Original Article

Rationale for Choosing the Basis for Early Coverage

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Abstract

Treatment of wounds of various genesis (surgical, purulent, gunshot wounds) remains a pressing problem today. Along with the improvement of treatment methods, the methods of combat operations are also being improved. At the same time, the change of approaches to traditional methods of wound treatment promotes the growth of resistant forms of microorganisms. All these complicate the treatment of wounds and the course of the wound process. For the treatment of wounds using a wide arsenal of drugs (antibiotics, local antiseptics) in various dosage forms (ointments, sprays, powders, solutions). Traditionally, the main elements of complex local therapy of wounds are antimicrobial drugs on a hydrophilic basis, in particular on a polyethylene glycol base with high osmotic activity. Therefore, the development of combined drugs with prolonged action with osmotic activity, which can absorb exudate but does not lead to the formation of a dry crust on the wound surface, is relevant.

Keywords: Base, Wounds, Excipients, Diffusion, Polymer mass

Introduction

The development of polymer chemistry has given impetus to their widespread use as a depot for drug substances in certain dosage forms: drug films, hydrogels, and gels [1, 2]. They can be considered as transdermal therapeutic systems [3, 4]. An important problem for the local treatment of wounds is to achieve a therapeutic effect of Active Pharmaceutical Ingredients (API) impregnated in polymeric media to prolong their action. After all, the local method of wound healing allows ensuring constant contact of API with the wound surface. Prolongers of API in the dosage form are polymers [5, 6].

Their main function is, on the one hand, the creation of a depot, and on the other - a modified release of API in quantities that are sufficient for therapeutic action over some time. This is achieved by creating hydrogels with a regulated structure and purposefully changed properties. Such properties are attractive, including sparsely crosslinked polymer hydrogels with a high degree of swelling.

Materials and Methods

We are interested in creating wound dressings that have antimicrobial, anti-inflammatory, anesthetic effect with sorption activity.

The scientific development of the drug is planned to be carried out in the areas that provide for the creation of medicinal films and hydrocolloids that will be activated under the action of saline (pure wound) and exudate (on the battlefield).

In the first case (drug film) we will comply with all the conditions for the creation of a polymer-drug film following the developments of the school of prof. L. Davtian [7, 8]. In this case, it is necessary to take into account the kinetics (in vitro, in vivo) of the release of API. Since the drug is planned to be used for the treatment of wounds, a prerequisite will be the design of the base so that in the first place the anesthetic is released.

In the second case - hydrocolloids - we will consider the issue of alternating freezing-thawing of the polymer composition [9]. The authors [10-12] substantiated the production of hydrocolloids by the method of ɤ-irradiation of a polymer solution. However, this method is expensive. Therefore, we have chosen the method of freezing-thawing.

One of the main requirements for the developed drugs is atraumatic. In our case, the drugs will not injure the wound surface, as they are biosoluble.

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Development of a Polymer Base

When developing a polymer matrix, it is necessary to take into account such indicators as physicochemical and physicomechanical properties of the system, the creation of a depot for API in the system, the selection of activators of release and absorption of API. We consider hydrophilic polymers as polymeric materials. This is because the rate of release of polar APIs from the matrix increases with increasing polarity of the polymer, which confirms the prospects for the use of a hydrophilic matrix. On the hydrophilic basis, the solubility of API is much higher than when using non-polar compositions, while increasing the diffusion coefficient and the partition coefficient between the membrane and the skin.

To create a scientifically and practically justified optimal composition with given physical, chemical, and technological properties, we decided to take as a basis for the development of polymer compositions the work of prof. L. Davtian. Therefore, the polymer base was obtained by combining polymer solutions with the subsequent addition of plasticizers. Polymer solutions were prepared in purified water. The addition of ethyl alcohol (to the final product) depends on the technological characteristics of the resulting composition. Thanks to ethyl alcohol, it is possible to regulate the viscosity of a solution of polymer and reduce the time of drying of finished goods.

Taking into account the medical and biological requirements for the composition under development, tack, biocompatibility, solubility - we selected natural polymers of sodium carboxymeylcellulose (Na-CMC) and carboxymeylcellulose (CMC). These polymers are widely used in medical practice as a gelling agent, stabilizer, and the like. As a plasticizer, we used Propylene Glycol (PG), glycerin, and PEG 400. The choice of concentrations of both polymers and plasticizers is based on experimental data [7]: for polymers 3 - 10%, plasticizers - 5 - 35%. In [7, 8] it is shown that the composition of one polymer can provide certain physical, mechanical, and technological characteristics of the finished product, but it is optimal to use in the composition of 2 or more polymers.

Results and Discussion

The composition and technological characteristics of the model composition are given in **Table 1**.

Table 1. Composition and Technological Characteristics of Model Compositions

№ Compound	The Composition of the Composition	Content of Components		Description
		g	%	
1	Solution Na-CMC 3% Solution CMC 3% PG PEG 400	10,0 10,0 2,5 2,5	40,0 40,0 10,0 10,0	Viscous, dense, stretching mass. Lots of air bubbles. The consistency is unsatisfactory. Poorly applied to the substrate.
2	Solution Na-CMC 5% Solution CMC 5% PG Glycerin	10,0 10,0 2,5 2,5	40,0 40,0 10,0 10,0	Viscous, dense, stretching mass. Lots of air bubbles. The consistency is unsatisfactory. Poorly applied to the substrate.
3	Solution Na-CMC 10 % Solution Na-CMC 10 % PEG 400 Glycerin	10,0 10,0 2,5 2,5	40,0 40,0 10,0 10,0	Viscous, dense, stretching mass. Lots of air bubbles. The consistency is unsatisfactory. Poorly applied to the substrate.
4.	Solution Na-CMC 15% Solution Na-CMC 15% PG Glycerin	10,0 10,0 5,0 5,0	33,3 33,3 16,6 16,6	Viscous mass. Lots of air bubbles. The consistency is not satisfactory. Poorly applied to the substrate.
5	Solution Na-CMC 10% Розчин КМЦ 10% PG	10,0 10,0 10,0	33,3 33,3 33,3	Viscous, plastic mass. There are air bubbles. The consistency is satisfactory. It is well applied on a substrate.
6	Solution Na-CMC 10% Solution Na-CMC 10% PG	15,0 15,0 15,0	33,3 33,3 33,3	Viscous, plastic mass. There are air bubbles. The consistency is satisfactory. It is well applied on a substrate.

7	Solution Na-CMC 10% Solution Na-CMC 10% PG	3,0 7,0 10,0	15,0 35,0 50,0	The mass is viscous, the consistency is more satisfactory. Lots of air bubbles. It is well applied on a substrate
8	Solution Na-CMC 5% Solution Na-CMC 10% PG	10,0 10,0 10,0	33,3 33,3 33,3	The mass is viscous, stretches sticky threads. There are air bubbles. The consistency is more satisfactory. It is well applied on a substrate.
9	Solution Na-CMC 10% Solution Na-CMC 5% PG	10,0 10,0 10,0	33,3 33,3 33,3	The mass is viscous, stretches sticky threads. There are air bubbles. The consistency is more satisfactory. It is well applied on a substrate
10	Solution Na-CMC 10% Solution Na-CMC 10% PG Ethyl alcohol 96 %	10,0 10,0 10,0 5,0	28,6 28,6 28,6 14,3	Very thick, viscous mass. The consistency is unsatisfactory. Application on the substrate is complicated.

Analysis of the composition 1-4 proves that the compositions are not optimal in their consistency. In our opinion, this is due to the unbalanced proportion between polymers and plasticizers. The description of compositions 5 and 6 is satisfactory: plastic, viscous mass, and air bubbles, that well applied to the substrate.

This is due to the optimal ratio of polymers and plasticizers. This hypothesis is confirmed by analyzing the composition of samples 7 - 9. The latter differ from each other and the composition 5 and 6 not only the ratio of polymer solutions in the base but also the concentration. At the same time, there is an increase in air bubbles, changes in the homogeneity and plasticity of the mass. That is, the optimal, from the point of view of technological indicators, is the composition of compositions 5 and 6. Subsequently, we introduced the composition of composition 5 ethyl alcohol 96% in the amount of 14.3%. Deterioration of characteristics of weight is observed, in particular, thanks to an increase in viscosity of weight the process of drawing on a substrate worsens. In this regard, we selected model samples 5 and 6.

The solution of the composition entering the stage of formation (application to the substrate) must not contain mechanical impurities and particles of undissolved polymer, as well as air bubbles that degrade the quality of the finished product. Therefore, for further formation of the composition, model samples were submitted to the stage of deaeration. In [7] the influence of centrifugation time on the quality of deaeration of samples was studied: centrifugation of polymer solutions at 3000 rpm for 20 - 25 min.

Deaeration of the model compositions was performed at a temperature of 15 – 25^{oC} for some time. The research results are given in **Table 2**.

Table 2. Deaeration of Compositions 5 and 6 at a Temperature of 15 to 25 ^{oC}

Deaeration Time, min	Description of the Composition	
	№ 5	№ 6
5	The mass is viscous and sticky, there are some air bubbles	
10	The mass is transparent, viscous and sticky, homogeneous, without air bubbles	The mass is viscous and sticky, there are some air bubbles
15	Not checked	The mass is transparent, viscous and sticky, homogeneous, there are individual air bubbles

Thus, the obtained results indicate that the deaeration time depends not only on the amount of mass of the base but also on the quantitative characteristics of the structuring substances and the plasticizer. Therefore, according to the set of technological characteristics, it was decided to choose a model composition of composition №5 for further development. The optimal time for deaeration of the model composition at a temperature of 15-25^{0}C is 5-10 minutes.

In the next stage of research, the composition was applied to the substrate to determine further physicochemical and technological characteristics.

One of the technological parameters that determine the quality of the polymer base is the homogeneity of mixing and uniformity of the thickness of the layer of polymer mass applied to the substrate. Due to the heterogeneity of mixing the composition may form an uneven layer on the substrates, due to which some parts of the same sample will have different physical and mechanical characteristics. Therefore, the guarantee of product quality is the homogeneity of mixing, which is achieved by mixing the polymer mass with an anchor stirrer for 5 to 10 minutes.

The technological indicators also include the thickness of the layer. The thickness of a layer is connected also with an indicator of homogeneity of mixing. Only a homogeneous polymer solution can ensure uniformity of the layer thickness. When obtaining dental drug films, the authors of [7, 8] substantiated the thickness of the film layer - 0.35 mm. It is proved that with increasing layer thickness the numerical indicators of their physical and mechanical characteristics increase. In particular, increasing the film layer thickness from 0.25 mm to 0.45 mm leads to an increase in the relative elongation from 83.2% to 99%, respectively.

To substantiate the optimal layer thickness, the diffusion of drugs from them at different layer thicknesses was studied.

It is known that the diffusion of drugs from the base depends on the thickness of the base layer applied to the substrate. In order to establish the optimal layer thickness, we studied the dependence of drug release from the base **(Figure 1)**. We introduced 0.1% ceftriaxone into the base. This concentration is due to the presence on the market of Ukraine of the drug Oflocaine (produced by JSC HFZ "Pharmaceutical Company" Darnytsia ", Ukraine) with a concentration of ofloxacin 0.1%.

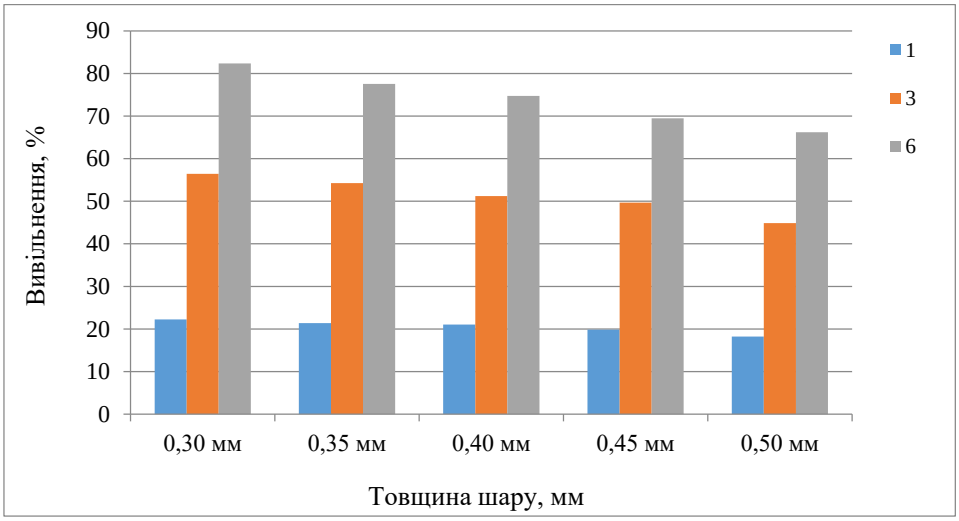

Figure 1. Diffusion of Ceftriaxone from the Layer Thickness after 1, 3, and 6 Hours

As can be seen from **Figure 1** with increasing thickness of the polymer base layer decreases the release of ceftriaxone. The substance diffuses most slowly from the base with a layer thickness of 0.50 mm, and faster - from films with a layer thickness of 0.30 mm. Thus, for 6 hours the diffusion of ceftriaxone from the base with a thickness of 0.30 mm averages 82.35%, while at a thickness of 0.35 mm - 77.56%, at a thickness of 0.40 mm - 74.75%, 0.45 mm - 69.48%, and at a thickness of 0.50 mm - 66.21% of the active substance. Therefore, increasing the thickness of the layer leads to a decrease in the release of ceftriaxone - a prolongation of the therapeutic effect.

We selected 0.40 mm for the optimal layer thickness. In the future, this indicator will be substantiated by physical and mechanical studies. In order to develop the optimal technology for obtaining polymer mass and establish technological indicators - mixing uniformity (mixing duration), deaeration quality (centrifugation duration), layer thickness - we studied the indicators of physical and mechanical properties, including tensile strength and elongation.

For this purpose, a series of polymer mass was modeled taking into account the above technological factors. **Table 3** shows the indicators of physical and mechanical properties of the polymer base depending on technological factors: model samples 1-5 centrifugation time 5-10 min at 3000 rpm, stirring homogeneity 15 min at 36 rpm, anchor stirrer, layer thickness 0.40 mm; model samples 6 and 7 - centrifugation time 15-20 min at 3000 rpm, stirring homogeneity 15 min at 50 rpm, anchor stirrer, layer thickness 0.50 mm; model samples 8-10 - centrifugation time 5-10 min at 3000 rpm, stirring homogeneity 15 min at 36 rpm, anchor stirrer, layer thickness 0.35 mm.

In the development of this dosage form, the main physical and mechanical indicator is the relative elongation and braking force. This is because the adhesive mass applied to the substrate must have elasticity.

Table 3. Physico-mechanical Properties of the Polymer Base (P = 95%; t = 2.78; $\bar{X}$; n = 5)

№ p/p	Series	Tensile Strength, kgf / cm^2	Relative Elongation,%
1	060219	80,4±0,8	90,2±0,1
2	130219	80,6±0,3	90,4±0,2
3	060319	81,1±0,3	91,3±0,1

4	280319	81,2±0,2	91,1±0,1
5	040419	81,1±0,3	91,4±0,3
6	060219	71,2±0,3	82,5±0,2
7	130219	70,4±0,2	81,8±0,1
8	060219	79,1±0,2	87,3±0,3
9	130219	79,4±0,1	89,4±0,1

The elasticity of the mass provides the application of the drug not only on the substrate but also on the wound surface. Besides, due to the elasticity, the drug can be applied to the substrate. Indicators of physical and mechanical properties - tensile strength and elongation depend on such technological characteristics as homogeneity, uniformity of application on the substrate, and the absence of air bubbles.

The latter reduces the numerical indicators of physical and mechanical characteristics due to the formation of voids in the mass, which leads to changes in the relative elongation and tensile strength. The higher the figures are given in **Table 3**, the better the polymer mass applied to the substrate. Therefore, after obtaining a homogeneous mass, it is necessary to deaerate the air bubbles by centrifugation (№ 1-5) at 3000 rpm for 5-10 minutes.

Next, we studied the ease of applying the polymer mass on the substrate **(Table 4)**.

Table 4. Technological Parameters for Applying the Polymer Mass

Technological Parameters of the Process	Characteristic of the Table
Samples **1-5**	
Application at room temperature	The mass is applied well, evenly
Drying at room temperature for 24 hours	Drying is uniform. Adhesion is sufficient.
Drying at a temperature of (50-60°C) for 2 hours	Drying is uniform. Adhesion is sufficient.
Samples **6-7**	
Application at room temperature	The mass is applied well, evenly.
Drying at room temperature for 24 hours	Uneven drying; There is mass adhesion.
Drying at a temperature of (50-60°C) for 2 hours	Drying is uniform. Adhesion is sufficient.
Samples **8-9**	
Application at room temperature	The mass is applied well, evenly.
Drying at room temperature for 24 hours	Drying is uniform. Adhesion is sufficient.
Drying at a temperature of (50-60°C) for 2 hours	Drying is uniform. Adhesion is sufficient.

The results of **Table 4** show that the drying process is affected by the thickness of the layer. It is proved that samples 1-5 have a uniform, adhesive layer and can be used in further studies.

The main technical indicators are the layer thickness of 0.40 mm, centrifugation time 5-10 min at 3000 rpm, homogeneity: stirring 15 min at 36 rpm, anchor stirrer. It was found experimentally that to obtain a layer thickness of 0.40 mm it is necessary to apply 0.03 g of sample per 1 cm2 of the substrate. In further studies to obtain a "crosslinked" polymer, we will transfer the finished mass before the drying stage to the freezing stage (for 12-24 h), followed by thawing. Hypothetically, the drying temperature of the polymer mass of 50-60°C can level the process of "crosslinking" of the polymer.

Therefore, the drying process will be carried out at room temperature.

Conclusion

Technological characteristics, physical and mechanical parameters of model compositions are studied. It is proved that the main technical indicators are the thickness of the polymer mass layer (0.40 mm), centrifugation time (5-10 min at 3000 rpm), homogeneity (stirring for 15 min at 36 rpm, anchor stirrer). It was found experimentally that to obtain a layer thickness of 0.40 mm it is necessary to apply 0.03 g of sample per 1 cm2 of the substrate.

The prospect of this study is to further study the freezing process on the physical and mechanical properties of the polymer mass.

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