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Plasticizers in Transdermal Drug Delivery Systems

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1. Introduction

Transdermal delivery is one of the non-invasive methods for drug administration. Patient compliance is improved and continuous, sustained release of drug is achieved by following the application of transdermal formulation on the skin (Guy 1996; Tanner & Marks 2008). Transdermal drug delivery systems, known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin in a predetermined time and controlled rate (Aulton 2007; Tiwary et.al., 2007; Vasil'ev et.al., 2001).

Transdermal drug delivery systems can be divided into three main groups : a) adhesive systems, in which the drug in adhesive, b) matrix type systems in which the drug in a matrix polymer and c) reservoir systems (Delgado-Charro & Guy 2001; Williams, 2003). Although there are differences in the design of transdermal therapeutic systems, several features are common to all systems including the release liner, the pressure sensitive adhesive, and the backing layer (Walters and Brain, 2007).

There are three critical considerations in the selection of a transdermal drug delivery system: adhesion to skin, compatibility with skin, and physical or chemical stability of total formulation and components (Walters and Brain, 2007). The adhesive nature of the patches is critical to the safety, efficacy, and quality of the product. Therefore the three important performance tests to monitor adhesive performance of patches are tack, shear strength and peel adhesion (Gutschke et al., 2010; Patel and Baria 2011; Ren et al., 2009). The choice and design of polymers, adhesives, penetration enhancers and plasticizers in transdermal patches are also critical because they have a strong effect on drug release, permeability, stability, elasticity, and wearing properties of transdermal drug delivery systems (Quan, 2011).

Plasticizers are low molecular weight resins or liquids, which cause a reduction in polymer-polymer chain secondary bonding, forming secondary bonds with the polymer chains instead (Gal and Nussinovitch, 2009; Rajan et al., 2010). The reasons for the use of plasticizers in transdermal drug delivery systems are the improvement of film forming properties and the appearance of the film, decreasing the glass transition temperature of the

polymer, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties (Wypych, 2004). One of the many advantages of plasticizers used in transdermal formulations is the controlling of the release rate of therapeutic compound which can be done by the selection of the plasticizer type and the optimization of its concentration in the formulation. The commonly used plasticizers in transdermal patches include phthalate esters, phosphate esters, fatty acid esters and glycol derivatives (Bharkatiya et al, 2010; Wypych, 2004).

The objectives of this chapter are to summarize the compositions and types of the transdermal drug delivery systems; to emphasize the role and effectiveness of plasticizers in transdermal drug delivery systems and to cover the research studies and current developments related to the development of transdermal formulations.

2. Transdermal drug delivery systems

Transdermal drug delivery systems, also known as "patches", are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin in a predetermined time at controlled rate and to maintain constant drug plasma concentration over a long period (Aulton 2007; Vasil'ev et.al., 2001). Transdermal patches have superiorities such as improved patient compliance and flexibility of dosage in which formulation can be removed immediately (Brown et.al. 2006; Guy 1996; Tanner & Marks 2008; Williams 2003). The transdermal systems of drugs including scopolamine, nitroglycerin, isosorbide dinitrate, clonidine, estradiol, fentanyl, nicotine, testosterone, norelgestromin+ethinyl estradiol, oxybutynin, selegeline, methylphenidate, buprenorphine, rivastigmine, rotigotine and granisetron have been approved (Guy 2010).

The major technical considerations by developing a transdermal formulation include (Meathrel, 2011; Quan, 2011):

- Size of the drug molecule and the required daily dose
- Drug compatibility with polymers, adhesives, plasticizers and other excipients used in the formulation
- Physical and chemical stability of the final formulation
- Size of the patch
- Balance between adhesion and easy patch removal depending on the duration of patch application.

2.1 Types of transdermal drug delivery systems

Although transdermal systems are classified in different types, transdermal patches can be divided into three main categories depending on the incorporation style of the drug in the system (Figure 1): (Delgado-Charro & Guy 2001; Padula et.al. 2007; Vasil'ev et.al., 2001; Williams, 2003).

- Reservoir Systems
- Matrix Systems
- Adhesive Systems

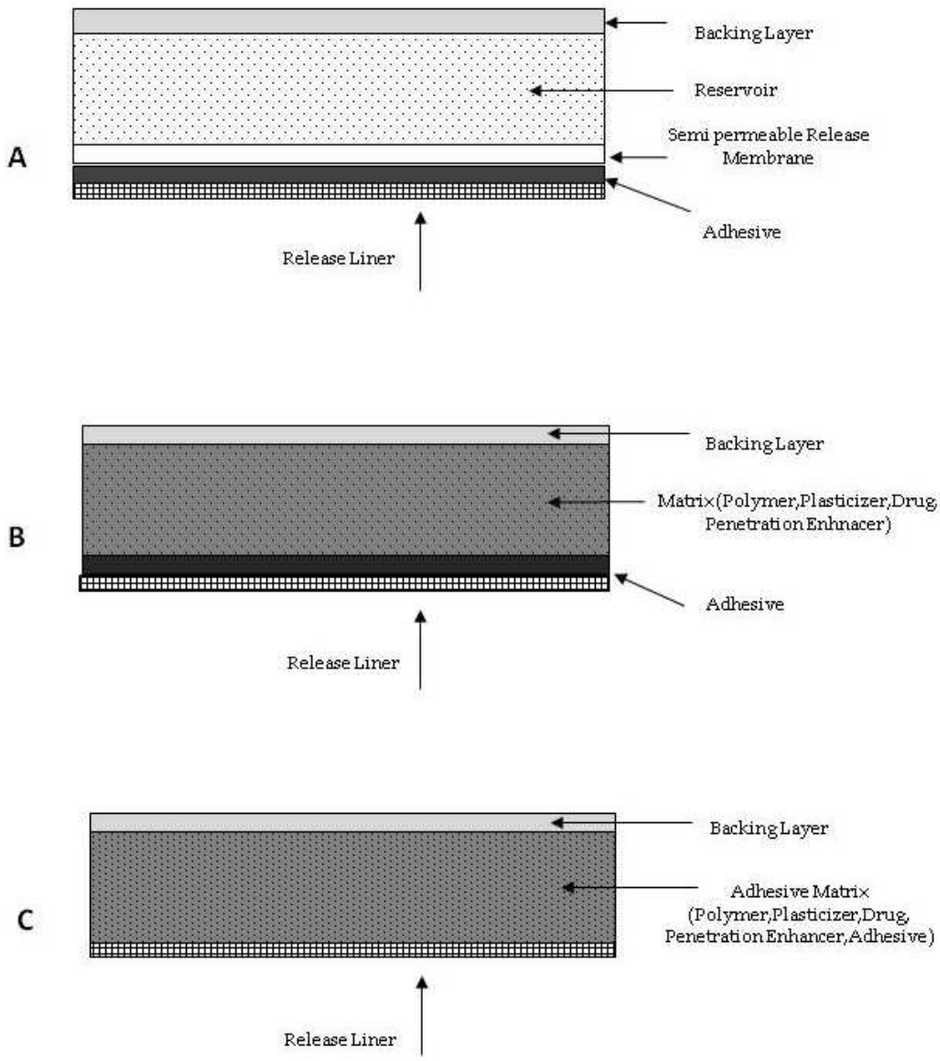


Fig. 1. Schematic representation of transdermal patch types: A. Reservoir, B. Matrix, C. Drug-in-Adhesive transdermal systems.

a. **Reservoir Systems:** In these systems, the drug is in a reservoir as liquid. Drug molecules are contained in the storage part, as a suspension in a viscous liquid or dissolved in a solvent. In the second type, there is a membrane made of a polymer with different structure, which separates the reservoir from the adhesive layer. In these systems, the membrane controls the release rate of the drug. The membrane can be porous or nonporous. The adhesive polymer on the exterior surface of the membrane enables the transdermal to adhere to skin. In these systems, drug release rate can be controlled by membrane thickness and adhesive layer (Delgado-Charro & Guy 2001; Padula et.al. 2007; Williams, 2003).

Transderm-Nitro (Nitroglycerin), Transderm-Scop (Scopolamine), Catapress-TTS (Clonidine), Estraderm (Estradiol) can be given as examples to the commercially available membrane diffusion controlled systems.

b. **Matrix Systems:** In this type of systems, the drug is dispersed homogeneously within a polymer matrix which has hydrophilic or lipophilic character. Outer side of the formulation is covered with a backing layer. In these systems, patch is held on the skin with a adhesive polymer as a strip. Matrix type formulations can also be prepared by dispersing the drug in an adhesive polymer that is sensitive to direct pressure and then covering this system with an impermeable backing layer. Since in matrix type formulations, release from semi-solid matrix of the drug is not controlled by any membrane, drug release from these systems is related to the surface area to which the patch is applied (Delgado-Charro & Guy 2001; Padula et.al. 2007; Williams, 2003).

Minitran (Nitroglycerin), Emsam (Selegeline), Exelon (Rivastigmine), Sancuso (Granisetron) and Oxytrol (Oxybutyne) can be given as examples to commercially available matrix diffusion controlled systems.

c. **Adhesive Systems:** In these systems, drug reservoir is prepared by dispersing the drug in an adhesive polymer. At the outmost, an impermeable backing layer takes place. Under the drug reservoir layer, there exists an adhesive membrane controlling the drug release rate. In this type of transdermal systems, drug release rate is controlled both by the matrix in which the drug is dispersed and also by a membrane. Although this type of systems can be designed with a single drug layer, they can be also designed as multi-layered (Delgado-Charro & Guy 2001; Padula et.al. 2007; Williams, 2003).

Nitrodur (Nitroglycerin), Daytarana (Methyl phenidate) and Duragesic (fentanyl) can be given as examples to commercially available adhesive systems.

2.2 Composition of transdermal drug delivery systems

Although transdermal systems can be design as different type systems mentioned above, following are the basic components which generally are used in the formulations of almost all type of transdermal patches (Williams, 2003).

- Drug
- Matrix
- Reservoir
- Semi-permeable (release) membrane
- Adhesive
- Backing layer
- Release liner
- Solvents, penetration enhancers
- Plasticizers

a. **Drug:** The drug, of which transdermal system will be designed, should possess some physicochemical characteristics. Drug should have relatively low molecular weight (<500 Dalton), medium level lipophilic character (log P 1-3.5) and water solubility (>100 mcg/ml). Also, the drug should be a potent compound, which is effective at low dose (<20 mg) (Guy 1996; Quan 2010).

b. **Matrix:** In the formulation of matrix type transdermal systems, the drug is dispersed or dissolved in a polymer matrix (Delgado-Charro & Guy 2001; Williams 2003). This matrix with polymer structure controls the release rate of the drug. Natural (e.g. pectin,

sodium alginate, chitosan), synthetic (Eudragit, polyvinyl pyrolidon, PVA) and semi-synthetic polymers (e.g. cellulose derivatives) are used as polymer (Amnuaikit et al., 2005; Güngör et al., 2008; Lin et al., 1991; Nicoli et al., 2006; Schroeder et al., 2007,a).

c. **Reservoir:** In this type of transdermal patches, a semi-permeable membrane controlling the drug release rate is used. The drug presents in a reservoir as liquid or solid (Delgado-Charro & Guy 2001; Williams 2003).
d. **Semipermeable (release) membrane:** It takes place in reservoir type transdermal systems and multi-layer adhesive systems. Ethylene-vinyl acetate copolymer, silicones, high-density polyethylene, polyester elastomers, cellulose nitrate and cellulose acetate are used as membrane. These membranes control the release rate of drugs (Williams 2003).
e. **Adhesive:** Adhesive should enable the transdermal system to easily adhere to the skin and should not be irritant/allergen for skin. Generally, pressure-sensitive adhesives are used in transdermal systems. Commonly used pressure-sensitive adhesives are collected under 3 classes as a) acylates, b) polyisobutilene adhesives and c) polysiloxan adhesives (Williams 2003).
f. **Backing layer:** It protects the system from external effects during administration and ensures integrity of the system in the storage period. For this purpose, the materials impermeable for drug molecule are used as backing layer. The backing layer must be inert and not compatible with the drug and other substances used in the formulation. Generally, ethylene vinyl acetate, polyethylene, polypropylene, polyvinylidene chloride and polyurethane are used as backing layer (Williams 2003).
g. **Release liner:** This is the part which protects the formulation from external environment and which is removed before the system is adhered to skin. Ethylene vinyl acetate, aluminum foil or paper can be used. Ideally, it should be easily peeled from the adhesive layer and should not damage the structure of adhesive layer. Also, silicone, fluorosilicone, perfluorocarbon polymers can be used (Williams 2003).
h. **Solvents, penetration enhancers:** Various solvents are used to solve or disperse the polymer and adhesive or drug used in preparation of the transdermal systems. Among those, chloroform, methanol, acetone, isopropanol and dichloromethane are used frequently. Also, various penetration enhancer substances are added to the formulations to increase permeation from skin of the drug. Terpenes, fatty acids, water, ethanol, glycols, surface-effective substances, azone, dimethyl sulfoxide are widely used in the transdermal formulations as permeation enhancer (Williams 2003).
i. **Plasticizers:** In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility (Williams 2003).

3. Plasticizers

Plasticizers are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material (Bharkatiya et al, 2010; Felton, 2007; Gooch, 2010; Meier et al., 2004).

3.1 The role of plasticizers in pharmaceutical formulations

The main reasons of adding plasticizers to polymers, improving flexibility and processability are counted (Harper, 2006; Höfer & Hinrichs, 2010; Rahman & Brazel, 2004; Whelan, 1994). Upon addition of plasticizer, flexibilities of polymer macromolecules or

macromolecular segments increase as a result of loosening of tightness of intermolecular forces (Bergo & Sobral, 2007; Höfer & Hinrichs, 2010).

The plasticizers with lower molecular weight have more molecules per unit weight compared to the plasticizers with higher molecular weight. These molecules can more easily penetrate between the polymer chains of the film forming agent and can interact with the specific functional groups of the polymer (Gal & Nussinovitch, 2009).

By adding plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase, on the other hand tensile stress, hardness, electrostatic chargeability, Youngs modulus and glass transition temperature are expected to decrease (Gal & Nussinovitch, 2009; Harper, 2006; Rahman & Brazel, 2004).

Plasticizers with low molecular weight, act by reducing the secondary bonds (e.g. hydrogen bond) of the polymer chains and themselves forming secondary bonds (Gal & Nussinovitch, 2009). While low molecular weight improves miscibility with the polymer, the second factor increasing the compatibility is the realization of strong mutual hydrogen bonding (Harper, 2006). Thus, weakening of interaction of the polymer chains decrease tensile strength and glass transition temperature and so the flexibility of polymer films increases (Felton, 2007; Rahman & Brazel, 2004).

3.2 Classification of plasticizers

Several substances, including water, can be used to plasticize the polymer. It is reported that, phthalate, sebacate and citrate esters are among the most commonly used plasticizers (Felton, 2007). Compatibility, general structure (being a monomeric or polymeric), functions and chemical structure are taken into account in classifying the plasticizer substances (Gooch, 2010).

Most used group of the plasticizer substances is the phthalic acid esters which have firstly put into use in 1920. Dioctyl-phthalate is the most commonly used phthalic acid ester and it constitutes 50% of the world's plasticizer consumption (Höfer & Hinrichs, 2010).

Aliphatic ester plasticizers are derived from esterification of adipic, sebacic and azelaic acids with linear or branched monofunctional alcohols of short or medium length of chain (e.g. dioctyladipate and dibutylsebacate). Adipate, azelate and sebacate plasticizers are distinguished from other groups by their low viscosity. They give flexibility to the polymers they are used together at low temperatures (Harper, 2006; Höfer & Hinrichs, 2010; Rahman & Brazel, 2004).

Phosphate esters and various glycol derivatives such as propylene glycol and polyethylene glycol are also employed to plastify the polymeric films (Felton, 2007; Harper, 2006; Meier et al., 2004; Rahman & Brazel, 2004).

It has been reported that, surfactants, preservatives and other compounds also function as plasticizer agent together with cellulosic and acrylic polymers (Felton, 2007).

3.3 Properties of plasticizers

A plasticizer is firstly expected to be compatible with the polymer substance. This means that, it can fully mix with the polymer and can remain permanently in the polymer.

Tendency to migration, exudation, evaporation or volatilization of the plasticizers employed in a polymeric system must be low (Felton, 2007; Harper, 2006).

Other properties expected from an ideal plasticizer are its workability, its ability to provide desired thermal-electrical and mechanical characteristics to the end product, its durability at high and low temperature values, its being effective over a wide temperature range and not being affected by ultraviolet radiation, its cost being low and its conformance to the health and safety arrangements (Rahman & Brazel, 2004).

3.4 Effectiveness of plasticizers

While some of approximately 600 commercial plasticizers are very effective in softening the polymers, the others do not exhibit efficiency in this area and are used for different purposes (Harper, 2006). To exhibit efficiency, the plasticizer should be able to transit from solvent phase to polymer phase and then it can diffuse into polymer and disrupt the intermolecular interactions (Felton, 2007).

Three factors determine the effectiveness of a plasticizer to be used with polymers (Harper, 2006):

1. A flexible plasticizer molecule with long $(CH_2)_n$ chains is more effective in increasing the polymer flexibility.
2. Low polarity and hydrogen bonding cause decrease in the interaction between the polymer and the plasticizer (borderline compatibility).
3. The plasticizers with low molecular weight are more active and they increase the flexibility more.

The forces affecting the polymer-plasticizer mixtures are identified as hydrogen bonds, dipole-dipole interactions and dispersion forces. The methods used in measuring the extent of polymer plasticizer interaction can be listed as follows (Felton, 2007):

- Torsion braid pendulum
- Vapor pressure depression
- Osmotic pressure
- Swelling tests
- Gas-liquid chromatography
- Viscometry
- Melting point depression
- Nuclear magnetic resonance (NMR) Spectroscopy
- Fourier Transform Infrared (FTIR) Spectrometry

Plasticizers are generally compared with a plasticizer with well known characteristics such as dioctylphthalate. A characteristic such as modulus or hardness is chosen and a value for this characteristic is determined. The ratio of plasticizer concentrations (test/dioctylphthalate) required to achieve this value is defined as the effectiveness of the plasticizer (Whelan, 1994). The effectiveness can also be measured by graphing the modulus versus plasticizer concentration and the graphs of various plasticizers can be compared (Harper, 2006). Most commonly used methods in measuring the effectiveness of the

plasticizer are DSC analyses and the decrease in glass transition temperature when plasticizer is added to polymer (Felton, 2007; Zhu et al., 2002).

In pharmaceutical formulations, effectiveness of a plasticizer agent substantially depends on its amount added to the formulation and on the polymer-plasticizer interaction. When an aqueous dispersion is in question, the proportion and amount of partition was found to be dependent on the solubility of the plasticizer in water and its affinity to the polymer phase. When water-insoluble plasticizers will be dispersed in an aqueous medium, they should firstly be emulsified and then added to the polymer (Felton, 2007).

4. Plasticizers in transdermal drug delivery systems

Many of the polymers used in pharmaceutical formulations are brittle and require the addition of a plasticizer into the formulation. Plasticizers are added to pharmaceutical polymers intending to ease the thermal workability, modifying the drug release from polymeric systems and improving the mechanical properties and surface properties of the dosage form (Felton, 2007; Lin et al., 2000; Wang et al., 1997; Wu & McGinity, 1999; Zhu et al., 2002).

The plasticizers used in pharmaceutical formulations present a) in coating material of solid dosage forms, and b) in transdermal therapeutic systems. The list of frequently used plasticizers in pharmaceutical formulations is given below (Table 1) (Wypch, 2004).

Group	**Hydrophilic/Lipophilic**	**Plasticizer**
Glycerol and esters	Hydrophilic	Glycerine, Glycerine triacetate, Glyceryltributyrate
Glycol derivatives	Hydrophilic	Propylene glycol, Poliethylene glycol
Phthalic acid esters	Lipophilic	Dibutyl phthalate, Diethyl phthalate
Sebacic acid esters	Lipophilic	Dibutyl sebacate, Diethyl sebacate
Oleic acid esters	Hydrophilic	Oleil oleate
Sugar alcohols	Hydrophilic	Sorbitol
Citric acid esters	Hydrophilic	Triethyl citrate, Tributhyl citrate
Tartaric acid esters	Lipophilic	Diethyl tartarate

Table 1. Plasticizers Used in the Pharmaceutical Formulations (Wypch, 2004).

It is observed that the plasticizers added to transdermal therapeutic systems are mostly used in the proportions between 5-20%. The chemical formulas of 6 plasticizers frequently used in transdermal drug delivery studies are given in Table 2.

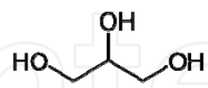
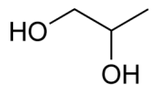
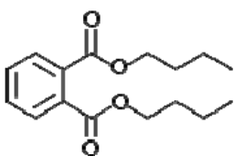
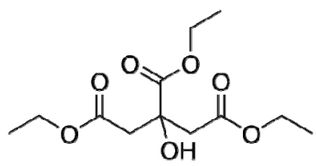
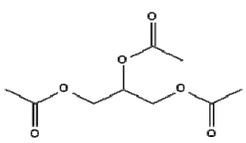
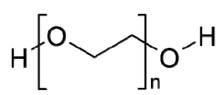
 Glycerine	 Propylene Glycol
 Dibutyl Phtalate	 Triethyl citrate
 Triacetin	 Polyethylene Glycol

Table 2. The chemical formulas of the frequently used plasticizers in transdermal formulations.

Among the plasticizers commonly used in the formulation of transdermal films, there are the phthalate and citrate esters and glycol derivatives (Gal & Nussinovitch, 2009). The plasticizers used in the studies conducted through last 20 years, their proportions and the polymers they are used with are given as a table (Table 3).

Following are the reasons which can be counted among those for adding plasticizers to the polymer films to be used in transdermal drug delivery systems:

- Reducing the brittleness
- Improving flow
- Ensuring flexibility
- Enhancing the resistance and tear strength of the polymer film (Bergo & Sobral, 2007; Felton, 2007; Rao & Diwan, 1997).

Plasticizer	% w/w	Polymer	Type of Transdermal Formulation	Reference
Triacetin	1.43-5.48	Eudragit E 100	Drug free film	Lin et al., 1991
Sorbitol Sucrose	20	Polyvinyl Alcohol: Chitosan	Drug free film	Arvanitoyannis et al., 1997
Dibutyl phthalate Propylene glycol Polyethylene glycol 600	40	Cellulose acetate	Drug free film	Rao & Diwan, 1997
Polyethylene glycol 3350	5	Hydroxypropylcellulose Hydroxypropylcellulose: Eudragit E 100 Hydroxypropylcellulose: Carbopol 971P Hydroxypropylcellulose: Polycarbophil	Matrix	Repka & McGinity, 2001
Polyethylene glycol 600	10-50	Cellulose Acetate	Membrane	Wang et al., 2002
Triethyl citrate Dibutyl phthalate	10	Eudragit E 100	Matrix	Gondaliya & Pundarikakshudu, 2003
Glycerine	4	Polyvinyl Alcohol 72000	Matrix	Padula et al., 2003
Polyethylene glycol 400	40	Carboxymethyl Guar	Matrix	Murthy et al., 2004
Dibutyl phthalate	30	Ethyl cellulose Polyvinylpyrrolidone	Matrix	Amnuaikit et al., 2005
Dibutyl phthalate	20	Ethyl cellulose: Polyvinylpyrrolidone Eudragit: Polyvinylpyrrolidone	Matrix	Mukherjee et al., 2005
Sorbitol Solution (70%)	2	Polyvinyl Alcohol	Matrix	Nicoli et al., 2005
Sorbitol Solution (70%)	4	Polyvinyl Alcohol 83400	Matrix	Femenia-Font et al., 2006
Sorbitol Solution (70%)	4	Polyvinyl Alcohol	Matrix	Nicoli et al., 2006
Dibutyl phthalate	30	Ethylcellulose: Polyvinylpyrrolidone	Matrix	Dey et al., 2007
Dibutyl phthalate Propylene Glycol	20	Polyvinyl Alcohol Xanthan Gum	Matrix	Kumar et al., 2007
Triethyl citrate	6	Hydroxypropylcellulose Eudragit RL PO Silicon Gum Acrylate copolymer	Film forming polymeric solution	Schroeder et al., 2007,a

Plasticizer	% w/w	Polymer	Type of Transdermal Formulation	Reference
Triethyl citrate Triacetin Dibutyl phthalate	1-6 2.1 4	Eudragit RL PO, E100, S100 and NE 40D Polyvinylpyrrolidone Hydroxypropylcellulose Acrylate copolymer Acrylate/Octylacrylamide copolymer Silicon Gum Polyvinyl Alcohol Polyisobutylene	Film forming polymeric solution	Schroeder et al., 2007, b
Tributyl citrate Triacetin	25-125	Eudragit NE40D	Matrix	Cilurzo et al., 2008
Propylene glycol	10	Pectin	Matrix	Güngör et al., 2008
Triacetin	20	Eudragit E 100: Eudragit NE40D	Matrix	Inal et al., 2008
Dibutyl phthalate Triethyl citrate	30	Hydroxypropyl methyl cellulose:Ethyl cellulose	Matrix	Limpongsa & Umprayn, 2008
Glycerin Polyethylene glycol 400 Propylene Glycol	20, 40	Polyvinyl Alcohol Polyvinylpyrrolidone	Matrix	Barhate et al., 2009
Triacetin	10-45	Eudragit E 100	Matrix	Elgindy & Samy, 2009
Glycerin Polyethylene glycol 200 Polyethylene glycol 400	10	Polyvinyl Alcohol : Polyvinylpyrrolidone	Matrix	Gal & Nussinovitch, 2009
Propylene Glycol Dibutyl phthalate	30 30	Polyvinyl Alcohol: Polyvinylpyrrolidone Ethyl cellulose: Polyvinylpyrrolidone	Matrix	Jadhav et al., 2009
Propylene Glycol Polyethylene glycol 400	5, 10	Eudragit L100 Eudragit L100-55 Eudragit S100	Matrix	Marzouk et al., 2009
Propylene Glycol	20, 30,40	Hydroxypropyl methyl cellulose Ethyl cellulose Carboxy methyl cellulose	Matrix	Pandit et al., 2009
Dibutyl phthalate	30	Ethyl cellulose: Polyvinylpyrrolidone Ethyl cellulose: Hydroxypropyl methyl cellulose	Matrix	Bagchi & Kumar Dey, 2010

Plasticizer	% w/w	Polymer	Type of Transdermal Formulation	Reference
Dibutyl phthalate Propylene Glycol Polyethylene glycol 400	40	Cellulose acetate Hydroxypropyl methyl cellulose Polyvinylpyrrolidone Polyethylene glycol 4000 Eudragit RL 100-RS 100	Matrix	Bharkatiya et al., 2010
Propylene Glycol	15	Hydroxypropyl methyl cellulose E15: Eudragit RS 100 Hydroxypropyl methyl cellulose E15: Eudragit RL 100	Matrix	Karunakar et al., 2010
Propylene Glycol	20	Hydroxypropyl methyl cellulose Eudragit RL 100	Bilayered Matrix	Madishetti et al., 2010
Propylene Glycol	20	Eudragit RL 100 Hydroxypropyl methyl cellulose	Matrix	Mamatha et al., 2010
Polyethylene glycol 400 Dibutyl phthalate Glycerin	15, 30,40	Gum Copal	Matrix	Mundada & Avari, 2010
Sorbitol Glycerin	4	Polyvinyl Alcohol 29, 83,115	Matrix	Padula et al., 2010
Dibutyl phthalate Dibutilsebacate	5, 10	Eudragit E100 Polyvinylpyrrolidone	Matrix	Rajabalaya et al., 2010
Dibutyl phthalate	5-25	Eudragit RS 100, Eudragit RL 100, Polyvinylpyrrolidone	Matrix	Rajan et al., 2010
Triethyl citrate	5	Hydroxypropyl methyl cellulose, Eudragit RL 100, Chitosan	Matrix	Shinde et al., 2010
Polyethylene glycol 400	5, 10	Eudragit RL 100 Eudragit RS 100	Matrix	Amgoakar et al., 2011
Glycerin	10	Polyvinyl Alcohol Polyvinylpyrrolidone Trimethoxysilane	Matrix	Guo et al., 2011
Glycerin	10, 20, 30	Hydroxypropyl methyl cellulose Polyvinylpyrrolidone Eudragit RS100	Matrix	Irfani et al., 2011
Glycerin	5	Polyvinyl Alcohol:Eudragit L30D55	Matrix	Nesseem et al., 2011
Dibutyl phthalate	10	Ethyl cellulose Hydroxypropyl methyl cellulose	Matrix	Parthasaraty et al., 2011

Table 3. The plasticizers used in the transdermal studies conducted through last 20 years, their proportions and the polymers they are used with.

The selection of plasticizers depends on the characteristics of polymer used to prepare transdermal formulation. When the composition of transdermal film/patch formulations in the patents was looked over, it was seen that polyvalent alcohols *e.g.* glycerin and 1,2 propandiol (propylene glycol) are generally used as plasticizers to softening the polymers in the formulation (Deurer et.al. 1999; Herrmann & Hille, 1999; Selzer 2001; Selzer, 2004). Higher alcohols such dodecanol, or mineral oil, silicone oil, isopropyl myristate; isopropyl palmitate; polyethylene glycol 400; diethyl sebacate and/or dibutyl sebacate; hydrocarbons, alcohols, carboxylic acids and derivatives thereof were also added into transdermal formulations as plasticizer (Petereit et.al. 2005; Salman & Teutsch 2011; Selzer, 2001).

Without a plasticizer, a very hard but brittle film is obtained. This means that, external forces such as bending, stretching and stripping from surface will cause tearing of the film without too much effort. However, when transdermal patches are in question, rather than reduction in the hardness of the patch, its endurance when positioned or repositioned on the skin is important (Gal & Nussinovitch, 2009).

In studying the mechanical properties of transdermal patches or films, tensile testing is the primarily interested subject. Tensile tests enable to study the mechanical properties of the formulation such as stress strain curves and stress at failure. These properties provide information about the resistance to damage during storage and usage. The effect of the type and proportion of the plasticizer in a formulation on the mechanical properties can also be understood by this way (Gal & Nussinovitch, 2009; Rajabalaya et al., 2010).

The tensile strength of the transdermal films varies with the type of the polymer and plasticizer used. Generally a soft and weak polymer is identified with low tensile strength and low elongation values, a hard and brittle polymer is identified with moderate tensile strength and low elongation values and a soft and tough polymer is identified with high tensile strength and high elongation values (Bharkatiya et al., 2010).

Barhate et al. have prepared matrix type transdermal patches using polyvinyl alcohol and polyvinyl pyrolidone as polymer and using glycerin, polyethylene glycol 400 and propylene glycol in proportions 20% and 40% as plasticizer and studied carvedilol permeation from these patches. Plasticizers used have ethylene oxide groups and display their effects thanks to the hydrogen bonds they form with polymer molecules. This interaction gives flexibility to the polymer. Tensile strength measures the ability to patch to withstand rupture. In the formulations prepared, highest tensile strength has obtained when glycerine was used as plasticizer. On the other hand, it was determined that in vitro permeation of carvedilol increased when polyethylene glycol 400 was used (Barhate et al., 2009).

Drug free polymeric patches have been prepared using various polymers (Eudragit, hydroxypropylmethyl cellulose, cellulose acetate, polyvinyl pyrolidone and polyethylene glycol 4000) and effect of various plasticizers on mechanical and physicochemical properties of the patches have been investigated. Polyethylene glycol 400, dibutyl phthalate and propylene glycol were used as plasticizer in proportion of 40% (w/w) of the weight of the dry polymer. Tensile strength and folding endurance properties of the patches prepared with dibutyl phthalate have been found higher compared to those prepared with propylene glycol and polyethylene glycol 400 (Bharkatiya et al., 2010).

In a study conducted with cellulose acetate transdermal films, it has been determined that when dibutyl phthalate and polyethylene glycol 600 have been used as plasticizer, the transparency of the films were not differing from the films not containing plasticizer, on the other hand, when propylene glycol has been used, it created a light opaqueness. Besides, the flexibility of the films plasticized with 40% plasticizer has been determined to be much better than unplasticized films and they could be removed without rupture from the surface they were adhered to (Rao & Diwan, 1997).

In a study where polyvinyl alcohol and polyvinyl alcohol-Xanthan gum mixture has been used as polymer, propylene glycol and dibutyl phthalate have been chosen as plasticizer. It has been observed that, addition of xanthan gum and dibutyl phthalate to the films prepared with only polyvinyl alcohol decreases the tensile strength and increases the percentage elongation. On the other hand, in polyvinyl alcohol films prepared with propylene glycol, tensile strength has been found higher. Besides, in vitro release of the terbutaline sulphate, which is an active substance, has been found higher in the propylene glycol containing films (Kumar et al., 2007).

Eudragit E 100, is a good polymer candidate in preparing transparent and self-adhesive transdermal films. However, its mechanical properties should be enhanced by adding a plasticizer. In a study evaluating drug free Eudragit E 100 films, it has been observed that elongation value of the films has increased depending on the increase of concentration of plasticizer. Triacetin used as plasticizer in combination with a cohesion promoter, succinic acid. It is thought that, the plasticizer ensures this effect with lubrication of the polymer chains. Differential Scanning Calorimetry (DSC) analyses have shown that, the crystallinity was decreased in plasticized Eudragit E 100 films when compared with those not plasticized. Increase in the mobility of the polymer chains and corresponding decrease in the crystallized area existing within the polymer are expected to enhance the active substance permeation. It has been concluded that, best cohesion promoter-plasticizer combination for Eudragit E 100 films was 7% succinic acid and 25% or 45% triacetine (Elgindy & Samy, 2009).

Although triacetin is considered as a good plasticizer for Eudragit E transdermal films, it has been determined that, addition of a secondary plasticizer such as polyethylene glycol 200, propylene glycol, diethyl phthalate or oleic acid to the system positively affects the transparency, flexibility and adhesive properties of the film (Lin et al., 1991).

Addition of plasticizer to the transdermal therapeutic systems may exhibit a facilitating effect in adhesion of the film to the other surfaces or membranes, by affecting the adhesiveness of the system (Gal & Nussinovitch, 2009; Rao & Diwan, 1997). Again in transdermal systems, humidity content and water absorption capacity of the system are measured and effect of the plasticizers on these values is researched (Rajabalaya et al., 2010). Water vapor transmission rate is closely related with the permeability characteristics of the transdermal films and can change according to the plasticizer and polymer type used (Bharkatiya et al, 2010).

It has been reported that, the plasticizers such as glycerine, sorbitol and polyethylene glycol can change release rate of the therapeutic components contained in the formula of transdermal drug delivery systems. Release rate of the drug can be adjusted by changing the type and concentration of the plasticizer (Lin et al., 2000; Wypch, 2004). Also it has been

found that, the effect of the plasticizer on drug transport is related to the physicochemical properties of the permeant, in particular to its solubility in the plasticizer (Padula et al., 2010).

In transition studies conducted with diltiazem hydrochloride and indomethacine, diffusion of the drug has been found as the films plasticized with polyethylene glycol 600 > dibutyl phthalate > propylene glycol, in order. It has been concluded that, permeation of the drugs and mechanical properties of the film were affected by the choice of suitable plasticizer and its concentration (Rao and Diwan, 1997).

In their study, Amgokar and coworkers have prepared transdermal films of budesonide. In the films, Eudragit RL 100: Eudragit RS and ethylcellulose-polyvinylpyrolidone (in proportions of 7:3 and 7:2, respectively) have been used as polymers and polyethylene glycol 400 has taken place as plasticizer. While drug release has found proportional to the polymer concentration, increase in the plasticizer amount has caused an increase in the weight of the film. It has also been observed that, increase in the plasticizer amount has also increased the humidity absorption of the transdermal films. It has been reported that, permeation of budesonide was the highest when polyethylene glycol 400 has been used in proportion of 10% (Amgaokar et al., 2011).

Irfani and coworkers have used different combinations of hydoxypropyl methylcellulose, Eudragit RS 100 and polyvinylpyrolidone, when preparing transdermal films of the active substance, valsartan. In the formulations, different proportions (10%, 20% and 30%) of glycerin have been tried as plasticizer. It has been found that, increasing plasticizer concentration was increasing the diffusion rate of the active substance. Besides, when also the polymer combination of Eudragit RS and hydroxypropyl methylcellulose has been used with 30% glycerine, an increase in the diffusion rate of valsartan has been determined (Irfani et al., 2011).

In a study, effects of two plasticizers, dibutyl phthalate and dibutyl sebacate, on the mechanical properties of the transdermal films prepared with Eudragit 100-polyvinylpyrolidone polymer mixture have been researched. It was shown that tensile strength was gradually decreased as the plasticizer concentration in the patch increased. It can be concluded from this result that plasticizer molecules disrupt the inter-chain cohesive forces of the polymer. Dibutyl phthalate and dibutyl sebacate have affected the mechanical properties of the transdermal system similarly. The finding that dibutyl sebacate is a suitable plasticizer for a more rapid release has been found in conformance with the finding of Siepmann and colleagues stating that dibutyl sebacate ensures faster release, whereas plasticizers containing phthalate group should be preferred when extended effect is required (Rajabalaya et al., 2010; Siepmann et al., 1999).

In the study where Gum copal has been used as polymer, hydrophobic dibutyl phthalate and hydrophilic glycerin and polyethylene glycol 400 have been preferred as plasticizer. It has been observed that, the films prepared by using dibutyl phthalate were more homogeneous and clear and also, their tensile strength and % elongation values have been found higher. In the study where verapamil hydrochloride has taken place as active substance, the release has realized longer and more controlled than the films containing 30% dibutyl phthalate (Mundada and Avari, 2010).

The characterization of the cellulose membranes where polyethylene glycol 600 has been used as plasticizer has been made and it has been determined that, besides the plasticizer concentration, preparation temperature was also effective on the membrane properties. It has been determined that, the membranes prepared at 40°C were more homogeneous and the diffusion of the active substance scopolamine, has realized through 3 days, controlled and constant, from the membranes containing 10% or 20% polyethylene glycol 600. It has been reported that, in order to improve the mechanical properties of the cellulose acetate membranes and to enable the linear release of the active substance, polyethylene glycol concentration should be optimized (Wang et al., 2002)

5. Conclusion

There are several considerations in the optimization of a transdermal drug delivery system. The choice and design of polymers, adhesives, penetration enhancers and plasticizers in transdermal systems are crucial for drug release characteristics as well as mechanical properties of the formulation. Beside the other components of transdermal patches, plasticizers also significantly change the viscoelastic properties of the polymers. The reasons for the use of plasticizers in transdermal drug delivery systems are the improvement of film forming properties and the appearance of the film, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties. Therefore, the selection of the plasticizer type and the optimization of its concentration in the formulation should be carefully considered.

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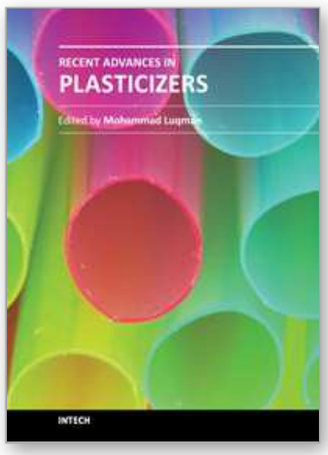

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Plasticizers are used to increase the process-ability, flexibility, and durability of the material, and of course to reduce the cost in many cases. This edition covers introduction and applications of various types of plasticizers including those based on non-toxic and highly effective pyrrolidones, and a new source of Collagen based bio-plasticizers that can be obtained from discarded materials from a natural source; Jumbo Squid (Dosidicus gigas). It covers the application of plasticizers in plastic, ion-selective electrode/electrochemical sensor, transdermal drug delivery system, pharmaceutical and environmental sectors. This book can be used as an important reference by graduate students, and researchers, scientists, engineers and industrialists in polymer, electrochemical, pharmaceutical and environmental industries.

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