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PHYSICAL CHARACTERISTICS OF RESERVOIR TYPE PATCH USING NANOSTRUCTURED LIPID CARRIERS (NLC) AS DRUG RESERVOIR, HPMC 606 AS RATE CONTROLLING MEMBRANE AND MELOXICAM AS DRUG MODEL

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ABSTRACT

The purpose of this research work was to create a meloxicam patch transdermal drug delivery system using Nanostructured Lipid Carriers (NLC**)** as drug reservoir and Hydroxy Propyl Methyl Cellulose (HPMC) as rate controlling membrane. Meloxicam, an anti-inflammatory non-steroidal drugs, was used as a drug model. The NLC was done by using high-shear homogenization method. In this formulation, monostearin and alpha-tocopherol were used as lipid matrix. The transdermal patches of meloxicam were prepared by using different percentages of rate controlling membrane. NLC Meloxicam was dispersed into 1 ml rate controlling solution and spread over the backing layer followed by drying at room temperature.The patches were evaluated for physical appearance, weight variation, moisture content, drug content uniformity and morphology. The patches demonstrated satisfactory characteristics with minimum weight variation among the patches that lead to give uniformity in the drug content.

KEYWORDS: Patch, meloxicam, NLC, transdermal.

1. INTRODUCTION

Meloxicam (MLX) is a non-steroidal anti-inflammatory drug, which inhibits cyclooxygenase-2 selectively. Therefore it was used orally to reduce the symptoms of rheumatoid arthritis and osteoathritis. Topical route administration is an alternative to overcome these problems and also provides many advantages; including avoiding gastrointestinal irritation, minimal systemic toxicity, avoiding hepatic metabolism, achieving stable plasma level, and improving

patient compliance.[1] MLX is classified as a BCS Class II drug (high permeability and low solubility), has a log p of 3.42, and has poor wettability in water, causing difficulties in the pharmaceutical formulations design. Therefore, in the development of the meloxicam transdermal delivery system, patch preparations – which is drug delivery systems that are given transdermally by delivering the drug percutaneously and intended for external use– are made.[2]

Transdermal patch is used for delivery of medications through the skin for treating local and systemic illnesses. Transdermal drug delivery systems, also known as patches offers a variety of benefits such as controlled release, reduced systemic side effects, user-friendly, painless, and patient compliance through multi-day dosing. The transdermal route vies with the oral treatment as a most successful innovative research area in drug delivery platform.[3]

Nanostructured Lipid Carriers (NLC) is a drug delivery system consisting a mixture of solid lipids and liquid lipids, which form a lipid core matrix that is stabilized by surfactants and has a particle size in the range of 10-1000 nm,[4,5] NLC also have several advantages such as increased absorption up to the stratum corneum, increase the rate of drug release, increase the penetration of lipophilic drug substance as it has occlusive properties and improve skin hydration.[5] In this study a reservoir patch type, patch preparations was made with HPMC 606 as rate controlling membrane and NLC was act as drug reservoir. Therefore, MLX was encapsulated in the NLC system to increase its penetration into the skin. This paper focuses on the physical characteristic on the resulted patch using NLC as drug reservoir and HPMC as rate controlling membrane.

2. EXPERIMENTAL

2.1. Materials and method

Meloxicam was gifted by PT. Combiphar (produced by SUN PHARMA), Hydroxypropyl methylcellulose 606 (HPMC 606) was purchased from Wuhan Senwayer Century Chemical Co.,Ltd, Monostearin (Cutina® GMS), Kolliphor® P 188 (poloxamer 188) waspurchased from BASF; alpha-tocopherol acetate was purchased from Xinchang pharma; Tween 80 was obtained from PT KAO; Ethanol p.a., and NaH_2PO4 (natrium dehydrogenate phosphate) p.a. was purchased from Merck. Aquabidestilata purchased from PT Bratachem, backing layer was gifted by Pharmaceutic laboratory of Universitas Airlangga.

2.2. ML-NLC preparation

High-shear homogenization was used as NLC preparation method in this research. MLX-NLC system was made by melting the lipid phase (monostearin and α-tocopherol) with different lipid ratio at 65°C temperature. At the same time, the surfactant solution (Kolliphor® P 188, Tween 80 and pH phosphate buffer 6.0 ± 0.05) was prepared and heated at the same temperature. Then, this heated surfactant solution was dispersed into heated lipid phase using ultra-turrax at 5000 rpm speed for 15 minutes. Furthermore, this surfactant solution was added with phosphate buffer with pH 6.0 ± 0.05 until the volume reaches 100% w/w. Subsequently, the NLC dispersions were formed by cooling the warm pre-emulsion to room temperature in the same container.[6]

2.3. Transdermal patch preparation

Meloxicam loaded NLC was used as drug reservoir. The rate controlling membrane (HPMC 606) was prepared by dissolving the polymer (5%, 10%, 15%, 20%) in demineralized water. Meloxicam loaded NLC was dispersed into 1 ml of rate controlling solution and Menthol (1%) was added to this solution. This mixture was Spread over to the backing layer followed by drying at room temperature. The dry patch was removed from the mold and kept in a desiccator containing silica and used for further analysis.

2.4. Evaluation transdermal patch

The evaluation of the prepared NLCs of particle size and size distribution was done by Delsa™ Nano Submicron Particle Size Analyzer. Subsequently, the tool was turned on and particle size menu was selected.[6] Patches were observed visually and inspected for smoothness, color and odor. Moisture content of patches was determined by weighing the patches and kept in desiccator containing activated silica at room temperature for 42 h. After that, patches were taken out and weighed individually every 30 minutes. The individual films were weighed on at designated interval until a constant weight was achieved. The percentage of moisture content was calculated by determining the difference between initial and final weight divided with final weight.[5]

Drug content uniformity assay was performed on patches. Each patch were dissolved in a phosphate buffer pH 7.4. The solutions were then stirred for 2 h and filtered. Meloxicam concentration was determined spectrophotometrically with multiple wavelength methods. Formulations were tested in triplicate to calculate the mean and standard deviation.[7]

Scanning Electron Microscopy (SEM) was used to determine surface morfology of patch. Patch were placed on an electron microscope stub and observed under designated magnification. Images were taken on random side of the patch.

3. RESULT AND DISCUSSION

The observation of particle size and size distribution was done by Delsa^{TM} Nano Submicron Particle Size Analyzer. Already in the method. Average droplet diameter and polydispersity index (PI) were observed. PI illustrates the variation on a sample. The small value of PI (<0.3) indicates that the sample was monodispersed (8). From the particle size observation of all six NLC system formulas, the result was less than 1000 nm. Table 1 shown the particle size of MLX-NLC system was about 445,8 -545.9 nm, with the average of 473.50 nm.

Table 1: The average of particle size and polydispersity index (PI) NLC system formula.

Replication	Particle size	Polydispersity index (PI)
	F1	F1
I	445.8	0.028
II	545.9	0.045
III	482.8	0.032
Total	1474.5	0.105
Average	473.50	0.035

All organoleptics data were shown in Table 2 and Figure 1. The yellow color of patches was occurred due to meloxicam colour. There was no significant differences on surface texture between F1, F2, F3 and F4. All formula shown smooth texture on their surface. Meloxicam patch preparations had the same characteristic menthol odor in every formula.

Morphological tests were carried out to determine the morphology of the patch surface in the preparation. Scanning Electron Microscopy (SEM) method was used in this assay .The pores on the patch were useful in the process of releasing the drug from the patch preparation, since large pores allow the drug to be released from the matrix more easily. SEM images were shown in Figure 2.

Weight uniformity was determined by weighing patches from each formulation. After each unit was weighed individually, the average weight of the patch was calculated.[1] From this calculation, there was no significant difference in weights of patches. Moisture content and weight of patches were show in Table 3.

Table 2: Organoleptic observation of meloxicam reservoir type patch.

Formula	Observation			
	Shape	Color	Odor	Consistency
F1 (HPMC 5%)	Round, thin, smooth surface texture	Yellow	menthol smell	little stiff and dry
F2 (HPMC 10%)	Round, thin, smooth surface texture	Yellow	menthol smell	little stiff and dry
F3 (HPMC 15%)	Round, thin, smooth surface texture	Yellow	menthol smell	little stiff and dry
F4 (HPMC 20%)	Round, thin, smooth surface texture	Yellow	menthol smell	little stiff and dry

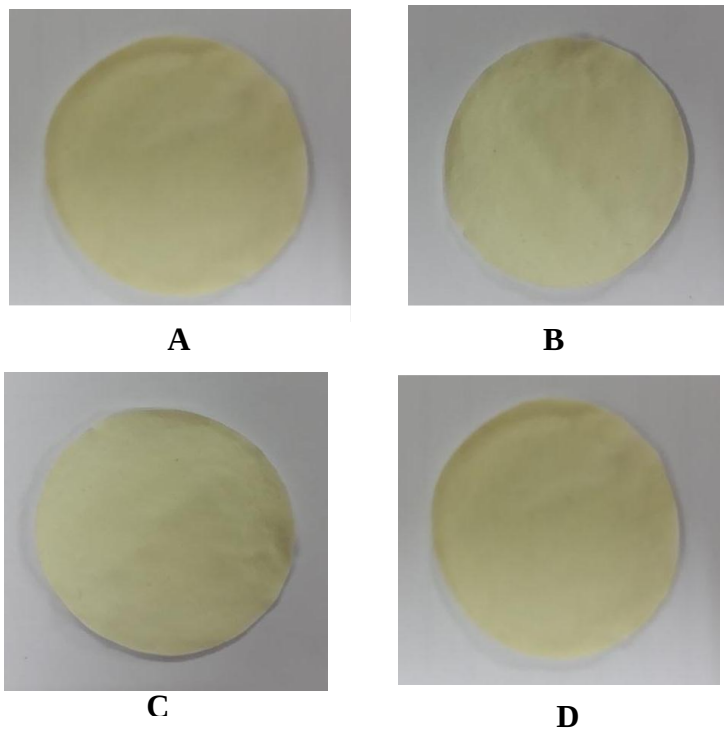
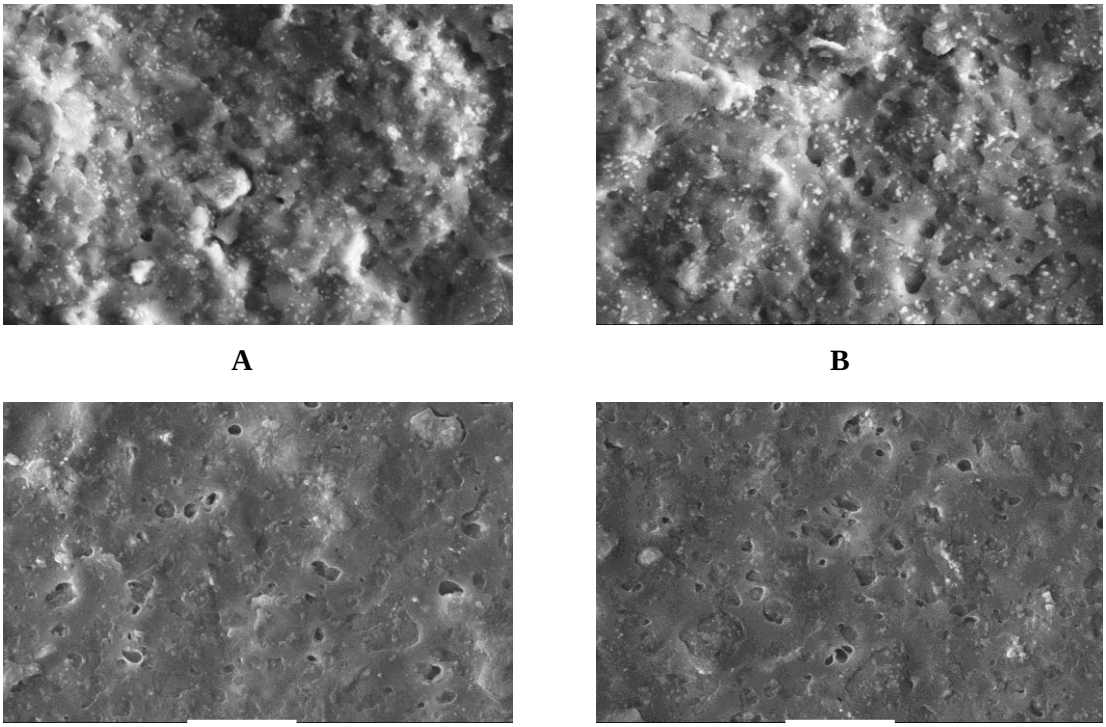


Fig. 1: Appearance of meloxicam reservoir type patch using NLC as reservoir and HPMC as controlled membrane with concentration A = F1(HPMC 5%) ; B = F2 (HPMC 10%) ; C = F3 (HPMC 15%) ; D = F4 (HPMC 20%). The Patch surface in the image looks as smooth.

Moisture content testing aims to determine the amount of water content in the patch preparation. The optimal formula for patch preparation hopefully contain less water with a range less than 10%. Moisture content in patches shown that patches were really stable and dry, with a low moisture content value that will protect the patch preparation from microbial contamination.[9] Moisture content of patch were 1.962 ± 0.433 for F1, 2.768 ± 0.901 for F2, 3.088 ± 0.579 for F3 and 2.667 ± 0.579 for F4. There was no significant difference in moisture content between the formulas.

Table 3: Weight (g) and moisture content (%) of meloxicam reservoir patches type.

Replication	Weight (g)				Moisture content (%)			
	F1	F2	F3	F4	F1	F2	F3	F4
I	0.610	0.641	0.613	0.763	1.475	3,744	3.099	3.670
II	0.650	0.661	0.719	0.740	2.307	1,967	2.503	2.432
III	0.618	0.593	0.628	0.752	2.103	2,592	3.662	1.900
Average	0.626	0.632	0.653	0.752	1.962	2.768	3.088	2.667
SD	0.021	0.035	0.057	0.011	0.433	0.901	0.579	0.579



A **B**

C **D**

Fig. 4: Photo of meloxicam reservoir type patch surface by Scanning Electron Microscopy (SEM) with 2000x magnification; A = F1(HPMC 5%); B = F2 (HPMC 10%); C = F3 (HPMC 15%); D = F4 (HPMC 20%).

The homogeneity test of patch was done to determine the uniformity of drug content in each patch section. The patch homogeneity observation was done by calculating the coefficient of variance (CV) of drug content. The level of preparation was said to be uniform if the CV value does not exceed 2%. Based on the test results (Table 4) it can be concluded that it has met the uniformity requirements guidance of drug uniformity.

Table 4: Homogenity drug content content of meloxicam reservoir patches type.

Replication	Homogenity Drug Content			
	F1 (HPMC 5%)	F2 (HPMC 10%)	F3 (HPMC 15%)	F4 (HPMC 20%)
I	97.52	99.15	95.90	97.52
II	97.52	97.52	95.90	95.90
III	97.52	97.52	99.15	97.52
IV	99.15	99.15	95.90	99.15
Average	97.93	97.52	96.71	97.52
SD	0.815	0.941	1.625	1.327
CV	0.832	0.965	1.680	1.361

Table 5: Drug content of meloxicam reservoir patches type.

Replication	Drug Content			
	F1 (HPMC 5%)	F2 (HPMC 10%)	F3 (HPMC 15%)	F4 (HPMC 20%)
I	98.17	97.23	96.91	96.91
II	97.23	97.23	98.17	98.17
III	98.17	98.17	97.23	96.91
Average	97.86	97.54	97.44	97.33
SD	0.543	0.543	0.655	0.727
CV	0.555	0.557	0.672	0.747

Drug content of patch formula was carried out to determine uniformity of meloxicam levels in patch preparations. Calibration curve of standard meloxicam was made, and sample absorbance value was calculated from the regression equation. Based on the test results (Table 5) it could can be concluded that all patches have met the same level of uniformity requirements, all of formulas had meloxicam concentration above 95% and was still within the range of levels received in the patch preparation (85-115%).[10] Statistical calculation was done by One Way Anova Test. Result shown that there was no significant difference between the drug content of meloxicam patch on formula 1, 2, 3, and 4 where $p > 0.05$.

4. CONCLUSION

Nanostructured Lipid Carriers (NLC) has potential as drug reservoir for patch system while using HPMC 606 as rate controlling membrane. Patch characteristic evaluation in terms of physical appearance, organoleptic, weight uniformity, drug content and uniformity shown that the characteristics had met the requirements and F1 was found as the optimal formula across all formulation.

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