Development of Composition and Technologies of Dental Gel of Meloxicam

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Abstract

BACKGROUND: Dental gels have several advantages over other oral dosage forms. Being a viscoplastic dosage form, the gel, when applied to the damaged area of the gum or mucous membrane, creates a protective film, preventing mechanical irritation, and providing a localized effect of the drug components.

AIM: The aim of this work was to develop the composition and technology of the dental gel of meloxicam, the study of the main technological and consumer characteristics, as well as the local irritating effect of the dosage form.

METHODS: Dental gels were prepared using purified water, alcohol, glycerol, and buckthorn oil as solvents, gelling agents and solubilizer Poloxamer 407 (Lutrol® F 127). The bioadhesive component and Noveon® Polycarbophil component were used for dental gel preparation. Aspartame was used as sweetener. Menthol and ascorbic acid were used to correct the organoleptic properties of the pharmaceutical composition. The formulated dental gel of meloxicam at a concentration of 7.5% was evaluated for organoleptic properties, pH, rheological characteristics, bioadhesive properties, and stability under the accelerated aging period. The in vivo local irritant effect was evaluated using ten rabbits by cutaneous, subcutaneous, subconjunctival administration, as well as application to the upper palate.

RESULTS: Based on the results of studying technological and organoleptic properties, the optimal composition based on the Natrosol® 250 HX hydroxyethylcellulose gelling agent, glycerol solvent, and purified water in the ratio 1/5 was selected, the composition contains Noveon® bioadhesive in an amount of 2%. The composition has good organoleptic properties, pH close to pH of saliva has high bioadhesive properties, satisfactory rheological characteristics. The shelf life of the experimental series by accelerated aging was 2 years. The selected composition does not have a local irritant effect.

CONCLUSION: A new dosage form of meloxicam was developed – a gel for use in dental practice.

Introduction

According to the WHO statistics, 98% of people in the world have a history of inflammatory diseases of the oral cavity, most of which are inflammatory periodontal diseases resulting in tooth loss with the absence of surgical intervention, as well as leading to morphofunctional changes in the masticatory apparatus, which are accompanied by a pain syndrome affecting the psychoemotional sphere patient activity, reduce resistance to the action of infectious and viral agents, increase the sensitization of the body, resulting in a decrease in the overall quality of life of the patient [1], [2].

In dental practice, the most common pharmacological group for relieving pain, as well as the part of complex therapy, is nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. The great popularity of NSAIDs is due to the fact that they have anti-inflammatory, analgesic and antipyretic effects, affect the symptoms observed in a wide range of diseases. According to the FDA, the proportion of dosage forms used in dentistry based on NSAIDs is as follows: Solutions (~60%), aerosols (~25%), pastes (~8%), and gels (~7%). Thus, there is no extensive nomenclature of dental gels, although they have several advantages, specifically, they have a point effect on the site of inflammation, the absence of systemic effects due to the small mucosal coating area, as well as ease of use.

Meloxicam – carboxamide with the primary inhibitory activity of COX-2 was chosen as the object of study. In vitro studies with human tissues confirmed a high affinity of meloxicam with COX-2, while COX-1 inhibited only at the highest concentrations (ratio of 50% inhibitory concentration to COX-2: COX-1 = 0.09 in whole blood tests). Meloxicam has a bioavailability of 89% after oral administration, is strongly associated with plasma proteins, and its half-life is 20–24 h. It easily penetrates into the synovial fluid, reaching 45–57% of plasma concentrations [4], [5].

At present, in the development of drugs, there is a tendency to search for new potent molecules, often targeting lipophilic receptors, which in general leads to an increase in the number of highly lipophilic
drugs with a limited therapeutic window (a low dose can be ineffective, and while a high dose leads to toxicity) [6], [7], [8], as a result of this, it was decided to use meloxicam as a weakly lipophilic drug with proven effectiveness and known toxicity.

The purpose of this study was to create a new dosage form of NSAIDs for use in dental practice, a comprehensive assessment of its physicochemical and biopharmaceutical characterization

Materials and Methods

Materials

The object of the study was the drug substance of meloxicam Boehringer Ingelheim (USP 39, Ph. Eur. 10); as solvents, the purified water (USP 39, Ph. Eur. 10), alcohol 96% (USP 39, Ph. Eur. 10), glycerin (USP 39, Ph. Eur. 10), and buckthorn oil (SPH RF XI) were used. Other excipients used were Poloxamer 407 Lutrol® F 127, BASF (USP 39, Ph. Eur. 10), Carbopol® 974P NF Polymer, Lubrizol (USP 39, Ph. Eur. 10), hydroxyethylcellulose Natrosol® 250 HHX Pharm, Ashland (USP 39, Ph. Eur. 10), Noveon® Polycarbophil, Ashland, menthol (USP 39, Ph. Eur. 10), ascorbic acid (USP 39, Ph. Eur. 10), and aspartame (USP 39, Ph. Eur. 10).

According to the published data, the concentration of NSAIDs in the developed dosage form was chosen, which amounted to 7.5% [5]. This concentration was calculated based on the average daily doses of meloxicam at the rate of 0.5 ml of gel per dose.

First, a suspension of the active pharmaceutical ingredient was made by dispersing meloxicam in water. Gel-forming agent samples were obtained by conventional methods [9]. A gel-forming agent, flavorings, and a mucoadhesive agent were added to the resulting dispersion with continuous stirring using the ECROS ES 6120 magnetic stirrer (Russia) and at a temperature of 20±2°C. The resulting composition was left for structuring for 1.5 h. At the end of the process, standardization was performed.

Methods

Organolectic properties

Two methods of organoleptic evaluation were used to determine the taste of experimental samples. To determine the taste characteristics of dispersions of NSAIDs in various solvents introduced into the model gel base, the organoleptic method of taste assessment according to A.I. Tentsova. A group of twenty volunteers assesses the taste of gel samples according to the proposed scheme. The following indicators are taken into account: “Sweetness” (1 – unsweetened, and 5 – very sweet), “presence of aftertaste” (1 – absent, and 5 – strong present), “character of aftertaste” (1 – unpleasant, and 5 – very pleasant), and “taste in general” (1 – unpleasant, and 5 – pleasant) [10]. To characterize the tastes of the experimental compositions after the initial taste correction and assess the influence of the solvent on the organoleptic properties of the finished dosage form, the profile method was used. This method is based on the construction of profilograms based on the results of assessing the taste of the compositions on a five-point scale according to indicators characterizing the taste of the compositions (acidic/bitter/sweet), the taste of the gelling agent. In addition, there is taking into account the texture indicator (numerical indices: 1 – the sign is absent; 2 – the sign is weakly expressed; 3 – a sign of normal intensity; and 4 – a sign is very pronounced) [10].

Evaluation of pH

When developing a dosage form for dental use, it is necessary to determine its pH, since a low pH value (pH 3–4) contributes to the demineralization of enamel [11]. To determine the pH, an aqueous extraction of the gel sample under study was prepared, the resulting extraction was dispersed on an ECROS ES 6120 magnetic stirrer (Russia) for 15 min at room temperature, and the pH was determined on an Aquilon pH-410 pH meter (Russia).

Rheological properties

A rheological study of the obtained samples was carried out on a coaxial rotational viscometer Lamy Rheology RM 200 (France) using the «cylinder-in-cylinder» geometry MS-DIN 33. The results obtained were approximated with the Casson model [12], recommended for pharmaceutical compositions in the form of gels, using the Rheomatic software. To conduct the experiment, the samples are tested one by one on a viscometer at a temperature of 20°C, which is the average temperature for storing the gel; and at a temperature of 37°C, which is temperature of the intended application site. The plastic viscosity of the samples was studied in the range of shear rates from 0 to 300 s⁻¹.

Evaluation of bioadhesive properties

Bioadhesion for oral dosage forms for the local use is one of the most important indicators because it determines the dose retention time on the mucous membrane, the completeness of absorption of the active substance, and the onset of the therapeutic effect.

In the experiment to determine the separation force, a lever mechanism was used, on the left shoulder of which there were movable (upper) and fixed (lower) parts, on the right – a place for cargo placement. Previously,
non-woven material of the spanbond type was attached to the lower and upper part of the lever mechanism. A 20% mucin solution was applied to the lower part, and a test gel sample was applied to the upper part. In this case, the mucin layer thickness was controlled, which was 0.1 mm, which lies within the range of the mucus layer thickness under physiological conditions. A load was placed on the platform and the weight was recorded at which the upper plate was completely detached from the lower one. Bioadhesion was determined at a temperature of 20 ± 0.5°C, which is the storage temperature of the tested gels. The amount of adhesion was calculated as the product of the mass of sand and the acceleration of gravity (g = 9.81 m/s²) and was expressed in newtons.

A modified model proposed by Puratchikody et al. [13] was used to determine in vitro retention times. A spanbond section (SPANLAB, Russia) with an area of 676 mm² was attached to a glass plate measuring 260 × 760 mm, onto which a 4% aqueous solution of type II porcine stomach mucin was applied (SIGMA, Sigma-Aldrich, USA, Cat. No. M 2378). On a disk made of spanbond, 26 mm in diameter, soaked in potassium phosphate buffer solution (pH 6.8), 1.0 g of the test sample was applied and uniformly distributed over the disk area. Treated spanbond membranes were combined with each other, thereby combining into a model system. Next, the resulting system was placed in the cell of the pharmacopeia apparatus of the disintegration tester of solid dosage forms ERWEKA ZT 220 “Swinging basket.” The dissolution medium was potassium phosphate buffer (pH 6.8); the medium temperature was 37°C. During the experiment, the time was noted after which the polymer disk with the test drug was torn off from the mucin-soaked spanbond.

Aggregate stability

The aggregate stability of the gel samples was assessed visually by the absence of visible changes (separation, sedimentation, and heterogeneity) and by the kinetic stability coefficient (Kk) after centrifugation for 5 min at a speed of 3000 rpm on a Biosan LMC-3000 centrifuge (Germany) 5 ml of sample gels in centrifuge tubes Greiner Bio-One 15 ml. The kinetic stability coefficient was calculated by the formula:

\[ K_k = \frac{I_1}{I_2}, \]

where

- \( I_1 \) – is the height of the layer of the precipitated phase;
- \( I_2 \) – is the height of the gel layer.

The indicator was determined in experimental samples during storage under natural conditions (temperature 20 ± 2°C, and humidity 55%).

The method of “accelerated aging” determined the shelf life of the developed dosage form. According to RSF XIV (Russia State Pharmacopoeia XIV), the limiting temperature of experimental storage was chosen + 40°C; the thermostat Binder ED 115 (Germany) was used.

**Local irritant effect**

The local irritating effect was determined by the methods of cutaneous, subcutaneous, conjunctival tests, and on the oral mucosa in chinchilla rabbits weighing 3.6–4.1 kg in accordance with the “Guidelines for the Preclinical Studies of Medicines” [14]. The care and maintenance of animals were carried out in accordance with the recommendations and requirements of Directive 2010/63/EU of the European Parliament and of the EU Council of September 22, 2010, on the protection of animals used for scientific purposes. All animal experiments were approved by the Sechenov University Ethics Committee.

Assessment of the local irritant effect on the skin was carried out on ten rabbits. Two days before the experiment, sections of 5 × 5 cm in size were trimmed on the back on symmetrical sections of the back on either sides of the spine, leaving a 2 cm hairline between them. The right side of the animal serves to apply the studied drug, the left to control. The exposure time is 4 h. Exposure is repeated every day for 7 days. The skin condition is recorded visually daily. Functional morphological disorders of the skin are noted in points (erythema, edema, cracks, necrosis, peeling, dryness, and ulceration). After the experiment, animals were monitored for 14 days. The test drug was added 0.5 ml per clipped area on the right side of the rabbit. The same amount of distilled water was applied to the left side.

Subcutaneous tests were conducted on ten rabbits. Injections were administered with 0.1 ml of gel once in shaved areas of the skin of the animal. The state of injections was noted immediately, 24, 48, and 72 h after administration. The degree of tissue reaction was evaluated, including erythema and edema. After the experiment, animals were also monitored for another 14 days.

The local irritant effect on the eyes was evaluated on ten rabbits. The gel in an amount of 0.1 ml was instilled 3 times a day for 7 days. One eye is used to apply the product, the other as a control; 0.1 ml of purified water was injected into it. The severity of hyperemia, conjunctival edema, vascular injection of the sclera, the condition of the cornea and iris, and the number and quality of discharge from the eye for 14 days, which were evaluated in points, were noted.

In addition, the local irritating effect of the gel on the mucous membrane of the oral cavity was evaluated. For this, 0.1 ml of gel was applied to the palate of 10 rabbits 3 times a day for 7 days. To the control rabbits in the amount of ten pieces to the palate, the purified
water was applied. The condition of the mucosa was recorded visually daily. Functional morphological disorders of the mucosa were noted in points (erythema, edema, fissures, necrosis, hyperemia, dryness, and expressions). After the experiment, animals were monitored for 14 days.

**Results and Discussion**

The experimental substantiation of the solvent is one of the most important steps in the development of a suitable gel formulation for local oral drug delivery. Meloxicam is practically insoluble (more than 10,000 g/ml) in oral solvents and has a sharp taste, which may limit its use in dental practice.

Therefore, it was introduced into the following solvents as a suspension: water, ethanol, glycerol, and buckthorn oil in the range of ratios 1:5, 1:10, 1:20, 1:30, and 1:40. Stable for 7 days dispersions were obtained in glycerol in a ratio of 1:40 and in oil in a ratio of 1:10. To obtain a sedimentation-stable suspension in ethanol the need for the introduction of a solubilizer was identified, which was used as Poloxamer 407 Lutrol® F 127 in the concentration range from 5% to 15%. It was shown that a stable dispersion is formed when a solubilizer is added at a concentration of 15%.

Based on the aggregate stable dispersions, experimental samples of dental gels were obtained, the composition of which is presented in Table 1. The most common and widely used gelling agents hydroxyethylcellulose Natrosol 250 HHX (Ashland) and Carbopol® 974P (Lubrizol) were obtained.

Dental gels must have significant bioadhesion to ensure their therapeutic effect; therefore, Noveon® Polycarbophil (Ashland) was additionally added to formulations 5, 6, and 8.

The next step was the determination of the organoleptic properties of the experimental gel samples, but to study the influence of solvents, solubilizer, and bioadhesive on taste, all gels were obtained on one gellant – Carbopol® 974P. To determine the taste used organoleptic method for assessing taste, according to A.I. Tentsova. The taste index was derived from the organoleptic method for assessing taste, according to the synthetic sweetener aspartame was used at a concentration of 0.1%, the acidity regulator ascorbic acid at a concentration of 0.05% and the odor flavor menthol at a concentration of 0.1% – the choice of concentrations was also carried out according to the organoleptic method A.I. Tentsova.

To characterize the tastes of the experimental compositions after conducting taste correction and assessing the effect of the gel on the organoleptic properties of the finished dosage form, the profile method was used. This method was rested on the construction of profilograms based on the results of assessing the taste of the compositions on a five-point scale according to indicators characterizing the taste of the compositions (acidic/bitter/sweet). In addition, the taste of the gelling agent and the indicator of texture were taking into account using numerical indices (1 – the sign is absent; 2 – the sign is weakly expressed; 3 – the sign of normal intensity; and 4 – sign is expressed very strongly) [10]. Profilograms of taste are presented in Figure 1.

All samples analyzed after adjusting the taste had satisfactory organoleptic characteristics. At the

![Figure 1: Profilograms of the taste of meloxicam gel samples](image)

**Table 1: The compositions of the experimental samples of meloxicam gels**

| Ingredients         | Number of composition | Amount of ingredients, % |
|---------------------|-----------------------|--------------------------|
|                     | 1         | 2         | 3         | 4         | 5         | 6         | 7         | 8         | 9         | 10        |
| Meloxicam           | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     | 7.50     |
| Ethanol             | 20.00    | 20.00    | -        | -        | -        | -        | -        | -        | -        | 20.00     |
| Purified water      | 57.50    | 71.70    | 80.20    | 76.75    | 76.75    | 76.75    | 69.00    | 74.75    | 83.60    | 69.25     |
| Poloxamer           | 15.00    | -        | -        | -        | -        | -        | -        | -        | -        | -         |
| Carboxol            | -        | 0.75     | -        | 0.75     | 0.75     | 0.75     | -        | -        | 0.75     | -         |
| Buckthorn oil       | -        | -        | 7.50     | -        | -        | -        | -        | -        | 8.20     | -         |
| Hydroxyethylcellulose| -    | -        | 4.50     | -        | -        | 4.00     | 4.00     | -        | 3.00     | -         |
| Glycerol            | -        | -        | -        | 15.00    | 15.00    | 15.00    | 19.60    | 15.00    | -        | -         |
| Bioadhesive         | -        | -        | -        | -        | 1.00     | 2.00     | -        | 2.00     | -        | -         |

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same time, a specific taste of the gel base was also noted in some formulations. This is more relevant for composition 4, which has a pronounced texture and a slightly bitter aftertaste. Compositions 2, 7, and 8 have a characteristic smack of a gel-forming agent of moderate intensity. According to the data obtained in the course of complex studies of the organoleptic properties of the compositions by the organoleptic method A.I. Tentsova and profile method, the most acceptable organoleptic characteristics are compounds 2, 7, and 8.

The most important indicator in the development of gels is their aggregative stability. A measure of stability was the kinetic stability coefficient calculated as the ratio of the separated phases after centrifugation of the sample. It was accepted that the samples are stable with a kinetic stability coefficient not exceeding 0.1 (Table 3).

Compositions with buckthorn oil began to exfoliate after a week of storage. Samples using ethanol as a solvent also did not show high stability. Samples 2, 4, 5, 7, and 8 had satisfactory stability, since their kinetic stability coefficient did not exceed 0.1. They also did not observe delamination, turbidity, discoloration, or gel consistency; there was no separation of the dispersion medium from the polymer network formed by the molecules of the dispersed phase (there was no syneresis).

At the next stage of the study, the physicochemical characteristics of stable meloxicam gel samples were evaluated.

According to the data obtained, it can be concluded that samples 7 and 8 have the most satisfactory pH values since their pH is as close as possible to the saliva pH (6.4–7.2) [15], which will not contribute to the destruction and demineralization of long-term use enamels [16]. However, the remaining samples satisfy the pharmacopeial requirements for this indicator.

**Table 2: The results of determining the taste of meloxicam gel samples by A.I. Tentsova**

| Indicator                   | Number of composition |
|-----------------------------|-----------------------|
| Sweetness                   | 1 2 3 4 5 6 7 8 9 10 |
| The presence of aftertaste  | 2.0 2.0 1.0 1.0 1.0 2.0 4.0 4.0 3.0 4.0 |
| Aftertaste character        | 5.0 5.0 1.0 4.0 4.0 2.0 2.0 3.0 5.0 5.0 |
| Taste in general            | 2.0 3.0 5.0 5.0 5.0 4.0 4.0 5.0 4.0 5.0 |

When studying the rheological characteristics of the experimental samples, it was shown that when using ethanol as a solvent of meloxicam, the yield strength characterizing the strength of the gel structure and plastic viscosity significantly differ from the performance of the samples, in which glycerol was used in various concentrations (Table 4). Thus, the introduction of ethanol in the pharmaceutical composition cannot ensure its stability during storage under shear stress (e.g., by extrusion from a tube by a patient). The rheological characteristics of the studied formulations 4, 5, 7, and 8 lie in the optimum range for dental gels defined by author [12].

Then, the bioadhesive properties of meloxicam gel samples were studied using two methods: The “peel” method, where the greater the peel force, the higher bioadhesion, and the “swinging basket” method, in which the longer the retention time, the higher bioadhesion.

According to Table 5, compositions 4 and 5 based on Carbopol® 974P have significantly lower bioadhesive retention properties than formulations 7 and 8 based on Natrosol® 250 HHX. The adhesion values of compositions 4 and 5 are 1.7 ± 0.164 s and 2.0 ± 0.11 s, and for compositions 7 and 8 more than 30 times higher: 65.0 ± 0.084 s and 77.0 ± 0.071 s, respectively. In addition, a noticeable effect on the bio-adhesion of Noveon® Polycarbophil administration (compositions 5 and 8). The adhesion value of composition 5 is higher by 5.6 N and the retention time is 0.3 s than that of composition 4. For composition 8, the adhesion value is higher by 1.2 N and the retention time by 12 s. Thus, compositions 7 and 8 have the best bio-adhesive properties.

To determine the shelf life by the method of “accelerated aging,” three series of samples of composition 7 and 8 were made as the most satisfactory for all previously studied indicators. For each series, the following quality indicators were evaluated during storage: Description, authenticity and quantification by HPLC, viscosity, particle size, pH, and microbiological purity.

**Table 4: Physicochemical characteristics of meloxicam gel samples**

| Sample No. | pH ± SD | Casson yield strength, Pa ± SD | Casson plastic viscosity, Pa.s ± SD |
|------------|---------|-------------------------------|-----------------------------------|
| 1          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 2          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 3          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 4          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 5          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 6          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 7          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |
| 8          | 1.37 ± 0.1 | 158 ± 0.084 ± 164 ± 0.11 |

The shelf life of sample 7 was 1.5 years and the shelf life of sample 8 was 2 years, so it was considered more promising for further development. In addition, bioadhesive characteristics are also higher for composition 8.

**Table 5: The results of the study of bioadhesion in samples of meloxicam gels**

| Sample No. | The amount of adhesion, N ± SD | Retention time, sec ± SD |
|------------|--------------------------------|-------------------------|
| 4          | 26.650 ± 0.004                 | 1.7 ± 0.164             |
| 5          | 31.713 ± 0.002                 | 2.0 ± 0.11              |
| 7          | 29.442 ± 0.002                 | 65.0 ± 0.084            |
| 8          | 30.682 ± 0.002                 | 77.0 ± 0.071            |

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For drugs applied to the mucous membrane, the absence of a local irritant effect is extremely important. For sample 8, the local irritant effect was evaluated in several ways.

When determining and evaluating the local irritating effect on the skin, the degree of erythema and edema was 0, which corresponds to the absence of a local irritating effect. With intradermal administration of a dental gel with meloxicam, the degree of intradermal reactions immediately after administration is 6 points out of 8. After 72 h, the degree decreases to 0, which corresponds to the absence of a local irritant effect. In the gel study to determine and evaluate the local irritant effect on the eyes, the degree of local irritant effect corresponds to "weak or absent." When this composition was applied to the mucous membrane of the oral cavity, a slight edema (0 or 1 point) or its absence, slight redness, or its absence (0 or 1 point) was observed, which also corresponds to the absence of a local irritant effect. Thus, a gel with meloxicam does not have a local irritant effect.

Conclusions

The meloxicam dental gel composition 8 was developed based on the Natrosol® 250 HHX hydroxyethylcellulose gelling agent, glycerol solvent and purified water in a ratio of 1/5 and 2% Noveon® Polycarbophil bioadhesive was present in the composition. The composition has good taste, a pH close to the pH of saliva, high bioadhesive properties, and satisfactory rheological characteristics. The shelf life of the experimental series by accelerated aging was 2 years. The selected composition does not have a local irritant effect.

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