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EFFECT OF HYDROPHILIZING ADDITIVES ON THE DESORPTION OF FURAZOLIDONE AND DICLOFENAC FROM SILICONE-BASED COMPOSITES

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The silicone composites, both bulk samples and films, were synthesized from hydroxyl terminated polydimethylsiloxane (PDMS-OH) and four-functional cross-linker tetraethoxysilane (TEOS) as carriers of two different drugs Furazolidone and Diclofenac sodium. To provide hydrophilic domains in the silicone elastomers, polyethylene glycol (PEG 200) and glycerol were used as hydrophylizing components. The effect of drugs'chemical structures and type of hydrophilizing components on film-forming (crosslinking-curing) duration, kinetics of drug release in vitro experiments and the composites morphology were studied. The properties of the composite films depend on both the drug's chemical structure and the type of hydrophilizing component. Both factors influence the distribution of the drugs in the composition and its morphology, which are ultimately responsible for the kinetics of the drug release and its amount.

Key words: silicone films, composite, Furazolidone, Diclofenac, PEG 200, glycerol

Fig. 4, tabl. 2, ref. 12.

1.Introduction

From the 1970s to nowadays transdermal drug delivery systems (TDDS, patches) are widely used in medicine. These systems are more comfortable for patients as compared with oral drug delivery and hypodermic injections allowing to avoid the irritation of the patient's gastrointestinal tract environment, providing prolonged drug penetration (for 1-7 days) through the skin [1].

It should be noted that not all drugs can be used in TDDS, it depends on the permeability of the drug through the outermost layer of the epidermis (*startum corneum, SC*) which is due to many factors, for example, the drug molecular weight (>500 Da), its solubility in water and oil (octanol-water partition coefficient, logPo/w), etc. [2].

From point of view of drugs distribution into the patches, the main types of transdermal patches are single-layer drug-in-adhesive, reservoir and matrix [3]. The structure of these patches is based on different polymers, which play an important role in sustaining, controlling, and targeting drug deliveries, providing mechanical strength to the formulations as well. In addition, different blends of hydrophilic and hydrophobic polymers were employed for achieving the controlled drug release behavior. Such polymers are silicones, acrylate ester/vinyl pyrrolidone copolymers, hydroxypropyl methyl cellulose (HPMC), HPMC/ Chitosan, HPMC/ PVP/ CP, lactic-co-glycolic acid (PLGA) etc [4].

Silicones or polydimethylsiloxane (PDMS) have a number of features: high oxygen permeability, biocompatibility, non-toxicity, and flexibility at low temperatures [5]. Silicon films or coatings, doped with different active substances, are extensively being applied as protective coatings on the surface of biomedical implants [6-8], in drug delivery systems due to self-adhering properties (adhesives). For this purpose, the crosslinked elastomers (networks) have been used, which are synthesized from industrially produced linear polymers, in particular, polydimethylsiloxane with terminal hydroxyl groups (PDMSOH), four-functional crosslinking agent – tetraethoxysilane (TEOS) and catalysts [9].

It is known that polysiloxanes are inherently hydrophobic; accordingly, elastomeric networks are also hydrophobic. Therefore, in order to introduce lipophilic or hydrophilic drugs into such networks, it is necessary to hydrophilize them with low and high molecular glycols (glycerol, polyethylene glycol, polyvinyl alcohol, polyethylene glycol, etc.).

Despite the big amount of research works performed, only a few drugs are still used in TDDS (approximately 17 drug molecules). These include Nitroglycerin (Nitro-Patch), Hormone (CombiPatch), Diclofenac (Flector Patch, Voltarol Gel Patch), Nicotine containing patches, which are approved by the US Food and Drug Administration (FDA). One of the features of the use of patches is the duration of their effect on the skin. The exposure time of known patches is 1-7 days, providing prolonged action of the drug.

The aim of our research work is as follows: a) to synthesize silicone composites based on hydroxyl terminated polydimethylsiloxane (PDMS-OH), as carriers of two different drugs Furazolidone and Diclofenac sodium salt, which have different chemical structures, physiological effects, and different logPo/w.; b) to study the effect of drugs' chemical structures and

type of hydrophilizing component on film-forming (crosslinking-curing) duration, kinetics of drug release *in vitro* experiments and percentage of swelling.

Furazolidon (Frz) antimicrobial drug, commonly used via oral administration, as a tablet, as a suspension, it also can be used as a spray, creams for external use for infected wounds and burns, as well as an antimicrobial agent for surgical sutures [10]. To our knowledge, furazolidon-containing patches or films are unknown so far.

Diclofenac sodium salt (Dcf) NSAID possesses anti-inflammatory, analgesic, and antipyretic properties through inhibition of COX isoenzymes and blockade of prostaglandin synthesis [11]. Diclofenac-containing patches are already available (for example, Voltarol 140 *mg* Medicated Plaster), but they have a complex composition containing two different types of polymers, butylated methacrylate copolymer and acrylate vinyl acetate copolymers, as well as several additives imparting the drug-containing layer, adhesive and membrane properties of the patch.

For the first time, we have synthesized and studied Furazolidone-containing (Frz) films, which are expected to be used for the treatment of external wounds. Also, patches with Diclofenac (Dcf) have been synthesized, which have a simpler composition as compared with the known ones.

2.Results and discussions

The elastomers films as crosslinked networks are synthesized from PDMSOH and TEOS, aminopropyl terminated polydimethylsiloxane ($PDMSNH_2$) is used as catalyst. In Fig.1 the reaction of synthesis and the formed network is schematically illustrated.

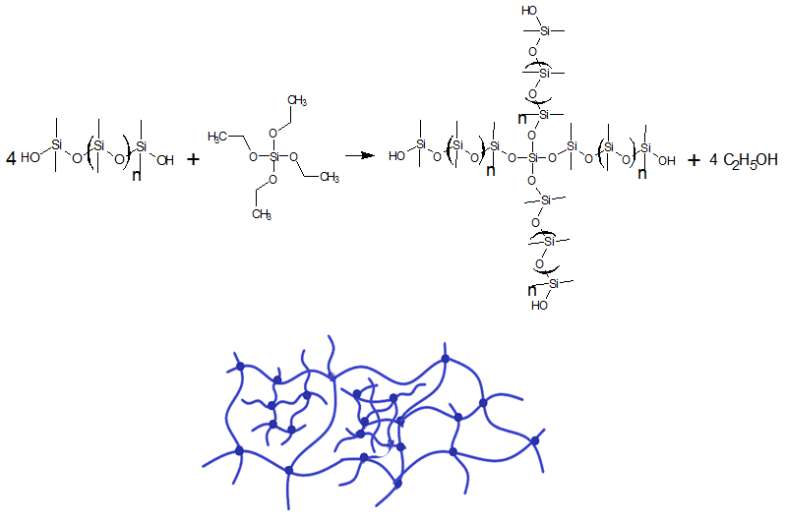


Fig. 1: Silicone elastomer formation:

A - reaction of synthesis (starting point); B - the formed network.

Recently we have found that crosslinking processes occur in different ways depending on sample volume: bulk or film forms. That is why we compare the kinetics of drugs release both from bulk and film samples.

Drugs chemical structures did not affect on cross-linking time of the matrixes (Frz -0, Dcf-0) - the matrices with both drugs were cross-linked and cured within 3-4 days. However, the percent of drugs release is slightly higher for Dcf (after 168 hours from matrix desorbed 15% Dcf and 3% Frz (Fig. 2a). At this, the percent of matrix swelling is higher in the case of Dcf, which may be a reason for the 15% drug release. The sample with Frz practically does not swell (Fig.2b).

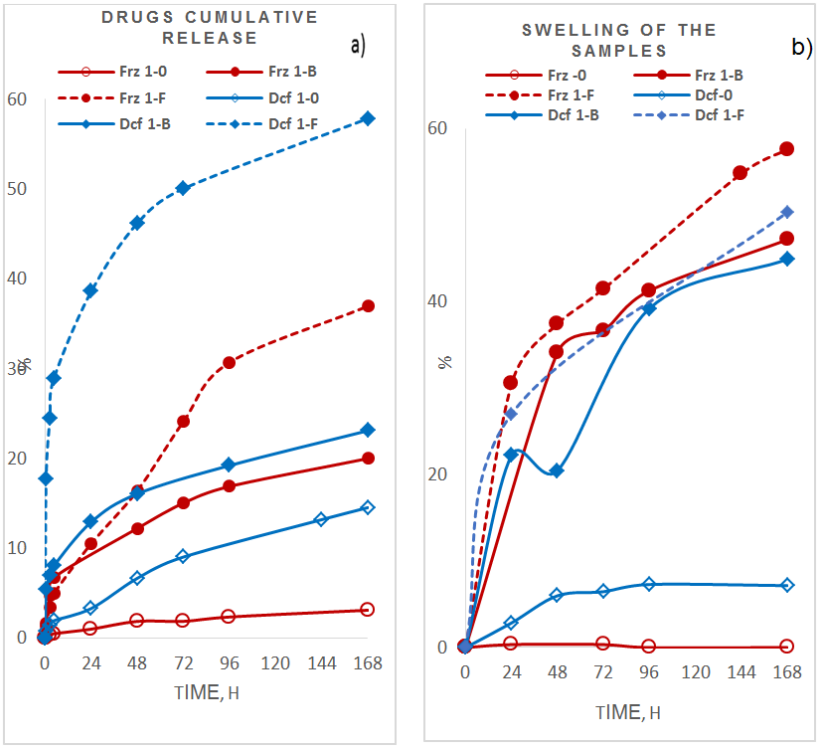


Fig. 2. a). Desorption kinetics of Frz and Dcf from matrixes (Frz-0, Dcf-0), bulk forms (Frz 1-B, Dcf 1-B) and films (Frz 1-F, Dcf 1-F);
b). Percent of swelling Frz and Dcf containing matrices (Frz-0, Dcf-0), bulk forms (Frz 1-B, Dcf 1-B) and films (Frz 1-F, Dcf 1-F).

For hydrophilization of the hydrophobic silicone matrices polyethylenglycol PEG 200 and glycerol were used in content of 11 and 23%, respectively. Their effect on the drugs release was examined. In Fig. 2 the kinetic curves for Dcf and Frz release from bulk samples and films containing PEG 200 are

provided. The presence of PEG 200 increases drugs release from both the bulk sample and the films, and this increase is more significant in case of film with Dcf. The percentage of swelling also increases for all samples with PEG, but almost to the same extent, regardless of the form of the samples and the drug. Judging by these data, the increase in drug release due to the presence of PEG is associated with the specific distribution of drugs in the composite, and not with an increase in the degree of swelling.

Based on the obtained results we synthesized new samples (films) in which the amount of PEG is 37%: film with Dcf was not cured, with Frz cured within 2 hours. The release of Frz from the sample after 168 hours is 57%.

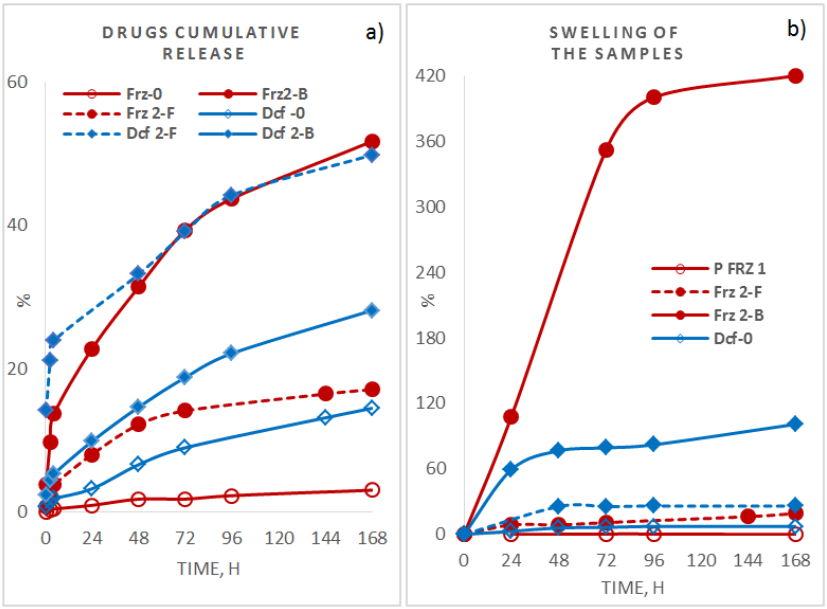


Fig.3. a).Desorption kinetics of Frz and Dcf from matrixes (Frz-0, Dcf-0), bulk forms (Frz 2-B, Dcf 2-B) and films (Frz 2-F, Dcf 2-F).
b).Swelling of Frz and Dcf containing matrices (Frz-0, Dcf-0), bulk forms (Frz 2-B, Dcf 2-B) and films (Frz 2-F, Dcf 2-F).

The presence of glycerol (23%) also provides an increase in the drugs release from both the bulk sample and the films (Fig.3a), but contrary to PEG 200, the release of Frz is sharply increased from bulk samples, but coincides with release Dcf from film, and the release of Frz from the film increases only slightly. The percentage of swelling is also sharply increased for bulk samples of Frz 2-B, Dcf 2-B (Fig.3b).

In Table 1 summarizes cross-linking time, percentage of drug release, and percentage of swelling in 168 hours.

Table 1

Cross-linking time, percentage of drug release and percentage of swelling in 168 hours.

PEG	*Dcf*		*Frz*	
	Bulk	*Film*	*Bulk*	*Film*
Cross-linking and curing duration	1 day	10 min	3 days	1 day
Drug release, %	23	58	20	37
Swelling, %	45	55	45	60
Glycerol				
Cross-linking and curing duration	4 days	4 days	2 days	1 day
Drug release, %	28	50	50	17
Swelling, %	50	23	360	23

Thus, an introduction of PEG into the matrices provides an increase in both drugs' release as compared to the matrices; for both drugs, the release from the film is higher than from the bulk samples (but Dcf > Frz), with the same swelling values.

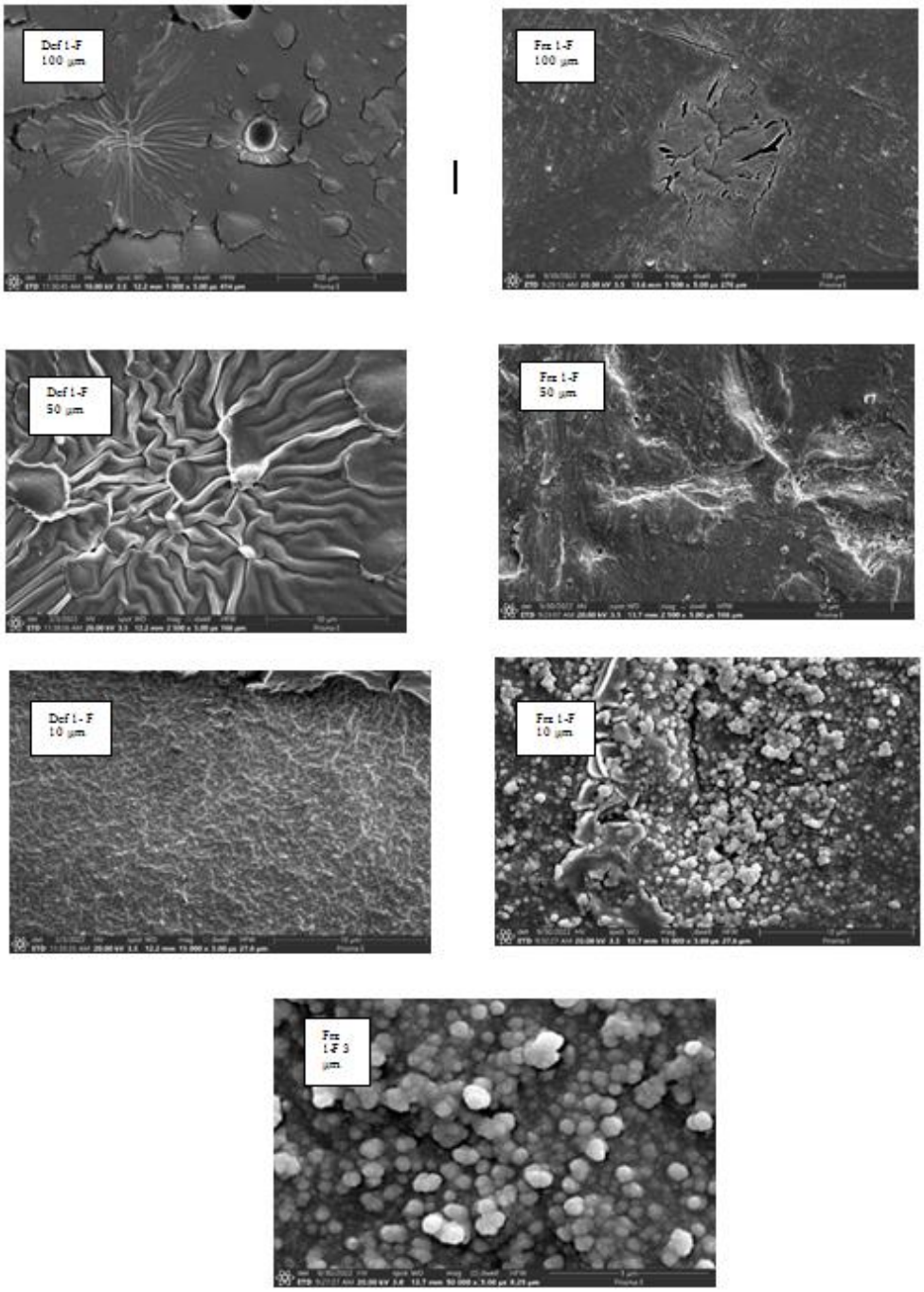
An introduction of glycerol into the matrixes also provides in general an increase in both drugs' release as compared to the matrices. However, contrary to PEG, in this case for both drugs, their release from the film and the bulk forms is different: Dcf release from the film is 2 times higher than from the bulk sample, although the swelling of the film is 2 times less. Frz release from the bulk sample is 3 times higher than from film, with very high swelling values.

Our studies have shown that glycerol in the composites under study is in a “free” state (TG-MS data, not published). As for PEG – it can participate in the formation of a polymer network like PDMSOH due to the end hydroxyl grou ps [12]. Therefore, these two hydrophilizing components can form composites distinguished by their morphology.

In order to understand whether the difference in the amount of drugs desorption and swelling is caused by the morphology of the synthesized films, we have carried out SEM studies of the samples Frz 1-F and Dcf 1-F. Different morphology may be caused by different distributions of drugs in the components of the composites.

SEM images showed a different distribution of films morphology (Fig. 4).

Fig.4



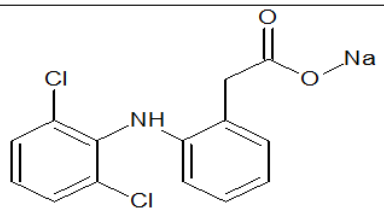
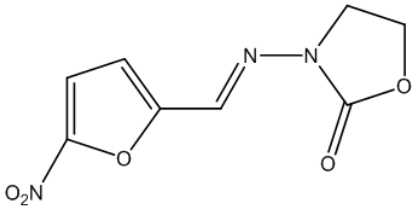
In case of the Dcf 1-F film inhomogeneities in the form of circles of 5-30 micron size and structured areas are observed. It is possible that the drug is surrounded by PEG, while the Frz 1-F film Frz is more evenly distributed throughout the composite, creating particles that have sizes 0.1-0.53 *micron*.

3.Experimental

Chemicals. Hydroxy-terminated PDMS (HO-PDMS, 1800-2200cSt,~36000 *g/mol,* Gelest), aminopropyl-terminated PDMS ($PDMSNH_2$, 10-15 cSt, 850-900 *g/mol*, (Gelest), tetraethoxysilane (TEOS,99,999% Aldrich), Polyethylene glycol (PEG 200, Aldrich) and glycerol (Aldrich) as hydrophilizing agents, Furazolidone (Aldrich), Diclofenac sodium salt (Aldrich) (table 2) were used as received.

Table 2

The drugs structure

Drug name	Chemical structure	MW	Log P o/w
Diclofenac sodium salt		318.13	4.49
Furazolidone		225.16	-0.05

Samples preparation

The following abbreviations are used to designate samples in the text:

Matrices - cured bulk cylinders with 0.5-0.6 cm height and 2.5 *cm* in diameter, containing Diclofenac or Furazolidone (Dcf -0, Frz -0).

Composites – a) bulk cylinders containing either PEG-200 (1) or glycerol (2), and drugs (named as Frz1-B, Dcf 1-B, Frz 2-B, Dcf 2-B). b) The films F- were synthesized with the same composition and sequence of composites, only after stirring, the liquid mixture was poured onto the surface of the plastic Petri dishes. The resulting films have diameter of 4.5cm and 0.3-0.5 *mm* thickness, containing either PEG-200 (1) or glycerol (2), and drugs (named as Frz 1- F, Dcf 1-F, Frz 2 -F, Dcf 2 –F).

Matrices. PDMSOH (1.8g/0.05mmol) was mixed with a cross-linker (TEOS 0.07g/0.34 *mmol*) and catalyst (aminopropyl terminated $PDMSNH_2$ 0.07g/0.078 *mmol*) [5,9] mixed for 1-2 minutes, and drugs were added (Dcf.0.06g/0.188 *mmol* or Frz.0.06g/0,267 *mmol*) to the mixture, stirred for 8-

10 minutes, and the matrices were allowed to cure at room temperature.

Composites. Polyethylene glycol 200 (0.25g/6.5mmol) or glycerol (0.6g) were mixed with (1.8 *g*/ 0.05 *mmol*) PDMSOH. After 1 min of stirring, an emulsion-like substance was obtained, which was mixed then with cross-linker (0.07g/0.34 *mmol*), catalyst (0.07g/0.078 *mmol*) and drug (Dcf.0.06 *g*/ 0.188 *mmol*) or (Frz.0.06 g/ 0.267 *mmol*) in the same subsequence as mentioned above. After stirring for 8-10 minutes, the composites were allowed to cure at room temperature (Table 1).

UV spectroscopy. The calibration curve of Furazolidone, Diclofenac sodium salt plotted using a 0.9 % NaCl solution. The drugs were analyzed spectrophotometrically (Cary 100 UV-Vis Spectrophotometer) and the curves were found to be linear in the range of 5-1.25 *mg*/ 100 *ml* and the regression coefficients were found to be 1.71 at 260 *nm* in case of Furazolidone,1.54 at 275 *nm* in case of Diclofenac.

In vitro drugs release was determined by UV spectrophotometry. Three samples of 0.03-0.04 *g* of the bulk or films samples were placed in Eppendorf tubes and filled with 2 *ml* of saline (0.9 % NaCl). After a specific time, the liquid was taken away and the drugs desorption was determined. The fresh portion of 0.9 % NaCl solution was added into the test tubes. The percentage of released drugs was calculated as an average of 3 measurements, relative to the amount of DCF in the sample. During the entire time of the drugs release tests, the samples were kept in a thermostat at 37-38 *°C*.

Measurements of the amount of desorbed glycerol from composites under study were performed according to GOST 7482-96 and are in the range of 2-4 %.

Swelling. The swelling of the samples was measured in following way - three small pieces (0.7-0.1 *g*) of each composite were weighed, 5 ml 0.9 % NaCl was added in each sample at a temperature of 37 ^{o}C. After 24 hours, the samples were taken away, dried with paper, and weighed. Then the new portion of the fresh solution was added. The swelling was determined by the equation given below:

$$\text{swelling ratio } = \frac{W - W_0}{W_0} * 100\%$$

Where Wo and W are the weights of silicon elastomer before and after swelling, respectively.

SEM images of the powders were obtained using Prisma E SEM (ThermoFisher) (in the Institute of Chemical Physics after A.B. Nalbandyan NAS RA):

Conclusions

The properties of composite films based on PDMSOH and TEOS depend on both the drug's chemical structure and the type of hydrophilizing

component. Both factors influence the distribution of drugs in the components of the composites and form different morphologies, which are ultimately responsible for the kinetics of the drug release and its amount.

Depending on the chemical structure of the drug, it is possible to choose the hydrophilizing agent that will ensure a short cross-linking-curing duration and controlled release of the drug desorption. But in order to achieve all this, it is necessary to carry out more extensive studies, collect statistical data, and to find out which parameters of the drugs are responsible for producing the above-mentioned results.

ՀԻԴՐՈՖԻԼԱՑՆՈՂ ԿՈՄՊՈՆԵՆՏՆԵՐԻ ԱԶԴԵՑՈՒԹՅՈՒՆԸ ՍԻԼԻԿՈՆԱՅԻՆ ՀԻՄՔՈՎ ԿՈՄՊՈԶԻՏՆԵՐԻՑ ՖՈՒՐԱԶՈԼԻԴՈՆԻ ԵՎ ԴԻԿԼՈՖԵՆԱԿԻ ԱՐՏԱԶԱՏՄԱՆ ՔԱՆԱԿՈՒԹՅԱՆ ՎՐԱ

Մ.Լ. ԱԹԱԲԵԿՅԱՆ

Հիդրօքսիլ ծայրային խմբով պոլիդիմեթիլսիլօքսանների և քառֆունկցիոնալ կարող ագենտ տետրաէթօքսիսիլանի հիման վրա սինթեզվել են սիլիկոնային կոմպոզիտներ (մեծ կտորներ և թաղանթներ)՝ որպես երկու տարբեր դեղերի՝ ֆուրազոլիդոնի և դիկլոֆենակի կրիչներ: Սիլիկոնային էլաստոմերներում հիդրոֆիլ դոմենների առաջացումն ապահովելու համար որպես հիդրոֆիլացնող կոմպոնենտներ օգտագործվել են գլիցերին և պրոպիլեն գլիկոլ200: In vitro էքսպերիմենտներով ուսումնասիրվել է դեղերի քիմիական կառուցվածքի և հիդրոֆիլացնող կոմպոնենտների ազդեցությունը թաղանթների առաջացման (կարման) ժամանակի և կոմպոզիտների մորֆոլոգիայի վրա:

Կոմպոզիտային թաղանթների հատկությունները կախված են և՛ դեղի քիմիական կառուցվածքից, և՛ հիդրոֆիլացնող ագենտի բնույթից: Այս երկու գործոններն էլ ազդում են կոմպոզիտների բաղադրիչներում դեղերի բաշխման վրա և ձևավորում են տարբեր մորֆոլոգիաներ, որոնք, ի վերջո, պատասխանատու են դեղամիջոցի թողարկման կինետիկայի և քանակի համար:

ВЛИЯНИЕ ГИДРОФИЛИЗИРУЮШИХ ДОБАВОК НА ДЕСОРБЦИЮ ДИКЛОФЕНАКА И ФУРАЗОЛИДОНА ИЗ КОМПОЗИТОВ НА СИЛИКОНОВОЙ ОСНОВЕ

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Синтезированы силиконовые композиты (в виде объемных образцов и пленок) на основе полидиметилсилоксана с концевыми гироксильными группами и тетраэтоксисилана, содержащие два разных лекарства (фуразолидон или диклофенак), а также полиэтиленгликоль или глицерин в качестве гидрофилизирующих компо-

нентов (ГК). Исследовано влияние лекарства и типа ГК на время образования сшитых образцов, их морфологию, и кинетику выделения лекарства в экспериментах *in vitro*. Показано, что свойства композитных пленок зависят как от химической структуры лекарства, так и от типа ГК. Оба фактора влияют на распределение лекарства в компонентах композита и формируют различную морфологию, которая определяет количество и кинетику выделения лекарства.

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