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Research Article

Preparation and characterization of amphiphilic cream formulations with meloxicam

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Abstract

The purpose of this study is to formulate and evaluate amphiphilic cream with meloxicam indicated for topical relief of pain, particularly because there are currently no available topical dosage forms on the market. Thus, the present research is focused on characterization of the capacity of the amphiphilic base, composed of glycerol monostearate, cetyl alcohol, Tagat® S2, Myritol® 318, propylene glycol, and white petrolatum, to be loaded with drug model meloxicam dissolved in propylene glycol. To enhance the solubility and penetration of meloxicam, menthol as a rubefacient was added to the meloxicam solution. The series of three formulations were prepared with variable content of added menthol. Obtained creams were characterized by drug content, pH, spreadability, viscosity, microbial purity, drug release, and stability. Results showed stable cream formulations with good spreadability and viscosity, suitable for topical application.

Keywords

amphiphilic base, cream, meloxicam, menthol

Introduction

Meloxicam is a well-known and widely used non-steroidal anti-inflammatory drug that preferentially inhibits cyclooxygenase-2 (COX-2) isozyme at its low therapeutic dose, which is attributed with fewer adverse reactions and a lower risk of gastrointestinal bleeding. Generally, it is indicated for treatment of rheumatoid arthritis and osteoarthritis (Vane and Botting 1997; Ahmed et al. 2005; Khalil and Aldosari 2020). Despite its selectivity, long-term use of meloxicam is associated with an increased incidence of severe adverse effects such as drowsiness, ulceration, swelling, and the risk of myocardial infarction and stroke (Lehmann et al. 1996; Moore et al. 2011). In addition, regarding the polarity of its molecular structure and the solid phases in which its crystal structures exist, meloxicam belongs to Biopharmaceutical Classification System class II, exerting low water solubility and high permeability. Therefore, an alternative approach to overcome these limitations of orally and parenterally administered meloxicam is the development of topical formulation since skin offers numerous advantages, such as minimal systemic toxicity, avoidance of hepatic metabolism, and risk of gastrointestinal bleeding (Moore et al. 2008; Saleem and Bala 2010).

The challenge for the development of a topical formulation of meloxicam is the fact that there is no currently available marketed topical formulation.

As a promising candidate for incorporation of meloxicam is an amphiphilic base, known as basis cream DAC, due to its composition that includes water/oil (w/o) and oil/water (o/w) emulsifiers with high capacity of emulsification of hydrophilic and lipophilic vehiculums/excipients of active substances. This emulsifier system contributes a superior characteristic biocoherent structure whereby hydrophilic and lipophilic phases are not separated but are adjacent to each other (Ivković et al. 2023). Under a polarized microscope, there is no difference between droplets in coexisting oil and the water phases. This base could also improve the stability of drugs, enable controllable drug release profiles, and reduce the production cost (Gloor 2004; Herwanto and Hutomo 2016).

According to literature data, combining non-steroidal anti-inflammatory drugs with rubefacients could significantly increase the drug release from the formulation. The mechanism of action of rubefacients is related to surface capillary dilation that causes irritation and redness to the skin and relieves minor pain (Pergolizzi et al. 2018). Despite the unreliability regarding classification of the compounds with rubefacient effect, most enhancers used for modifying drug permeation patterns are menthol, capsaicin, camphor, isopropanol, and salicylates (Mason et al. 2004).

Topical formulations with non-steroidal anti-inflammatory drugs that are currently available on the market contain a single active ingredient associated with several disadvantages, including lower potency and frequent application that reduces patients' compliance. To overcome these limitations, an intriguing approach is to formulate meloxicam with rubefacient into a suitable base for topical application. Therefore, the aim of this study is to formulate and evaluate amphiphilic cream with meloxicam in combination with menthol.

Materials and methods

Materials

All materials used were kind donations from Replek JSC-Skopje and were of pharmaceutical grade. Meloxicam (active ingredient) was purchased from Apex Healthcare Limited, India, and menthol (rubefacient and penetrator) was procured from Alkaloid JSC-Skopje. Other excipients for formulation of amphiphilic base were propylene glycol (solubilizer), triethanolamine (pH adjuster), Myritol® 318 (medium-spreading emollient) that were purchased from BASF Pharma, Tagat® S2 (emulsifier) procured from Evonik, glycerol monostearate 60 (emulsifier) purchased from Thermo Scientific Chemicals, cetyl alcohol (emulsifier, surfactant) procured from Ward's Science, and white petrolatum procured from Alkaloid JSC-Skopje.

Preparation of amphiphilic cream with meloxicam

Preparation of amphiphilic cream with meloxicam was achieved through a two-step process of formulation, and the obtained creams were packaged in an aluminum tube as a single batch of 100 grams.

Step 1. Preparation of amphiphilic base

The amphiphilic base was prepared according to the monograph Basis cream DAC obtained from DAC/NRF 2013 (DAC/NRF. 2013). The composition is listed in Table 1.

Table 1. Composition of amphiphilic base (DAC/NRF. 2013).

Components	Amount (g)
Glycerol monostearate 60	4.0
Cetyl alcohol	6.0
Myritol® 318	7.5
White petrolatum	25.5
Macrogol-20-monostearate	7.0
Propylene glycol	10.0
Aqua purificata	40.0

Glycerol monostearate 60, cetyl alcohol, Myritol® 318, and white petrolatum were heated in a water bath at 60 °C. With continuous stirring, the mixture of macrogol-20-monostearate, propylene glycol, and aqua purificata was added to the previously prepared mixture and heated at 2–5 °C higher temperature. The stirring continued until cooling to room temperature and the formation of a homogenous cream base.

Step 2. Incorporation of meloxicam and menthol into amphiphilic base

The composition of the final preparation is presented in Table 2.

Table 2. Composition of amphiphilic cream formulations with different amounts of menthol.

Substance	Amount (g)		
	F1	F2	F3
Meloxicam	1.0	1.0	1.0
Propylene glycol	15.0	15.0	15.0
Menthol	1.0	5.0	9.0
Amphiphilic base	70.0	70.0	70.0
Triethanolamine	q.s	q.s	q.s
Aqua purificata	q.s	q.s	q.s

Meloxicam and menthol were dissolved in propylene glycol under constant stirring at slightly elevated temperature. Deionized water was added to the amphiphilic base with continuous stirring. The oil phase was then added to the water phase using homogenizer Ultraturex (IKA T 18 Digital ULTRA-TURRAX® Homogenizer) until formation of homogeneous cream, after which a few drops of triethanolamine were introduced to adjust the pH of the formulations.

Evaluation of amphiphilic cream

Physical properties of prepared formulations

The developed formulations were examined visually for color, odor, agglomeration, and potential phase separation.

Identification

Identification of meloxicam in amphiphilic cream was performed using a UV-visible spectrophotometer (UV-1600PC-VWR) at a wavelength range of 240–600 nm. The sample was dissolved in phosphate buffer (pH 7.4), and the absorption maximum was compared with the absorption maximum of the standard solution of meloxicam at a concentration of 16 µg/mL. Phosphate buffer was used as a blank probe.

pH measurements

Determination of pH value was obtained using a digital pH meter (Benchtop pH Meter, PH-B200E/PH-B200EM) calibrated with standard buffer solution (pH 7.4). Aliquots of 1 gram of amphiphilic cream were diluted to 100 mL with deionized water and left at room temperature for 2 hours (Panday et al. 2015; Mwangi et al. 2021).

Determination of meloxicam content

Drug content was obtained using a method adopted by Mwangi et al. (2021). One gram of the amphiphilic cream was dispersed in 100 mL phosphate buffer pH 7.4 and placed in an ultrasonic bath for 2 hours, and then centrifuged at 5000 rotations/min for five minutes. The supernatant was filtered through a Whatman filter with a pore size of 0,45 µm, and 5 mL of the solution was diluted with 50 mL of phosphate buffer. The drug content was determined at 362 nm using a UV-visible spectrophotometer (UV-1600PC-VWR).

Determination of viscosity

The viscosity of prepared formulations was determined using Brookfield DVT2 and an RV viscometer at 25 ± 0.5 °C using an RV-6 spindle at a rotation speed of 10 rpm with torque readings obtained in the range 15–85% of the base scale.

Spreadability of amphiphilic cream

A 1 g sample of amphiphilic cream was weighed on a graduated glass plate. Another glass plate was then placed on top, and a weight that totaled 1 kg was put on the upper glass plate for five minutes. The obtained diameter of the spread circle was measured using Vernier calipers (Bachavv et al. 2010; Mwangi et al. 2021).

Microbiological examination

Microbiological quality of amphiphilic cream formulations was examined at the Center for Public Health in Stip, North Macedonia, according to the monograph from USP Pharmacopoeia "Microbiological Examination of Non-Sterile Products," supplement 62 (Dabbah et al. 2001; Ratajczak et al. 2015). Test strains and culture media used for microbiological testing are listed in Table 3.

Table 3. Test mediums and strains for microbiological examination.

Test medium	Test strains
MacConkey Agar	*Escherichia coli*
Rappaport Vassiliadis	*Salmonella enterica* ssp.
Xylose Lysine Deoxycholate Agar	
Selenite F bujon	
Cetrimide agar	*Pseudomonas aeruginosa*
Columbia Agar	*Staphylococcus aureus*
Columbia Agar	*Clostridium sporogenes*
Sabouraud Dextrose Agar with Chloramphenicol	*Candida albicans*

A 1 gram of tested formulations was inoculated into the listed test mediums and incubated at a temperature of 30–35 °C for a duration of 18–48 hours, depending on the specific microbial species.

In vitro drug release

The release of meloxicam from amphiphilic cream was performed using the method from Bachhav et al., with slide modifications (Bachhav and Patravale 2010). For determination of drug release, we used Dissolution Apparatus 1 (basket type) under sink conditions with a total volume of 500 mL of freshly prepared dissolution medium. Phosphate buffer solution (7.4) was used as a test medium, primarily based on the official editions of British Pharmacopoeia and United States Pharmacopoeia. Additionally, literature evidence further supports that drug release from semisolid dosage forms is notably higher at pH 7.4 than at lower pH values, as meloxicam as an acidic compound demonstrates increased solubility in alkaline conditions. 500 mg of amphiphilic cream was placed on a cellulose membrane attached to a basket. The study was performed at 32 ± 0.5 °C with a paddle rotation speed of 50 rpm. At predetermined time intervals, aliquots of 2 mL were withdrawn and scanned spectrophotometrically at a wavelength of 362 nm, followed by the addition of an equal volume of fresh dissolution medium to maintain constant volume.

Stability of amphiphilic cream formulations

Stability testing of prepared formulations was studied according to International Council for Harmonization (ICH) guidelines. Samples of amphiphilic cream were stored at 25 °C/60% RH for a period of 6 months and then evaluated for pH, physical characteristics, and drug content.

Results and discussion

Physical characterization and pH determination

The aim of the study was to prepare amphiphilic cream with meloxicam and different concentrations of menthol. Upon visual examination, no phase separation was de-

tected. The formulated preparations were homogenous, pale yellow with creamy consistency. The pH values were within the optimal pH range of 5–7 without risk of skin irritation and suitable for topical application.

Identification

Obtained results showed that the absorption maximum of the tested sample is overlapped with the spectra of standard meloxicam solution (16 μg/mL) at a wavelength of 362 nm, which clearly demonstrates successful incorporation of meloxicam into the amphiphilic base. Results are presented in Fig. 1.

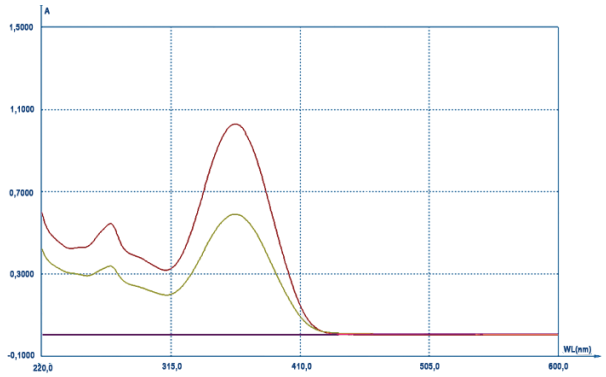

Figure 1. UV spectrum of blank probe (phosphate buffer pH 7.4-purple), standard solution of meloxicam (concentration = 16μg/mL – yellow), amphiphilic cream with meloxicam (red).

Viscosity measurements

Results from viscosity measurements are listed in Table 4, ranging from 21 435 cP to 25 500 cP, respectively. The third formulation with the highest menthol concentration had the lowest viscosity, which is in accordance with literature data that menthol concentration can significantly reduce the viscosity of topical preparations (Litaiem and Dhahbi 2012).

Table 4. Viscosity of tested formulations.

Sample	Ind. value	AVE	SD	RSD
F1	25 515	**25 500**	**16.0935**	**0.0631**
	25 483			
	25 502			
F2	23 258	**23 246**	**13.2035**	**0.0568**
	23 249			
	23 232			
F3	20 129	**20 125**	**14.8436**	**0.0738**
	20 109			
	20 138			

Spreadability studies

The spreadability of topical formulations is an important factor that is attributed to the increased surface area of the skin and higher drug permeation, which significantly improves patients' compliance (Bachhav and Patravale 2010; Rao et al. 2013; Mwangi et al. 2021). It is considered that spreadability above 7.5 cm is acceptable for topical application (Lardi et al. 2000). Spreadability is directly correlated with polymer concentration and viscosity. The results are presented in Table 5.

Table 5. Spreadability of amphiphilic cream formulations.

Sample	Ind. value	AVE	SD	RSD
F1	7.7	**7.8**	**0.0577**	**0.7434**
	7.8			
	7.8			
F2	8.5	**8.5**	**0.1528**	**1.8042**
	8.3			
	8.6			
F3	9.1	**9.2**	**0.1000**	**1.0870**
	9.2			
	9.3			

Based on the obtained results, it is evident that the F3 formulation has the highest diameter of the obtained circle that can be correlated with a higher menthol concentration and a lower viscosity of the formulation (Al Haushey 2024).

Determination of drug content

Drug content in tested formulations was 103.5% for the F1 sample, 103.0% for the F2 sample, and 102.8% for the F3 sample, respectively, which is according to requirements from the European Pharmacopoeia, indicating full incorporation of meloxicam into the amphiphilic base. Detailed results are presented in Table 6.

Table 6. Content determination.

F1		F2		F3	
Sample	**Ind. content (%)**	**Sample**	**Ind. content (%)**	**Sample**	**Ind. content (%)**
1	103.45	1	103.03	1	102.94
2	103.55	2	103.00	2	102.42
3	103.52	3	102.86	3	102.99
AVE	**103.5**	**AVE**	**103.0**	**AVE**	**102.8**
SD	0.05	**SD**	0.09	**SD**	0.31
RSD	0.05	**RSD**	0.09	**RSD**	0.31

Microbiological examination

According to the examination for microbiological quality protocol from the Monograph of USP Pharmacopoeia, no colonies of tested strains were detected in prepared amphiphilic cream formulations with meloxicam. These tests confirmed that prepared formulations are of acceptable microbiological quality and are safe for topical applications.

In vitro drug release

The results from meloxicam release from prepared amphiphilic preparations are listed in Table 7 and illustrat-

Table 7. *In vitro* drug release from tested formulations.

Time (min)	F1		F2		F3	
	Average release (%) (n = 3)	SD	Average release (%) (n = 3)	SD	Average release (%) (n = 3)	SD
0	0.0	0.00	0.0	0.00	0.0	0.00
30	27.0	0.20	35.0	0.35	42.6	0.76
60	43.0	0.49	52.0	0.32	57.3	0.50
90	55.0	0.15	63.2	0.23	68.0	0.08
120	67.5	0.17	74.6	0.06	78.7	0.29
180	78.4	0.32	86.8	0.29	92.3	0.06

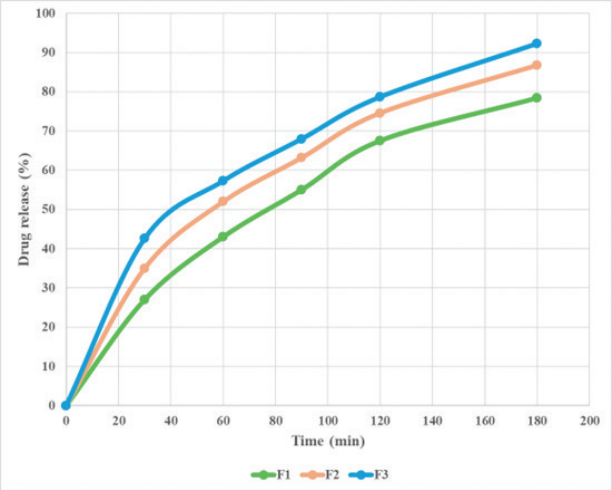

Figure 2. Drug release from amphiphilic formulations with different amounts of menthol.

ed in Fig. 2. The corresponding release of meloxicam after 30 and 60 minutes was found to be 27.0% and 57.3%, respectively. After 180 minutes, the amount of released meloxicam was found to be high, ranging between 78.4% and 92.3%. The difference in drug release between the tested three formulations is related primarily to higher menthol concentrations. Conforming to the literature data, menthol can significantly increase the amount of drug released from the formulation, probably by the formation of an eutectic mixture with the active substance or by synergism with propylene glycol included in the formulation, resulting in an additional amount of released meloxicam available for partitioning into the stratum corneum (Sinha and Kaur 2000; Murthy 2020; Mwangi et al. 2021). Viscosity is another factor affecting the drug release from semi-solid formulations. Reduction in viscosity due to variation in menthol concentration led to an increased amount of released drug (Roy et al. 2017).

Hence, referring to the meloxicam amorphous solid dispersion formulation, the correlation of the increased dissolution profile of meloxicam with increased menthol content implies the influence of menthol in controlling the phase transition of dissolved meloxicam and hydrophilic menthol in propylene glycol, which is used as a solution incorporated in amphiphilic vechiculum/base within. In addition, the lipid phase impacts the dissolved drug distribution towards the emulsified phase, controlling the rate of recrystallization by its deposition as an amorphous phase. (Choonara et al. 2015; Cordeiro et al. 2017; Sulaiman Hameed et al. 2022).

Stability studies

After six months of storage of amphiphilic formulations with meloxicam, no observable changes in consistency and homogeneity were detected. The stability data regarding drug content, pH, and spreadability are listed in Table 8. Obtained results showed only slight changes in pH value and drug content without difference in the appearance of tested formulations that imply the physicochemical stability of amphiphilic creams.

Table 8. A six-month stability data of prepared formulations.

Formulation		Parameter		
		pH	Drug content (%)	Spreadability (cm)
F1	AVE	**6.38**	**103.3**	**7.6**
	SD	/	0.25	0.1000
	RSD	/	0.24	1.3158
F2	AVE	**6.22**	**102.7**	**8.4**
	SD	/	0.13	0.0577
	RSD	/	0.13	0.6846
F3	AVE	**6.18**	**102.5**	**9.0**
	SD	/	0.07	0.1732
	RSD	/	0.06	1.9245

Conclusion

Meloxicam amphiphilic creams were physicochemically stable, homogenous formulations with a pH suitable for topical application. Increasing menthol concentration led to a decrease in viscosity as well as a significant difference in the amount of released drug. To the best of our knowledge, there is currently no available topical formulation with meloxicam and menthol. Thus, according to the obtained results, amphiphilic base could be a promising delivery system for topical meloxicam. Our further research perspective will be focused on the biopharmaceutical characterization of topical formulations with menthol, aiming to address the correlation of bioavailability with menthol's role in increased perfusion of directly provoked or non-provoked skin regions due to a

complex interplay of increased nitric oxide (NO), endothelium-derived hyperpolarization factors (EDHFs), and sensory nerve responses.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

All authors contributed to the study design and manuscrpit preparation. All authors read and approved the final version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.

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