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Formulation and Evaluation of Lornoxicam Suppositories

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Lornoxicam suppositories were prepared by using water soluble and oil soluble suppository bases. All the prepared suppositories were evaluated for various physical parameters like weight variation, drug content, hardness, Liqification time and temperature, disintegration and macro-melting range. In-vitro release study was performed USP type I apparatus (Basket type) using phosphate buffer pH 7.4 as dissolution media. The suppositories prepared were within permissible range of all physical parameters. In vitro drug released from water soluble bases (like PEG) was greater than that from oil soluble bases. Addition of HPMC, Glyceryl Behenate in agar suppositories to controlled release. The results suggest that of PEG of low molecular weight with high molecular weight in different percentage of release. The Sustained release suppositories can be prepared by addition of HPMC, Glyceryl Behenate in agar based suppositories and by use of bees wax in cocoa butter as base.

Keyword: Lornoxicam, Agar, PEG, Cocoa Butter, *In- vitro* Evaluation.

1. Introduction

Suppositories are medicated solid bodies suitably shaped for rectal administration. Rectal drug delivery has a number of advantages such as reduced hepatic first pass elimination of high clearance drugs, improved enzymatic drug stability, higher drug load, avoidance of gastric irritation associated with certain drugs in case of nausea, vomiting and when the patient is unconscious [1].

Rectal route of administration is specifically useful for infants and children who have difficulty in swallowing oral medicine. Drug administered in suppository form can produce not only local effect but also systemic therapeutic action. Suppositories can be prepared by using lipophilic bases or by hydrophilic bases. These suppositories melt or dissolve in body fluids and release the drug [2].

Lornoxicam, (3*E*)-6-chloro-3-[hydroxy (pyridin-2-ylamino) methylene]-2-methyl-2, 3-dihydro-4*H*-thieno [2, 3-*e*] [1,2] thiazin-4-one 1,1-dioxide , a potent nonsteroidal anti-inflammatory drug has been used effectively in the management of moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, surgery and inflammatory diseases joints [3].

Lornoxicam has side effects similar to other NSAIDs most commonly mild ones like gastrointestinal disorders (nausea and diarrhea) and headache. Severe but seldom side effects include bleeding, bronchospasms and the

extremely rare Stevens–Johnson syndrome, CNS effect, Abdominal Pain, Nephrotoxicity, Photo-sensitivity, Hypertension, Insomnia, Palpitation, fluid retention [4].

Now the majority of the drugs are formulated in the form of suppositories to produce systemic effect. The suppository may be useful for long-term treatment of chronic diseases like essential hyper-tension, rheumatoid arthritis, asthma, diabetes, AIDS, anemia, etc. Many researchers have concentrated their efforts in rectal drug absorption on those drugs which currently must be injected parent rally, to provide effective therapy (e.g., antibiotics and polypeptides) [5,6].

2. Experimental

2.1. Material

Lornoxicam was a gift sample from (FDC Limited, Mumbai), PEG 4000, 6000 (FDC Limited, Mumbai), PEG 400 (Fine Chem. Ind, Mumbai), Agar (Fine Chem. Ind, Mumbai), Methyl & Propyl Paraben (Modern Lab, Nasik), propylene Glycol (Fine Chem. Ind, Mumbai), HPMC K4M & E15 (FDC Limited, Mumbai), Glyceryl Behenate (Gattefosse Pvt. Ltd. Mumbai), Cocoa Butter (Fine Chem. Ind, Mumbai), Bees Wax (Fine Chem. Ind, Mumbai) All other chemical used were of analytical grade.

2.2. Method

2.2.1 Preparation of Lornoxicam Suppositories

Agar suppositories were prepared by molding method, dissolving methyl and propyl paraben in hot water and then drug along with other additives like propylene glycol, HPMC, Glyceryl Behenate was added and mixed well. Finally agar was incorporated at 75-80 ℃ and mixed thoroughly. The molten mass was poured into previously calibrated by stainless steel mould of 1gm and allowed to set and kept in freeze for cooled for some time and removed it. The PEG suppositories were prepared by using fusion method by melting PEG (400, 4000, and 6000) in different ratios and then drug was incorporated. Cocoa butter suppositories were prepared by melting cocoa butter and bees wax on water bath and then the drug was incorporated[7]. The details of all formulations are tabulated in table 1 and 2. All the Prepared suppositories were packed in Aluminum foil kept in refrigerator and used in the evaluation.

Table 1: Formulation of lornoxicam suppositories (Agar base)

Ingredients (% w/w)	Formulation Codes						
	A1	A2	A3	A4	A5	A6	A7
Lornoxicam(mg)	10	10	10	10	10	10	10
Agar	5	5	5	5	5	5	5
Propylene glycol	10	10	10	10	10	10	10
Methyl Paraben	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Propyl Paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02
HPMC(K4M)	--	1	1.5	--	--	--	--
HPMC (E15)	--	--	--	2	4	--	--
Glyceryl Behenate	--	--	--	--	--	2	4
Water (q.s)	--	--	--	--	--	--	--

Table 2: Formulation of lornoxicam suppositories (PEG & Cocoa butter)

Ingredients (% w/w)	Formulation Codes						
	P1	P2	P3	P4	C1	C2	C3
Lornoxicam(mg)	10	10	10	10	10	10	10
PEG 6000	60	80	--	--	--	--	--

PEG 4000	--	--	60	80	--	--	--
PEG 400	40	20	40	20	--	--	--
Bees wax	--	--	--	--	--	1	3
Cocoa butter(q.s)	--	--	--	--	q.s	q.s	q.s

3. Calibration of Mould

Before preparing the suppositories, the mould should be calibrated because the moulds may vary in their capacity. The base was melted alone and then filled into the mould and weighed after removing the suppositories; the mean weight was taken as true capacity of the mould. The procedure was repeated for different bases. The calibrated mould capacities ranged from 1.02 to 1.195 g [8].

4. Evaluation of Suppositories

The prepared suppositories were evaluated for official and unofficial parameters viz weight variation, content uniformity, hardness, Liquefaction time and temperature, dissolution test, disintegration and Macro-melting range test. The tests were carried out in triplicate [9, 10, 11].

4.1. Weight Variation

All the suppositories (made by the respective bases), were weighed and average weight was calculated. Then all the suppositories were individually weighed and the variation from the average was calculated. No suppositories should deviate from average weight by more than 5% except two which may deviate not more than 7.5 %.

4.2. Hardness (fracture point)

Hardness of the prepared suppositories was tested using Monsanto hardness tester model. The weight required for suppository to collapse was taken as measure of hardness of the suppository. Hardness test or fracture point test was carried to determine the tensile strength of the suppositories to access whether they will be able to withstand the hazards of packing and transporting.

4.3. Disintegration Test

The disintegration test was performed on six suppositories of each type using USP tablet disintegration (Electro lab, ED 2L) test apparatus. 160ml of distilled water was used as medium at 37 ℃. Suppositories prepared with water soluble bases the time required for complete disintegration and in case of oily bases, the time required for complete Disintegration of suppository was determined

4.4. Macro Melting Range Test

For macro melting range test the formulation was filled to about 1cm height in capillary tubes of 10 cm length and dipped in a beaker containing water. The temperature was raised slowly and the temperature at which the mass liquefies was recorded [12].

4.5. Liquefaction Time & Temperature

For Liquefaction time and temperature was done using fabricated instrument. A big pipette was taken having a narrow opening on one side and broad opening on another side. The pipette was dipped in hot water maintained at 37 ℃. So that narrow end faces toward hot water. The sample suppository was introduced from the top of the pipette through broad end and carefully pushed down its length until it reaches narrow end. A glass rod was then inserted so that it rests over the suppository. The temperature at which the glass rods just come down was noted that represents the liquefaction temperature. The time at which glass rod reaches to narrow end after complete melting of suppositories represents the liquefaction time [13].

4.6. Drug Content

For determination of drug content the suppositories were dissolved in 100 ml phosphate buffer of pH 7.4 by stirring through magnetic stirrer slowly at 37 ℃ for 1 hr. After the solution

was filtered; and the filtrate was diluted suitably and absorbance was measured against blank at 371nm [14].

4.7 Dissolution Test

In vitro dissolution studies of lornoxicam suppositories were carried out in USP tablet dissolution test apparatus (Electro lab-TDT 08L) employing a rotating basket apparatus (Type I) at 100 rpm and using 500 ml of phosphate buffer (pH 7.4) at 37±0.5 ℃ as dissolution medium. One suppository was used in each test. At predetermined time intervals 5 ml sample were withdrawn by means of syringe fitted with a pre filter then filtered through watman filter paper. The volume withdrawn at each interval was replaced was replaced with same quantity of fresh dissolution medium and maintained at 37±0.5 ℃. The sample were analyzed for drug release by measuring the absorbance at 371 nm using UV-visible spectrophotometer after suitable withdrawn sample cumulative percent of lornoxicam released was calculated and plotted against time. All the studies were run in triplicate (n=3).

5. Stability studies

Short term stability studies were performed at a room temperature and refrigeration temperature (4 ℃) was kept for 6 w on the promising formulation. The suppositories were individually wrapped in aluminum foil and packed in card-board boxes. Sample are taken after 6 w for drug content estimation and dissolution test also performed to determine the drug release profile [15].

6. Result and Discussion

The weight variation studies for all suppositories were found to be within the acceptable range of <5 %.which indicates that calibration of mold was perfect.

All the prepared suppositories showed uniformity of drug content was within the permissible range (95 to100 %) indicating uniformity of drug dispersion in suppositories.

The suppositories should have good mechanical strength for handling and transportation. All suppositories were having good mechanical strength in the range of (1.5 to 2.5 kg/cm^2) showing optimum hardness. In PEG suppositories increasing the concentration of Peg 4000 and PEG 6000 increased the mechanical strength. In cocoa butter suppositories mechanical strength was increased as the amount of bees waxes increased up to 3% w/w and beyond this concentration brittle were formed.

The macro melting range test was performed for agar based suppositories ranges (54 to 60 ℃). In PEG suppositories the macro melting range time was increased as the amount of PEG 4000 and PEG6000 (40 to 44 ℃). In cocoa butter suppositories the macro melting range was (36 to 40 ℃). increasing the amount of bees wax.

The liquefaction time is the time necessary for suppository to liquefy under pressure similar to those found in the rectum. In agar based suppositories liquefaction temperature and time range (52 to 58 ℃) and time (8 to 12 min). In PEG suppositories ranges liquefaction temperature and time range (46 to 50 ℃) and time (12 to 20 min) as the amount of PEG 4000 and PEG 6000 increased. In Cocoa butter Suppositories liquefaction temperature and time range (36 to 40 ℃) and time (4 to 6 min) as the amount of bees wax was increased.

The disintegration test for agar based suppositories ranges more than 9 min. In PEG suppositories were disintegrated within a time period of (6 to 8 min). Suggesting that PEG it was a good disintegrant. In cocoa Butter Suppositories showed loss in shape of the suppository within ranges (6 to 7 min).

The in vitro release profile of lornoxicam from different bases are shown table 4. The overall release of lornoxicam from different bases was as follows, PEG > Agar > Cocoa butter Suppositories

In Dissolution study agar based suppositories indicated that the suppository does not disintegrate, melt or dissolve in the dissolution medium but remain intact. The drug diffuses out from the hydrophilic matrix with time. It was observed that more than 50% of the drug was released from plain agar based formulation.

In agar based formulation addition of HPMC K4M (1, 1.5 % w/w), E15 (2, 4 % w/w) and Glyceryl Behenate (2, 4 % w/w) retard the release significantly, which may be due to increase in the viscosity and gel strength of the polymer matrix. Hence HPMC and Glyceryl Behenate polymer in higher concentration can be used to formulate sustained release suppositories.

The drug released from the PEG suppositories as a consequence of the progressive dissolution of PEG in the dissolution media.

Suppositories prepared with the combination of PEG (P1-P4) showed maximum release of 90 % within 60 min.

In cocoa butter suppositories the drug release very slowly within 6 hrs. Addition of bees wax (1 %, 3 % w/w) further increase the drug release. This may be due to increase in the hardness and liquefaction temperature and time. Slow release of lornoxicam from cocoa butter base was due to high lipophilicity of the base, non miscibility of the base with the dissolution media absence of additive or surface active agents. The mechanism of drug release was chiefly diffusion controlled following first order kinetics.

Agar suppositories shows drug release by peppas kinetic model, cocoa butter shows drug release by higuichi, peppas model and PEG shows drug release by higuichi, first order and peppas model.

On stability studies showed that there was no significant change in drug content, physical character and dissolution profile of suppositories after storing them 6 w at refrigeration and room temperature. Lornoxicam suppository was stable in physical characteristics such as Hardness, Macro melting test, Liquefaction test, disintegration were satisfactory for practical use.

Table 3: Evaluation of suppositories for various parameters

Formulation Code	Drug Content (Mean±SD) (%)	Weight variation (mean±SD) (gm)	Hardness (Kg/cm^2)	Disintegration Time (min) (37.5±0.5℃)	Macro melting (℃)	Liquefaction	
						Time (min)	Temp. (℃)
A1	95.44±0.036	1.000±0.011	1.5	> 9	54-56	8-10	52-54
A2	96.58±0.045	1.005±0.012	2.0	> 9	56-58	8-10	52-54
A3	96.36±0.060	1.007±0.026	2.0	> 9	56-58	10-12	54-56
A4	95.44±0.025	1.001±0.029	1.5	> 9	54-56	10-12	54-56
A5	95.90±0.025	1.003±0.026	2.0	> 9	56-58	14-16	56-58
A6	96.81±0.035	0.999±0.022	1.5	> 9	56-58	12-14	52-54
A7	97.72±0.050	1.002±0.026	2.0	> 9	58-60	16-18	54-56
P1	99.94±0.068	1.030±0.019	2.0	8.17	42-44	14-16	46-48
P2	99.59±0.055	1.040±0.015	2.5	8.56	40-42	18-20	46-48
P3	99.75±0.041	1.030±0.012	1.5	6.45	40-42	12-14	48-50
P4	99.36±0.051	1.010±0.011	2.5	7.54	42-44	16-18	46-48

C1	98.64±0.010	0.998±0.010	1.5	6.20	36-38	4	36-38
C2	99.16±0.080	1.000±0.012	2.0	6.52	38-40	4-6	38-40
C3	99.77±0.070	1.001±0.013	2.0	7.35	38-40	4-6	38-40

Table 4: In–Vitro drug release data

S.N	Formulation Code	Time (min)	Cumulative (%) Drug Release
1	A1	360	90.45
2	A2	360	73.28
3	A3	360	62.61
4	A4	360	82.72
5	A5	360	78.17
6	A6	360	81.93
7	A7	360	76.26
8	P1	60	90.68
9	P2	60	91.93
10	P3	60	95.56
11	P4	60	91.23
12	C1	360	43.06
13	C2	360	44.88
14	C3	360	47.87

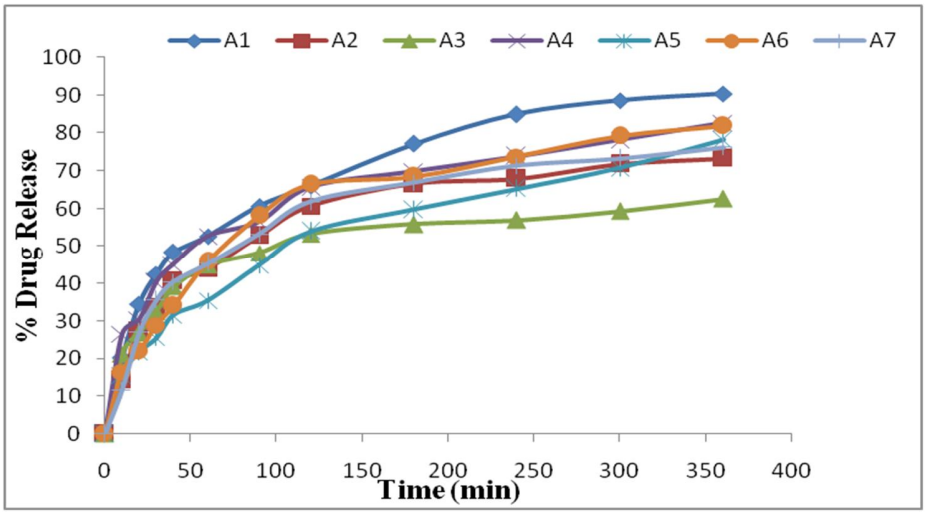

Fig 1: *In vitro* release of lornoxicam from agar based Suppositories

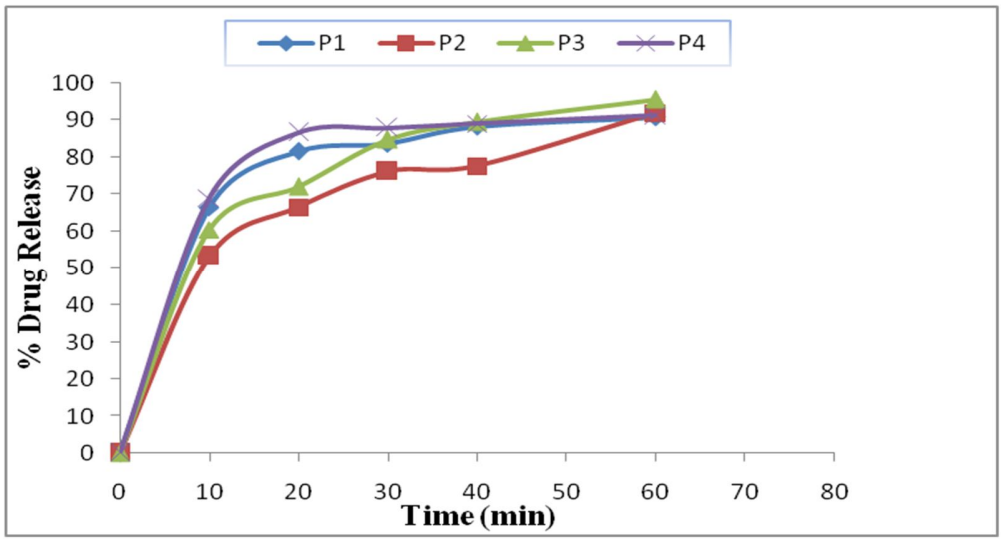

Fig 2: *In vitro* release of lornoxicam from PEG based Suppositories

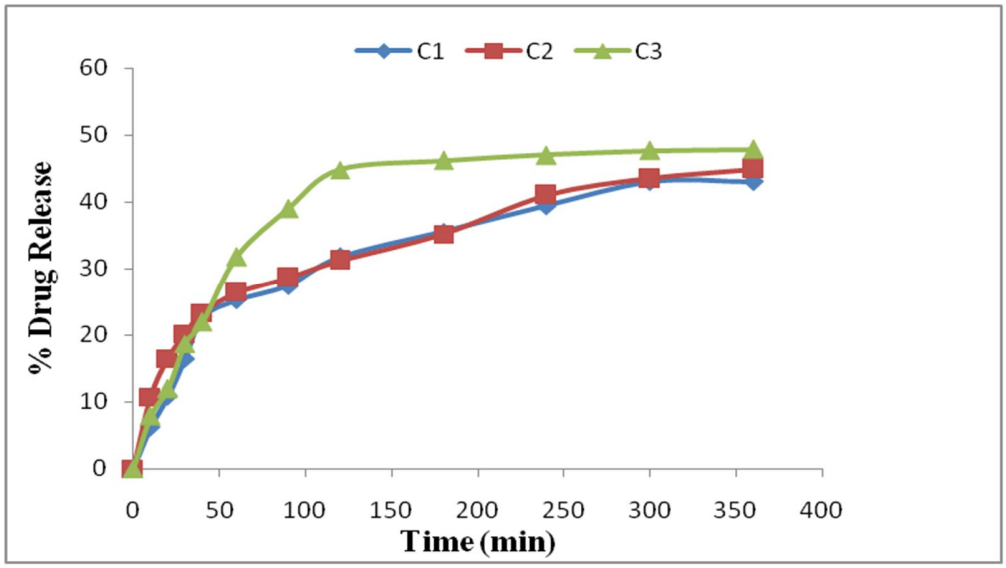

Fig 3: *In vitro* release of lornoxicam from Cocoa butter based Suppositories

7. Conclusion

It can be concluded that lornoxicam suppositories can be prepared by utilizing both hydrophobic and hydrophilic bases like the PEG of low molecular weight with high molecular weight in different percentage and cocoa butter base suppositories also very slow drug release and agar base used to formulate conventional rapid release where as agar based suppositories prepared by addition of HPMC, Glyceryl Behenate shows sustained release suppositories. Agar suppositories shows drug release by peppas kinetic model, cocoa butter shows drug release by higuichi, peppas model and PEG shows drug release by higuichi, first order and peppas model. Refrigeration storage is better than room temperature for lornoxicam suppositories storage.

Table 5: Drug release kinetic study

Sr. No.	Formulation code	Zero-order	Peppas	Higuichi	First order
1	A1	0.8608	***0.9905***	0.9813	0.9839
2	A2	0.7865	***0.9650***	0.9449	0.8882
3	A3	0.7613	***0.9310***	0.9198	0.8343
4	A4	0.8506	***0.9627***	0.9624	0.9555
5	A5	0.9198	***0.9901***	0.9848	0.9813
6	A6	0.8205	***0.9443***	0.9407	0.9334
7	A7	0.7857	***0.9660***	0.9474	0.9047
8	P1	0.7630	0.9563	***0.9809***	0.8974
9	P2	0.9475	0.9566	0.9507	***0.9587***
10	P3	0.8936	0.9437	0.9502	***0.9956***
11	P4	0.5944	***0.9781***	0.9092	0.7248
12	C1	0.8329	0.9258	***0.9594***	0.8814
13	C2	0.8954	0.9887	***0.9890***	0.9324
14	C3	0.6910	***0.8682***	0.8636	0.7303

8. Acknowledgements

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