**ANNOTATION**

Of the dissertation work on the topic **"Development and conformity assessment of *Rosa platyacantha* Schrenk based perfumery and cosmetic product"**

for the degree of Doctor of Philosophy (PhD) in the specialty

6D074800 - Pharmaceutical manufacturing technology by

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**Relevance of the research topic.**

The mission for improving the health of the population is established as a priority within the framework of the "Quality and affordable healthcare for every citizen "Healthy Nation" National project. Despite the growth rates of the Kazakhstan's domestic pharmaceutical industry, which includes the perfumery and cosmetics industry, import dependence remains an urgent problem, expressed by the share of domestic production of medicines and cosmetic products to import, respectively, 83% and 90%. Thus, the domestic production of perfumery and cosmetic products, according to the Statistics Agency of the Republic of Kazakhstan, is less than 10% of total consumption.

Within the framework of the Strategic Plan for Industries Development "Kazakhstan - 2030" and the State Program for Infrastructure Development "Nurly Zhol" for 2020-2025, the creation of new domestic production of consumer goods, including perfumery and cosmetic products, received the status of a state priority as one of the main drivers of growth in the economic well-being of the population. A necessary condition for ensuring the competitiveness of perfumery and cosmetic products manufacturing at the world level is the development of knowledge-intensive full-cycle industries.

The production of a full cycle of perfumery and cosmetic products, carried out in accordance with the requirements of GACP and GMP practices, will ensure the consistency and uniformity of product quality.

In recent years, in the Republic of Kazakhstan, there has been an active formation and development of such a field of activity as cosmetology. Cosmetology centers of aesthetic medicine providing cosmetic services have formed a strong cluster of small and medium-sized businesses. The market demand trends for these products fully demonstrate the annual growth in consumption by the population, which includes both an increase in turnover and an expansion of the range of products. At the same time, there is a tendency to develop original formulations of perfumery and cosmetic products through the introduction of the achievements of modern pharmaceutical science and new manufacturing technologies.

For the purposes of creation of original perfumery and cosmetic products, plants of the genus *Rosa* of the *Rosaceae* family are a valuable source of biologically active substances.

Pharmacopoeial wild rose species (*Rosa acicularis* Lindl., *Rosa beggeriana* Schrenk., *Rosa corymbifera* Borkh., *Rosa fedtschenkoana* Regel., *Rosa majalis* Herrm.) are widely used as an antibacterial, anti-inflammatory, hepatoprotective, antioxidant, hypoglycemic, choleretic and immunostimulating agent. Non-

pharmacopoeial species are widely used in folk medicine as a tonic and vitamin remedy. One of the numerous species of wild rose species used for the above-mentioned purposes, which still remains unstudied is a representative of the genus *Rosa,* same as the wild rose (*Rosa platyacantha* Schrenk.), which grows widely on the territory of the Republic of Kazakhstan and is not inferior in its valuable properties to other species.

The development of herbal pharmaceutical substances and innovative cosmetic products based on *Rosa platyacantha* Schrenk. seems to be a promising direction in pharmaceutical and manufacturing research.

**Purpose of the study.**

Development of a technology for obtaining a herbal pharmaceutical substances from *Rosa platyacantha* Schrenk. and the creation of an original cosmetic product based on it.

**Research objectives:.**

1. Carry out marketing researches of the Kazakhstani market of perfumery and cosmetic products.
2. Harvesting, pharmaceutical and technological research and standardization of raw materials from *Rosa platyacantha* Schrenk.
3. Development of a technology for the production of herbal pharmaceutical substances from *Rosa platyacantha* Schrenk. and the establishment of a profile of their pharmacological activity.
4. Development of the composition, technology and standardization of cosmetic cream with *Rosa platyacantha* Schrenk. extract.
5. Technology transfer and validation evaluation of pilot production of cosmetic cream with *Rosa platyacantha* Schrenk. extract.
6. Feasibility study for the production of cosmetic cream and a plan for its commercialization.

**Objects of research:** *Rosa platyacantha* Schrenk. and its morphological organs (leaves, stems, flowers / buds and fruits), extract from *Rosa platyacantha* Schrenk., cosmetic cream.

**Research methods:** pharmacopoeial and non-pharmacopoeial methods (physical, physico-chemical, pharmacognostic, pharmaceutical-technological, pharmacological, biological, information-analytical and statistical), as well as marketing research methods.

**Scientific novelty.**

For the first time:

– marketing analysis of the domestic market of perfumery and cosmetic products with herbal pharmaceutical substances was carried out in order to justify the production of new products.

– pharmaceutical and technological study of the raw material of *Rosa platyacantha* Schrenk. was carried out. Mmorphological and anatomical diagnostic features of leaves, flowers and fruits were determined in order to standardize raw materials.

– comprehensive characterization of the chemical profile and individual biological properties of extracts obtained from various parts of the *Rosa platyacantha*

Schrenk. species has been determined. The presence of gallic and ellagic acids and their derivatives, quercetin, rutin, kaempferol and their derivatives as the most characteristic components of the chemical composition of the plant was established. The presence of brevifolin derivatives in *Rosa platyacantha* Schrenk species has been confirmed for the first time.

– it was found that the extract from *Rosa platyacantha* Schrenk buds has a significant antioxidant potential, confirmed by conventional DPPH and ABTS radical scavenging assays, as well as in vitro studies on HaCaT keratinocytes. The extract from the buds is effective against human melanoma cells, while it exhibits significantly less cytotoxicity against non-cancerous skin cells, and effectively inhibits the monophenolase and diphenolase activity of tyrosinase. Based on the biological activity profile of *Rosa platyacantha* Schrenk flower bud extract should be considered as an effective active ingredient in skin brightening, anti-aging and protective cosmetics.

– a new method for obtaining an extract from the raw material of *Rosa platyacantha* Schrenk has been developed, which makes it possible to increase the yield of biologically active substances. The novelty of the developed method is confirmed by utility model patent No. 6574 “Method for obtaining rosehip extract”, registered in the State Register of Utility Models of the Republic of Kazakhstan on 10/29/2021.

– safety and the local irritating and allergenic effect of *Rosa platyacantha* Schrenk extracts have been established.

– an original recipe and an optimal technology for obtaining a cosmetic cream with *Rosa platyacantha* Schrenk have been developed. An application has been filed for a patent of the Republic of Kazakhstan for a utility model No. 2022/0626.2 dated 07/15/2022 "Cream with antioxidant, brightening, anti-collagenase, anti-elastase, anti-tyrosinase, anti-melanoma actions".

**The main provisions of the dissertation research submitted for defense:**

- results of the marketing analysis of the Kazakhstani market of perfumery and cosmetic products and the rationale for the production of new products based on domestic resources of *Rosa platyacantha* Schrenk.;

- results of the development of a technology for obtaining herbal pharmaceutical substances from *Rosa platyacantha* Schrenk. as a source of biologically active compounds for cosmetic purposes;

- results of the development of a rational composition, and technologies for obtaining, standardizing and evaluating the conformity of a cosmetic cream. A feasibility study for the production of the cream and a plan for its commercialization.

**The practical significance of the study.**

Technological instructions for the collection, processing and storage of *Rosa platyacantha* Schrenk raw materials have been developed and implemented. for pilot series at the pharmaceutical company Fitoleum LLP, Esik, Republic of Kazakhstan (Act of Implementation No. 8 dated August 15, 2017).

A method for obtaining an extract from *Rosa platyacantha* Schrenk raw materials has been introduced, which makes it possible to obtain a product with the maximum release of biologically active substances on a pilot scale at Fitoleum LLP, Esik, the Republic of Kazakhstan (Act of implementation No. 9 of 09/07/2017).

Technological regulations for manufacturing and production of herbal pharmaceutical substances from raw materials (fruits, flowers/buds and leaves) of *Rosa platyacantha* Schrenk have been developed and approved at Fitoleum LLP, Esik, Republic of Kazakhstan, validation tests of the production process were carried out.

Quality specifications for herbal pharmaceutical substances have been developed: medicinal herbal raw materials (fruits, flowers/buds, leaves) *Rosa platyacantha* Schrenk. and extracts from it, approved by Fitoleum LLP, Esik, Republic of Kazakhstan.

A regulatory document STANDARD OF ORGANIZATION "Zhayik - AS" LLP for cosmetic products "Cream with wild rose hip (*Rosa platyacantha* Schrenk.)", ST LLP 040840006381-01-2022 was developed and approved. A technology transfer and a validation evaluation of the pilot production of a cosmetic cream with *Rosa platyacantha* Schrenk. extract were carried out. Approbation of pilot series of cosmetic cream with *Rosa platyacantha* Schrenk. was carried out at the pharmaceutical enterprise Zhayik-AS LLP, Almaty, Republic of Kazakhstan (Act of Approbation).

A feasibility study and a plan for the commercialization of a cosmetic cream with *Rosa platyacantha* Schrenk. have been developed.

Implemented in the scientific and educational program of the Department of Cosmetology of the University of Information Technology and Management in Rzeszow (Rzeszow, Poland) the results of the development of the composition and production technology of a cosmetic cream with *Rosa Platyacantha* Schrenk., as well as the assessment of its quality.

**Personal contribution of the author.**

All the results of the dissertation research were obtained by the author independently, which testifies to the personal contribution of the applicant to science in the field of pharmaceutical manufacturing technology.

The reliability of the results, the main provisions submitted for defense, the deductions and conclusions formulated in the dissertation work are substantiated by a significant amount of experimental material, and are fully confirmed by the results of our own research conducted in laboratory and production conditions, using modern instruments and accurate measurement methods, as well as comparison with literary data.

**Approbation of the work.**

The main provisions of the dissertation work were reported and published in the following materials: International scientific and practical conference "Modern methods of correction of acne and other skin problems in the practice of a

cosmetologist" (October 2018, Ukraine, Kharkiv); VI All-Russian scientific and practical conference with international participation "Innovations in the health of the nation" (November 2018, Russian Federation, St. Petersburg); VII Scientific and practical conference with international participation "Priorities of pharmacy and dentistry: from theory to practice" (November 2018, Republic of Kazakhstan, Almaty); VI International scientific conference of young scientists and students "Prospects for the development of biology, medicine and pharmacy" (December 2018, Republic of Kazakhstan, Shymkent); Second Austrian Summit on Natural Products "Phytovalley 2019" (January 2019, Seefeld in Tirol, Austria); XIV International scientific and practical conference of young scientists and students "Scientific discussion: current issues, achievements and innovations in medicine" (April 2019, Tajikistan, Dushanbe); IV International Scientific Conference "Scientific Discoveries" (January 2019, Czech Republic, Karlovy Vary - Russian Federation, Moscow); International scientific-practical conference of students, young scientists and teachers "Akanovskie readings: The role of PHC in achieving universal health coverage" (April 2019, Republic of Kazakhstan, Almaty); VIII Scientific and practical conference with international participation "Priorities of pharmacy and dentistry: from theory to practice", dedicated to the memory of Abdullin K.A. (November 2019, Republic of Kazakhstan, Almaty); International scientific and practical conference "Pharmaceutical education, modern aspects of science and practice" (May 2019, Russian Federation, Ufa); X All-Russian scientific conference of students and graduate students with international participation "Young pharmacy - the potential of the future" (April 2020, Russian Federation, St. Petersburg); International conference “Modern science. Management and standards of scientific research”, “Modern science. Management and standards of scientific research” (October 2020, Czech Republic, Prague); IV International Scientific and Practical Conference "Innovative Technologies in Pharmacy" (April 2021, Czech Republic, Prague); International Scientific and Practical Conference "Modern Pharmacy: New Approaches and Current Research" (October 2021, Republic of Kazakhstan, Almaty); V International Scientific and Practical Conference "Innovative Technologies in Pharmacy" (March 2022, Czech Republic, Prague).

**Information about publications.**

Based on the results of the research, 16 scientific papers were published, including: an article in an international peer-reviewed scientific journal included in the Scopus database and Web of Science Core Collection - 1; articles in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan - 3; abstracts and articles at international scientific and practical conferences (Russia, Austria, Czech Republic, Tajikistan, Kazakhstan) - 10; articles in international journals (Russia) - 1; utility model patents of the Republic of Kazakhstan - 1.

**Research objectives and the scientific programs plan connection.**

The dissertation work was carried out within the framework of the International Project "Cosmetic Valley - International Scientific and Implementation Cooperation at the Cosmetology Department" No. PPI/APM/2018/1/00042/U/001 (Narodowa Agencja Wymiany Akademickiej - NAWA).

**The volume and structure of the dissertation.**

The dissertation work is presented on 149 pages of typewritten text in a computer set, contains 40 tables, 53 figures, a list of references, including 247 sources, and 35 appendices. The work consists of an introduction, a literature review, a section on research materials and methods, three sections of own research, conclusions and a conclusion.

**Conclusion.**

The dissertation work is devoted to the systematic study, standardization of raw materials of *Rosa platyacantha* Schrenk., proper development of herbal pharmaceutical substances and cosmetic product based on it. This research work was carried out on the bases of NJSC “KazNMU named after S.D. Asfendiyarov" (Almaty, Republic of Kazakhstan), Lublin Medical University (Lublin, Poland), Research Institute of FPM named after. B.A. Atchabarova (Almaty, Republic of Kazakhstan), Fitoleum LLP (Esik, Republic of Kazakhstan), Zhayik-AS LLP (Almaty, Republic of Kazakhstan). Approbation, validation and pilot production of herbal pharmaceutical substances and cosmetic products were carried out at local pharmaceutical enterprises "Fitoleum" LLP, "Zhayik-AS" LLP.

According to the Agency on Statistics of the Republic of Kazakhstan, more than 90% of Perfumery-cosmetic products (“PCP”) is produced in the countries of near and far abroad. The procedure for assessing conformity of PCP and permitting the circulation of these products on the territory of the EAEU is carried out by declaring based on the requirements of the technical regulation TR CU 009/2011 "On the safety of perfumery and cosmetic products". For some types of PCP, a state registration procedure is provided for by the authorized body of the EAEU member state. Specific requirements for PCP manufactured for the common market are regulated by unified sanitary rules and regulations, and requirements for production facilities, storage and sale of PCPs in the territory of an EAEU member state, in particular, the Republic of Kazakhstan, are regulated by national rules. Thus, the modern production of PCPs according to the original recipes based on natural raw materials of Kazakhstan seems to be a new vector for the development of the domestic perfumery and cosmetics industry.

Plants of the genus *Rosa* are part of the *Rosacea* family and are widely distributed throughout the world. On the territory of the Republic of Kazakhstan, there are 24 species of wild rose, of which wild rose (*Rosa acicularis* Lindl.,), Begterovsky wild rose (*Rosa beggeriana* Schrenk.), Shield-bearing wild rose (*Rosa corymbifera* Borkh.), Fedchenkovsky wild rose (*Rosa fedtschenkoana* Regel.), Cinnamon rose hip (*Rosa majalis* Herrm.) are pharmacopoeial, and *R. Pavlovii, R. Iliensis, R. Dsharkentii* are endemic species.

Among the plants of the genus *Rosa* growing in Kazakhstan, a special place is occupied by wild rose hip (*Rosa platyacantha* Schrenk.), whose distribution areas

determine sufficient reserves. This species is cultivated on the plantations of Fitoleum LLP. The plant is poorly studied, pharmacognostic studies have not been conducted, and the profile of pharmacological activity has not been described.

In accordance with GOST 32048-2020 “Perfume and cosmetic products. Terms and definitions" the concept of "perfume and cosmetic products" corresponds to the term "cosmetics". Economic activity related to the production, consumption, foreign and domestic trade of PCPs in the Republic of Kazakhstan is defined within the framework of a single concept of "perfumes and cosmetics". Accordingly, the macroeconomic indicators of the market of cosmetic products in the Republic of Kazakhstan are determined together with perfumery products.

Domestic PCP market in Kazakhstan in physical terms within 2016 shows a steady trend towards stabilization, averaging 73.1 thousand tons. The exception is 2021, in which the macroeconomic impact of the global COVID-19 pandemic was critical. In 2021, the volume of PCP production in Kazakhstan reached 6.7 thousand tons, which is more than 2 times higher than in 2016. The maximum increase in production occurred in the pre-pandemic year of 2019, amounting to 66% compared to the same period last year. By 2021, the percentage ratio of PCP produced in Kazakhstan to the total market volume reached a “record” of 9%, which indicates the prevailing (91%) presence of imported products. Domestic production occupied only an average of no more than 5% of its volume. Thus, the market of Kazakhstan in this segment is largely dependent on imports.

Within the framework of this study, an integrated concept of the full cycle of production of cosmetic products was developed in accordance with the requirements of international standards of good practices (GACP, GMP, GSP), as well as the Technical Regulations of the Customs Union (CU TR 009/2011), the State Standard (ST RK 1076-2002) and sanitary regulations of the Republic of Kazakhstan. The production process of a full cycle cosmetic products based on herbal pharmaceutical substances from *Rosa platyacantha* Schrenk consists of successive stages, the main of which are: preparation and standardization of raw materials, obtaining standardized herbal pharmaceutical substances, safety assessment, creation of a cosmetic product, technology transfer, conformity assessment of finished products and feasibility study.

Based on the morphological features and dynamics of the accumulation of biologically active substances in the raw material of *Rosa platyacantha* Schrenk. laboratory and pilot regulations for the collection, processing and storage of fruits, flowers/buds and leaves of this species were developed. The development of an appropriate technology for the collection and processing of raw materials, the establishment of optimal conditions for its storage was carried out within the framework of GACP.

For the first time, macroscopic and microscopic diagnostic features of each type of raw material (fruits, flowers/buds, stems, leaves) of *Rosa platyacantha* Schrenk. have been determined.

Pharmaco-technological study of *Rosa platyacantha* Schrenk. raw materials. made it possible to determine the optimal concentration of the extractant and the degree of grinding of raw materials for extraction. The maximum yield of extractives

was obtained with ethyl alcohol in the concentration range of 30-70% with a raw material fineness of 1.0-1.5 mm.

Phytochemical analysis by GC-MS of fruits, flowers/buds, stems and leaves of *Rosa platyacantha* Schrenk. showed the presence of 31 compounds. The presence of components of hydrolysable tannins (gallotanins and ellagitannins) was found. In the chromatographic analysis of extracts obtained from different parts (flowers/buds, stems, leaves) of *Rosa Platyacantha* Schrenk., it was found that the most characteristic compounds are quinic acid, methoxygallic acid isomer and methylbrevifoline carboxylate. Ellagic and gallic acids were identified in the methanol extracts. For the first time, the presence of brevifolin derivatives was found in the *Rosa platyacantha* Schrenk. Species. Among other characteristic components, the presence of derivatives of gallic and chlorogenic acids, as well as flavonoids, which determine the significant antioxidant activity of the extracts, was established.

Quality specifications for medicinal plant raw materials of *Rosa platyacantha* Schrenk have been developed and approved at Fitoleum LLP. (Fruits, flowers/buds, leaves). Real-time stability studies made it possible to establish the shelf life in packaging for each type of raw material (three-layer bags of kraft paper) of 24 months at a temperature not exceeding 25±2 °C and relative humidity not exceeding 60±5%.

A rational technology for extracting biologically active substances from fruits, flowers/buds and leaves has been developed. Production method based on the maceration method using ultrasound in the optimal range of 20-35 MHz for 20-30 minutes, allows you to increase the yield of biologically active substances in the finished product (patent No. 6574 dated October 29, 2021). The proposed technology for obtaining extracts was tested at the production site of Fitoleum LLP. The parameters of critical stages of the technological process are regulated.

Conducted non-clinical studies of acute and subacute toxicity, local irritant and allergenic effects, that indicate the safety of the studied extracts, which allows them to be attributed to the fifth class of toxicity. Studies of the pharmacological activity profile of fruit, flower/bud and leaf extracts of *Rosa platyacantha* Schrenk. determined their pronounced antioxidant, anti-collagenase, anti-elastase, anti-tyrosinase and anti-melanoma effects. Thus, the obtained results confirm the possibility of using extracts of *Rosa platyacantha* Schrenk. as active pharmaceutical ingredients in the development of new dosage forms and cosmetics.

The standardization of herbal pharmaceutical substances obtained from the fruits, flowers/buds and leaves of *Rosa Platyacantha* Schrenk. was carried out in accordance with the requirements of the State Pharmacopeia of the Republic of Kazakhstan. Quality indicators and criteria for their acceptability have been established, quality specifications for herbal pharmaceutical substances have been developed, approved by Fitoleum LLP. Thus, the quality requirements for herbal pharmaceutical substances from *Rosa Platyacantha* Schrenk raw materials. meet the general requirements of the State Pharmacopeia of RK for extracts.

Herbal pharmaceutical substances remain stable for 27 months at a temperature not exceeding 25±2 °C and relative humidity not exceeding 60±5%. Thus, their shelf life (shelf life) is 2 years under the specified conditions.

A prognostic evaluation of the pharmacological activity of the obtained herbal pharmaceutical substances from *Rosa platyacantha* Schrenk. was carried out, based on the results of predicting the pharmacological effect performed using computer simulation of chemical objects *in silico* in the database of the PASS-online program. The results obtained confirm the high antioxidant effect of herbal pharmaceutical substances, as well as a significant degree of their anti-inflammatory activity. It has been established that biologically active compounds contained in herbal pharmaceutical substances inhibit the expression of matrix metalloproteinases (MMP9) and intercellular adhesion molecules (ICAM-1) involved in skin aging processes, and are also capable of absorbing UV radiation in the range of 200-400 nm (UVA and UVB) as natural alternative sunlight filters. The results of the study of the pharmacological activity of herbal pharmaceutical substances, as well as the analysis of the data of computer modeling of the forecast, were the basis for the development of a cosmetic cream with *Rosa platyacantha* Schrenk.

In the formulation of the cosmetic cream, the required content of the herbal pharmaceutical substance was determined taking into account the results of the safety study and amounted to 1-2%. Cosmetic cream includes hydrophilic and lipophilic phases. The composition of the hydrophilic phase includes a concentrate of herbal pharmaceutical substances in glycerin and excipients (purified water, rose hydrolate and xanthan gum). The lipophilic phase contains, as excipients, rosehip oil, traditionally used in the manufacture of pharmaceutical products, isononyl isononanoate, cetearololivat, sorbitanolivat and sucrose stearate. The last three substances are used as emulsifiers. *Rose* essential oil, added to the finished mass, acts as a preservative and flavoring agent.

In the process of developing the technology, the rheological properties of the cosmetic cream were studied. The plastic type of its flow and viscoelastic properties have been established, which justify the uniform distribution of the cream over the surface of the skin, that is, its easy spreadability.

The technology for obtaining a cosmetic cream includes the stages of preparation of raw materials, preparation of hydrophilic and lipophilic phases, preparation of an emulsion and homogenization, followed by packaging and packaging of the finished product.

The critical stages of the technological process for obtaining a cosmetic cream have been fully validated. The technology was transferred to a pilot scale at the production site of Zhaiyk-AS LLP, and a pilot industrial regulation was developed.

To standardize the quality of a cosmetic cream with wild rose hips, a regulatory document for perfumery and cosmetic products− organization standard ST LLP 040840006381-01-2022 has been developed and approved. Consumer qualities and safety of a cosmetic cream are ensured by checking its organoleptic and physico-chemical parameters, determining the impurities of elements, pesticides and microbiological purity. On the basis of this document, the quality of pilot samples of cosmetic cream was assessed. The quality of the product is confirmed by test reports in the accredited laboratory of NPKAL of Fitoleum LLP.

Long-term stability tests of the cosmetic cream with *Rosa platyacantha* Schrenk in the proposed consumer packaging showed that there were no significant changes in

quality indicators over the study period (12 months), and the results were within the regulated limits. Based on the data obtained, the recommended storage conditions for the cosmetic cream were established (temperature not more than 25 °C and relative humidity not more than 75%). Shelf life of the product before completion of long-term stability testing was 1 year.

A feasibility study for an investment project for the production of a cosmetic cream with *Rosa platyacantha* Schrenk. has been carried out. Implementation of the investment project "Production of perfumery and cosmetic products - cosmetic cream with extracts of *Rosa Platyacantha* Schrenk." is assumed to be implemented on the basis of the "Zhaiyk AS" LLP company of the corresponding profile. The implementation of the project is envisaged on the basis of the current legislation in the field of labor protection and regulatory documents regulating the quality, safety and efficiency of products. The conducted financial analysis showed high profitability of the developed investment project. The payback period for the project is 1.4 years.

Thus, as a result of the studies carried out withing dissertation work, herbal pharmaceutical substances from *Rosa platyacantha* Schrenk. and an original cosmetic product in the form of a cream with antioxidant, anticollagenase, antielastase, antityrosinase, antimelanoma and light-protective effects were developed and obtained.