Development of Composition and Technologies of Dental Film with Ketorolac Trometamine

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ABSTRACT

The report presents the results of the development of dental films with ketorolac trometamine based on the natural biodegradable polymers from the groups of sodium alginates and xanthan gums in combination with lightly crosslinked acrylic polymer carbopol. Physicochemical properties, such as moisture, mucoadhesion, thickness, tensile strength, disintegration in phosphate buffer were determined in obtained samples of this dosage form. A comparison of physicochemical properties of experimental samples and commercial model of dental film has allowed establishing the perspective composition of complex matrix of films with ketorolac trometamine for use in dentistry.

Introduction

There are diseases that require long-term maintenance of concentration of active substances, occurring frequently in dental practice. Such conditions include periodontal disease, oral mucosal trauma, cankers and erosive lesions etc. In these cases, it is recommended to use local drug delivery systems [1], which aims to deliver an active substance into the affected spots with minimal interaction with oral cavity in general and with reduced side effects.

Films as a dosage form are most appropriate for the solution this problem. They have good adhesion properties to the tunica mucosa of mouth. With their help, it can not only prolong the therapeutic effect, but also combine the drug substances, belonging to different pharmacotherapeutic and physicochemical groups, in one composition. Furthermore, thin films are convenient and harmless to use, and patients can use them themselves. If it is necessary, it possible to remove films from the place of application easily [1–3]. The last advantage is significant in terms of consumer preferences in selecting drug delivery system in dental practice.

Among all these drugs for using in dentistry non-steroidal anti-inflammatory drugs play an important role. Pain is the major symptom faced by patients in the process of endodontic treatment in extraction of teeth or part of the gum, after dental implant insertion etc [3–5]. Ketorolac is used successfully in dentistry because of strong analgesic effect comparable with narcotic analgesics, but unlike them, ketorolac does not affect at opiate receptors. Hence, it does not depress breathing and intestinal motility, does not produce sedative effect and, the most important, it does not produce euphoria and addiction [5, 6]. In numerous clinical trials ketorolac has shown the effectiveness in the treatment of inflammation in oral cavity and sharp pain, when it was administered orally, buccally, parenterally and intranasally [7–9]. However, using the ketorolac trometamine in such dosage form as a dental film will allow providing targeted treatment of the affected areas, as well as to modify release and correct the intensity of the side effects.

Thus, the purpose of this research was development of composition, technology and study of physicochemical properties of dental film with ketorolac trometamine.

Materials and Methods

The research object was the active substance of ketorolac trometamine produced by Chemo Iberica, Spain (Ph. Eur. 10).

Materials

Xanthan gum Grindsted Xanthan 80 (Dupont Nutrition & Health, Ph. Eur. 10); Carbopol® 971P NF (Lubrizol, Ph. Eur.10); sodium alginate Protanal® CR8133 (FMC BioPolymer, Ph. Eur.10); sodium alginate Manucol® LKX (FMC BioPolymer, Ph. Eur.10); glycerin (Ph. Eur.10).

Thin films were obtained by solvent casting method onto the glass substrate, hydrophobized by liquid paraffin, with subsequent drying at a temperature of 50 ± 0.5 °C for 48 h in a BINDER KBF 115 constant climate chamber. The polymer dispersions for bases of thin films were prepared by mixing the polymers and purified water using IKA tropolino mobil magnetic stirrer. The carbopol dispersion were neutralised by sodium hydroxide to pH 7.5. Glycerin was added to solution of polymers. For the production of thin film based on carbopol and xanthan gum, the solution of components were prepared separately, mixed and then the glycerin was added to final blend.

There were monitoring during casting thin films, so that the bases distributed evenly on the surface of glass substrate.

Methods

Features screened the experimental samples: moisture content, moisture absorption, thickness, flexural strength, tensile strength, pH, biodegradation, mucoadhesion.

Range of pH, which is affecting biopharmaceutical properties, was determined in the dispersions and the polymer solutions on the ion meter Mettler Toledo S220-Kit (Mettler Toledo) before drying. Drying of thin films based on different polymers was conducted under the same conditions. But the residue moisture of thin film, defining many processing characteristics in the future, depends not only on the condition of drying but also on specific polymer. So it is important to determine this rate of experimental samples. Moisture of thin films was determined by the gravimetric method on Moisture Analyzer MS-70 (AND) during the drying process until a constant mass at temperature 105 ± 0.5 °C. Moisture absorption and swelling properties, were also determined by the gravimetric method after putting of the thin films into the dessicator with constant relative humidity 97 % at 25 ± 0.5 °C for 24 h. Tensile strength of samples was determined by using the axial extensometer (Reliant Technology LLC) at 20 ± 0.5 °C (Method 1), and in folding endurance experiment by repeatedly folding of the sample of the thin film measuring 9 by 15 centimeters with next visual evaluation of the integrity. If there were no cracks on the test film sample after folding, the sample was considered as "strong" at this number of additions (Method 2). Thickness of the thin films was determined by using the micrometer GRIFF MKC 25 (GRIFF). Disintegration were explored in the disintegration tester ZT 122 (Erweka GmbH) into phosphate buffer solution pH 6.8 at temperature 37 ± 0.5 °C. Time necessary for losing the shape and the structure with the subsequent dissolution or jellification of the thin film was determined as the disintegration time.

Mucoadhesion properties of the experimental samples were explored in vitro in the experiment of determining the force of separation the sample from the mucous tissue model composed of 20 % gel mucin from porcine stomach type II (SIGMA, Sigma-Aldrich) applied to the membrane.

There was used the commercial sample of the self-adhesive dental thin film Diplen Denta with chlorohexidine (0.01 – 0.03 mg/cm^2) of "Nord OST", Russia, for comparison and monitoring the quantified indications (as a control sample).

Results

The experimental samples of thin films were produced using the one polymer-matrix or the combination of polymers in the following concentrations: xanthan gum Grindsted Xanthan 80 – 1.0 %; Carbopol® 971P NF–0.05 – 0.5 %; sodium alginate Protanal® CR 8133–1.0 %; sodium alginate Manucol® LKX–1.0 %; glycerin –0.03 – 3.0 %. The study demonstrated that the thin films made with a high concentration of glycerin (above 0.03 %) were distinguished by higher tack, were formed and separated from the substrate poorly after the end of drying. The samples produced on the basis Carbopol 971P NF and Manucol LKX dispersions did not provide a homogeneous distribution of ketorolac trometamine and lacked the necessary elasticity. As a result, the five samples were selected for further study - the multi-component compositions with the adding of glycerin 0.03 % based on polymers Grindsted Xanthan 80, Manucol® LKX and Protanal® CR 8133. Also combined compositions of thin films were selected, which based on the same polymers with addition of Carbopol® 971P NF in concentration of 0.05 % (▶ **Table 1**). There were added 0.02 g ketorolac trometamine to produce the thin film covering 78.5 cm^2 at 25 ml of purified water, concentration of ketorolac is equivalent to the recommended effective single-dose [6, 7].

For producing the thin films, pH of polymers dispersions was in neutral ranging between 6.8 and 7.5. Ketorolac trometamine was

▶ **Table 1** Compositions of experimental samples of thin films with ketorolac trometamine.

Sample number	Concentration, % (w/v)				
Components	**1**	**2**	**3**	**4**	**5**
Carbopol® 971P NF	–	0.05	0.05	–	0.05
Protanal® CR 8133	1.00	1.00	–	–	–
Manucol® LKX	–	–	1.00	–	–
Grindsted® Xanthan 80	–	–	–	1.00	1.00
Glycerin	0.03	0.03	0.03	0.03	0.03
Purified water	to 25 ml				

distributed homogeneously in the dosage form. The results of screening characterizations of experimental samples in comparison with commercial sample of thin film "Diplen Denta X" are presented in ▶ **Table 2**. It has been shown that nature of the polymers has a significant impact on the technology indicators of thin films. Thus, the samples based on alginate (1, 2, 3) had the higher moisture content but the lower tensile than the sample based on xanthan gum (4). Adding of Carbopol 971P NF in the compositions (2, 3, 5) had different impact on properties of this dosage form – it increased tensile and mucoadhesion for the samples based on xanthan gum and decreased adhesion property and disintegration time for the sample based on alginate. For the alginate Manucol LKX the adding of 0.05 % Carbopol 971P NF in the composition contributed to homogeneously distribution of the substance in the thin film and also made it elasticity.

Among the compositions selected for studying the samples 3, 4 and 5 exceeded the technological indications of the control sample or were close to it.

▶ **Figure 1** shows the trend in water absorption of the explored samples. The value of water absorption can be used to determine the storage conditions and the type of primary packaging of the dosage form. The sample 5, based on xanthan gum and carbopol (98 %), and the sample 1, containing Protanal® CR 8133 (112 %), along with the control sample was characterized by the lowest water absorption. The sample 2 absorbed three-fold number of liquid for 24 h of the experiment compared with the initial mass it limits its further development.

Discussion

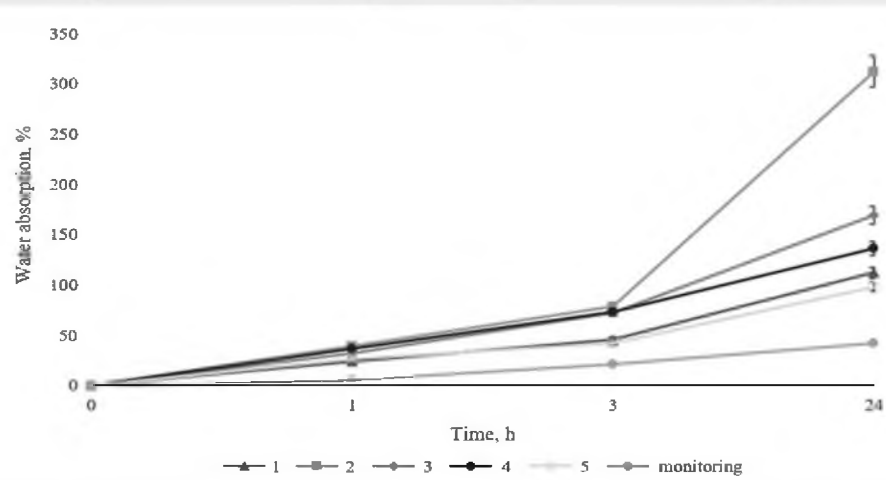
In this work the biodegradable polymers such as sodium alginates and xanthan gum and synthetical lightly crosslinked polymer were used.

Selected polymers have less irritating effect and are biocompatible with mucosal membrane. Using their combinations, it also can be reached the high technology characteristics (tensile, mucoadhesion), are not inferior to polyvinyl alcohol and polyvinylpyrrolidone, which often apply for producing the thin films [3, 9]. Furthermore, dental films, keeping the same shape during the exposition for a long time, could cause discomfort among the patients in applying or could be displaced involuntary by movements of the tongue. The samples 4 and 5 based on xanthan gum did not disintegrate during the biodegradation and made the gel on the application place. It can increase both the patient compliance of therapy and effectiveness of medicine using this dosage form. Mucoadhesive gel layer on the application place will be not only contributing to the protection of the affected area of gum from mechanical and microbial impacts but it also can provide the modified release of an active substance.

▶ **Table 2** Technological characteristics of the compositions.

Composition number	Moisture, % ± SD	Thickness, mm ± SD	Strength		Muchoadhesion, N ± SD	Disintegration time, sec ± SD
			Method 1, MPa ± SD	Method 2, number ± SD		
1	15.0 ± 0.2	0.03 ± 0.01	1.16 ± 0.02	6 ± 1	14.84 ± 0.13	180.0 ± 3.5
2	20.0 ± 0.3	0.03 ± 0.01	2.98 ± 0.05	≥ 20	8.98 ± 0.14	40.0 ± 2.4
3	9.3 ± 0.5	0.03 ± 0.01	2.65 ± 0.03	20 ± 2	29.78 ± 0.08	120.0 ± 2.1
4	9.0 ± 0.4	0.03 ± 0.01	3.18 ± 0.02	≥ 30	18.24 ± 0.07	*30.0 ± 2.2
5	5.4 ± 0.3	0.03 ± 0.01	3.67 ± 0.03	≥ 30	23.42 ± 0.08	*26.0 ± 2.6
Control	5.3 ± 0.3	0.05 ± 0.02	2.43 ± 0.02	6 ± 1	18.21 ± 0.07	30.0 ± 3.2

* the formation of a gel during disintegration.



▶ **Fig. 1** Kinetics of water absorption of the experimental compositions.

Conclusion

The promise of using the biodegradable polymers from the group of alginate and xanthan gum in combination with carbopol was shown in the process of developing the dosage form with ketorolac trometamine for dental applications. The optimal features in such parameters as tensile, moisture content, bioadhesion and disintegration were had the sample based on the complex matrix of xanthan gum (1.0 %) with carbopol (0.05 %) containing glycerin (0.03 %).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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