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Research Design of the Release of Amizon, Decametoxine, and Chlorhexidine from the Composition of Dental Medicinal Films

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ABSTRACT

Introduction: The treatment of most diseases in dentistry is related to the local application of antiseptic drugs that regulate the microbiocenosis in the oral cavity. The study of pharmacodynamic and kinetic parameters of the release of active pharmaceutical ingredients (APIs) from the dosage form (DF) is an important task. In this study, we tried to evaluate the release of APIs from developed dental medicinal films (DMF) produced on a polymeric basis.

Methods: To confirm the antimicrobial activity of the three developed DMF with amizon, decamethoxine and chlorhexidine digluconate, a statistical analysis and mathematical processing of the research results were carried out.

Results: Statistical processing made it possible to organize the results of our earlier studies, in which the concentrations of three APIs (amizon, decamethoxine, and chlorhexidine digluconate) were determined during their diffusion from the polymer base of the DMF to the aqueous dispersion medium (0.9% sodium chloride solution). Due to performed statistical calculations, regarding the reliability of APIs release, it was determined that the time duration of complete release of the three active substances from the polymer base was different, which will ultimately affect the duration of the pharmacological effect of the APIs in the patient's body.

Conclusion: In the manufacture of DMF on a polymeric base of hydrophilic type, it is necessary to take into account the release time of each API, according to the composition of the polymeric coatings.

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Introduction

Oral and dental ailments, including tooth decay, dental caries, gingivitis, periodontitis, commonly occur on the globe and are often caused by bacterial infections. Different antiseptics of synthetic and natural origin as well as other groups of medicines are applied in periodontal diseases and tooth infections, due to their inhibitory effect on the growth of *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacillus spp.*, *Candida ssp.* and other microorganisms, anti-inflammatory,

analgesic and wound-healing activities, ability to prevent dental plague formation (Wang et al., 2014; Gasmi Benahmed et al., 2020; Manouchehri, 2022; Gasmi Benahmed et al., 2022a; Santacroce et al., 2022; Mandil et al., 2023; Manouchehri et al., 2023; Mandil et al., 2023). Antimicrobial properties of applied dental biomaterials can decrease pathogenic contamination and local inflammatory processes (Gasmi Benahmed et al., 2022b).

Anatomical and physiological features of the oral cavity complicate the use of most DF, since the oral cavity is lined with smooth epithelial tissue (mucous membrane), which is constantly washed with oral fluid (saliva). As a result, the local application of any medicinal products (solutions, ointments, gels or pastes) is accompanied by the washing out from the mucous surface and impossibility of long-term fixation, as well as a decrease in the concentration of the active substance (in the composition of the medicinal product) due to its dilution with oral fluid (Kida et al., 2021).

Therapeutic assistance to dental patients is an important component when considering human health as a whole (Lamster and Eaves, 2011; Sanders et al., 2021; Katakura, 2022). It is possible to optimize and facilitate the therapy of dental patients due to the development of a new DF in the form of DMF, which after application to the mucous membrane undergo a gradual bio-destruction and release of API (Rokaya et al., 2018; Petrescu et al., 2022; Zhang et al., 2022).

The reliability of the release of API from the DMF in the test solution, allows mathematical and statistical evaluation of the experiment *in vitro*, which can predict the optimal time of their dissolution in the human mouth under physiological norms and to simulate the results of research close to *in vivo* conditions (Vasylenko and Sencha, 2011).

Analysis of the results for statistical evaluation of the release of amizon, decametoxine and chlorhexidine will allow the production of DF applied in the form of DMF, the advantage of which comprise a controlled period for the API release and their diffusion through the oral mucosa without compromising the integrity of epithelial tissues.

Therefore, the aim of this work was to perform statistical processing, using previously obtained results of sampling studies, and to determine the concentrations of three API that diffused to the dispersion medium (aqueous sodium chloride 0.9%) from the produced DMF with amizon, decametoxine and chlorhexidine digluconate.

Materials and Methods

Comparison of the release from the composition of DMF containing amizon, decametoxine and chlorhexidine digluconate, depending on the time in the dynamics was performed by mathematical confirmation of the results obtained from three studied groups of DMF, with different active substances - 6 test samples in each group, totally eighteen polymer films were prepared on a polymeric hydrophilic basis.

Statistical data processing, based on the Tukey method, was used to study and compare the time periods of API release, from the composition of DMF, yielding amizon, decametoxine and chlorhexidine digluconate, since these indicators can affect their pharmacokinetics and pharmacodynamics.

Results:

Statistical evaluation of the rate of API release was performed by studying three DMF of the following compositions (Table 1).

Application of mathematical, statistical processing was used to confirm the preliminary results of the study on DMF sampling, in which the concentrations of amizon, decametoxine and chlorhexidine digluconate, diffused to the dispersion medium (aqueous sodium chloride 0.9% solution), were determined.

Comparison of the time parameters of release from the composition of DMF containing amizon, decametoxine or chlorhexidine digluconate in the dynamics was performed by statistical comparison of eighteen test samples in the form of polymeric films made on a polymeric hydrophilic basis (Hrynovets, 2013). Thus, sampling was carried out in time periods through 3, 5, 10, 15, 20, and 25 min (Table 1).

The average values of the ingredients at each fixed time after the release of API into the composition of an aqueous Na Cl (0,9% solution) were also determined (Figure 1). Estimation of residual variances was performed by formulating a hypothesis and further comparison of received experimental and tabulated F-values of Fischer-Snedekor distribution for reliability P < 0,05 (Horoneskul, 2009).

During the experiment from each DMF, where the content of test samples of API is expressed as a percentage, depending on the time, sampling was performed after application to the base of the polymer carrier by analysis of variance using the method of Tukey (Vasylenko and Sencha, 2011), the optimal time of dissolution of the polymer base and the transition of the gel form into a solution form were estimated. The result of the research is a statistical analysis of the ratio of time indicators, in accordance with the concentration of the active substance in the composition of the DMF in the test solution, are represented (Tables 2, 3, and 4).

The table 2 summarizes the results of the release of three investigated API from DMF into the tested solution.

To obtain a statistical conclusion based on analysis of variance, the API amizon is taken here as an example.

Formulation of hypotheses and set the level of significance:

$H_0: \mu_1 = \mu_2 = \mu_3 = \mu_4 = \mu_5 = \mu_6$,

there is no significant difference between the average values of amizon release over time;

H_1: the difference between the average values is significant; level of significance $\alpha = 0{,}05$.

The criteria for testing hypotheses, using statistical processing of the obtained data, is determined as follows:

$F = MS_A / MS_W$,

with the number of degrees of freedom

$\nu_1 = I - 1,\ \nu_2 = n - I$,

where the time factor is variable ($\nu_1 = 5;\ \ \nu_2 = 35$).

According to the algorithm, calculations on the results of statistical analysis were performed (Table 3).

Calculation of the residual variance was conducted using formulae (Bakhrushyn, 2006):

$$SS_A = \sum_{i=1}^{I} n_i (\overline{Y}_{i*})^2 - n\overline{Y}^2$$

$$SS_W = Y_{**}^2 - \sum_{i=1}^{I} n(\overline{Y}_{i*})^2 \qquad MS_A = \frac{1}{\nu_A} SS_A$$

$$MS_W = \frac{1}{\nu_W} SS_W$$

The variance analysis with empirical criterion value calculation (Anistratenko and Fedorov, 1993) is shown (Table 5).

According to the Fischer-Snedekor tables, the following results will be critical:.

$$f^* = f(p = 0{,}95, \quad \nu_1 = 5, \quad \nu_2 = 30) = 2{,}65$$

$$f^* = f(p = 0{,}999, \quad \nu_1 = 5, \quad \nu_2 = 30) = 4{,}182$$

Since $f_e > f^*$, the difference between the average values is significant, i.e. amizon release is accurate at the time ($p<0.001$).

To assess amizon release over time, the method of Tukey (Vasylenko and Sencha, 2011) was used, as the number of values in the groups are the same.

Formulation of hypotheses:

H_0: $\mu_k - \mu_l = 0$, $(k, l) = 1, 2, 3, 4, \quad k \neq l$;

H_1: there are non-zero slope; level of significance

The criterion of statistical hypothesis testing (Herasymenko et al., 2000) is:

$$Q_{kl} = \frac{\overline{Y_{k*}} - \overline{Y_{l*}}}{\sqrt{MS_W / m}}$$

The numbers of degrees of freedom:

$$\nu_1 = 5, \quad \nu_2 = 30$$

$$q^* = q(p = 1 - \alpha_1;\ \nu_1 = \mathrm{I};\ \nu_2 = \mathrm{I}(m-1)$$

$$q^* = q(p = 0{,}95; \quad \nu_1 = 6; \quad \nu_2 = 30) = 4{,}30$$

The half-width of the probability range is:

$$q^* \sqrt{MS_W / m} = 5{,}59$$

The received data comparison is given in Table 4.

Analysis of variance showed that the content of amizon, decametoxine, and chlorhexidine digluconate in the tested solution for each of the films significantly increased ($p < 0{,}001$).

Most quantity of amizon was released during the first 10 minutes ($p < 0{,}001$), by 15 minutes the reliability of the release decreased ($p < 0{,}05$), and subsequent its release was insignificant and included in the parameters of insignificant maintenance of concentration for 30 min from the beginning of the experiment.

Dexametoxinum is released faster during the first 10 minutes ($p < 0.001$), after the release is insignificant and its subsequent release was insignificant and included in the parameters of insignificant maintenance of the concentration for 30 min from the beginning of the experiment.

Chlorhexidine digluconate is released to the greatest degree in the first 15 minutes ($p < 0{,}001$), up to 20 minutes the reliability decreases ($p < 0{,}05$), and after 20 minutes it becomes not statistically significant ($p > 0{,}05$), insignificant and included in the parameters of insignificant maintenance of concentration for 40 minutes from the beginning of the experiment.

Table 1. Release of active pharmaceutical ingredients from the composition of the dental medicinal films into the experimental aqueous solution (NaCl 0,9%).

Time sampling (min)	The content of API in the experimental samples,% of the content in the DMF		
	Amizon	Decamethoxinum	Chlorhexidine digluconate
3	49.7 ± 0.01	70.0 ± 0.1	7.0 ± 0.01
5	71.4 ± 0.01	85.0 ± 0.05	17.0 ± 0.03
10	86.8 ± 0.01	90.0 ± 0.1	28.0 ± 0.02
15	90.6 ± 0.01	95.0 ± 0.05	49.0 ± 0.01
20	92.7 ± 0.01	96.7 ± 0.1	75.0 ± 0.02
25	93.0 ± 0.01	97.0 ± 0.1	80.0 ± 0.01

API: Active pharmaceutical ingredients; DMF: Dental medicinal films; Solution was NaCl 0.9%.

Table 2. Release of amizon, decametoxine and chlorhexidine digluconate from dental medicinal films into the tested solution

Time sampling after preparation of DMF, min	The average value of the content of the API in experimental samples of different DMF		
	Amizon	Decamethoxine	Chlorhexidine digluconate
3	49.7±0.01	70.0±0.1	7.0±0.01
5	71.4±0.01	85.0±0.05	17.0±0.03
10	86.8±0.01	90.0±0.1	28.0±0.02
15	90.6±0.01	95.0±0.05	49.0±0.01
20	92.7±0.01	96.7±0.1	75.0±0.02
25	93.0±0.01	97.0±0.1	80.0±0.01

API: Active pharmaceutical ingredients; DMF: Dental medicinal films.

Table 3. Calculations, based on the results of statistical processing

Time rate	Sample size	Number at the level	Number of squares	Average value at the level	Average number of square
	n_i	$Y_{i*}=\sum_{j=1}^{n_i} Y_{ij}$	$Y_{i*}^2=\sum_{j=1}^{n_i} Y_{i*}^2$	$\overline{Y}_{i*}=\frac{1}{n_i}Y_{i*}$	$n_i(\overline{Y}_{i*})^2=\frac{1}{n}(Y_{i*})^2$
3	6	298	14800.98	49.667	14800.67
5	6	428.3	30573.83	71.383	30573.48
10	6	520.6	45171.1	86.767	45170.73
15	6	543.5	49232.31	90.583	49232.04
20	6	556.3	51578.53	92.717	51578.28
25	6	558	51894.44	93	51894
Number	36	2904.7	243251.2		243249.2
Number by levels	$n=\sum_{i=1}^{I} n_i$	$Y_{**}=\sum_{i=1}^{I} Y_{i*}$	$Y_{**}^2=\sum_{i=1}^{I} Y_{i*}^2$	-	$\sum_{i=1}^{I} n_i(\overline{Y}_{i*})^2$

Table 4. The comparison between the received data of release of amizon, decametoxine and chlorhexidine

Groups	Average value at the level	25 min	20 min	15 min	10 min	5 min	3 min
	93	92.717	90.583	86.767	71.383	71.383	
3	49.667	-43.333	-43.05	-40.92	-37.1	-21.716	0
5	71.383	-21.617	-21.334	-19.2	-15.384	0	21.716
10	86.767	-6.233	-5.95	-3.816	0	15.384	37.1
15	90.583	-2.417	-2.134	0	3.816	19.2	40.916
20	92.717	-0.283	0	2.134	5.95	21.334	43.05
25	93	0	0.283	2.417	6.233	21.617	43.333

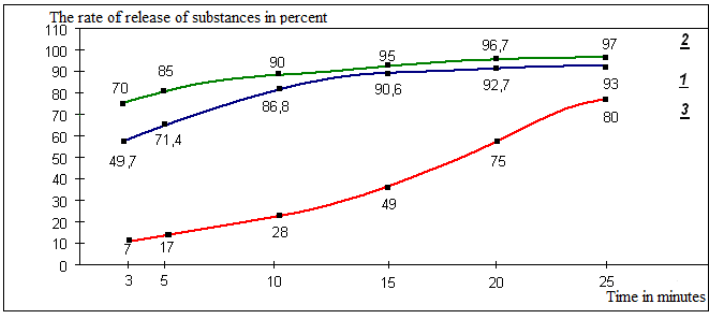

Figure 1. Dynamics of active pharmaceutical ingredients release from the composition of dental medicinal films in aqueous NaCl (0.9% solution). 1: Amizon content in the tested sample (%); 2: Decametoxine content in the tested sample (%); 3: Chlorhexidine digluconate content in the tested sample (%)

Discussion

Polymeric materials and polymeric films have found a wide application in dentistry as antimicrobial and drug delivery agents due to their excellent surfaces, appropriate mechanical and biological characteristics, affordable cost, and ease in production. Oral films as carriers of antibacterial or antimycotic API for their gradual and direct release at the target surface of the oral cavity are suitable for prolonged local effects and enhancement of treatment effectiveness (Rokaya et al., 2018; Zhang et al., 2022).

Films are basically produced from a polymeric matrix which can release the API. The degradable or nondegradable films can contain a mixture of polymers, additives, API, and a solvent which can be hydrophilic or hydrophobic (Petrescu et al., 2022).

The films for dental application can be defined as hard or soft preparations of the appropriate size and shape, consisting of a matrix, in which the active substance is incorporated, or active principle, surrounded by a membrane that controls the rate of release. This DF is used in the therapy of periodontitis for incorporation into the gum pocket, as well as for applications on the gums and mucous membrane of the mouth. Depending on the composition of the polymer matrix, dissolution of such a film occurs within 1 to 30 days, and *in vitro* research showed the possibility of release of API for about 90 days (Davtyan and Golod, 2013).

Chlorhexidine is a well-known safe agent for infection control in dentistry, able to reduce plaque formation, gingival inflammation and bleeding. The search and development of various chlorhexidine containing DF for application in dental clinic is an active research area (Heling et al.,1992; McBain et al., 2003; Varoni et al., 2012; Sawada et al., 2016; Rodriguez Zorrilla et al., 2020).

PerioChip films, containing 2.5 mg chlorhexidine gluconate, are produced in Israel, on a soluble matrix, based on hydrolyzed gelatine cross linked with glutaraldehyde (Mandlik and Jha, 2007). Up to 40% of the active substance after the introduction of the film into the gum pocket is released within the first 24 hours, the rest within 7–10 days (Davtyan and Golod, 2013). Carmellose mucoadhesive oral films incorporated modified nanocomposite enriched by chlorhexidine diacetate and digluconate inhibit the growth of *Staphylococcus spp.* and *Candida spp.* (Gajdziok et al., 2015).

The performed by us current study demonstrates, that in the manufacture of dental medicinal films on a polymeric basis of hydrophilic type it is necessary to take into account the release time of each of the active pharmaceutical ingredients, in accordance with the composition of the polymeric basis. The statistical calculations on the reliability of the release of API confirm that the time of complete release of the three active substances from the polymeric base was different, which ultimately affects the time periods of pharmacological impact of the active substance in the body.

Conclusions

Due to the lack of standardization and considering individual properties of different API in DMF, a statistical analysis was performed to assess the pharmacodynamic properties of the finished products, because during the manufacture of DMF on a polymeric basis of hydrophilic type it is necessary to take into consideration the release time for each API.

The development of polymer-based dosage forms allows the creation of new drugs with antiseptic effects for the dentistry that have a prolonged type of release of active pharmaceutical ingredients compared to other forms of local action (ointments, gels or rinsing solutions).

Declarations

Conflict of interest

There is no conflict of interest among the authors.

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Consent for publications

The author approved the manuscript for publication.

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None.

Authors' contributions

IH contributed in conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, original draft preparation, review and editing, visualization, supervision, and project administration. VH contributed in conceptualization, methodology, investigation, resources, review, and editing. RL contributed in conceptualization, original draft preparation, review, and editing.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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