

Available online on 15.07.2021 at <http://ujpr.org>**Universal Journal of Pharmaceutical Research***An International Peer Reviewed Journal*

Open access to Pharmaceutical research

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial Share Alike 4.0 License which permits unrestricted non commercial use, provided the original work is properly cited

**Volume 6, Issue 3, 2021**

Open Access

**REVIEW ARTICLE****A CRITICAL STEP FOR THE COSMETIC INDUSTRY: SCALE-UP****Meltem Ezgi DURGUN<sup>1</sup> , Evren ALGIN YAPAR<sup>2\*</sup> **<sup>1</sup>*Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Istanbul, Turkey.*<sup>2</sup>*Ministry of Health, Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratory, Ankara, Turkey.***ABSTRACT**

The perception of aesthetics directs the daily life of people from ancient times to the present. While the desire to be beautiful turns into a passion for some, it can also become a medical necessity for some people, such as war veterans. The historical documents examined show that both men and women use different materials either to change their appearance or to care their skin or hair. These materials still lead the way in the development of today's cosmetic products. The cosmetics industry is an important business line developed based on this aesthetic perception of societies. Starting from the research and development (R&D) process of a cosmetic formulation and becoming a final product, health authorities control the industry by various regulations that are based on safety evaluation and good manufacturing practices. In this process, where each step must be meticulously fulfilled, perhaps the most critical step is the scale-up process. In this review, cosmetic products, scale-up and critical parameters in scale-up process are discussed.

**Keywords:** Critical transfer parameters, cosmetics, manufacturing, optimization, quality control, scale-up.

**Article Info:** Received 7 May 2020; Revised 16 June; Accepted 23 June, Available online 15 July 2021

**Cite this article-**

DURGUN ME, ALGIN YAPAR E. A critical step for the cosmetic industry: scale-up. Universal Journal of Pharmaceutical Research 2021; 6(3):77-82.

**DOI:** <https://doi.org/10.22270/ujpr.v6i3.611>

**Address for Correspondence:**

**Assoc. Prof. Evren ALGIN YAPAR**, Ministry of Health, Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratory, Ankara, Turkey, Tel- +903125655370; E-mail: [evren.yapar@yahoo.com](mailto:evren.yapar@yahoo.com)

**INTRODUCTION**

The concepts of "aesthetics" and "beauty" have been two elements that affect people's daily lives since ancient times. Contrary to popular belief, these concepts have not been a part of our lives after modern technology's convenience and living standards. Since ancient times, human beings have always attached importance to their appearance and aimed to increase their appreciation in society by enriching their clothing with an accessory or using any cosmetic product<sup>1</sup>. In the historical documents, it is seen that people resort to many ways to preserve their beauty and bodily integrity. For example, it is known that in ancient Egypt, Cleopatra put atropine, obtained from *Atropa belladonna*, into her eyes to make her eyes look bigger and more attractive<sup>2</sup>. When the tomb of Pharaoh Pharaoh Tuthmosis III (1400BC) was examined, it was determined that materials intended to increase beauty were used<sup>3,4</sup>. Another important finding obtained from this tomb was that these materials used for cosmetic purposes also protect the eyes and skin against the African desert winds. Henna is also one of the cosmetic

and medicinal materials used in a widespread geography since ancient times<sup>5,6</sup>. Henna, which is thought to have a history of close to 9000 years, is one of the oldest traditional products known in India, Persia, North Africa, the Arabian Peninsula, Mesopotamia, and the Mediterranean. Simple cosmetic formulations prepared by people at home in ancient times continued to be produced in small workshops over the years, and today they have turned into a large industry<sup>7</sup>. Undoubtedly, the fact that the concepts of beauty and aesthetics affect all people plays an important role in the background of this great industrial development. Because when people think of beauty, which is expressed as "a combination of qualities that satisfy the aesthetic senses", women come to mind first, but it is actually an important concept for both genders<sup>4</sup>.

While the cosmetics industry was developing, some problems also arose<sup>8</sup>. These problems are listed in generally;

- A significant increase in the amount of these products, which were previously produced in small quantities,

- Changes to be made in manufacturing equipment as the batch size increases,
- The need for products to meet the needs of a wider audience, not a single person,
- Based on the time difference between the preparation and consumption of the product, the ability to maintain its stability in processes such as shelf life and transfer.

“Scale-up” and “scale-down” are the most critical steps in an industry where production is concerned<sup>8</sup>. The preparation of a final product in different quantities than it is worked on during the research and development (R&D) process is expressed as “scale-up” or “scale-down”. Generally, when we look at the pharmaceutical or cosmetic industry, R&D batch sizes are made in possible minor quantities<sup>9</sup>. For this reason, the concept of scale-up appears more frequently in these areas when transferring from R&D processes to mass production. However, scale-down can also be done in cases such as a decrease in the need for an existing product or a market shrinkage. With a properly performed feasibility study, the scale-up process of a product's transferring from R&D laboratories to the production line is successfully completed.

## OVERVIEW OF COSMETICS

### Identification and classification of cosmetics

The FDA defines a “cosmetic” as a product (excluding pure soap) intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance<sup>10</sup>. According to the regulation of the Council of the European Union: “cosmetic product means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition, or correcting body odours”<sup>11</sup>. In the Far East the scope of cosmetics differ from the EU according to the Korean Cosmetic Products Act divides cosmetic products into the following three categories<sup>12</sup> and between those functional cosmetics and quasi-drugs are subjected to premarket license of competent authority.

- General cosmetics
- Functional cosmetics; sunscreens, skin-whitening products, etc.
- Quasi-drugs; anti-acne preparations etc.

Cosmetic products are generally used to correct body odor, change the appearance, to protect and care for the skin<sup>12-14</sup>. Through the diversity of definition and scope, there are various classes and expressions attributed to cosmetics even in the legislations or the literature. Of these expressions, some of which can be found in legislations and global scientific articles are; cosmeceuticals, dermocosmetics, functional cosmetics, dermatocosmetics, active cosmetics, etc. In fact, cosmetics are considered a subgroup of pharmaceutical sciences. Albert Kilman, a dermatologist, coined the term “cosmeceutics” (or active cosmetics) in the 1984,

which was not thought to have a clear biological therapeutic effect while having a beneficial effect on the skin. Dermocosmetics are considered as products related to the aesthetic appearance of the skin, which can be on the border of cosmetics and medicines such as skin care products, avoid superficial skin problems and improves skin appearance and health<sup>15-17</sup>. The uses of cosmetics can be grouped according to their main functions as follows<sup>11-17</sup>:

- Products for changing appearance (decorative cosmetics)
- Products for personal care (cleaning and caring)
- Products for perfuming
- Active cosmetics (cosmeceutics, dermocosmetics, etc.)

### Cosmetics, Camouflage, and Rehabilitation

The fact that appearance is always important for people from ancient societies to the present brings aesthetic concerns and psychological problems. It is known that people may experience a lack of self-confidence and have difficulty in social life in cases such as a scar on the visible part of the body, skin color unevenness, or acne. Wars also have led to the development of different industries. The effect of make-up on camouflage and rehabilitation developed as a result of such a situation. It was featured as a medical aid for the rehabilitation of seriously burned pilots after World War II<sup>18-22</sup>. Whether these external appearance disorders are congenital or acquired later, the negative feeling it creates on people is the same. In this situation, people first seek a permanent solution to the problem by choosing a medical or surgical intervention. However, medical or surgical intervention is not always possible. This is where cosmetic products come into play. It is combined with medical practice to help patients hide congenital or acquired deformities that are not suitable for medical or surgical treatment<sup>23</sup>. Studies have shown that the camouflage provided by cosmetics has a profound improvement effect on the quality of life of patients<sup>24</sup>. These camouflage cosmetics, which are different from normal make-up products, reinforce the fact that cosmetic science is a sub-branch of pharmaceutical sciences.

### Cosmetics and Novel Technology

Industrial developments occur due to the inadequacy of existing products to produce solutions, competition in market share, changes in people's needs or consumption habits. Although a positive step has been taken with new technological developments, always aiming for the better ensures the continuity of science. The pharmaceutical and cosmetic industry is one of the areas that constantly renew itself. The most important technological development for pharmaceutical and cosmetic products is the changes in formulations. Conventional products such as creams, solutions, gels, and ointments have disadvantages such as not having high efficacy, not being able to cross body barriers, rapid elimination, applying frequently, and having high side effects. Thus, drug delivery systems have been developed. These systems ensure that the drug is delivered to the target area thanks to a suitable carrier. With similar logic, these carrier systems can also be

used for cosmeceutics. Active ingredients used in cosmeceuticals are minerals (fluoride in toothpaste), vitamins (vitamin A-retinol and vitamin E-tocopherol), peptides (dermal collagen derivatives such as pal-KTTKS and Cu-GHK), herbal products (ginseng, ginkgo biloba, soy, silymarin, and green tea) or growth factors<sup>25</sup>. With a suitable carrier, these active cosmetics can pass through dermal barriers and reach the target tissue directly, improve pigmentation, and have a sustained effect. For this purpose, innovative systems frequently used in the cosmetic field are nanocrystals, micelles, liposomes, solid lipid nanoparticles, cubosomes, transferosomes, phytosomes, etosomes, transdermal patches, micro and nanoemulsions, micro and nanoparticles, dendrimers, carbon-based nanoparticles (fullerenes), and micro-needles<sup>4, 26-30</sup>.

## SCALE-UP PROCESS

### Scale-up Definition and Steps

Process scale-up is an increase in batch size or production capacity, usually in response to increased product demand, concerns about high production costs, or an increased need for supplies. The first process in the emergence of pharmaceutical or cosmetic products is the preformulation studies carried out in the R&D departments. In preformulation studies, parameters such as active ingredient, compatibility of all synthetic and natural materials in the formulation, and preparation method are examined<sup>31</sup>. According to the results, the final formulation is decided. In all these processes, the batch sizes should be as small as possible in order to reduce the cost. However, once the final formulation has been selected, the production batch size must be modified so that the product can meet market needs. However, as the production size increases, it must be proven that the product maintains its quality. For this reason, the manufacturing of a formulation is basically divided into three different batch sizes. These are laboratory-scale batches, pilot-scale batches, and production-scale batches<sup>32</sup>.

**Laboratory-scale batches:** These are the batches carried out in R&D departments in sizes 100-1000 times less than the actual production scale. They are carried out for preformulation studies and determination of the final formulation. On the other hand, the evaluation and identification of critical quality attributes (CQA) for the final formulation are also determined in these series.

**Pilot-scale batches:** It is used as an intermediate step for transferring from laboratory-scale batches to production-scale batches. If it supports official registration, a pilot batch size must correspond to at least 10% of the production scale batch. In fact, it is the indispensable intermediate step of the time that takes a product from the R&D process to its marketplace as a commercial product. Reasons for producing pilot-scale series:

- It facilitates the transition from laboratory to production,
- It provides the characterization of the product,
- Used in tests and evaluations,

- Provides information about the product,
- It provides foresight about the problems that may be encountered in production, process, packaging and storage conditions.

**Production-scale batches:** It is the size of a formulation that will actually be produced during routine production and marketing in production departments.

### Scale-up of Cosmetics

The R&D process in cosmetics production includes raw materials, formulation, scale-up, production, and equipment, and that the formulation and process team should carry out together. The turning point for industrial production is the scale-up phase.

The Purpose of Scaling Up<sup>33,34</sup>;

- Reproducible production/manufacturing
- Successful large-scale production of the physical characteristics of the formulation,
- It is proof that scaling up from laboratory to pilot scale and industrial production does not change quality.

Optimizing the transfer of formulation from laboratory scale to industrial production scale in the production of cosmetics is an important process that requires the achievement of many steps. While the trials carried out in the laboratory during the cosmetic product development phase are generally aimed at determining the best mixing ratios of different ingredients, scale-up operations require the definition of the correct procedures (mixing time, temperature, order of addition of the ingredient, time, equipment need, etc.) to obtain the same formulation at an industrial scale, and requires a thorough understanding of similar aspects of the processes. Therefore, in scaling up, it is important to define and control critical phases by ensuring the continuity of product formulation quality. Thus, the same product with the same properties (viscosity, pH, color, etc.) will be successfully produced on a larger scale<sup>35,36</sup>. At the step of cosmetic product development; while in laboratory scale, generally production and stability of the formulation are targeted for detecting components and mixing ratios, in scale-up operations, studies are made to identify and transfer critical operation parameters (the order of addition of content, mixing time and speed, temperature, equipment characteristics, etc.) for the same formulation can be produced in industrial scale in the same properties. In this context, identification of critical steps and keeping them under control is intended by ensuring the continuity of the quality and the stability of the formulation.

Things to know for equipment subject to almost any scale-up operation:

- Having sufficient data on the properties and performance of the equipment.
- Using geometrically (shape and size) similar production equipment is important for transferring the production.
- However, geometric similarity cannot provide individual results from the scale and cannot guarantee mechanical, thermal, or chemical similarity.



Figure 1: Critical steps in the cosmetic production.

### Risk Assessment Approach in Cosmetic Scale-up

The risk assessment approach has gained importance at evaluating the process of research-development, pilot, and commercial-scale production of pharmaceutical and cosmetic products<sup>37,38</sup>. To make it easier the transfer from laboratory to commercial production, it is important to study at a pilot scale. By this means, probable assumptions are provided about the characterization, production, packaging, and stability of the product, data for testing and evaluation is obtained. In scale-up, repeatable production, provision of the physical characteristics of the formulation, and proving there has not been any change in the quality must be done. Scale-up and repeatable production in single-phase products like solutions, shampoos, and hair sprays is easily achieved comparing with multiple phase products, products that contain particle systems, and powder products. The product development formulators in the laboratory are then charged with meeting the performance objectives and product parameters set by management. They have to be concerned with a host of considerations, ranging from safety issues, global regulations, raw material cost and availability, awareness of the competitive climate, patent status, adequate preservation, stability and compatibility issues, product scale-up and production problems, to cosmetic elegance considerations, such as fragrance selection, colour, and packaging. Finally, there is the medical fraternity, often dermatologists, devising and supervising efficacy and safety tests concerned with the performance of the products<sup>39</sup>.

The risk assessment approach is increasing its importance in the evaluation of cosmetics from research and development (R&D) to scale-up processes and market launches. Focusing on the critical parameters of the products and developing products that are resistant to process conditions; will help to eliminate shelf life and other related potential problems<sup>37,38</sup>. The risk parameters in cosmetic products vary according to the dosage form of the formulation:

**Single-phase products:** For example, scale-up and reproducible production of single-phase products such as solutions, shampoos, and hairsprays are more easily

achieved compared to multi-phase systems and powder products<sup>40</sup>.

**Liquid cosmetic formulations:** The problem of transporting solutions or suspensions prepared at laboratory scale to industrial scale is prominent<sup>40</sup>. The critical process parameters are usually the optimization of mixing speed, mixing time, and temperature. In addition, if there are components sensitive to the processing steps or ambient conditions in the formulation, the processing process should be evaluated by considering these. Possible interactions of the final formulation with the packaging material should be considered during the formulation development phase. Quality control tests performed on finished liquid products include taste, odour, and colour controls, pH measurement, viscosity determination, stability tests, and critical component quantification, in addition to assertive efficacy tests are usually among the tests performed.

**Cosmetic emulsions:** The success of the production processes, during the development phase and the selection of optimal formula components, the selection of production equipment suitable for specific operation sizes should be made together with experts who produce at pilot and industrial production scale<sup>41</sup>. The properties expected from the formulation (droplet size and distribution, rheological properties) should be determined, and its stability at room temperature and higher temperatures and after freezing thawing tests should be tested. Other factors that affect the final product quality include preventing contamination, ensuring the uniformity of the composition, viscosity, color, and sensory properties of the product intended for topical application. The cosmetic emulsion producer must consider the rheological behaviour of the product (Newtonian or non-Newtonian behaviour, etc.), factors affecting rheology, and the time-dependent stability of the product during the industrial production process. The order and timing of the addition of the formulation ingredients during production, controlling the pH, ensuring the volumetric uniformity of the emulsifiers to be added to the internal and external phases before or during the process are other important points of a successful production

process. During cosmetic processes, proper operation of this equipment is as important as the selection of emulsion components and the right equipment. The knowledge of rheology and fluid dynamics for manufacturers and formulation developers will be very useful in overcoming the difficult task of large-scale production of uniform and homogeneous emulsions. Mixing with conventional agitators and propellers may be insufficient to provide the expected micro-uniformity in high-quality cosmetic products. In addition, natural/synthetic polymers, which modify the product rheology and are generally added to the system in powder form, are added to the mixing system very quickly, and the agglomerated material will disrupt the homogeneity. Such problems can be overcome by optimizing factors such as temperature and mixing time, as well as the use of new and improved technology equipment<sup>33-35</sup>.

Since cosmetic emulsions are generally thermodynamically unstable systems, they are highly dependent on variables (temperature and composition) and method (process method, equipment) during their production. Therefore, the successful and reproducible production of a cosmetic emulsion on a large scale is closely related to the required production design based on well-documented specifications.

**Novel technology used cosmetics:** In order to examine the critical parameters in micro or nano-sized carrier systems, first of all, it is necessary to know how these systems are produced. Although there are many carrier system subtypes in the literature, their preparation is basically done by similar methods. We can divide these preparation methods into two basic classes: bottom-up (i.e., starting from a dissolved molecule to a precipitate) and top-down processes (i.e., starting from a macro-size drug powder to be reduced to a smaller one)<sup>42</sup>. Although bottom-up methods are often preferred in the production of laboratory-scale batches, industrial production is challenging. In this method, where formulation components are generally dissolved in organic solvents, high costs and remaining organic solvent residues are among the critical risk factors. On the other hand, the biocompatibility of the carriers (polymer or surfactant) used in these carrier systems, the particle size, and the toxicological properties of the micro or nano-system are other critical risk parameters. On the other hand, choosing the suitable preparation method also determines the time loss-gain balance<sup>43</sup>.

The most important critical risk factor of the scale-up process of novel cosmeceuticals is the adjustment of particle or droplet size. The main risk assessment factor on the efficacy and toxicity of these systems is particle size<sup>44</sup>. However, particles of desired sizes may not always be produced when scaling up. The main reason for this situation is that the laboratory and manufacturing equipment do not have similar characteristics. Parameters such as mixing speed and time to reach the required temperature may vary. In this case, the characteristic features of the products change. For example, in a study on scaling up the nanoparticle prepared using the emulsion method, it was observed that the increase in mixing speed and

time did not change the loading efficiency, but the particle size decreased<sup>45</sup>.

## CONCLUSION

Cosmetic products are used not only to beautify the appearance but also to provide personal hygiene, protection, care, and supporting medical treatments. The world cosmetics market changes every year in line with new needs. The cosmetics industry, which develops in direct proportion to these needs, should be considered as a whole from the R&D process to the production process. Scale-up is one of the important parameters in the process of transforming a cosmetic formulation from R&D labs to a commercial product. Cosmetic formulations are mainly dependent on the factors such as variations related to temperature, composition, process, and equipment. In this direction, for a successful scale-up, it is essential to consider thus define, evaluate, control, validate and document in writing the parameters related to the formulation, equipment, process, and final product.

## REFERENCES

1. Dureja H, Kaushik D, Gupta M, Kumar V, Lather V. Cosmeceuticals: An emerging concept. *Indian J Pharmacol* 2005; 37(3):155. <https://doi.org/10.4103/0253-7613.16211>
2. Al B. The Source-Synthesis- History and Use of Atropine. *J Acad Emerg Med* 2014 Mar 25; 13(1):2-3. <http://www.akademikacilitip.com/sayilar/234/buyuk/2-3.pdf>
3. Ben-Noun L. *Medical Effets of Cosmetics*. 1<sup>st</sup> ed. Ben-Noun L, editor. B.N. Publication House; 2016.
4. Ahmad U, Ahmad Z, Khan A, Akhtar J, Singh S, Ahmad F. Strategies in development and delivery of nanotechnology based cosmetic products. *Drug Res (Stuttg)* 2018; 26;68(10):545-52. <https://doi.org/10.1055/a-0582-9372>
5. Gallo FR, Multari G, Palazzino G, *et al*. Henna through the centuries: a quick HPTLC analysis proposal to check henna identity. *Rev Bras Farmacogn* 2014; 24(2):133-40. <https://doi.org/10.1016/j.bjp.2014.03.008>
6. Sharma RK, Goel A, Bhatia AK. *Lawsonia Inermis* Linn: A Plant with Cosmetic and Medical Benefits. *Int J Appl Sci Biotech* 2016; 31; 4(1):15-20. <https://doi.org/10.3126/ijasbt.v4i1.14728>
7. Azoth Analytics. *Global Prestige Beauty Market Analysis by Product (Skincare, Fragrance, Makeup, Haircare), Distribution Channel, Region and Country (2020 Edition): Market Insights, COVID-19 Impact, Competition and Forecast to 2025* [Internet]. 2020. <https://www.researchandmarkets.com/reports/5232418/global-prestige-beauty-market-analysis-by-product#rela0-546301>
8. Zlokarnik M. *Dimensional Analysis and Scale-Up in Theory and Industrial Application*. In: Levin M, editor. *Pharmaceutical Process Scale-Up*. 1<sup>st</sup> ed. New York, NY: Marcel Dekker; 2001;1-42.
9. Helal NA, Elnoweam O, Eassa HA, *et al*. Integrated continuous manufacturing in pharmaceutical industry: current evolutionary steps toward revolutionary future. *Pharm Pat Anal* 2019; 8(4):139-61. <https://doi.org/10.4155/ppa-2019-0011>
10. FDA. *Cosmetics Overview* <https://www.fda.gov/industry/regulated-products/cosmetics-overview>
11. The European Parliament and the Council of the European Union. Regulation (EC) No. 1223/2009 of the European parliament and of the council of 30 November 2009 on cosmetic products. *Off J Eur Union* 2009; 342:59-209.

12. Cosmetics Act No. 15947, Dec. 11, 2018. [https://elaw.klri.re.kr/eng\\_service/lawView.do?hseq=50282&lang=ENG](https://elaw.klri.re.kr/eng_service/lawView.do?hseq=50282&lang=ENG) Accessed 24 May 2021.
13. Halla N, Fernandes I, Heleno S, *et al.* Cosmetics preservation: a review on present strategies. *Molecules* 2018 Jun 28; 23(7):1571. <https://doi.org/10.3390/molecules23071571>
14. Siemer E. Preparations for cleansing and caring for blemished skin. In: Umbach W, editor. *Cosmetics and Toiletries-Development, Production and Use*. 1<sup>st</sup> ed. New York, NY: Cosmetics and Toiletries—Development, Production and Use; 1991; 124–8. <https://doi.org/10.3390/molecules23071571>
15. Pandey A, Jatana GK, Sonthalia S. *Cosmeceuticals*. Stat Pearls. 2021. PMID: 31334943
16. Draelos ZD. *Procedures in cosmetic dermatology series: Cosmeceuticals*. 3rd ed. Canada: Elsevier 2016; 11-150.
17. Dreno B, Araviiskaia E, Berardesca E, *et al.* The science of dermocosmetics and its role in dermatology. *J Eur Acad Dermatol Venereol* 2014; 28(11): 1409-17. <https://doi.org/10.1111/jdv.12497>
18. Murthy RS, Lakshminarayana R. Mental health consequences of war: a brief review of research findings. *World Psychiatry* 2006; 5(1):25–30. PMID: 16757987 <http://www.ncbi.nlm.nih.gov/pubmed/16757987>
19. Farhood L, Zurayk H, Chaya M, Saadeh F, Meshefedian G, Sidani T. The impact of war on the physical and mental health of the family: The Lebanese experience. *Soc Sci Med* 1993 Jun; 36(12):1555–67. <https://linkinghub.elsevier.com/retrieve/pii/0277953693903444>
20. Korinek K, Loebach P, Teerawichitchainan B. Physical and mental health consequences of war-related stressors among older adults: an analysis of posttraumatic stress disorder and arthritis in Northern Vietnamese war survivors. *J Gerontol Ser B Psychol Sci Soc Sci* 2016; 12;gbv157. <https://doi.org/10.1093/geronb/gbv157>
21. LeRoy L. Camouflage therapy. *Dermatol Nurs* 2000; 12(6):415–6.
22. Ngaage M, Agius M. The psychology of scars: a mini-review. *Psychiatr Danub* 2018; 30(7):633–8.
23. Antoniou C, Stefanaki C. Cosmetic camouflage. *J Cosmet Dermatol* 2006; 5(4):297–301. <https://doi.org/10.1111/j.1473-2165.2006.00274.x>
24. Holme SA, Beattie PE, Fleming CJ. Cosmetic camouflage advice improves quality of life. *Br J Dermatol* 2002 Nov; 147(5):946–9. <https://doi.org/10.1046/j.1365-2133.2002.04900.x>
25. Martin KI, Glaser DA. *Cosmeceuticals: the new medicine of beauty*. *Mo Med* 108(1):60–3. PMID: 21462614
26. Rosen MR. *Delivery system handbook for personal care and cosmetic products-technology, applications, and formulations*. Rosen MR., Norwich, NY, USA: William Andrew Publishing; 2005.
27. Raghava Srivalli KM, Mishra B. Drug nanocrystals: A way toward scale-up. *Saudi Pharm J* 2016; 24(4):386-404. <https://linkinghub.elsevier.com/retrieve/pii/S1319016414000383>
28. Puglia C, Santonocito D. *Cosmeceuticals: nanotechnology-based strategies for the delivery of phytochemicals*. *Curr Pharm Des* 2019; 26; 25(21):2314–22. <http://www.eurekaselect.com/173360/article>
29. McCrudden MTC, McAlister E, Courtenay AJ, *et al.* Microneedle applications in improving skin appearance. *Exp Dermatol* 201; 24(8):561–6. <https://doi.org/10.1111/exd.12723>
30. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. *Br J Pharmacol* 2015; 172(9):2179–209. <https://doi.org/10.1111/bph.13059>
31. Ahuja S. *Modern pharmaceutical analysis: An overview*. In 2001; 1–22. <https://doi.org/10.1016/j.puhe.2019.12.009>
32. Long C, Mc Quaid J. *Strategic Approaches to Process Optimization and Scale-up*. *Pharm Technol* 2010;34(9).
33. Gibson M. *Product Optimization*. In: *Formulation PP and editor. Pharmaceutical Preformulation and Formulation*. New York, NY: Informa Healthcare USA, Inc; 2009; 290–324.
34. Holl P, Rosen M. Improving cosmetic formulation quality through innovative processing technology. *Eurocosmetics*. 2012; 7(8):24–9.
35. FDA. *Guidance for Industry, Cosmetic Good Manufacturing Practices*. 2013;
36. Gibson M. *Pharmaceutical and Formulation*.
37. Felton LA. *Pharmaceutical Process Scale-Up*, 3<sup>rd</sup> edition. *Drug Dev Ind Pharm* 2012 Apr 16; 38(4):512–512. <https://doi.org/10.3109/03639045.2011.633523> <http://www.tandfonline.com/doi/full/10.3109/03639045.2011.633523>
38. Muller F, Latimer J. Anticipation of scale up issues in pharmaceutical development. In: *European Congress of Chemical Engineering (ECCE-6)*. Copenhagen; 2007. <https://doi.org/10.1016/j.compchemeng.2008.09.015>
39. Draelos Z, Thaman L. *Cosmetic formulation of skin care products*. Draelos Z, Thaman L, editors. New York, NY: Taylor & Francis Group; 2006. <https://doi.org/10.3109/9781420020854>
40. Block LH. Scale up of liquid and semisolid manufacturing processes. *Pharm Technol* 2005; 26:26–33.
41. Salager JL. Emulsion properties and related know-how to attain them. In 2000; 73–125. <https://doi.org/10.1201/b14839-19> <http://www.crcnetbase.com/doi/abs/10.1201/b14005-4>
42. Müller R, Junghanns. Nanocrystal technology, drug delivery and clinical applications. *Int J Nanomedicine* 2008 Oct; 295. <https://doi.org/10.2147/IJN.S595>
43. Galindo-Rodríguez SA, Puel F, Briançon S, Allémann E, Doelker E, Fessi H. Comparative scale-up of three methods for producing ibuprofen-loaded nanoparticles. *Eur J Pharm Sci* 2005; 25(4–5):357–67. <https://doi.org/10.1016/j.ejps.2005.03.013>
44. Paliwal R, Babu RJ, Palakurthi S. *Nanomedicine scale-up technologies: feasibilities and challenges*. *AAPS PharmSciTech* 2014; 22; 15(6):1527–34. <https://doi.org/10.1208/s12249-014-0177-9> <http://link.springer.com/10.1208/s12249-014-0177-9>
45. Colombo AP, Briançon S, Lieto J, Fessi H. Project, design, and use of a pilot plant for nanocapsule production. *Drug Dev Ind Pharm* 2001 30; 27(10):1063–72. <https://doi.org/10.1081/DDC-100108369>