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Veterinary compounding: the impact of different gelling agents on the rheological characteristics and release kinetics from meloxicam oral gels in the treatment of cats

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ABSTRACT

Worldwide, the growing number of pets has increased the use of veterinary drugs, as well as individualised therapy such as compounded drugs. If a suitable formulation or drug is not registered for veterinary species, drugs are compounded. This also includes pharmaceutical forms which are easy to administer, such as semi-solid preparations (gels and pastes) for oral use in order to enhance drug administration and adherence. The number of non-steroidal drugs (NSAIDs) approved for use in cats is relatively small. NSAIDs represent the largest group of drugs with adverse drug experience, but meloxicam has advantages in relation to all of them because of its safety for use in cats. In this study, the pharmaceutical-technological characterisation of oral gels for cats made with different gelling agents (carbomer, xanthan gum, carmellose sodium and hypromellose) was undertaken. Subsequently, four different samples were prepared and designed for veterinary use (using meloxicam, gelling agents and taste enhancer), and then the pH value, rheological characterisation and drug release were determined. The results demonstrated that addition of the taste enhancer influenced the rheological properties of the tested oral gels. It was found that the rate of meloxicam release was the highest from the oral gel prepared with carbomer (Carbopol® 974P), where complete meloxicam dissolution was observed after 5 minutes. On the basis of these results, it was concluded that Carbopol 974P has a certain advantage over the other gelling agents used in this study. Further work is required to assess the palatability of the oral gel for cats in clinical settings.

Key words: oral gel; cats; meloxicam; veterinary compounding

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Introduction

Drugs have been compounded for veterinary practice for many years to enhance drug administration and adherence. Further, it is expected for compounding to increase. Veterinary compounding is necessary and beneficial for optimal treatment of animal patients if a suitable formulation, especially a drug is not approved for use in veterinary species, or if products approved for use in certain species may be commercially available in dosage forms (e.g., large chewable tablets) that are not suitable for use in other species (e.g., cats or exotic animal patients), and particularly in species which are difficult to medicate (e.g., cats) (PAPICH, 2015; DAVIDSON, 2017). What was given two decades ago in the field of veterinary compounding is still valid, where in fact the aim of compounding is to obtain a drug formulation that can be administered in a more suitable way, such as: an injectable drug when only a pill source is available, a larger bolus when only small pills are available, or a drug in a powdered form to mix in a grain supplement when only pills are available (JONES, 1999).

A drug administered in a therapeutic dose and in the same formulation may show differences in pharmacokinetic profile in different animal species (LIN, 1995) due to anatomical-histological differences, and physiological and genetic reasons (the absence or reduced activity of certain enzymes responsible for drug metabolism, as well as the different sensitivity of receptor systems (JEZDIMIROVIC et al., 2015). Moreover, most nonsteroidal anti-inflammatory drugs (NSAIDs) are metabolized in cats by glucuronidation in the liver, and the lack of the enzyme glucuronyl transferase in these animals may lead to a prolonged elimination half-life of some of these drugs (LASCELLES et al., 2007; MADDISON, 2007).

In addition, use of NSAIDs in human and veterinary medicine dates from the second half of the 19th century. Besides anti-inflammatory properties, these drugs have antipyretic and analgesic effects (GREEN, 2001). Compared to other NSAIDs, meloxicam is more advantageous in terms of safety when administered to cats (GUNEW at al., 2008; GOWAN et al., 2011). Consequently, on the European veterinary drug market, meloxicam has been licensed for oral use in cats but only as a suspension (SmPC, Inflacam; SmPC, Loxicam; SmPC, Melosus; SmPC, Meloxaid; SmPC Meloxidy, SmPC Meloxoral, SmPC, Metacam).

Some active pharmacological substances are only available as commercial preparations in solid dosage forms, such as capsules and tablets, suitable for use in humans, but difficult to use in animals. Moreover, it is permitted to use human medicines in animal treatment, and this is regulated by the law on medicines and medical devices (LAW ON MEDICINES AND MEDICAL DEVICES REPUBLIC OF SERBIA, 2017). Veterinary medicine could benefit from this, since extemporaneous compounding enables the provision of appropriate formulations specific for a species and dosage when no commercial preparations are available on the veterinary drug market (JULIANO et al., 2016).

In the era of personalized medicine, drug compounding for specialized needs will continue to play an important role, providing optimum therapy for veterinary patients (KARARA et al., 2016). While the benefits of veterinary compounding are well-established (PAPICH, 2005), there is a need for practitioners to recognise the inherent limitations of these therapeutic options regarding the challenges related to these drugs (LUST, 2004). Some of them are the differences in anatomy, physiology, metabolism, behaviour, genetics, diet, and toxicology for the prescribed species (DAVIDSON, 2017). In order to overcome these challenges, close cooperation between veterinarians and pharmacists is needed. In fact, increased education on the best practices in veterinary pharmacy for veterinarians and pharmacists, and continued communication between the professions have been highlighted (LUST, 2004).

Pharmacists could play an important role in veterinary compounding since they are well trained in pharmaceutical-technological characterisation and preparation of appropriate pharmaceutical formulations. The pharmacist's participation in the practice of veterinary pharmacy in the United Kingdom is minimal, so O'DRISCOLL et al. (2014) suggested enhanced knowledge of veterinary

pharmacy to be included in undergraduate veterinary curricula, thereby facilitating greater participation in this area. Moreover, similar research in the same country revealed poor interaction between pharmacists and veterinary pharmacy, due to a lack of knowledge of veterinary medicines (O'DRISCOLL et al., 2015). In New Zealand, McDOWELL et al. (2017) noticed that interest exists in expanding the pharmacist's role to work with veterinarians, stating that wider collaboration between the two professions is implied in the application of One Health principles, and the implementation of appropriate education and training.

ALPI et al. (2020) stated that veterinary pharmacy and pharmacology literature relies primarily on human medicine and veterinary journals, veterinary conference proceedings, as well as books and drug manufacturer information. Lack of information in this field of research opens room for improvement in veterinary compounding practice. There is increasing interest in the development of guidelines that could guide veterinary compounding in Serbia. Amongst other factors, this country has a small drug market and pharmaceutical companies do not have any interest in licencing all veterinary drugs. Since the lack of these regulatory documents can put animals at risk, researchers and relevant stakeholders from veterinary compounding practice should be encouraged to fill this gap. In the meantime, pharmacists must self-educate to become aware of the unique species idiosyncrasies of animals, and use all available resources to provide safe, effective, and high quality compounded preparations (DAVIDSON, 2017). Also, one of the possible solutions is pharmaceutical-technological testing of veterinary compounded drugs as a first step to ensure the quality of the prepared drugs.

In a study conducted in a large independent community pharmacy in the USA the majority (88%) of compounded preparations were administered by the oral route, whereas suspensions were the most frequently used (47%), with extemporaneously compounded dosage forms, followed by solutions (28%), and capsules (10%) (KARARA et al., 2016). Among all the pharmaceutical formulations intended for veterinary use, oral pastes and gels as semi-fluid masses have the advantage since they cannot be expelled from the animal's mouth as readily as a tablet or liquid. Besides, they can be administered from a flexible tube, syringe, package, or other specialized dosing device (RAMTEKE et al., 2014). In line with the individual approach to treating animals and adjusting the dose, the administration of these drugs allows correction of odour and taste (KOVACEVIC et al., 2020). In addition, although these pharmaceutical forms have been used in veterinary practice for a number of years, they have only recently been included in the European Pharmacopoeia for veterinary use (EUROPEAN PHARMACOPOEIA, 2016). Therefore, the aim of this study was the development and pharmaceutical-technological characterisation of an oral gel for cats, with meloxicam as the active substance, made with different gelling agents (carbomer, xanthan gum, carmellose sodium and hypromellose). Oral gel pharmaceutical-technological characterisation included examination of the rheological characteristics and examination of the rate of release of the active substance from the prepared oral gels.

Materials and methods

Material and experimental design. The following substances and reagents were used in the research: carbomer (Carbopol® 974P, BF Goodrich, USA); xanthan gum (Jungbunzlauer, Austria); carmellose sodium (Fluka AG, Switzerland); hypromellose (Metolose 60SH, Shin-Etsu Chemical Co., Ltd., Japan); triethanolamine (Centrohem, Serbia); sodium benzoate (Centrohem, Serbia); propylene glycol (Centrohem, Serbia); Aroma fish flavour enhancer (Avitasa, Spain); Movalis® tablets 15 mg (Boehringer Ingelheim Ellas A.E., Greece).

Potassium dihydrogen phosphate (Merck, Germany) and sodium hydroxide (Merck, Germany) were used to make the phosphate buffer (pH 6.8) used as a medium for the active substance release rate testing.

Preparation of oral gels for cats. After preliminary research, the following gelling agents and their concentrations were selected: sample F1 - carbomer gelling agent (Carbopol® 974P), in a

concentration of 1%; sample F2 - gelling agent Xanthan gym, in a concentration of 4%; sample F3 - carmellose-sodium gelling agent, in a concentration of 5%; sample F4 - hypromellose gelling agent, in a concentration of 5%. All gel substrates contained propylene glycol in a concentration of 10% as a humectant, and sodium benzoate as a preservative, in a concentration of 0.175%. In preparation of gels with carbomer, triethanolamine (as a solution in a concentration of 10%) was used as a neutralizing agent, in a concentration of 1.4% in the final gel. Samples labelled "A" contained meloxicam in a concentration of 0.05% (0.5 mg/ml). Samples labelled "B" contained 2% flavour enhancer, and samples labelled "C" contained both meloxicam (0.05%) and flavour enhancer (2%).

Due to the impossibility of procuring the active substance meloxicam on the drug market in the Republic of Serbia, the active substance was added in the form of crushed/powdered Movalisâ 15 mg tablets, labelled for use in humans, in the amount corresponding to a share of 0.05%. The composition of Movalis® 15 mg tablets includes the following excipients: sodium citrate, dihydrate; lactose monohydrate; cellulose, microcrystalline; povidone K25; silica, colloidal, anhydrous; crospovidone and magnesium stearate. The amount of lactose in Movalis® 15 mg tablets is 20 mg per tablet (SmPC, Movalis). This amount of lactose is acceptable for use in cats (KIENZLE, 1993). The sample composition is given in Table 1.

Table 1. Composition of tested samples

Sample	Meloxicam (%)	Flavour enhancer (%)	Type and concentration of gelling agent
F1	-	-	Carbopol® 974P 1%
F1A	0.05	-	
F1B	-	2.0	
F1C	0.05	2.0	
F2	-	-	Xanthan gum 4%
F2A	0.05	-	
F2B	-	2.0	
F2C	0.05	2.0	
F3	-	-	Carmellose-sodium 5%
F3A	0.05	-	
F3B	-	2.0	
F3C	0.05	2.0	
F4	-	-	Hypromellose 5%
F4A	0.05	-	
F4B	-	2.0	

Within the Biopharmaceutical Classification System (BCS), meloxicam belongs to BCS class II, with low solubility and high permeability (SIRISOLLA, 2015)

Determination of the pH value of the oral gels. Measurement of the pH value of the oral gels for cats was performed potentiometrically, by direct immersion of a glass electrode in the tested samples, at room temperature (20±2°C). Prior to the measurement, the apparatus was calibrated (pH meter HI 9321, Hana Instruments, Portugal) with standard buffers with a pH value of 4.0 and pH 7.0. The pH of the tested samples was measured 48 hours and 30 days after preparation. These results are presented in Table 2.

Determination of the rheological characteristics of the oral gels. Continuous (rotational) rheological measurements were performed using a rheometer (*Rheolab MC120*, *Paar Physica*, Germany), with a MK 22 measuring system cup/plate (cup diameter 50 mm, angle of inclination 1˚, distance between the cup and plate 50 μm), at a temperature of 20±0.2˚C. This device contains the software package *US 200*, which enables electronic control of measurements and automatic processing of the obtained results. During the measurement, the shear rate was increased in the range 0-200 s^{-1} (ascending curve) and from 200-0 s^{-1} (descending curve).

For rheological analysis, the values of maximum (η_{max}) and minimum (η_{min}) apparent viscosity were used, read from the ascending viscosity curves at the lowest (4.0 s^{-1}) and maximum (200,0 s^{-1}) shear velocities. The hysteresis area (ΔH) represented the area between the ascending and descending curves, and was calculated using *US 200* software. The values of apparent viscosities and hysteresis surfaces obtained represent the mean value of three consecutive measurements. These results are presented in Table 3 and Fig. 1-7.

Determination of the active substance release rate from the oral gels. Determination of the meloxicam release rate in samples F1A, F2A, F3A and F4A was performed in a mini blade type apparatus (Erweka DT 700) using 250 ml of medium, at a blade rotation speed of 50 rpm, at a temperature of 37±0.5°C. Phosphate buffer (pH 6.8) was used as medium. At the beginning of the examination, the quantity of 10 ml of sample was introduced into the medium vessel using a plastic syringe. A meloxicam-free gel sample was used as a blank. Medium samples were taken after 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes and filtered through quantitative filter paper. The amount of dissolved meloxicam in the samples was determined by UV spectrophotometry (UV spectrophotometer Thermo Fisher Scientific, USA) by measuring the absorbance of the solution at a wave length of 222 nm. The standard method was used to calculate the concentration of meloxicam in the samples (the concentration of the standard solution (C_{st}) was 0.014 mg/ml; and its absorbance (A_{st}) was 0.444). The results presented show the mean value for the three replicated samples (Fig. 8).

Results

Determination of pH value. Initial pH values were measured 48 hours after sampling. In order to assess the stability of the samples, the measurements were repeated after 30 days. These the results are shown in Table 2. The measured pH value of the 2% dispersion of the flavour enhancer was 5.15.

pH values of the samples made with different gelling agents (without the addition of meloxicam and flavour enhancers) were similar to each other: from 6.35 for the substrate with xanthan gum to 6.96 for the substrate with carmellose sodium.

Table 2. pH values of tested samples 48 hours and 30 days after preparation

Sample	pH values after 48 h	pH values after 30 days
F1	6.74	6.68
F1A	7.23	7.25
F1B	6.01	6.03
F1C	6.05	6.09
F2	6.35	-*
F2A	6.57	-*
F2B	5.17	-*
F2C	5.35	-*
F3	6.96	6.86
F3A	6.90	6.91
F3B	5.45	5.62
F3C	5.55	5.61
F4	6.91	6.25
F4A	6.86	5.65
F4B	5.26	5.21
F4C	5.55	5.50

* pH measurement was omitted due to visible microbiological contamination of samples

Determination of the rheological characteristics of the oral gels. The rheological characteristics of the oral gels were measured 48 hours and 30 days after preparation. Further, all tested oral gels, 48 hours and 30 days after preparation, showed a non-Newtonian thixotropic flow (the ascending and descending curves on the graph do not coincide, but close a certain surface, called the hysteresis surface) (Fig. 1-7, Table 3). Of all the tested gel substrates, the highest value of maximum apparent viscosity, 48 hours after the preparation, was recorded in the case of carbomer gel F1 (39700 mPas), and the lowest in the case of F3 gel, made with carmellose sodium (16800 mPas). The addition of crushed tablets to meloxicam gel substrates had no significant effect on the values of maximum apparent viscosity (samples marked A, Table 3).

Control measurement of the maximum apparent viscosity of the samples, 30 days after preparation, showed that there were no significant changes in these values compared to the values measured after 48 h, in the case of carbomer gels (F1-F1C). Since there was microbiological contamination of the samples, the measurement of gel with xanthan gum was not performed.

In the case of gels from series 3 and 4, aging of the gels (30 days) led to significant changes in the rheological parameters examined, i.e. to a significant increase in the maximum apparent viscosities, indicating some structuring of these samples over 30 days. Therefore, in the case of the gel with carmellose sodium, i.e. hypromellose, all the samples showed an increase in the value of the maximum apparent viscosity. The largest change was observed in the samples with the addition of the combination of meloxicam tablets and flavour enhancers, from 19300 mPas to 34800 mPas (sample F3C) and from 47200 mPas to 66900 mPas (sample F4C) (Table 3).

All tested sample rheograms are shown in Fig. 1-7.

Examination of the rheological characteristics of samples made with xanthan gum (samples F2-F2C) 30 days after preparation was omitted due to the visible microbiological contamination of the samples.

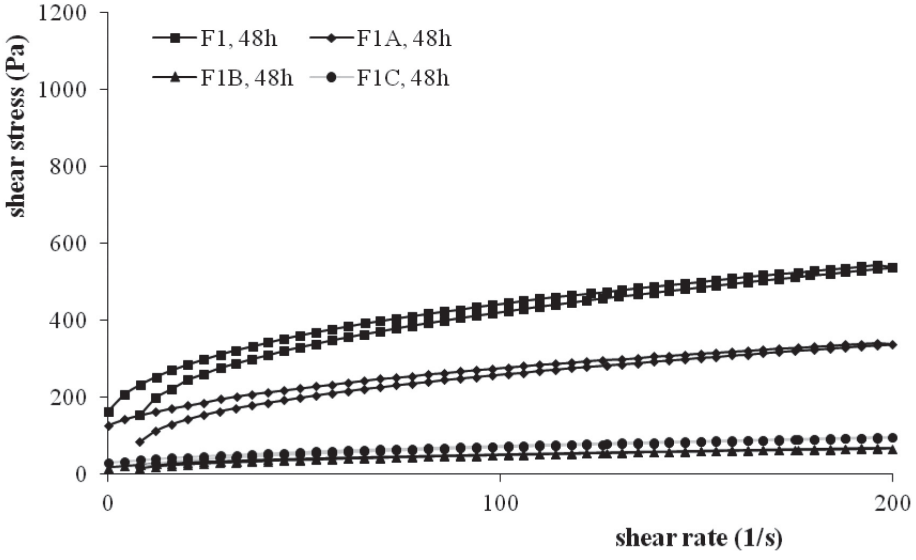

Fig. 1. Rheograms of tested samples F1, F1A, F1B and F1C, 48h after preparation

Table 3. Values of the examined rheological parameters of gel substrates and oral gels with meloxicam

	48 h			30 days		
	η_{max} (mPas)	η_{min} (mPas)	Δ H (Pa/s)	η_{max} (mPas)	η_{min} (mPas)	Δ H (Pa/s)
F1	39700	2720	1370	34000	2750	516
F1A	31200	1700	2010	29200	1740	1680
F1B	4010	337	26	5160	436	33
F1C	7360	477	180	10500	511	533
F2	28600	1230	3075	/*	/*	/*
F2A	29100	1250	3265	/*	/*	/*
F2B	41500	1580	4114	/*	/*	/*
F2C	42200	1570	3761	/*	/*	/*
F3	16800	2120	3875	27100	2570	4609
F3A	14800	1920	3505	21800	2230	4145
F3B	18000	2040	4520	26600	2440	5902
F3C	19300	2090	5029	34800	2730	7033
F4	33400	3500	5757	48200	4480	5342
F4A	29500	3270	4135	40000	4040	3829
F4B	36000	3770	4419	43900	4360	3356
F4C	47200	4570	1610	66900	5780	5298

* Measurement was omitted due to visible microbiological contamination of the samples

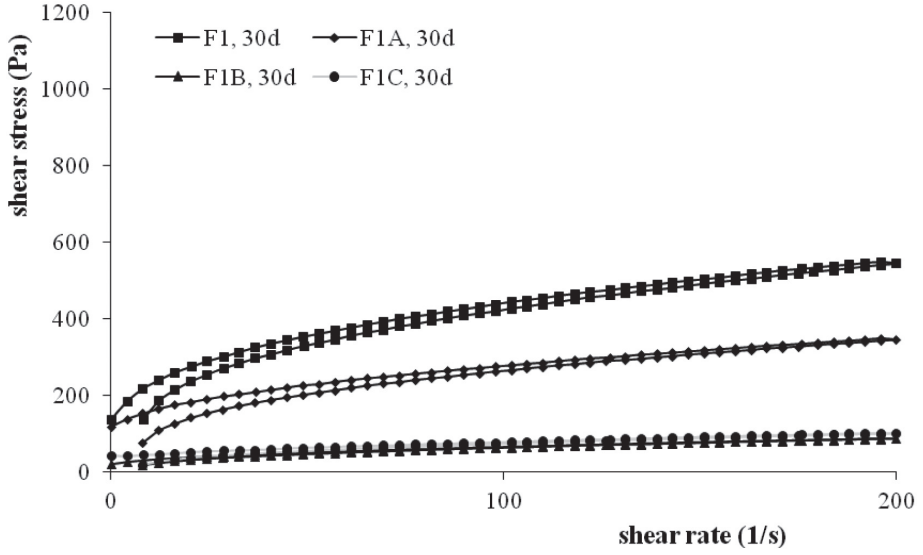

Fig. 2. Rheograms of tested samples F1, F1A, F1B and F1C, 30 days after preparation

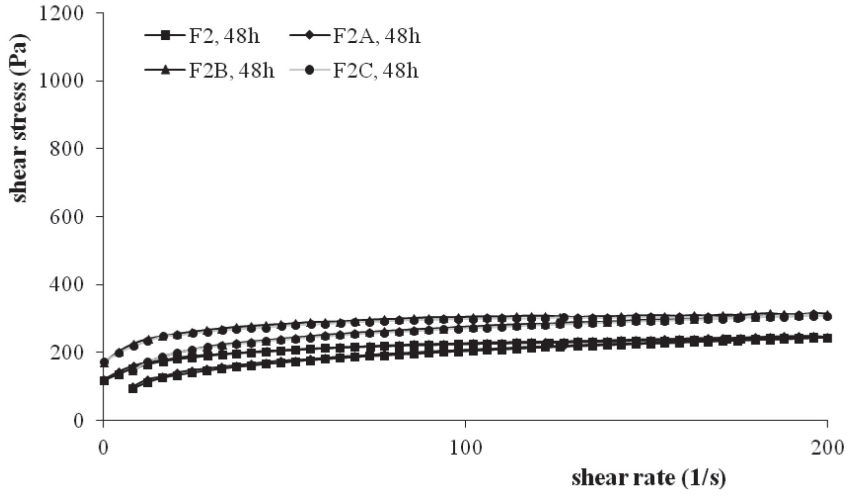

Fig. 3. Rheograms of tested samples F2, F2A, F2B and F2C, 48h after preparation

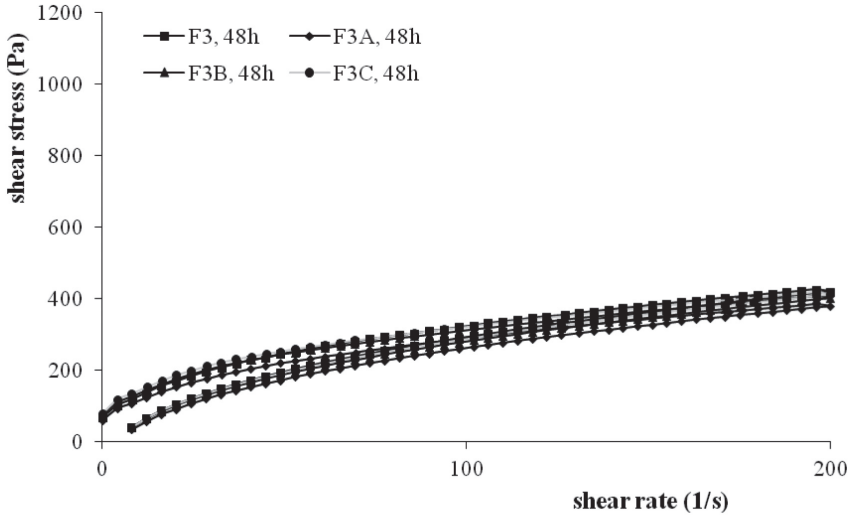

Fig. 4. Rheograms of tested samples F3, F3A, F3B and F3C, 48h after preparation

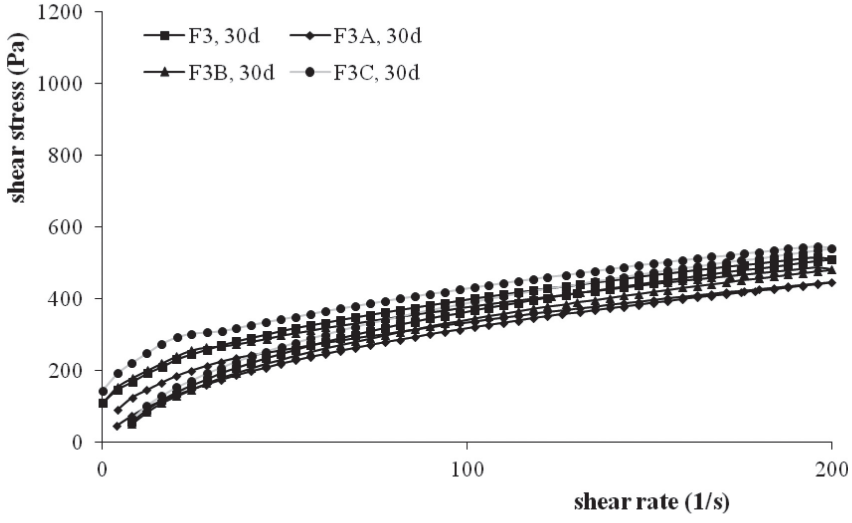

Fig. 5. Rheograms of tested samples F3, F3A, F3B and F3C, 30 days after preparation

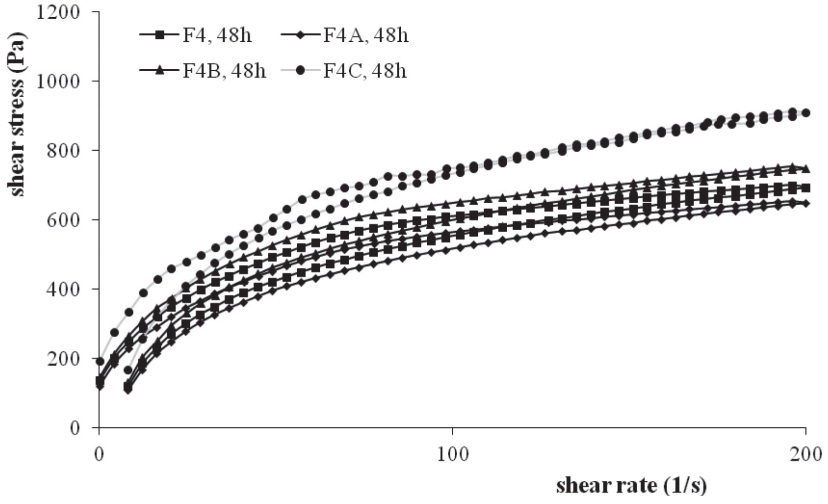

Fig. 6. Rheograms of tested samples F4, F4A, F4B and F4C, 48h after preparation

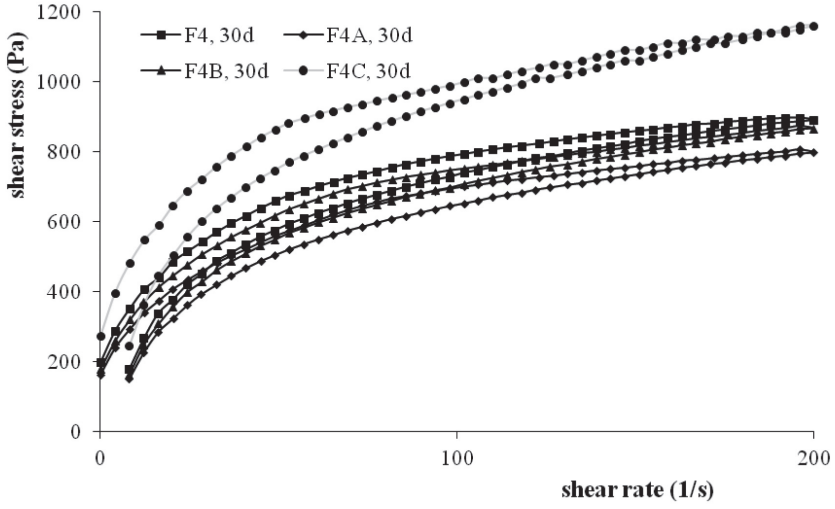

Fig. 7. Rheograms of tested samples F4, F4A, F4B and F4C 30 days after preparation

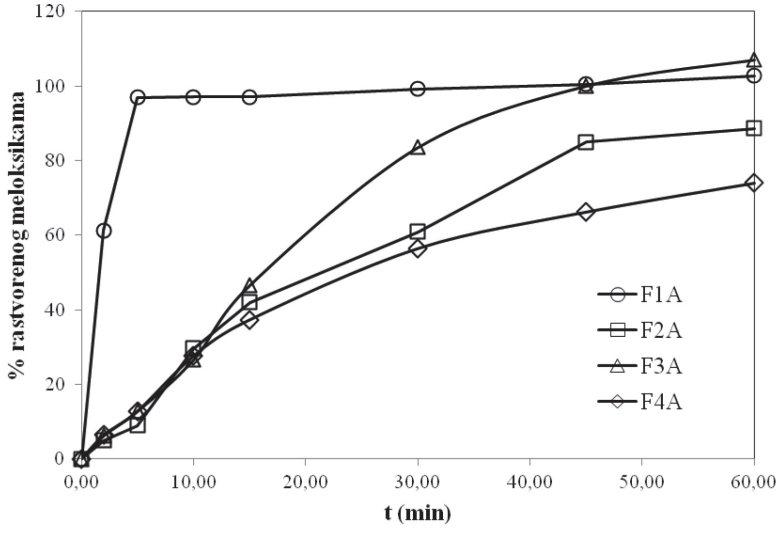

Fig. 8. Meloxicam dissolution rate from oral gels for cats

Determination of the active substance release rate from the oral gels. The results of the meloxicam release rate test from the oral gels are shown in Fig. 8. The results obtained indicate significant differences in the release rate of meloxicam from the tested samples. The sample made with Carbopol 974P (F1A) showed the fastest active substance release rate, since after 5 minutes of testing the total amount of meloxicam was dissolved due to the very rapid dispersion of the gel in the dissolution rate test medium. In contrast to this finding, the slowest release of meloxicam was recorded in the case of the sample made with hypromellose (F4A). In this case, despite the relatively high degree of agitation at a mini blade rotation speed of 50 rpm, the dispersion of the gel was relatively slow and limited, with about 55% released after 30 minutes, and about 75% with meloxicam after 60 minutes. Interestingly, the release rate of meloxicam from samples F2A, F3A and F4A was almost identical during the first 15 minutes, with about 40% of the substance being released after 15 minutes. During the examination of the F2A sample, made with xanthan gum, the formation of a spherical gel residue was observed in the space under the blade of the device.

Discussion

In order to address the medical needs of animal patients, veterinary compounding is becoming more and more interesting. In a study conducted in New Zealand, dogs (64%) were the animals most commonly requiring veterinary compounding, followed by cats (58%) and cattle (46%) (GARGIULO et al., 2013). Although some cases of deaths were recorded after administration of compounded drugs, such as some errors in 21 polo ponies in Florida (BELAINESH et. al., 2011) and in three horses in Maine and Ohio (THOMPSON et al., 2011), interest in veterinary compounding has not waned. Certainly, risk-based assessment of the pharmaceutical quality of these drugs is essential, as well as specific strategies. These strategies should recognise the shared responsibility of prescribers, dispensers and regulators to achieve contemporary quality, safety, and efficacy standards, and support the quality use of compounded drugs (FOIS et al., 2009).

Although extensive studies have been conducted to demonstrate the safety, efficacy, and bioavailability of drugs approved for animal use, there are no equivalent assurances for these attributes in compounded preparations (DAVIDSON, 2017).

Since these preparations do not undergo bioavailability testing, it is essential to focus our attention on testing compounded drugs for veterinary patients. Proper pharmaceutical-technological characterisation of formulations could potentially ensure drug safety. As JONES (1999) states, there are many considerations to take into account, requiring an entirely new way of thinking about drug dosing and administration. This author noticed that besides the type of animal and their unique metabolic functions that must be considered, as well as the determination of the most appropriate dosage form, it is important to determine the flavours they like and how to ensure the adherence. This is why taste the enhancer used in our study is made in a flavour suitable for cats. Interestingly, the majority of veterinary pharmacists questioned in a study conducted in the United States of America incorrectly answered the question regarding the proper flavouring for a medication for a ferret (GOCHENAUER et al., 2019). In addition, it has been established that compounding should be based on approved dosing forms (UMSTEAD et al., 2012). Hence, meloxicam tablets licensed for human use (Movalis® tablets) were used in this study.

Besides examination of the rheological characteristics and the rate of release of the active substance from the prepared oral gels, pharmaceutical-technological characterisation of the oral gels prepared in this study also included pH value measurement. Our study results indicated that the pH values of the samples made with different gelling agents (without the addition of meloxicam and flavour enhancers) were similar to each other: from 6.35 for the substrate with xanthan gum to 6.96 for the substrate with carmellose sodium. In fact, the addition of flavour enhancers to the gels with and without meloxicam led to a noticeable decrease in pH, which was lower by one pH unit in almost all the tested samples. The same trend was observed in the results obtained 30 days after sample

production, except for samples made with xanthan gum (samples F2-F2C) where pH measurement was omitted 30 days after preparation due to the visible microbiological contamination of samples.

Systems are described as non-Newtonian when the viscosity depends on the applied shear rate. Thixotropy is a consequence of the existence of a three-dimensional internal structure in the system, which collapses under the influence of an external force, i.e. shear, and is renewed after the cessation of the action of the external force. Moreover, thixotropy is a desirable property of pharmaceutical preparations, because the action of an external force (e.g. shaking, mixing, squeezing from a syringe, smearing, etc.) on such systems leads to a decrease in viscosity, and after the cessation of that external force, the initial viscosity is restored after a certain time (MEZGER, 2014; BRUMMER, 2007).

The values of minimum and maximum apparent viscosities are indicators of different states of the system structure. The maximum apparent viscosity (measured at a minimum shear rate - in these tests 4 s^{-1}) is an indicator of the structure of the system at rest, while the value of the minimum apparent viscosity (measured at maximum shear rate, in these tests 200 s^{-1}) is a measure of the destruction of the structure of the system, i.e. the ease of application of the preparation (MALKIN and ISAYEV, 2012).

Of all the gel substrates tested, the lowest value of maximum apparent viscosity, 48 hours after the preparation, was recorded in the case of F3 gel, made with carmellose sodium (16800 mPas). These results are in agreement with the gels' appearance since the gel with carmellose sodium was the softest. The addition of crushed tablets to meloxicam gel substrates had no significant effect on the values of maximum apparent viscosity (samples marked A, Table 3). PAPICH (2015) also noticed that adding different chemicals, flavourings and vehicles may result in a compounder that interferes with the stability of the drug, thereby decreasing its potency, compromising its oral absorption, and consequently reducing its efficiency. Contrary to these findings, in our study the addition of flavour enhancers to gel substrates (samples labelled B, Table 3) had a significant effect on the values of the maximum apparent viscosity of the carbomer gel (F1B) and the xanthan gum gel (F2B). It is certain that in both cases there was some interaction between the gelling agents and the flavour enhancers, which, however, cannot be explained since detailed information on the composition of the flavour enhancers used is not available. Interestingly, the addition of flavour enhancers to gel substrates made with carmellose sodium (F3B) and hypromellose (F4B) had an almost negligible effect on the values of maximum apparent viscosity. Control measurement of the maximum apparent viscosity of the samples, 30 days after preparation, showed that there were no significant changes in these values compared to the values measured after 48 h, in the case of carbomer gels (F1-F1C). Furthermore, the largest change in the examined rheological parameters was observed in the samples with the addition of a combination of meloxicam tablets and flavour enhancers, from 19300 mPas to 34800 mPas (sample F3C) and from 47200 mPas to 66900 mPas (sample F4C) (Table 3).

When it comes to determination of the active substance release rate from the tested oral gels, the sample made with Carbopol 974P (F1A) showed the fastest active substance release rate, since after 5 minutes of testing the total amount of meloxicam had been dissolved due to the very rapid dispersion of the gel in the dissolution rate test medium.

Veterinary pharmacists are at the forefront of comparative medicine, as the only health care professionals legally permitted to provide pharmaceutical care to all species. Treating veterinary patients often requires data extrapolation from human medicine, and therefore access to relevant human and veterinary medicine resources is paramount (ALPI et al., 2020). Therefore, providing more research including veterinary compounds that are tested in a pharmaceutical laboratory could fill this gap in our country given the lack of pharmacists trained in veterinary medicine.

In conclusion, pharmaceutical formulations for veterinary patients have an important role in preserving and enhancing animal health. Hence, safe and effective compounded veterinary drugs could be essential to maintenance animal health and productivity, and especially to treat a range of diseases where drugs are not approved for use in specific animal species.

The pharmaceutical-technological results of this study indicate that acceptable the rheological characteristics and adequate dissolution rate of meloxicam from oral gels were noticed in the case of oral gels made with Carbopol 974P. Hence, it can be concluded that this polymer shows a certain advantage over the other gelling agents used in this study. Further research, including palatability testing of this gel in cats, is needed to validate our findings in the clinical setting.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

ALPI, K. M., E. STAFFORD, E. M. SWIFT, S. DANEHOWER, H. I. PAXSON, G. DAVIDSON (2020): Mapping the Literature of Veterinary Pharmacy and Pharmacology. Am. J. Pharm. Educ. 84, 7314.
DOI: 10.5688/ajpe7314

BELAINESH, D., G. MALDONADO, H. REID (2011): Acute selenium toxicosis in polo ponies. J. Vet. Diagn. Invest. 23, 623-628.
DOI: 10.1177/1040638711404142

BRUMMER, R. (2007): Rheology essentials of cosmetic and food emulsions. Springer, Berlin, Heidelberg.
DOI:10.1515/arh-2007-0030

DAVIDSON, G. (2017): Veterinary Compounding: Regulation, Challenges, and Resources. Pharmaceutics 9, 5.
DOI: 10.3390/pharmaceutics9010005

EUROPEAN PHARMACOPOEIA (2016): 9th edition. European Directorate for the Quality of Medicines and Health Care. Council of Europe, Strasbourg Cedex, France.

FOIS, R. A., B. T. MEWES, A. J. MCLACHLAN, I. RAMZAN (2009): Compounded Medicines and 'Off Label' Prescribing a Case for More Guidance. Aust. Fam. Physician. 38, 16-20.

GARGIULO, D. A., C. CHEMAL, L. JODA, Y. J. LEE, M. PILKINGTON, A. HAYWOOD, S. GARG (2013): Extemporaneous compounding in veterinary practice: A New Zealand perspective. N. Z. Vet. J. 61, 311-315.
DOI: 10.1080/00480169.2013.773853

GOCHENAUER, A. E., E. R. HOLMES, K. E. BARBER, L. R. FORSYTHE (2019): The current landscape of veterinary compounding in the Pharmacy setting. Int. J. Pharm. Compd. 23, 422-427.

GOWAN, R. A., A. E. LINGARD, L. JOHNSTON, W. STANSEN, S. A. BROWN, R. MALIK (2011): Retrospective case-control study of the effects of long-term dosing with meloxicam on renal function in aged cats with degenerative joint disease. J. Feline Med. Surg. 10, 752-761.
DOI: 10.1016/j.jfms.2011.06.008

GREEN, G. A. (2001): Understanding NSAIDs: from aspirin to COX-2. Clin. Cornerstone 3, 50-60.
DOI: 10.1016/s1098-3597(01)90069-9

GUNEW, M., V. MENRATH, R. MARSHALL (2008): Long-term safety, efficacy and palatability of oral meloxicam at 0.01–0.03 mg/kg for treatment of osteoarthritic pain in cats. J. Feline Med. Surg. 10, 235-241.
DOI:10.1016/j.jfms.2007.10.007

JEZDIMIROVIĆ, M., V. ĆUPIĆ, S. IVANOVUĆ, B. DIMITRIJEVIĆ, N. JEZDIMIROVIĆ (2015): Factors that affect therapeutic efficacy and safety of drugs. Vet. Glas. 69, 401-415. (in Serbian)
DOI: 10.2298/VETGL1506401J

JONES, W. E. (1999): Veterinary compounding fulfills a need. J. Equine Vet. Sci. 19, 10-655.
DOI: 10.1016/S0737-0806(06)82165-9

JULIANO, C., P. MANCONI, M. COSSU (2016): Characterisation of commercial Perna canaliculus samples and development of extemporaneous oral veterinary paste formulations containing Perna. Nat. Prod. Res. 30, 1-8.
DOI:10.1080/14786419.2015.1107557

KARARA, A. H., R. HINES, Z. DEMIR, B. NNOROM, R. HORSEY, G. TWIGG (2016): Evaluation of the Most Frequently Prescribed Extemporaneously Compounded Veterinary Medications at a Large Independent Community Pharmacy. Int. J. Pharm. Compd. 20, 461-467.

KIENZLE, E. (1993): Carbohydrate metabolism of the cat. 3. Digestion of sugars. J. Anim. Physiol. Anim. Nutr. 69, 203-210.
DOI: 10.1111/j.1439-0396.1993.tb00806.x

KOVAČEVIĆ, Z., D. STOJANOVIĆ, I. DAVIDOV, M. ERDELJAN, M. RADINOVIĆ (2020): The importance of palatability of compounded veterinary drugs. Vet. Rev. 1, 61-67. (in Serbian)

LASCELLES, B. D. X., M. H. COURT, E. M. HARDIE, S. A. ROBERTSON (2007): Nonsteroidal anti-inflammatory

drugs in cats: a review. Vet. Anaesth. Analg. 34, 228-250. DOI: 10.1111/j.1467-2995.2006.00322.x

LAW ON MEDICINES AND MEDICAL DEVICES REPUBLIC OF SERBIA (2017): ("Official Gazette of RS", No. 30/2010, 107/2012, 113/2017 - other law and 105/2017 - other law) (in Serbian).

LIN, J. H. (1995): Species similarities and differences in pharmacokinetics. Drug Metab. Dispos. 23, 1008-1021.

LUST, E. (2004): Compounding for animal patients: contemporary issues. J. Am. Pharm. Assoc. 44, 375-386. DOI: 10.1331/154434504323064011

MADDISON, J. E. (2007): Cats and NSAIDs – what are the issues? Ir. Vet. J. 60, 174-178.

MALKIN, A. Y., A. I. ISAYEV (2012): Rheology Concepts, Methods and Applications. 2nd ed., Chem.Tech. Publishing, Toronto.

MCDOWELL, A., R. BEARD, A. BRIGHTMORE, L. W. LU, A. MCKAY, M. MISTRY, K. OWEN, E. SWAN, J. YOUNG (2017): Veterinary Pharmaceutics: An Opportunity for Interprofessional Education in New Zealand? Pharmaceutics 9, 25. DOI: 10.3390/pharmaceutics9030025

MEZGER, T. G. (2014): Applied Rheology. Anton Paar GmbH, Graz.

O'DRISCOLL, N. H., C. JUWAH, O. LABOVITIADI, A. J. LAMB (2014): Veterinary pharmacy within the United Kingdom: Review of current practice and education. Pharm. Educ. 14, 26-30.

O'DRISCOLL, N. H., O. LABOVITIADI, A. J. LAMB (2015): Evaluation of the practice of veterinary pharmacy. Curr. Pharm. Teach. Learn. 7, 606-613. DOI: 10.1016/j.cptl.2015.06.017

PAPICH, M. G. (2015): Saunders handbook of veterinary drugs-e-book: small and large animal. 4th ed., Elsevier Health Sciences, England, p.932.

PAPICH, M. G. (2005): Drug compounding for veterinary patients. AAPS. J. 7, E281-E287. DOI: 10.1208/aapsj070229

RAMTEKE, K. H., S. A. JOSHI, P. A. DIGHE, A. R. KHARAT (2014): Veterinary Pharmaceutical Dosage Forms: A Technical Note. Austin Therapeutics 1, 10.

SIRISOLLA, J. (2015): Solubility Enhancement of Meloxicam by Liquisolid Technique and Its Characterization. Int. J. Pharm. Sci. Res. 6, 835-840. DOI: 10.13040/IJPSR.0975-8232.6(2).835-40

THOMPSON, J. A., M. H. MIRZA, S. A. BARKER, T. W. MORGAN, R. W. BAUER, R. S. MCCONNICO, R. S. (2011): Clenbuterol Toxicosis in Three quarter horse racehorses after administration of a compounded product. J. Am. Vet. Med. Assoc. 239, 842-849. DOI: 10.2460/javma.239.6.842

UMSTEAD, M. E., D. M. BOOTHE, C. CRUZ-ESPINDOLA, J. M. MACDONALD, R. KENNIS, D. ANGARANO (2012): Accuracy and precision of compounded ciclosporin capsules and solution. Vet. Dermatol. 23, 431-482. DOI: 10.1111/j.1365-3164.2012.01078.x

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SAŽETAK

Sve veći broj kućnih ljubimaca u cijelom svijetu utječe na sve učestaliju upotrebu veterinarskih lijekova, također i na primjenu individualizirane terapije u obliku magistralne izrade složenih lijekova. Ako odgovarajuća formulacija ili lijek nije registriran za neku životinjsku vrstu, lijekovi se izrađuju magistralno. Ova izrada obuhvaća farmakološke oblike koji se lako primjenjuju, kao što su polučvrsti preparati (gelovi i paste) za oralnu upotrebu radi poboljšanja njihove primjene i adherencije. Broj nesteroidnih protuupalnih lijekova (NSPUL) odobrenih za upotrebu u mačaka relativno je mali. NSPUL-ovi čine najveću skupinu lijekova s potencijalno štetnim djelovanjem, a među svima njima prednost ima meloksikam jer je njegova primjena u mačaka sigurna. U ovom su istraživanju opisane farmakološko-tehnološke značajke oralnog gela za mačke pripravljenog s različitim gelirajućim sredstvima (karbomer, ksantan-guma, natrij-karmeloza i hipromeloza). Pripremljena su četiri različita uzorka koja su dizajnirana za veterinarsku upotrebu (primjenom meloksikama, gelirajućih sredstava i pojačivača okusa), a potom su određeni pH-vrijednost, reološka svojstva i brzina oslobađanja lijeka. Rezultati su pokazali da dodatak pojačivača okusa utječe na reološka svojstva analiziranih oralnih gelova. Utvrđeno je da je brzina oslobađanja meloksikama najveća iz oralnoga gela pripravljenog s karbomerom (Carbopol® 974P), gdje je potpuno rastvaranje meloksikama primijećeno nakon pet minuta. Na osnovi dobivenih rezultata zaključeno je da Carbopol® 974P ima stanovitu prednost u odnosu na druga sredstva za geliranje primijenjena u ovom istraživanju. Potreban je daljnji rad na procjeni palatabilnosti oralnoga gela u mačaka u kliničkim uvjetima.

Ključne riječi: oralni gel; mačke; meloksikam; magistralna izrada