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Optimization of transdermal patch on parameters of composites of hyaluronic acid and zinc oxide nano particle filler

Kolawole S. Dada[1], Mayya V. Uspenskaya[2], Roman O. Olekhnovich[3]

[1, 3] ITMO University, Saint Petersburg, Russian Federation
[3] Peter the Great Saint Petersburg Polytechnic University, Saint Petersburg, Russian Federation
[1] dadakolawole1978@gmail.com
[2] mv_uspenskaya@mail.ru
[3] r.o.olekhnovich@mail.ru

Abstract. Transdermal drug delivery has gained popularity as a non-invasive method for controlled drug release compared to traditional delivery routes. Transdermal patches have emerged as a promising platform for delivering a variety of drugs due to their ease of use. The objective of this research was to create and characterize transdermal patches using various compositions and ratios of hyaluronic acid and zinc oxide nanoparticles. A micro molding technique was utilized to fabricate the patches which were subsequently characterized using Optical microscopy, FTIR, TGA and tensile strength testing. The study found that the mechanical strength and dissolution properties of the patches were influenced by the hyaluronic acid and zinc oxide nanoparticle ratios used in the fabrication process. Moreover, the patches demonstrated controlled filler dispersion in the polymer matrix as a function of the concentration of each filler. The results suggest that transdermal patches can be tailored to meet specific requirements for drug delivery applications using different compositions and ratios of hyaluronic acid and zinc oxide nanoparticles. This development has the potential to improve treatment outcomes and patient compliance in various therapeutic areas.

Keywords: hyaluronic acid, zinc oxide, transdermal patch, composite materials, drug delivery

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Научная статья
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Оптимизация трансдермального патча по параметрам композитов гиалуроновой кислоты и наночастиц цинка-наполнителя

К.С. Дада[1], М.В. Успенская[2], Р.О. Олекнович[3]

[1, 3] Университет ИТМО, Санкт-Петербург, Россия
[3] Санкт-Петербургский политехнический университет Петра Великого, Санкт-Петербург, Россия
[1] dadakolawole1978@gmail.com
[2] mv_uspenskaya@mail.ru
[3] r.o.olekhnovich@mail.ru

Аннотация. Трансдермальная доставка лекарств приобрела популярность как неинвазивный метод контролируемого высвобождения лекарств по сравнению с традиционными способами доставки. Трансдермальные пленки стали перспективной платформой для доставки различных лекарств благодаря простоте использования. Цель этого исследования – создание и изучение трансдермальных пленок с использованием различных составов и пропорций наночастиц гиалуроновой кислоты и оксида цинка. Для их изготовления использовалась технология микроформования, а далее они были изучены с помощью оптической микроскопии, ИК-Фурье-спектроскопии, термогравиметрии и испытаний на растяжение. Исследование показало, что на механическую прочность и растворимость пленки влияет соотношение гиалуроновой кислоты и наночастиц оксида цинка, используемых в процессе изготовления. Более того, пленки демонстрируют контролируемую дисперсию наполнителя в полимерной матрице в зависимости от концентрации каждого наполнителя. Результаты показывают, что трансдермальные пленки можно адаптировать под конкретные требования к доставке лекарств, используя различные составы и соотношения гиалуроновой кислоты и наночастиц оксида цинка. Эта разработка может улучшить результаты лечения и повысить приверженность пациентов к терапии в различных областях.

Ключевые слова: гиалуроновая кислота, оксид цинка, трансдермальная пленка, композитные материалы, доставка лекарств

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1. Introduction

The conventional method of drug administration through injections, intravenous and oral routes are quite expensive, demanding dosage frequencies and time consuming. Resolving to simpler and more cost-effective drug delivery methods, such as transdermal dissolvable patches made from composite materials of hyaluronic acid and ZnO, will open more research opportunities in drug kinetics.Various non-

invasive and painless methods of drug administration have been researched to improve drug delivery efficacy, with the aim of bypassing the gastrointestinal tract and avoiding the first-pass metabolism effect [1], [2]. The main benefits of these methods are the precise control of drug dosage [3], steady drug plasma concentration, and potential drug release mechanism. Transdermal administration is a popular method for delivering drugs due to its benefits compared to other routes. It is commonly utilized for various medical conditions such as to quit smoking, management of chronic pains and motion sickness, and hormone therapy application [4–6] The patches deliver drugs through a process of diffusion, that make small channels in the Stratum Corneum, which is a layer located in the epidermis of the skin tissue. Typically, the stratum corneum is 10 mm thick when it is not hydrated and consists of 10 to 15 layers of dead cells. The corneocytes are tightly packed together and are separated by lipid bilayers made of free fatty acids and ceramides. These corneocytes are keratinized cells. [7, 8] the difussion process create an opening through this layer where drugs are directly transported to the systemic circulation.

In the present times, innovative technologies like liposomes, nano emulsions, nanoparticles, and various other nanotechnologies have emerged to effectively deliver cosmetic and medicinal components into the stratum corneum [9, 10]. The above listed methods show a great possibility in the administration of drugs directly through the Stratum cornuem to the systemic circulation. However, among these technologies, transdermal patches are anticipated to be a safe and efficient method for delivering water-absorbing substances [11–15].

These patches are designed to effectively treat a variety of skin conditions. In respect of this are further references from articles like [16–20]. The general configuration of a patch, which consists of a backing laminate done to prevent hydrolisys , a drug-loaded adhesive matrix, and a release liner. The discovery of ZnO drug kinetic release mechanism with its advantageous and innovative properties has been used in recent times for administration of insulin and other viable drugs. Numerous studies have reported on the antibacterial properties of zinc oxide (ZnO) with different morphologies at the nano-scale level [21–25].

Presently, the potential of using ZnO as an antibacterial agent in both microscale and nanoscale configurations. As the particle size of ZnO is reduced to the nanometer range during dispersion in distilled water and polymer solution, it exhibits notable antimicrobial properties against a diverse range of bacterial species. Likewise, the potentials of Hyaluronic acid which is a natural existing polysaccharide can be used as a drug courier in transdermal application.

Moreso, Due to its biodegradable and biocompatible characteristics, Hyaluronic acid (HA), which is a type of polysaccharide, is commonly employed in research related to skin diseases [26]. Hyaluronic acid (HA) is a heteropolysaccharide and a type of naturally occurring polymer that can be found in various parts of the human body, such as the skin, connective tissue, joints, rooster comb, and umbilical cord. The structure of HA contains carboxyl and acetamido groups that can form H-bonds with water molecules, leading to the stabilization of its secondary structure. This feature allows HA to be biodegradable, especially in water-based environments [27–28].

The study will aim at understudying the physicochemical, mechanical and drug release properties of the dissolvable patch, various methods of characterization will be employed in this regards FTIR analysis, TGA, Polarized/Optical microscope, mechanical and physical analysis device and so on.

2. Materials and methodology

2.1. Materials

Hyaluronate (HA, HMW ~ 1000kDa), was provided by Huaxi Biotechnology Co., Ltd. (Shandong, China), Zinc Oxide Nanoparticles / Nano powder (ZnO) 99.8% purity of size 10-30 nm was prepared at the center for chemical engineering laboratory , ITMO University. The ultrapure water was prepared in the laboratory and used for the preparation of all aqueous solutions.

2.2. Method of Experiment

Hyaluronic acid is measured separately within 0.5-3 wt.% and zinc oxide, 0.1-0.3 wt.%. of various concentrations, they are placed in measuring cylinder and 15 ml of distilled water was added. The solution of Hyaluronic acid is first stirred to attain a clear solution at room temperature and after about 45mins of stirring, the ZnO prepared solution is adjusted to a favourable pH for easy dispersion through electrostatic repulsive effect.The pH is reduced using citric acid corresponding to a measured percentage by weight of the HA ,precisely 20 percent and carefully titrated into the ZnO solution untill a pH of 5-6.5 is attained, which precisely reduces the Zeta potential and creates a positive charge around the ZnO for easy dispersion in the polymer matrix. The magnetic stirrer is left on for another three hours in order to ensure some percentage of homogeneity. The solution is allowed to settle down and then placed again in ultrasonic homogenizer for another 45-60 minutes for final dispersion of the ZnO in the polymer soultion , this ensures proper bonding of the molecules .The solution of Hyaluronic acid and ZnO nano particles is then placed inside a substrate for casting and kept safely under room temperature (25 ℃) for four days for proper drying process and for the final formation of the composite film.

2.3. Characterization techniques used

The Characterization techniques used are not limited to observing the surface morphology, film thickness to understand its mechanical relevance, dissolution rate measurement as a dependant of its hydrophilic nature. Hence the relevant characterization method used in this synthetization of dissolvable patch are FTIR Analysis, Optical Microscope, Dissolution test, TGA analysis for Thermal stability and degradation and Mechanical analysis to understudy the mechanical strength, tensile stress and strain which will define the expected deformity of the film to suit the skin texture. The characterization was done severally on various categories

of the produced patched samples in order to project the optimum value for application.

3. Results and Discussion

The results obtained from the characterization techniques are crucial in determining the optimal value for the various ratios of the combination of the Polymer and Nanoparticles used in the fabrication of the transdermal patch. However, the determination of the optimal value is also influenced by other factors such as the type of drug application and the duration of application. Therefore, it is important to take into consideration the results of the solubility test as seen on table 1 below, which provides additional technical information regarding the longevity of the patch and the potential release rate of the drug.

3.1. Moisture content percentage in the sample

For a thin film composite containing hyaluronic acid and zinc oxide, the degree of swelling refers to the extent to which the film absorbs a solvent or moisture. A degree of swelling of 0.54 indicates that the film absorbs 54% of its original dry weight when exposed to a specific solvent or moisture. In this case, the composite film with a degree of swelling of 0.54 suggests that it has a moderate ability to absorb moisture or solvent. This property can be advantageous for applications such as transdermal drug delivery, as it allows the film to absorb and retain a certain amount of moisture or solvent, facilitating the controlled release of drugs through the skin. Additionally, the moisture absorption of 2.7% indicates the percentage of moisture the film absorbs from the surrounding environment. This property is important as it affects the film's stability and mechanical properties. A moisture absorption of 2.7% suggests that the film can absorb a moderate amount of moisture, which can potentially impact its physical and chemical characteristics. Overall, the degree of swelling and moisture absorption properties of the composite film containing hyaluronic acid and zinc oxide provide insights into its behavior in different environments and its potential applications in areas such as drug delivery and wound healing. The expression is seen below.

$$Q = [ws - wd(1 - \gamma)], \quad (1)$$

$$swelling\ \% = \frac{ws - wd}{wd} \cdot 100 = 2.7\%, \quad (2)$$

Ws = Weight of the polymer film after it has swollen in the solvent; Wd = Weight of the dry polymer before swelling; 'γ' (gamma) is the sol fraction of the film.

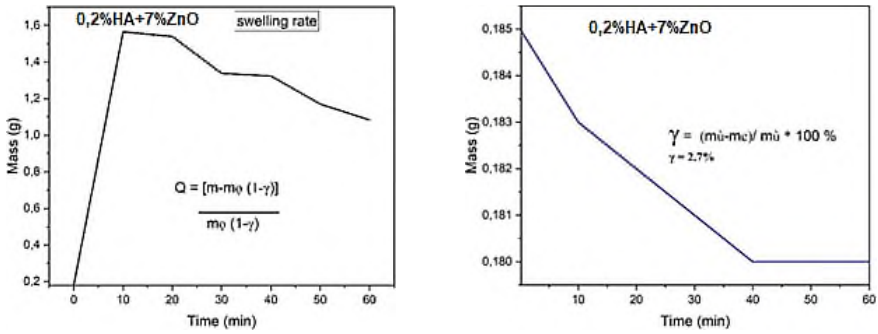
3.1.1. Swelling and Mositure absorption data

Drying temperature for the set up experiment was between 22-25 degrees room temperature; after removing the film from the solvent, it was held vertically over a pre-weighted beaker and was allowed to drip for 10-15 seconds to remove free surface solvent. It was gently blotted once with lint free filter paper and it was weighed immediately to record Ws.

Table 1

Data Summary

Time (min)	Ws (g) mass after swelling	Ws (g) drying mass (before immersing)	Degree of swelling (g/g) Ws–Wd/Wd	Moisture Absorption (%)
10.0	2,48	1,80	0,377778	37,778
20.0	2,21	1,80	0,227778	22,778
30.0	2,04	1,80	0,133333	13,333
40.0	1,80	1,80	0,000000	0,000
60.0	1,75	1,80	–0,027778	–2,778



a *b*

Fig. 1. The swelling rate (*a*); the sol fraction of the film (*b*)

Table 2

Solubility Test for Sample 3 (0.2% HA + 7% ZnO)

Step	Procedure	Time Interval, min	Conclusion
1	Place the thin film biopolymer patch in a beaker containing 100 mL of distilled water at room temperature	0	Observe the initial appearance of the patch
2	At specific time intervals, remove the beaker from the stir plate and examine the patch for any changes	10	Observe any changes in the patch, such as swelling or dissolution
3	After each observation, return the beaker to the stir plate and continue stirring at a constant speed	20	Check for any further changes in the patch
4	Repeat step 2 and 3 until the patch is completely dissolved or a maximum time of 60 minutes has been reached	40	Record any changes in the appearance of the patch, such as shape, size, and transparency
5	Once the patch has completely dissolved or 60 minutes have passed, remove the beaker from the stir plate and analyze the solution for drug content using a suitable analytical technique	60	Calculate the dissolution rate of the patch and evaluate its drug release profile
6	Repeat the experiment with different patch formulations or dissolution media to compare the performance of the biopolymer patch	–	Draw conclusions about the suitability of the composite of hyaluronic acid and zinc oxide nanoparticles as a thin film material for drug delivery

3.2. Thermogravimetric analysis

The central piece of equipment for the Thermogravimetric analyzer (TGA), was a specific model PerkinElmer TGA 4000, TA instruments TGA Q50.This has a microbalance an ultra-sensitive balance with precision ±0.1μg, housed inside the instrument for measuring the sample weight. This equipment also houses a furnace which heats precise controlled rate. Samples are placed inside a crucible made of platinum and heated from 30 ℃ to 800 ℃ at constant heating rate of 10 ℃ per minute. The entire set up is also purged with Nitrogen (N_2) at a flow rate of 20-60mL/min for the entire heating ramp.This prevents oxidation and allows the visibility of the material during inherent thermal degredation.At the final high temperature, the gas is swicthed form N_2 to synthetic air .This will combust any carbon based residue ,leaving only the inorganic ash, giving a clean measure of the filter.

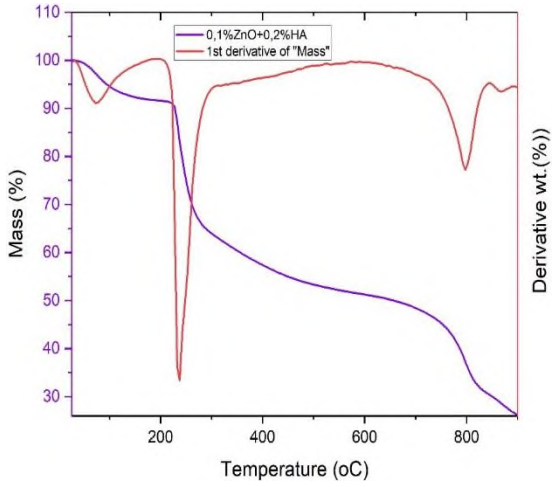


Fig. 2. Thermogravimetric analysis (TGA) and Derivative thermogravimetric (DTG) curves combined, of composite material of HA-ZnO film of 0.1% ZnO 0.2% HA

Table 3 provides a clear overview of the two main phases of mass loss observed during the TGA analysis, specifying the temperature ranges, the percentage of mass loss, and an interpretation of what these changes indicate about the behavior of the film under heat.

Table 3

Mass % loss

Temperature Range (°C)	Mass Loss (%)	Interpretation
0 to 227.72	100 to 90.96	Removal of water associated with HA, possibly in the form of bound or adsorbed water
227.72 to 820.69	90.46 to 32.41	Decomposition of HA, releasing oxygen and leaving behind a residue of ZnO NPs or carbonized material

Table 4

The mass percentage loss for HA 0.2% and ZnO (1, 3, 5, and 7%)

	0.2% HA + 1% ZnO	0.2% HA + 3% ZnO	0.2% HA + 5% ZnO	0.2% HA + 7% ZnO
Sample Mass (g)	6,4049	6,5066	7,2066	8,3195
Temperature Range (°C)	25°C to 900°C	25°C to 900°C	25°C to 900°C	25°C to 900°C
Mass Loss (%)	67.57%	65.21%	65.46 %	68.83%
Decomposition Range (°C)	Significant mass loss occurs between 0 to 227.72°C and 227.72 to 820.69	Significant mass loss occurs between 0 to 228.66°C and 191.80 to 638.29	Significant mass loss occurs between 0 to 226.63°C and 224.42 to 670.64	Significant mass loss occurs between 0 to 228.66°C and 191.80 to 638.29°C
Thermal Behavior	Release of volatile components or decomposition of the film	Release of volatile components or decomposition of the film	Release of volatile components or decomposition of the film	Release of volatile components or decomposition of the film
Stability	Relatively stable at lower temperatures	Relatively stable at lower temperatures	Relatively stable at lower temperatures	Relatively stable at lower temperatures

3.3. Polymer surface morphology

The polymer films as shown in Fig. 3, Fig. 4, Fig. 5 where placed under the optical microscope at various magnification using objective lens from 5x to 100x. and it shows an even polymer reinforcement while in some sample are agglomeration of zinc oxide cluster whose particles exhibited different contrast, which requires dessaturation through proper dispersion to improve their distribution in the polymer matrix .The decision was to focus on high ZnO concentration above %.

Fig. 3. The morphology of the composite film HA-ZnO 3%

Fig. 4. The morphology of the composite film HA-ZnO 5%

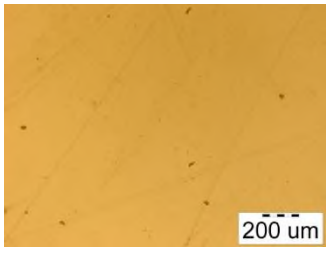


Fig. 5. The morphology of the composite film HA-ZnO 7%

The effect of the zinc oxide cluster could impact on the mechanical properties of the polymer membrane, thereby affecting its strength, antibacterial properties and flexibility.

Sample observation: HA0,2% + ZnO7%

Observation of the texture: By viewing under the optical microscope, the Film obviously exhibits a smooth surface with a slight sheen, which is indicative of the hygroscopic nature of hyaluronic acid (HA). Moreso, the presence of ZnO nanoparticles (NPs) must have introduced an ultra-fine, evenly scattering formation across the polymer matrix, this is observed as a light, powdered texture. This is suggesting a good dispersion of ZnO NPs within the HA matrix, which is important for deciding the reinforcement patterns and areas of usefulness of the film.

3.4. FTIR Analysis

Fourier Transform Infrared Spectroscopy, also known as FTIR Analysis or FTIR Spectroscopy, is an analytical technique used to identify organic, polymeric, and, in some cases, inorganic materials. The FTIR analysis method uses infrared light to scan test samples and observe chemical properties.The FTIR instrument sends infrared radiation of about 10,000 to 100 cm-1 through a sample, with some radiation absorbed and some passed through. The absorbed radiation is converted into rotational and/or vibrational energy by the sample molecules. The resulting signal at the detector presents as a spectrum, typically from 4000 cm-1 to 400cm^{-1}, representing a molecular fingerprint of the sample. Each molecule or chemical structure will produce a unique spectral fingerprint

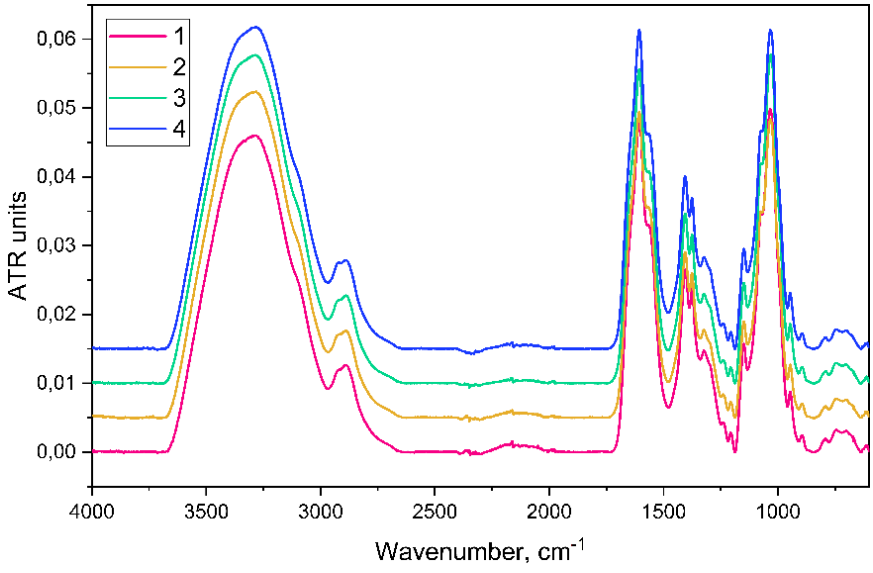


Fig. 6. The FTIR (1-4) describing the samples of composites films of HA-ZnO 1, 3, 5 and 7 percent respectively

The presence of O-H stretching vibration around the peak value of 3277 cm cm^{-1} is associated with the hydroxyl groups that are present in the glucuronic acid and N-acetylglucosamine components of Hyaluronic acid, the C=O stretching vibration at 1692 cm^{-1} aligns with ester C=O stretching in the ester linkages in Hyaluronic acid. In addition the wavenumber 1020 cm^{-1} is also consistent with the ester linkages in Hyaluronic acid. In conclusion, the spectra completely depicts the presence of the defining functional groups of Hyaluronic acid.

4. Interpretation of results

The nearly similar results is interpreted that the variation of the percentage concentrations of ZnO NPs in the polymer film up to 7% concentration does not in any way significantly alter the fundamental properties of the polymer matrix. This shows that the base material which is the HA was able to maintain its structure and well stable ,irrespective of the introduction of fillers of various concentrations .The limitation at the moment is the long term stability of the structure due to the high swelling rate when exposed to atmospheric conditions and the stability rate under the possible introduction of nanoparticles of different size distributions. The future direction of the research will focus more on investigating the biological responses during in vivo application of the samples.

5. Conclusion

In conclusion, based on the analysis and characterization of various samples of compositions and ratios of hyaluronic acid and zinc oxide nanoparticles for transdermal patches fabrication, various indicative measures of defining the properties of the films for various application is very possible, for wound dressing, drug delivery and tissue regeneration process, especially for preparing a scaffold. The optimum values are as described using the basis of characterization. This research further creates an indicative approach to studying the impact of HA as a stable and base material for biomedical applications with specific tailored properties.

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***Information about the authors*:**
Dada Kolawole S. – PhD Student, Chemical Engineering Center, ITMO University (Saint Petersburg, Russian Federation). E-mail: dadakolawole1978@gmail.com
Uspenskaya Mayya V. – Doctor of Technical Sciences, Professor, Institute of Civil Engineering, Peter the Great Saint Petersburg Polytechnic University (Saint Petersburg, Russian Federation). E-mail: mv_uspenskaya@mail.ru
Olekhovich Roman O. – Candidate of Technical Sciences, Associate Professor, Faculty of Control Systems and Robotics, ITMO University (Saint Petersburg, Russian Federation). E-mail: r.o.olekhnovich@mail.ru

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***Сведения об авторах*:**
Дада Колаволе С. – аспирант Химико-технологического центра Университета ИТМО (Санкт-Петербург, Россия). E mail: dadakolawole1978@gmail.com
Успенская Майя Владимировна – доктор технических наук, профессор Инженерно-строительного института Санкт-Петербургского политехнического университета Петра Великого (Санкт-Петербург, Россия). E mail: mv_uspenskaya@mail.ru
Олехович Роман Олегович – кандидат технических наук, доцент факультета систем управления и робототехники Университета ИТМО Университета ИТМО (Санкт-Петербург, Россия). E mail: r.o.olekhnovich@mail.ru

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