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A REVIEW ON: "CHARACTERIZATION AND TOPICAL DELIVERY OF PHENYL-ETHYL RESORCINOL

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ABSTRACT

The potent skin-lightening agent phenyl-ethyl resorcinol (PER) is frequently utilized in dermatological and cosmetic formulations because it inhibits tyrosinase and lower the formulation of melanin. The physical and chemical characterization of the molecule, such as it's molecular structure solubility and stability have a significant impact on the formulations creation and topical distribution. The results of differential scanning calorimetry (DSC) and thermogravimetric analysis nuclear magnetic resonance (NMR), high- performance liquid chromatography (HPLC), and thermal gravimetric analysis (TGA) have all shown the following.The stability profile of PER and it's compatibility with a number of excipients .The he limitations of traditional topical therapies, such as creams and gels, have led to the development of complex delivery methods. Photostability has improved significantly studies nanocarriers such as liposomes, nanoliposomes, niosomes, ethosomes, invasomes and Nanostructured Lipid Carriers (NLCs), to demonstrate enhanced skin penetration for PER delivery and controlled release.In vitro research has demonstrated that the qualities of the product improve stability and bioavailability when compared to conventional formulations. In vivo studies have shown how effectively since these vesicular systems boost PER while having low cytotoxicity. And enhancing penetration across the stratum, they are ideal for cosmetic applications . Relative studies of various solvents and formulations have also aided in optimizing PER-loaded delivery systems, ensuring optimal efficacy and stability. Highlighting the need of combining advanced nanocarrier systems as a review thoroughly covers the topical delivery methods, formulating approaches and characterization techniques of PER. Strategies to solve problems overcome conventional delivery limitations and achieve superior and outstanding skin-lightening.

KEY WORDS: *Phenylethyl resorcinol (PER),topical delivery, skin-lightening agent, tyrosinase inhibition, liposomes, nanoliposomes, niosomes, ethosomes, invasomes, nanostructured lipid carriers (NLCs), physicochemical characterization, high-performance liquid chromatography (HPLC) analysis, Deferential scanning calorimetry (DSC), Thermogravimetric analysis (TGA), Nuclear magnetic resonance (NMR), in vitro skin permeation, photostability, cosmeceutical formulation, controlled release, vesicular systems.*

1.INTRODUCTION

A powerful skin-lightening ingredient, phenyl-ethyl resorcinol (PER) has drawn a lot of attention in dermatological and cosmetic research due to its exceptional inhibitory effect. Tyrosinase is the main enzyme in charge of melanin synthesis. [3,6]. It has special physicochemical properties, including poor water solubility, mildness and susceptibility to caused by its chemical consumption, which includes phenylethyl substitution resorcinol moiety. Because of these characteristics, topical products need to be carefully defined and enhanced to be safe, stable and efficient [1,7]. The physical and chemical characteristics of PER in mixtures have been investigated using a range of analytical techniques. Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) are techniques for evaluating thermal stability, while nuclear magnetic resonances (NMR) and high-performance liquid chromatography (HPLC) provide data, provide ideas on that topic, HPLC allows for accurate quantitative and chemical analysis [1,10].This type of study is important to ensure product stability, establish consistent quality standards, and enable consistent effectiveness in local applications. Despite frequent issues with traditional formulations like creams and gels, such as low solubility, limited skin penetration and photostability they are nonetheless commonly utilized for the distribution of PER. Advanced topical delivery methods have been the subject of growing research in an effort to overcome these limitations which can reduce efficacy and shelf life [2,5]. Liposomes, nanoliposomes, niosomes, ethosomes, invasomes and Nanostructured Lipid Carriers (NLCs) are examples of vesicular transporter systems that have demonstrated improved skin absorption, increased solubility, regulated release, and protection against photodegradation, because these systems increase PER's bioavailability while maintaining low cytotoxicity, they are particularly suitable for cosmeceutical applications and uses.

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[7,8,9]. The formulation methods along with the carrier makeup and solvent selection, have been shown to have a significant impact on both the penetration of PER through the stratum corneum and its overall stability. [7]. Comparative research has provided guidelines on the most effective combinations for optimizing topical delivery while maintaining the compound's activity. The combination of sophisticated systems is one of the main trends in current skin-lightening research, offering positive solutions to the challenges associated with traditional topical treatment. This review compiles the current knowledge on the topic, highlighting the scientific methods utilized to enhance stability, skin penetration and overall PER characterization and topical administration, efficacy. Drawing on the findings of several studies, it provides a comprehensive overview of how formulation advances can optimize the practical application of this powerful cosmetic agent [1,10].

2.CHEMISTRY AND PHYSICO-CHEMICAL PROPERTIES

Phenylethyl resorcinol (PER) is a synthetically produced or derivative of resorcinol where a phenylethyl group is linked to the base structure of resorcinol. This small change in structure results in more effectiveness as skin-lightening and depigmenting agent it blocks tyrosinase, the important enzyme in melanin production, while still keeping its toxicity on cells quite low. [3,6]. The molecular formula of PER is **$C_{14}H_{14}O_2$,** with a molecular weight approximately **214.264 g/mol.** It gives moderate lipophilicity and poor water solubility .[1,7]. Because of this PER works well with lipid type carriers but doesn't dissolve easily in water-based formulation. It's solubility matters a lot for topical application. PER dissolve easily in polar solvents like ethanol and propylene glycol but in water barely dissolves. That means you often need solubilizers or delivery systems like nanocarriers to make it work effectively on skin .[2,5,7]. Science it is lipophillic shown by partition coefficient values (log_p), It mixes well with lipid vesicles, which is helpful for penetrate in skin layers and show longer duration of action.[7.] On the other hand, it is quietly sensitive to light and can degrade under much exposure. That's why protective methods such as putting it inside liposomes or lipid nanoparticles are recommended. [6,7,8]. Another good point is that PER fits well with common excipients used in cosmetic products. Studies reveals that loading it into nanoliposomes, ethosomes, or niosomes are guards against oxidation and photodegradation as well as improving solubility and absorption through skin.[2,4,8]. These systems usually have particle sizes in the 100-300 nm range with strongest entrapment efficiency and controlled release properties which are useful for long-lasting or longer duration topical delivery and improved all results. [2,3,9].Overall the unique structure and chemical properties of PER makes it a strong potent and solid candidate for cosmetic formulations. Its moderate fat solubility and ability to reduce melanin synthesis by inhibition tyrosinase and good compatibility with new carrier technologies together support its use in effective and stable skin-lightening agent that reduces degradation and side effects.[1,10].

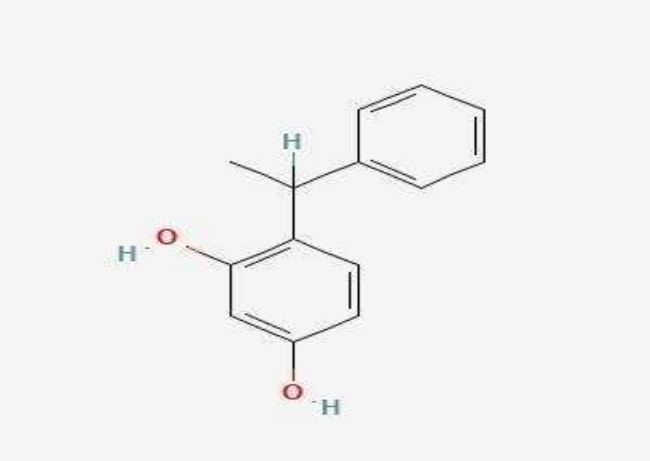

Fig.1(4-(1-phenylethyl)-1,3-benzenediolPhenylethyl resorcinol) or (Symwhite 377) [11].

3. MECHANISM OF ACTION

Phenylethyl resorcinol (PER) acts as a skin lightening agent, primarily by blocking tyrosinase, a copper enzyme that is important in melanin production. Tyrosinase converts L-tyrosine to L-DOPA and to melanin, so by slow down this step, PER works to reduce the overall amount of pigment produced in skin cells [3,6]. Due to its chemical structure, with a phenylethyl group attached on the resorcinol ring, PER actually binds more abundantly to the active site of tyrosinase after that simple resorcinol compounds, making it more effective [1,6]. In addition to blocking the enzyme, PER also has antioxidant activity. During melanin production, reactive oxygen species (ROS) are produced, which can lead to increased pigmentation and oxidative stress in the skin. Thanks to its phenolic structure, PER can neutralize free radicals, cutting down this stress and indirectly reducing melanin production [3,6,7]. So it doesn't just stop tyrosinase, it also helps by calming the oxidative environment that pushes melanogenesis forward.When PER is applied topically, its performance improves a lot if it's put into advanced carriers like liposomes, nanoliposomes, niosomes or nanostructured lipid carriers [2,6,8]. These delivery systems help it cross the outer skin barrier and reach the melanocytes in the basal epidermis. Studies have shown that these

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carriers increase the amount of PER reaching the target site and their release process is slow, thus prolonging the inhibitory effect.[4,6,8]. The type of solvent or base / Base systems used in the formulation is also important. Studies comparing different solvent systems have shown that the solubility and stability of PER are important for achieving a stronger tyrosinase inhibiting action and better penetration into the skin layers.[7]. Another advantage of vesicular carriers is that they shield PR from light and oxidation, which otherwise would weaken its activity [6,8].All together, PER's action combines direct inhibition of tyrosinase, antioxidant support, and better skin delivery when loaded into smart carriers. These features explain why it is seen as a strong cosmeceutical option for lightening skin and managing hyperpigmentation disorders [1,10].

4. FORMULATION STRATEGIES FOR TOPICAL DELIVERY

4.1 Conventional Formulations

Phenylethyl resorcinol (PER) has usually been added into simple products like creams, gels or lotions for use on the skin. These basic types of formulations are easy to use and let people apply the ingredient directly, but they also have limits because PER doesn't dissolve well in water and it breaks down easily when exposed to light [1,2,5]. Studies on stability have shown that when PER is put into plain cream or gel bases, it can oxidize or lose some of its activity with time, which lowers its effect as a skin-lightening agent [1,5]. To deal with this, solubilizing agents such as ethanol, propylene glycol or polyethylene glycol are often included to help PER spread better in the formula [2,7].While these conventional formulations are fine for short-term use, they don't go deep into the skin very well and can't really protect PER from outside factors like light or air. Because of this, there's a clear need for more advanced delivery systems to improve stability and results [2,5,7].

4.2 Advanced Delivery Systems

To make PER work better on the skin, different advanced delivery systems have been designed. The main goals are to get it to penetrate deeper, stay stable, and release in a more controlled way over time.

Liposomes and Nanoliposomes: PER-loaded liposomes and nanoliposomes are studied the most because they can hold the hydrophobic molecule inside and push it through the skin better. These vesicles are usually between about 100 and 300 nm in size and show high entrapment efficiency, which helps protect PER from light damage and oxidation [3,4,6]. Since they release PER in a controlled manner, they keep blocking tyrosinase activity longer, which leads to more effective lightening results [2,3,4].

Niosomes and Ethosomes: Niosomes and ethosomes a similar way, both protecting PER and boosting penetration. Niosomes are made with non-ionic surfactants, which gives them good stability and allows slow release. Ethosomes, on the other hand, have ethanol that helps them slip through the stratum corneum by making skin lipids more fluid [3,4]. Both have been shown to increase how much PER actually deposits in the epidermis compared to regular creams or gels [4,6].

Invasomes and Nanostructured Lipid Carriers (NLCs: Invasomes combine terpenes with ethanol inside vesicular systems, which makes the skin barrier more fluid and lets more PER get through [2,3]. NLCs mix solid and liquid lipids, which not only stabilize PER but also improve its solubility and allow a steadier release, all while keeping cytotoxicity low [7,8]. Research shows that NLCs are especially helpful for keeping PER stable when exposed to heat or light, and they make sure it gets deposited in the skin layers where it's most needed [6,8].

Optimization Parameters: The success of these systems depends on several factors like particle size, zeta potential, entrapment efficiency, and the type of solvent or lipid used. Smaller vesicles usually go deeper into the skin, while higher encapsulation efficiency means more PER is available for action [2,6,9]. The solvent also matters ethanol and propylene glycol not only improve solubility but also make it easier to load PER into these carriers [7].In short, while simple creams and gels are still useful for basic applications, advanced delivery systems such as liposomes, nanoliposomes, niosomes, ethosomes, invasomes and NLCs clearly perform better. They make PER more stable, improve penetration, and allow for controlled release. Choosing the right system and optimizing its parameters are key to getting the most out of PER for cosmetic and therapeutic skin uses [1,10].

5.ANALYTICAL AND CHARACTERIZATION TECHNIQUES

Getting the characterization of phenylethyl resorcinol (PER) right is important to make sure it stays stable, works effectively, and is actually suitable for skin delivery. A range of analytical and physicochemical methods have been used to study PER in both its pure form and when it's inside different formulations, giving a clearer idea of how it behaves and how well it fits into delivery systems.

Physicochemical Characterization

The basic physical and chemical features of PER, like particle size, shape, and surface charge, are key for loading it into advanced carriers. Dynamic light scattering (DLS) is often used to check particle size and distribution, which has a direct effect on how well PER

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can pass through skin and how it releases [2,4,6]. For looking at the shape and structure of vesicles, transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide clear images that confirm whether liposomes, nanoliposomes, niosomes or nanostructured lipid carriers (NLCs) keep their structure when loaded with PER [3,6,8]. Zeta potential measurements are also done to check surface charge, since this influences the stability of the formulation and helps prevent vesicles from clumping together over time [2,3,4].

Chemical Analysis

High-performance liquid chromatography (HPLC) is still the most reliable way to measure PER levels in formulations. It allows precise checking of concentration, entrapment efficiency, and how fast PER is released [1,10]. Nuclear magnetic resonance (NMR) spectroscopy is used to confirm the chemical structure and purity, making sure that the molecule doesn't degrade during formulation [1]. Fourier-transform infrared (FTIR) spectroscopy is also helpful for understanding functional groups and possible interactions with excipients, which is important for predicting compatibility and long-term stability [1].

Stability and Release Studies

Since PER is sensitive to light, oxidation, and heat, testing stability is an important step. Thermal analysis methods like differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) help to find out the temperature ranges where PER stays stable or starts to break down [1]. Photostability studies also show that putting PER inside systems like liposomes, ethosomes, or NLCs gives much better protection against light, keeping its biological activity intact [2,7,8].For release testing, in vitro methods like dialysis, Franz diffusion cells, and skin-PAMPA assays are often used. These provide useful data on how quickly PR comes out of the carrier, how much is released, and how well it passes through the outer skin layer [3,4,7]. Results usually show that advanced vesicular carriers not only slow down release but also increase how much PR collects in the epidermis, which makes it more bioavailable compared to plain creams or gels [4,7,8]. Overall using these different analytical and characterization tools helps make sure that PER formulations are optimized for stability, controlled release, and effective skin delivery. By combining physical, chemical, and release studies, researchers are able to design delivery systems that get the most out of PER's cosmetic potential, while also keeping safety and effectiveness in mind [1,10].

6.Biological Evaluation

Looking at the biological evaluation of phenylethyl resorcinol (PER) is important to prove its safety, effectiveness, and how suitable it really is for skin use in cosmeceutical products. Both in vitro and in vivo studies have been carried out to check its depigmenting effect, possible toxicity, and how well it penetrates the skin.

In Vitro Studies

Most in vitro work focuses on how PER blocks tyrosinase and lowers melanin production in cultured melanocytes or melanoma cell lines. Results show that PER has strong tyrosinase inhibition and this directly reduces melanin levels, making it a powerful depigmenting compound [3,6]. Antioxidant tests also reveal that PER can remove reactive oxygen species (ROS), which are usually produced during melanin formation. This lowers oxidative stress and adds to its skin-lightening activity [6,7].Studies on permeation and deposition using human or animal skin (often with Franz diffusion cells) show that advanced delivery systems—like liposomes, nanoliposomes, niosomes, ethosomes, invasomes and nanostructured lipid carriers (NLCs)—help PER get past the stratum corneum more effectively while still releasing it in a controlled way [3,6,8]. These carriers increase how much PER stays in the epidermis, keeping the effect going for longer. Comparisons with normal creams or gels suggest that nanocarriers-loaded PER has better penetration and higher deposition overall [3,4,7].

In Vivo Studies

Animal models and human trials have been used to see how PER works directly on skin. Topical use of PER formulations shows a clear reduction in melanin levels and noticeable brightening of skin tone, without serious irritation or cytotoxicity [3,4,6]. When nanocarrier-based PER systems are used, the effect lasts longer because of better skin retention and controlled release, proving these advanced carriers work better than conventional ones [3,6,8].Toxicity studies further confirm that PER is safe at concentrations needed for tyrosinase inhibition, with very low cytotoxic effects [3,6]. In vivo work also shows that formulations with protective carriers lower the risk of PER breaking down, which improves its stability and makes it more reliable for topical use [3,4,,8]. Altogether, both in vitro and in vivo evidence show that PER, especially when delivered through advanced nanocarriers, offers strong skin-lightening effects, steady release, and good safety. These findings give a strong base for developing PER-based cosmeceutical products with improved biological performance [1,10].

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7.CHALLENGES AND LIMITATIONS

Even though phenylethyl resorcinol (PER) shows strong promise as a skin-lightening and cosmeceutical agent, there are still a number of challenges that affect how well it can be formulated, how stable it is, and how effective it works once applied on skin. One of the biggest problems is its poor water solubility, which makes it difficult to mix directly into simple creams, gels, or other water-based products [2,5,7]. Because of this, PER can sometimes spread unevenly through a product, lowering its availability to the skin and reducing its overall lightening effect.Photostability is another key limitation. PER tends to break down quickly when exposed to light, which shortens its shelf life and weakens its biological activity [6,7,8]. Standard creams and gels usually don't offer enough protection against this kind of degradation, so advanced carriers or stabilizing excipients are often needed to keep it effective for longer [4,8]. Heat and oxidation make the situation harder, since both can cause chemical changes during storage or even during manufacturing [1,7].Skin penetration is also a real challenge. The stratum corneum is a tough barrier and limits how much PER can actually reach melanocytes deeper in the skin [3,4,6]. Basic topical products don't penetrate well, so the inhibition of tyrosinase and the whitening effect can end up weaker. Advanced carriers like liposomes, nanoliposomes, ethosomes, invasomes, and nanostructured lipid carriers (NLCs) have shown much better penetration and retention, but fine-tuning things like particle size, encapsulation, and formulation design is still needed to get the best results.[3,8,9].Safety is another concern. While PER is usually safe at normal concentrations, wrong formulation choices or using too much can raise the risk of irritation, especially if applied for long periods or on sensitive skin [3,6]. On top of that, safety regulations limit the concentrations and excipients that can be used, which narrows down formulation flexibility.Scaling up production also adds complications. Advanced delivery systems often work well in the lab, but they usually require complex manufacturing processes that are harder and more costly to reproduce at commercial scale [2,3,7]. Keeping particle size, encapsulation levels, and stability consistent in large batches is still a big obstacle.In short, the main difficulties with PER include poor solubility, instability under light and heat, weak skin penetration, possible irritation, and formulation or production complexity. Getting around these issues needs careful excipient selection, optimized advanced carriers, and strong physical and biological testing to make sure products are both effective and safe for practical, commercial use [1,10].

8.FUTURE PERSPECTIVES

The future of phenylethyl resorcinol (PER) as a cosmeceutical ingredient depends largely on improving its stability, penetration into skin, and ability to release in a controlled manner through advanced delivery systems. While creams and gels are the simplest way to apply PER topically, they often fall short. Recent work shows that vesicular carriers like liposomes, nanoliposomes, niosomes, ethosomes, invasomes, and nanostructured lipid carriers (NLCs) can boost its bioavailability, photostability, and retention in the skin layers [6,8,9]. Going forward, research can fine-tune these carriers to get better encapsulation, more consistent particle sizes, and sustained release that allows PER to inhibit tyrosinase for longer without causing irritation [4,6,7].Nanotechnology offers even more options. Hybrid lipid–polymer carriers, for example, could help bypass PER's poor solubility in water and its tendency to break down when exposed to light [7,8]. Stimuli-responsive systems that trigger release based on conditions like pH, body temperature, or even UV light could further improve effectiveness, making sure PER is used only when it's needed and not wasted [7,8].There is also promise in pairing PER with other skin-brightening or antioxidant compounds. Delivering these together in vesicular systems might create synergistic effects, achieving stronger results at lower doses, which in turn lowers the risk of skin irritation and improves safety [3,6,7]. Still, more in vivo studies and clinical trials are needed to confirm these benefits in humans. Research should pay close attention to not just the whitening effect but also long-term safety, tolerability, and consumer acceptability [3,4,6]. Developing standardized methods for stability testing, permeation studies, and biological evaluation will also help generate consistent data to guide product development and regulatory approval [1,10].Another hurdle is scale-up. Manufacturing advanced delivery systems at commercial levels without losing stability, particle uniformity, or encapsulation efficiency is challenging. Future work should explore easier and more cost-effective production methods so PR-based products can reach wider markets [3,7,8]. In short, the future of PER is closely tied to advances in nanotechnology, novel hybrid carriers, and smart combination strategies. With continued progress in optimizing formulations, running real-world clinical tests, and making production scalable, PER can evolve into one of the most effective and widely used cosmeceutical agents for skin-lightening [1,10].

9.CONCLUSION

Phenylethyl resorcinol (PER) has become one of the most promising cosmeceutical ingredients because of its strong tyrosinase inhibition and antioxidant activity, which makes it highly useful in treating hyperpigmentation and skin-lightening concerns. Studies on its characterization have helped outline its physicochemical properties such as moderate lipophilicity, poor water solubility, good thermal stability and sensitivity to light, all of which are important when designing effective formulations. Tools like HPLC, NMR, DSC, TGA and FTIR are widely applied for stability checks, structural confirmation and quality control, both for raw PER and its final formulations. Traditional creams and gels have struggled to deliver PER effectively because of its low solubility, weak skin penetration and degradation when exposed to light. To overcome this, researchers have turned to advanced delivery systems like liposomes, nanoliposomes, niosomes, ethosomes, invasomes and nanostructured lipid carriers (NLCs). These systems not only boost solubility and protect the molecule from breakdown but also allow for controlled and more targeted delivery to melanocytes. In general, nanocarriers

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show higher entrapment, better stability and sustained release profiles, which together lead to stronger results and safer topical use. Evidence from both in vitro and in vivo studies also points to the fact that optimized formulations, when paired with the right solvents, are crucial for improving PER's penetration through the skin, its bioavailability and overall therapeutic outcomes. This shows how closely formulation development needs to be linked with understanding the molecule's basic properties to ensure reliable performance. In summary, combining detailed physicochemical knowledge with innovative topical delivery strategies has positioned PER as a reliable and versatile cosmeceutical. With continued effort in developing smarter nanocarriers and more user-friendly formulations, there is strong potential to further enhance its stability, effectiveness and consumer acceptance, making PER a clear model for future work in skin-lightening therapies.

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