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RESEARCH ARTICLE

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FORMULATION AND IN VITRO & IN VIVO EVALUATION OF ORAL DISPERSIBLE FILMS OF LORNOXICAM

ABSTRACT

The aim of the present study is to formulate and evaluate the Immediate release oral dispersible film formulation of lornoxicam with different ratios polymeric combinations by the solvent evaporation technique. . Lornoxicam, a potent non-steroidal anti-inflammatory drug (NSAID) with shorter half life, makes the development of immediate release dosage forms extremely advantageous. These formulations are named as F1 to F7 and studied for Thickness, mean weight(mg), drug content(mg),% hydration, % moisture loss , surface PH, Tensile strength, % elongation at break, folding endurance, mucoadhesion time, disintegration time. And these are also studied for *In vitro* dissolution and *In vivo* dissolution studies. Among all the formulations F4 with combination of polymers (1:1) showed maximum release of 98 % in 15min, with peak plasma concentration 10.54 mcg/ml emerging to be ideal formulations. The developed Oral dispersible films increase the efficacy of Lornoxicam for the therapy of arthritis and other painful muscular conditions.

Key words lornoxicam , Oral dispersible film, solvent evaporation technique, NSAID.

INTRODUCTION

Despite the tremendous advancement in the drug delivery system, oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage form [1-3] but now they experienced several limitations like chocking and swelling discomforts in the geriatric and paediatric patients [4-5].

A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists[6].

Fast dissolving drug delivery system (FDDS) was introduced in late 1970 as the alternative to conventional tablet, capsule and syrups especially for the geriatric and paediatric patients suffering from the dysphasia problem [7]. Fast dissolving tablets are the solid dosage form which disintegrates rapidly in the oral cavity without the need of water [10-8]. Some problems are associated with the OFDF like they are sometime difficult to carry, storing and handling (friability and fragility), these are prepared using the expensive lyophilisation method [9-11]. To overcome these problems oral films were developed, which are very popular now a days. Oral films as dosage form are getting more attention for the delivery of active pharmaceutical ingredients (API). It offers distinct advantages like an easy application, no degradation of API by gastrointestinal fluids, bypassing the first-hepatic metabolism and potentially improved bioavailability ensuring rapid invasion and fast onset. Many advantages of this route have been recently recognized and various products are under development. There is no single definition of oral films so for practical purpose it is defined as “A thin flexible, non-friable polymeric film having dispersed active pharmaceutical ingredient which is intended to be placed on the tongue for rapid disintegration and dissolution in the saliva prior to swallowing for delivery into GIT[12]. Lornoxicam is a newer NSAID of oxicam class. It is a strong analgesic and anti- inflammatory agent. Its analgesic activity is comparable to that of opioids (more effective than 10 mg morphine when used at doses > or =8 mg to control pain after oral surgery). Clinical investigations have established it as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions including Rheumatoid arthritis and postoperative pain [13,14,15] .

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MATERIALS AND METHODS

Materials

All the polymers of the formulation like HPMC E5 and others are purchased from Indian scientific, Hyderabad. Lornoxicam is obtained as a gift sample from Ranbaxy Pvt limited,Gurgaon . All the other laboratory chemicals used in the study were of analytical reagents grade. Double distilled water was used throughout the study.

Method

Preparation of Lornoxicam Oral dispersible Film

Water is heated to 80^0C and then 23gms is taken in a beaker. To this 1.5gms of HPMC and 0.8gms of pullauan is added under continues stirring for 10mim and keep it aside for 10hrs to get viscous lump.To this lump again add 8gms of purified water and 5gms of IPA under stirring for 2hrs . And then add SLS and Mannitol for 10min. Then add the remaining excipients one by one under continuous stirring for 30min.Keep it aside for 10hrs then pour into prtiplate in the form of film and allow the film for drying at 80^0C for 15min. Cut the desired size and evaluate the films for physical and chemical properties. The composition of films are mentioned in Table

Ingredients mg/film	F1	F2	F3	F4	F5	F6	F7
Lornoxicam	8	8	8	8	8	8	8
Polacrillin potassium	30	30	30	30	30	30	30
SLS	15	15	15	15	15	15	15
Mannitol	10	10	10	10	10	10	10
HPMC E5	15	15	15	15	15	15	15
Pullulan	8	8	8	8	8	8	8
Glycerol	10	10	10	10	10	10	10
Neotame	5	5	5	5	5	5	5
Tartazine	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mint flavor	10	10	10	10	10	10	10
SSG	-	5	10	15	-	-	-
CCS	-	-	-	-	5	10	15
Purified water	80	80	80	80	80	80	80
IPA	50	50	50	50	50	50	50

Table No: 1

Evaluation of Oral Dispersible Films

1. Physical appearance: All the prepared Films were visually inspected for colour, clarity, flexibility and smoothness. The physical and chemical parameters of different formulations of lornoxicam from F1 to F7 studied are represented in Table 2 & 3.
2. Thickness Uniformity: The thickness of the formulated film was measured at 3 different places and average thickness of three readings was calculated.
3. Weight Uniformity: For each formulation, three randomly selected films were used. For weight variation test 3 films from each

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batch were weighed individually and the average weight was calculated.

4. Folding endurance: The folding endurance was measured manually for the prepared films. A strip film (3X3 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.
5. Percentage moisture absorption: The films were weighed accurately and placed in the desiccators containing 100ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3days, the films were taken out and weighed. The study performed at room temperature. The percentage moisture absorption was calculated using the formula

$$\text{Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

1) Percentage moisture loss: The films were weighed accurately and kept in a dessicator containing anhydrous calcium chloride. After 3days the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\%\ \text{Moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

2) Tensile Strength: Tensile strength of the film was determined with Universal strength testing machine (Hounsfiled, UK). The sensitivity of the machine was 1gm. It considered of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4X 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. It can be calculated from the formula:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

3) Drug content uniformity of films:The films (1cm^2)were cut and added to a beaker containing 100ml of phosphate buffered saline of pH 6.8. The medium was stirred with magnetic bead. The contents were filtered using Whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films at 375nm spectrophotometrically. The experiment was repeated to validate the result.

4) In vitro drug release studies:The In vitro drug dissolution of films were performed using Phosphate buffer pH6.8 at 37±5^{0}C. 5ml of Sample was withdrawn periodically for every 10min upto 50min by replacing with dissolution medium and these samples were again diluted and examined spectrophometrically at 375nm. The values obtained were shown in **Table 4** and **graph No: 1**

5) In vivo studies of **LORNOXICAM** Oral Dispersible Films: In vivo studies were carried out for Male Wistar rats weighing 250- 400gms. 24 rats were dividied into 4 groups of each group containg 6 rats .

Group 1: Pure drug is administered by calculating the dosage based on animal weight. the animal dose for the drug is 1.3mg/kg by oral route by preparing a suspension of drug in sodium cmc.
Group 2: Marketted formulation is given with same dose calculation as above by oral route.

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Group 3: Tablet formulation is given onto mouth mucosa. For the administration of sample (tablet or film) preparation, 50 µl aliquot of distilled water was dropped into the rat oral cavity under light ether anesthesia, then two halves (1 cm×0.5 cm) of the film preparation were applied to the buccal cavity bilaterally. Blood specimens were taken (every 0.5 ml) in a centrifuge plastic capillary tube by the intraorbital route at 0 min, 30 min, 1 h, 2 h, 4 h, 6h, and 12 h after drug administration. Blood was subjected to centrifugation at 10,000 rpm for 15 min, then plasma was taken in a polyethylene tube to the plasma of 100 microlitres, 100 microlitres of acetonitrile is added and mixed by vortexing for 15min, then centrifuged at 15,000 rpm for 30min and the supernatant was injected into HPLC.
Group 4: film formulation is given onto mouth mucosa.

The sampling intervals remain the same for all the animals, later the kinetic data is processed in software for all the pharmacokinetic parameters.

RESULTS AND DISCUSSION

1) Physical appearance: All the prepared films were transparent, smooth, uniform and flexible.
2) Thickness Uniformity: The thickness of the formulated film were varies from 13.21± 0.09mm to 14.21±0.023mm. Low standard deviation values ensured uniformity of the patches.
3) Weight Uniformity: The weights ranged between 111.1 to 128.7mg as mentioned in **Table No:2**
4) Folding endurance: The folding endurance was found to be < 100 which was sufficient **Table No:2**
5) Percentage moisture absorption: The films were found to between 1.945 ± 0.09 to 2.77±0.01 and it increases with increasing concentration of hydrophilic polymers.
6) Percentage moisture loss: Water vapour transmission rate for prepared films were found to be 0.0463± 0.01 to 0.0543 ± 0.03 as mentioned in **Table No 3.**
7) Tensile Strength: The Tensile strength of films is found to be in order F2>F1>F5>F6>F3>F4>F7. As the concentration of hydrophilic polymer was increased there is increase in tensile strength. It was found to be in **Table No.3.**
8) Drug content uniformity of films: Drug content was found to be 90.36% to 99.13% as mentioned in **Table No.3**.
9) In vitro drug release studies: The result indicated that the release of drug from films having HPMC E5 shows better dissolution. The cumulative percentage of immediate release Oral Dispesible Film was 98% in 15min from formulation F4 (Table No 4) and minimum was 72% from F1 formulation.
10) In vivo studies:

From the results F4 formulation of Oral Dispersible Film showed Cmax of 10.54 mcg/ml concentration.It was shown in **Graph No:2**

Formulation	Thickness	Mean weight(mg)	Drug content(%)	%hydration ratio	% moisture loss	Surface pH
F1	13.23	111.1	96.54	0.546	2.774	6.65
F2	14.33	123.4	93.45	0.634	1.087	6.63
F3	14.21	124.4	99.13	0.723	1.567	6.45
F4	13.45	127.3	86.34	0.808	2.243	6.34
F5	14.87	119.4	90.36	0.624	1.945	6.81
F6	14.67	121.4	86.23	0.505	2.342	7.03
F7	13.95	128.3	94.34	0.463	2.016	6.61

Table No:2 Thickness, mean weight(mg), drug content(mg),% HYDRATION, %moisture loss & surface pH

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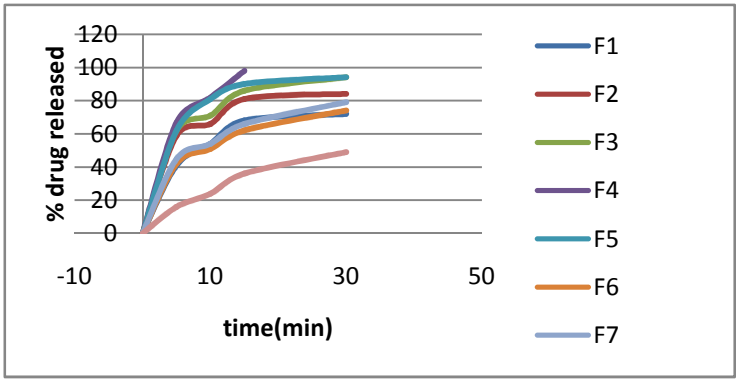
Formulation	Tensile strength	%elongation at break	Folding endurance	Mucoadhesion time(SEC)	Disintegration time(s)
F1	0.706	6.34	46	150	31
F2	0.807	5.21	57	90	24
F3	0.616	5.13	55	120	28
F4	0.517	4.34	43	153	26
F5	0.701	5.34	40	128	36
F6	0.687	4.12	45	145	24
F7	0.463	4.08	39	270	28

Table No: 3 Tensile strength, %elongation at break, folding endurance, mucoadhesion time, disintegration time

Time/ Formulation code n code	5 min	10 min	15 min	30 min
F1	41	54	68	72
F2	59	66	81	84
F3	62	71	86	94
F4	67	82	98	-
F5	72	81	90	94
F6	42	51	62	74
F7	46	54	66	79
Marketted	16	24	36	49

Table No: 4 In vitro dissolution profile



Graph No: 1 In vitro dissolution graph

In vivo animal studies

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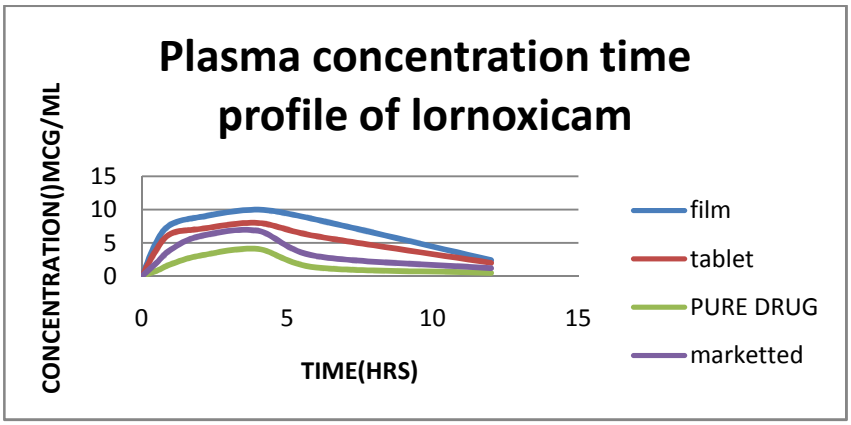
Parameters	Tablet	Film	Marketed	Pure drug
Cmax(mcg/ml)	8.22	10.54	6.17	3.20
Tmax(hrs)	2.64	2.83	2.74	2.8
AUC(mcg/ml*h)	62.9	81.7	42.91	22.8
MRT(h)	7.2	7.2	5.4	65.69

Graph No 2



CONCLUSION

In conclusion the formulation of Oral Dispersible film with F4 have better physical chemical properties with good dissolution proflile. Hence it is further studied for release kinetics and it showed peak plasma comcentration of 10.54 mcg/ml. Hence it was the best formulation.

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