CONTRIBUTIONS CONCERNING THE IMPROVEMENT OF QUALITY INDICATORS OF COSMETIC PRODUCTS WITH NATURAL INGREDIENTS USING MATHEMATICAL MODELING TECHNIQUES AND NUMERICAL SIMULATION

PhD Thesis – Abstract

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People must accord great importance caring to the cutaneous organ (skin) from the moment of birth until the age of senescence. A healthy and well-cared skin gives everyone a state of comfort, both physically and mentally (it gives self-confidence).

In recent years, the frequency of dermatological diseases has increased worldwide, for various reasons, both in children and in adults. These health problems cannot always be cured, but the use of emulsions/creams in applied treatments can alleviate certain unpleasant effects and prevent their recurrence, thus improving people's health [1].

For these reasons, worldwide, the field related to the manufacture of cosmetic and dermato-cosmetic products has developed, as well as research related to the improvement of their quality indicators. Research has been carried out on new raw materials, i.e. revolutionary active ingredients (natural and synthetic) with clinical efficacy studies, which aim to restore and maintain the natural beauty and health of the skin. In this way, those active substances, called cosmeceuticals, which are considered cosmetic ingredients and which improve the appearance of the skin thanks to a pharmacological effect that can be identified at the intracellular level. The name "cosmeceuticals" appeared by combining the terms "cosmetic" and "pharmaceutical". An example from the cosmeceuticals category are synthetic peptides that have a bioactive effect on the skin [2-5].

The development of the cosmetics industry has led to a significant diversification of the types of products, whose main purpose is to increase attractiveness, as well as promote health and beauty. The basic objective of the cosmetic preparation specialist is to create a product that is as stable as possible from both a physico-chemical and microbiological point of view.

A wide range of products are marketed under the general name of cosmetic products, which belong to distinct categories, namely [1]:

- Skin care products: cleaning preparations, preparations with astringent action, moisturizing preparations, cosmetic masks, creams, sun protection preparations (creams, lotions).

- Hair care products: shampoos, conditioners, combination shampoo - conditioner, styling products, products for changing hair color.

- Toiletries: soaps, shampoos, bath products, shaving products, conditioners, toothpaste, deodorants and antiperspirants.

- Make-up products (decorative cosmetics): foundation, powder, eye and skin make-up, lipsticks, nail varnishes.

- Perfumery products: perfumes and colognes, "after shave" type lotions, bath powders.

Even if cosmetic products are numerous and belong to different categories, and their net classification is difficult and generates disputes, they must obey some basic rules mentioned bellow [1,4]:

• chemical compatibility of the components used in their preparation;

• aesthetic appearance and pleasant smell;

• innocuousness (that is, harmlessness, with as low an index of allergenicity as possible, without causing irritation);

• easy application and removal on / and from / the skin;

• maintaining physical, chemical, rheological and microbiological purity and stability as long as possible.

Compared to the rest of the human body, the face is directly exposed to the action of external agents (dust, radiation, wind, etc.). Exposure to sun and wind can make skin dry and rough and over-washing removes the natural - oily layer that protects the skin. Therefore, the cosmetic product intended for the skin organ exposed to the environment (face, hands, feet) must meet several requirements: be nutritious and moisturizing, protective and able to screen solar radiation. The role of cosmetic emulsions is to protect and nourish the skin, but also to soothe the unpleasant sensations of irritation.

The specialists responsible for the research, development and application of cosmetic and dermato-cosmetic products (pharmacists, chemists, chemical engineers, doctors, biologists) carry out their work in accordance with the rules and requirements imposed by the legislation in force.

Regarding the research and studies carried out in this paper, the main proposed objectives were taken into account. Among these, the most important are the study of the dynamics of the physico-chemical and microbiological indicators of cosmetic emulsions, as well as the systemic approach to problems related to maintaining their stability, using mathematical modeling and numerical simulation methods. Thus, as a novelty in the work, the principles of Systems Theory were used in the study of cosmetic creams. This allowed benefiting from the scientific, applied and economic advantages obtained by studying creams considered "systems with distributed parameters". These benefits allow a series of major simplifications related to the manufacture of creams (based on determined mathematical models), which are directly reflected by the drastic decrease in manufacturing expenses (raw materials, obtaining technologies, stability, etc.) and therefore in the price of the finished product and last but not least as means of prediction regarding the possibility of obtaining the most optimal quality indicators of the finished products (creams placed on the market).

In accordance with the Systems Theory principle, in Fig.1 the cosmetic emulsion is represented as a system, with input variables (u), output variables (y) and disturbances (z) [6].

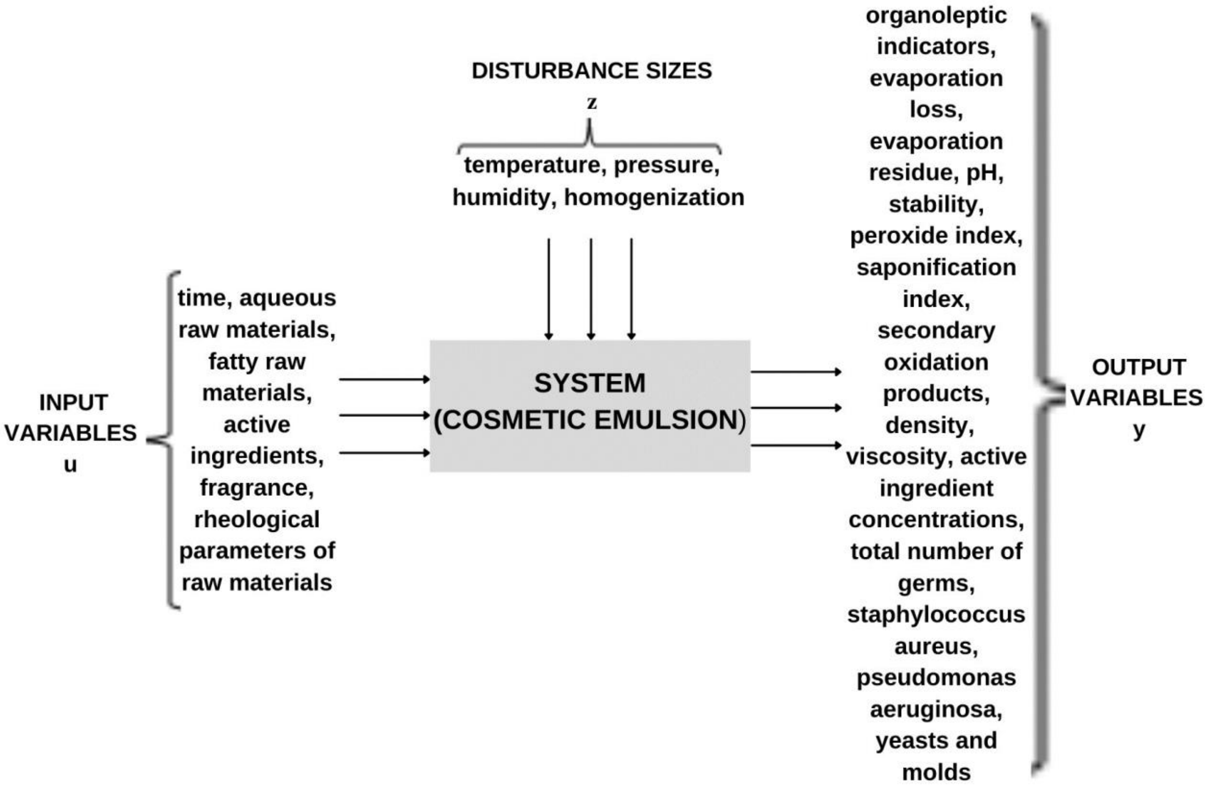

Fig. 1. Representation of the cosmetic emulsion as a system

The thesis is structured in 7 chapters:

1. The current state of knowledge in the field of emulsified creams
2. Systems theory, mathematical modeling and numerical simulation, modern ways of achieving knowledge
3. Synthesis of the main national and international laws and regulations regarding the quality of cosmetic products
4. Experimental research
5. Stages of launching cosmetic products on the market
6. General conclusions
7. Personal Contributions

The first chapter presents a review of the available literature, highlighting the motivation for choosing this topic, as well as the fundamental aspects regarding the need to approach and develop these studies.

This first chapter also contains a presentation of the current state of research in the field of obtaining cosmetic products, especially creams and emulsions, including the description of technological flows, Fig. 2, and of all categories of raw materials found in their composition.

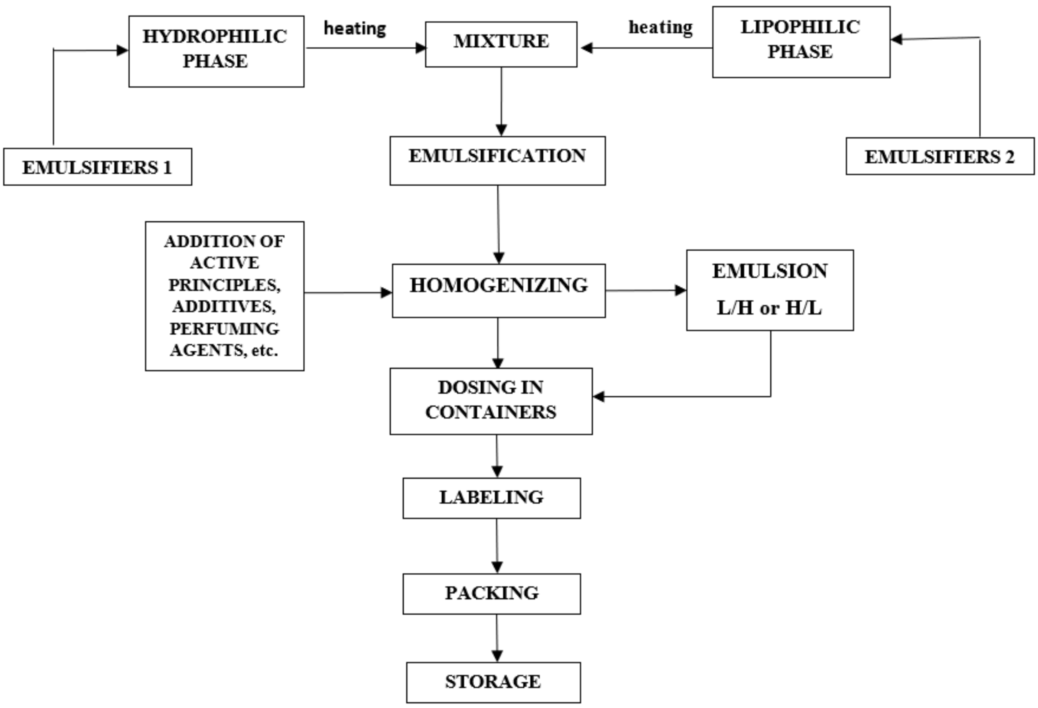

Fig. 2. Organization chart of the technological flow operations for obtaining cosmetic emulsions

Important notions related to the stability of these products are also presented, as well as the methods of determining and maintaining it over a certain well-specified period of time, Fig. 3. The instability of emulsions can manifest itself in several ways: skimming, coagulation (flocculation), coalescence and Oswald ripening. These phenomena can influence each other or coexist [4,7,8].

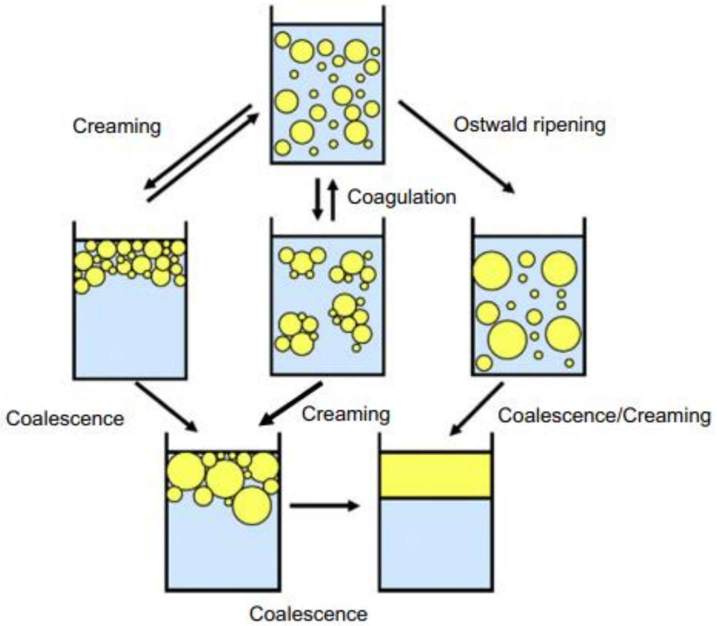

Fig. 3. The instability phenomena of cosmetic emulsions [4]

This chapter also describes the fields of use and the benefits of cosmetic creams on the skin organ, as well as notions about the structure and functioning of the skin organ [9].

Chapter 2 presents the bibliographic documentation related to use the Systems Theory in the research related from this thesis, to the techniques of mathematical modeling, numerical simulation and to the statistical-computational methods of processing the experimental data obtained from the studies carried out on cosmetic emulsions [4,10,11,12,13].

Chapter 3 contains the legal provisions regarding the authorization and marketing of cosmetic products. These include laws, decisions, ordinances and standards, which are: general, national, European and international. The national and international regulations regarding the authorization and commercialization of cosmetic products include the following objectives: harmonization, organization, differentiation, maintenance and continuous improvement of quality indicators [14].

Chapter 4 presents the research and experimental studies carried out within this thesis, which were carried out in the laboratories of the Department of Applied Chemistry and Engineering of Organic and Natural Compounds from the Faculty of Industrial Chemistry and Environmental Engineering, Politehnica University of Timișoara and in the laboratory of the company S.C. Virago Beauty S.R.L., on several types of cosmetic creams: anti-wrinkle cream, moisturizing cream, body milk and other types of cosmetic emulsions.

In the research and experimental studies, the following directions were approached:

4.1. Determining the stability of cosmetic creams in order to predict their optimal shelf life [15]

In this study, the variation over time of the physico-chemical parameters (residue on evaporation RE, pH) and microbiological parameters (total number of NTG germs, BC coliform bacteria, Pseudomonas Aeruginosa, Staphylococcus aureus) influencing the stability of some cosmetic emulsions (moisturizing cream 1, moisturizing cream 2, body milk 1, body milk 2) with the aim of determining the life span, respectively their optimal term of validity.

Based on the experimental data obtained by direct measurement for 4 years for four creams, the equations of the statistical mathematical models were calculated using the program OriginPro 2021b (Table 1). With the same program, the adequacy indicators of the models determined for the studied creams were calculated, respectively: the standard deviation σ, the model precision indicator R2 and the correlation coefficient, R (Table 2).

Table 1. Equations of statistical mathematical models obtained for the 4 creams studied

Emulsions	Equations of statistical mathematical models
Moisturing cream 1	$RE = 34.18947 – 0.2485 \cdot T + 0.0024 \cdot T^2$
Moisturing cream 2	$RE = 40.18267 – 0.31457 \cdot T$
Body milk 1	$RE = 32.7615 + 6.70792 \cdot 10^{-4} \cdot T – 0.00843 \cdot T^2 + 1.04447 \cdot 10^4 \cdot T^3$
Body milk 2	$RE = 43.7335 – 0.21894 \cdot T + 0.00756 \cdot T^2 – 1.03475 \cdot 10^{-4} \cdot T^3$

Table 2. Adequacy indicators of the determined statistical mathematical models

Adequacy indicators	Moisturing cream 1	Moisturing cream 2	Body milk 1	Body milk 2
Standard deviation, σ	0.1196	0.0586	0.3044	0.2214
Model accuracy indicator, R^2	0.9986	0.9960	0.9965	0.9920
Correlation coefficient, R	0,9993	0,9979	0,9982	0,9960

According to the values of the quality indicators measured for 4 years and based on the indicators of calculated adequacy of the determined mathematical models, the optimal term of validity of the 4 studied emulsions can be a maximum of 3 years period of time.

4.2. Stability studies of cosmetic creams according to environmental temperature variations, using the mathematical modeling technique [16]

As we stated in the previous study, the chemical and microbiological stability of cosmetic creams is an important factor in determining their lifespan.

The factors that can influence the chemical and microbiological stability of cosmetic creams are: temperature, homogenization, the amount of emulsifier used, chemical agents, phase inversion and storage conditions.

In this study, the time variations of the physico-chemical and microbiological parameters of a number of 10 cosmetic emulsions, under normal conditions, for 12 months, were followed, compared to the behavior under stress conditions, at a temperature of -15°C, for 10 days. According to the actual standards, cosmetic creams are stored in rooms where the temperature and humidity are monitored; these two parameters must fall within the following limits: temperature between 15 - 25°C and humidity between 55 - 65%. Tables 3 and 4 present the equations of the obtained mathematical models, as well as the calculated adequacy indicators.

Table 3. The equations of the statistical mathematical models obtained for the 10 samples stored under normal conditions and the calculated suitability indicators

Sample	Equations of statistical mathematical models	Model accuracy indicator, R^2	Correlation coefficient, R
1	$PE=54,111+0,0017 \cdot T^3-0,0429 \cdot T^2+0,4565 \cdot T$	0,9863	0,9931
2	$PE=56,966+0,0028 \cdot T^3-0,0538 \cdot T^2+0,4986 \cdot T$	0,9831	0,9915
3	$PE=56,824+0,0009 \cdot T^3-0,0095 \cdot T^2+0,1889 \cdot T$	0,9872	0,9935
4	$PE=57,827-0,0005 \cdot T^3-0,0008 \cdot T^2+0,3400 \cdot T$	0,9869	0,9934
5	$PE=50,849+0,0002 \cdot T^3+0,0077 \cdot T^2+0,0463 \cdot T$	0,9852	0,9925
6	$PE=52,117+0,0007 \cdot T^3-0,0700 \cdot T^2+0,0911 \cdot T$	0,9820	0,9909
7	$PE=58,883-0,0004 \cdot T^3+0,0186 \cdot T^2+0,0986 \cdot T$	0,9900	0,9949
8	$PE=58,617-0,0011 \cdot T^3+0,0202 \cdot T^2+0,1373 \cdot T$	0,9892	0,9945
9	$PE=57,679+0,0016 \cdot T^3-0,0301 \cdot T^2+0,0331 \cdot T$	0,9819	0,9909
10	$PE=56,882-0,0003 \cdot T^3-0,0097 \cdot T^2+0,0935 \cdot T$	0,9848	0,9923

Table 4. Equations of statistical mathematical models obtained for the 10 samples stored under stress conditions and the calculated adequacy indicators

Sample	Equations of statistical mathematical models	Model accuracy indicator, R^2	Correlation coefficient, R
1	$PE=56{,}343+0{,}0019\cdot T^3+0{,}0174\cdot T^2+0{,}1529\cdot T$	0,9999	0,9999
2	$PE=60{,}006-0{,}0006\cdot T^3+0{,}0359\cdot T^2+0{,}1906\cdot T$	0,9978	0,9988
3	$PE=59{,}161-0{,}0051\cdot T^3+0{,}0968\cdot T^2+0{,}0555\cdot T$	0,9981	0,9990
4	$PE=61{,}044+0{,}0019\cdot T^3+0{,}0181\cdot T^2+0{,}1509\cdot T$	0,9999	0,9999
5	$PE=52{,}943+0{,}0024\cdot T^3+0{,}0207\cdot T^2+0{,}0537\cdot T$	0,9994	0,9996
6	$PE=53{,}482+0{,}0028\cdot T^3+0{,}0095\cdot T^2-0{,}0007\cdot T$	0,9989	0,9994
7	$PE=62{,}069-0{,}0010\cdot T^3+0{,}0449\cdot T^2-0{,}0475\cdot T$	0,9962	0,9980
8	$PE=61{,}213-0{,}0039\cdot T^3+0{,}0863\cdot T^2+0{,}0343\cdot T$	0,9954	0,9976
9	$PE=60{,}180+0{,}0008\cdot T^3+0{,}0425\cdot T^2-0{,}0902\cdot T$	0,9970	0,9984
10	$PE=58{,}797+0{,}0015\cdot T^3+0{,}0202\cdot T^2+0{,}0089\cdot T$	0,9921	0,9960

From the first part of this study, it can be observed that for the ten samples stored for 12 months under normal conditions, the quality indicators fall within the limits imposed by the national standards in force.

In the second part of the work, in which the other 10 samples were subjected to stress conditions for ten days, the microbial load at the end of the study was much higher, exceeding the maximum allowed values. And the values of the physico-chemical quality indicators increased, but they fell within the limits imposed by the specific standards.

The statistical mathematical models obtained in both cases of the study describe the physico-chemical processes that take place in cosmetic emulsions. These processes can lead to the modification of the value for some parameters and of course the quality indicators specific to the legislative requirements. The testing of the mathematical models was carried out by calculating the adequacy indicators: the model precision indicator R2 and the multiple correlation coefficient R. The latter has values close to 1, therefore the developed mathematical models characterize with a good approximation the real systems, respectively the creams for which performed the measurements.

In conclusion, by extrapolation, cosmetic creams made in the form of emulsions with a composition similar to those taken in the study must be kept in optimal conditions, i.e. at temperatures between 15 - 25°C and humidity between 55 - 65%. Failure to comply with these conditions and requirements definitely leads to a decrease in the validity period.

When stored creams are subjected to stress factors, auxiliary physico-chemical phenomena appear in their structure that can modify their chemical and phase composition.

Thus, destruction of the bonds between the emulsion particles can occur, which leads to demulsification phenomena, respectively the separation of the liquid-solid phases and finally to the destruction of the emulsion. Due to this phenomenon, the emulsion loses all its rheological and organoleptic properties stipulated in national and international legislation.

4.3. Determination of mathematical models characterizing the rheological behavior of cosmetic creams

Cosmetic creams are semi-solid emulsions containing mixtures of oils and water, having a consistency that varies between liquid and solid form. For this reason rheological characterization is more difficult, as both mathematical models for solid and liquid systems must be considered.

The rheological behavior of cosmetic emulsions can be influenced by temperatures of their preparation and cooling, the amount of emulsifier in the composition and that of principlesassets added at the end of the technological process.

The rheological properties of emulsions, especially viscosity, intervene in ensuring their stability by reducing the mobility of the droplets of the internal phase in the external phase, thus reducing the possibility of the droplets approaching and joining (coalescence), which will ultimately lead to the separation of the emulsion.

This study refers to the rheological behavior and stability over time of four oil-in-water emulsions (A, B, C, D) in correlation with the parameters (temperature, composition and active principles) expected to be respected within the manufacturing processes of cosmetic creams [17].

As regards the preparation of these emulsions, the procedure was as follows: the first two phases were heated to 70°C for emulsions A, B and D, respectively to 90°C for emulsion C. Then the fatty phase was added over the aqueous one and homogenized for 10 minutes with a Lab High-shear Homogenizer at 10,000 rpm. After homogenization, emulsions A, B, C were gradually cooled under slow stirring (5000 rpm) to 40°C, and emulsion D was suddenly cooled in ice water to the same temperature.

At a temperature of 40°C, in emulsions B, C and D, phase 3 (active principles) was added, these being: Lactobacillus ferment (probiotic used in anti-wrinkle, anti-aging, anti-wrinkle creams), tea tree leaf extract (Camelia Sinensis), pomegranate extract (Punica Granatum) and caffeine.

The experimental results show that the rheological properties of the analyzed emulsions depend to a large extent by the preparation conditions (temperature and cooling rate), by the temperature at which the measurements are made, as well as by the presence of active principles in the composition.

All four emulsions show a non-Newtonian behavior at the yield point, and the obtained rheological equations fit into Bingham and/or Herschel-Burkley mathematical models.

The decrease in viscosity of emulsions B and D containing active principles is generated by the composition and concentration of the four incorporated ingredients, even if the amount of water in the aqueous phase is identical in both emulsions.

The increase in the viscosity of emulsion C could be the consequence of the partial evaporation of the watery phase, due to the high temperature during its preparation (90˚C).

All measurements carried out in this line of research led to determination of mathematical equations that describe the rheological behavior of the studied emulsions.

These are shown in Tables 5, 6 and 7.

Table 5. Rheological equations for emulsion A

Temperature, ˚C	Equation $\boldsymbol{\tau = \tau_0 + \eta_p \cdot \dot{\gamma}}$	R^2
25	$\tau = 11.17 + 13.24 \cdot \dot{\gamma}$	0.99969
37	$\tau = 9.98 + 8.23 \cdot \dot{\gamma}$	0.99927
46.5	$\tau = 4.81 + 4.11 \cdot \dot{\gamma}$	0.99651

Table 6. Rheological equations for emulsions B, C, D (Bingham model)

Emulsion	Temperature, ˚C		
	25	37	46.5
	Equation $\boldsymbol{\tau} = \boldsymbol{\tau}_0 + \boldsymbol{\eta}_{\boldsymbol{p}} \cdot \dot{\boldsymbol{\gamma}}$		
B	$\tau = 17.3 + 1.49 \cdot \dot{\gamma}$ (R^2=0.96868)	$\tau = 9.74 + 0.61 \cdot \dot{\gamma}$ (R^2=0.94597)	$\tau = 4.25 + 0.27 \cdot \dot{\gamma}$ (R^2=0. 88417)
C	$\tau = 9.46 + 13.61 \cdot \dot{\gamma}$ (R^2=0.99495)	$\tau = 5.15 + 6.35 \cdot \dot{\gamma}$ (R^2=0.99585)	$\tau = 2.31 + 0.75 \cdot \dot{\gamma}$ (R^2=0.9657)
D	$\tau = 20.9 + 6.56 \cdot \dot{\gamma}$ (R^2=0.98489)	$\tau = 11.48 + 3.6 \cdot \dot{\gamma}$ (R^2=0.9528)	$\tau = 3.59 + 0.7 \cdot \dot{\gamma}$ (R^2=0.97074)

Table 7. Rheological equations for emulsions B, C, D (Herschel-Bulkley model)

Emulsion	Temperature, ˚C		
	25	37	46.5
	Equation $\boldsymbol{\tau} = \boldsymbol{\tau}_0 + \boldsymbol{k} \cdot \dot{\boldsymbol{\gamma}}^{\boldsymbol{n}}$		
B	$\tau = 13.08 + 5.29 \cdot \dot{\gamma}^{0.582}$ (R^2=0.99877)	$\tau = 5.92 + 3.80 \cdot \dot{\gamma}^{0.485}$ (R^2=0.99954)	$\tau = 0.04 + 4.14 \cdot \dot{\gamma}^{0.283}$ (R^2=0. 88417)
C	$\tau = 8.15 + 15 \cdot \dot{\gamma}^{0.937}$ (R^2=0.9951)	$\tau = 2.56 + 8.87 \cdot \dot{\gamma}^{0.838}$ (R^2=0.9979)	$\tau = 0.215 + 2.64 \cdot \dot{\gamma}^{0.585}$ (R^2=0.99481)
D	$\tau = 9.17 + 18.75 \cdot \dot{\gamma}^{0.454}$ (R^2=0.99799)	$\tau = 0.023 + 15.23 \cdot \dot{\gamma}^{0.399}$ (R^2=0.99711)	$\tau = 1.39 + 2.48 \cdot \dot{\gamma}^{0.594}$ (R^2=0.99336)

From the structure of these equations, the rheological parameters that improve the behavior of cosmetic emulsions (viscosity, deformation rate, shear stress, etc.) can be approximated with sufficient precision when they are applied to the human skin organ, in order to improve or cancel some allergic or toxic actions for the human organism. Also, the rheological properties are important for the comfort of the users, comfort related to the uneven distribution of the more liquid creams used (which do not have the appropriate rheological properties), which can lead to quantitative loss and a reduction in the effectiveness of the product upon application.

4.4. Studies related to the modification of the stability of cosmetic emulsions in the case of their oxidation processes [19-22]

One of the physico-chemical processes that can influence the stability from the point of view of composition and organoleptic properties is the phenomenon of oxidation, which occurs when creams are exposed to air (oxidation and autooxidation) at different stages of the technological process, storage and use of the finished product. The oxidation stability of cosmetic emulsions is influenced by the type of lipids included in their composition and by their method of preparation.

The oxidation stability of the four emulsions (A,B,C,D) presented previously was followed for 420 days, by determining the peroxide values and the presence of oxidation products both at the beginning and at the end of the study.

To determine the peroxide values, two samples were taken from each of the four emulsions packed in airless polypropylene bottles. Samples marked A,B,C,D were kept in closed vials throughout the study period, and samples A1, B1, C1, D1 were exposed to air for 420 days.

The spectrophotometric method was used to determine the occurrence of secondary oxidation products. Thus, the presence of hydroperoxides, conjugated dienes and trienes and carboxylic compounds resulting from oxidation in cosmetic emulsions was characterized by the value of the specific extinction coefficient K232, and the presence of secondary oxidation products by the extinction coefficient K270.

Thus, it has been proven that cosmetic emulsions preserved and stored properly, when not exposed to air, have a high oxidation stability for a long time. Emulsions exposed to air, even if preserved and stored under appropriate conditions according to existing standards, have limited stability, depending on the composition, active principles and other ingredients liable to be oxidized.

4.5. The study of cosmetic creams based on statistical mathematical models that reflect the existing dependencies between different quality indicators [6,23]

Within the present research direction, cosmetic creams in the form of emulsions prepared according to own recipes by the phD candidate were chosen as the object of study.

Usually, the quality of a cosmetic cream is evaluated in specific laboratories by classical methods, respectively by physico-chemical, microbiological and organoleptic analyses.

Considering the advantages obtained by using mathematical modeling methods, frequently encountered in the systemic analysis of some materials, I proposed to study the emulsions prepared through the prism of Systems Theory.

The main property of a cosmetic emulsion that gives it a high quality is its stability (chemical-physical, rheological and microbiological) both during the manufacturing phase and during storage and use. In accordance with the legal norms provided by national and international legislation, stability is quantified through the values of specific quality indicators.

Within this direction of research, experimental determinations were made on the following physico-chemical and microbiological quality indicators: evaporation residue (RE), pH, total number of germs (NTG), as well as organoleptics.

The stages of carrying out this research activity were the following:

- The preparation of the 4 emulsions, which was made in accordance with the technology of obtaining water-in-oil (A/U) emulsions in the laboratory of S.C. Virago Beauty S.R.L.;
- Dosing and placing them in boxes with lids, made of plastic material (PP - polypropylene) and their storage in a suitable room with daily monitoring of temperature and humidity (15÷25ºC, 55÷65%) according to the requirements of the legislative norms available;
- Carrying out physico-chemical and microbiological analyses, as well as detection possible organoleptic changes (appearance, color, smell) on emulsions E1, E2, E3, E4, every month, for 4 years;
- Following the experimental measurements performed, a database was obtained regarding the characteristics of the studied emulsions, which can be found in tabular form in Annex 1 of the thesis;
- The Statistica 14.0 program was used to process the experimental data with help of which both the graphic representations in 3D format and the mathematical expressions of equations representing the statistical models characterizing the emulsions under study were obtained. Within this program, the values of the adequacy indicators for the determined equations were also obtained;
- The last operations performed were those of testing and verification of authenticity, the veracity and precision of the obtained mathematical models.

The graphic representations in 3D format, obtained by processing the experimental data, are

presented in the thesis for each individual emulsion.
Based on the conducted study, timely conclusions were drawn up on the existing dependencies between different quality indicators that majorly influence the properties of the studied emulsions.

The use of experimental-computational mathematical models determined can replace the classical monitoring of the characteristic parameters of cosmetic emulsions, as well as allowing the determination of predictions for the optimal values of the quality indicators, which will ensure the physico-chemical and microbiological stability of the creams.
Given the accelerated development of the use of artificial intelligence, I believe that the future technologies for obtaining cosmetic emulsions will be realized very soon only on the basis of computational mathematical models through the robotization of all technological phases in the manufacturing process of cosmetic products.

4.6. The complete study on the 24-month shelf life for the "Remineralizing anti-wrinkle cream" manufactured in S.C. Virago Beauty S.R.L.'s own laboratory.

Database processing (physico-chemical analysis results) obtained in the report delivered by the S.C. laboratory. Genmar Cosmetics S.R.L. using the methods of mathematical modeling and presenting the graphs obtained, the respective equations and the values of the calculated adequacy indicators

4.6.1. Complete study on the 24-month shelf life for "Remineralizing anti-wrinkle cream" manufactured in the company's own laboratory SC Virago Beauty S.R.L.

In order to approve the dossier for placing the "Remineralizing Anti-Wrinkle Cream" on the market, the services of testing its stability over time at a nationally accredited laboratory, namely the "LAFC Testing Laboratory of S.C. Genmar Cosmetics S.R.L.". Based on the Laboratory Report and an Analysis Bulletin in accordance with the national legislation available, the cream can be put on the market with a validity period of 24 months.

To ensure the health of people who use cosmetic products under normal conditions and in accordance with the instructions for use specified in the product leaflet, it is essential that they undergo a safety assessment to avoid unwanted effects on the human body.

According to Regulation (EC) no. 1223/2009, companies producing cosmetics must have a well-trained specialist in charge of product safety evaluation and the entire process of putting them on the market. This person is called the "responsible person" who also draws up the report on the safety of the cosmetic product based on the relevant information and in accordance with the requirements of the aforementioned regulation (this report is mandatory to be part of the product's notification and accreditation file so that it can be put on the market).

All the values of the physico-chemical quality indicators obtained fell within the admissibility conditions provided by the national legislation on the conformity of cosmetic products.

Regarding the material from which the packaging is made (polypropylene), it can be stated that it did not influence the physico-chemical behavior of the analyzed cream.

The obtained results confirm that the product "Remineralizing anti-wrinkle cream", tested from from the point of view of the stability of the physico-chemical parameters, according to the described methodology, it was stable during the entire test period, in the original packaging.

According to the study carried out (Annex 2 of the thesis), a validity period of 24 months is allowed for the "Remineralizing Anti-Wrinkle Cream", batch 01/2022, manufactured in 07/2022, with the mandatory requirement to comply with the storage conditions. These conditions are imposed both on the manufacturer and on its placing on the market (in pharmacies, specialized stores where it is sold and to the final consumer). The mentioned conditions refer to keeping the product in the original packaging, which does not allow the penetration of light and air, in clean and dry rooms, at temperatures between 5-25ºC.

The recommendations mentioned above must also be written on the product's inner (primary) and outer (secondary) packaging, according to the legislative norms available.

4.6.2. Database processing (physical-chemical analysis results) obtained in the report delivered by the S.C. laboratory. Genmar Cosmetics S.R.L. using the methods of mathematical modeling and presenting the graphs obtained, the respective equations and the values of the calculated suitability indicators [24]

To extend the utility of the experimental data obtained within the LAFC Test Laboratory of S.C. Genmar Cosmetics S.R.L. and to find out a series of additional information on the behavior of the "Remineralizing anti-wrinkle cream" I processed the data communicated by above mentioned laboratory in the "Analytical study report on the testing of the physical-chemical stability Remineralizing anti-wrinkle cream - batch 01/2022" using the experimental-computational mathematical modeling technique . Specifically, the Microsoft Excel program was used for data processing, with the help of which the mathematical models were developed in the form of equations of the 2nd degree.

Thus, the equations of the mathematical models representing the variation of mass loss, pH and density as a function of time were calculated at the working temperatures of 40±2°C and 4±2°C for the sample sent for approval.

The appropriateness indicators of the determined models were also calculated with the program used, obtaining acceptable values for them, which indicates that the determined models accurately reflect the behavior of the real cream during the tests performed.

Table 8 shows the equations of the obtained mathematical models and the calculated adequacy indicators.

Table 8. Equations of mathematical models obtained and the calculated adequacy indicators

Physico-chemical quality indicators	Equations of mathematical models	Model accuracy indicator, R^2	Correlation coefficient,, R
Evaporation loss %, at 40±2°C	$PM_{40} = 62{,}893-0{,}0275\cdot T^2 + 0{,}0596\cdot T$	0,9952	0,9976
Evaporation loss %, at 4±2°C	$PM_4 = 62{,}977-0{,}0271\cdot T^2 - 0{,}0364\cdot T$	0,9968	0,9984
pH at 40±2°C	$pH_{40} = 6{,}1557-0{,}0062\cdot T^2 - 0{,}0305\cdot T$	0,9936	0,9968
pH at 4±2°C	$pH_4 = 6{,}2386-0{,}0015\cdot T^2 - 0{,}1063\cdot T$	0,9812	0,9905
Relative density at 40±2°C	$d_{40} = 0{,}9279-8E^{-05}\cdot T^2 - 0{,}0008\cdot T$	0,9760	0,9880
Relative density at 4±2°C	$d_4 = 0{,}9274-0{,}0002\cdot T^2 - 0{,}0004\cdot T$	0,9941	0,9970

The adequacy indicators of the determined mathematical models fall within the limits of a good approximation, which can be noted in the correlation coefficient R, which has values very close to 1.

The obtained results lead to the conclusion that the mathematical models derived in this study are truthful and reproduce with a good approximation the behavior of the real system, respectively "Remineralizing anti-wrinkle cream".

Based on the conclusions drawn following the realization of these graphic

representations and the determination of the equations of the representative mathematical models for the studied cream, some recommendations can be made to the specialized laboratories that deal with the testing and approval of cosmetic products, especially creams in the form of emulsions, preparations according to the recipes of the products to be put on the market.
Chapter 5 contains the presentation of the necessary and mandatory steps that must be taken carry out the manufacturer in order to approve a new cosmetic product in order to launch it on the market. These stages were also completed in order to launch the "Remineralizing Anti-wrinkle cream" product on the market manufactured in "S.C. Virago Beauty S.R.L"'s own laboratory, by the phD candidate and of course for the other products that are obtained under this brand.

Chapter 6 presents the general conclusions formulated on the basis of the results obtained in the framework of the experimental research carried out during the elaboration of this thesis.

The studies carried out refer to theoretical and experimental research on cosmetic products used for different purposes. In general, cosmetic products are used to maintain the beauty of the human body, especially the epidermis.

In the specialized literature, many materials are presented that refer to the properties of the cosmetic products, the manufacturing technologies, as well as the parameters that represent the quality indicators that must be ensured, in accordance with the national and international legislation in force.

The worldwide increase in the frequency of dermatological problems for various reasons, both in children and in adults, has determined the diversification and development of cosmetic productions, which can alleviate or cure certain skin diseases, thus improving people's health.

The theoretical research, the obtained experimental results and their processing within the work highlighted the following aspects:

• The use of mathematical modeling techniques in order to improve the indicators of quality and microbiological is beneficial for the more in-depth study of the physico-chemical processes that take place during the manufacture, storage and use of cosmetic creams;

• Systemic approach to problems related to maintaining the stability of cosmetic creams using mathematical modeling and numerical simulation makes important improvements in their study, technology and marketing;

• By using the principles of Systems Theory it successfully benefits from the advantages scientific, applied and economic in the manufacturing techniques, the choice of raw materials and the necessary quantities, therefore financial savings on the price of the finished product, a very important thing in the competition of cosmetic products on the national and international market.

• The elaborated work has an interdisciplinary character, based on both the principles theories of cosmetology, chemical engineering and, last but not least, Systems Theory. At the same time, it is also based on other fields, such as: organic chemistry, physical chemistry, microbiology, mathematics, statistics, informatics, pharmacy, medical engineering, artificial intelligence, etc. As far as the experimental part is concerned, it can be stated that general and specific research tools were used to study the physico-chemical processes that take place in the characterization, manufacture and use of cosmetic creams.

• The obtained experimental database was processed with appropriate programs and software, obtaining mathematical models with good and very good accuracy, which allowed the identification of the most optimal manufacturing conditions and the most advantageous values for the quality indicators of cosmetic creams.

• At the end of the work, the necessary documentation is presented to obtain approvals at the placing on the market of a product prepared on the basis of an own recipe by the undersigned, in the S.C. Virago Beauty S.R.L. laboratory, in accordance with the legislation in force. When manufacturing the product, we took into account the conclusions drawn from all the studies carried out and applied the obtained solutions to improve the quality of this cream.

• The studies carried out in this paper are personal contributions to the research of the field of cosmetic creams, using both modern mathematical modeling techniques and classical research methods.

Chapter 7 contains the presentation of personal scientific contributions which are further presented as follows:

• Realizing of a documentation with bibliographic data regarding the current state of cosmetic products knowledge field: general notions about cosmetic emulsions and creams, their qualities and properties, raw materials and manufacturing technologies, fields of use and the benefits of their use, main and mandatory quality indicators for approval and marketing.

• Making a synthesis of the main norms and standards related to emulsions and cosmetic creams provided for by national and international legislation on manufacturing, authorization and marketing, as well as their mandatory control methods.

• Creating a bibliographic documentation with reference to the use of the Theory Systems in the studies and research carried out within the thesis, to the techniques of mathematical modeling, numerical simulation and to the analytical-statistical-computational methods of experimental data processing.

• Preparation of cosmetic emulsions, as well as their stability study them over time and performing periodic physico-chemical and microbiological analyzes with the measurement of parameters that are considered mandatory quality indicators.

• Obtaining some databases following the measurements carried out within 6 directions of research with objectives related to: stability, rheological properties, oxidation phenomena, shelf life and interdependencies between quality indicators.

• Analyzing the experimental results obtained on the emulsions prepared by the undersigned leads to the formulation of important considerations related to their composition, respectively the influence that the amount of active principles and perfume ingredients, as well as that of added preservatives, has on the desired properties of an emulsion, respectively a cosmetic cream. Thus, the increase or decrease of the amounts of active principles and perfume ingredients in the cream composition influences the viscosity and other rheological properties, a phenomenon that conditions the application process of the cream on the skin surface. The amount of preservative used in the prepared emulsion recipes influences another important parameter of the emulsion, namely its shelf life. However, when preparing emulsions, the limitations for the amount of preservatives imposed by national and international legislation must be taken into account.

• Experimental data processing was carried out using modeling techniques mathematics, so that the systemic approach to problems related to the maintenance of stability and other properties will bring important improvements to the study of the technology of obtaining and marketing cosmetic products.

• By using the principles of Theory Systems, it was benefited in the studies carried out of the scientific, applied and economic advantages, in the manufacturing techniques, the choice of raw materials and the necessary quantities, so that financial savings occur at the price of the finished product, an important factor in the competition of cosmetic products on the national and international market.

• The concrete development of some packages of mathematical models within the 6 directions of research was carried out using specific calculation programs: OriginPro 2021b, Microsoft Excel, TIBCO Statistica 14.0.0.15, TableCurve 2D.

• Testing and validation of the obtained mathematical models was performed based on the values adequacy indicators σ2, σ, R2, R, respectively of the classical method of calculating the absolute error E, as the difference between the value calculated from the model equation and the actual measured one.

• The elaborated work has an interdisciplinary character considering that I tried to apply the principles of Systems Theory in the study of cosmetic emulsions, benefiting in this way from the advantages related to the possibility of predicting some physico-chemical and microbiological behaviors of emulsions, which cannot be detected by classical methods.

• The conclusions obtained at the end of the conducted studies provide new information regarding the possibilities of improving the quality of cosmetic creams, respectively of developing manufacturing recipes that ensure the most advantageous benefits for the creams to be put on the market by the specialists in the field.

• At the end of the thesis, the documentation produced by the undersigned is presented obtaining approvals for the production and placing on the market of a product, namely "Remineralizing anti-wrinkle cream" batch 01/2022, manufactured in July 2022, in the S.C. own laboratory. Virago Beauty S.R.L.. This cream was manufactured according to a proprietary recipe, designed in accordance with the conclusions obtained from the studies covered in the paper.

• Processing the experimental data provided by the Genmar Cosmetics S.R.L. Laboratory, who tested the physico-chemical stability under accelerated conditions of the previously mentioned product, through the mathematical modeling technique (Microsoft Excel program) we obtained the mathematical equations and their graphic representations. The resulting adequacy indicators fell within the limits provided by the legislation in force, which proves once again that the systemic approach technique used is beneficial in the studies of cosmetic products. I will pass these conclusions on to the Genmar Cosmetics S.R.L. laboratory.

• As part of the undersigned's collaboration with the Faculty of Industrial Chemistry and Engineering Environment, CAICON Department, I specify that during 2019-2020 in the laboratory S.C.Virago Beauty S.R.L. the student Carpa Daiana, currently a chemical engineer, carried out her practical activity at the end of the third year, provided for in the education plan.

• I mention that the works published based on the studies carried out in the thesis were appreciated in Specialty literature. As such, at the end of the thesis, the published works are annexed in full, as well as the emails received from some collectives or specialists in the field of cosmetic products, who appreciated the results presented in these articles.

Taking into account the content and approach to the established objectives, this work with a strong interdisciplinary character, tries to satisfy the current requirements of a doctoral thesis, responding to scientific, theoretical and applied demands, both from the point of view of the science of cosmetology, and and from that of Systems Theory.

It should also be mentioned that the work addresses a series of specific aspects related to Chemical Engineering and Rheology directly involved in the studies of the physico-chemical processes that take place in the manufacturing technologies, as well as in ensuring the values of the quality indicators of the imposed cosmetic products by national and international legislation in force.

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