International Journal of Current Trends in Pharmaceutical Research

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Research Article **Open Access**

Formulation and Evaluation of Meloxicam Mucoadhesive Films

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A B S T R A C T

The Mucoadhesive films are also known as patches, containing dispersed or dissolved drug with plasticizers, polymers, etc are intended to deliver a therapeutically effective amount of drug across the skin. The aim of the present study was to prepare and evaluate Mucoadhesive films containing Meloxicam by using to different formulations codes like Film I like Drug, HPMC (15cps), glycerin, Ethanol. Film II shows Drug, HPMC (15 cps), Eudragits, tween 80, Acetone, Ethanol. Transdermal patches of Meloxicam with Film I and II by varying the blend ratios were prepared by solvent casting method. The films were tested for their potential to cause skin irritation in few human beings. Thin, flexible, smooth Patches of Meloxicam were obtained with various Films I and II blends. The FT-IR confirmed no interaction between the drug and polymers. Thickness, Tensile strength, Swelling studies, Weight variations, Content uniformity, *In Vitro* Release Studies of Meloxicam Films in Sorensen's Phosphate Buffer *(*pH 6.2*)* were found to be uniform and reproducible. It could be concluded that the polymeric matrix-type transdermal patches of biopolymer based transdermal Patches are potential vehicles for improved transdermal delivery of Meloxicam.

Keywords: Meloxicam, HPMC (15 cps), Eudragits, Mucoadhesive films.

A R T I C L E I N F O

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Article History: Received 10 June 2015, **Accepted** 27 July 2015, **Available Online** 15 September 2015

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PAPER-QR CODE

Citation: Veerapuram Kumar Reddy, et al. Formulation and Evaluation of Meloxicam Mucoadhesive Films. *Int. J. Curnt. Tren. Pharm, Res.*, 2015, 3(5): 1013-1018.

1. Introduction

The Meloxicam Mucoadhesive films used for the treatment of NSAIDS. The oral mucosa has been studied extensively for a potential route of systemic drug delivery. As early oral mucosal drug delivery work focussed on the phenomena that drugs can be absorbed via the oral mucosa. This interest had diminished somewhat with the finding that only a few drugs are clinically needed and practically feasible to be delivered via the oral mucosal route[1]. More recently, interest has been renewed with the finding that certain penetration enhancers are effective in improving the permeability of oral mucosal tissue, coupled with more appropriate ways to deliver drug to this site, for example, buccal patches, chewing gum, bioadhesive tablets etc.

Advantages of Drug Delivery through Buccal Mucosa

a. It permits easy accessibility
b. It is a passive system and does not require activation.
c. Enzymatic activity is very low as compared to stomach.
d. Buccal mucosa is highly perfused with blood vessels and offers greater permeability than skin.
e. It can be easily removed in case of emergency
f. Therapeutic serum concentration can be achieved rapidly.

Limitations of drug delivery through Buccal Mucosa[2]

a. Drug that is impermeable to the oral mucosa cannot be used.
b. Surface area available for absorption is less.
c. Patient may swallow the patch.
d. It may be difficult to convince the patient because of unpleasant taste, odour and irritability to the mucosa.
e. The drug should be stable at buccal pH.

Some simple drug delivery systems to oral mucosa include solutions, mouth washes, mouth paints, chewable tablets, buccal and sublingual tablets and capsules. Bioadhesive multilayered compacts containing cetylpyridinium chloride have been formulated and evaluated in vitro. The device produced more uniform and effective plasma levels with adequate comfort and less irritancy for 3 hours when compared to proprietary lozenge formulation. Bioadhesive slow-release tablets containing miconazole were used in the treatment of oral candidosis in irradiated cancer patients [3]. The prepared buccal adhesive medicated patches of benzydamine and lidocaine using tamarind gum as bioadhesive polymer for obtains controlled release of these drugs.

2. Materials and Methods

Meloxicam is the gift sample Hetero Pharma Ltd, Hyderabad, HPMC (15 cps), Eudragit-RS 1 was obtained from Spectrum Chemicals and Reagents, Cochin, India Glycerin, Tween – 80, Acetone, Ethanol was ontained from Micro labs Pvt. Ltd, Pondicherry, India.

Film 1: Preparation of Meloxicam -HPMC Films

Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent [4]. The buccal mucoadhesive films of Meloxicam were prepared using hydroxypropyl methylcellulose (HPMC 15 cps) polymer by casting method. 200 mg of HPMC polymer was weighed accurately and dissolved in 2 ml of ethanol. The beaker containing polymer was kept aside for 5 minutes for swelling of polymer. Ten mg of Meloxicam was weighed separately and dissolved in 1 ml of ethanol. Further 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then one drop of (0.0294g) of glycerin was added to the polymer solution. The drug solution was added to the polymer solution. The whole solution was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5 × 3 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. A cardboard sheet was placed over the mould to avoid sudden evaporation. The mould was kept for 12 hours at room temperature for drying. After this period, the film was removed from the mould and preserved in butter paper and in a desiccator.

Film 2: Preparation of Mucoadhesive Films

The mucoadhesive film of Meloxicam was prepared by using hydroxypropyl methylcellulose (15 cps) polymer and eudragit RS 100 polymer by using casting method. 100 mg of HPMC was weighed and transferred into a beaker and 1 ml of ethanol was added. 10 mg of eudragit RS 100 was weighed separately into another beaker and 1 ml of acetone was added. The polymer dispersions were kept for swelling for 5 minutes. 10 mg of Meloxicam was weighed and dissolved in 2 ml of ethanol[5]. After swelling, both the polymers were mixed together one drop (0.0294 g) of glycerin and one drop (0.0315 g) of Tween 80 was added to the polymer dispersion.The drug solution was added to the dispersion and mixed thoroughly with the help of magnetic stirrer. The speed of the magnetic stirrer was kept low to avoid air bubbles. A glass mould of size 5 x 3 cm^2 was placed over a perfectly flat surface. The drug polymer viscous dispersion was poured into the glass mould, a cardboard sheet was placed over the glass mould to avoid any sudden evaporation. The mould was kept at room temperature for 12 hours for drying. After this period, the film was removed from the mould and preserved in butter paper in a desiccator.

Table 1: Formulation of Meloxicam Mucoadhesive Films

Formulation code	Ingredients	Quantity
Film I	HPMC (15 cps)	200 mg
	Glycerin	1 drop
	Ethanol	6 ml.
	Meloxicam	10 Mg
Film II	HPMC (15 cps)	100 mg
	Eudragit-RS 100	100 mg
	Glycerin	1 drop
	Tween – 80	1 drop
	Meloxicam	10 mg
	Acetone	1 ml
	Ethanol	6 ml

Evaluations

Thickness Uniformity of the Films: The thickness of each film was measured using Thickness Tester at different positions of the film and the average was calculated [6].

Swelling Studies of the Films: A drug loaded film of 1 x 1 cm^2 was weighed on a preweighed cover-slip. It was kept into a petridish and 50 ml of Sorensen's phosphate buffer, pH 6.2 was added. After every two minutes, the cover-slip was removed and weighed again. The difference in the final and initial weight gives the weight increase due to absorption of water and swelling of film [7].

Area Increase due to Swelling: A drug loaded film size of 1 x 1 cm^2 was cut and placed in a petridish. A graph paper was placed beneath a petridish, to measure the increase in the area. The film was placed in the petridish. 50 ml of Sorensen's phosphate buffer, 6.2 pH was poured into the petridish. An increase in the length and breadth of the film was noted at suitable time intervals and the area was calculated.

Tensile Strength of the Film: Tensile strength of the films was determined with Digital Tensile Tester (DY-20, 1986). The sensitivity of the machine is 1 to 10 Newton's. It consists of two load cell grips. The upper one is fixed and lower one is movable (Figure 9). The test film of specific size (4.5 × 3 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in Newtons, which is converted into kilograms [8]. Weight Variation of the Films: Film size of 1 x 1 cm^2 was cut. The weight of each film strip was taken and the weight variation was calculated [9]. Drug Content Uniformity of Films: A film of size 1 × 1 cm^2 was cut and placed in a mortar. 10 ml of 0.1 N sodium hydroxide solution was added and triturated for 20 minutes. The temperature was maintained at 37^0C. The contents were transferred to a volumetric flask (50 ml). The volume was made upto 50 ml with 0.1 N sodium hydroxide solution. The dispersion was kept in a dark place for overnight. Next day the dispersion was filtered and the absorbance was measured against the corresponding blank solution at 292.2 nm [10].

In-Vitro* Release Studies of Meloxicam Films in Sorensen's Phosphate Buffer *(*pH 6.2*): A film of 1 x 1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.2). This slide was kept at an angle 45^0 in a 250 ml beaker containing 100 ml of buffer solution. The beaker was kept in circulating water bath in which the temperature was maintained at 37^0C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. 5 ml of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid. The samples were taken at predetermined intervals and analysed for drug content at 284.4 nm. The release studies were conducted for three times and average was determined [11].

3. Results and Discussion

Drug – Excipient compatibility studies:

As described in the methodology section the FT-IR studies were carried out for pure drug alone and in combination with polymers. Similarly FT-IR spectra of Meloxicam in combination with polymers. The peaks are given in the characteristic peaks of Meloxicam. These peaks were not affected and prominently considered as observed in FT-IR spectra. This indicates that there is no interaction between Meloxicam and polymers and the drug was compatible with the formulation components.

Buccal Mucoadhesive Films of Meloxicam:

Meloxicam films in polymers were prepared by casting method as described in the previous chapter. The films of HPMC (15 cps) were prepared with a purpose of releasing the drug rapidly. Attempts were also made to extend the release of drug by including endragit RS 100. Plasticizer such as glycerine was used to get a film of good strength and less brittleness. Tween 80 was used for dispersing the drug uniformly in the film.

Physical Characteristics Study of Films:

The films were translucent, having good strength and visually smooth surface. The drug and polymer distribution was uniform. For the purpose of discussion, Film I means HPMC film and Film II means a combination of HPMC and eudragit RS 100

Thickness Uniformity of Films:

The thickness of drug loaded films was measured with the help of thickness tester by combining 4 films for Film I and 3 films for Film II together, as it was difficult to measure the thickness of a single film. The results were given below.

Film I: Average thickness (n = 6) uniformity of films = 0.405667 + 0.02151 mm.

Film II: Average thickness (n = 4) uniformity of films = 0.340 + 0.007071 mm.

Weight Variation of Films:

Drug loaded films (1 x 1 cm^2) were tested for weight variation and the results were given below.

Film I: The average weight of the films of size (n= 3) = 11.0 + 1.0 mg.

Film II: The average weight of the films of size (n=3) = 14.0 + 1.0 mg.

Swelling Studies of Films

The swell ability of the drug loaded films (1 x 1 cm^2) was observed up to specific time. Swelling was determined in terms of area as well as weight of the films. The swelling of the films was observed in Sorensen's phosphate buffer solution (pH 6.2). The data for increase in area and weight due to swelling. It indicated that the increase in area and weight are agreeing with each other. The swelling changes are more predominent in Film I than in Film II. This was justified because HPMC film (Film I) were having greater affinity to take up water than HPMC-eudragit films (Film II).

Tensile Strength of Meloxicam Films:

Tensile strength was determined using Digital Tensile Tester DY-20 for the blank and drug loaded films. The average of three determinations is given below.

- Tensile strength of HPMC films (Blank)(n = 3) = 2.7336 ± 0.4650 kg.
- Tensile strength of HPMC films (with drug)(n =3) = 3.47136 ± 0.282 kg.

- Tensile strength of HPMC-eudragit RS 100 (Blank)(n =3) = 1.632 ± 0.34642 kg.
- Tensile strength of HPMC-eudragit RS 100 (with drug)(n=3) = 2.19636 ± 0.551936 kg.

Perusal to the data indicated that the tensile strength of drug loaded films were higher than control (blank) films. This is justified because Meloxicam is hydrophobic and strengthened the bonding polymer chains. The tensile strengths of Films II are lower than Films I. In other words, eudragit does not produce effective cross linking with the HPMC chains at the working concentrations. Still Film II has shown extended drug release.

Content Uniformity of Meloxicam Films:

The content uniformity tests are commonly employed for unit dosage forms such as tablets, capsules etc**.** In order to make sure about the uniform dispersion of drug in films, the films of size 1 x 1 cm^2 were cut and dissolved in 0.1 N sodium hydroxide solution, the temperature was maintained at 37^0C. The drug content was analysed at 292.2 nm. The results were expressed in AM ± SD and given below along with percent in paranthesis.

Film I (HPMC): Concentration of drug present (n=3) = 0.639 ± 0.0154410 mg (96.01%)

Film II (HPMC-Eudragit): Concentration of drug present (n=3) = 0.6566 ± 0.239449 mg (98.60%)

In vitro Release Studies of Meloxicam:

The release kinetics of Meloxicam from films may follow the mechanisms such as diffusion controlled, dissolution controlled or a combination of both. The release of drug may follow a zero order or a first order kinetics. *In-vitro* Release Studies of Meloxicam Films in Sorensen's Phosphate Buffer (pH 6.2). The release data of Meloxicam were given Table % and 6 and Figure 4 *In-vitro* release of Meloxicam from Film I and Film II respectively

Release Kinetics of Meloxicam

The release kinetics of Meloxicam for Film I was first order and Film II was zero order. However, understanding the zero order release is difficult to reconcile for this brief period of study. Therefore, for the purpose of uniformity in calculations, first order is considered for HPMC-eudragit film *in vitro* release. The coefficients of 't' indicated that the release is faster from Film I compared to Film II.

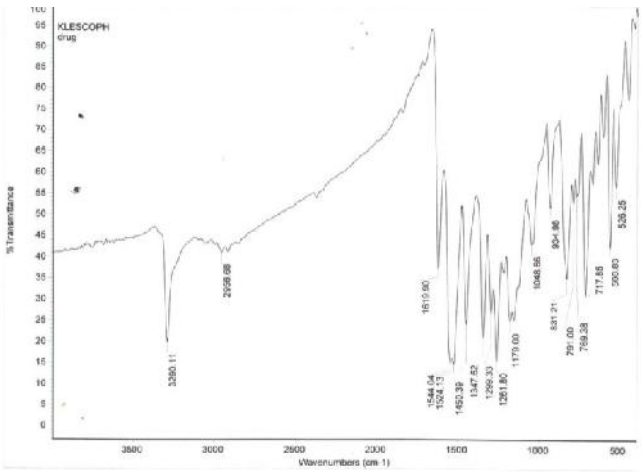

Figure 1: FT-IR spectrum of pure Meloxicam

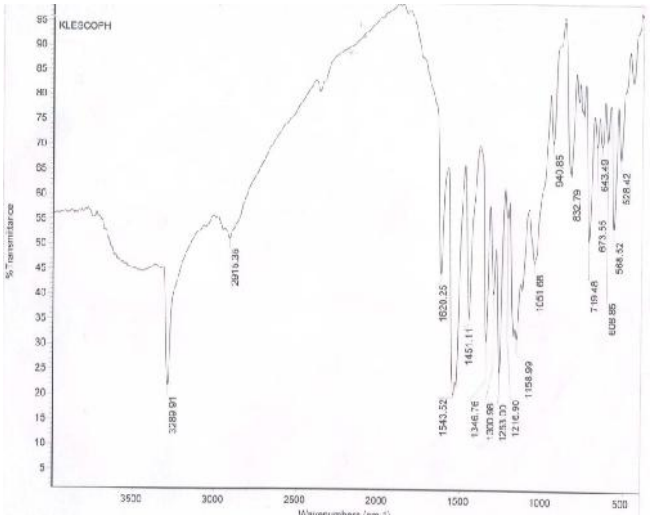

Figure 2: FT-IR spectrum of pure Meloxicam+ Eudragit

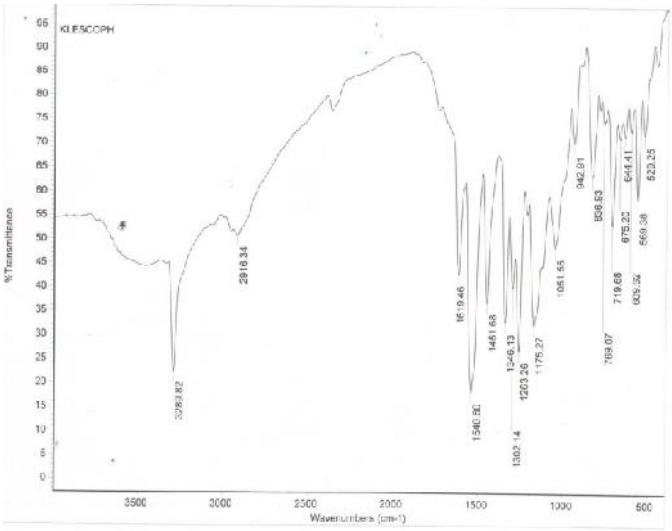

Figure 3: FT-IR spectrum of pure Meloxicam + Eudragit + HPMC

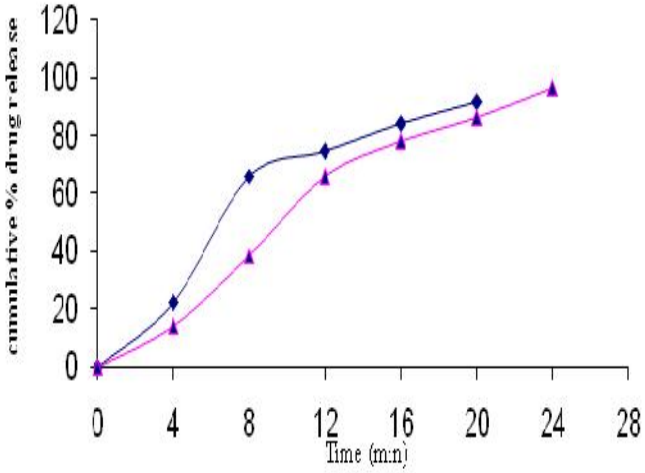

Figure 4: *In-vitro* release of Meloxicam from Film I and Film II.

Table 2: Data of the FT-IR spectra of pure Meloxicam and polymers

IR Spectra	Peak of functional groups [Wave length (cm^{-1})]			
	C=O (Amide)	CH- stretching	OH-	NH-
Meloxicam	1619.90	2956.68	3458.10	3290.11
Meloxicam + Eudragit	1620.25	2915.35	3440.12	3289.91
Meloxicam + Eudragit + HPMC	1619.64	2916.34	3453.29	3289.82

Table 3: Swelling studies of films-Changes in area

S.No	Time (min)	Film I (HPMC) (cm^2)	Percent increase in volume	Film II (HPMC-eudragit)(cm^2)	Percent increase in volume
1	0	1.00	-	1.00	-
2	5	1.10	10	-	-
3	10	1.20	20	1.10	10
4	20	---	-	1.20	20

Each reading was done in triplicate.

Table 4: Swelling studies of Meloxicam films-Change in weight

S.No	Time (min)	HPMC films (Film I) (mg)	Percent increase in weight AM ± SD	HPMC-Eudragit RS 100 (Film II) (mg)	Percent increase in weight AM ± SD
1	0	11.0 ± 1.00	-	14.0 ± 1.00	-
2	2	51.0 ± 3.6055	364 ± 14	38.66 ± 0.5092	175 ± 12
3	4	60.33 ± 4.041	449 ± 14	47.00 ± 4.3588	235 ± 13
4	6	66.0 ± 4.5825	500 ± 14	58.66 ± 0.7859	319 ± 11
5	8	-	-	66.33 ± 3.5118	372 ± 7
6	10	-	-	70.33 ± 1.5275	403 ± 25

Each reading was done in triplicate.

Table 5: *In-vitro* release of Meloxicam from Film I in Sorensen's phosphate buffer (pH 6.2)

Time (min)	Cumulative * drug released (mg) AM ± S.D	% Drug released	% Drug remain unreleased	log% drug remain unreleased
0	0.000 ± 0.000	00.00	100.00	2.0000
4	0.1433 ± 0.0879	22.42	77.58	1.8897
8	0.4211 ± 0.0660	65.85	34.15	1.53339
12	0.4765 ± 0.0711	74.52	25.48	1.40619
16	0.5381 ± 0.0499	84.15	15.85	1.20029
20	0.5856 ± 0.0437	91.59	8.41	0.92479

*Each reading is an average of three readings. Initial drug concentration = 0.639 mg.

Table 6: *In-vitro* release of Meloxicam from Film II in Sorensen's phosphate buffer (pH 6.2)

Time (min)	Cumulative* drug released (mg) AM ± S.D	% Drug released	%Drug remain unreleased	Log % drug remain unreleased
0	0.000	00.00	100.00	2.0000
4	0.0925 ± 0.02478	14.09	85.91	1.93404
8	0.2511 ±0.04793	38.25	61.75	1.79063
12	0.4326 ± 0.07007	65.88	34.12	1.53301
16	0.5100 ± 0.04855	77.67	22.33	1.34888
20	0.56689 ± 0.0336	86.33	13.67	1.13577
24	0.6317±0.01605	96.20	3.80	0.57978

*Each reading is an average of three readings. Initial drug concentraion = 0.656 mg.

Table 7: Comparison of orders of *in vitro* release of Meloxicam from

Formulation	***In-vitro* release in Sorensen's buffer pH 6.2 Regression equations**	
	Zero order	**First order**
Film I	y = 4.655786 t + 9.86381, R^2 = 0.89762	Log y = -0.05408 t + 2.0332, R^2 =0.984178
Film II	y = 4.21875 t + 3.435, R^2 = 0.962474	Log y = -0.05624 t + 2.1494, R^2 = 0.931195

4. Conclusion

Meloxicam can pass through the buccal mucosa, Meloxicam patches were found to be ideal for immediate as well as delayed release of drug. The adhesive nature of the polymers was taken advantage for better delivery of the meloxicam. Mucoadhesive patches of meloxicam containing 10 mg of drug were prepared successfully using HPMC polymer for Film I and HPMC-eudragit RS 100 polymers for Film II with an intention to obtain immediate as well as delayed release of meloxicam. The *in vitro* release of meloxicam from HPMC films was about 91% in 20 minutes in Sorensen's phosphate buffers, pH 6.2. About 86% of the drug was released from HMPC-eudragit films in 20 minutes. The release kinetics indicated first order release of drug from Film I, where as zero order release from Film II. Hixon-Crowell cube root law was applied to test the release mechanism. A plot of ($M_0^{1/3}$ - $M^{1/3}$) versus time, t, gave a straight line for both HPMC (Film I) as well as HPMC-eudragit (Film II) films indicating that the release was dissolution rate limited.

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