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FORMULATION AND DEVELOPMENT OF TRANSDERMAL FILMS OF MELOXICAM WITH B-CYCLODEXTRIN COMPLEX AND ITS *IN-VITRO* RELEASE STUDIES

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ABSTRACT
Skin delivery of NSAIDs offers several advantages over the oral route associated with potential side effects. The present research has been undertaken with the aim to develop transdermal films of Meloxicam, which would attenuate the gastrointestinal relater toxicities associated with oral administration. Meloxicam is a nonsteroidal anti-inflammatory drug. It has anti-inflammatory, analgesic and antipyretic activity through inhibition of prostaglandinsynthetase, via inhibition of cyclooxygenase enzymes. This study was designed to enhance the solubility of Meloxicam by preparing its inclusion complex with β-cyclodextrin and formulating films using HPMC E 6 and ethyl cellulose. The films were evaluated for release through cellophane membrane. It was observed that the formulation containing complex (DCP 3) was good in all respects.

KEYWORDS : Meloxicam, β-cyclodextrin, Meloxicam-β-CD-Complex, films, cellophane membrane etc.

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INTRODUCTION

Skin is man's largest organ providing around 10% of the body mass of an average individual. An average human skin is known to contain, on an average 40-70 hair follicles and 200-250 sweat ducts per every square centimeter of the skin. These skin appendages, however actually occupy grossly only 0.1% of total stratum corneum surface henceforth the transappendageal route of percutaneous absorption has provided only a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecule at steady can thus be considered as primarily diffusion through the intact stratum corneum in the interfollicular region. So, for fundamental understanding of TDD (Transdermal drug delivery), the structure should be understood[1]. Skin has many essential functions, including protection,

thermoregulation, immune responsiveness, biochemical synthesis, sensory detection, and social and sexual communication. Although the skin is a large and easily accessible area for the administration of therapeutic agents, it also forms a highly efficient barrier between internal and external parts of the body. Skin is highly resistant to the penetration by any exogenous compound including chemicals and also organisms such as bacteria and viruses. The transverse section of the human skin is shown in fig. 1. The structure of human skin can be divided into three distinct layers, which are epidermis, dermis and hypodermis (subcutaneous adipose tissue). Permeation through can occur by diffusion[2,3] via:

1. Transcellular permeation, trough the stratum corneum
2. Intracellular permeation, through the stratum corneum
3. Transappadageal permeation, via the hair follicles, sebaceous and sweat glands.

Permeation pathways are shown in fig. 2.

First two mechanisms require further diffusion through the rest of the epidermis and dermis whereas third mechanism allow diffusional leakage into the epidermis and direct permeation into the dermis. The appendages may be important at short diffusional time and for polar molecules. For drugs penetrating directly across the intact stratum corneum, entry may be transcellular or intercellular.

Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Advances in modern technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules. In recent times, development of transdermal delivery system started in 1970s, and in 1979, the first transdermal film of scopolamine was approved by USFDA for the treatment of motion sickness and later on nitroglycerine film was marketed for the management of angina pectoris[4]. Since then numbers of drugs viz. clonidine, nitroglycerine, fentanyl, oxybutonin, scopolamine, lidocaine and testosterone have been successfully delivered through transdermal route[5].

Use of non-steroidal anti-inflammatory drug is well recognized for regional inflammatory disorders such as muscle pain, osteoarthritis and rheumatoid arthritis[6,7]. Meloxicam[8] is a non-steroidal anti-inflammatory drug from oxicam group that exhibits anti-inflammatory, analgesic and antipyretic activities. Oxicams shows all diverse functions shown by other NSAIDs and oxicam is highly effective class of NSAIDs, mainly used in various arthritic condition and post-operative inflammation. Meloxicam, which is described chemically as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. It is potent, highly selective COX-2 inhibitor from BCS –II class. It has very poor aqueous solubility so its solubility has to be enhanced. There are several methods to enhance solubility. One of the methods of increasing bioavailability is by preparing its inclusion complex with Beta-cyclodextrin.

Cyclodextrins (CD) are known to improve the solubility of insoluble drug by forming inclusion complexes[9]. Cyclodextrins are widely used as "molecular cages" in the pharmaceutical, agrochemical, food and cosmetic industries[10]**.** Cyclodextrins increase the water solubility of poorly soluble drugs to improve their bioavailability, light, thermal and oxidative stability of actives can be improved through the formation of cyclodextrin complexes. Cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability[11]. The most common cyclodextrins are α -cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, which consist of six, seven, and eight glucopyranose units, respectively. Among α-, β-, γ-; β-CD was used for the study, as it has bigger cavity size and is the least toxic among the other natural cyclodextrin[12]. Cyclodextrins were reported to enhance topical drug delivery in the presence of water. The interior environment of cyclodextrin cavity is hydrophilic; hence it can entrap unionized form of the molecule which too is hydrophilic[13].

Several techniques are used to form cyclodextrin complexes **s**uch as co-precipitation method, solution method, the neutralization method, the kneading method, the slurry complexation method, and the grinding method[14].

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, cream, gel, ointments, liquids, aerosols and

injectables as drug carriers. Delivery of drugs through the skin is an effective and targeted therapy. This route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Due to the first past effect only 25-45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages the film formulations have been proposed.

The aim of the present study was to enhance the solubility of Meloxicam by its inclusion complexation with β-cyclodextrin by kneading method, to formulate and develop transdermal films containing complex and its *in-vitro* release studies.

Materials and Methods

The materials used include Meloxicam (gift sample from Cipla Pharmaceuticals, Kurkumbh), β-cyclodextrin (gift sample from Macleods Pharma, Kachigam, Daman), HPMC-E-6 (gift sample from Piramal limited, Ahmedabad). Ethyl cellulose, Glycerine, Dibutyl phthalate, Dichloromethane and all others chemicals of analytical reagent grade were procured from S.D Fine Chemicals Ltd, Mumbai.

Preformulation studies

Preformulation studies were performed on free drug and complexes to assess the suitability of the complexes for the dosage forms. Solubility of the drug and the complex in phosphate buffer pH 7.4 were determined. The results were as shown in table 1. FT-IR studies of the pure drug, β-CD and drug-β-CD complex were recorded using Fourier Transform Infrared (FTIR) spectroscopy (Jasco FT-IR-460 Plus). Thermo grams of the pure drug, β-CD and β-CD complex were recorded by analyzing the samples by DSC using Mettler-DSC-30S, Mettler Toledo India Pvt. Ltd., Switzerland, using crucible Al 40µL, at of 10°C /min heating rate, under nitrogen environment. The temperature range used was 0 – 400°C. The DSC thermograms of Meloxicam exhibited an endothermic peak at 263 corresponding to its melting point. β-cyclodextrin alone showed a broad endothermic representing a loss of water molecule, a dehydration process. The thermograms of complexes are different from the pure drug; thereby giving clear evidence that there is formations of the complex. As the concentration of the β-cyclodextrin is increased in the in the complex it was observed that the height of endothermic peak at 263 diminished gradually and it disappeared at the concentration of 1:5, indicating complex formation at all these concentrations. However, maximum deflection in the peak height was found to occur while changing the concentration ratio from 1:1 to 1:2, indicating maximum inclusion at this concentration. Hence, other characterizations were performed in complexes bearing drug:β-cyclodextrin, 1:3, 1:4 and 1:5 in molar concentration. The molecular volume of β-cyclodextrin is 346 Å where as molar volumes of, Meloxicam is 412 Å, which is greater than the molecular volume of β-cyclodextrin. Therefore two molecules of β-cyclodextrin may be required for making true inclusion complex. Practically, it has been found that for making inclusions, two molecules of β-cyclodextrin were to enclose one molecule of drug. On the basis of molecular volume itself it is suggestive that drug could not be covered by the cavity of one molecule of β-cyclodextrin. Therefore for further studies 1:2, drug: β-cyclodextrin ratio were used. The prepared complexes were studied for its solubility in phosphate buffer pH 7.4.

Preparation of Meloxicam- β -Cyclodextrin Complex

Kneading Method: The inclusion complex of Meloxicam with β-CD was prepared by the kneading method[15]. Calculated amounts of Meloxicam and β-CD were accurately weighed and

transferred in a glass mortar, triturated with a small volume of distilled water and methanol (1:1 volume ratio) and then kneaded for 60 minutes. The product was kept at room temperature for 24 hrs. Distilled water and methanol (1:1 volume ratio) was used as wetting agent to achieve better interaction of Meloxicam with β-CD during kneading method. The kneaded formulations were prepared at 1:0.5, 1:1, 1:2, 1:3, 1:4 and 1:5 molar ratios. These complexes were used for the formulation of films.

Preparation of Transdermal Films: The transdermal films containing Meloxicam and Meloxicam- β-cyclodextrin complex were prepared by solvent evaporation method using polymers HPMC and Ethyl Cellulose as mentioned in formulation table 2. For HPMC film, casting solution was prepared by dissolving the polymer in solvent blend of dichloromethane and chloroform and glycerine (30 % w/w of polymer) was added. Drug was dissolved in above solution. For EC film, casting solution was prepared by dissolving the polymer in 5 ml blend of chloroform and dichloromethane (3:2) and dibutyl phthalate (30 % w/w of polymer) was added. Drug was dissolved in above solution. Penetration enhancers like eugenol (5 % w/w of drug) were dissolved in respective solvent blends. The resulted clear solution was poured on the mercury surface on the surface of a Petri dish (5 cm). The rate of evaporation was controlled by inverting cut funnel over the Petri dish. The films were dried at 40^0 C in an oven for 24 hr. After 24 hr, the films were cut into a 3.14 cm^2 area and backing membrane (biaxial oriented polyethylene film) was then glued. A glossy paper having a smooth surface was used as a release liner. The films were stored in desiccators until used. For the preparation of films containing Meloxicam-β-CD complex, casting solution was prepared by dissolving the polymer in 10 ml of distilled water and 90 mg glycerine (30 % w/w of polymer) was added. Meloxicam-β-CD complex equivalent to the 8 mg of Meloxicam was added. Then above solution was stirred for 2 hr. and followed by sonication for 2 hrs. Finally the mixture was poured on the mercury surface on the surface of the Petri plates and dried in an oven at 35ºC for 24 hr. The rate of evaporation was controlled by inverting cut funnel over the Petri dish. The films were dried at 40^0 C in an oven for 24 hr, the films were cut into a 3.14 cm^2 area and backing membrane (biaxial oriented polyethylene film) was then glued. A glossy paper having a smooth surface was used as a release liner. The films were stored in desiccators until used.

Characterization of Films : Hydroxy propyl methyl cellulose and ethyl cellulose were utilized to incorporate a water insoluble drug Meloxicam. Films of each polymer were prepared with different concentration of polymer 200, 250, 300, 350 and 400. Formulation with 200 mg of polymer could not form a proper film with both HPMC and EC. Formulation with 400 mg of polymer forms a thick film for both HPMC and EC. Therefore 300 and 350 mg quantity of polymers was used. Formulations with 300 and 350 mg polymer have produced uniform, smooth, transparent and reproducible films. The weight and thickness of films were also uniform and reproducible and proportionate with polymer concentration in each batch. Drug content of the films determines the amount of drug entrapped in matrix. The drug content estimated with 1cm^2 of various films in phosphate buffer saline of pH 7.4 was carried from 94.14 to 98.18. The low RSD values indicate uniform distribution of the drug in each batch of the film. The drug contents of both HPMC and EC films were also uniform and reproducible in each batch. The films were characterized for different physicochemical characteristics[16,17] of films like physical appearance, weight uniformity, thickness uniformity, folding endurance and drug content uniformity of films. The films were further studied for their *in-vitro* drug release through cellophane membrane. The results are given in table no. 3.

Results and Discussion: Present study involves the study of release of drug from films prepared using inclusion complexes of β-cyclodextrin to increase the solubility of Meloxicam. The solubility of the drug was found to be increased considerably by complexation. The results were as shown in table

2. The drug and complexes were characterized for solubility, DSC, FT-IR studies. The IR spectras were shown in fig. 3. Thermograms of pure drug, β-CD and β-CD complex were shown fig 2. Results of characterization of films for different physicochemical characteristics of films like physical appearance, weight uniformity, thickness uniformity, folding endurance and drug content uniformity of films are given in table no. 3. The results of *in-vitro* drug release across the cellophane membrane using fabricated Keshary-Chien diffusion cell were indicated in table 4 and graphically shown as graph 1**.**

Conclusion: Dissolution profile of Meloxicam was improved by complexation with β-CD by kneading method. This complex with the ratio of 1:2 (drug: complex) has contributed for better drug release profile. The physicochemical of properties of complex was amenable for film formation. Films prepared with EC and HPMC E-6 were good in all aspects with respect to all the physicochemical characteristics. However, the films prepared with HPMC E-6 (formulation DCP-3) proved to be the formula of choice, since it showed the highest percentage of % drug content, % drug release and other properties. Hence it can be concluded that *In vitro* release of Meloxicam from films was enhanced because of inclusion complex.

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Tables & Figures

Table 1: Solubility analysis of pure drug and of complex

	Solubility (mg/ml)	Concentration (mg/10ml)	Molar conc. Of Meloxicam.	Enhancement in solubility
Plain drug in PBS	0.346	3.460	0.001005	1 fold
Drug- β-CD complex	1.005	10.00	0.002906	2.89 folds

Table No. 2: Formulation Table of films

Sr. No.	Ingredients	Formulation codes								
		DP 1	DP 2	DP 3	DP 4	DCP 1	DCP 2	DCP 3	DCP 4	DP 5
1.	Meloxicam (mg)	7.5	7.5	7.5	7.5	--	--	--	--	7.5
2.	Drug-β-CD complex (mg)	--	--	--	--	55.96	55.96	55.96	55.96	--
3.	HPMC (mg)	--	--	300	350	300	--	350	--	--
4.	EC (mg)	300	350	--	--	--	300	--	350	300
5.	Glycerine (ml)	--	--	0.073	0.085	0.073	0.073	0.085	0.085	--
6.	Dibutyl phthalate (ml)	0.088	0.102	--	--	--	--	--	--	0.088
7.	Dichloromethane (ml)	4	6	--	5	--	--	--	4	4
8.	Chloroform (ml)	6	4	6	5	--	--	--	6	6
9.	Distilled water (ml)	--	--	4	--	10	10	10	10	--
10.	Eugenol	--	--	--	--	--	--	5%	5%	5%

Note: DP 1, DP 2, DP 3, DP 4, DP 5: Films containing plain Drug
DCP 1, DCP 2, DCP 3, DCP 4: Films containing Drug-β-CD complex

Table 3: Physical parameters and drug content of transdermal films of Meloxicam through cellophane membrane

Sr. No.	Formulation Codes	Physical appearance	Weight* (mg)	Thickness* (mm)	Folding endurance*	Drug Content**
1	DP 1	++	329 (0.61)	0.118 (1.57)	71 (1.17)	95.28 (0.43)
2	DP 2	++	391 (0.47)	0.144 (1.62)	66 (1.74)	97.25 (0.48)
3	DP 3	++	457 (0.30)	0.170 (1.23)	58 (1.75)	94.21 (0.67)
4	DP 4	++	329 (0.47)	0.110 (1.22)	103 (0.79)	97.21 (0.80)
5	DCP 1	++	394 (0.61)	0.132 (1.56)	113 (0.98)	96.19 (1.02)
6	DCP 2	++	459 (0.63)	0.156 (1.41)	112 (1.56)	96.21 (0.97)
7	DCP 3	++	422 (0.73)	0.136 (1.28)	122 (1.29)	98.11 (0.49)
8	DCP 4	++	423 (0.50)	0.134 (1.85)	58 (1.75)	96.91 (0.81)
9	DP 5	++	439 (0.71)	0.137 (1.17)	54 (1.89)	95.13 (0.49)

* Average of five observations

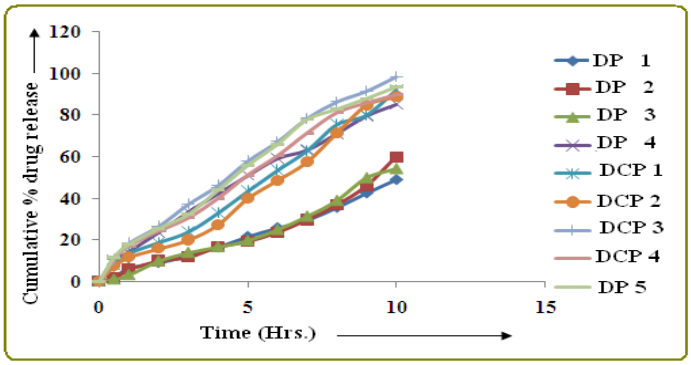
** Average of three observations

++ Satisfactory

Table 4: *In vitro* release of Meloxicam from films through cellophane membrane in PBS pH 7.4.

Time (hr)	% Cumulative amount of drug released*								
	DP 1	DP 2	DP 3	DP 4	DCP 1	DCP 2	DCP 3	DCP 4	DP 5
0	0.000	0.000	0.000	0.00	0.00	0.00	0.000	0.000	0.000
0.5	2.032	1.426	0.965	9.88	8.14	7.24	10.478	10.911	11.694
1	6.487	5.661	3.115	14.38	13.56	11.67	18.387	17.191	17.928
2	8.979	9.879	9.781	23.68	18.78	15.75	26.455	24.301	25.485
3	12.534	11.604	13.863	33.44	23.89	19.92	37.079	30.657	32.359
4	16.522	16.600	16.594	42.23	32.98	27.29	46.041	40.036	43.939
5	21.614	19.230	19.643	50.87	43.47	39.95	57.794	51.222	55.892
6	25.772	23.588	24.885	59.11	53.53	48.61	67.081	60.45	65.969
7	29.646	29.662	31.32	63.12	62.98	57.55	78.254	71.423	77.885
8	35.656	36.798	38.946	71.07	75.63	71.47	86.266	81.178	82.836
9	42.613	45.917	49.886	79.52	80.19	84.84	91.411	85.858	87.938
10	49.132	59.910	54.282	85.03	92.23	88.96	98.321	89.843	93.56

*Average of three determinations



Graph 1 : Graphical representation of *In vitro* release of Meloxicam from films through cellophane membrane

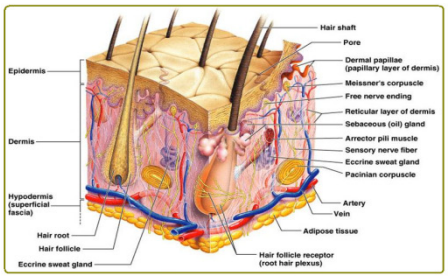


Figure 1: Transverse section of the human skin

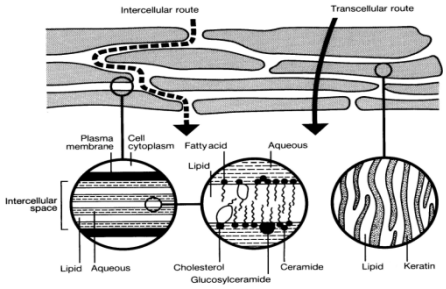
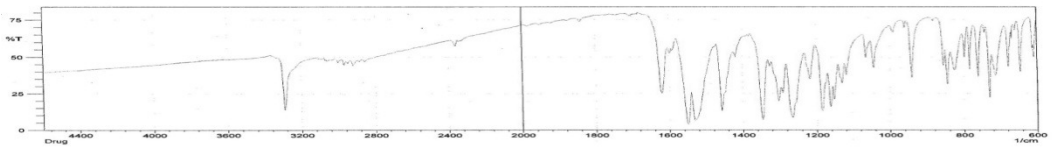


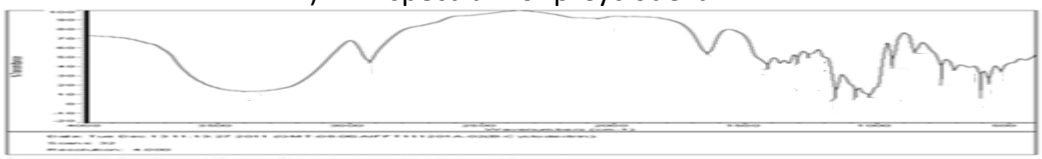
Figure 2: Permeation pathways of skin.

Figure. 3: IR spectra of Meloxicam, β-CD and Meloxicam-β-CD complex

i) FTIR spectrum of plain Meloxicam



ii) FTIR spectrum of β-Cyclodextrin



iii) FTIR spectrum of Meloxicam: **β**-cyclodextrin inclusion complex

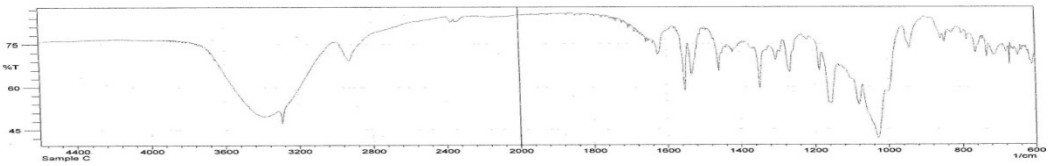
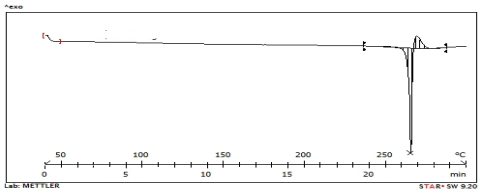
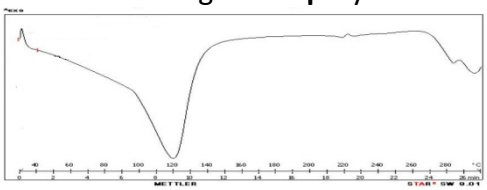


Figure 4 : DSC thermograms of Meloxicam, β-CD and Meloxicam-β-CD complex

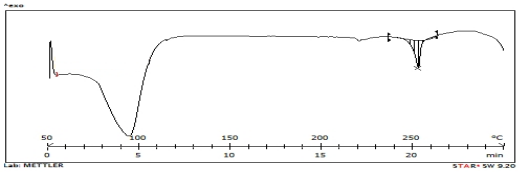
i) DSC thermogram of plain Meloxicam



ii) DSC thermogram of **β**-Cyclodextrin,



iii) DSC thermogram of Meloxicam: **β**-cyclodextrin inclusion complex



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