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# Hydrogel in Novel Drug Delivery_A Review

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**ABSTRACT**
A hydrogel is a water-insoluble three-dimensional polymer network that has the ability to absorb body fluids in a biological environment. These products constitute a group of polymeric material, the hydrophilic structure of which render them capable of holding large amount of water in their three-dimensional networks. Hydrogels now have attracted a growing interest from most of the scientists in various research fields in novel drug delivery system. Hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. Due to its structural similarity with extracellular matrix (ECM) and its ability to absorb water, hydrogen is used in various medical applications including drug delivery systems, diagnostics, tissue engineering, Cellular immobilization, optics and imaging. Hence the hydrogel biomaterial preparation techniques and properties evaluations are of extreme significance. The main objective of this article is concerned with the classification of hydrogel on different bases, properties of hydrogel and its method of preparation and the physical and chemical characteristics of the products.

**KEYWORDS:**Hydrogels, Tissue engineering, Biomaterial.

## I. INTRODUCTION

Hydrogelsare polymeric networks that have been heavily inflated with water.[1] Hydrophilic gels, also known as hydrogels, are networks of polymer chains that are sometimes found as colloidal gels that are dispersed in water.[2]

Hydrogels can absorb and retain large amounts of water. The polymeric network contains hydrophilic groups that become hydrated in aqueous environments, generating a hydrogel structure. Because of their high-water content, they have a degree of elasticity that is extremely similar to natural tissue. The hydrophilic functional group connected to the polymeric backbone gives hydrogels their ability to absorb water, while crosslinks between network chains provide them resistance to disintegration. [3,4]

Natural hydrogels have been phased out in favor of synthetic hydrogels, which have a longer service life, a higher water absorption capacity, and a higher gel strength. Synthetic polymers have a well-defined structure that can be altered to produce tail or functional degradability. If molecular entanglements and/or secondary forces such as ionic, H-bonding, or hydrophobic forces play a major part in building the network, then such hydrogels are referred to as "reversible" or "physical" gels.

Hydrogels are water-retentive carboxylic acid polymers that can hold many times their weight of water. They are carboxylic acid polymers. In water, the acid groups ionize, leaving the polymer with several negative charges running throughout the length of it.This has two effects. First one is that, the negative charges repel each other due to which polymer is forced to expand. Other one is that the negative charges attract the polar water molecules.This will increase the viscosity of the resulting mixture and the polymer chain takes up more space and resists the movement of solvent molecules around it. The polymer and the water around it are in balance, but this equilibrium may be disrupted in a variety of ways. Positive ions link themselves to the negative sites on the polymer when the ionic concentration of the solution is raised, like by adding salt. As a result, the polymer collapses in on itself once more. Adding alkali causes the point of equilibrium to shift to the right by removing the acid ions; adding acid has the reverse effect.

Hydrogels come in a variety of shapes and sizes, and they expand and contract in response to changes in pH, temperature, and ionic concentration. These properties may be fine-tuned by utilizing a blend of monomers to make the polymer.Hydrogels are being studied to learn more

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about the fundamentals of swollen polymer networks because of their ability to absorb water. They also have a wide range of applications in science and technology, including materials for protein separation and contact lenses, dies for encapsulating cells, and devices for controlled release of proteins and drugs. [5,7]

**ADVANTAGES OF HYDROGEL** [8]

- ✓ Hydrogels are biocompatible
- ✓ Modification is easy
- ✓ Hydrogels also possess good transport properties.
- ✓ Growth factors and other nutrients are released at specific times to guarantee optimal tissue growth.
- ✓ Microbial cells are entrapped within polyurethane hydrogel beads, which have a low toxicity.
- ✓ Environmentally sensitive hydrogels can detect changes in pH, temperature, or metabolite concentration and release their load as a response of the change.

**DISADVANTAGE OF HYDROGEL**[9]

- ✓ Hydrogels are expensive.
- ✓ They are non-adherent; they may need to be secured by a secondary dressing and also cause sensation felt by movement of the maggot.
- ✓ Difficult to sterilize.
- ✓ Hydrogels used as contact lenses causes lens deposition, hypoxia, dehydration and red eye reactions.
- ✓ Difficulty in handling.
- ✓ Difficulty in loading.

**CLASSIFICATION OF HYDROGEL PRODUCTS**

**I. CLASSIFICATION BASED ON SOURCE**[10,11]

- ➢ **Natural hydrogels**: These hydrogels are biodegradable, biocompatible and havegood cell adhesionbehavior. Proteins like collagen, gelatin, and lysozyme, as well as polysaccharides like hyaluronic acid, alginate, and Chitosan, are two of the most common natural polymers utilized to make natural hydrogels.
- ➢ **Synthetic hydrogels**:Synthetic hydrogels are more useful when compared to natural hydrogels because they have a much wider range of chemical and mechanical properties than their natural counter parts. Because of its non-toxicity, compatibility, and low immunogenicity, polyethylene glycol-based hydrogels are a commonly utilized material in biomedical applications.
- ➢ **Hybrid hydrogels**:These are polymer hydrogels made up of combination between natural and manmade polymers.

**II. ACCORDING TO POLYMERIC COMPOSITION**[12]

- ➢ **Homo-polymeric hydrogels**: Homo-polymeric hydrogels are referred to polymer network derived from a single species of a monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.
- ➢ **Co-polymeric hydrogels**: Co-polymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network. These hydrogels were pH and temperature sensitive, and are described for use in drug delivery.
- ➢ **Multi-polymer interpenetrating polymeric hydrogel** (IPN): An important class of hydrogels, having two independent cross-linked natural polymer or synthetic polymer component.Because of the permanent interlocking of network segments, the interpenetrating polymeric hydrogel approach can overcome thermodynamic incompatibility, allowing for minimal phase separation.

**III. ACCORDING TO THE BIODEGRADABILITY**[13]

- ➢ **Biodegradable hydrogels**

Many natural polymers, such as fibrin, Chitosan, and agar are biodegradable. Synthetic biodegradable polymers include poly (aldehyde glucoronate), poly (N-isopropyl acrylamide) and polyanhydrides.

- ➢ **Non-biodegradable hydrogels**

These hydrogels are commonly made with vinylated monomers or macromers such as 2-hydroxypropyl methacrylate, 2- hydroxyethyl methacrylate, methoxy poly (ethylene glycol) (MPEG)and acrylamide.

**IV. CLASSIFICATION BASED ON PHYSICAL APPEARANCE [**[13]

Physical appearanceof hydrogel depends on the polymerization technique involved in the preparation of hydrogel, which appearance as film, matrix, or microsphere

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## V. CLASSIFICATION ACCORDING TO NETWORK ELECTRICAL CHARGE[15]

They can be categorized into 4 groups on the basis of electrical charge onthe cross-linked chains:

- Nonionic (Neutral).
- Ionic (anionic or cationic).
- Zwitterionic (cationic or anionic group both) or polybetaines
- Amphoteric (acidic and basic group both) or Ampholytic

## VI. CLASSIFICATION BASED ON CONFIGURATION[16]

This classification is based on the chemical composition and physical structure of hydrogels, which includes;

- Amorphous (which are non-crystalline).
- Semicrystalline: A complex of amorphous and crystalline phases.
- Crystalline.

## VII. CLASSIFICATION BASED ON TYPE OF CROSS-LINKING [16]

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions. These hydrogels include

- Chemically cross-linked networks having permanent junctions.
- Physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions as hydrogen bonds, or hydrophobic interactions.

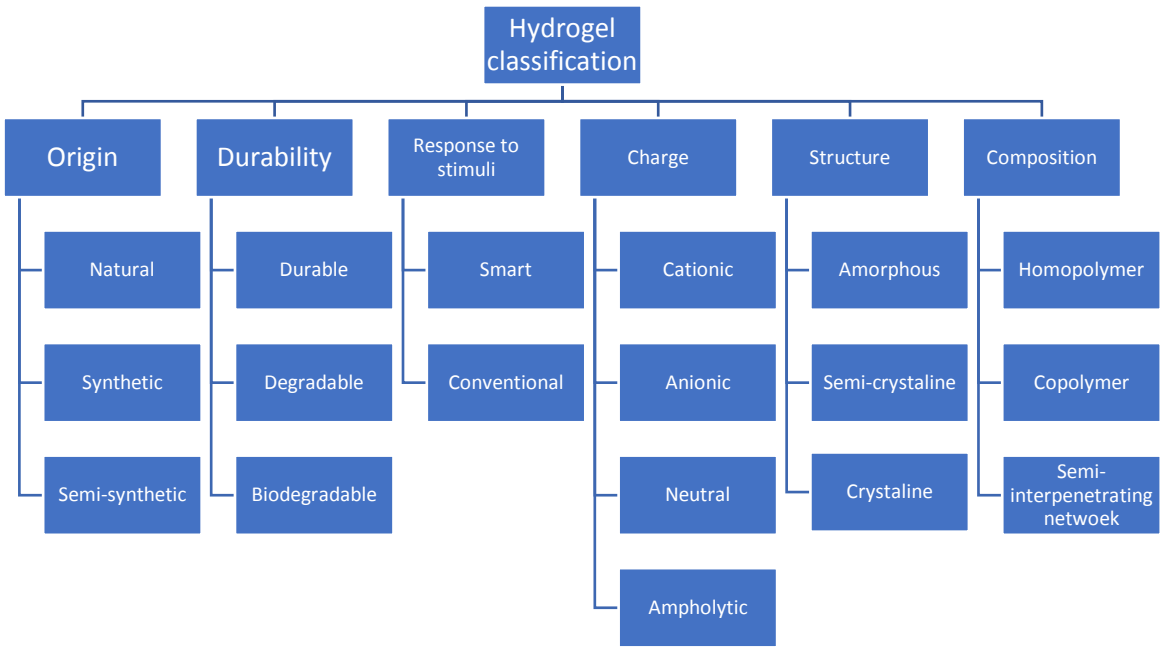


Table 1: classification of hydrogels products

## HYDROGEL PREPARATION METHODS

Hydrophilic as well as hydrophobic monomers are sometimes used in hydrogel preparation to regulate the properties for specific applications.

Several methods are utilized in formulation of hydrogels. Both synthetic and natural polymers can be used for preparation. In comparison to natural polymers, synthetic polymers are hydrophobic and chemically stronger.

Their mechanical strength results in a delayed rate of decomposition, but mechanical strength also enhances durability. In general, the integral parts of the hydrogel's formulation are monomer, initiator, and cross-linker.

The general methods toproduce physical and chemical gels are described below.

### 1. Emulsion cross-linking [1]

The ionic or neutral monomers are combined with the multifunctional crosslinking agent in solution copolymerization/crosslinking operations. UV irradiation or a redox initiator system are used to start the polymerization process. The existence of a heat sink condition in the form

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of a solvent is the primary advantage of solution polymerization versus bulk polymerization.To eliminate the monomers, oligomers, cross-linking agent, initiator, soluble and extractable polymer, and other contaminants from the produced hydrogels, by washing rinsed them with distilled water.When the amount of water used during polymerization is more than the amount of water used duringpolymerization, phase separation occurs and a heterogeneous hydrogel is created.

Rokhade APet al.,[41]formulate and evaluated hydrogel microspheres of chitosan (CS) and Pluronic F127 (PF-127) by emulsion-crosslinking method employing glutaraldehyde (GA) as a crosslinker. 5-Fluorouracil (5-FU), an anticancer drug, was encapsulated into hydrogel microspheres. Various formulations were prepared by varying the ratio of CS and PF-127, % drug loading and amount of GA. SEM showed that microspheres have smooth shiny surfaces. Encapsulation of the drug up to 86% achieved was measured by UV spectroscopy. In vitro release studies indicated the dependence of release rate on the extent of crosslinking. The release data were also fitted to an empirical equation to compute the diffusional exponent (n), which indicated that the release mechanism followed the non-Fickian trend. The formulation F12 was selected as best formulation because of maximum encapsulation efficiency

**2. Free radical polymerization**[18]

For formulation of free radical polymerization variety of monomers, such as acrylates, vinyl lactams, and amides, are used. These polymers are functionalized with radically polymerizable groups or include appropriate functional groups. The chemistry of conventional free-radical polymerizations is used in this approach, which includes phases like propagation, chain transfer, initiation, and termination. A number of thermal, ultraviolet, visible, and redox initiators can be used to generate radicals in the initiation stage, and the radicals react with the monomers to convert them to active forms.

Panda NI et al.,[42]formulated hydrogels in a specifically built jacked reaction vessel with a steady flow of nitrogen, a graft copolymer of guar gum-g-poly (acrylamide) was produced by free radical polymerization. The reaction was initiated by using Ceric ammonium nitrate (CAN). FTIR, TGA, and SEM were used to evaluate the graft copolymer. The SEM analyses revealed that the pAAm-g-GG/sodium alginate microbeads were virtually spherical in form. The largest swelling index was reported in Phosphate buffer pH 7.4 and the lowest in Phosphate buffer pH 9.2. The release of doxofylline was found to be controlled as the polyacrylamide content in the copolymer and sodium alginate content in microbeads increased, with larger release in pH 7.4 medium than in pH 1.2 media was observed.

**3.Bulk polymerization** [17]

Bulk hydrogels can be made using one or more types of monomers. The most common is vinyl monomers for hydrogel formation. For most hydrogel formulations, a small amount of cross-linking agent is used. The polymerization reaction is started by radiation, ultraviolet light, or chemical catalysts. The selection of an appropriate initiator relies upon the type of monomers and solvents being used. Rods, particles, membranes emulsions, as well as films, are all possible forms of the polymerized hydrogel through this method.

**4.Solution polymerization** [19]

The multifunctional crosslinking agent is combined with ionic or neutral monomers. UV-irradiation or a redox initiator system are used to start the polymerization. The inclusion of a solvent functioning as a heat sink is a major advantage of solution polymerization versus bulk polymerization. The soluble monomers, initiator, cross-linking agent, oligomers, extractable polymer, and other contaminants are rinsed out of the produced hydrogels using distilled water. Water–ethanol blends, water, ethanol, and benzyl alcohol were utilized as solvents.
Ahmed S et al.,[43]formulated and characterizeda topical membrane treating bacterial skin infections using chitosan-based hydrogel membranes. Modifications to the free radical solution polymerization process were used to create the polymeric membranes. Through the cross-linker N, N-methylenebisacrylamide, high molecular weight chitosan polymer was cross-linked with monomer 2-acrylamido-2-methylpropane sulfonic acid. The antibiotic mupirocin was employed as a model medication. Characterization of hydrogel membranes was performed by FTIR, SEM, DSC, TGA, swelling behavior, drug release, irritation study, and ex vivo drug permeation and deposition study. Permeation flux was up to 104.09μg $cm^{-2}$ $h^{-1.}$ And significant retention of drug in skin up to 2185μg 1.5 $cm^{-2}$.

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**5.Suspension polymerization**[20]

This approach is used to make spherical hydrogel microparticles that range in size from 1m to 1mm. The monomer solution is dispersed in non-solvent to create thin droplets that are stabilized by using stabilizer. The polymerization process is started when a free radical is thermally decomposed. Unreacted monomers, cross-linking reagent, and initiator were rinsed out of the produced microparticle.

Razzaq R et al.,[44]formulated and evaluated a series of novel pH-sensitive copolymeric butyl acrylate-co-itaconic acid (p(BA-co-IA) hydrogel microspheres using modified suspension polymerization of butyl acrylate and itaconic acid with the addition of 5% ethylene glycol dimethacrylate as a cross-linker and 1% benzoyl peroxide as an initiator. Nifedipine, an antihypertensive drug, was successfully encapsulated into these hydrogel microspheres by the equilibrium swelling method. Prepared hydrogel microsphereswere evaluated by different parameters.The percentage yield was about 72 and percentage entrapment efficiency of nifedipine was found 67. The maximum in vitro release studies of drug-loaded microspheres, which is 94.4% for the pH 7.4 buffer solution.

**6.Polymerization by irradiation** [21]

In this method initiators likeionizing high energy radiation, such as gamma rays and electron beams, have been employed to create hydrogels of unsaturated molecules. The production of radicals on the polymer chains occurs when an aqueous polymer solution is irradiated. The production of covalent bonds arises from the recombination of macro-radicals on distinct chains, resulting in the formation of a cross-linked structure.

Iqbal FM et al.,[45]formulated and evaluated hydrogel by using crosslinking polyvinyl alcohol (PVA) with 2-acrylamido-2-methyl-1-propanesulfonic acid yielded a copolymeric hydrogel product (AMPS). Microwave radiation was used to help crosslink polymers utilizing N, N′-methylenebisacrylamide (MBA) as a crosslinker and extremely small amounts of potassium persulfate (KPS) as an initiator. The prepared hydrogels were loaded with captopril and subjected to in vitro and in vivo evaluation. The crosslinking in components was confirmed by FT-IR, XRD, TGA and DSC analysis.Captopril-loaded hydrogels had their Tmax extended to 4 hours, while their Cmax was reduced to 661.853 ng/ml. The polyvinyl alcohol and AMPS polymeric hydrogels developed may be able to release captopril for a longer period of time.

**7.Grafting to support** [23]

Hydrogels made via bulk polymerization are known for having a fragile structure. A hydrogel's mechanical characteristics can be improved by grafting it onto a stronger support surface. This process requires generating free radicals on a more durable support surface and then polymerizing monomers directly onto it, resulting in a chain of monomers that are covalently bound to the support. Grafting techniques have been utilized to create hydrogels from a variety of polymeric supports. An example of this type of technique is starch grafted with acrylic acid using N-vinyl-2-pyrrolidone.

Kajjari PBet al.,[46]used the emulsion cross-linking method and glutaraldehyde (GA) as a cross-linker, acrylamide-grafted-guar gum (pAAm-g-GG) was produced and combined with chitosan (CS) to form interpenetrating polymer network (IPN) hydrogel microspheres. The microspheres encapsulated up to 74% of ciprofloxacin (CFX), an antibiotic with a plasma half-life of 4 hours, and the CFX release was extended to 12 hours. SEM showed their spherical shape with smooth surfaces, and FTIR confirmed the grafting reaction as well as the chemical stability of CFX in the blend IPN hydrogel microspheres.Invitro release data was analyzed using empirical equations, namely, Korsmeyer–Peppa's whose value ranged between 0.19 and 0.33 was observed.

## CHARACTERIZATION OF HYDROGELS

Hydrogels are characterized for their morphology, swelling property, chemical structure and elasticity

**1. pH:** [22,24]

pH of hydrogels is measured by using calibrated digital pH meter

**2. Scanning Electron Microscopy (SEM):**

The sample's composition, surface topography, and other properties such as electrical conductivity can all be determined using SEM.

**3.Spreadibility study:**[25]

The instrument used in this method consists of wooden block with a scale and two glass slides with a pan fixed on a pulley made up the equipment. Excess formulation was sandwiched between two glass slides, and a 100-gm weight was placed on the upper glass slide for 5 minutes to compare the thickness of the formulation. The time

International Journal of Pharmaceutical Research and Applications
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it took to separate the two slides was used as the spreadibility time.

S= (m × l) / t
Where S is spreadibilty,
m is weight tied on upper slide,
l is length of glass slide and
t is time taken in seconds

**4. In -Vitro drug release study:** [26]

Release studies are carried out to understand the mechanism of release over a period of application. Since hydrogels are inflated polymeric networks, the interior of which is occupied by drug molecules. The parameters are matched with the standard plot to ensure that the medication solutions are equivalent.

**5. Rheology:**[27, 28]

The viscosity of the gel formulations is determined using Brookfield viscometer with spindle no. 7 at 100 rpm at the temperature of 25°C. or by using Cone plate type viscometer under constant temperature at 4ºC.

**6. Skin irritancy test:** [29]

Rabbits are used in skin irritancy studies. Two rabbits are given the preparation, which is then covered with gauze or a bandage. The formulation is removed after 24 hours and the region is examined for evidence of edema and erythema.

(Erythema scores + edema reaction scores) / time interval = average irritation scores

**7. Drug Content Determination:**[30]

The drug concentration of Hydrogel was determined by dissolving one gramme of hydrogel formulation in 100 ml methanol, making suitable dilutions, and filtering the resultant solution through a Millipore filter (0.45 m). A UV spectrophotometer was used to detect absorbance at 296 nm (Shimadzu UV 1800). The slope and intercept derived from a linear regression study of a standard calibration curve were used to calculate drug content.

**8. Stability studies:** [29]

The hydrogel was packed in aluminum tubes (5 grams) and subjected to stability studies at 25°C/60% relative humidity (RH) and 40°C/75% RH for period of 3 months. Samples were withdrawn at time intervals of 15 days and evaluated for physical appearance, pH, rheological properties, drug content and drug release

**APPLICATIONS**

Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application. A number of strategies have been proposed to achieve drug delivery systems for efficient therapy. Hydrogels have attracted considerable attention as excellent candidates for controlled release devices, bio adhesive devices, or targetable devices of therapeutic agents.Oral, rectal, ophthalmic, epidermal, and subcutaneous applications are all possible using hydrogel-based delivery systems.

✓ **Drug delivery in the oral cavity** [31]

Hydrogels containing drug are used to deliver the drug into oral cavity for local treatment of diseases of the mouth, such as, fungal diseases, viral infections, stomatitis, periodontal disease, and oral cavity cancers

✓ **Drug delivery in the GItract [**[32, 33]

Hydrogels delivers drugs to specific site in the GIT. It is the most popular route of drug delivery because ease of administrationof drugs for compliantthерapy, and itslarge surface area for systemic absorption. Drugs can be delivered locally to specific areas in the GI tract using hydrogel-based devices. For example. Antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease.

✓ **Wound healing**[34,35]

Hydrogels which are cross linked materials, have the ability to hold water and drug in them and due to this water holding ability they can hold and retain wound exudates. Gelatin and sodium alginate-based hydrogelswhen applied havethe ability tocover and protect the wound from bacterial infection. For example, Polyvinyl pyrrolidine or polyacrylamide in the form of a gel containing 70-95% water

✓ **Rectal Delivery** [26]

Hydrogels which are having bio adhesive properties are mainly used in rectal drug delivery

✓ **Transdermal Delivery:** [37]

Hydrogels used trasdermally, exhibit various advantages, like bypassing hepatic metabolism, which improves bioavailability and medicinal efficacy. To achieve a consistent drug release, a

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transdermal drug delivery method is used. Various hydrogel-based drug delivery devices have been developed for transdermal medication delivery.

✓ **Ocular delivery:** [38]

Traditional ophthalmic preparations, such as eyedrops, are quickly excreted from the eye, and the medications delivered have little absorption, resulting in low ocular bioavailability. Whereas hydrogels control or sustain the release to minimize dosage frequency or boost drug effectiveness by localizing the drug to its site of action, lowering the dose necessary, or ensuring uniform drug delivery.

✓ **Topical drug delivery:** [40]

Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. The hydrogels have been formulated for better patient compliance having moisturizing properties therefore scaling and dryness is not expected with this drug delivery system.

## II. CONCLUSION

Controlled drug delivery and site-specific delivery have made rapid advances in drug development. Several studies indicated the usefulness of gels especially hydrogels. Hydrogels balance the drug concentration in body within therapeutic limitation for long duration. Hydrogel based delivery devices can be used for oral, ocular, epidermal, subcutaneous application due to their high-water contents and soft consistency. They resemble natural living tissue more than any other class of synthetic biomaterials and thereby are the excellent type of DDS that can be used nowadays.

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