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POLYVINYL ALCOHOL BASED TRANSDERMAL DEVICES FOR ENHANCED SKIN PERMEATION

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ABSTRACT: Skin is the most easily accessible organ which has been used as a route for the delivery of therapeutic agents into the systemic distribution. The chief component of a transdermal (TND) drug delivery system is a controlled release device consist of polymers. Hence the selection of appropriate polymer is a key step during the development of TND patch. In recent years, polyvinyl alcohol (PVA) have gained tremendous attention in the field of TND drug delivery because of their favorable features such as biocompatibility, hydrophilicity, biodegradability and excellent film forming ability. In this article the applicability of PVA in developing TND patches are discussed. The application of PVA through chemical modification as TND device is also detailed. The potential of PVA based devices such as microneedles, TND films, organic-inorganic hybrid patches, nanocomposites etc to delivery drug molecules across the skin are described.

KEYWORDS: Transdermal drug delivery, Polyvinyl alcohol, Microneedles, Nanocomposites.

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1.INTRODUCTION

With the constant progress in the development of novel materials and urgent pharmaceutical needs, the fabrication of effective drug delivery system has become a predominant section of the whole biomedical industry. For the pharmacological management of diseases, drugs are generally delivered either orally or intravenously. The administration of drugs via conventional oral strategies suffers serious drawbacks such as first pass hepatic metabolism, gastro intestinal absorption etc. On the other hand injection induces pain, infection, hypothermia etc [1]. In this scenario, researchers

searched for an alternate route for drug administration and TND drug delivery has received the ample attention. Although TND approach promises to revolutionize biomedical field, it is still a novel strategy to be completely exploited. TND delivery avoids first pass hepatic metabolism, offers sustained drug release for prolonged time period, prevents pain and emotional trauma related to needle injection and improves patient's compliances [2]. However, the utilization of skin as a portal for the transport of drug molecules is limited because of the presence of extremely hydrophobic lipid packing called stratum corneum (SC), the outermost layer of skin [3]. Vanquishing the SC hindrance harmlessly and reversibly by disorganizing the lipid packing is a principle issue existing in this area. Recently polymeric materials have gained significant attention in TND drug delivery system due to their noticeable effect on local skin penetration. The most fundamental building constituent of a TND patch is the matrix which holds the therapeutic entities in the final phase and allows it to diffuse straight into the skin surface. PVA is a linear semicrystalline synthetic polymer obtained by the partial or complete hydrolysis of poly(vinyl acetate). It is a versatile material highly soluble in water and biodegradable under aerobic and anerobic conditions. PVA has been regarded as a functionalizing agent to impart hydrophilic surrounding to other materials. The favorable site for the functionalization of PVA is the secondary hydroxyl group which furnish novel properties and extend the area of applications [4]. PVA displays outstanding thermomechanical properties, flexibility, recyclability and biocompatibility. It is worth noticing that the reinforcement of nanosized particles like carbon nanotube, nanographene oxide, nanodiamond, nanocellulose, titanium nanotube etc into PVA remarkably enhance its thermomechanical properties. The biomedical applications of PVA involves drug delivery, tissue engineering, wound dressing etc [5]. PVA can be categorized into two class namely: partially hydrolyzed and completely hydrolyzed. The properties of PVA such as molecular weight, solubility and flexibility can be altered by varying the conditions of hydrolysis [6]. Recent investigations have shown the significance of PVA as a matrix for the development of TND patches due to its excellent film forming capacity, moisture permeability, flexibility and adhesiveness. Kumar et al prepared PVA-Xanthan gum blend membranes and used for the TND delivery of terbutaline sulfate. The device was stable for six weeks and DSC thermograms disclosed no variation in the chemical identity of the incorporated drugs [7]. Another research group loaded testosterone into PVA based hydrogel containing polyisobutylene. *In vitro* skin permeation test disclosed that the prepared PVA based patch incorporated with 3.0 % dodecylamine showed excellent skin permeability [8]. Literature stated that PVA based TND devices have been widely investigated and these patches have successfully delivered progesterone, ketorolac tromethamine, indomethacin, verapamil and isosorbide-5-mononitrate across the skin [7]. The investigations involving PVA have begun to pave the pathway towards the development of highly efficacious TND patches.

PVA in TND Drug Delivery Systems

An et al fabricated a soft hydrogel to deliver testosterone across the skin. Testosterone was embedded in hydrogel prepared from PVA and polyisobutylene [8]. Polyisobutylene was incorporated in PVA to improve the skin adhesion properties of the device. The capacity of various penetration enhancers such as dodecylamine, lauric acid and oleic acid to improve the skin permeation was studied in details. *In vitro* and *in vivo* examination revealed that the skin permeability of the device was remarkably increased in presence of penetration enhancers. PVA hydrogels with 3.0 % dodecylamine showed the best results. Bhunia et al evaluated the ability of PVA incorporated with nanosilica to deliver diltiazem hydrochloride across the skin [9]. Tensile measurements displayed that a variation in molecular weight of PVA markedly affected the mechanical properties of the film mainly at low filler concentration compared to high concentration. They reported that addition of 1.0 % nanosilica to low molecular weight polymer produced uniform distribution of fillers which ultimately resulted in the improvement of mechanical properties. These changes in physicomechanical behavior finally influenced the release of drug from the patches. The article concluded that PVA with low molecular weight showed highest diltiazem hydrochloride retention and steady diltiazem release compared to pristine PVA and high molecular weight PVA film. Bhunia et al reported another TND device based on PVA for the delivery of diltiazem hydrochloride [10]. To enhance the mechanical strength and elongation at break, they added multi-walled carbon nanotube to PVA film and evaluated their drug release profile. PVA with high molecular weight displayed excellent matrix-filler interaction than that of low molecular weight PVA. Addition of 1.0 % nanofiller has significantly improved the elongation at break (196 %) and tensile strength (6 %) than pristine PVA while such enhancement was less pronounced in low molecular weight PVA. However addition of 0.5 % nanotube to low molecular weight PVA has displayed comparatively better behavior than with 1.0 % nanofiller. Skin permeation test revealed that substantially sustained diltiazem release was observed in high molecular weight PVA with 1.0 % nanotube and low molecular weight PVA at 0.5 % nanotube ascribed to high encapsulation efficiency. The mechanism of drug release was “relaxation” based ascribed to slow hydroswelling behavior of the device due to PVA-nanotube interaction. Engelkc et al reported a device fabricated from PVA for the delivery of molecules upon fractional skin laser microporation [11]. They prepared PVA blends with carboxymethyl cellulose or cross-linked carbomer. The laser microporation produced a four to five times enhancement in water transport through excised skin than intact skin. The improved water treatment enhanced the dissolution of PVA based formulations with in 6 h. The application of device on laser microporated site resulted in remarkable enhancement in the delivery of model molecules, which was superior for pristine PVA membranes than PVA- carboxymethyl cellulose and PVA-carbomer blends. Feith et al effectively delivered ketorolac tromethamine across the skin using PVA based film [12]. A Different variety of films were fabricated using PVA, sodium

carboxymethyl cellulose and chitosan. To improve the skin adhesion behavior plastoid E35L and polyvinyl pyrrolidone were incorporated. Penetration enhancers such as oleyl alcohol, propylene glycol and sodium glycocholate were added to evaluate their potential as enhancers. *In vitro* permeation test showed that PVA based film displayed the best performance followed by sodium carboxymethyl cellulose than chitosan. PVA patch consisting plastoid E35 displayed the highest permeability and skin adhesion. Further the effect of penetration enhancer in PVA film was studied and they reported that the order of enhancing skin permeation was sodium glycocholate > oleyl alcohol > propylene glycol. An organic-inorganic hybrid patch was reported by Guo for the TND delivery of drug molecules [13]. Polyvinyl alcohol was modified using γ-(glycidyloxypropyl) trimethoxysilane. Polyvinyl pyrrolidone and glycerol were respectively added as tackifier and plasticizer. The patches showed excellent transparency, cosmetic inconspicuous and comfortable feel. The addition of 20-30 % of γ-(glycidyloxypropyl) trimethoxysilane into PVA remarkably improved the tensile behavior and skin adhesiveness. Furthermore, the addition of inorganic species reduced the crystalline sites of PVA and thus assisted the permeation of water vapor and diffusion of drug molecules. *In vivo* skin irritation test proved the non-skin irritancy of the PVA based film. They evaluated the release of 5-fluorouracil and ibuprofen from the prepared film. They stated that the addition of PVA enhanced the drug release ascribed to its anti-nucleating effect which changes the crystalline drug into amorphous. Furthermore glycerol produced a space within the patch, facilitating better molecular mobility, hence improved the diffusion of drug. The drug release was significantly improved when the γ-(glycidyloxypropyl) trimethoxysilane/PVA+ γ-(glycidyloxypropyl) trimethoxysilane ratio was between 10 and 34 %, but reduced swiftly with further addition of γ-(glycidyloxypropyl) trimethoxysilane. These outcomes displayed that a particular amount of γ-(glycidyloxypropyl) trimethoxysilane could productively enhanced the amorphous sites of PVA and improved diffusion of drug. However excess γ-(glycidyloxypropyl) trimethoxysilane resulted in self-crosslinking reaction which made the patch more compact and prevent the easy diffusion of drug molecules. Kataria et al prepared ciprofloxacin loaded TND device using PVA and sodium alginate by electrospinning technique [14]. The cumulative drug release profile of PVA and PVA/ sodium alginate patch revealed that at first 1 h PVA showed highest drug release ascribed to the burst release of drug molecules from the surface of patch, followed by the degradation of water soluble PVA happened until 7 h of application. However the drug release rate of PVA/ sodium alginate was slow initially as sodium alginate furnished better stability to the fiber architecture because of intermolecular hydrogen bonding between drug and matrix. The test displayed that the release pattern within 7-8 h was better for acute injuries where a continuous ciprofloxacin supply is necessary. The drug release kinetics showed Higuchi and Kosermayer-Peppas model. The ability of the device to deliver drug molecules was evaluated by *in vivo* wound healing performance. The investigations showed that compared to PVA patch, PVA- sodium alginate

patch furnished better physiological environment for wound epithelialization. Kumar et al prepared a number of terbutaline sulphate loaded TND patches using PVA and the influence of xanthan gum and plasticizers on drug release rate was studied [7]. The developed membranes were flexible, smooth and displayed excellent tensile properties. FTIR mapping suggested that no reaction between terbutaline sulphate and matrix was happened. Furthermore terbutaline sulphate was homogeneously dispersed throughout the PVA matrix. Tensile test showed that the patch fabricated using propylene glycol as plasticizer showed remarkable mechanical strength compared to device with dibutyl phthalate. Release studies showed that the patches without xanthan gum displayed a slow release profile compared with that with xanthan gum. Compared to dibutyl phthalate film as plasticizer, the one with propylene glycol showed the best performance. Stability test indicated that the patch was stable for around six weeks and DSC studies suggested that no change in the chemical identity of terbutaline sulphate was observed. Finally it was concluded that the drug release mechanism was non-Fickian and the drug diffusion was remarkably enhanced by the addition of xanthan gum and polyethylene glycol. PVA and gelatin based devices were fabricated by Kunal et al [15]. They incorporated salicylic acid as filler but its amount was maintained less than 10 % to reduce the influence of filler on the behavior of the device. The incorporation of salicylic acid after the esterification of PVA with gelatin before solution casting of device displayed to cause slow drug release when compared to the device fabricated by dipping in salicylic acid solution. The drug molecules encapsulated in the device was crystalline. The kinetics of the drug release was found to be Higuchian-Fickian model suggesting a diffusion-controlled release. Kwon et al studied the applicability of PVA membranes as TND device for the delivery of erythromycin for acne treatment [16]. The drug encapsulated PVA membranes were fabricated using solution of PVA containing varying content of drug. They tested glycerin, Tween 80, CCT oil, polyethylene glycol and carboxymethyl cellulose as additives in the device. The prepared devices displayed sustained release of drugs and revealed that by varying the amount of drug and additive, the drug release could be controlled. The skin permeation was evaluated using the devices containing glycerin and polyethylene glycol as additives. The device first showed initial blow out. But the patch filled with glycerin continuously released approximately 5-6 % drug even at 15 h. Glycerin slow down the drug release ascribed to the interaction between glycerin and PVA or drug. In the case of device incorporated with polyethylene glycol, until 8 h, polyethylene glycol absorbed the release media inside the membrane, producing decreased drug release. After 8 h, fine cracks in the device produced enhanced release of drug. They concluded that the device continuously released drug to the acne area. Mahadevina prepared cefazolin loaded biocompatible nanocomposite based on chitosan and PVA by the addition of sepiolite [17]. TEM and SEM images revealed that the distribution of sepiolite in the matrix in a needle-type fashion. The membrane incorporated with high amount of chitosan displayed greater swelling capacity. Furthermore, the membrane displayed pH dependent

swelling properties and under acidic pH the water absorbency reached the maximum. The drug release was influenced by the content of chitosan/PVA ratio and sepiolite. The sepiolite loaded membrane showed more release compared to neat membrane. In addition, the rate of drug release was increased by increasing the amount of chitosan. Nayak et al developed nebivolol loaded TND device composed of ethyl cellulose with PVA and ethyl cellulose with hydroxylpropylmethyl cellulose [18]. PVA was employed to develop the backing membrane. Tween 80 and polyethylene glycol was respectively added as permeation enhancer and plasticizer. The prepared device showed enhanced skin permeability. Prabhu et al fabricated papaverine hydrochloride loaded TND patches using PVA and compared its potential with ethyl cellulose-polyvinyl pyrrolidone, eudragit RL-100 and eudragit RS-100 [19]. The device prepared from PVA and polyvinyl pyrrolidone displayed faster drug release compared to device prepared from eudragit RL-100: eudragit RS-100 or combination of ethyl cellulose and PVA. A remarkable variation in the release of drug was found from device prepared from high amount of PVA and showed faster release. The observation was ascribed to the hydrophilic nature of PVA which ultimately produced improved thermodynamic activity of drug in the membrane. The stability test revealed that the device showed better physicochemical behavior and drug contend after storing the device at varying conditions. Compatibility test confirmed the absence of drug-polymer interaction. Maji et al prepared maleic anhydride cross-linked chitosan-PVA membrane and evaluated its potential to transport alprazolam across the skin [20]. The patch prepared from high concentration of PVA displayed enhanced swellability and tensile strength. FTIR mapping displayed the absence of drug-polymer interaction. The skin permeability of drug was enhanced with increasing the concentration of PVA. The kinetic studies showed that the membrane followed Fickian transport diffusion. Furthermore, the device was found to be non-skin irritant. Kumar et al prepared metraprolol tartarate loaded hydroxypropylmethyl cellulose and eudragit S-100 [21]. The presence of PVA increased the moisture absorption. The Higuchi's plot displayed that the drug release followed diffusion mechanism. The skin permeation test showed that the device efficiently transport metroprolol tartarate across the skin. Kulkarni et al developed PVA based patches for the TND delivery of salbutamol sulphate [22]. They efficiently loaded drug molecules into glutaraldehyde cross-linked films of PVA, sodium alginate and chitosan. The device was thin, transparent and showed enhanced mechanical properties. Furthermore, the patches displayed enhanced water vapor permeability and swelling ratio. The article reported that the blending of PVA with other polymers and cross-linking with glutaraldehyde resulted in remarkable increase in drug encapsulation efficiency. *In vitro* skin permeation test showed that the PVA-sodium alginate film showed more drug release compared to that of PVA-chitosan film. Finally, skin irritation test indicated that the prepared patches were compatible to skin and fit for TND application. Ginting and coworker developed TND film from PVA and chitosan cross-linked tripolyphosphate sodium for the delivery of diclofenac sodium [23]. The weight of the device, thicknes and diclofenac contend were

found to be uniform. The device followed zero-order release pattern. The optimized device showed release flux of 89.42 μg/cm^2 at 10 h. The moisture absorption rate of the device was found to be 1.07 ± 0.193. The FTIR data of rabbit skin showed that the developed device enhanced the skin permeation of drug molecules. Sivaraman studied the applicability of PVA in developing a topical gel for the TND delivery of diclofenac salt [24]. PVA based formulations were prepared using isopropyl alcohol, propylene glycol, Transcutol P and hydroxypropyl cellulose. The fabricated device delivered an average cumulative drug amount of 22.85 ± 9.41 μg/cm^2 and 10.30 ± 9.09 μg/cm^2 respectively across the skin and in the skin over 24 h. The skin irritation test proved that the device was non-irritant to skin. Nguyel et al developed microneedles based on PVA to deliver doxorubicin across the skin [25]. The device was prepared using the micromolding strategy with doxorubicin loaded in different sites within the microneedle array. The device was found to be sharp and mechanically strong. The skin permeation test displayed that the skin applied with microneedle furnished a remarkably higher doxorubicin permeability compared to the untreated group. Lee et al developed a microneedle patch based on PVA and polyvinyl pyrrolidone [26]. The rate of drug release can be controlled by changing the ration of PVA and polyvinyl pyrrolidone. Confocal images suggested that Rhodamine 6G and bovine serum albumin used as model molecule could efficiently move from punctured site to deeper layers of skin. The penetration depth shown were about 190 and 380 μm, respectively for PVA- polyvinyl pyrrolidone. *In vitro* skin penetration test revealed that the device could significantly enhance the TND delivery of hydrophilic macromolecules.

2. CONCLUSION

TND drug delivery system has been developed or being developed to vanquish the downsides associated with conventional strategies. This review established the promising application of PVA based materials in TND drug delivery. The major findings and accomplishments arrived in this article may open new avenues in TND drug delivery.

CONFLICT OF INTEREST

Authors have no any conflict of interest.

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