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A Comprehensive Review on Role of Polymers in Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug delivery system has been emerged as one of the most effective controlled drug release system in topical formulation as it doesn't undergo first pass metabolism in liver and can be directly absorbed into the systemic circulation. Polymers are used in TDDS as to increase its effectiveness in the control release of drug from the transdermal patch. Use of polymers in the TDDS has decreased the control release rate of drug from the patch. Use of polymers in combination has given more effectiveness of the drug release. This article gives a quality of information about the use of polymers in the Transdermal drug delivery system. Polymers also help in the adhesive nature of the drug to the skin and promote more extent of drug release from the dosage form. An advance in the use and amount of polymers used in the TDDS has been increased recently. This article provides the information about the use of Natural, semisynthetic and synthetic polymers in the TDDS. Use of natural polymers has been showed more impact in the TDDS and their use has showed fewer side effects like irritation, allergy, and this has been increased patient compliance and more effectiveness in drug release. Semisynthetic and synthetic polymers has been developed and used excessively in the TDDS for effective control release of the drug from the patches. A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a pre-determined dose of medication via skin with a predetermined rate of release to reach into the bloodstream.

KEYWORDS: Stratum corneum, Polymers, Controlled release, Hydrogels, TDDS.

ARTICLE DETAILS

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INTRODUCTION

A polymer is a large molecule or macromolecule composed of repeated units called monomers that are connected on to a long chain. These are back bone in pharmaceutical formulation. Polymer word derived from Greek roots –"poly" means many "mer"-parts. Polymers have very large molecular weight made up of repeating units (monomers) throughout their chain (1). Transdermal patches are rate controlled drug delivery systems designed to deliver a therapeutically effective amount of drug in systemic circulation. Polymers play a very crucial role in controlling drug release from Transdermal patch. Polymers are the back bone of TDDS.TDDS are multilayered polymeric laminates in which a drug source or matrix is placed between the polymeric layers; outer prevents loss of drug and inner polymer has adhesive to membranes of skin. The higher proportion of hydrophilic polymer in patches provides rapid release of higher percentage of drug. Transdermal drug delivery systems are prepared to deliver drugs through skin at predetermined rate escaping the first-pass effect by liver. (2) The disadvantage of oral drug delivery systems is improved by transdermal drug delivery. This gives the controlled release of the drug into the systemic circulation to target organs through the skin.

The current article assembles comprehensive information on the suitability of various types of polymers are used.

Fig 1: Transdermal patch

CLASSIFICATION OF POLYMERS

1. Based on origin of source: (4)

- Natural polymers: ex: Xanthan gum, Sodium alginate, Chitosan, Sodium CMC, Natural Rubber.
- Semi synthetic polymer: ex: HPMC [hydroxyl methyl cellulose], Ethyl cellulose,
- Synthetic polymers: ex: PVP [Poly Vinyl Pyrrolidone], PVA [Poly Vinyl Alcohol]

2. **Based on structure**

- Linear polymers
- Branched chain polymers

3. Based on molecular force

- Elastomers
- Fibers
- Thermoplastics
- Thermosetting polymers

4. **Based on mode of polymerization**

- Addition polymers
- Condensation polymers

HISTORY

- Polymers are widely used in the formulations of pharmaceuticals and health care products. The use of polymers in the medical field is not a –novelty. Natural polymers have been used as components of herbal remedies for centuries and synthetic polymer however the situation is difficult. The first work in the 1960s concentrated on using polymers as blood plasma expanders, injectable or implantable deports, and wound dressing. Helmut Ringsdorf, in 1975, proposed the first pattern for pharmacologically effective polymers. (2)
- In 1994, the first polymer- drug conjugate design to treat cancer was clinically tested it consisted on a HPMA {N-(2-hydroxy propyl meth) acrylamide} copolymer conjugate of Doxorubicin.
- In the 2000's two polymer-protein conjugates, PEG-interferon-α (an antiviral drug intended to treat chronic hepatitis C and hepatitis B) and PEG- GCSF were placed in the market and five years later the first therapeutic nanoparticles was approved as a treatment for metastatic breast cancer.(3)
- The first Transdermal drug delivery system transderm scope developed in 1980 contained the scopolamine for treatment of MOTION SICKNESS.
- Hydrogels and other polymers based carriers have been developed to provide safe passage for pharmaceuticals.

ADVANTAGES: (3, 11)

1. Controlled drug release: polymers allow for precise control over the release rate of drugs, leading to sustained and controlled therapeutic effects, reducing the need for frequent dosing.
2. Improved bioavailability: polymers can enhance the solubility and stability of poorly soluble drug, increasing their bioavailability and effectiveness.
3. Targeted delivery: polymers enable targeted drug delivery to specific cells, tissues, or organs, minimizing side effects and maximizing therapeutic outcomes.
4. Reduced toxicity: by encapsulating drugs with in polymers, the toxicity of certain drugs can be reduced, improving their safety profile.
5. Minimization of dosage frequency: extended- release polymer formulation can reduce the frequency of administration, improving patient compliance.
6. Transdermal route provides advantages like elimination of gastro intestinal absorption problems and hepatic pass effect, reduction of dose and dose interval.
7. Extends duration of activity, improved patience compliance.
8. Quick termination from the skin.
9. Topical patches are a painless, non-invasive way to deliver substances directly into the body.
10. Self-administration is possible with these systems.
11. It reduces systemic drug interactions.
12. It offers longer duration of action.

DISADVANTAGES

1. High cost: developing polymer- based formulation can be costly, especially when dealing novel polymers or complex delivery systems.
2. Complex formulation: designing polymer- based drug delivery systems can be complex and require specialized knowledge in polymer chemistry and material science.
3. Regulatory challenges: regulatory approval for novel polymer- based drug delivery system can be challenging due to concerns about safety, biocompatibility and long term effects.
4. Potential immunogenicity: some polymers especially those derived from natural sources might trigger immune responses in some individuals.
5. Variable release profiles: achieving consistent and predictable drug release rates from polymer matrixes can be challenging due to factors like polymer degradation and variability in physiological conditions.

PHYSIOLOGY OF SKIN: (19)

Skin is the most expansive and readily accesable organ of the human body. It has been used as an administration site of pharmaceutical drugs.

Transdermal delivery may be defined as the delivery of drug through intact and skin, so that the drug reaches systemic circulation.

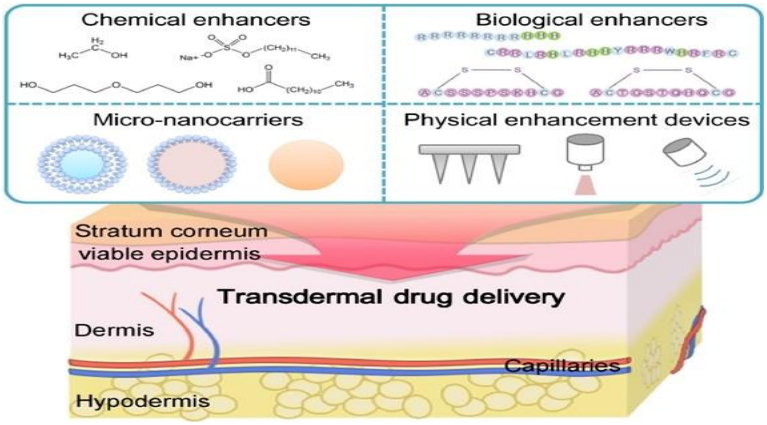

Fig 2: Structure and layers of the skin

PATHWAYS FOR TRANSDERMAL DRUG DELIVERY SYSTEM: (17).

When drugs are applied on the skin surface, drug penetration into the skin can occur in various routes like,

- Membrane penetration controlled system
- Matrix diffusion controlled systems
- Adhesive dispersion type system
- Micro reservoir type diffusion system

Drugs can enter via stratum corneum or via appendages. During penetration through the stratum corneum, two possible routes can be seen,

1. Penetration through corneocytes and Trans cellular route.
2. Penetration through along the inter cellular spaces.

Polymers Used In Transdermal Drug Delivery System (TDDS):

Natural Polymers in Transdermal Drug Delivery Systems:

Natural polymers can be used as the means of achieving predetermined rates of drug delivery. Natural polymers are basically polysaccharide, so they are biocompatible without any side effects, biodegradability and low toxicity. (9).

EX: Xanthan Gum, Sodium alginate, Chitosan, Sodium CMC, Natural rubber.

1. XANTHAN GUM: (13)

Xanthan gum is obtained from by fermentation of *Xanthomonas campetris* found in the leaves or green parts of the plant.

- It is high molecular weight polysaccharide containing sugars like d-mannose and d-glucose.
- XG has high stability in both acidic and alkaline medium.
- The rate of release of drug can be controlled by changing the pH of the release medium.
- Combining of XG with other polysaccharides increases and improves the controlled release of drugs in TDDS.
- XG has a very good muco adhesive property which is important for the formulation like TDDS.
- XG based patches shows an extended drug release of 98.65% over a period of 12 hrs.
- XG has used with the Topical nanoemulgel and formulated using clove oil, PEG-400, and tween-80 for increased bioavailability.

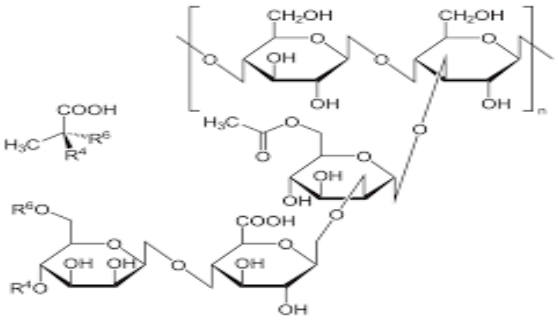

Fig 3: Structure of xanthan gum

SODIUM ALGINATE: (9-10)

Sodium alginate consists of sodium salt of Alginic acid which is a mixed of polychromic acid and composed of residues of D-mannuronic acid and L-glucoronic acid.

- The sodium alginate is a versatile functional biomaterial for increasing of viscosity, stability, and also used as matrixing [adhesive] agent in transdermal drug delivery system.
- Alginic acids and it's salt are abundantly present in brown algae{Pheophyta}
- It is haemo-compatible and does not accumulate in any organ and as it is biodegradable, there is no need for surgical removal after the drug is completed.
- Aqueous solutions of sodium alginate with concentrations ranging from [0.5% to 2.5%] can be employed for the treatment of smooth skin.
- It is used to increase blood volume and maintain blood pressure conditions in conditions like burns, blood loss and circulatory system stability.

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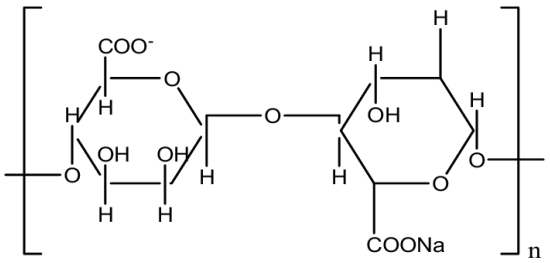

Fig 4: Structure of sodium alginate

CHITOSAN:

- Chitosan is one of the most important naturally occurring polymer, which is chemically (1, 4**)** - 2-amino -2-deoxy beta D- glycan.

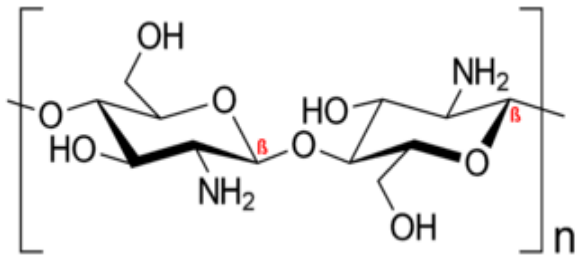

Fig 5: Structure of chitosan

- It is produced from chitin by alkaline deacetylation of chitin from the shells of crab, shrimp.
- Chitosan is widely used in transdermal drug delivery due to its variety of properties like non-cytotoxicity, biocompatibility, and non-allergic behavior.
- Chitosan greatly enhances the transport of polar drugs across epithelial surface.
- The increase in water content of the stratum corneum increases the drug permeation in chitosan, as well as in another derivative of monoclonal acetyl chitosan (MCC). This increases cell membrane fluidity and decreases cell membrane potentials.
- Chitosan, and its derivatives, have a hygroscopic and three-dimensional network structure that allows water to seep into the stratospheric corneum in a short amount of time and soak into the skin for an extended period.

NATURAL RUBBER:

- Cis 1, 4-polyisoprene, the major polymer from Natural Rubber Latex (NRL), obtained from *Hevea brasiliens* has interesting properties such as biocompatibility, high mechanical resistance capability to form a film. (13).
- The NRL from *Hevea brasiliens* has low cost and has high mechanical strength resistance. It is biocompatible material which can stimulate natural Angiogenesis and capable of adhering cell on its surface.(14)
- Natural rubber latex is a colloidal dispersion of polymer particles in a liquid. It is harvested from rubber trees by a tapping process.
- Reservoir type nicotine transdermal patches (NTP) were manufactured by heat-sealing. The nicotine solution is embedded between the backing layer and the controlling layer membrane. The goal of this study was to develop a new controlling layer membrane made from deproteinised natural rubber latex.(16)

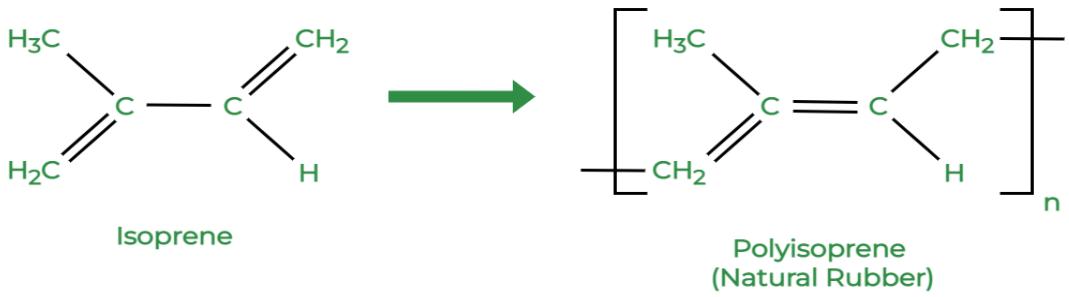

Fig 6: Structure of natural rubber

SODIUM CARBOXY METHYL CELLULOSE (SCMC): (21)

- Sodium carboxy methyl cellulose is one of the most important products of cellulose ethers which are cellulose derivatives.
- The acid form of CMC has low water solubility hence show high lipophilic and can penetrate through lipid layers.
- CMC binds to the surface of corneal epithelial cells via its glucopyranose subunits binding to glucose receptors and show the action of controlled drug delivery system as in transdermal drug delivery system.
- CMC is a penetration enhancer polymer used to enhance the penetration of drugs into the skin. The polymer plays a vital role in the drug delivery system of transdermal drugs. CMC plays a critical role in the drug release propensity of the drug from the drug delivery system. CMC is also known as non-reactive, non-toxic, biocompatible and biodegradable.(18)

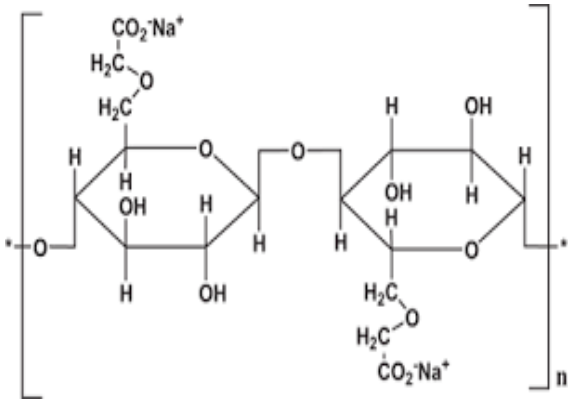

FIG 7: Structure of sodium cmc polymer.

SEMI-SYNTHETIC POLYMER USED IN TRANSDERMAL DRUG DELIVERY SYSTEM:

1. HPMC (Hydroxy Propyl Methyl Cellulose): (6)

HPMC is semi-synthetic polymer belonging to the category of hydrophilic and swelling polymer. HPMC has also been explored to fabricate a matrix type of transdermal patches. It has an extensive application in oral controlled drug delivery system. HPMC has the potential to yield clear film due to adequate solubility of polar drugs in the polymer. HPMC chain dissolution from the matrix surface involves two main steps the first step involves change in the entanglement of individual polymer chain at the matrix surface which depends on the rate of hydration. The second step; involve the diffusion of drugs molecule from the surface of the polymeric matrix structure of the bulk of medium.

Organogels and some nonionic surfactants such as Sorbitane monosterate, lecithin, and Tween80 tend to associate into reverse micelles. 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 drug with greater influx.

Organogels can cause slight disorganization of the skin an outcome that is attributing to the organic solvent that is used to make the gel. Thus organogels can enhance the permeation of various substances.

Guyotelal {2000} formulated an adhesive matrix for transdermal delivery of propanol by employing two different polymers via HPMC and poly isobutylene. Uceryl polymer, an acryline polymer was employed as an outer rate controlling membrane. Propylene glycol is used as a plasticizer was found to have a positive effect on the release rate of drug more than 70% of the initial drug load was released within the first hour ; whereas release from the coated matrices become more regular and slow .

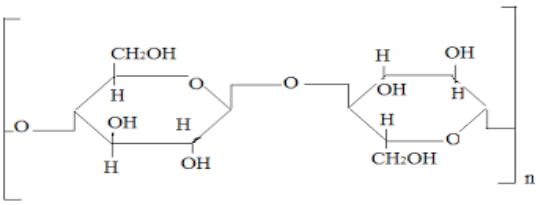

FIG 8: Stucture of HPMC

2. ETHYL CELLULOSE: (6)

EC is a water insoluble polymer used in controlled release drug forms. As it can't undergo swelling EC compatibility becomes a key factor in such systems, as release kinetics would depends largely on the porosity of the hydrophobic compound. Although EC is considered insoluble, it can take up water. This is because of its hydrogen bonding capacity with water.

Idress etal (2014) attempted to formulate a matrix patch of flubiprofen by employing EC as matrix former. Propylene glycol or di-butyl phthalate [DBP] was used as plasticizer and span 20, Tween 20, Sodium lauryl sulphate, iso propyl myristate(IPM) or ethanol were employed as permeation enhancer's. the drug release from patches followed the HIGUCHI model where maximum drug permeations from the patch containing EC as matrix forming polymer, DBP as plasticizer and IPM as penetration enhancer was found to be 903 micrograms in 48 hrs.

Mukherjee .el.al (2005) developed a suitable matrix type TDDS of dexamethasone using blends of polymeric combinations PVP and EC and Eudrgit with respectively. Therefore both the polymer combinations containing suitable plasticizer could be used for developing matrix type. TDDS exhibits controlled drug release.

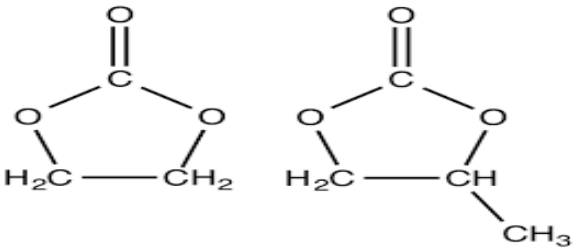

Fig 9: Structure of ethyl cellulose

Synthetic polymers in TDDS:

1. Poly Vinyl Pyrrolidone (PVP):

PVP is basically a water soluble polymer it is obtained by the polymerization reaction of monomer namely N-vinyl pyrrolidone. It is water soluble, inert, non-toxic, biocompatible and biodegradable polymer. PVP is also found to be used in transdermal patches due to its inherent film forming characteristics. However the challenges associated with the use of PVP include its inherent hydrophilicity and hygro-scopicity issues. This hygroscopic nature of PVP films exhibit high water vapors absorption which in turn leads to microbial contamination to overcome this issue and to improve the properties and performance PVP was blended with EC .It has played a pivotal role in the development of topical formulation.

The procedure uses a laser to perform photosensitive vaporization of the prostate .The PVP in EC films drug release rate increases by increasing the concentration of hydrophilic and the PVP, EC in the ratio of 2:1 the highest cumulative %of drug release of 88.35% lasting drugs.(6).

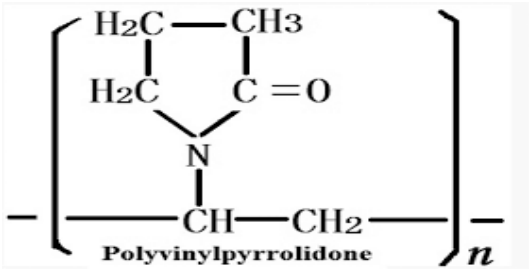

Fig 10:Structure of PVP

2. Polyvinyl alcohol(PVA): (6,20)

PVA is a color less water soluble synthetic resin employed principally in the treating of textiles and paper and the PVA solution can be gelled through repeated freezing thawing yielding highly strong. The PVA is used in a variety of medical applications.

Because of its biocompatibility low tendency for protein PVA based polymers are used widely in additive manufacturing for example 3D printed oral dosage forms demonstrate.

Skin is unaffected by PVA which is incompatible with inorganic salts it based on multi responsive hydrogel was prepared by introducing the dynamic and reversible supra molecular complexation.

Polyvinyl Alcohol (PVA) is a synthetic polymer that is bio-compatible, biodegradable, and non-toxic. It can be used as a matrix form for sustained release drug delivery systems based on hydrogel formulations. PVA is used in a variety of pharmaceutical applications, including solid, liquid or semi-solid formulation.

The PVA films with xantham gum and plasticizers had their mechanical performance tested as well when compared to polyvinyl alcohol films alone. Polyvinyl alcohol xantham gum mixes demonstrated a high rate of drugs release. Skin is unaffected by PVA which is incompatible with organic salts.

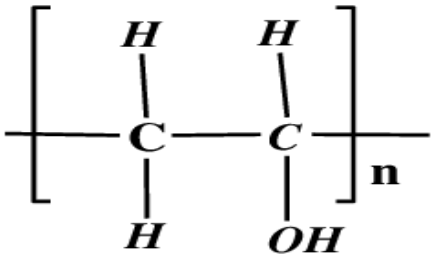

Fig 11: structure of PVA

3. CARBOPOL:

Carbopol is synthetic polymer which is widely used in TDDS and gels to enhance drug delivery efficiency. Carbopol also known as polyacrylic acid is a cross linked polymer that forms a gel like consistency when dispersed in water. One of the primary functions of Carbopol in TDDS is to act as gelling agent when incorporated into the formulation; it can increase the viscosity of the drug release. The gel forming ability of Carbopol ensures that the drug is evenly distributed within the matrix, reducing the risk of dose dumping where a large amount of drug released once. Carbopol are acrylic acid-cross-linked polymers that are either polyethylene glycol (PEG) or polyvinyl ether (PV). Carbopol have a hydrophilic structure, which makes them suitable for topical use as a gel-type formulation.

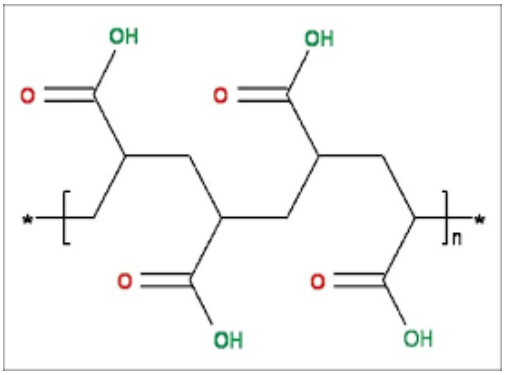

FIG 12: Structure of carbopol

CONCLUSION

Polymers are generally most important excipients in the pharmaceutical formulations Polymers are used to increase the release time and reserve time of drug in the body in transdermal drug delivery systems. The above review article gives a quality of information of different polymer used in TDDS and their effectiveness in the drug release in TDDS system. Polymer significantly shown more effectiveness in TDDS when they are used in combined with other polymers. Use of polymer in TDDS has not shown any decrease in activity and also no side effects with the drug. TDDS are the system which comes under the category of controlled drug delivery system, use of the polymer combination gives more effectiveness for the controlled release. Polymers also used as plasticizers, blends, cross linking agents in the TDDS and pharmaceutical formulation. Thus the above review article can be used as base information for the study of polymers in TDDS.

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