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The study of properties of the matrix for periodontal films based on Metronidazole, Chlorhexidine and Glucosamine

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Abstract: Selection of optimal matrix is one of the most important stages for new semi-solid medicines creation. Biopharmaceutical properties of periodontal film completely depend on the properties and composition of the matrix. The purpose of the present study was selection of proper composition and technology of film base for obtaining of necessary physical-chemical and technological parameters. Periodontal films with various compositions based on different natural and semi-synthetic polymers or their combinations were made according to different technologies. Physical- chemical properties and osmotic action of obtained matrixes were studied. Microscopy of periodontal films was performed. After selection of the matrix study of metronidazole release was performed. The collected data showed that chitosan and agar-agar matrix are the most promising base for the future research of the investigated composition of periodontal film. Technology of films was modified according to the technological properties of selected polymers.
Keywords: periodontal film, chitosan, agar-agar, metronidazole, chlorhexidine, glucosamine.

Introduction:

People of all ages widely suffer from periodontal diseases. According to WHO data from 10% to 15% of adult population worldwide has advanced disease with deep periodontal pocket[1]. One of the promising medicinal forms for treatment of periodontal diseases is stomatological films. Its main advantage is direct contact of medicine with periodontal pocket during all time of films use while other medicines for gums inflammation treatment have short period of action and are washed away by saliva quickly.

The impact on all inflammation stages is crucial for increasing the treatment effectiveness. Thus medicinal matters with antimicrobial effects (metronidasole and chlorhexidine) on various pathogens and with antiphlogistic and reparative effect (glucosamine) were selected for creation of new combined drug.

The development of new drugs in film form starts with the matrix choice. First we conducted comparative investigation of compatibility of medicinal matters with different polymers used for film production according to the data available[2-3]. Then the compatibility of bases and medicinal matters was investigated in vitro; we chose natural and semi-synthetic polymers for this research. Then we conducted compounding of films using different compositions of polymers and different technologies[4]. As a result 36 films compositions were obtained. Using organoleptic and microscopic investigation from these films two compositions of matrix were chosen: one of them contained semi-synthetic (Sodium carboxymethylcellulose and Sodium alginate) and natural (chitosane) polymers (#1) and another one – just natural polymers (chitosane

and agar-agar) (#2). First one was compounded using special technology of «three layers» to protect chlorhexidine from interaction with sodium alginate and sodium carboxymethylcellulose.

Table 1. Film forming solutions and films matrixes compositions

Composition/Films matrix	Quantitative content, %			
	for film-forming solution		for film	
	#1	#2	#1	#2
Chitosane	1	1	11,36	11,019
Sodium alginate	0,5		5,68	
Sodium carboxymethylsellulose	0,5		5,68	
Agar-agar		2		22,039
Lactic acid (80% solution)	1	1	11,36	11,019
Glycerine	5	5	56,81	55,096
Water	91	90	2,43	0,83

The aim of the present study was to investigate the physical-mechanical and physical-chemical properties of these two compositions and select one of these matrixes for periodontal films production.

Experimental:

The objects of study were films matrixes. Methods: microscopic, organoleptic, modified dynamometric method, spectrophotometric method. The study used the following equipment: biological microscope (PRIZE, by "Sigeta" company), spectrophotometer (SF-46, by LOMO company), laboratory balances (TBE, by "Technowagy" ltd.).

After preparing the films their physical-mechanical and physical-chemical properties were investigated. Mass and average thickness of the films were measured. We cut the samples of prepared film matrixes and measured their tension resistance and relative extension. Obtained data are available (Table 2).

For both matrixes osmotic activity at 34°C through semi-permeable membrane until the constant mass obtaining was investigated. For the matrix with better results we also conducted the study of metronidasole release through semi-permeable membrane using the spectrophotometric method.

Results And Discussion

For selection of matrix we compared physical-chemical and physical-mechanical properties of designed films (Table 2). The data showed that matrix with Composition#2 had the higher tension resistance. Relative extension varied insignificantly. Microscopic and organoleptic analysis showed smoother surface for Composition#2 matrix (Fig.1.,Fig.2).

Table 2: Physical and mechanical properties of films matrixes with different compositions

Matrix composition	Average thickness, mm	Tension resistance, kg/cm²	Relative extension, %
Composition#1	0,28±0,0048	79,25	105,83
Composition#2	0,32±0,0064	129,7	104,7

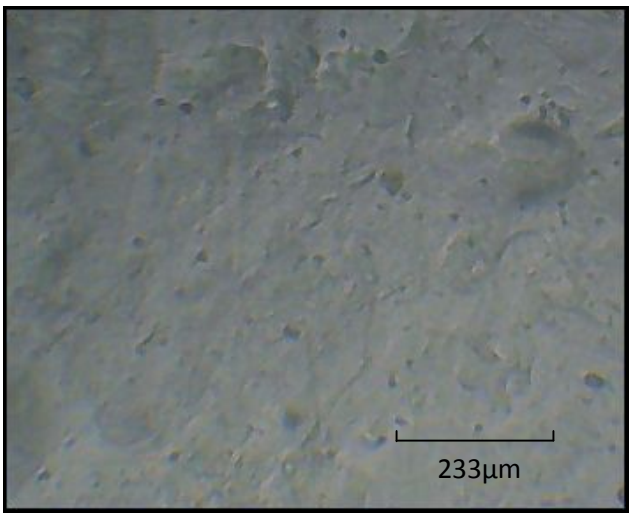

Figure 1: Result of microscopy for Composition#1 film

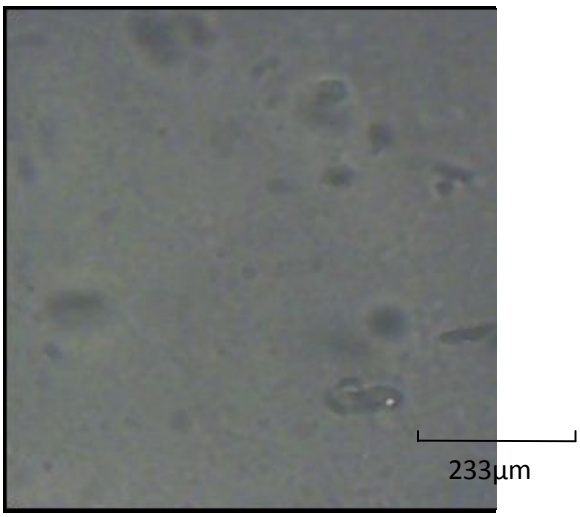

Figure 2: Result of microscopy for Composition#2 film

Optimal osmotic activity level is important for dental medicinal forms. Available results showed higher osmotic activity that partly comes to dissolution for Composition#1 matrix (Figure 3). For Composition#2 matrix change of osmotic activity stopped in 150 minutes, instead of partial evaporation of solvent (Figure 4).

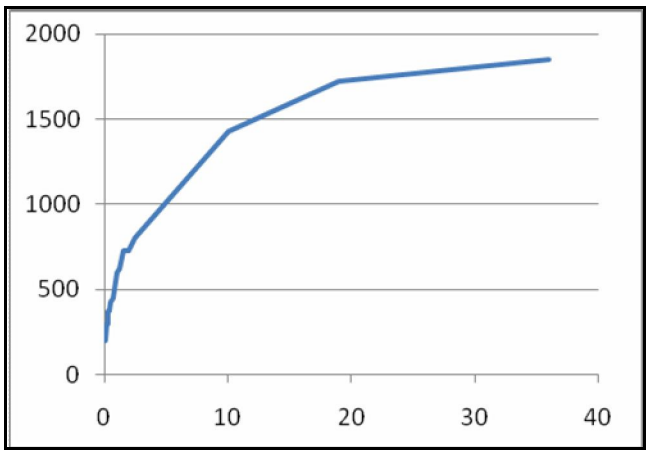

Figure 3: Osmotic properties for Composition 1 matrix, %

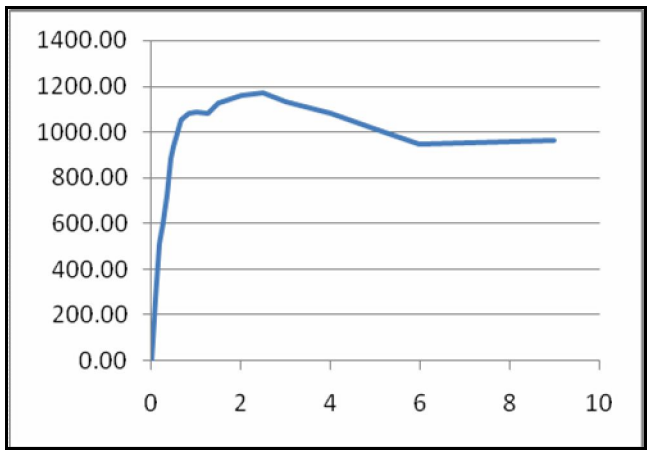

Figure 4: Osmotic properties for Composition 2 matrix, %

Taking into account optimal physical-mechanical (smother surface, higher tension resistance) and physical-chemical properties - osmotic activity (slower dissolution) for future work we selected matrix with Composition#2 (based on natural polymers - chitosan and agar-agar). To confirm opportunity of use for the films based on this matrix the kinetic of release of metronidazole in vitro was investigated.

Metronidazole dissociated from matrix through semi-permeable membrane into solution during the first hour (Fig. 5). At the same time the highest osmotic action of film was noticed (Fig. 4), so we can suppose both dehydrating and antimicrobial effects on bacterial cells.

Available data showed the best release of metronidazole in alcaline medium. In weak acid medium only 80% of metronidazole dissociated. The fullness of metronidazole release is increased with pH increasing (Fig. 5)

This shows that the investigation of glucosamine release kinetic in vivo is worth researching because it can correct metabolic acidosis in periodontal pocket and modify metronidazoles diffusion.

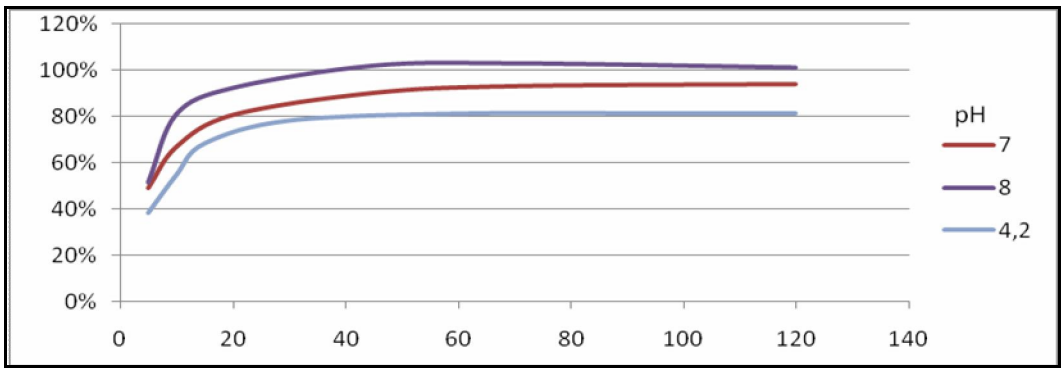

Figure 5: Dissociation of Metronidazole from matrix through semi-permeable membrane into solutions with different pH

We selected matrix containing agar-agar for future investigation. Thus it is important to take into account the technological properties of these polymers. Agar-agar dissolves at 90°C and forms thermoreversible gel. Therefore it is necessary to maintain temperature not less than 40°C during all process after agar-agar dissolution while preparing the film-forming solution. Subsequent heating up of gel for liquefaction can cause decomposition of thermolabile substances, as chlorhexidine.

Conclusion:

Two different compositions of matrixes for stomatological films were selected as possible base for semi-solid medicinal form with metronidasole, chlorhexidine and glucosamine for treatment of inflammatory periodontal diseases. It was experimentally confirmed that one of that matrixes based on natural polymers (Chitosan and agar-agar) has better physical and osmotic properties comparing to another one and is more promising for further investigation. Obtained data showed that natural matrix has at the same time highest osmotic action and fast metronidasole release, which can be continued while correcting the metabolic acidosis. Thus, this matrix is optimal from all studied bases for preparing of films with selected composition. At the same time technology of this matrix needs special temperature regime to prevent premature gelation and expansion of heat-labile substances.

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