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REVIEW

Biodegradable Polymer Based Nanoparticles: Dermal and Transdermal Drug Delivery

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Skin is an extensively employed route for drug delivery to provide the local and systemic effects. *Stratum corneum* (SC) is the upper layer of the skin, which makes a natural physical obstacle against penetration of the drugs. Polymer based nanoparticles are one of the approach to overcome this barrier. Biodegradable polymers are ideal carriers to a broad range of drugs for therapeutic applications. The biodegradable polymer based nanoparticles reduce the strength, dosing period and side effects of pharmaceutical dosage forms. Furthermore, these polymers based nanoparticles show interesting applications in novel drug delivery systems due to their versatility and harmless degradation. The smart polymers might release the captured molecule in response to a particular physiological trigger (pH, temperature etc.) in a proper time and site of action. The choice of polymer based nanoparticles depends on the skin condition to be treated, the type of drug to be loaded and the desired drug release profile.

Keywords: Nanoparticle, Polymer, Argan Oil, Dermal, Transdermal, Drug, Delivery.

CONTENTS

1. INTRODUCTION

The skin has previously been employed for the local drug delivery, but since 1970 it has broadly been used like a route for systemic drug delivery.[1] Transdermal Delivery Systems (TDS) or Transdermal Therapeutic Systems (TTS) are the topical formulations, which include drug and provide systemic action. TDS could also be defined as the drug penetration through the skin to the systemic circulation in enough quantity to produce therapeutic effect. The advantages of TDS are taking away from gastrointestinal absorption problems and hepatic first pass effect. Moreover, the reduction of strength and dosing period, predictable and extended duration of activity, better patient compliance, and immediate termination by simple removal of the system from the skin surface, and possible self-application are also from its advantages.[2]

It is revealed that nanoparticles are now finding large applications in different fields.[3] The innate structural diversity and the need to understanding the polymer surface and bulk intended properties make the choice and the polymer design difficult task.[4] Biomaterials being used for drug delivery and enlargement or replacement of any tissue, organ or function of the body through interfacing with biological systems. In the light of degradation properties biomaterials are divided into biodegradable and non-biodegradable biopolymers. The discovery of biomaterials with new characteristics lead to fundamental breakthroughs in tissue engineering, regenerative medicine, gene therapy, and controlled drug delivery. Biologically derived and synthetic biodegradable biopolymers particularly drew researchers' attraction.[5] Protein and polysaccharides are representative biologically derived biopolymers, whereas

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polyphosphoester (PPE) and aliphatic polyesters are representative synthetic biopolymers. Synthetic biodegradable polymers have lower immunogenicity than biologically derived polymers. Additionally, it is easier to modify and functionalize them.[6]

Skin is the largest organ in the body that forms 16 percent of total body weight.[7] It is essential for all mammalian life,[8] and could be used for both local and systemic drug delivery.[2] One of the major functions of skin is to avoid the organism invasion against threats from the exterior environment. The skin act as a physical, metabolic, immunological, and UV protective barrier against microbes, UV radiation, toxic chemicals and particulate materials (e.g., nanoparticles naturally occurring in the surrounding environment) attacks. On the other hand, the skin is able to be employed like a "port for entry" for therapeutic molecules such as drugs and vaccines if the mechanisms governing the barrier features are understood and by passed.[1] The skin barrier include two principal layers as dermis and epidermis. The penetration of

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macromolecules and particulate materials in diseased skin, due to the damaged SC and/or activated immune system, with respect to healthy skin is frequently changed.[1] In general it is known that the probability of nanoparticle and microparticle to penetrate the skin is negligible. The substance permeating across the skin, diffusion through the SC is the rate limiting step because SC is the main physical obstacle of the skin.[1] The aim of this review is to give an overview of the biodegradable polymers used as nanoparticulates for TDS.

2. BIODEGRADABLE POLYMERS

2.1. Polymer Degradation and Drug Release

Polymeric biomaterials after application on the skin might be degraded through chemical and/or enzymatic reactions. Polymer degradation pathway depends on the nature of the polymer.[9] In ideal world the decomposition products of polymers must be non-toxic. Usually the degradation of polymeric particles is a complex procedure and the encumbered drug release has a non-linear kinetic.[10] Factors influencing the biodegradation kinetic of the selected polymer are the chemical structure, size, shape, chain defects, ion exchange, ionic strength, pH, morphology (amorphous, semicrystalline, crystalline, microstructure, residual stress), mechanism of degradation (enzymatic, hydrolysis, microbial), molecular-weight distribution, processing conditions and sterilization process, annealing and storage history, route of administration and site of action.[4]

2.2. Commonly Used Polymers for Encapsulation

There are numerous polymers which have been employed for drug encapsulation but just biodegradable and biocompatible ones could be used in biomedical fields. The existence of a labile function such as ester, anhydride, orthoester, carbonate, amide, urea or urethane in the backbone of biodegradable polymers made them biodegradable. Moreover, these polymers can be natural (polysaccharides and protein based polymers) or synthetic (polyesters).[4] In biomedical applications biodegradable polymers are the best carrier systems. The characteristics such as controlled and sustained delivery, improved drug pharmacokinetics, reduced undesirable effects and safe degradation make the use of these materials very smart in the most of medical areas, with dermatology included. According to the number of studies, which have been done, particle-based formulations can enhance the skin penetration of locally administrated drugs.[10]

2.2.1. Natural Polymers

Generally, natural polymers are biodegradable and provide exceptional biocompatibility.[4] Nowadays, the manufacturers due to the availability of different types of natural polymers have gained a large achievement regarding the development of the most promising therapeutic systems

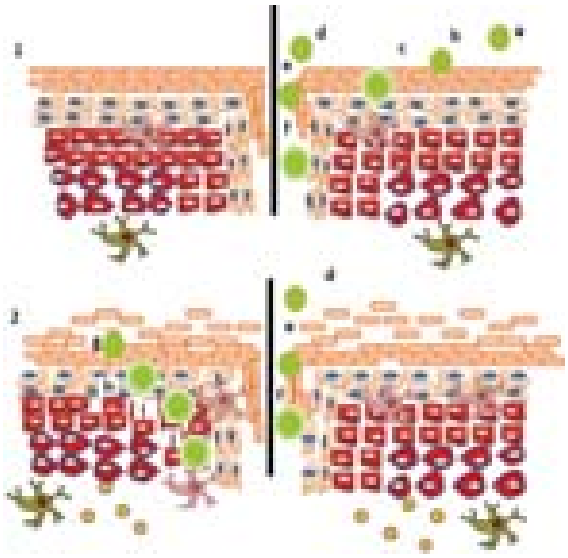

Fig. 1. The penetration of polymer based nanoparticles (PBNPs) through the skin and release of drug in (1) healthy skin and (2) theory of polymer based particle behavior in diseased skin. SC cell (skin barrier), polymer based nanoparticle, nanoparticles undergo degradation and/or release the loaded substances, macrophage, dendritic cell, and, , , shows skin viable layers in this photo. (a) When the skin barrier is unbroken, topically applied carriers interact with the surface of the skin (a, d) and accrue in the SC (b) and in the hair follicle canal (e). Where-nanoparticles undergo degradation and/or release the loaded substances, (c, f). (2) In the majority of the skin conditions, the skin barrier is interrupted and the skin immune system is activated. Topically applied substances interact with the altered skin surface (g), penetrate across the SC (h), go into the skin viable layers (i), and might be carried on by activated dendritic cells or macrophages (j). PBNPs can degrade and/or deliver their loads in the SC (h), in the intercellular space (i), or upon internalization in the cells (j).

(drug delivery system) that supply long-term effective therapy to the patients.[12] Moreover, it should keep in mind that natural polymers undergo from batch to batch diversity.[4]

2.2.1.1. Chitosan. Chitosan is gained through deacetylation of chitin which is structural component of cell walls of fungi and exoskeleton of crustaceans (shrimp, crabs, etc.) (Fig. 2). Chitosan is a non-toxic polymer which might be digested in the physiologic condition either through chitinases or lysozymes enzymes which exist in the blood and human intestine. These characteristics led to augment the interest to this polymer in the field of pharmaceutical research and industry as a vehicle for the drug delivery.[4] Moreover, chitosan has the positive charge consecutively permit interaction with the negatively charged mucosal surface. However, for increasing the residence time and absorption of active molecules through mucosa [3, 12] and also for targeting in drug delivery[14] the utilization of the chitosan as a matrix[15] or as a coating material[16] in drug encapsulation demonstrated promising tactic. Chitosan is also a potential and usually employed candidate to change the surface because of its biocompatibility[17] and

Fig. 2. Chemical structure of chitosan.

positive charge.[18] Because of their exceptional biological features Chitosan-based nanoparticles have attracted more attention.[19]

2.2.1.2. Dextran and Its Derivatives. Dextrans are the polymers which are synthesized in bacteria from sucrose (Fig. 3). Moreover, in these polymers predominantly the glucosidic linkages are α-(1–6) kind. It can be synthesized chemically as well.[4] The low toxicity, biodegradability and good biocompatibility are the principles features which encouraged the use of this polymer in the biomedical and pharmaceutical fields.[20] Diethyl aminoethyl dextran is a dextran derivative.[4]

2.2.1.3. Gelatin. Gelatin is a natural polymer, which is derived from collagen. As Gelatin is biodegradable and biocompatible in physiologic environments so it is mainly used in pharmaceutical and medical fields. The cross-linking degree of gelatin has important role in its mechanical and thermal properties and swelling comportment. Because of nontoxic, bioactive properties and its reasonable price, Gelatin is interesting polymer for employing in controlled release.[4]

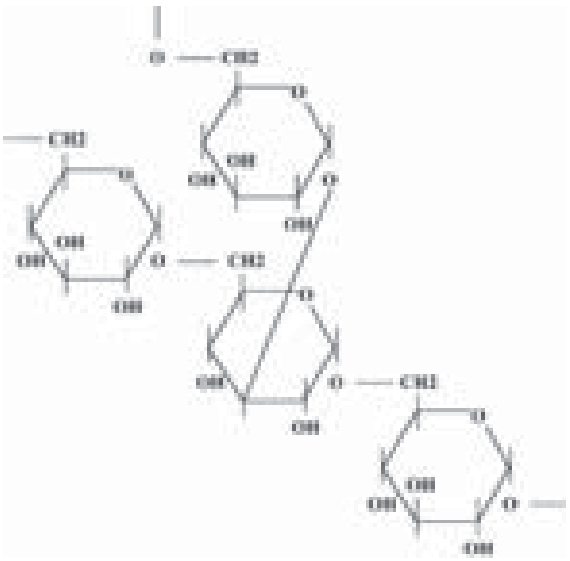

Fig. 3. Chemical structure of dextran polymers.

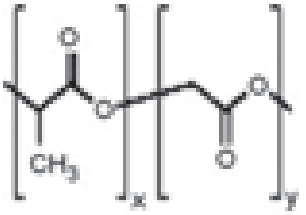

Fig. 4. Chemical structure of Poly (lactic-co-glycolic acid) (PLGA), X = number of units of lactic acid; y = number of units of glycolic acid.

2.2.2. Synthetic Polymers

Synthetic polymers present a broad variety of composition with easily adjustable characteristics.[21] Currently; in both academic and industrial field of the pharmaceutics synthetic polymers are the most active areas of biomedical research.[22]

2.2.2.1. Poly(lactic-co-glycolic acid) (PLGA). Poly (lactic-co-glycolic acid) (PLGA) is one of the most successfully used biodegradable polymers because its hydrolysis leads to metabolite monomers, lactic acid and glycolic acid. (Fig. 4). They are endogenous and metabolized with minimum systemic toxicity that depends on the drug delivery or biomaterial applications through Krebs cycle, so PLGA is one of the most successfully employed biodegradable polymer.[23] In different drug delivery systems for humans the PLGA is approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA). PLGA is commercialized having various molecular weights and copolymer compositions. The time necessary for degradation of PLGA according to molecular weight and used ratio of copolymer is different from several months up to several years. The used ratio of monomers identified the PLGA.[24] PLGA is the most commonly used polymer for the preparation of these carriers which is well known to be biocompatible, safe, non-toxic and is restorable by natural pathways.[25] It has been shown that PLGA microparticles could give elevated encapsulation efficiency (91%) and better release kinetics than PLA.[26]

2.2.2.2. Poly(lactic acid) (PLA). PLA which is demonstrated in Figure 5, is a biocompatible and biodegradable synthetic polyester that suffer scission in the body to monomeric units of lactic acid. PLA have a good mechanical properties and it is mainly used for the preparation of particles.[27] The solvent evaporation, solvent displacement[28] salting out[29] and solvent diffusion are the methods which are mainly employed for the preparation of the PLA based nanoparticles.[23]

2.2.2.3. Polycaprolactone (PCL). PCL is a biocompatible, biodegradable, hydrophobic and semicrystalline polymer. Its slow degradation makes it favorable polymer for extended drug delivery system over a period of time. Its chemical formula is indicated in the Figure 6. The relative inexpensive price of PCL and its authorization by

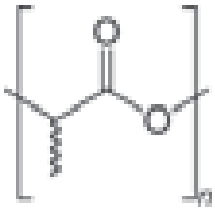

Fig. 5. Chemical structure of PLA.

FDA, offer an opportunity to the design and fabricate the extended term drug delivery system, consecutively it might decrease the toxicity and side effects of drugs. The low melting point, good solubility and exceptional mixing-compatibility has provoked wide research into its huge application in the biomedical field.[4] The compatibility of PCL with the majority of drugs facilitates drug distribution over the formulation matrix and its long period degradation allows the release of drug up to several months.[27, 28]

2.2.2.4. 'Smart' Polymers. They are known as "smart" polymers due to the conformational changes that they undergo in response to changes in environmental conditions such as temperature, pH etc.[33] Smart polymers are able to employ in different fields. Intelligent systems of delivery have been investigated through smart polymeric systems of drug delivery. Moreover, they are able to release the entrapped drugs in response to the specific physiological trigger in a suitable site of action and time. The replays of smart polymers are extensively different from the swelling/contraction to disintegration. The present applications would be enhanced and increased through synthesis of new polymers and cross-likners with better biocompatibility and greater biodegradability. Main attractive characteristics of these polymers are formed by their versatility and tunable sensitivity. The numerous reactive properties of nanoparticles, such as those composed of poly(*N*-isopropylacrylamide) (PNIPAM) have guided them to become the base of significant interest in the area of drug delivery.[33] It would be possible to design more accurate and programmable drug delivery systems with the progress of the smart polymers.[34]

3. KEY PROCESS OF BIODEGRADABLE POLYMER BASED NANOPARTICLES AFTER TOPICAL APPLICATION

The explosion of modern nanotechnology in pharmaceutics gave rise to a trend of taking several advantages from single preparation.[35] Lately, nanotechnology through controlling the release rate of the irritant substance and avoiding of direct contact between the substance and skin like an approach to reduce the irritation and allergenicity of active ingredients after application to the skin, has been recommended.[36]

Fig. 6. Chemical structure of Polycaprolactone (PCL).

PBNPs are particles with diameter of less than 1 μm which are prepared from natural or synthetic polymers (Table I).[37] According to the structural organization; biodegradable nanoparticles are classified as nanocapsule, and nanosphere. The drug molecules are either entrapped inside or adsorbed on the surface.[23] The release pattern of polymeric nanoparticles are one of the most important features when used as sustained drug delivery systems.[38] The drug transport through skin by passive diffusion are the pararcellular, the transcellular and the appendageal routes (Fig. 7).[1]

Nevertheless, biodegradable nanoparticles used to enhance the therapeutic significance of different water soluble or insoluble pharmaceuticals and bioactive molecules through improving solubility, retention time and consecutively bioavailability.[39] The achievement of optimal drug loading of carriers, control of drug release, delivery and design of stable materials which do not release dangerous degradation products are challenging the nanoparticles design and characterization. However the PBNPs propose the advantages of being stable, controlled and sustained drug release.[36, 37, 42] Their further advantages over lipid-based vehicles include the storing over months, encapsulation of both kinds of molecules (hydrophobic and hydrophilic), functionalization and furthermost their physicochemical properties can be adjusted which is most important.[10] The penetration incapability of polymeric nanoparticles to the SC is from their restriction however, they accumulate in skin furrows and hair follicles and increase the local concentration by loaded drugs that can more diffuse to the viable layers of the skin.[11] It should kept in mind that for improving drug delivery to the deeper skin layers the composition and surface charge of nanoparticles are to be considered.

3.1. Biodegradable Polymer Based Nanoparticles Interaction with Stratum Corneum

This layer of the skin is built from the protein-rich cells surrounded in a lipid extracellular matrix. Moreover, corneocytes are attached together through the intracellular proteic structure that named corneodesmosmes.[10] It has been demonstrated that lipid-based particles have the ability to fuse with the skin lipid layers, whereas polymeric particles, being more hydrophilic, might have unlike interactions with the extracellular lipids of the SC.[43] The three-dimensional conformation of SC that leads to the adsorption, destabilization, or agglomeration would change its interaction with polymeric carriers while they

Fig. 7. Sites in skin for nanoparticle delivery. Topical nanosize particle drug delivery occurs in three major sites such as stratum comeum (SC) surface (panel 1), furrows (dermatoglyphs) (panel 2), and openings of hair follicles (infundibulum) (3). The nanoparticles are shown in green and the drug in red. Other sites for delivery are the viable epidermis (E) and dermis (D).

do not fuse with the lipids of the SC. The normal microbial flora of skin surface will interact with applied materials. Moreover, the sebum which formed a shell to the SC is rich in lipids and proteins. It is able to interact with administered polymer based materials changing their approach to interact with the other skin components or destabilizing them. The pH of the skin surface is between 4.2 and 5.6.[10] The stability of the colloidal particles can be influenced through this acidic pH. The degradation of the polymer based carriers might increase by acidic pH of the skin.[44] The paracellular, the transcellular, and the transfollicular route are the three described pathways of penetration for locally applied materials. Generally, the penetration pathway and amount of diffusion of released drugs influenced through their lipophilicity/hydrophilicity, molecular weight, and the carrier type.

3.2. The Pathway of Hair Follicle

The hair follicle canal of the pilosebacous unit demonstrate a reservoir in where micro-, submicron-, and nano sized substances are able to penetrate and accumulate.[10] The size of the hair follicle orifices ranges between 102–242 μm in terminal hair follicles and 49–123 μm in vellus hair follicles.[45] Indeed, as demonstrated only the 0.1% of the skin surface is formed through the hair follicle orifices.[10] Since last decades through certain studies the importance of the transfollicular pathway, particularly for the preferential penetration of particulate substances has been shown. Particles that accrue in the hair follicle are safe from SC turnover and persist for days before they are cleared.[46] The interaction surface of hair follicle infundibulum about 0.68 for empty follicles and 0.068 cm^2 for full follicles was calculated.[47]

Therefore, the hair follicle infundibulum demonstrates not only a reservoir but also large surface area where interaction among accumulated substance and skin structures can take place. The hair follicle is a by-pass for a more rapid penetration of substances. After the selectively closing of hair follicle orifice, the administered drug materials reached the equal blood values in volunteers with open hair follicles.[48,49] This could be because of the fact that the SC barrier in deep infundibulum is thinner and molecules might be diffuse more promptly here than on the skin surface where the SC consists of certain more layers. Additionally, the accumulated carriers in the hair follicle canal release the encumbered drug, thus creating high local concentration of the drug that is a dynamic force for its diffusion to the viable skin. The elimination of sebum, cells debris, and eventually bacteria from the hair follicle that formed its content improve the penetration of locally administrated particulate materials.[50]

3.3. Translocation Across the Stratum Corneum

According to the general believe the molecules which can pass through the skin are, lipophilic drugs having the molecular weight of less than 500 Dalton, on the contrary the penetration of drug through the skin as macromolecules, hydrophilic molecules, and nanoparticles is too reduced.[51,52] The penetration of loaded substances has been improved by liposomes, solid lipid nanoparticles, and polymeric drug delivery system but it should keep in mind that there is no prove of the intact particles translocation across the intact SC of healthy skin. Inversely, it appears that constituent of lipid-based particles dissolve in the lipids of the SC enhancing its permeability.[2,53] In fact, in the acceptor medium of the Franz diffusion cell the biocompatible polymeric vehicles were detectable through the Transmission Electron Microscopy (TEM).[10]

3.4. Carriers Penetration Across Disrupted Constituent Skin Barriers

In order to develop drug delivery systems to use in skin disorders, the various characteristics of the diseased skin should be considered. In the most of skin diseases the SC

Table I. Examples of recent polymeric nanoparticles for application on the skin.

Type of particle	Used polymer	Average particle size (nm)	Intended application	Drug	Reference
Cationic lipid-polymer hybrid nanoparticle	PLGA	163	Improvement of efficacy transport into the deeper dermal medium	Anti-TNFα siRNA and capsaicin	[55]
Hydrogel nanoparticle	Hydrogel	37	Proposition of the hydrogel nanoparticles delivery as efficacy enhancement technique	HA	[56]
Polymeric nanoparticle	PLGA-Chitosan	153, 173 and 169	Delivery enhancement to deep epidermis	Spantide II and Ketobrofen	[57]
Polymeric nanoparticle	Chitosan	138	Reducing of skin irritation	Capsaicin	[36]
Polymeric nanoparticle	Dextran	69–453	Drug release ajustement	Ibuprofen	[58]
Polymeric nanoparticle	PLA	210	Development of novel investigating drug release method in a dynamic manner	Beclomethosone-dipropionate (BDP) and Indomethacin	[30]
Polymeric nanoparticle	PCL	344.6	Increasing of anti-inflammatory activity of nimesulide in topical application	Semi-solid topical formulations containing nimesulide-loaded nanocapsules showed *in-vivo* anti-inflammatory activity in chronic arthritis and fibrovascular tissue models	[59]
Cross-linked gelatin nanoparticle	Gelatin	168	Increasing of the stability and decreasing the release of the drug	Cycloheximide	[60]

function is disturbed in different degrees.[10] However, in the normal skin particulate carriers penetrate in the SC and in the canals of hair follicle releasing there the loaded drugs, in diseased skin, that the integrity of the SC is changed, carrier systems could passe the SC obstacle and go into the epidermis and dermis. To bypass the SC numbers of methods have been developed, for instance through disrupting it with abrasion and adhesive tapes.[54] The physiology, morphology, and biology of healthy skin are different from the diseased skin, see Figure 1. Thereby, for attainment of more selective drug delivery various approaches might be developed taking into account the special states that characterize affected skin and exploiting them. According to the majority of the authors the inflamed skin has considerably higher drug permeability than diseased skin. These findings are demonstrated that the structure of tight junctions might be altered because of the swelling of the tissue and increased intercellular fluid in the epidermis. Based on the studies which employed the ultraviolet, irradiation or mechanical techniques to interrupt the SC and activate the immunity system in the viable skin layers the nano-materials can be detected. After passing the SC, they could touch the subcutaneous lymph nodes after being taken up through skin antigen presenting cells or by passive transport behind the drainage of lymph. All these results highlight the requirement for more information about the interactions and fate of the vehicle system after local administration on the abnormal skin. Nevertheless, there is no available data concerning the penetration of softer particle as polymeric nanocarriers. The barrier properties of the skin changing at the time of its infection.

Generally, in the period of the bacterial and fungal based infections, the permeability of the SC is increased and the immunity system of the skin is activated as well. However, according to the category of pathogen and the phase of the disease, there are different degrees of skin dryness, inflammation and desquamation. It has been found that the elderly skin is scaly and dry. Acne vulgaris is an example that is characterized though a hyper-proliferation of keratinocytes in the hair follicle at the level of the sebaceous gland duct and an amplified production of sebum that cause a strong obstruction to the penetration of hydrophilic molecules and nanoparticles.[10]

As shown in the table hydrogel polymer produced the smallest particle size among all polymers which has an important role in passage via the skin.

Literature shows that in general materials having specific characteristics are better able to penetrate human skin such as particles up to size of 2 μm and materials with molecular weight less than 500 kDa, having adequate oil solubility and high partition coefficient, showed enhanced skin penetration.[61,62] Furthermore, according to a research, negatively charged liposomes have improved skin penetration of betamethasone and betamethasone dipropionate than liposomes containing the same active ingredient with positive and neutral charge. [63]

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4. CONCLUSION

Nowadays, nanotechnology through controlling the release rate of the irritant molecules and avoiding of direct contact between the substance and skin has been recommended. It is an approach to reduce the irritation and allergenicity of active ingredients after application to the skin. In this article we reviewed the interest of different used biodegradable polymers in Dermal and Transdermal Delivery Systems. Nonetheless, the polymer based nanoparticles (PBNPs) suggest the advantages of being stable, controlled and sustained drug release. Moreover, storing over months, encapsulation of both kinds of molecules (hydrophobic and hydrophilic), functionalization and furthermost adjustment of their physicochemical properties, are the advantages of polymer based nanoparticles (PBNPs) over lipid-based vehicles. The penetration inability of polymeric nanoparticles across the SC is their restriction, though they accumulate in skin furrows and hair follicles consecutively increase the local concentration by loaded drugs that can diffuse more easily to the viable layers of the skin. It must be bear in mind that the composition and surface charge of nanoparticles play a key role in the enhancement of drug delivery to the deeper layer of the skin. Being carriers for both hydrophilic and lipophilic drugs, biodegradable polymers based nanoparticles are employed to treat different diseases such as skin cancers (melanoma), and inflammatory diseases (e.g., rheumatoid arthritis). Usually synthetic biodegradable polymers have lower immunogenicity than biologically derived polymers, and they are easier to be modified and functionalized. In the preparation of nanoparticles the most employed polymers are PLA, PGA and their copolymer, PLGA. PLGA is the main approved polymer for the skin application. They can increase the bioavailability, permeability and solubility of many potent drugs that are difficult to deliver orally. The relatively low price, authorization by FDA, offering of a chance to the design of extended term drug delivery systems, low melting point, good solubility, exceptional mixing-compatibility, long period degradation that allows the release of drug up to several months and compatibility with the most of drugs are from the advantages of the PCL. Biodegradable polymer based nanoparticles (PBNPs) decrease dosage frequency of drug and will increase the patient compliance. In fact, innovative polymeric carriers being developed and that the number of their applications in dermatological field is augmenting at stable manner. A better understanding of interaction between skin and applied biodegradable polymer based nanoparticles (PBNPs) needs more studies. The concentration and molecular weight of the employed polymer affect the nanoparticles colloidal properties. The used polymer in formulation of nanoparticles might influence the properties, structure, and uses of the particles. The kinetic of release in polymer based nanoparticles (PBNPs) are one of the most significant features of the formulations due to proposed application in sustained drug delivery. Surface modification approaches in polymeric nanoparticles are crucial and need further investigations.

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