995	0.998	1.04	0.899

Effect of membrane thickness:

Membrane thickness has a profound effect over the release rate of drug from osmotic pump tablet. To evaluate and quantify the effect of membrane thickness, batches of different membrane thickness was fabricated and their release profile is compared in Figure 2.

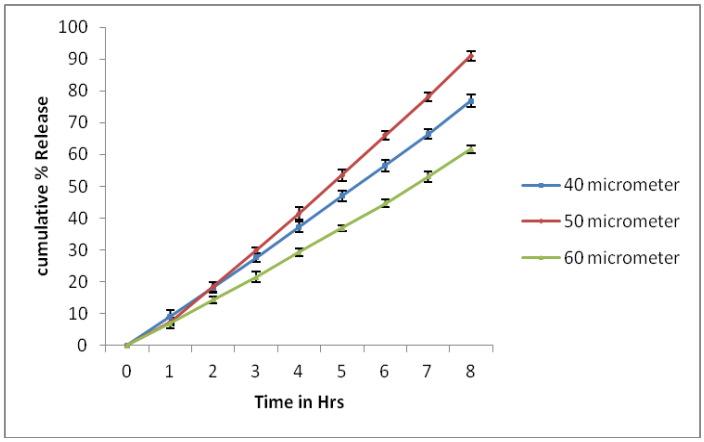

Figure 2: Effect of membrane thickness on release profile of Lornoxicam from EOPs in Phosphate buffer 7.4.

The membrane thickness is inversely proportional to the release rate and eventually with the overall release profile which can express by following equation[17]:

$$dm/dt = (AS/h)\ L p \sigma \Delta\pi \text{ ----------(3)}$$

Where, dm/dt is the zero-order release rate of the drug,

A is the surface area of the film coated membrane, his the membrane thickness,

$\Delta\pi$ is the osmotic pressure difference across the membrane at saturation,

S is the solubility,

Lpis the hydraulic permeability of the membrane and

σ is the reflection coefficient having the value of one for an ideal SPM like cellulose

acetate and zero for a non-selective membrane.

The weight of the membrane (W) was shown to be related with the membrane thickness as follow:

$$W = \rho m A h \quad \text{----------} \quad (4)$$

Where ρm is the membrane density.

This is one of the important test to mark the distinguishing characteristic of osmotic pump and advantage over other delivery system The semipermiable membrane was truly ion selective, ions are not allowed to diffuse through the membrane while solvent molecules are allowed to pass through it.

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 tablet 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 semipermiable membrane coated osmotic pump was unaffected by hydrodynamic condition as well by the pH of dissolution medium, which confirmed the nature of membrane was a semipermiable which in addition confirmed by release rate as it was inversely proportional to the membrane thickness. The semipermiable membrane coated batches as 2a, 3a, 5b and as well as 6b behaved as a true semipermiable. The semipermiable 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.[18] The kinetics of drug release remains linear as long as the transport mechanism was unidirectional.[19]

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 12 hour. This can lead to the development of these formulations as potential candidate for twice 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 microporous and semipermiable membrane and their thickness considerably play important role in controlling the release of lornoxicam from elementary osmotic pumps.

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