Annals of Pharmacy Practice and Pharmacotherapy
2021, Volume 1, Page No: 9-15
Copyright CC BY-NC-SA 4.0
Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Justifying the Foundation for Early Coverage Decisions

Shmatenko Oleksandr[1], Kazmirchuk Anatolii[1], Solomennyy Andrii[1], Syrota Petro[1], Plieshkova Olga[1], Davtian Lena[1]*

[1]Ukrainian Military Medical Academy, Kyiv, Ukraine.

***E-mail** ✉ alinasposts@gmail.com

Received: 19 January 2021; **Revised:** 28 March 2021; **Accepted:** 02 April 2021

ABSTRACT

The management of wounds from many causes, such as surgical, purulent, or gunshot wounds, is still a major issue in modern times. Not only are treatment procedures advancing, but combat operations techniques have also been enhanced. The development of resistant microbes is also encouraged by the shift away from conventional wound care techniques. All of these make it more difficult to treat wounds and monitor their progression. This research aims to investigate the effects of the freezing procedure on the mechanical and physical characteristics of the polymer mass. An analysis of the mechanical, physical, and technical properties of the model compositions reveals that the thickness of the polymer mass layer (0.40 mm), centrifugation time (5–10 min at 3000 rpm), and homogeneity (stirring for 15 minutes at 36 rpm with an anchor stirrer) are the primary technical indicators. According to experimental studies, 0.03 g of sample must be applied for every 1 cm² of substrate to achieve a layer thickness of 0.40 mm. A broad range of medications (antibiotics, local antiseptics) in different dose forms (ointments, sprays, powders, solutions) for the treatment of wounds. Antimicrobial medications based on hydrophilic bases, namely polyethylene glycol bases with significant osmotic action, have historically been the primary components of complicated local treatment for wounds. Consequently, the creation of combination medications with osmotic activity and extended action that can absorb exudate without causing a dry crust to form on the surface of the wound is pertinent.

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

How to Cite This Article: Oleksandr Sh, Anatolii K, Andrii S, Petro S, Olga P, Lena D. Justifying the Foundation for Early Coverage Decisions. Ann Pharm Pract Pharmacother. 2021;1:9-15.

Introduction

As polymer chemistry has advanced, they have become increasingly popular as a depot for medicinal compounds in specific dosage forms, such as gels, hydrogels, and drug films [1, 2]. Such systems can be regarded as transdermal therapeutics [3, 4]. A significant challenge in the local management of injury is to extend the therapeutic impact of active pharmaceutical ingredients (APIs) by impregnating them in a polymeric medium. It is, after all, possible to guarantee continuous contact between the API and the wound surface using the local approach to wound healing. Polymers extend API in the dose form [5, 6].

The establishment of a depot and the subsequent discharge of API in amounts enough for therapeutic activity over a while are their primary functions. This is accomplished by producing hydrogels with controlled structure and intentionally altered characteristics. These characteristics are appealing, such as hydrogels made of sparsely crosslinked polymers that have a great level of swelling. This research aims to investigate the effects of the freezing procedure on the mechanical and physical characteristics of the polymer mass.

Materials and Methods

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

© 2021 Annals of Pharmacy Practice and Pharmacotherapy

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.

Development of a polymer base

While creating a polymer matrix, it is important to consider indicators including the system's physicochemical and physicomechanical characteristics, the establishment of an API depot within the system, and the choice of API release and absorption activators. Hydrophilic polymers are regarded as polymeric compounds. This is because the potential for using a hydrophilic matrix is confirmed by the fact that the rate at which polar APIs are released from the matrix rises as the polymer's polarity improves. API is far more soluble on a hydrophilic foundation than when non-polar formulations are used, and the diffusion and partition coefficients between the membrane and the skin are also increased.

We decided to use Prof. L. Davtian's work as a foundation for the creation of polymer compositions to produce an ideal composition with specified physical, chemical, and technical attributes that are both scientifically and practically justifiable. Polymer solutions were thus combined, and plasticizers were then added to create the polymer base. The water used to produce the polymer solutions was purified. Depending on the technical features of the final formulation, ethyl alcohol may or may not be included. The viscosity of a polymer solution may be controlled and the drying time of final products shortened with the help of ethyl alcohol.

We chose natural polymers of sodium carboxymethyl cellulose (Na-CMC) and carboxymethyl cellulose (CMC) based on the composition's biological and medical needs, tack, biocompatibility, and solubility. These polymers are frequently utilized as gelling agents, stabilizers, and similar substances in medical treatment. Propylene glycol (PG), glycerin, and PEG 400 were utilized as plasticizers. Based on experimental results, the concentrations of plasticizers and polymers were chosen to be 3–10% for polymers and 5–35% for plasticizers [7]. Although it is best used in the composition of two or more polymers, it is demonstrated in [7, 8] that the composition of one polymer can give certain physical, mechanical, and technical features of the final product.

Results and Discussion

Table 1 lists the model composition's composition and technical attributes.

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%	10.0	40.0	A viscous, thick, stretched material with a lot of air bubbles and an undesirable consistency that was applied to the substrate poorly.
	Solution CMC 3%	10.0	40.0	
	PG	2.5	10.0	
	PEG 400	2.5	10.0	
2	Solution Na-CMC 5%	10.0	40.0	Inadequately placed to the substrate; viscous, dense, expanding mass; numerous air bubbles; inadequate consistency.
	Solution CMC 5%	10.0	40.0	
	PG	2.5	10.0	
	Glycerin	2.5	10.0	

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	Thick, stretched mass that is viscous. Many bubbles of air. There is a lack of uniformity. Applied to the substrate poorly.
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 substance. Many bubbles of air. The consistency isn't up to par. Applied to the substrate poorly.
5	Solution Na-CMC 10% Розчин КМЦ 10% PG	10.0 10.0 10.0	33.3 33.3 33.3	Plastic is a viscous substance. Air bubbles are present. The consistency is adequate. It applies to a substrate well.
6	Solution Na-CMC 10% Solution Na-CMC 10% PG	15.0 15.0 15.0	33.3 33.3 33.3	Plastic is a viscous substance. Air bubbles are present. The consistency is adequate. It applies to a substrate well.
7	Solution Na-CMC 10% Solution Na-CMC 10% PG	3.0 7.0 10.0	15.0 35.0 50.0	It has a more suitable consistency and a viscous bulk. Many bubbles of air. It is applied to a substrate effectively.
8	Solution Na-CMC 5% Solution Na-CMC 10% PG	10.0 10.0 10.0	33.3 33.3 33.3	The material stretches sticky threads and is viscous. Bubbles of air are present. The consistency is better. It is applied to a substrate effectively.
9	Solution Na-CMC 10% Solution Na-CMC 5% PG	10.0 10.0 10.0	33.3 33.3 33.3	The material stretches sticky threads and is viscous. Bubbles of air are present. The consistency is better. It applies to a substrate well.
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 viscous and dense substance. It is not consistent enough. It is difficult to apply on the substrate.

The compositions are not optimally consistent, as demonstrated by the analysis of compositions 1-4. We believe that the imbalanced ratio of plasticizers to polymers is the cause of this. Compositions 5 and 6 are well described as having plastic, viscous mass, and air bubbles that are properly added to the substrate.

This results from the ideal proportion of plasticizers to polymers. The makeup of samples 7–9 is examined to verify this theory. The latter is different from one another, and compositions 5 and 6 differ in terms of both concentration and the ratio of polymer solutions in the base. Air bubbles are growing, and the mass's homogeneity and flexibility are changing all at once. The composition of compositions 5 and 6 is therefore the best from the perspective of technological indicators. We then presented component 5, which contains 14.3% ethyl alcohol and 96%. Particularly, deterioration of weight features is seen, as the process of drawing on a substrate becomes more difficult due to an increase in weight viscosity. We chose model examples 5 and 6 in this context.

To enhance the quality of the final product, the composition's solution must be free of air bubbles, mechanical contaminants, and particles of undissolved polymer as it enters the forming stage (application to the substrate). A stage of deaeration was thus applied to model samples to further shape the composition. The impact of centrifugation duration on the caliber of sample deaeration was examined in Lena and Alyona [7]. Polymer solution centrifugation @ 3000 rpm for 20–25 minutes.

The model compositions were deaerated for a while at a temperature between 15 and 25 °C. **Table 2** presents the findings of the study.

Table 2. Deaeration of compositions 5 and 6 at a temperature of 15-25 °C

Deaeration Time, min	**Description of the composition**	
	№ 5	**№ 6**
5	The mass is viscous and sticky, there are some air bubbles	

10	The bulk is homogenous, translucent, sticky, and viscous with no air bubbles.	There are some air bubbles in the thick, sticky material.
15	Not checked	The mass is uniform, clear, sticky, and viscous, with individual air bubbles.

Accordingly, the findings show that the deaeration time is dependent on the quantitative properties of the plasticizer and the structural compounds as well as the mass of the base. Thus, it was determined to select a model composition of composition №5 for potential growth based on the set of technological features. At temperatures between 15 and 250 °C, 5 to 10 minutes is the ideal amount of time to deaerate the model composition.

The mixture was then put to the substrate in the following study phase to additionally ascertain physicochemical and technical properties.

The regularity of the thickness of the layer of polymer mass added to the base and the homogeneity of combining are two technical factors that affect the quality of the polymer base. Certain portions of the same sample will have distinct mechanical and physical properties because of the composition's propensity to create an unequal layer on the substrates as a result of heterogeneity in combining. Therefore, homogeneity of mixing—achieved by combining the polymer mass for five to ten minutes with an anchor stirrer—is the assurance of product quality.

The layer's thickness is another of the technical markers. An indication of mixing homogeneity is also related to a layer's thickness. The homogeneity of the layer thickness can only be guaranteed by a homogenous polymer solution. The authors of [7, 8] confirmed that the film layer was 0.35 mm thick when they obtained dental medication films. It has been demonstrated that as layer thickness increases, so do numerical indicators of their mechanical and physical properties. In particular, when the film layer thickness is raised from 0.25-0.45 mm, the corresponding elongation rises from 83.2%-99%.

The diffusion of pharmaceuticals from them at various layer thicknesses was investigated to support the ideal layer thickness.

Medication diffusion from the base is known to be influenced by the thickness of the base layer that is added to the substrate. The dependency of medication release from the base was examined to determine the ideal layer thickness **(Figure 1)**. 0.1% ceftriaxone was added to the base. This concentration results from the fact that the medication Oflocaine, which is made by JSC HFZ “Darnytsia Pharmaceutical Company”, is available on the Ukrainian market and has a 0.1% ofloxacin content.

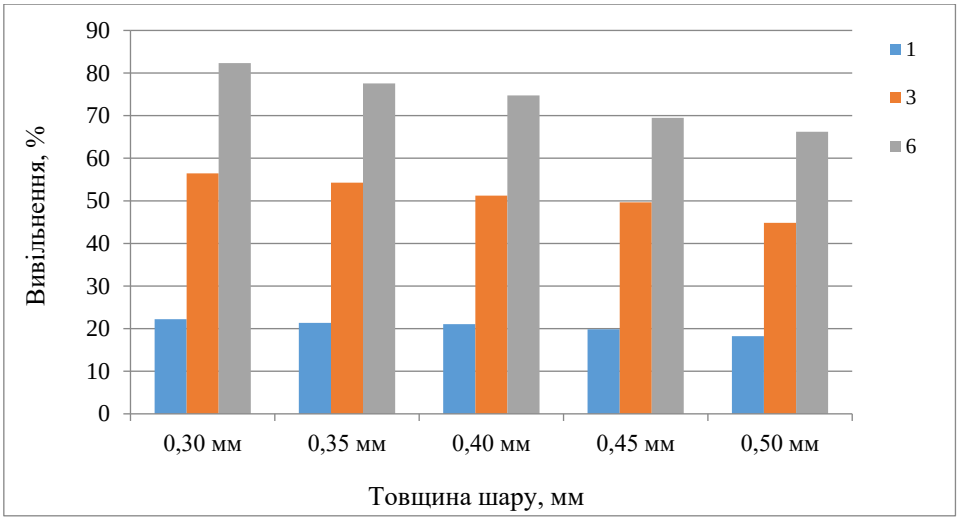

Figure 1. Diffusion of ceftriaxone from the layer thickness after 1, 3, and 6 hours

As the thickness of the polymer base layer increases, ceftriaxone discharge drops, as shown in **Figure 1**. Films with a layer thickness of 0.30 mm show the quickest diffusion of the material, while bases with a layer thickness of 0.50 mm show the slowest. Because the substance which works is 77.56% at a thickness of 0.35 mm, 74.75% at a thickness of 0.40 mm, 69.48% at a thickness of 0.45 mm, and 66.21% at a thickness of 0.50 mm, the diffusion of ceftriaxone from its base with a thickness of 0.30 mm the mean 82.35% over 6 hours. Thus, a thicker layer results in less ceftriaxone being released, extending the therapeutic impact.

To determine the ideal layer thickness, we chose 0.40 mm. In the future, mechanical and physical research will support this indicator. To maximize the procedure to acquire polymer mass, we looked into physical and mechanical property indicators like tensile strength and elongation. We also established technological indicators like mixing uniformity (duration of mixing), deaeration quality (duration of centrifugation), and layer thickness.
The aforementioned technological considerations were taken into consideration when modeling a series of polymer masses for this purpose. The physical and mechanical property indicators of the polymer base are displayed in **Table 3** based on technical factors: samples of the model 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.
The relative elongation and braking force are the primary mechanical and physical indicators used in the formulation of this dosage form. This is due to the requirement for flexibility in the adhesive mass applied to the substrate.

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 mass's flexibility enables the medicine to be applied to the wound surface as well as the substrate. The medicine can also be applied to the substrate because of its flexibility. Tensile strength and elongation are indicators of mechanical and physical attributes that rely on technical features, including homogeneity, homogeneous application on the substrate, and the lack of air bubbles.
This reduces the numerical indications of physical and mechanical qualities because of the gaps forming in the mass, resulting in variations in relative elongation and tensile strength. In **Table 3**, a higher number indicates a bigger amount of polymer added to the substrate. After attaining a homogenous mass, deaerating the air bubbles by centrifugation (№ 1-5) at 3000 rpm for 5-10 minutes is critical.
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, and 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, and 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, and 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.

Table 4 findings demonstrate that the layer's thickness has an impact on the drying process. It has been demonstrated that samples 1–5 have a consistent, sticky coating and are suitable for use in additional research.
The layer thickness of 0.40 mm, centrifugation period of 5–10 minutes at 3000 rpm, homogeneity: stirring for 15 minutes at 36 rpm, and anchor stirrer are the primary technical markers. Experimental research revealed that 0.03 g of sample must be applied for every 1 cm² of substrate to achieve a layer thickness of 0.40 mm. In further research, we will move the completed mass from the drying step to the freezing stage (for 12–24 hours) and then thaw to produce a "crosslinked" polymer. Theoretically, the polymer's "crosslinking" process can be leveled by drying the polymer mass at 50–60 °C.
Consequently, the drying procedure will be conducted at room temperature.

Conclusion

An analysis of the mechanical, physical, and technical properties of the model compositions reveals that the thickness of the polymer mass layer (0.40 mm), centrifugation time (5–10 min at 3000 rpm), and homogeneity (stirring for 15 minutes at 36 rpm with an anchor stirrer) are the primary technical indicators. According to experimental studies, 0.03 g of sample must be applied for every 1 cm² of substrate to achieve a layer thickness of 0.40 mm.

Acknowledgments: We would like to show our gratitude and appreciation to Prof. Shmatenko Oleksandr, colonel of medical service for sharing his pearls of wisdom with us and collaboration in writing that greatly improved the manuscript.

Conflict of Interest: None

Financial Support: None

Ethics Statement: All measures accomplished in this scientific trial containing human supporters remained similar through the ethical principles of the institutional advisory group.

References

1. Shrivastava KB, Gopaiah GV, Rao S. Lipid-polymer based nanoparticles as a new generation therapeutic delivery platform for ulcerative colitis in Vitro/In Vivo evaluation. Pharmacophore. 2019;10(4):15-27.
2. Dib N, Sebba FZ, Sebti H, Kada SO. Preparation and characterization of macroporous hydrogels from copolymers networks. Int J Pharm Res Allied Sci. 2019;8(1):202-6.
3. Narimene EK, Zohra SF, Mustapha R. In Vitro study of the antimicrobial effect of synthesized copolymer compounds against Staphylococcus aureus and Escherichia coli strains. Pharmacophore. 2019;10(3):82-8.
4. Ashjaran A, Sheybani S. Drug release of bacterial cellulose as antibacterial Nano wound dressing. Int J Pharm Res Allied Sci. 2019;8(3):137-43.
5. Khan KI, Akmal M, Waqas A, Mahmood S. Role of prophylactic antibiotics in Milligan Morgan hemorrhoidectomy–a randomized control trial. Int J Surg. 2014;12(8):868-71.
6. Gottrup F. Trends in surgical wound healing. Scand J Surg. 2008;97(3):220-5.
7. Lena D, Alyona V. The study of properties of the matrix for periodontal films based on Metronidazole, Chlorhexidine and Glucosamine. Int J Pharm Tech Res. 2016;9(2):9-12.
8. Vlasenko IA, Davtyan LL. Technological method creations of dable-layer medicinal films on the polymeric basis. Farm Zh. 2010(6):53-4. Available from: https://pharmj.org.ua/index.php/journal/article/view/747
9. Konovalova MV, Kurek DV, Litvinets SG, Martinson EA, Varlamov VP. Preparation and characterization of cryogels based on pectin and chitosan. Prog Chem Appl Chitin Deriv. 2016;21:114-21.
10. Konovalova MV, Markov PA, Durnev EA, Kurek DV, Popov SV, Varlamov VP. Preparation and biocompatibility evaluation of pectin and chitosan cryogels for biomedical application. J Biomed Mater Res A. 2017;105(2):547-56.

11. Shmatenko O, Tarasenko V, Davtian L, Drozdova A, Shmatenko V. Problems of the highest health care. 2012;(31):306-9. Available from: http://nbuv.gov.ua/UJRN/prvozd_2012_31_44
12. Davtyan L, Reva D, Maletska Z. Technological aspects of dental medical films with chlorhexidine and decamethoxine. Int J Pharm Tech. 2015;7(1):8166-73.