REVIEW ARTICLE

# A Review of Gelatine Formulations for Topical Skin Cancer Treatment

**S. Kale, Sunita N. Vaidya, S. Agrawal, V. Satote, V. Gulghane, S. Waghade, S. Kale**

*Department of Pharmaceutics, Datta Meghe College of Pharmacy Salad (H), Data Meghe Institute of Higher Education and Research (D.U.), Wardha, Maharashtra, India*

**Abstract**

Regarding both regional and widespread drugs, cancer of the skin, regardless of its manifestations, is the disease with the highest incidence rate in the world. Topical chemotherapy is an intriguing therapeutic approach due to its low cost and lack of invasiveness. Nonetheless, it is difficult to distribute antineoplastic drugs through the skin due to the numerous methodologies that have been utilized to ascertain the physicochemical features, including solubility, ionized molecular weight, and melting point, as well as the efficacy of the stratum corneum's protective barrier, utilized to increase drug absorption, retention, and effectiveness. Its objectives are to determine the most popular methods for topical medication administration using gel-based medications for the treatment of skin cancer. The preparation methods, the excipients employed, and the techniques for characterizing gels are briefly explained. Safety considerations are also emphasized.

**Key words:** Chemical hydrogel, composite gel, skin cancer, systematic literature review

## INTRODUCTION

The skin, the body's largest organ, serves a multitude of vital functions, encompassing metabolism and defense. Within the realm of global health, skin cancer stands as the most prevalent form of cancer, characterized by abnormal skin cell growth.[1] Skin cancer exists in both benign and malignant forms, including moles, squamous cell carcinoma, and basal cell carcinoma (BCC), among others.[2] It is worth emphasizing that while the mortality rate for melanoma cancer is relatively low, accounting for just 2% of cases, more aggressive forms, when left undetected, lead to fatalities in over eighty percent of instances.[3]

Treatment approaches for skin cancer encompass radiation therapy, topical therapies, surgical excision, oral therapy, and medication administration.[4] Although surgery commonly serves as the primary treatment option, topical treatments hold their own set of advantages in certain cases.

The topical dermal method offers simple administration, minimal discomfort, improved patient compliance, and minimized systemic effects with minimal side effects.[5] A significant portion of pharmaceutical formulations are in semisolid dosage forms because they can be given externally to the epidermis, nasal passageways, vagina, rectum, cornea, etc. How effectively they adhere to the application depends on their specific rheological behavior. The fundamental benefit of this dosage formulation is the formulation's adaptability and simplicity of incorporation of multiple. It should be noted that gels have numerous advantages over other partially solid forms. These benefits include longer retention duration, superior spreadability, and fewer long-term stability issues. In addition, active moieties are also present, as stated in reference.[6]

Nonetheless, constraints emerge from the inherent API characteristics, complex structure, and physiological functions of the skin. This complexity hampers the universal applicability of conventional gel formulations for treating diverse skin conditions. Specifically, when combating malignant cells situated in the skin's deeper layers, the efficacy of conventional

**Address for correspondence:**
Sunita N. Vaidya, Datta Meghe College of Pharmacy Salod (H), Datta Meghe Institute of Higher Education and Research (D.U.), Wardha - 442 002, Maharashtra, India. Phone: 9284591082.
E-mail: sunitavaidya06@gmail.com

**Received:** 28-11-2023
**Revised:** 12-02-2024
**Accepted:** 08-03-2024

semisolid formulations in delivering chemotherapeutic agents is limited.[7] In response to these challenges and to optimize cutaneous drug delivery, a contemporary tactic has emerged, leveraging a synergistic strategy. Larger molecules or extremely hydrophilic chemicals may be delivered using nanoformulations, which also guarantee regulated drug release and resolve significant issues with API solubility and skin layer penetration. Their direct application, however, is linked to potentially reduced stability and short retention times.[8]

The purpose of this paper is to conduct a thorough evaluation of gel-based solutions for skin cancer therapy, as well as to highlight the key shortcomings and future elements of gel development. The most prevalent characterization techniques are briefly addressed, together with the excipients that are most frequently utilized and their functions. The reported methods for topical chemotherapeutic drug administration using gel-based formulations are summarized in the current article.

## SYSTEMATIC SEARCH

### Search strategy

According to PRISMA recommendations, a systematic analysis was conducted.[9] Significant scientific databases include Science Direct, Google Scholar, PubMed, and Scopus. The World Wide Web of Science and this were searched to find the records. Without access to the complete text, the search was restricted to the headings, keywords, and abstracts. The publishing year was restricted to 2022 and beyond. With the use of the Zotero program (v. 6.0.22), the duplicates were eliminated from the recognized papers, and the remaining ones' relevancy was browsed.

### Inclusion and exclusion criteria

All remedial guidelines for medical routine, clinical standards, the proceedings of conferences, book chapters, therapeutic strategies, updates, and all review papers were disregarded, and only research articles were thought to be pertinent. Articles that failed to mention the potential application of gel in treating skin cancer topically were eliminated from consideration. The search did not exclude any publications released in 2023. The search method currently being utilized does not have any language restrictions**.**

## SKIN CANCER TREATMENT: CHALLENGES IN DELIVERING DRUGS

Chemo for cancer of the skin can be administered orally, intravenously, or topically. When administered orally, however, only a limited quantity of the medication reaches the desired place, while the remainder might induce undesirable adverse reactions in other tissues, cells, and organs. Injection has comparable difficulties in terms of applicability and intrusiveness. As a result, local application to diverse skin types is possible. Many cancer types' therapeutic efficacy and safety can be improved. There are, however, a lot of them. Because of drug penetration obstacles, topical medicine distribution is a tough task.

### Skin structure

The skin, a marvelously intricate organ, stands as a formidable shield, entrusted with the task of preserving internal sanctity while staunchly repelling external intrusions.[31] Its triumvirate layers – epidermis, dermis, and hypodermis – unveil distinct compositions and attributes, each an emblem of its unique role.[10] The innermost hypodermis, ensconced in adipose tissue, largely wields minimal sway over drug delivery dynamics.[11] Constructing the dermis is a complex interplay of collagen, elastin, and a mucopolysaccharide gel, fashioning a hydrogel-like structure with dimensions spanning 2–4 mm.[12] Noteworthy is the dermis's lavish vascular bed, orchestrating a transdermal symphony and ushering medicinal molecules into the bloodstream by capitalizing on a resolute concentration gradient. Hair follicles, sebaceous glands, and sweat glands – offshoots of this layer – enrich the narrative, although their dominion resides predominantly in early cutaneous diffusion narratives. Aloft, the epidermis takes center stage, a tapestry woven predominantly with keratinocytes, poised as the linchpin in orchestrating the performance of topical medication delivery.[13] The functional skin and the skin layer corneum (SC), both non-vascular and hydrophobic bastions, rule supreme inside the epidermal domain. The live epidermis contains melanocyte cells called Merkel, cells from Langerhans, and keratinocytes in layers of varying maturation. As the tale progresses from the center outward, the epidermis begins its voyage of differentiation, resulting in the production of corneocytes – lifeless, non-nucleated, flatter creatures rich in keratin.[14] Ceramides, unsecured long-chain fatty acids, and cholesterol make up the lipid matrix that surrounds corneocytes. These structures are the principal hindrance. The delivery of medicine is limited because the skin has a restricted ability to absorb anticancer substances, both on a macro and micro level.[15]

Recent studies conducted on skin cancer have discovered that elevated levels of keratin are present in cancerous cells. lipid than cells in good health, leading to a deeper SC layer and an increased drug entry barrier, making accessing the tumor site considerably more challenging for anticancer drugs.[16] For successful treatment of active isotretinoin actinic keratosis (AK) and tumors of basal cells, or BCC, dermal dosage forms of drugs must be carefully designed to get to the deeper epidermal layers.[17] Between 200 and 400 nm is the ideal particle diameter for transdermal dispersion.[18] The transappendageal channel enables the delivery of nanoparticles as tiny as 300 nm to the skin. It is worth noting that the skin is thicker.

## Routes of skin penetration and factors that affect it

The physical and chemical properties of the active ingredient are very important. Drugs may enter cells through one of three different entry points: the stratum corneum, the lipid matrix between cells, or skin appendages like sweat glands or hair follicles. Figure 2 shows that the lipid matrix facilitates the transport of hydrophobic molecules, while skin appendages are more important for hydrophilic molecules.

Numerous obstacles, frequently described as "brick walls," are present along the intercellular passage that the medicine must get through. Before entering the lipophilic intercellular lipid matrix, the material must first partition among corneocytes having hydrophilic properties, followed by diffusion across these corneocytes. Lipophilic medicines are suitable for transdermal administration because they can move around effectively in these lipid-rich environments.

Regrettably, not all anticancer drugs exhibit the hydrophilic-lipophilic balance that is desirable.[19] This pronounced hydrophilicity hampers its ability to traverse the hydrophobic stratum corneum, effectively, thereby compromising the efficacy of treatments targeting deeper-seated ailments.[20] Furthermore, the poor epidermal penetration of 5-fluorouracil necessitates continued administration of higher doses, culminating in potential adversities such as skin irritation.[21] Similar challenges are encountered with imiquimod, used for BCC treatment. Infiltration within the hydrophilic dermal milieu poses difficulties due to its limited water solubility. Moreover, the amine groups in the drug molecule interact with the negatively charged skin components, hindering the absorption of imiquimod and reducing its therapeutic efficacy.

It is an undeniable fact that the molecular mass of a substance has a significant impact on its capacity to infiltrate the skin through passive diffusion along a concentration gradient, as explained by Fick's law. The scientific formula is commonly referred to as the Stokes-Einstein equation. States that as a molecule's approximate radius grows, so does its diffusion coefficient. As a result, a heavier molecular weight (MW) is correlated with a larger approximate radius, resulting in a decreased overall diffusion coefficient and less effective diffusion. It is challenging for anticancer medications with greater MWs to penetrate the skin due to the requirement for optimal results. It is advised to keep the MW of the drug below 500 for transdermal administration.[22]

The problem of multidrug resistance (MDR) is of utmost importance and should be given careful consideration in the realm of cancer treatment. Cancers may show notable resistance to different compounds due to the complicated interaction between the medicine and tumor medium. MDR, which is a significant issue that lowers the efficacy of chemotherapies, is described as the decline in a drug's efficacy and potency to provide a therapeutic impact.[23] It is important to note that drug resistance in skin cancer can manifest as either intrinsic or acquired. The first response to therapy is poor because primary resistance develops without previous exposure to anticancer drugs.[24] When using cytostatic medication, acquired resistance develops and is linked to disastrous outcomes following initially positive ones.[25]

Numerous processes, including adjustments to the efflux pump and drug transport, alterations to enzyme activity and DNA repair, and modification of the apoptotic pathway, among others, are linked to intrinsic resistance.[26] Genetics or external variables that promote the development of therapeutic-resistant lines of cancer cells or result in enzyme mutations are the primary contributors to acquired drug resistance.[27] Understanding the molecular mechanisms responsible for treatment resistance is imperative for advancing the development of more effective therapeutic interventions for skin cancer.

The small amount of medicine that reaches the tumor cells is one of the possible causes of drug sensitivity. Due to this, it is crucial to establish the "maximum tolerated dose", which is the largest amount of a medicine that does not result in appreciable or intolerable adverse effects.[28] Enhancing the efficacy of cancer treatment is possible by improving the ability of anticancer drugs to penetrate through the skin.

## Possibilities for improving skin penetration

One of the biggest challenges of treatment, taking into account all of the concerns raised and the components that go into managing the diffusion of chemotherapy medicines through the skin,[29] is an enhancement in drug absorption, which allows the medication to move through the most packed layers of the skin and within cancerous cells.

One method to increase the absorption of substances is through the use of "penetration enhancers".[30] These enhancers include alcohol, a zones, fatty alcoholic drinks, glycols, and DMSO. When these chemicals communicate with each other within proteins, they mostly disrupt lipid bilayer packing.[31] Water has enhancer properties that are critical to comprehend since wet skin has higher drug absorption rates, necessitating occlusion for the best possible treatment.

Powders, aerosols, emulsions, and creams are among the dosage forms utilized for topical administration of skin anticancer medicine. Hydrogels, on the other hand, exhibit excellent characteristics.[32] Their structure enables molecular control, which may be utilized to adjust features such as degradation rate, long-term discharge, adjustable pores, and biochemical and biological responsiveness to stimuli such as pH, enzymes, and temperature to desired values.[33] In addition, hydrogel-based medication dosage forms improve chemotherapy results by extending drug half-lives, allowing

for regulated drug release, and lowering non-targeted exposure.[34]

The growth of advanced drug delivery methods like nanogels and liposomes, whose ethosomes are nuclei, or transferases, that improve skin penetration and accessibility, has a chance to be used in current cancer therapy, which is achieved through the combination of gel formation and nanotechnology.[35] The present review delves into the examination of these approaches both independently and in combination, as detailed in the subsequent sections.

## FORMULATIONS THAT USE THE GEL AS A BASE

As per the European Pharmacopoeia, gels are semi-solid preparations primarily intended for topical application, formed by effectively transforming liquids into a gel-like state.[36] These gels exhibit a three-dimensional network structure due to the various linkages formed between the polymer and the surrounding medium, which can be either covalent or non-covalent.[37] Moreover, the Pharmacopoeia classifies gels into two categories based on the polarity of the liquid: hydrophobic and lipophilic gels.[38] Gels can be characterized by factors such as their financial viability, colloid properties, rheology, the source of the gelling agent, and various other parameters, as referenced in existing literature.

Furthermore, the method of crosslinking allows us to differentiate gels into three fundamental types: physical gels, covalently cross-linked gels, and entanglement network gels.[39] In this review, we explore the unique characteristics of each of these gel types and examine how they can be harnessed for the delivery of chemotherapeutic agents in the treatment of skin cancer.

Various types of polymers, including natural, synthetic, and semi-synthetic options such as gelatin, carbomers, ocean polysaccharides, and plant carbohydrates, can be employed in the formulation of physical gels for this purpose.

These gels are often transitory since they involve temporary cross-linking. Covalently cross-linked gels, also known as chemically cross-linked gels, fall under the second category. Their cross-linker and the macromolecules are connected by chemical bonds in their structure, and only heat can break these ties. Due to the adaptability of the polymer chain, these gels exhibit considerable elasticity. A subclass of this class created by cross-linking is polymeric hydrogels. As presented here, only heat deterioration may damage these connections. Because the solvent volume is larger and the polymer chain is more flexible, these gels have a high degree of elasticity. A multidimensional hydrophilic polymeric network that has been swelled in water is used to create the polymeric hydrogels, a subset of this class. Gels develop in the final class (entanglement networks) when the polymer's content and MW are higher than the entanglement's critical molecular mass. In the absence of it, they produce diluted polymer solutions. The 156 pertinent entries that the systematic search turned up\ display the distribution of publications among the various gel types. 25% ($n$ = 39) of the articles are about the creation and description of physical hydrogels. None of the records that were located mention how organogels are made. This is most likely a result of hydrogels' benefits, which include their simplicity in production, lack of greasiness, and cooling feeling after application.

The 156 relevant items that the systematic search uncovered are displayed in Figure 1. The breakdown of articles across different gel types is shown in articles, or 25% of the total, on making and describing physical hydrogels. None of the discovered documents discuss the production process for organogels. This is most likely a result of hydrogels' benefits, which include their ease of manufacture, no greasiness, and cooling sensation after application.

Physical hydrogels: Physical hydrogels are dosage forms whereby an ingredient in creams is directly linked together by electrostatic forces, bonds made up of hydrogen, and ions in interchain paths, crystallizing intersections. Water-resistant association or additional processes. They can be made regardless of the inclusion of other polar liquids and use fluid as the medium. The key attributes commonly associated with these gels include their reversible nature and their responsiveness to temperature, leading to a sol-gel transition. The polymers utilized in creating these gels also provide a high level of safety when compared to chemical hydrogels. These polymers are environmentally benign, biocompatible, and inert, thereby eliminating the presence of any leftover cross-linking agents. In this section of the review, we explore the application of different naturally occurring, synthetic, and partially synthetic polymers that are well-suited for developing physical gels capable of delivering chemotherapeutic agents for the treatment of skin cancer.

### Carbomers gelling agent

Physical hydrogels are dosage forms that involve an individual whose creams are emotionally linked together by

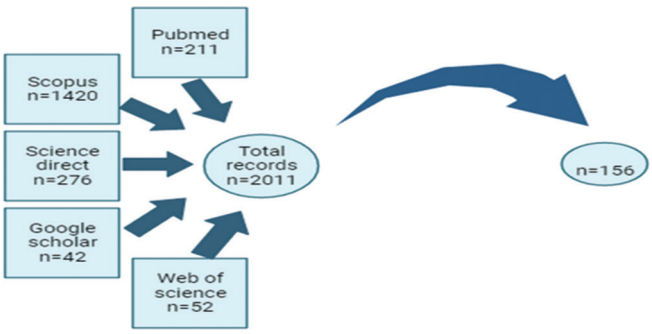


**Figure 1:** Flow chart of the systemic search strategy

electrostatic attraction, hydrogen bonding, charged interchain roadways and formation crossings, repellent connection, or additional channels. They can be made by containing or refraining from the inclusion of other polar fluids and using fluid as the medium.[40] The influence of temperature on the sol-gel transition and the reversal of these gels are common properties. In addition, compared to chemical hydrogels, the polymers utilized in their synthesis have an excellent safety profile since they're environmentally friendly, compatible with life, and inert, so zero leftover cross-linkers can be identified. This portion of the review discusses the utilization of various made-up, organic, and partially synthetic polymers suitable for the production of physical gels carrying chemotherapeutic medicines for skin cancer. It is common knowledge that the technological method for producing carbomer gels involves soaking polymers in water to generate a very acidic mixture with a range of pH levels of 2.5–3.5. After that, neutralizing by hydroxide of sodium, triethanolamine, or another base causes the carboxylic functional groups to ionize, which causes the polymer chains to partially detangle and the creation of irreversible agglomerates. In place of fluid, polyethylene glycol (PEG 400) or glycerol are frequently included in the medium of carbomer gels, which may impact the rheological and mucoadhesive characteristics. The substance found to be most often employed in the current study to create conventional physical gels was Carbopol® 934. The concentrations ranged from 0.5% to 3%. w/w.[41]

The watery medium in which carbomer-based physical gels are made is one of their disadvantages. This emphasizes the need for additional excipients, including preservatives, to increase microbiological stability. On the other hand, a sizable number of medications, like Resatorvid, that are employed to treat skin cancer are not water soluble. According to Ruiz *et al*., an appropriate co-solvent must be added to do this. Phenethyl, a solution of a phytochemical, PEIT, which was synthesized in 0.5% Carbopol® 940, was compared to an analogous gel that included 5-fluorouracil by Osipitan *et al*. Similar to the PEIT, the PEIT had to be dissolved in DMSO before gel production. Due to its widespread usage as a penetration enhancer, DMSO can further amplify the impact. It is compatible with carbomer gel, according to the research.[42] Abkin *et al*. added human thermal shock protein (Hsp70) to 1% carbomer, while 1% glycerol and 10% DMSO were also present. Their analysis revealed that the protein was protected during storage against denaturation and/or proteolysis. Using 10% glycerol, Bharadwaj *et al*. were able to successfully integrate a frozen methanol-extracted root of Annona reticulata inside Carbopol® 940 solution (1% w/w). The formulation's potential as a cutaneous anticancer therapy was demonstrated by the authors. The use of physical gels might potentially be advantageous for photodynamic treatment (PDT). Photosensitizers, non-toxic compounds, are given topically or orally to create visible fluorescence when triggered by the right wavelength of light. Porphyrins and 5-aminolevulinic acid (5-ALA), which is its pre-cursor, are well-known examples of medications used in PDT. Despite being a tiny molecule, 5-ALA's hydrophilic nature prevents it from penetrating the stratum corneum. The problem may be solved by chemically altering it to become esters of methyl or hexyl ester. Utilizing penetration enhancers like DMSO is an alternative. Merclin and colleagues looked at the viability of utilizing iontophoresis to deliver carbomer compounds. Actual gel comprises 5-ALA or methyl-ALA. Hydrogels might be employed as a means of transporting API to the underneath layers of the skin since they reach jelly on skin layers and electrodes during iontophoresis. In addition, carbomer, an anionic polymer with high buffering capabilities, can help maintain a steady pH. It is interesting that the authors looked into this and found that uncharged drug diffusion on a 1% w/w carbomer compound gel is comparable to that in water. Positively charged medicines are also partially maintained at the same time. The physical gels based on carbomers are demonstrated to have an adaptable structure, allowing rapid putting of philic and lipophilic compounds, and may be used in conjunction with iontophoresis, phototherapy, and radiotherapy. However, there are still barriers that prevent APIs from penetrating deeper into the epidermal layers, and these barriers in these kinds of gels heavily rely on the characteristics of the medication itself. Therefore, if adequate drug solubilization is accomplished, physical gels made using carbomers are appropriate semisolid carriers for the treatment of surface skin cancer.

## Cellulose derivatives as gelling agents

Studies that describe the features, processes, and applications of various hydrogels made from cellulose derivatives have previously been reported. Their usage of dosage forms for topical chemotherapeutic administration is the main theme of the current paper.

A polysaccharide, cellulose, can be derived from a variety of plants, animals, or microbes. It is suitable for a wide range of applications because of its biodegradability, biocompatibility, environmental friendliness, and good mechanical properties because it is renewable and widely available around the world. Like many organic solvents, cellulosic is a semicrystalline proportional polymer of glucose that has no taste or odor but is insoluble in water. The use of cellulose in biomedicine is hampered by its insolubility in water. As a result, etherification and esterification of their hydroxyl groups lead to the production of substances with increased solubility. Most drug delivery techniques, including water, semisolid, and solid ones, use various cellulose derivatives, as well as the more recent nanocomposites and solid traditional dose forms. The bonding of hydrogen, ionic relationships, and hydrophobic forces all contribute to the cellulose derivatives' capacity to create physical hydrogels.[43]

A cellulose derivative with meth and hydroxypropyl side groups attached is called hypromellose, also known as

hydroxypropyl methylcellulose (HPMC). According to the extent and ratios of substitution, the polymer offers a wide variety of viscosity classes. A careful search revealed four papers that examined the use of HPMC as a gelling agent in physical hydrogels. The incorporation of APIs and cyclodextrin compounds into a semisolid gel was the subject of two of their studies. Given that the dissolution rates between a gel comprising an API and a gel containing the API-cyclodextrin complex are equal, Ceschel and colleagues show that the HPMC-based gel has its own soluble action. However, the cyclodextrin complex demonstrated improved permeability. The authors speculated that this is because of an absorbent layer that is present. According to the authors' theory, this is because the skin surface has a diffusion layer and, in addition to acting as a transporter across it to a liquid skin layer, cyclodextrin. Similar cellulose combinations of the liquid antioxidant 3-O-methyl flavonoid were used in a different, more recent investigation conducted by Doneda and collaborators to enable its integration into an anhydrous topical formulation. In the presence of 1%, a mixture of prop HPMC at a concentration of 3.5% was utilized as a gelling agent. All of the suggested gels displayed properties that made them appropriate for cutaneous application, including pseudoplastic rheological behavior and a pH range of 4.49–4.87. Even though the formulations contained hydroxypropyl-cyclodextrin or -cyclodextrin, bioadhesion was also confirmed. Due to interactions with HPMC, they lose some of their bioadhesive potential. *In situ* gelling and bioadhesive characteristics are provided by the carboxylate moiety of carboxymethyl cellulose (CMC), which is pH-sensitive. However, low mechanical stability is a characteristic of physical gels made with CMC. This problem can be resolved without chemical cross-linking by including naturally occurring nanoclays like sepiolite. Palem *et al*. produced a physical gel from CMC, which is made up of agar, PVP, and sepiolite, using a straightforward moisture-heat treatment. The platform released 5-fluorouracil steadily and continuously and was non-toxic.[44] *In situ* gelling and bioadhesive details are provided by the carboxylate moiety of CMC, which is pH-sensitive.[11] However, limited mechanical stability is an aspect of physical gels made with CMC. This problem can be resolved without chemical cross-linking by including naturally occurring nanoclays like sepiolite. Palem *et al*. produced a physical gel from CMC, an agar, PVP, and sepiolite using a straightforward moisture-heat treatment. The platform released 5-fluorouracil steadily and continuously and was non-toxic. Another cellulose derivative used in the management of 5-ALA or glycoalkaloids is hydroxyethyl cellulose (HEC), which is used in quantities between 2 and 3 percent. HEC is a water-soluble form of non-ionic cellulose ether.[11] In comparison to dry lotion, lipophilic ointment, and DMSO-free gel, 5-ALA was more deeply absorbed when administered as a 3% HEC gel with 40% Mda as an absorption enhancer. Low-chain alcohols were discovered to be more effective as penetration enhancers when used with 5-ALA. Its solution of PEG, tetraethylene glycol ether, ethanol, and isopropanol penetrates the skin more effectively than the recently created physical gel. Tiossi and colleagues used commercial 2% HEC physical hydrogel.[45]

### Poloxameras gelling agent

Poly (ethylene oxide) and poly (propylene oxide) building blocks make up the synthetic copolymer known as poloxamers, which is sold under the trade name Pluronics. These copolymers have unusually responsive temperature characteristics. Poloxamers are made up of three segments: PEO, which likes water; PPO, which doesn't; and PEO once again. Poloxamers' behavior varies depending on the temperature. They behave more like PPO, which despises water, at lower temperatures. They start to behave more like PEO, which prefers water, as the temperature rises. Poloxamers have a tendency to aggregate and form micelles, which are microscopic spheres that float around in water. Different temperatures cause these micelles to develop in different ways, which can have useful implications. Poloxamers are used in the real world in the pharmaceutical, cosmetic, and other industries. They have a number of functions, including assisting with medication dissolution and enhancing cream textures. Micellization is the aggregation of certain molecules, such as poloxamers, in a liquid. Poloxamers do this by having a PPO portion that becomes less moist and moves to the center, and a PEO portion that surrounds the exterior. Unique compounds known as poloxamers are produced by BASF. They are made up of two parts: PEO, which likes water, and PPO, which does not. Larger poloxamers can produce gels at lower temperatures and require fewer of them to do so. Micellization is the process by which specific molecules called poloxamers, which have two components and may readily form gels when they are larger, group together in liquids. They are thermoresponsive, and temperature affects how they micellize, aggregate, and gel.[46] The dehydration of PPO blocks, which are then found in the core while the hydrated PEO chain forms an outside shell, causes micellization. Poloxamers' critical gelation concentration and gelation temperature decrease as their MW increases. Poloxamer 400 (Pluronic® F127) is referred to as producing a reversible gel at levels over 20% and temperatures close to 19°C. The greater the polymer concentration, the lower the gelation temperature. To distribute 5-fluorouracil or doxorubicin topically, poloxamer gel has been studied since 1984. The researchers found that the seeming discharge of the APIs through the gels is influenced by the amount of gelling component. The in vitro dissolving test's released quantity increased when the temperature was raised. These results imply that the polymer micelles' aqueous channels that surround them are where the release takes place. The channels get smaller when more polymer is added to the gel, and the micro-viscosity of the channels gets lower as the temperature rises. Redpath and colleagues discovered that a 30% empty poloxamer 407 gel, despite API loading, somewhat delayed cell migration in the C8161 cancer cell

lines without hurting cell survival, but they did not pursue the discovery further. Furthermore, their research showed that the drug's slow diffusion in the gel, which is the rate-limiting phase, delayed the accidental discharge of silibinin from the gel. Because of the gel's less permeable crystalline structure than a liquid, test results showed that Poloxamer 407 gels had a comparatively modest drug flow into the skin. The polymers did not compromise the lipid integrity of the skin, despite decreased penetration. Another study suggests that 7% poloxamer 40 and 40 percent poloxamer 188 might be utilized to create an in vivo gelling formulation. *In situ* gels offer several advantages, including easy application, great therapeutic agent penetration, and strong adhesion to the skin's surface. However, dissolution of drugs was a limiting issue for the accidental discharge rate of hydrophilic APIs like curcumin, according to studies by Sun and colleagues. The capacity to deliver curcumin to melanoma cells successfully was considerably increased by using the cyclodextrin complex.[47]

Batista and colleagues looked at the stability of a poloxamer 407 gel when hydroalcoholic extract was added. In contrast to HEC-based gel, the gelling agent is ethanol-compatible. Poloxamer 407 gels do, however, have certain drawbacks, including poor mechanical strength, short durability, and quick drug release. Sun and associates showed that an in situ determination by poloxamer 188 and 407 degraded by around 40% in just 3 h. As a result, poloxamers are commonly used with other gelling polymers. In the current investigation, combinations of poloxamer and carbomer were found for the topical delivery of anticancer drugs. The poloxamer gel's stability and consistency might both be enhanced by the addition of carbomer, which would also give it more bioadhesive qualities. This could increase medication delivery and extend the contact time. To obtain suitable in situ gelation without runoff upon application, Borghi-Pangoni and colleagues demonstrated that a mixed poloxamer/carbomer gel must have a concentration of 20% or 0.15%, respectively. In the suggested gel, the low solubility of hypericin in aqueous solutions might be somewhat mitigated. Despite the drug's quick release (within 2 h), there was no sign of penetration.[48] As a result, PDT may be appropriate for the suggested dosage form. The investigation carried out by Campanholi and colleagues lends more weight to these conclusions. It was shown that the authors' gel mixture of 20% poloxamer and 0.2% carbomer may dissolve chlorophyll for use in photodynamic therapy.

In addition, expanding the time spent in contact through bioadhesive polymers like carbomer could enhance the functionality of such drug-delivery devices since; otherwise, the drugs are just released and fail to penetrate. In the setting of photodynamic therapy, this could be advantageous because it could boost the gel stability and solubilization of hydrophilic APIs.[49]

## Other physical hydrogels

Chitosan and chitin are naturally occurring substances created from glucose and acetamide. Chitosan is produced when it is only partially deacetylated (<50%). Chitosan cannot be dissolved in water; hence, a suitable solvent is required to turn it into a physical hydrogel. To create physical hydrogels, chitin or chitosan must first undergo hydrolysis or cross-linking. The hydrogel becomes stronger as the concentration of the gelling ingredient is increased, changing it from a liquid to a solid. Enhancing Stability: different temperatures or the use of certain coagulants can increase the stability of hydrogels. Iota-Carrageenan: Another natural polymer that has the ability to form physical gels due to molecular interactions like hydrogen bonds and electrical attractions is iota-carrageenan. These hydrogels have the potential to transport medicines, such as methotrexate and cyclodextrin inclusion complexes. The cyclodextrin complex had no impact on the rheology of the gel or its mechanical stability.

According to the information from the literature search, scientists have been working to create innovative polymers that can gel physically and carry lipophilic APIs to skin cancer cells. The cationic triblock polymer of the synthesized ABA type produced by Taktak *et al*. illustrates this. By facilitating the entry of lipophilic medications like paclitaxel, the polymer's amphiphilic character and positive charge may interact with the stratum corneum.[50]

## Chemical hydrogels

Water-loving polymers are unique substances that can absorb water without melting. Consider these products, which can hold a lot of water, as sponges built from these materials. Customizable Gels: By altering the components in these sponges, we can change how they function. Skin Cancer Research: Researchers are looking at the usage of these sponges in the treatment of skin cancer (additional information is in a table). When CMC and citric acid are combined, a safe, breakable sponge is produced. Medication Sponge: Doxorubicin is attached to CMC, which allows for a gradual release of the medication inside cancer cells. Hybrid Sponge: CMC is also mixed with silver particles, which improve the drug's ability to combat bacteria and cancer. Essentially, researchers are investigating water-holding sponges. For stimulus-triggered 5-fluorouracil release, Okay and Alemdar created a gelatin-based electro-responsive hydrogel. Methacrylic anhydride was used to change the gelatin, and then, it underwent UV cross-linking. Because 5-fluorouracil contained a polymer that controlled drug release and led to anisotropic gel distortion when 1.5 V was applied, the dosage utilized to treat skin cancer was appropriate.[51]

Kudacik-Kramarczyk *et al*. constructed and studied a transdermal system based on hydrogel for an achievable cure for skin cancer and burn wounds brought on by radiation. The chitosan-based

formulation was cross-linked using PEGDA (diacrylate PEG). To coagulate and produce distinctive rheological behavior, chitosan hydrogels require an alkaline medium. Ionic cross-linkers that increase their strength while also giving them pH sensitivity include sodium citrate and tripolyphosphate. The produced gel's biocompatibility was established by the authors' extensive physicochemical characterization.[52]

The hydrogels' limited capacity to transport hydrophobic medicines is a result of their hydrophilic nature. Due to the decreased and unequal distribution of the loaded quantity over the gel structure, there is inadequate release in this instance. Pour-Manouchehri *et al*. recommended resolving this issue by incorporating deoxycholic acid micelles containing 5-fluorouracil into a hydrogel. At pH = 9, it has been shown that the glutaraldehyde-crosslinked carboxymethyl chitosan is more insoluble than the original polymer. The researchers found that an acidic environment (pH = 6.8 and pH = 5) allowed for a better and more thorough release of 5-fluorouracil. Deoxycholic acid micelles' destabilization was also halted by the hydrogel formed, and it had no burst effect. Overall, these findings showed that the API was effective in treating cancer and that it had a five-fold greater cytotoxic effect than free 5-fluorouracil.[53]

Dummer *et al.* created a polymer to make an ingredient hydrogel that could be filled with green indocyanine and used together with photodynamic therapy to cure cancer.[11] Treatment for this type of skin cancer is exceedingly difficult since it spreads swiftly to nearby skin tissue. The developed hydrogel is mechanically stable and skin-adhesive. The recommended formulations appear to be more suitable for PDT than an intravenous hydrogel because they shield the packed indocyanine from irradiation and produce less irritation at the application site. Scientists demonstrated that all cells of melanoma have been eradicated in the animal model under study.[54]

Oktay and Alemdar have suggested a novel method for topical antineoplastic medication administration using chemically cross-linked hydrogel. The authors created a 5-fluorouracil-loaded electro-responsive hydrogel. Methacrylic anhydride was used to alter the gelatin before it was further UV-cross-linked. The internalization of a polymer with conductivity that controlled drug release led to anisotropic gel deformation when 1.5 V electricity was applied. The 5-fluorouracil that came out was therefore sufficient for treating skin cancer.

This category of hydrogels has received very few publications, which might be attributed to the fact that they usually lack the rheological properties required for topical application. Thus, they are administered directly into the malignant cells or used as plasters.[55]

## NANOGELS

Nanogels are a subclass of hydrogels that have a 3D porous structure with nanoparticles that are 20–250 nm in size. According to some definitions, nanogel particles range in size from 10 to 1000 nm.[38] They may also be cross-linked chemically or physically. The second can be produced by either monomerization or cross-linking of pre-existing polymers. In comparison to regular nanoparticles, nanogels are more sensitive to many environmental factors (such as pH, temperature, ionic strength, etc.) and have changeable particle size and form. As a result, they mainly provide pharmaceutical delivery methods for systemic treatment. Nanogels can also be used for topical distribution because of their unique structure and mechanical features, which resemble those of the matrix of cells in the skin.[56]

Di-ethylene glycol monoethyl ether, sometimes known as Transcutol®, can disrupt stratum corneum cell membranes, enhancing penetration. It improves the absorption of drugs and may be added to simple gel formulations in dosages between 1 and 50%. The recommended dose of 22% v/v facilitates dispersion throughout the skin's lipid matrix. Together, Poloxamer 407 and Transcutol® create an inert nano-gel formulation that eliminates the irritation-causing potential of the penetration enhancer. Matsui *et al*.[38] suggest using natural penetration enhancers as an alternative strategy to lessen irritation, edema, and inflammation. These substances include the terpenes and terpenoids found in oak and chenopodium essential oils. They can significantly increase the extent of penetration, raising the formulation's therapeutic value.

For the administration of API through the skin, nanogels composed of chitosan showed enhanced drug release in an environment that is acidic (pH = 4.5–6.0). The primary cause of this phenomenon is thought to be the polymer molecule's potential protonation of free amino groups. This is also beneficial in terms of the potential for ionic interaction with tumor cells due to their acidic composition (pH > 5.5–6.5), and as a result, regulated release may be anticipated.

### Nanocarrier-loaded gels

Nanotechnology and gel formulations are two technical approaches that are combined in this kind of medication delivery system. Gel supports the nanocarriers and ensures that they are applied and released continuously. Due to their unique qualities and traits, the nanocarriers can further allow the adjustment of medication release. As a result, the multimodal approach can boost the therapeutic effectiveness of several drugs and delivery systems. The topical administration of chemotherapy is highlighted in the current review. It became clear from the systematic search that various nanocarriers may be put onto physical hydrogels to cure skin cancer.[57]

## REFERENCES

1. Linares MA, Zakaria A, Nizran P. Skin cancer. Prim Care 2015;42:645-59.

2. Craythorne E, Al-Niami F. Skin cancer. Medicine 2017;45:431-4.
3. Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, *et al*. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer 2019;118:10-34.
4. Nawaz A, Ullah S, Alnuwaiser MA, Rehman FU, Selim S, Al Jaouni SK, *et al*. Formulation and evaluation of chitosan-gelatin thermosensitive hydrogels containing 5FU-alginate nanoparticles for skin delivery. Gels 2022;8:537.
5. Barrera MV, Herrera E. Topical chemotherapy for actinic keratosis and nonmelanoma skin cancer: Current options and future perspectives. Actas Dermosifiliogr Engl Ed 2007;98:556-62.
6. Safwat MA, Soliman GM, Sayed D, Attia MA. Fluorouracil-loaded gold nanoparticles for the treatment of skin cancer: Development, *in vitro* characterization, and *in vivo* evaluation in a mouse skin cancer xenograft model. Mol Pharm 2018;15:2194-205.
7. Ghezzi M, Pescina S, Delledonne A, Ferraboschi I, Sissa C, Terenziani F, *et al*. Improvement of imiquimod solubilization and skin retention via TPGS micelles: Exploiting the co-solubilizing effect of oleic acid. Pharmaceutics 2021;13:1476.
8. Lapteva M, Mignot M, Mondon K, Möller M, Gurny R, Kalia YN. Self-assembled MPEG-HexPLA polymeric nanocarriers for the targeted cutaneous delivery of imiquimod. Eur J Pharm Biopharm 2019;142:553-62.
9. Capanema NS, Mansur AA, Carvalho SM, Carvalho IC, Chagas P, de Oliveira LC, *et al*. Bioengineered carboxymethyl cellulose-doxorubicin prodrug hydrogels for topical chemotherapy of melanoma skin cancer. Carbohydr Polym 2018;195:401-2.
10. Gamal FA, Sayed OM, El-Ela FI, Kharshoum RM, Salem HF. Treatment of basal cell carcinoma via binary ethosomes of vismodegib: *In vitro* and *in vivo* studies. AAPS PharmSciTech 2020;21:51.
11. Dummer R, Ascierto PA, Basset-Seguin N, Dréno B, Garbe C, Gutzmer R, *et al*. Sonidegib and Vismodegib in the treatment of patients with locally advanced basal cell carcinoma: A joint expert opinion. J Eur Acad Dermatol Venereol 2020;34:1944-56.
12. Nagendran S, Pimpale A. Advances and prospects in antimicrobial research using nanomedicines. Curr Drug Ther 2023;18:194-204.
13. Mousa IA, Hammady TM, Gad S, Zaitone SA, El-Sherbiny M, Sayed OM. Formulation and characterization of metformin-loaded ethosomes for topical application to experimentally induced skin cancer in mice. Pharmaceuticals 2022;15:657.
14. Kollipara RK, Tallapaneni V, Sanapalli BK, Kumar GV, Karri VV. Curcumin loaded ethosomal vesicular drug delivery system for the treatment of melanoma skin cancer. Res J Pharm Technol 2019;12:1783-92.
15. Priya P, Raj RM, Vasanthakumar V, Raj V. Curcumin-loaded layer-by-layer folic acid and casein coated carboxymethyl cellulose/casein nanogels for treatment of skin cancer. Arab J Chem 2020;13:694-708.
16. Alhakamy NA, Aldawsari HM, Ali J, Gupta DK, Warsi MH, Bilgrami AL, *et al*. Brucine-loaded transliposomes nanogel for topical delivery in skin cancer: Statistical optimization, *in vitr*o and dermatokinetice valuation. 3 Biotech 2021;11:288.
17. Iqbal B, Ali J, Ganguli M, Mishra S, Baboota S. Silymarin-loaded nanostructured lipid carrier gel for the treatment of skin cancer. Nanomedicine 2019;14:1077-93.
18. Nagaraja S, Basavarajappa GM, Attimarad M, Pund S. Topical nanoemulgel for the treatment of skin cancer: Proof-of-technology. Pharmaceutics 2021;13:902.
19. Kaplan A, Cetin M, Orgul D, Taghizadehghalehjoughi A, Hacimuftuoglu A, Hekimoglu S. Formulation and *in vitro* evaluation of topical nanoemulsion and nanoemulsion-based gels containing daidzein. J Drug Deliv Sci Technol 2019;52:189-203.
20. Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics 2015;7:438-70.
21. Jose A, Labala S, Ninave KM, Gade SK, Venuganti VV. Effective skin cancer treatment by topical co-delivery of curcumin and STAT3SiRNA using cationic liposomes. AAPS PharmSciTech 2018;19:166-75.
22. Gupta P, Garg S. Semisolid dosage forms for dermatological application. Pharm Technol 2002;3:144-62.
23. UnNabi SA, Sheraz MA, Ahmed S, Mustaan N, Ahmad I. Pharmaceutical gels: A review. RADS J Pharm Pharm Sci 2016;4:40-8.
24. Goyal N, Thatai P, Sapra B. Skin cancer: Symptoms, mechanistic pathways and treatment rationale for therapeutic delivery. Ther Deliv 2017;8:265-87.
25. Yuan L, Pan M, Shi K, Hu D, Li Y, Chen Y, *et al*. Nanocarriers for promoting skin delivery of therapeutic agents. Mater Today 2022;27:101438.
26. Akhter MH, Ahsan MJ, Rahman M, Anwar S, Rizwanullah M. Advancement in nanotheranostics for effective skin cancer therapy: State of the art. Curr Nanomed 2020;10:90-104.
27. Farhana A. Enhancing skin cancer immunotheranostics and precision medicine through functionalized nanomodulators and nanosensors: Recent development and prospects. Int J Mol Sci 2023;24:3493.
28. IkedaImafuku M, Wang LL, Rodrigues D, Shaha S, Zhao Z, Mitragotri S. Strategies to improve the EPR effect: A mechanistic perspective and clinical translation. J Control Release 2022;345:512-36.
29. Gierlich P, Mata AI, Donohoe C, Brito RM, Senge MO, Gomes-da-Silva LC. Ligand-targeted delivery of photosensitizers for cancer treatment. Molecules 2020;25:5317.
30. Rizwanullah M, Ahmad MZ, Garg A, Ahmad J. Advancement in design of nanostructured lipid carriers for cancer targeting and theranostic application. Biochim Biophys Acta Gen Subj 2021;1865:129936.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I,

Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
32. Taylor KM. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 4th ed. Amsterdam, The Netherlands: Elsevier; 2013.
33. Shende P, Vaidya J, Gaud RS. Pharmacotherapeutic approaches for transportation of anticancer agents via skin. Artif Cells Nanomed Biotechnol 2018;46:S423-33.
34. Depieri LV, Praça FS, Campos PM, Bentley MV. Advances in the bioanalytical study of drug delivery across the skin. Ther Deliv 2015;6:571-94.
35. Khan NH, Mir M, Qian L, Baloch M, Khan MF, Rehman A, *et al*. Skin cancer biology and barriers to treatment: Recent applications of polymeric micro/nanostructures. J Adv Res 2022;36:223-47.
36. Bolzinger MA, Briançon S, Pelletier J, Chevalier Y. Penetration of drugs through skin, a complex rate-controlling membrane. Curr Opin Colloid Interface Sci 2012;17:156-65.
37. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 2004;3:115-24.
38. Matsui T, Amagai M. Dissecting the formation, structure, and barrier function of the stratum corneum. Int Immunol 2015;27:269-80.
39. Sahu P, Kashaw SK, Jain S, Sau S, Iyer AK. Assessment of penetration potential of PH responsive double walled biodegradable nanogels coated with eucalyptus oil for the controlled delivery of 5-fluorouracil: *In vitro* and *ex vivo* studies. J Control Release 2017;253:122-36.
40. Georgescu SR, Tampa M, Mitran CI, Mitran MI, Caruntu C, Caruntu A, *et al*. Tumour micro environment in skin carcinogenesis. Adv Exp Med Biol 2020;1226:123-42.
41. Barua S, Mitragotri S. Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects. Nano Today 2014;9:223-43.
42. McGrath JA, Eady RA, Pope FM. Anatomy and organization of human skin. In: Rook's Textbook of Dermatology. Vol., Ch. 3. Hoboken, NJ, USA: Wiley; 2004. p. 1-84.
43. Taveira SF, Lopez RF, Taveira SF, Lopez RF Topical Administration of Anticancer Drugs for Skin Cancer Treatment. London, UK: IntechOpen; 2011.
44. Sahu P, Kashaw SK, Sau S, Kushwah V, Jain S, Iyer AK. Discovering PH triggered charge rebound surface modulated topical nanotherapy against aggressive skin papilloma. Mater Sci Eng C 2020;107:110263.
45. Amasya G, Aksu B, Badilli U, Onay-Besikci A, Tarimci N. QbD guided early pharmaceutical development study: Production of lipid nanoparticles by high-pressure homogenization for skin cancer treatment. Int J Pharm 2019;563:110-21.
46. Williams A. Transdermal and Topical Drug Delivery from Theory to Clinical Practice. London, UK: Pharmaceutical Press; 2003.
47. National Research Council (US) Commission on Engineering and Technical Systems, Wartell MA, Kleinman MT, Huey BM. Appendix E, percutaneous absorption. In: Strategies to Protect the Health of Deployed U.S. Forces: Force Protection and Decontamination. Washington, DC: National Academies Press, US; 1999. Available from: https://www.ncbi.nlm.nih.gov/books/NBK225150 [Last accessed on 2023 Mar 01].
48. Touitou E, Barry BW, editors. Enhancement in Drug Delivery. Boca Raton, FL, USA: CRC Press; 2006.
49. Wenande E, Olesen UH, Nielsen MM, Janfelt C, Hansen SH, Anderson RR, *et al*. Fractional laser assisted topical delivery leads to enhanced, accelerated and deeper cutaneous 5-fluorouracil uptake. Exp Opin Drug Deliv 2017;14:307-17.
50. De Oliveira BE, Amorim OH, Lima LL, Rezende RA, Mestnik NC, Bagatin E, *et al*. 5-Fluorouracil, innovative drug delivery systems to enhance bioavailability for topical use. J Drug Deliv Sci Technol 2021;61:102155.
51. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. Clin Pharmacokinet 1989;16:215-37.
52. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: A systematic review. Arch Dermatol 2009;145:1431-8.
53. Dangre PV, Borase HP, Gunde MC, Pethe AM, Borkar MR. Deep eutectic solvents: Fundamental aspect, characterizations and applications. Recent Adv Drug Deliv Formul 2022;17:3-12.
54. Dangre P, Sonawane K, Moravkar K, Pethe A, Chalikwar S, Borse V. Design of layer-by-layer lipid-polymer hybrid nanoparticles to elicit oral bioavailability of buspirone hydrochloride. Int J Polym Mater Polym Biomater 2023;4:1.
55. Agrawal SS, Nagendran S, Pimpale A. Advances and prospects in antimicrobial research using nanomedicines. Curr Drug Ther 2023;18:194-204.
56. Kalode V, Gagarani M, Awari D, Mankar S, Armarkar A, Gawali R, *et al*. A comprehensive review on therapeutic potential on *Euphorbia hirta* Lin. J Pharm Res Int 2021;33:713-8.
57. Jirwankar P, Khobragade D, Agrawal S, Agrawal R, Chambhre N. Preclinical estimation of effect of piperine on anti-Parkinsons activity of berberine estimated by behavior modification scale. Int J Pharm Qual Assur 2023;14:143-8.

**Source of Support:** Nil. **Conflicts of Interest:** None declared.