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POLYMERS AND PLASTICIZERS USED IN TRANSDERMAL DRUG DELIVERY: AN OVERVIEW

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ABSTRACT

The use of polymers for skin preparations is manifold. Advances in transdermal delivery systems and the technology involved have been rapid because of the sophistication of polymer science which now allows incorporation of polymeric additives in transdermal systems in adequate quantity. Polymer selection and design are of prime importance in formulating various criteria of new transdermal systems. In this review paper, typical polymers and plasticizers in topical drug formulations and their usefulness is discussed.

KEYWORDS: Backing Membrane Polymers, Plasticizers, Transdermal System

INTRODUCTION

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics. It enables us to withstand a considerable range of environmental challenges. There are different considerations to be taken into account depending on whether the drug is to be delivered for local action or for systemic action. For a drug to be administered transdermally, it has to be very potent. To a first approximation, feasibility can be accessed from the daily dose. The second criteria, the molecules should be small, have a low melting point (good solubility properties), and have a log K_{oct} of ~ 2. Another factor that needs to be taken into consideration is the nature of the functional groups on the molecule the ionization potential, and hence pKa, of the drug. Many drugs are weak acids or bases. The skin has a surface pH of around 4 to 5 and a good buffer capacity, probably owing to the free fatty acids that make up an important component of the stratum corneum lipids. When a drug is applied to the skin surface, its ionization state could change because of the acidic environment. For a compound like nitro-glycerine, which has ideal physicochemical properties for transdermal delivery from a reasonable patch area, no more than 40 to 50 mg per day can be delivered.

COMPOSITION OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Although transdermal systems can be design as different type systems, 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

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).

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 semisynthetic polymers (e.g. cellulose derivatives) are used as polymer (Amnuaikit et al., 2005; Gungor et al., 2008; Lin et al., 1991; Nicoli et al., 2006; Schroeder et al., 2007,a).

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).

Semi Permeable (Release) Membrane

It takes place in reservoir type transdermal systems and multi-layer adhesive systems. Ethylene-vinyl acetate copolymer, silicones, high sdensity polyethylene, polyester elastomers, cellulose nitrate and cellulose acetate are used as membrane. These membranes control the release rate of drugs (Williams 2003).

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).

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). Commercially available backing materials are as given in Table 1.

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, aluminium 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, per fluorocarbon polymers can be used (Williams 2003).

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).

Plasticizers

In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility (Williams 2003).

There are chemicals known to improve diffusion through the skin. In general, these compounds have similar structures in that they possess a polar head group and a long alkyl chain. This indicates that they tend to have surface-active properties. The polarity of the head groups, however, tends to be quite low (they are not charged) and they are therefore less irritant than cationic and anionic surfactants. Compounds such as oleic acid are known to intercalate into the structured lipids of the skin (Santoro A et al., 2000). Here they reduce the diffusion resistance to permeation and aid drug transport.

Polymers used in transdermal delivery systems should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. They also should provide consistent, effective delivery of a drug throughout the product's intended shelf life or delivery period and have generally-recognized-as-safe status. From an economic point of view, a delivery tool kit rather than a single delivery tool is most effective (Davis SS *et al*., 1998). Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation (Mountain View, CA) mainly concentrates on ethylene vinyl acetate (EVA) copolymers or micro porous polypropylene, and Searle Pharmacia (Barceloneta, PR) concentrates on silicone rubber (Baker RW et al., 1989).

MATRIX FORMERS

Polymer selection and design must be considered for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin (Wolff HM et al., 2000).

A monolithic solid-state design often is preferred for passive transdermal delivery systems because of manufacturing considerations. Although polymeric matrices are used for rate control, adhesion (e.g., a PSA), or encapsulation of a drug reservoir in transdermal delivery systems discussion in this section is limited to polymers that have

been used in the design of matrices with or without rate control.

CROSS-LINKED POLY (ETHYLENE GLYCOL) (PEG) NETWORKS

The polyethylene glycols (Macrogols) are liquids over the molecular weight range 200-700. The liquid members and semisolid members of the series are hygroscopic. They are used as solvent for drugs such as hydrocortisone. The macrogols are incompatible with phenols and can reduce the antimicrobial activity of other preservatives.

Acrylic-Acid Matrices

Acrylic-acid matrices with plasticizers have been used to make drug–polymer matrix films for transdermal delivery systems. Some of the polymers that have been reported are Eudragit RL PM, Eudragit S-100, Eudragit RS PM, and Eudragit E-100 (Costa P et al., 1997). Eudragit NE-40D (a copolymer of ethyl acrylate and methyl methacrylate), a no adhesive hydrophobic polymer, also has been used as a matrix former (Minghetti P et al., 1999). The release rates of drugs from these matrix systems are more closely described by the square-root-of-time model.

Ethyl Cellulose (EC) and Polyvinylpyrrolidone (PVP)

EC and PVP matrix films with 30% dibutyl phthalate as a plasticizer have been fabricated to deliver diltiazem hydrochloride and indomethacin. The addition of hydrophilic components such as PVP to an insoluble film former such as ethyl cellulose tends to enhance its release-rate constants. This outcome can be attributed to the leaching of the soluble component, which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium. The result is higher dissolution rates. Substances such as PVP act as ant nucleating agents that retard the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilisation by penetration of the dissolution medium (Ramarao P et al., 1998).

Hydroxypropyl Methylcellulose (HPMC)

HPMC, a hydrophilic swellable polymer widely used in oral controlled drug delivery, also has been explored as a matrix former in the design of patches of propranolol hydrochloride. HPMC has been shown to yield clear films because of the adequate solubility of the drug in the polymer. Matrices of HPMC without rate-controlling membranes exhibited a burst effect during dissolution testing because the polymer was hydrated easily and swelled, leading to the fast release of the drug (Guyot M et al., 2000).

Organogels

Some non-ionic surfactants such as sorbitane monostearate, lecithin, and Tween tend to associate into reverse micelles (Florence AT et al., 1982). These surfactants in an organic solvent, upon the addition of water, undergo association reorientation to form a gel. These organogels can be used as a matrix for the transdermal delivery of drugs with greater influx (Walde P et al., 1990). Bhatnagar and Vyas proposed a reverse micelle-based microemulsion of soy lecithin in isooctane gelled with water as a vehicle for transdermal delivery of propranolol. The transdermal flux of propranolol from this organogel increased 10-fold over a vehicle composed of petrolatum (Bhatnagar S et al., 1994). Pluronic lecithin organogels also have been used as transdermal delivery systems because both hydrophobic and hydrophilic drugs can be incorporated into them. Oil-soluble drugs are miscible with the lecithin phase, and water-soluble drugs are miscible with the aqueous phase.

RATE-CONTROLLING MEMBRANES

Reservoir-type transdermal drug delivery systems contain an inert membrane enclosing an active agent that diffuses through the membrane at a finite, controllable rate. The release rate– controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid-filled microspores — in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membranes, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the membrane thickness. Hence, the choice of membrane material must conform to the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per area of the device can be controlled.

Ethyl Vinyl Acetate

EVA frequently is used to prepare rate-controlling membranes in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting the vinyl acetate content of the polymer. For example, when ethylene is copolymerized with vinyl acetate, which is not isomorphism with ethylene, the degree of crystallinity and the crystalline melting point decreases and amorphousness increases. As the solutes permeate easily through the amorphous regions, the permeability increases. The copolymerization also results in an increase in polarity. Hence, an increase in the vinyl acetate content of a copolymer leads to an increase in solubility and thus an increase in the diffusivity of polar compounds in the polymers.

Silicone Rubber

The silicone rubber group of polymers has been used in many controlled-release devices. These polymers have an outstanding combination of biocompatibility, ease of fabrication, and high permeability to many important classes of drugs, particularly steroids. The high permeability of these materials is attributed to the free rotation around the silicone rubber backbone, which leads to very low microscopic viscosities within the polymer.

Polyurethane

The commonly used polyurethanes are of the polyether type because of their high resistance to hydrolysis (Boretos JW et al., 1971), polyester polyurethanes recently have become the focus of attention because of their biodegradability (Kambe JW et al., 1999). These polyester or polyether urethanes are rubbery and relatively permeable. The hydrophilic–hydrophobic ratio in these polymers can be balanced to get the optimum permeability properties (Lyman DJ et al., 1967). Polyurethane membranes are suitable especially for hydrophilic polar compounds having low permeability through hydrophobic polymers such as silicone rubber or EVA membranes (Baker RW, 1979).

PRESSURE-SENSITIVE ADHESIVES (PSAS)

A PSA is a material that adheres with no more than applied finger pressure, is aggressively and permanently tacky, exerts a strong holding force, and should be removable from a smooth surface without leaving a residue (Pocius AV et al., 1991). Adhesion involves a liquid-like flow resulting in wetting of the skin surface upon the application of pressure, and when pressure is removed, the adhesive sets in that state. For an adhesive bond to have measurable strength, elastic energy must be stored during the bond-breaking process. Therefore, pressure-sensitive adhesion is a characteristic of a visco-elastic material. The balance of viscous flow and the amount of stored elastic energy determine the usefulness of a PSA material (Franz TJ., 1991). Acrylic-, polyisobutylene-, and silicone-based adhesives are used mostly in the design of

transdermal patches (Barnhart S et al., 1998 & Tan HS, 1999). The selection of an adhesive is based on a number of factors, including the patch design and drug formulation. For reservoir systems with a peripheral adhesive, an incidental contact between the adhesive and the drug or penetration enhancers must not cause instability of the drug, penetration enhancer, or the adhesive. In the case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive.

Polyisobutylene (PIB)

Isobutylene polymerizes in a regular head-to-tail sequence by low-temperature cationic polymerization to produce a polymer having no asymmetric carbons. The physical properties of the polymer change gradually with increasing molecular weight. Low molecular weight polymers are viscous liquids. With increasing molecular weight, the liquids become more viscous, and then change to balsam-like sticky masses and finally form elastomeric solids. PIB PSAs usually comprise a mixture of high molecular weight and low molecular weight fractions. High molecular weight PIB has a viscosity average molecular weight between 450,000 and 2,100,000, and low molecular weight. PIB has the chemical properties of a saturated hydrocarbon. It is readily soluble in nonpolar liquids. Cyclohexane is an excellent solvent, benzene is a moderate solvent, and dioxane is a nonsolvent for PIB polymers (Kruge E et al., 1991).

Polyacrylates

Polymers of this class are amorphous and are distinguished by their water-clear colour in solution and stability toward aging. Acrylic polymers are highly stable compounds. Unless they are subjected to extreme conditions, acrylic polymers are durable and degrade slowly. Oxidative degradation of acrylic polymers can occur in high-pressure and high-temperature conditions by the combination of oxygen with the free radicals generated in the polymer to form hydro peroxides (Burgess AR et al., 1952). Acrylic polymers and copolymers have a greater resistance to both acidic and alkaline hydrolysis than do poly (vinyl acetate) and vinyl acetate copolymers. In extreme conditions of acidity or alkalinity, acrylic ester polymers can be made to hydrolyze to poly (acrylic acid) or to an acidic salt and the corresponding alcohol. Acrylic polymers are insensitive to normal UV degradation because the primary UV absorption of acrylics occurs below the solar spectrum.

Silicones

Silicone PSAs comprise polymer or gum and a tackifying resin. Medical-grade silicone adhesives contain a low viscosity dimethylsiloxane polymer (Pfister W.R et al., 1989), which has a terminal silanol group. The silicone resin has a three-dimensional silicate structure that is end capped with trim ethyl siloxy groups and contains residual silanol functionality (Woodard JT et al., 1987). The adhesive is prepared by cross linking the reactants in solution by a condensation reaction between silanol groups on the linear poly (dimethylsiloxane) polymer and silicate resin to form siloxane bonds (Si-O-Si). Unlike acrylic-, rubber-, and PIB-based adhesives, medical-grade silicone adhesives do not contain organic tackifiers, stabilizers, antioxidants, plasticizers, catalysts, or other potentially toxic extractable.

Some of the silicone PSAs contains a significant degree of free silanol–functional groups. Certain amino-functional drugs can act as catalysts to cause further cross-links between these silanol groups. This unwanted reaction can be reduced, thus enhancing a PSA's chemical stability, by end capping the silanol groups with methyl groups by means of a trim ethyl silylation reaction. Some of the trace components in acrylic-adhesive blends reacted with a variety of drugs and caused colouring, which deepens with time. This problem was overcome when 2-mercaptobenzimidazole and/or

propyl gal late were incorporated into the adhesive composition (Muraoka T et al., 2000). Different polymers and plasticizers used in transdermal system are given in the Table 2.

Hot-Melt PSAs (HMPSAs)

Typical PSAs include a volatile organic solvent for reducing the viscosity of the composition to a coat able room-temperature viscosity. After the product is coated, the organic solvent is removed by evaporation. When they are heated, HMPSAs melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flawless state. HMPSAs are advantageous over solvent-based systems because they

- Do not require removal and containment of the solvents
- Do not require special precautions to avoid fire
- Are amenable to coating procedures other than those commonly used with solvent-based systems
- Are more easily coated into full thickness with minimal bubbling, which often results with solvent-containing PSAs

Of these polymers, EVA copolymers are most widely used. Polybutenes, phthalates, and tricresyl phosphate often are added as plasticizers to improve mechanical shock resistance and thermal properties. Antioxidants such as hindered phenols are added to prevent oxidation of ethylene-based hot-melt adhesives. Fillers opacify or modify an adhesive's flow characteristics and reduce the cost. Paraffin and microcrystalline wax are added to alter the surface characteristics by decreasing the surface tension and the viscosity of the melt and to increase the strength of the adhesive upon solidification. Moisture-curing urethanes have been attempted as cross-linking agents to prevent creep under the load of these thermoplastic materials. Silicone-based adhesives also are amenable to hot-melt coating.

BACKING LAYER

When designing a backing layer, the developer must give chemical resistance of the material foremost importance. Excipient compatibility also must be seriously considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug, or penetration enhancer through the layer. However, an overemphasis on the chemical resistance often may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long-term wear. The most comfortable backing may be the one that exhibits the lowest modulus or high flexibility, good oxygen transmission, and a high moisture-vapor transmission rate (36). In a novel modification to the conventional design, a patch was fabricated in which the backing itself acted as a reservoir for the drug. The upper internal portion of the drug reservoir infiltrated the porous backing and became solidified therein after being applied so that the reservoir and the backing were unified. This modification enabled the backing itself to act as a storage location for the medication-containing reservoir (Rolf D et al., 2000).

RELEASE LINER

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form delivering the active principle (Santoro A et al., 2000). However, because the liner is in intimate contact

with the delivery system, it should comply with specific requirements regarding the chemical inertness and permeation to the drug, penetration enhancer, and water. In case cross-linking is induced between the adhesive and the release liner, the force required to remove the liner will be unacceptably high (Pfister WR et al., 1990). Manufactures release liners made of fluoro polymers (Scotchpak 1022 and Scotchpak 9742, 3M Drug Delivery Systems, St. Paul, MN).

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 et al., 2007; Gooch et al., 2010; Meier et al., 2004).

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 (Table 3) present;

- in coating material of solid dosage forms, and
- In transdermal therapeutic systems.

It is observed that the plasticizers added to transdermal therapeutic systems are mostly used in the proportions between 5-20%. 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)

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).

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).

CONCLUSIONS

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.

Table 1: Commercially Available Backing Materials

Product	Polymer
CoTrans 9701	Polyurethane film
Co Trans 9706	Ethyl vinyl acetate
CoTrans 9720 CoTrans 9722	Polyethylene
Foam tape 9772L	Poly vinyl chloride foam
Foam tap 9773	Polyolefin foam
Scotchpak1006	Poly ethylene, Poly(ethylene terephthalate) (polyester), Ethyl vinyl acetate
Scotchpak 1109 Scotchpak 9723 Scotchpak 9732 & 9733	Poly ethylene, Poly(ethylene terephthalate) (polyester)

Table 2: Different Polymers and Plasticizers used in Transdermal Systems

Polymer	Plasticizer (%w/w)	Type of Transdermal System	References
PVA:Chitosan	Sorbitol (20%) Sucrose	Drug free film	Rao & Diwan 1997
PVA72000	Glycerine (4%)	Matrix	Padula et al 2003
PVA	Sorbitol solution (2%)	matrix	Nicoli et al 2005
HPMC Eudragit RLPO Silicon gum Acrylate polymer	Triethylcitrate (6%)	Film forming polymeric solution	Schroeder et al 2007a
Eudragit E100:Eudragit NE40D	Triacetin (20%)	Matrix	Lin et al 2008
HPMC:EC	Dibutyl phthalate (30%) Triethyl citrate	Matrix	Limponge et al 2008
PVA PVP	Glycerine (20%) PEG 400 (40%)	Matrix	Barhate et al 2008
Eudragit E100	Triacetin (10%) Propylene glycol	Matrix	Elgindy et al 2009
PVA:PVP EC:PVP	Propylene glycol (30%) Dibutyl phthalate (30%)	Matrix	Jadhav et al 2009
EC:PVP EC:HPMC	Dibutyl phthalate (6%)	Matrix	Bagchi et al 2010

Table 3: Plasticizers Used in Pharmaceutical Formulations (Wypch 2004)

Group	Hydrophilic(H) /Lipophilic (L)	Plasticizer
Glycerol & esters	H	Glycerine, glycerine triacetate, glyceryl tributyrate
Glycol derivatives	H	Propylene glycol, polyethylene glycol
Oleic acid esters	H	Oleil oleate
Sugar alcohol	H	Sorbitol
Citric acid esters	H	Triehtyl citrate, tributyl citrate
Phthalic acid esters	L	Dibutylphthalate, Diethylphthalate
Sebacic acid esters	L	Dibutyl sebacate, Diethyl sebacate
Tartaric acid esters	L	Diethyl tartarate

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