

# Polymeric Nanoparticles Based Topical Drug Delivery: An Overview

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## Review Article

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### ABSTRACT :

Human skin not only functions as a permeation barrier (mainly due to the stratum corneum layer), but it also provides a unique delivery pathway for therapeutic and other active agents. Skin is a widely used route of delivery for local and systemic drugs and is useful as a route for their delivery as nanoparticles. The skin behaves as a natural physical barrier against particle penetration, but there are opportunities to deliver therapeutic nanoparticles, especially in diseased skin and to the openings of hair follicles. These compounds penetrate via intercellular, intracellular and transappendageal routes, resulting in topical delivery (into skin strata) and transdermal delivery (to subcutaneous tissues and into the systemic circulation). Active and passive permeation enhancement methods have been widely used to increase cutaneous penetration. Recent literature has demonstrated that nanoparticles-based topical delivery systems can be successful in treating skin conditions as they combine the advantages of both the nano sized drug carriers and the topical approach.

**Keywords:** polymeric nanoparticles, nanospheres, nanocapsules, topical delivery.

## INTRODUCTION:

Development of successful topical drug delivery systems has been limited in scope due to the significant penetration barrier provided by stratum corneum (SC), the top most skin layer [1]. Stratum corneum comprises of a multi-layered "brick and mortar" like structure, where mortar is an intercellular matrix of a unique composition of lipids and the bricks are composed of keratin-rich corneocytes [2]. To overcome this barrier, numerous passive and active penetration enhancement methods have been evaluated. Chemical penetration enhancers have been intensively investigated over the years, but the concentrations required for improved penetration often lead to sensitization or irritation [3]. Nano-sized drug carriers have attracted much attention in the past decade as options in formulations for topical therapy. Nano-sized carriers such as polymeric nanoparticles (nanospheres, nanocapsules), solid lipid nanoparticles, liposomes, and nano-emulsions have been widely applied as topical formulations to enhance cutaneous drug delivery. Chemical and physical features of these nanosized carriers can effectively protect unstable drugs from degradation/denaturation, thereby decreasing the side effects of toxic drugs by producing controlled release, and enhance the cutaneous penetration of the drugs across the skin barrier by increasing the concentration gradient. Nanoparticles based on biocompatible and

biodegradable synthetic or semi-synthetic polymers, including poly (lactide-co-glycolide) (PLGA), poly ( $\epsilon$ -caprolactone), chitosan, and a combination of chitosan and poly (gamma-glutamic acid) and (gamma-PGA), have shown promise in dermal drug delivery. These carriers can potentially (i) protect labile compounds from premature degradation, (ii) provide controlled and sustained release via modification of polymer composition [4-6], (iii) increase localized targeting thereby reducing systemic absorption, and (iv) reduce irritation [7]. Dispersion of polymer-based nanoparticles in hydrophilic gels can further improve drug delivery to the skin. Gels can aid in creating uniform dispersion of the carriers in the matrix, increase contact time and deposition of the carriers on the skin resulting in enhanced skin penetration of the payload. It has been reported that these nanoparticles significantly enhance the permeation of highly lipophilic molecules into the lower skin strata, even though the delivery of such compounds is typically restricted to the upper most layers [8]. These results indicate that nanoparticles can be used as effective skin penetration enhancers. In this article an attempt is made to review the published literature pertaining to novel polymeric nanoparticles based drug delivery systems.

Nano-sized carriers have been extensively studied in the past decades for various biomedical applications

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including drug delivery, gene delivery, vaccination and disease diagnostics. Benefits of such nano-sized carriers include (a) enhanced Permeation and Retention (EPR) effect due to higher concentration in tumors. (b) Tissue specific targeting by conjugating antibodies and peptides to carrier surfaces (c) sustained and controlled release of drugs (d) chemical and physical protection due to stabilization of compounds.

Polymeric nanoparticles are prepared from biodegradable and biocompatible polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticles matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed [1, 2.]. These systems are represented in the following diagram.

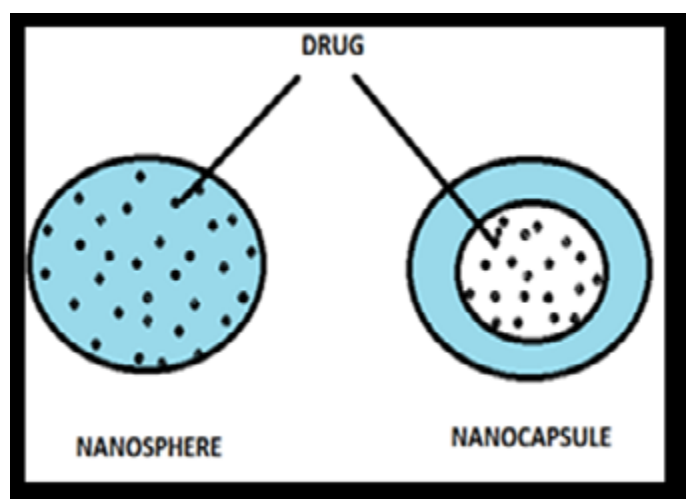


Figure1. Nanospheres and nanocapsules

## METHOD OF PREPARATION OF NANOPARTICLES

Several methods have been developed during the last two decades for preparation of Polymeric nanoparticles. These techniques are classified as follows:

### 1. Nanoparticles obtained from dispersion of preformed polymer:

Dispersion of drug in preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA), poly (D, L-glycolide) (PLG), poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA). These can be accomplished by different methods described below.

- Solvent evaporation
- Nanoprecipitation / Solvent displacement technique
- Emulsification/solvent diffusion
- Salting out
- Dialysis

### 2. Methods for preparation of nanoparticles from polymerization of monomers:

- Emulsion
- Interfacial polymerization

### 3. Ionic gelation or coacervation of hydrophilic polymers:

#### 1. Nanoparticles obtained from dispersion of preformed polymer:

##### a) Solvent evaporation:

In this method, polymer solutions are prepared in volatile organic solvents (e.g. dichloromethane and chloroform) and emulsions are formulated by high-speed homogenization or ultrasonication and converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion [9]. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water (w/o)/w.

##### b) Solvent displacement technique / Nanoprecipitation:

In solvent displacement technique polymer is dissolved in an organic, water miscible solvent and then added into the aqueous phase in presence or absence of a surfactant. Addition of organic solvent from the oil phase to aqueous phase can diffuse immediately by which precipitation of polymer occurs and nanospheres are formed. Thus, the solvent diffusion towards the aqueous phase, generating nano-emulsions causes the polymer to precipitate uniformly within the nano-emulsion template. This method is mainly applicable to lipophilic drugs because of the miscibility of the solvent with the aqueous phase, and it is not an efficient means to encapsulate water-soluble drugs [10, 11]

##### c) Emulsification / solvent diffusion (ESD):

In Solvent diffusion method encapsulating polymer is dissolved in a partially water soluble solvent and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. This technique presents several advantages, such

as high encapsulation efficiencies (generally >70%), high batch-to-batch reproducibility, easy scale-up, simplicity, and narrow size distribution [12, 13].

**d) Salting out:**

Salting out is based on the separation of a water miscible solvent from aqueous solution via a salting out effect. Polymer and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent and a colloidal stabilizer thus inducing the formation of nanospheres [13]. The salting out procedure can be considered as a modification of the emulsification/solvent diffusion method.

**e) Dialysis:**

Polymeric nanoparticles by the dialysis method are prepared as follows: the polymer and drug are dissolved in a suitable organic solvent (acetone or DMF). The resulting solution is introduced into a dialysis tube and dialyzed against deionized water. Water is exchanged at suitable intervals to remove the solvent [13].

**2. Preparation of nanoparticles by polymerization of a monomer**

To attain the desired properties for a particular application, suitable polymer nanoparticles must be designed, which can be obtained during the polymerization of monomers. Processes for the production of polymeric nanoparticles through polymerization of monomers are discussed below.

**a) Emulsion polymerization:**

Emulsion polymerization is one of the fastest methods for nanoparticles preparation and is readily scalable. The method is classified into two categories, based on the use of an organic or aqueous continuous phase. The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse micro emulsion, or into a material in which the monomer is not soluble (non-solvent) [13]. In the aqueous continuous phase the monomer is dissolved in a continuous phase that is usually an aqueous solution, and surfactants or emulsifiers are not needed. The polymerization process can be initiated by different mechanisms. Initiation occurs when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical [14].

**b) Interfacial polymerization:**

Interfacial polymerization is one of the well-established methods used for the preparation of polymeric nanoparticles. It involves step

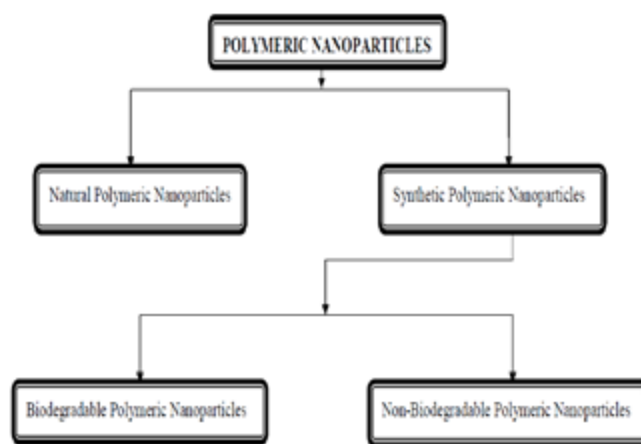
polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., continuous- and dispersed-phase), and the reaction takes place at the interface of the two liquids. Nanometer-sized hollow polymer particles synthesized by employing interfacial cross-linking reactions as poly-addition and poly-condensation or radical polymerization, methods are reported [15, 16, 17].

**3. Ionic gelation or coacervation of hydrophilic polymers:**

Polymeric nanoparticles prepared using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Involves a mixture of two aqueous phases, positively charged amino group of chitosan interacts with negatively charged triphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature [17, 18, 19].

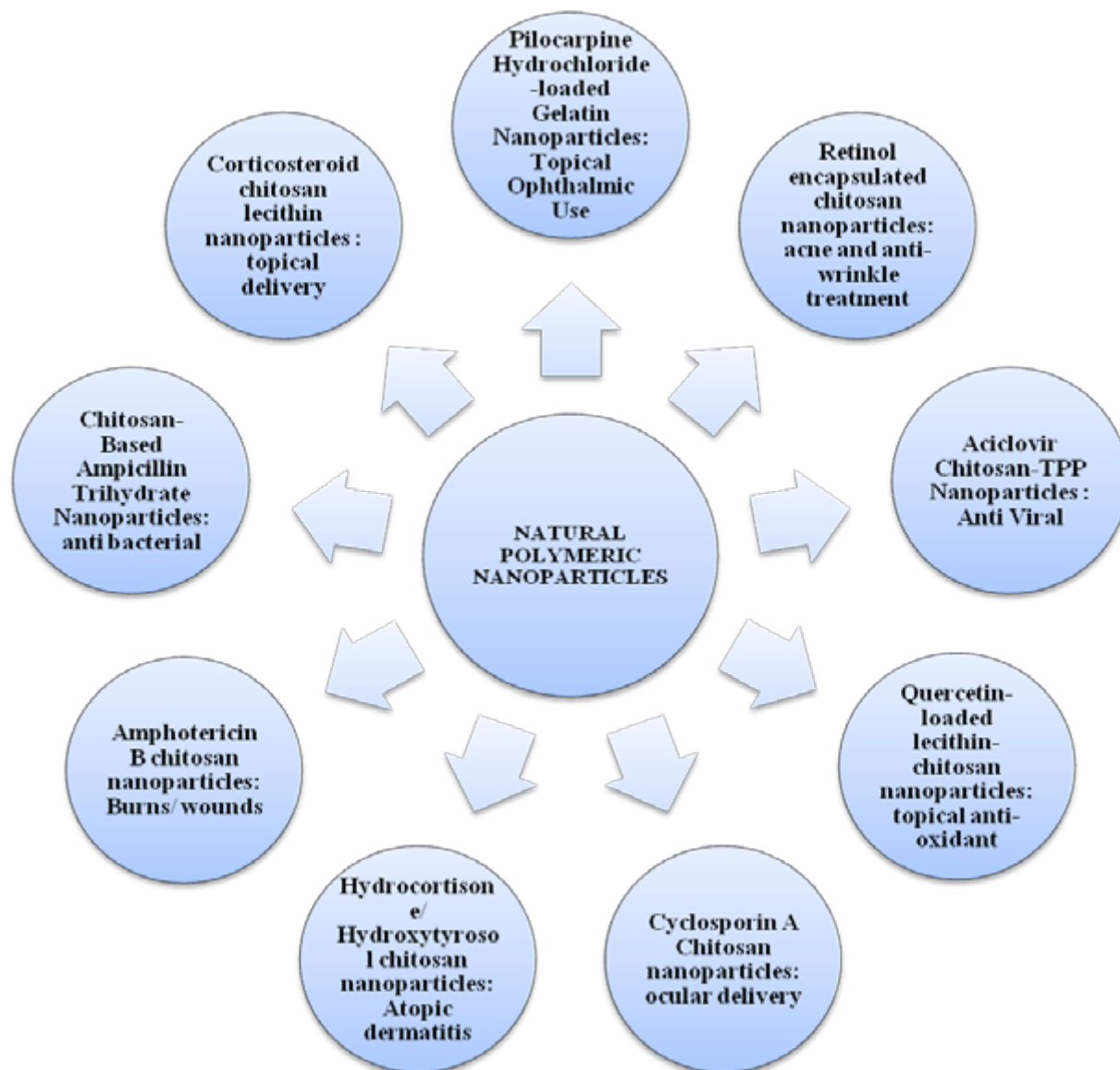
**POLYMERS USED IN PREPARATION OF NANOPARTICLES**

Polymers used in preparation of nanoparticles should be non-toxic, non-antigenic and should be biodegradable and biocompatible [16]. Polymeric nanoparticles are classified as follows:



**NATURAL POLYMERIC NANOPARTICLES:**

The most commonly used natural polymers in preparation of polymeric nanoparticles are Chitosan, Gelatin, Sodium alginate and Albumin. These polymers are usually obtained by extraction followed by various purification procedures. The tendency of these natural polymers to form hydro gels makes them ideal carriers for oligo nucleotides, peptides, proteins and water-soluble drugs. Following is a summary of reported literature using such polymers. The following figure represents examples of carrier systems containing natural polymers.



#### a) Gelatin Nanoparticles:

Pilocarpine hydrochloride-loaded gelatin nanoparticles have been reported by Vandervoort et al. (2004) for topical ophthalmic use. Collagen, the native protein from which gelatin is derived is biocompatible and biodegradable is present in the eye and employed in ocular applications. Gelatin nanoparticles encapsulating Pilocarpine HCl or hydrocortisone as model drugs were produced using a desolvation method. A high Pilocarpine HCl entrapment was established and compared to aqueous drug solutions, a sustained release profiles for both drugs is reported [20].

Oxybenzone-loaded gelatin microspheres reported by Patel M et al. (2006), although not in the nano-sized range, were used for sunscreen applications [21].

#### b) Chitosan Nanoparticles:

Among various natural polymeric nanoparticles, chitosan-based nanoparticles have been most frequently applied for topical skin delivery. Chitosan, the N-deacetylated derivative of chitin, is a natural biodegradable, cationic polymer composed of mainly glucosamine units. Its anti-oxidant, anti-

inflammatory and anti-microbial properties make it a suitable vehicle for delivering therapeutics to treat dermatological disorders. Moreover, at physiological pH, the primary amine groups of chitosan are protonated, and therefore chitosan is positively charged. The positive charge can be used to form nanoparticles in solution via cross-linking with poly anions, to efficiently encapsulate negatively charged drugs via electrostatic interaction, and to promote cellular internalization of drug-containing chitosan nanoparticles. The interesting biopharmaceutical characteristics of this polymer are accompanied by its well documented biocompatibility and low toxicity [22]. Many articles on the potential of chitosan for pharmaceutical applications have been published. A few examples of topically applied, chitosan-based nanoparticle systems are given below.

Kim *et al.* (2006) have reported a formulation of retinol (Vitamin A derivative) encapsulated chitosan nanoparticles. Retinol and its derivatives are extensively used in the pharmaceutical and cosmetic area. The encapsulation of retinol in chitosan nanoparticles minimizes its irritation and toxicity,

and these nanoparticles can be potentially used for acne and anti-wrinkle treatment. Also, solubility of retinol increases by encapsulation into chitosan nanoparticles as concluded by the report [22]

Hasanovic et.al (2009) demonstrated that the encapsulation of Acyclovir into chitosan-TPP nanoparticles resulted in significantly increased drug stability, decreased photo degradation, and enhanced drug penetration through porcine skin [23]

Şenyigit et al. (2010) reported that chitosan lecithin nanoparticles in a chitosan gel formulation delivered a corticosteroid clobetasol-17- propionate to epidermis and dermis as effectively as a commercial cream [24]

Tan et al. (2011) investigated, Quercetin-loaded lecithin-chitosan nanoparticles containing D- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate (TPGS) with a conclusion that addition of TPGS into the nano system resulted in increased entrapment efficiency and drug-loading of Quercetin [25]

Ampicillin trihydrate loaded chitosan nanoparticles prepared by modified ionic gelation method was studied by Rath et al. (2010) Nanoparticles prepared using chitosan as polymer and sodium tripolyphosphate (TPP) as cross-linking agent produced particles of good stability and exhibited sustained drug release behavior. While chitosan has its own antibacterial activity, the investigator exhibited that incorporation of Ampicillin trihydrate in the chitosan nanoparticles produced synergism [26].

Campos A. M. De et al (2001) *have* described the potential of Chitosan nanoparticles for the delivery of drugs to the ocular mucosa, using the immunosuppressive peptide Cyclosporin A as a model drug. Ionic gelation technique was conveniently modified in order to produce Cyclosporin A-loaded Chitosan nanoparticles for the treatment of these local diseases [27].

Sanchez D.A. et al (2014) investigated encapsulation of Amphotericin B within Chitosan nanoparticles. Which can effectively transport encapsulated molecules across diverse and complex biological barriers and tested the efficacy of Amphotericin B within Chitosan nanoparticles as a vector for cutaneous delivery in the settling of a murine burn wound infection [28]

Polymeric nanoparticle for percutaneous co-delivery of hydrocortisone/hydroxytyrosol is reported by Z. Hussain et al (2013) providing additional anti-inflammatory and antioxidant benefits in the treatment of atopic dermatitis (AD). This delivery system is proposed as a promising system for the percutaneous co-delivery of anti-inflammatory and antioxidative agents in the treatment of atopic dermatitis AD [29].

#### **SYNTHETIC POLYMERIC NANOPARTICLES**

The most widely used polymeric nanoparticles are prepared from synthetic polymers. Since natural polymers vary in purity and often lack the batch-to-

batch consistency, it is difficult to obtain reproducible particles and controlled release pattern for the encapsulated drug(s). On the contrary, synthetic polymers can be supplied with good purity and batch-to-batch reproducibility; [30]. Also compared to nanoparticles based on natural polymers, nanoparticles from synthetic polymers have been applied predominantly for hydrophobic/lipophilic drugs.

Hydrophilic, biologically active molecules can be loaded into synthetic polymer-based nanoparticles by using the double emulsion method; the limitation being that when volatile organic solvents are used, it is a challenge to maintain the biological activity of the molecules. Commonly used synthetic polymers for drug delivery applications include biodegradable aliphatic polyesters such as polylactides (PLA), poly (lactide-co-glycolide) copolymers (PLGA), and poly ( $\epsilon$ -caprolactone) as well as non-degradable polymers such as poly (methyl methacrylate) and polyacrylates. Following is a representation of published synthetic polymer based nanoparticle drug delivery system.

#### **NANOPARTICLES BASED ON BIODEGRADABLE SYNTHETIC POLYMERS**

##### **1. Poly (D, L-Lactide-Co-Glycolide) (PLGA):**

PLGA copolymers are biocompatible and biodegradable, the final degradation compounds i.e. lactic acid and glycolic acid is eventually removed by citric acid cycle [30]. These copolymers are the most commonly applied synthetic polymers for nanoparticle preparation, and PLGA nanoparticles have been widely employed for topical delivery.

Gomez Gaete C. et al. (2007) have encapsulated dexamethasone polymeric nanoparticles of biodegradable poly (d,l-lactide-co glycolide) (PLGA). In addition, encapsulated dexamethasone nanoparticles might be sufficient for therapeutic purposes since nanoparticles internalization within retinal pigment epithelial cells would increase the drug efficacy [31].

Poly (D, L-lactide-co-glycolide) and poly (D, L-lactide-co-glycolide) with poly (ethylene glycol) nanospheres (NSs) incorporating Flurbiprofen have been reported by Vega et al. (2012). A possibility of combining the advantages of polymeric Nanospheres in terms of increasing flurbiprofen permeability through corneal epithelium with the solubilizing properties of hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD) in order to be an effective system for increasing the bioavailability of flurbiprofen is suggested.

Shah et al. (2012) developed bilayered nanoparticles (NPS) using Poly-(lactide-co-glycolic acid) and chitosan for the simultaneous topical delivery of two anti-inflammatory drugs, spantide II (SP) and ketoprofen (KP). Surface was modified with oleic

acid. It was concluded that *In vitro* human skin permeation study of this nano gel system exhibited significant increase in penetration of spantide II and ketoprofen in epidermis and dermis layers as compared to the control groups. Similar approach could be extrapolated to treat other skin diseases like fungal, bacterial, viral infections and skin cancers like melanoma [33].

Tsujimoto H. et al. (2007) investigated PLGA nanospheres by encapsulating Hinokitiol by emulsion solvent diffusion method. Hinokitiol is known for its antibacterial and anti-inflammatory effects; but, it is also often used in the over-the-counter hair restorers, because it can normalize the metabolism of matrix and papilla cells. This study shows that hair growth was enhanced by using the encapsulated PLGA nanospheres, which transformed the hair growth cycle from the resting phase to the growing phase. As a result, the degree of hair growth was improved significantly [34].

Flurbiprofen loaded poly (d,l-lactide-co-glycolide) (PLGA) with poly(ethyleneglycol) (PLGA-PEG) nanospheres were studied by E. Vega et al. (2013) as skin controlled delivery systems. These studies indicate that after 24 hrs, Flurbiprofen retained in the skin was about 9-fold higher with nanospheres compared with the control solution, attributed to the reservoir effect of nanospheres acting as a depot, sustaining the drug and limiting its systemic absorption [35]

## 2. Poly- $\epsilon$ -Caprolactone (PCL):

Poly ( $\epsilon$ -caprolactone) is another synthetic polymer that is widely employed for the preparation of nanoparticle formulations due to its biocompatibility, biodegradability and mechanical properties. In addition, due to its semi-crystalline structure, its degradation is delayed compared with amorphous polyesters.

Alvarez-Roman et al. (2001) reported the preparation of octyl methoxy cinnamate-loaded poly ( $\epsilon$ -caprolactone) nanoparticles for epidermal delivery and their results suggest better sun protection and partial protection against erythema [36].

Hydrophilic gel containing nanocapsules of Diclofenac described by D. Milao et al. (2003) were prepared by Nanoprecipitation [37].

Alves PM et al (2005) investigated nanocapsules suspensions of poly ( $\epsilon$ -caprolactone) (PCL) containing Nimesulide by nanoprecipitation and spontaneous emulsification. It was concluded that different nimesulide loaded nanocarriers (nanoemulsion, nanocapsules, nanospheres) can be incorporated in semisolid hydrophilic gels. In general, the incorporation of nanoemulsion, nanocapsules or nanospheres did not affect the non-Newtonian behavior and pseudo plastic character of gels [38].

Tretinoin-loaded nanocapsules were prepared by

interfacial deposition of preformed polymer (poly- $\epsilon$ -caprolactone) by Ourique AF et al. (2008) which improved Tretinoin photo stability, independent of the type of oil phase used and represent a potential system to be incorporated in novel topical dosage forms containing Tretinoin [39].

Głowka E et al. (2014) developed and evaluated a semisolid formulation containing polymeric nanoparticles suitable for follicular targeting of Roxithromycin using Poly ( $\epsilon$ -caprolactone). The encapsulation of Roxithromycin into biodegradable, biocompatible and inexpensive polymeric nanoparticles and *ex-vivo* human scalp skin penetration studies proved that it is possible to achieve preferential targeting to the pilosebaceous unit by using polymeric nanoparticles [40].

## 3. Tyrosine:

Tyrosine-derived nanospheres have been reported by Sheihet L. et al. (2008) prepared by the self-assembly of a biodegradable, non-cytotoxic ABA triblock copolymer [A-blocks Poly (ethylene glycol) and B-blocks were oligomers of suberic acid and desamino tyrosyl-tyrosine alkyl esters]. Tyrosine-derived nanospheres significantly enhanced skin penetration of highly lipophilic model compounds (DAF and Nile Red) in human cadaver skin as compared to conventional formulation which can be a promising tool for the topical skin delivery of lipophilic drugs and personal care agents such as Vitamins A and D, sunscreens, glucocorticoids, or retinoid [41].

Batheja P et al. (2011) have investigated Tyrosine-derived nanospheres containing Diclofenac sodium having potential as effective carriers for the topical delivery of lipophilic molecules. Tyrosine-derived nanospheres are biocompatible and are safe for topical delivery systems. Tyrosine-derived nanospheres dispersed in gels offer promise for the topical delivery of lipophilic drugs and personal care agents to skin for treatment of cancers, psoriasis, eczema, and microbial infections [42]

## NANOPARTICLES MADE OF NON-DEGRADABLE SYNTHETIC POLYMERS

Nanoparticles formulated with non-degradable polymers have also been studied for cutaneous delivery of active compounds. Following is a compilation of non-degradable synthetic polymers.

### 1. Ethyl Cellulose:

Venkatesh et al. (2005) and Abdel-Mottaleb M.M.A. et al. (2012) developed and evaluated Betamethazone Loaded Ethyl Cellulose Nanospheres by a modified method of desolvation and cross linking. The drug Betamethazone was incorporated into nanospheres as a carrier for targeting corticosteroids to the skin. The comparative *in vitro* diffusion study between commercial cream and the formulated cream showed a marked reduction in release rate from nanospheres-

based cream. It was found to be a potential dermal delivery system for sustaining the release of the drug. They conclude that smaller particles had around 3-fold stronger and deeper penetration tendency with a preferential accumulation in inflamed skin hair follicles and sebaceous glands [43, 44]

## 2. Polystyrene:

Alvarez-Roman R. et al. (2004) proposed non-biodegradable polystyrene nanoparticles for topical administration to enhance percutaneous transport into and across the skin barrier and thus accumulated preferentially in the follicular openings in a time-dependent manner, and the smaller nanoparticles demonstrated higher accumulation in the follicular regions. Apart from follicular uptake, localization of nanoparticles in skin furrows was apparent from the surface images [45].

## CONCLUSION

Topical administration of active substances offers several attractions compared to traditional routes viz, it avoids hepatic first-pass metabolism, has the potential of long term controlled release with avoidance of the frequent dosage regimens, Direct as well as indirect evidences substantiate the early reports on the usefulness of nanoparticles as carriers for topical administration. Though, the mechanisms by which prolonged release occurs are not completely understood, novel approaches in nanomedicines are able to extend the therapeutic effect of the embedded active molecules providing their prolonged release in the epidermis. This review provides an insight to reported evidences of novel nanoparticulate delivery systems that exhibit a targeting and prolonged release effect with great potential in dermal delivery. On studying the reported literature, it is observed that topically applied, polymeric nanoparticles-based drug delivery systems for the treatment of skin diseases exhibit advantages which include enhanced skin permeation, especially of poorly water-soluble / lipophilic drugs, increasing the drug concentration gradient across the skin with improved drug stability. Side effects such as skin irritation can be minimized also; drugs can be directly delivered to the diseases site with minimal systemic absorption.

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