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REVIEW PAPER

Polymers in topical delivery of anti-psoriatic medications and other topical agents in overcoming the barriers of conventional treatment strategies

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Abstract
In recent decades, topical treatments to dermal disorders have shown ineffectiveness in delivering the medication at a particular location without a suitable drug carrier. Psoriasis treatment is hindered because of the ineffective delivery and efficacy of conventional pharmaceutical treatment. In conventional medication formulation approach, it is difficult to breach the transdermal layer of a skin membrane for topical drugs, i.e. cyclosporine, methotrexate. This problem is further complicated by extreme disease-associated conditions such as hyperkeratosis and irritation. Intending to assure better drug delivery carriers, this review emphasizes the therapeutic efficacy of polymers and their potential to deliver the drug into the deeper layer of the skin membrane. The polymers are essential in structural and physiochemical perspectives as it works as a carrier for the medication. A vast variety of delivery carriers is available nowadays but their applicability in such dermal cases like psoriasis is still lacking due to less knowledge on an appropriate polymer. The current investigation of suitable polymer would assist in brushing our expertise to optimize the advantages of a wide spectrum of polymers to fulfill the topical targeting of psoriasis.

Keywords Psoriasis · Hyperkeratosis · Inflammation · Polymeric carrier · Immune-mediated skin disorder

Introduction

Psoriasis is an inflammatory, chronic autoimmune disorder of the skin that affects epidemiologically 1–3 percent of the world's population with a negative effect on patient life (Yadav et al. 2018b; Pradhan et al. 2018). Psoriasis is a multiple-factor disease regulated by abnormal keratinocyte proliferation and migration of T cells to the skin by stimulated immune systems. Later, the T cell release cytokines and chemokines, which ultimately regulate disease etiology including aggravating inflammation and premature hyperkeratosis (Elder et al. 2010; Rahman et al. 2015; Yadav et al. 2018a).

The initiation and progression of the disorder are regulated by the immune system in individuals with a genetic susceptibility to psoriasis. The pathomechanism is orchestrated to stimulate various mediators, such as cytokines, chemokines, and growth factors, to facilitate hyperkeratosis, epidermal thickening, neovascularization, and keratinocyte proliferation (Sala et al. 2018). Physiologically, induction of T lymphocytes and inflammatory infiltrates into the skin is responsible for hyperkeratosis in which antigen-presenting cells conjugate with MHC, leading to large cytokines being recruited, i.e. TNF-α, Interleukin-23 (IL-23), and IL-17 playing key functions in the production of inflammatory psoriatic lesions (Roberts et al. 2017). The studies revealed that IL-17 and IL-23 are crucially involved in psoriasis pathogenesis (Tonel et al. 2010; Kuwabara et al. 2017). A sequential process that occurred during the pathogenesis of psoriasis has been demonstrated in Fig. 1.

The treatment of psoriasis involves topical application through the cream, lotion, gel as well as phototherapy, or/and systemic therapy depending on the rigorousness of disease as mild to severe. Topical therapy was frequently utilized for psoriasis treatment but the major challenge includes deliverance of active constituents into the transdermal layer (Chandrashekara 2012; Pradhan et al. 2018; Abed et al. 2019). Several specific drugs are now commonly used for topical treatment of psoriasis in variable dosage formulations. Despite all challenges of topical treatment including low

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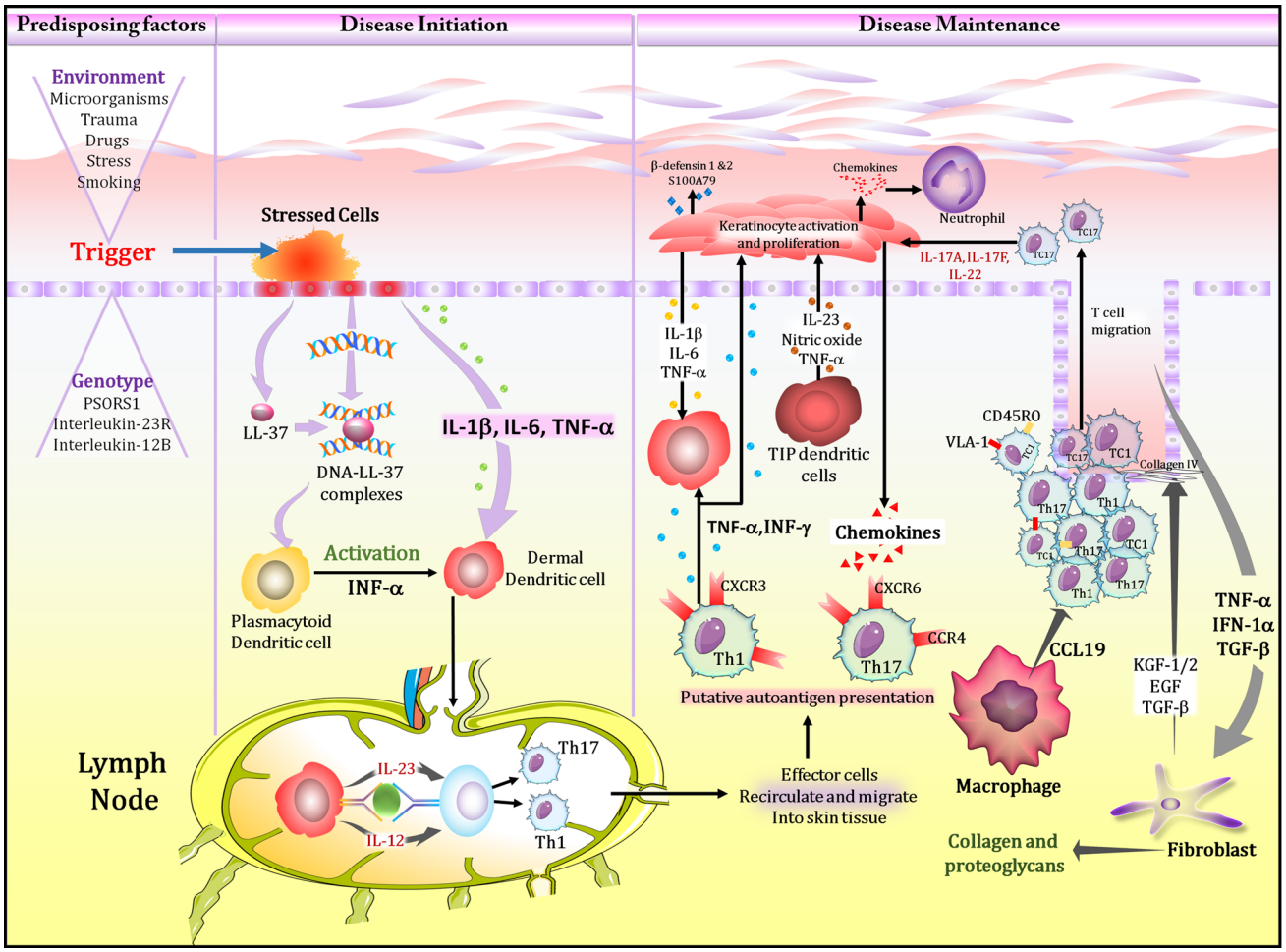

Fig. 1 Schematic representation of psoriasis pathogenesis: triggering, initiation, and maintenance of disease through the various immunological array. Adopted from (Keijsers et al. 2014)

absorption, poor permeability, uneven distribution, deprived tolerability, and cutaneous side effect, it is the preferable route of drug administration. The barrier function of the stratum corneum stops the drug from entering the skin due to the weak physicochemical properties of the medication that are even more complicated in the case of psoriasis (Abdelgawad et al. 2016).

Polymers have been found as a reliable and versatile component while focusing on the transdermal drug delivery system. The versatility and flexibility of the polymer structures provide multi-dimensional opportunities toward different delivery routes. Rationally several features considering improved drug penetrability, bioavailability controlled, and targeted release to the specific site make polymers a choice of nanomaterial in functionalized drug delivery (Venditti 2019). The physicochemical characteristics of the therapeutic activity and its carriers are key factors for efficient medication delivery. Polymers must grant an internalization and intracellular localization to enable active movement to penetrate the depth of the skin's membrane to achieve effective skin drug delivery (Venditti 2019). A significant amount of work on the strategy has been reported to increase polymers as an effective nanocarrier to overcome the limitations associated with psoriasis drug delivery to achieve improved physicochemical properties with the better therapeutic performance (Gong et al. 2012; Pandey et al. 2013; Gabriel et al. 2016; Lotfi-Attari et al. 2017). This review is an attempt to explore the use of polymers in the delivery of psoriasis medications, with an emphasis on efficient nanocarriers for various topical drugs used in therapy. This summarizes different polymers used to represent their role as a promising carrier in nanoformulation.

Challenges faced in topical delivery of therapeutic in psoriasis and other related skin issues

The histological transformations of psoriasis are expressed as intensely inflamed silvery scales with demarcated erythematous plaque adhering to them. Such lesions develop epidermal acanthuses under the command of over proliferative immature keratinocyte regulated by neutrophil migration, and angiogenesis causing dermal and epidermal inflammation (Tonel et al. 2010; Di Meglio et al. 2014).

The conventional strategies of treating psoriasis mostly consider skin and systemic routes for therapeutic delivery. The issues of oral bioavailability are typically faced with traditional systemic agents because of the first past metabolism and rapid body clearing and inadequate skin distribution. Their use in psoriasis is also limited as a consequence of the adverse effects associated with psoriasis and drug reactions that threaten their use and involve close monitoring (Hoffman et al. 2016). A key strategy for the treatment of mild to moderate psoriatic skin is a topical treatment. Numerous nanoformulations, including liposomes, niosomes, NLCs, SLNs, and nanoparticles, have been developed for the delivery of psoriasis drugs over a decade. Nanotechnology has arisen as an effective and versatile treatment to preserve medication safety and patient compliance (Morganti et al. 2001; Raza et al. 2013). The modification of the barrier properties of the skin at multiple sites contributing to the exacerbation of disease pathology is the primary problem for the topical administration of psoriatic medications. Stratum corneum is not only an inert layer but also a 'solid wall' that becomes thicker in psoriasis, making it the rigid obstacle for transdermal therapy (Morganti et al. 2001; Khadka et al. 2014). Heterogeneity in percutaneous absorption is also one of the big problems that impede the penetration of drug moiety into the deeper skin sites due to the diseased and metabolic impact of the skin. In addition, the physicochemical and pharmacokinetic properties of the drug compound are themselves a significant impediment to its transdermal distribution. Drug partitioning, molecular weight, dosing frequency, half-life, skin toxicity, metabolism, and bioavailability are the main features of drug molecules considered in transdermal drug delivery. The key concern is differences in the physicochemical properties of the carrier and the active moiety used, resulting in a discrepancy in drug penetration and drug effectiveness (Prausnitz et al. 2012). To solve problems applicable to traditional vehicles, the use of a suitable delivery carrier with the functionalization of various polymers might be a preferred alternative. Polymers are capable of shielding and allowing the escape from the physical/chemical degradation of encapsulated drugs. With a primary supporting factor, i.e. penetration, product distribution, and controlled release rate, the polymer-drug carrier is useful, and promising in transdermal delivery (Kumari et al. 2010; Prausnitz et al. 2012; Jijie et al. 2017). The polymer is the mainframe of the carrier that safely encapsulates and transports the medication. This drug delivery carrier has an enormous capacity and the use of prescient polymers can improve drug conveyance and reduce the side effects associated with these therapeutic agents resulting in increased therapeutic efficacy (Yadav et al. 2020a).

To control the therapeutic load of skin disease, nanocarriers with their many benefits can aim at transdermal and subcutaneous layers of the skin (Prosperi et al. 2017). Such kinds of dermal pathologies like skin cancer, cutaneous infections inflammatory disorder and psoriasis, are difficult to cure with the oral and parenteral route with conventional drug formulation (Katare et al. 2010). Even though medication compounds were delivered topically, a cream, gel, and lotion formulation did not allow the drug ingredient to be absorbed completely and penetrated the deep skin layer (Pradhan et al. 2013). Correspondingly, skin treatments that are widely available for psoriasis are associated with a number of problems, including decreased penetration through the stratum corneum layer due to greater particle size, failure to achieve controlled delivery in the tissue or desired cell, inability to transmit the drug to intracellular operational areas, and failure to pass the functional epithelium through medicine. This topical route also causes problems due to thick flaky plaques, decreased ceramides, and increased cholesterol levels that enable psoriasis to "obstinate" the skin. In addition, there is an inadequacy of moisturizing stimuli such as skin water, which restricts the drug's entry to a relatively high amount. A variety of ground-breaking nanotech therapies have been developed to overcome a wide range of constraints associated with traditional psoriasis treatment therapies. The problem of introducing the medication into psoriatic skin barriers has been overcome by nanoformulations drug therapy over the past decade with a particular intent and different place of action that can be solved by the use of a versatile range of polymers with desired properties.

Therapeutic targets in psoriasis

There is no cure available for psoriasis, so medication is the only way left to control such a debilitating condition. The choice of psoriasis treatment depends on the severity of the condition. Topical and systemic treatment accompanied by phototherapy is considered in moderate to severe conditions (Yadav et al. 2018b). Most of the therapeutic methods are based on the regulation of the immune response that controls different dermal manifestations. Based on the

approaches of delivery, i.e. topical or systemic the therapeutic candidates are selected. In initial treatment approaches, the immunomodulators are promising to control the various inflammatory mediator however the systemic delivery exhibits a more pronounced adverse effect on other body tissues. On the other hand, long-term exposure to phototherapy (i.e., UVA, UVB) may cause a cancerous effect on the skin itself. In such cases, topical delivery is the most promising choice of delivering anti-psoriatic medication to the pathological site (Pradhan et al. 2018). Biologists and biofields are emerging in psoriasis management by targeting the specified pathways for attaining accurate treatments. Frequently utilized therapeutic agents in the treatment of psoriasis and their therapeutic targets have been consolidated in Table 1. It also includes the small molecule inhibitors as newer and promising therapeutic approaches for futuristic targeting of the various possible mechanisms involved in psoriasis progression.

Nanotechnology for the delivery of therapeutics in the treatment of psoriasis

Nanotechnology encompasses all the systems in which the physical, chemical, and biological attributes are transformed to turn out to be essentially new, which ultimately stimulates the enhanced processes owing to the nanosized particle scale (Md et al. 2018). These methods offer distinct significant advantages over traditional therapy, such as increased efficacy, capacity to deliver a specific amount of drug over a long period at the individual location, and reduced unfriendly reactions (Jackson et al. 2013). In the treatment of dermatologic problems, nanotechnologies have shown significant improvement. As the body's exterior organ, the skin is in close communication with the external surroundings. Because of the fusion of epidermal cells with lipids in the stratum corneum layer, most of the drugs are almost impermeable (Gupta et al. 2013). The skin's epidermal obstruction increases more with keratinocyte hyperproliferation, and strategies are then required to resolve this threshold of skin penetration when treating psoriasis (Rahman et al. 2015). Nanotechnology-based carriers not only have a direct interaction between the therapeutics and the stratum corneum and other skin appendices, but they also improve their physical and chemical longevity by increasing their shelf life across the surface of the tissue (Gupta et al. 2013). Penetration of the nanocarrier into the skin may occur intercellularly through corneocytes and other dermal appendages such as hair follicles (Palmer and DeLouise 2016). The nanoparticles are pharmaceutically defined as particles with a size range of 1–1000 nm and incorporate solid colloidal particles which help to achieve distinctive pharmacokinetic profiles based on the patient's need (Md et al. 2018). The numerous methods by which therapeutic agents may be incorporated into these nanocarriers build in encapsulation and conjugation of drugs with these carriers (Rahman et al. 2015).

Often conventional therapy is used topically in the treatment act by forming a thin film on the surface of the skin. Nonetheless, when nanocarriers are used they avoid the deposition of free drugs from this perspective. The accretion of medicines into nanocarriers results in the deposition of medicines on the skin surface for extended periods and, having prolonged half-lives, the films produced a concentration gradient which, through diffusion, brings the medicine into the skin layers (Rahman et al. 2015). The carriers used in psoriasis therapy in previous years can be divided into three major groups of solid/liquid/crystalline nanocarriers (Palmer and DeLouise 2016). The nanotechnology-based drug delivery system is a growing avenue for resolving numerous cutaneous challenges, and thereby diverse nanocarriers such as liposomes, transfersomes, niosomes, aquasomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and polymeric nanoparticles have been extensively studied for their role in psoriasis treatment (Yang et al. 2015). Polymeric nanocarriers (PNCs) are versatile in nature, offering biocompatible and reliable homing to drug molecules for transport and delivery. The polymeric nanocarriers offer several advantages of drug transportation over other carriers that include the following:

- Relatively high medicine payloads for transportation
- Permit targeted delivery of medications
- Improving drug safety in the biological environment
- Permeate through diverse biological obstacles
- Facilitate controlled delivery of drugs
- Escalating the bioavailability of medicines that are inadequately soluble
- Allow surface modifications to increase interaction with biological targets

Polymeric carriers as promising transdermal drug delivery system for anti-psoriatic and other topical agents

The PNCs for transdermal drug delivery are less studied than lipid nanoparticles. PNCs are frequently used for topical ingress to deliver the drug into the transdermal layer (Kumari et al. 2010; Kapoor and Dhawan 2013; Paredes and Alarcón 2019). Polymeric drug delivery systems to cure psoriasis exhibit numerous advantages that comprise enhanced skin permeation, especially of poorly water-soluble/lipophilic drugs, and also provide enhanced drug stability with upgraded drug concentration gradient across the skin (Palmer and DeLouise 2016). Numerous scientific studies have shown that polymers not only perform encapsulation

Table 1 Various treatment approaches for targeting psoriasis, their therapeutic targets, and different delivery options

Therapeutic agent	Therapeutic targets	Delivery options	References
Broad-spectrum treatment approach			
Folic acid antagonist	Methotrexate	Lipid nanoparticles, niosomes, liposomes	Srisuk et al. (2012); Abdelbary and Aboughaly (2015), Ferreira et al. (2016), Ramanunny et al. (2020), Bakshi et al. (2020)
Calcineurin inhibitors	Tacrolimus and Pimecrolimus	Microemulsion, lipospheres, polymeric nanoparticles	Jain et al. (2016), Wan et al. (2017), Yu et al. (2018), Bakshi et al. (2020)
Retinoic acid analogs	Tazarotene	Polymeric emulsion, proniosomes, cerosomes	Abdelgawad et al. (2017), Prasad and Chaurasia (2017), Dayal et al. (2018), Tanghetti et al. (2019)
Vitamin D receptor analogs	Calcipotriol, calcitriol, hexafluoro-1,25(OH) D, maxacalcitol, and tacalcitol	Nanoemulsion, liposomes, Nanostructured lipid carriers	Knudsen et al. (2012), Zuchi et al. (2015), Kaur et al. (2017), Pradhan et al. (2020)
Steroid receptor analogs	Triamcinolone acetonide, fluocinolone acetonide	Liposomes, nanostructured lipid carriers	Yadav et al. (2020b), Pradhan et al. (2021)
Novel treatment approach: biologists			
TNF blockers	Infliximab, Golimumab	Nanocomposites	Urdaneta et al. (2017), Kim et al. (2020)
IL-12/23 inhibitors	Ustekinumab	Monoclonal antibody, prefilled syringe (solution, subcutaneous)	Papp et al. (2013)
IL-23 p19 inhibitors	Risankizumab, tildrakizumab, and guselkumab	Monoclonal antibody, prefilled syringe (solution, parenteral)	Chan et al. (2018)
IL-17 Inhibitor	Ixekizumab Secukinumab	Monoclonal antibody, prefilled syringe (solution, parenteral)	Gordon et al. (2016); Mease et al. (2017)
LFA-3/CD-2 Antagonist	Alefacept	Monoclonal antibody, prefilled syringe (solution, parenteral)	Rønholt and Iversen (2017); Saleem et al. (2020)
Inosine-5′-monophosphate dehydrogenase (IMPDH) inhibitors	Mycophenolic Acid	Nanoparticle	Lou et al. (2019)
Newer approaches: small molecule inhibitor			
Signal transducer and activator of transcription intracellular signaling pathways	Ruxolitinib	Tablets	Ludbrook et al. (2016); Yadav et al. (2018b); Irey et al. (2019)
Tumor necrosis factor-like weak inducer of apoptosis	Tacrolimus and pimecrolimus	Microemulsion, lipospheres, polymeric nanoparticles	Jain et al. (2016); Wan et al. (2017), Yu et al. (2018), Bakshi et al. (2020)
Phosphodiesterase 4 (PDE 4) inhibitors	Apremilast (Otezla)	Tablets	Zhao et al. (2018), Gul et al. (2018)
Janus kinases inhibitor	Tofacitinib citrate	Tablets	Papp et al. (2016)
IκB kinase inhibitor	Acetyl-11-keto-β-boswellic acid	Nanogel	Goel et al. (2009), Wang et al. (2009)

tasks but also provide several favorable physicochemical properties for a drug group. Natural as well as synthetic polymers have been considered beneficial for the manufacturing and conveyance of transdermal medications and have a better therapeutic profile (Palmer and DeLouise 2016; Kamoun et al. 2017). The application of polymers utilized in various transdermal drug delivery approaches for topical treatment of skin diseases including psoriasis is listed in Table 2.

Application of various polymers in topical drug delivery

Chitosan and derivatives

Chitosan is one of the versatile biodegradable copolymers used for almost all purposes of drug delivery. It is structurally formed by a repetitive chain of *N*-acetyl-*D*-glucosamine entities bound by β (1–4) glycosidic bonds. A higher impact was found on the ratio of both *N*-acetyl-glucosamine and *N*-glucosamine components, where the percentage covers half of the structure in the biopolymer chain to be concluded in chitin or chitosan derivatives (Sumit et al. 2012; Domínguez-delgado et al. 2014). It has been used for the construction of many regenerative medical components because of its crystallinity, biocompatibility, and biochemical significance (Prabaharan and Mano 2005; Colladо-González et al. 2017). Chitosan is acid-soluble, forming a rigid crystalline structure (around pH 2). This facilitates the loading of a large number of drugs via enriched functionalities – OH and NH–CO–CH (de Britto and Campana-Filho 2007; Kumirska et al. 2011). Nanocarriers made up of chitosan polymer can enhance the pharmacological activity of drugs as well as retain their physicochemical effectiveness in topical delivery. Existing antibacterial and other consistent properties like solubility, penetrability in varieties of its derivatives such as quaternary chitosan (Q-chitosan), C-E l chitosan, and N–O-carboxymethyl chitosan have been vastly studied (Mourya and Inamdar 2009; de Britto et al. 2011). Several studies have shown that chitosan has multifaceted physicochemical characteristics, including greater skin penetration, pH-related swelling, controlled drug properties, hemocompatibility, and cytocompatibility, which shows that it is a potent drug carrier (Mourya and Inamdar 2009; Kumirska et al. 2011). It also provides high encapsulation efficiency and high physical stability to a number of therapeutics. Chitosan is suitable for the transport, through the transdermal and mucous layers, of the macromolecule-like protein by opening an epithelial membrane at a tight intersection. Owing to its cationic nature, it increases the penetration through the membrane, works together with the cell membrane, and enables the tight intersections to be opened. Schipper et al. investigated the influence of the use of chitosan hydrochloride salts in pH 5.5 for their in vitro penetration into Caco-2 cell-monolayers (Schipper et al. 1999). It was discovered that chitosan can efficiently improve mannitol conveyance based on their M_w and the degree of deacetylation (DD). Appropriately, chitosans with a high DD were effective as penetration enhancers at low and high M_w, those with low DD were effective just at high MW. Accordingly research investigations showed > 80% deacetylation allows the best promoter impact on cells in culture (Dodane et al. 1999; Alama et al. 2019). A progressively articulated cationic character being accomplished by trimethylation of the essential amino groups (Mourya and Inamdar 2009). Thanou et al. examined the viability of chitosan as a pH enhancer close to the intestinal tract. Trimethyl chitosan chloride (TMC) was synthesized to varying degrees of quaternization. These quaternized polymers form complexes with anionic macromolecules and gels with cationic or neutral composites at neutral pH. TMC has been shown to substantially boost the permeation of both neutral and cationic peptide analogs through Caco-2 intestinal epithelia. In contrast to the phenomena of protonated chitosan, TMC increased intestinal permeability. It works reversibly together with a closely intersected part, allowing the intercellular spaces to stretched (Fig. 2). It was also found that TMC did not cause damage to the cell layer and did not affect the viability of the intestinal epithelial cells. Delivery of peptide drugs with TMC has been shown to improve the bioavailability of peptides by comparing pigs and rats without polymers (Thanou et al. 2001; Mourya and Inamdar 2009). Chitosan has also been shown to be a potent drug carrier factor in psoriasis by the studies. By formulating chitosan-lipid nanoparticles, Ridolfi and coworkers studied the effectiveness of chitosan with the anti-psoriatic drug tretinoin. They discovered the drug's optimum encapsulation with high stability, permeability and less toxicity. The carrier system has been shown to be effective for supplying tretinoin to keratinocytes on topical basis (Ridolfi et al. 2012). In another study Panonnummal et al. investigated the ability of chitosan-based nanogel to distribute methotrexate in an Imiquimod mouse model. Preferably a gel-like flow property, excellent skin permeability was found to be a good alternative than control group and conventional methotrexate gel. In addition, increased drug preservation in epidermal and dermal layers of the skin has been noted allowing for more effective use of chitosan for topical psoriasis (Panonnummal and Sabitha 2018). On the other hand, the Lakshmi et al. experiments for methotrexate loaded niosomal nanoparticles of chitosan gel were found to be more effective than placebo and methotrexate gel (Lakshmi et al. 2007). They also suggested that chitosan gel per se be useful for symptoms recovery. Chitosan has been shown to decrease the symptom of nail dystrophy if it is composed of hydroxyl propyl-chitosan (HPCH) with the potential to treat the patients (Ghannoum et al. 2015). The whole result suggests

Table 2 The polymeric nanocarriers and polymers utilized in the transdermal delivery of anti-psoriatic drugs

Polymers for drug delivery of anti-psoriatic agents	Therapeutics agent delivered	Delivery systems	Therapeutic drug delivery approach	Investigation phase	References
1,2-Dioleoyl-sn-glycero-3-phospho-choline	Anti-TNF-α siRNA and capsaicin	Nanoparticles	Proficiently deliver si-TNF-α and Cap into the profound dermal layer	In vitro and In vivo	Desai et al. (2013), Jose et al. (2018)
ABA triblock copolymer: PEG, oligomers of suberic acid, desaminotyrosyl-tyrosine alkyl esters	Vitamin D3	Tyrospheres	Improve skin delivery and drug stability	In vitro and Ex vivo	Ramezanli et al. (2017)
Chitosan	Tacrolimus	Chitosan-nicotinamide Nanoparticles	Improved drug solubility, drug entrapment, and stability, better permeability	In vitro and In vivo	Yu et al. (2018)
	Clobetasol-17-propionate	Polymeric nanoparticles	Better accumulation of drug in epidermis with no permeation across the skin	In vitro and Ex vivo	Şenyiğit et al. (2010)
Eudragit RS 100	Dexamethasone	Nanocapsules	Skin penetration and permeation	In vitro, In vivo	Beber et al. (2016)
Methoxy-poly(ethylene glycol)-dihexyl substituted polylactide diblock copolymer	Tacrolimus	Polymeric micelles	Enhancement of skin penetration potential of drug	In vitro, In vivo	Gabriel et al. (2016)
	Tacrolimus	Polymeric micelles	Dermal delivery and deposition of drug	In vitro, In vivo	Lapteva et al. (2014)
N-Isopropylacrylamide	Methotrexate	Nanogel	Improved skin deposition with a reduced lag time, Lesser transdermal side effects	In vitro, Ex vivo and In vivo	Singka et al. (2010)
Pluronic® F-127 (copolymer)	Cyclosporine	Solid lipid nanoparticles	Improved dermal delivery	In vitro, Ex vivo	Essaghraoui et al. (2019)
Poly (ethylene glycol)-*b*-poly(L-lysine)-*b*-poly(L-leucine)	C-Rel specific sirna	Polymeric micelles	Delivery of the therapeutic gene reduced the expression of susceptibility locus (c-Rel)	In vitro and In vivo	Fan et al. (2016)
Poly(*D,L*-lactic-co-glycolic acid)	Curcumin	Polymeric nanoparticles	Deposition of the drug in the stratum corneum and sustained release	In vitro and In vivo	Sun et al. (2017)
	Clobetasol propionate	Microsphere	Prolonged release of drug and to diminished systemic absorption	In vitro	Badıllı et al. (2011)
	Betamethasone phosphate	Nanoparticles	Encapsulation of water-soluble corticosteroid, sustained release, targeting to inflammatory sites	In vitro	Ishihara et al. (2005)

Table 2 (continued)

Polymers for drug delivery of anti-psoriatic agents	Therapeutics agent delivered	Delivery systems	Therapeutic drug delivery approach	Investigation phase	References
Poly(ε-caprolactone)	Hydrocortisone	Polymeric nanoparticles	Upright polymer biocompatibility	In vitro, Ex vivo	Rosado et al. (2013)
	Dexamethasone	Polymeric nanocapsules (interfacial deposition of preformed polymer)	Controlled drug release following the Higuchi release pattern	In vitro and Ex vivo	Marchiori et al. (2010)
	Tretinoin	Nanocapsules	Enhanced antiproliferative activity and improvement of photostability of drug	In vitro	Ourique et al. (2008)
	Tretinoin	Polymeric nanocapsules (interfacial deposition of preformed polymer)	Prolonged drug retention on the surface of the skin	In vitro, Ex vivo	Ourique et al. (2011)
Poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone)	Tacrolimus	Polymeric micelle (self-assembly of the triblock copolymer)	Controlled and sustained release of drug	In vitro	Wang et al. (2011)
Poly(ethylene glycol)	Amphiphilic zinc Phthalocyanine	Polymeric micelle	Phototherapy (Anti-psoriasis effects of light)	In vitro and In vivo	Jin et al. (2015)
Polyacrylamide	Methotrexate	Nanogel	Iontophoretic conveyance of MTX	In vitro and Ex vivo	Alvarez-Figueroa and Blanco-Méndez (2001), Nguyen and Banga (2018)
Polyamidoamine	8-Methoxypsoralene	Dendrimers (Divergent, in situ branch cell method)	Increased drug localization and deposition in epidermis and dermis	In vitro, Ex Vivo and In vivo	Borowska et al. (2012)
Polylactic acid	Quercetin	Nanoemulsion	Great encapsulation efficacy, less toxicity, precise delivery with improved transdermal drug pervasion	In vitro, and Ex Vivo	Bennet and Kim (2013), Hussain et al. (2014b)
Polypropylene Imine	Dithranol	Hyperbranched dendritic nanocarriers	Maximum drug encapsulation, constant permeation rate, improvement in drug permeation and pilosebaceous deposition of drug	In vitro, Ex Vivo and In vivo	Agrawal et al. (2013)
RRR-α-tocopheryl succinate grafted ε-polylysine conjugate	Curcumin	Polymeric nanoparticles	Sustained drug release and better	In vitro, In vivo	Mao et al. (2017)

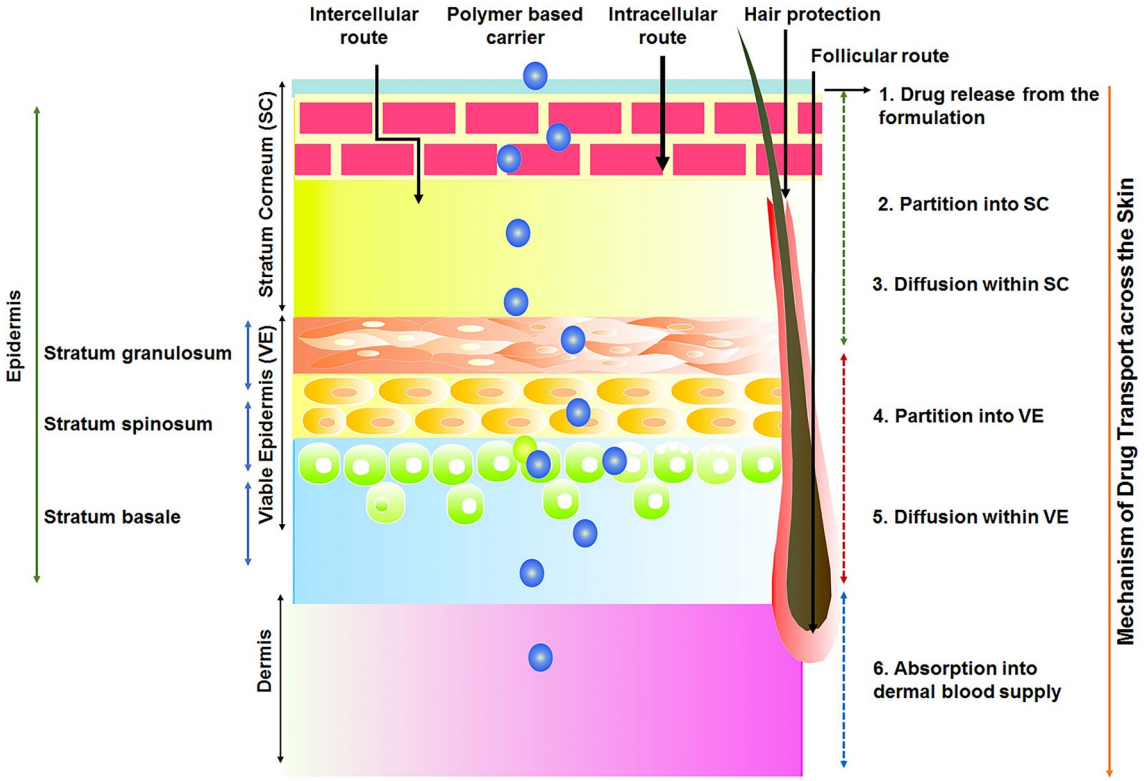

Fig. 2 The transport mechanism of polymeric nanocarriers across the tight junction of the skin and mucosal layer under the influence of polymer-like chitosan and TMC

chitosan and its derivative as an appropriate and promising polymer for managing the complexity of the psoriatic skin with valid, effective and safe conjugation in topical delivery.

Poly-(lactic-co-glycolic acid) (PLGA)

One of the most valuable synthetic biodegradable polymers used in the medical field is PLGA, approved by the USFDA and the European Medicines Agency for a variety of remedial assessment activities (Danhier et al. 2012). The key advantages of this polymer are biocompatibility, biodegradability, and the least side effects which make it more effective for biomedical applications. PLGA scaffolds are used as the most suitable biomaterials and are also useful for drug delivery carriers and medical devices (Kapoor et al. 2015). Emphasizing the research opportunity of PLGA scaffolds already exists as a potential candidate for cardiac and, bone tissue regeneration, and wound healing (Patel et al. 2020). The PLGA is used in microparticles and nanoparticles in the manufacture of targeted drug delivery systems to reduce the effects of the use of free medicine (Makadia and Siegel 2011; Prosperi et al. 2017). Nanoparticles provide a broad variety of benefits, for example, minimum inhibitory concentration (MIC), the half-maximal inhibitory concentration (IC50) may promote penetration into the cells employing small particle size for extended-release of medicine with better capturing abilities. PLGA materials have been studied extensively for cancer drug delivery, wound healing treatment, cardiovascular diseases, due to their biocompatibility (Mathew et al. 2012; Sun et al. 2017; Farajzadeh et al. 2018). Tomoda and co-investigators developed PLGA nanoparticles and studied their effectiveness on rat skin to resolve low transdermal penetration of Estradiol. The transdermal permeability of estradiol nanoparticles was found to be higher than the free drug overcoming problems associated with the free drug such as high hydrophobicity, low permeability building itself a viable method for the delivery of topical drugs (Tomoda et al. 2012). Apart from it, PLGA had been reported for psoriasis management widely in the form of various nanoformulations. PLGA had also shown promising results for topical delivery of Psoralen reported by Tolbaand co-workers (Wang et al. 2008; Sun et al. 2017). Overcoming dearth of penetration efficacy, the hydrogel of PLGA loaded curcumin nanoparticles was investigated for topical delivery and studied successfully for the skin penetrating efficacy on psoriasis mouse model reported by Kaili Mao and associates (Mao et al. 2017). A topical carrier's efficiency depends on its penetration capacity against the thick corneum that was found to be the maximum for curcumin nanoparticles (CUR-NPS) gel on psoriatic mice. As

a result, PLGA has been proven to be efficient in encapsulating the drug as well as enabling it to provide transdermal and therapeutic effects. Methotrexate (MTX) is well known for anticancer and immunomodulatory efficacy, as well as being one of the most commonly available medicines for psoriasis treatment. Singh and colleagues developed MTX as PLGA-soya lecithin micelles with enhanced pharmacokinetic profile and reduced cytotoxicity (Singh et al. 2017). The an imiquimod-induced psoriasis mouse model was investigated for the effectiveness of drug and drug penetration into the skin. The improved dispersion and continuous release of drugs were noticed when encapsulated with PLGA showing it to be a versatile polymer for drug delivery through psoriatic skin (Wang et al. 2008; Sun et al. 2017). Exploring the understanding of unique features exploited by PLGA-based nanoparticles concentrating on the treatment of psoriasis by transdermal drug delivery allows PLGA, a major drug carrier.

Polyethylene glycol (PEG)

PEGylation is tangible in characterizing PEG as one of the finest therapeutic bridging polymers that tend to be a versatile means of drug delivery, consisting of dynamic properties such as crosslinking, conjugation, with some therapeutic potential (Li et al. 2001; Suk et al. 2016). PEG is a polyether compound that considers the substantial uses as a carrier in numerous drug deliveries in pharmaceutics. PEG consists of a process of connecting repeated units of ethylene glycol to form polymers with linear or branched shapes of different atomic masses (Vyas et al. 2006; Suk et al. 2016). PEG has been investigated for various kinds formulations of consisting of nanoparticles, hydrogels, emulgel, etc. These PEG configurations are chemically related to the product of choice in a process called PEGylation. Many PEGylation research, including conjugations of PEG-biomolecule, PEG-based hydrogels, and Liposomes modified with PEG and so forth, have been observed. In many pathologies, including obesity, neurodegeneration, rheumatoid arthritis, PEGylation's clinical effectiveness is shown to be a versatile polymer for novel methods of delivery. Despite having vast potential for topical delivery its utility in psoriasis is still unexplored. Numerous research work has been carried out in recent years, addressing several PEG studies in the treatment of psoriasis and anticipating to reduce the problems that occurred in the subsequent section of transdermal delivery (Milton Harris and Chess 2003; Veronese and Pasut 2005; Vyas et al. 2006; Abbina and Parambath 2018). A study by Mirtic and colleagues has proposed that PEG-based medicated foams are used in combination to deliver incompatible hydrophilic and lipophilic drugs (Mirtič et al. 2017). The clinical practice was tested by the investigators for further conversion to therapeutic values with such kinds of relevant parameters as propellant free-foam with sufficient foaming properties, physicochemical stability, and less inflammation on topical exposures. Proposing the enhancement of the percutaneous delivery of tacrolimus (TAC), Tao Wan, and colleagues reported the potential of D-α-tocopherol polyethylene glycol (TPGS) microemulsion (Wan et al. 2017). Due to its superior hydrophobicity and high molecular weight, the inadequacy of the percutaneous delivery of the marketed TAC formulation remains a concern. High transdermal permeation via psoriatic skin formation has made the TPGS a promising carrier of drugs. Another research indicated that PEG in the form of a conjugated nanoparticle was also worthwhile to control the gene cycle in psoriasis. Small interfering RNA (siRNA) has been developed to deliver small spherical nucleic acid nanoparticles for psoriasis targeting. Subsequently, a mouse model was developed to test the effectiveness of epidermal growth factor receptor (EGFR) siRNA medication. The findings showed stable and non-toxic spherical nucleic acid nanoparticle conjugates (SNA-NC), dramatically decreasing gene expression in cells that facilitate symptomatic relief (Nemati et al. 2017). In another research by Acharya et al., PEG-400 was used to treat psoriasis by creating a stable formulation of MTX into a nano-emulsion gel (MNG). MTX nanoemulsions demonstrated an impending delivery of drugs with good stability and controlled release of drugs (Avasatthi et al. 2016; Acharya 2017). Eventually, PEG could be considered as a flexible carrier of choice for the delivery of transdermal drugs and to be able to overcome the deficit in psoriasis drug delivery.

Dextran

The most promising method for topical delivery is to add excellent physicochemical properties to macromolecules as carrier material. Dextran is an important polysaccharide carrier for a varied range of therapeutics and bioactives. It is the undefined name applied as a part of their fundamental atomic chain to a large class of α-*D*-glucans with anhydrous-*D*-glucopyranose units (Dhaneshwar et al. 2006). An alpha-1, 6-linkages in a dextran structure are found in variation composed of 95 percent α-1,6-glucopyranosidic linkages, and 5 percent 1.3 linkages. The 1,3-linkages manifesting connexion of side chains, about 85% of which are 1 or 2 residues of glucose in length, and the remaining 15% of side chains have an average length of 33 residues of glucose evenly distributed in the molecule (Huang and Huang 2018). Vast potent therapeutic characteristics would be key aspects for dextran to be considered as the most acceptable drug carrier. The importance of dextran as a drug carrier has been reported in various disorders, including cancer, ocular disease, hyperpigmentation, and some topical diseases. Crosslinking and conjugation are the primary strategies for delivering the drug to a polymer carrier such as

dextran (Huang and Huang 2018, 2019; Zhang et al. 2020). Numerous research eventually indicates dextran as an effective targeted drug nanocarrier for skin cancer, but the topical delivery of anti-psoriatic drugs with dextran polymer is still being studied. To minimize the dosing level of mycophenolate mofetil (MMF), Lou and associates investigated the structural importance of dextran. MMF is a mycophenolic acid (MPA) prodrug that acts as an immune suppressant used in various immune conditions including psoriasis. They produced dextran-based MPA nanoparticles and found that it was very effective in the treatment of the imiquimod-incited murine psoriasis model (Lou et al. 2019). The MPA was conjugated to dextran an ester bond to form nanoparticles called dextran-based MPA nanoparticles (DMNPs). The biopharmaceutical investigation after DMNPs intraperitoneal injection showed controlled long-term release of MPA to improve symptomatic relief at the histological level, like IL-17a, Ki-67 from psoriasis. Dextran is effective in conjugating with drugs and providing controlled release of MPA making it suitable for the delivery of antipsoriatic drugs. (Lou et al. 2019). The studies are still under operation for exploring the versatility of dextran in psoriasis.

Carbopol

In different medicinal formulations, Carbopol is of interest as an excipient. It is a polymer which is prepared by crosslinking acrylic acid and divinyl glycol or polyalkenyl ethers (Proniuk and Blanchard 2002; Sivaram et al. 2015). Carbopol is potential a candidate for the delivery of controlled releases of pharmaceutical products, having particles of around 0.2 to 0.6-micron diameter, complex hydrophobic nature, and a cross-linked composition which is appropriate for the problem of conventional drug therapy to be used as a viable alternative (Kim et al. 2003; Gaikwad et al. 2012; Sivaram et al. 2015). Numerous research studies for assessing existing Carbopol intervention for the significant effect on topical delivery have been reported. By formulating tacrolimus loaded polymer nanocarriers for the treatment of psoriatic lesions, Gabriel and co-investigator tested the loading property of Carbopol. The research stated that the integration of Tacrolimus into a Carbopol Hydrogel made the topical administration more feasible and convenient (Gabriel et al. 2016). Carbopol allowed the moisture content to be given to thickened and dry psoriatic skin. It also enabled the carrier loaded with the medication to travel through the transdermal route making it the most suitable alternative for topical hydrogel formulation. A similar approach was also adopted in another Carbopol hydrogel test to co-provide MTX and Etanercept from lipid nanoparticles to improve their fluidity to deliver high transdermal permeation to the skin (Ferreira et al. 2017). Naga and co-investigators have also investigated the effectiveness of Carbopol as emulgel in supplying anti-psoriatic treatment. The research was done with the hydrophobic medication Calcipotriol. Via rat skin diffusion kinetics, the topical emulgel showed significant drug release and permeation properties showing improved thickness, spreadability, extrudability, controlled drug release, and more stability (Naga et al. 2014). Unilamellar liposomes loaded to gel using Carbopol facilitated the maximum permeation of the skin and consequently provided the successful psoriasis treatment verdure (Hussain et al. 2014a; Damiani et al. 2019). Shah et al. contributed to the endeavor in another study to investigate the percutaneous distribution of a melanocyte-stimulating hormone for the treatment of psoriasis on the imiquimod induce model (Shah et al. 2016). They observe the pseudoplastic flow and thixotropic behavior arising from uniform dispersion on α-melanocyte-stimulating hormone (α-MSH) in Carbopol Ultrez 10. A reduction in psoriasis-assisted inflammation was found by the improvement of skin permeation due to α -MSH-based formulation (Shah et al. 2016). Studies have also indicated Carbopol's efficiency in the form of nanogel exhibited its dynamic ability to regulate the release of a trapped medication directly at the inflammatory site by changing the nanogel's surface charge with appropriate polymers. This may boost the topical delivery of entrapped drugs with an affinity to target keratinocytes (Shah et al. 2012; Talele et al. 2017). These shreds of evidence suggest Carbopol as a proactive carrier for treating psoriasis by delivering the drug via the transdermal route.

Hydroxypropyl methylcellulose (HPMC)

The HPMC is a versatile polymer and an excipient for controlled delivery with a sturdy adhesive, semi-synthetic, inert, viscoelastic appearance. Typically used as a solvent in the ophthalmic formulation (Siepmann 2001; Vlaia et al. 2016). HPMC is non-ionic, water-loving, and soluble in polar organic solvents and offers the basis for the advancement of topical drug delivery (Siepmann 2001; Cai et al. 2016). Numerous clinical tests have shown that HPMC is suitable for therapeutic purposes, including improving solubility properties in gastrointestinal fluids, drug protection non-interference, resilience to disintegrate, resistance-free, tasteless, and odor-free. Pharmaceutically, it is utilized as an ophthalmic agent, film, membrane, and patch in transdermal and topical formulations. Kilfoyle et al. to ensure a topical treatment of psoriasis was investigated HPMC in the paclitaxel nanosphere based on tyrosine. The aim of the research was on the development of TyroSphere, the loading of paclitaxel, and its distribution through the HPMC gel to increase its solubility (Kilfoyle et al. 2012). As a good polymer with no incompatibility with the skin and drug molecule, HPMC was found to be very efficient in the delivery of drugs through the skin. In another study, Jain and coworkers investigated

the efficacy of HPMC polymer-based liposphere gel preparation to resolve the low solubility, poor skin penetration, and irregular absorption of TAC and curcumin in topical delivery for effective psoriasis targeting (Jain et al. 2016). The results indicated that the polymer was suitable for psoriatic skin delivery. The topical supply of anti-psoriatic drugs made up of HPMC with flexibility for controlled release and efficient management of psoriasis were also recorded as transdermal patches (Anselmo and Mitragotri 2014; Palmer and DeLouise 2016; Yadav et al. 2020c). In one approach, Viviana De Caro et al. stated that triamcinolone acetonide buccal tablets formulated with HPMC would better control oral and intraoral psoriasis (Caro et al. 2017). The tablet was able to produce a controlled release of medications, which tailored to the drug's therapeutic benefits. Besides, HPMC was also used to prepare the nanoemulsion-based gel to increase the viscosity of betamethasone dipropionate with Omega-3 unsaturated fat to maximize nanoform anti-psoriatic efficacy. The HPMC nanogel was successful for percutaneous delivery and decreased psoriatic inflammation by enabling the delivery of medicine through the skin (Batheja et al. 2011; Cai et al. 2016). All these clinical results on HPMC indicate a good candidate in the treatment of psoriasis for topical drug delivery.

Toxicological concern of polymeric nanocarriers

Due to its relatively stable nature and capacity to encapsulate various active ingredients, PNCs have several benefits over other carriers. Therefore, the concern of their nanotoxicity is very critical (Zielińska et al. 2020b). Particularly for those nanomaterials that can induce unintended toxicities (Chenthamara et al. 2019). To assert the toxic potential of PNCs and to respond to the appropriate animal model that closely reflects the pathophysiology of the human condition, it is important to evaluate preliminary efficacy in vitro followed by in vivo tests (Jain and Thareja 2019). The defining features of PNCs are biodegradability, biocompatibility, and non-toxicity. PNCs are non-toxic for human utilization, according to Maurya and co-investigators (Maurya et al. 2019), and the biocompatibility of the loaded medications can be enhanced. Because of their good stability and the capacity to encapsulate a high variety of therapeutics, it is gaining an increasing interest in clinical and medical science (Zielińska et al. 2020a).

The chemical, biocompatible and mucoadhesive attributes of natural polymers such as dextran, chitosan, heparin, or hyaluronic are most widely used in drug delivery research (Lombardo et al. 2019). In addition, the concept of biomimetics has been applied in the design of materials to create more sophisticated and highly efficient nanocarriers. The poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-*co*-glycolide) (PLGA) are widely utilized for medicinal purposes and were authorized by the Food and Drugs Administration (US) and the European Medicine Authority (Zielińska et al. 2020a) because of their safety, effectiveness, assurance of biocompatibility, and low immunogenicity standard.

According to recent research studies, the active targeting of tumor tissue through ligand bounded PNCs offer less toxicity to healthy tissue making it less toxic to the body (Chenthamara et al. 2019). The ex vivo and in vivo investigation of topical polystyrene NPs revealed the efficient deposition of PNCs in follicular openings. The transdermal drug delivery system is capable of bypass the first-pass metabolism effect of the medications, so a lower dose of the drug can be delivered successfully with decreased toxicity (Zielińska et al. 2020a). It has been noted that polymeric nanogel often possess a low degree of toxicity, serum persistence, and stimuli tolerance since they have a high potential for drug encapsulation, varied size, and are comparatively easy to produce. Apart from the delivery of drugs, they are also commonly used in tissue engineering, biosensing, and the production of biomimetic materials (Lombardo et al. 2019; Pinelli et al. 2020). The cytotoxic spectrum of polymers is usually assessed in vitro for the cell viability of specified cell lines utilizing colorimetric laboratory tests such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). Cell viability of over 70 percent is commonly regarded as confirmation of the low cytotoxicity of the polymer matrix being examined (Zielińska et al. 2020a).

At present, the impacts of polymer NPs in medicine is important, but due to the possible toxicity of their constituents, their clinical utilization needed to be strictly monitored, while polymers are largely biodegradable and enable the fast excretion of their oligomers through different metabolic pathways (Lima et al. 2020). Toxicity must be tested for the intrinsic toxicity of all ingredients of the mixture (i.e., polymers, medications, and other excipients) (Calzoni et al. 2019).

Discussion

The present study aims to provide details on the potential of polymers, offering a significant amount of troubleshooting to resolve the shortcomings supported by the topical delivery of psoriasis. The effectiveness of the anti-psoriatic medication in the delivery of anti-psoriatic drugs was tested for significant penetration and improved dermatokinetics. The topical approach to psoriasis therapy has been stated in the current activity by demonstrating the importance of polymers such as chitosan, HPMC, PLGA, carbopolymers, and so on. Some of the key issues with conventional drug

formulations have been reported i.e. polymeric nanocarriers have essentially affected solubility, penetration, and permeation of skin barrier. The polymer as an excipient also retains its stability with decent drug bioavailability. The work discussed would promote readers to develop new delivery approaches with polymeric carriers to improve the effectiveness of the anti-psoriatic drugs.

Conclusion

In the current scenario, nanoformulations have emerged as a promising choice for dealing with various delivery-related problems. The barrier function of skin becomes more rigid under the influence of psoriasis making topical delivery of medication more challenging. A vast variety of delivery carriers are available nowadays but their applicability in such dermal cases is still lacking due to less known facts about the appropriate polymer. The polymers are essential in structural and physiochemical points of view as it works as a carrier for the medication. It not only provides a homing task for the medication but also delivers it to the desired site therefore study of polymer behavior before the carrier fabrication becomes apparent. This will help in improvising our knowledge domain for achieving the maximum benefits of available polymers to meet the therapeutic goals towards targeting psoriasis.

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Declarations

Conflict of interest The authors report no conflicts of interest.

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