*International Journal of Research in Engineering and Science (IJRES)*
*ISSN (Online): 2320-9364, ISSN (Print): 2320-9356*
*www.ijres.org Volume 10 Issue 6 ǁ 2022 ǁ PP. 852-857*

# A Review Study on Artificial Biological Fluids

Sumit Dahiya
*Biomedical metrological division, CSIR-National Physical Laboratory, New Delhi*

***Abstract:***
*Biological fluids, also known as bio-fluids, are crucial in our bodies because they transfer chemical compounds, hormones, medications, signaling molecules, and waste items out of the body. These artificial biological fluids have compositions that are similar to, but not identical to, those of natural biological fluids. These artificial biological fluids are not the same as the real fluids found in the human body, but they are close enough in some ways. Artificial biological fluids must be assured for a variety of objectives, including drug testing, the production of reference standards, the detection of molecules, the preparation of biosensors for detection, the impact of biological fluids on various surfaces, and so on. Artificial biological fluids are being used in a wide range of scientific, pharmaceutical, and medical studies. Artificial biological fluids are utilized for a variety of applications around the world. The main contribution of this paper is a comparison of available artificial biological fluids synthesis methods and their applications in previous research, such as artificial blood, urine, saliva, tear, and perspiration. This study will benefit the researcher in the creation of biological fluid standard materials as well as the development of newer procedures for testing biological standards.*
***Keywords**: Artificial biological fluids, artificial blood, synthetic urine, artificial Saliva.*
---------------------------------------------------------------------------------------------------------------------------------------
Date of Submission: 01-06-2022 Date of acceptance: 12-06-2022
---------------------------------------------------------------------------------------------------------------------------------------

## I. Introduction:

Biological fluids, often known as body liquid, are liquids secreted or expelled by the human body. The nature of biological fluids is complicated, with solid-like and liquid-like phases. Blood, urine, sperm, vaginal secretions, tears, sweat, saliva, synovial fluid, tissue fluid, amniotic fluid, nasal fluid, milk, and other bodily fluids are all included. The human body contains a variety of fluids or liquids, some of which are present in minute amounts while others are found in huge quantities. Total body water to body weight in a healthy adult man is approximately 60-70 % and slightly less in women (50-55 percent). The body's fluids are divided into two categories: internal fluid (28-32 liters) and extracellular fluid (10-14 liters).[1]

Artificial biological fluids are imitators of actual biological fluids, not the real thing. These fluids are created for a variety of reasons, including determining the amount of uric acid in human urine and designing biosensors for uric acid detection using fake urine. For example, fake blood can be made to detect the quantity of glucose in the blood or to assess the resistance of protective gear materials used in the testing and fabrication of PPE kits and masks. As a result, various artificial biological fluids perform various activities depending on their requirements.

The Blood, urine, saliva, tears, and other bodily fluids are the most commonly tested nowadays. There are literally dozens of elements in biological fluids that are evaluated nowadays, but the majority of laboratory tests are done on blood, which is studied both in terms of its liquid and cellular features. Today, blood components are examined for hundreds of different things. Urine and blood tests are frequently used to identify the sick organ in the body. Blood is typically found in a wide range of crimes, not just violent crimes, but also where any form of injury has happened, such as cutting on broken glass or nasal bleeds where the perpetrator has suffered from high blood pressure. This review paper comprises all the possible artificial biological fluids found in the market and their recent discoveries and their applications.

**Intended audience of the article**

The reader should have a basic understanding of biotechnology science and reference standards in order to properly comprehend the core of the review article. This article considers artificial biological fluids, advancements, and challenges that have occurred to date.

**Conceptual/Empirical/Review Article**

This is a review article since it summarises recent improvements in artificial biological fluids standards technologies that can be used as a point of reference materials. By analysing and discussing previously published studies, we recapitulate the existing understanding of the topic.

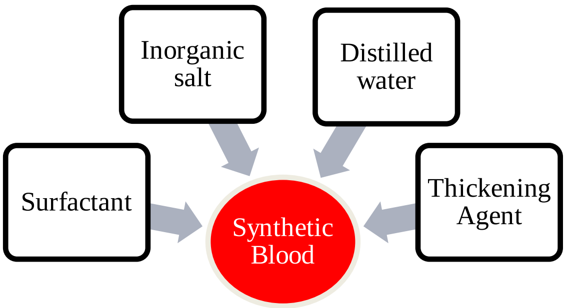
**Brief summary**

**Artificial biological fluids**

Artificial biological fluids are biological fluids that are prepared or created by man rather than by the human body. These are used all around the world for product testing and research. They're made to meet the product testing requirements of ISO, NIST, and other recognized standards bodies. Synthetic blood, artificial saliva, synthetic urine, and synthetic sweat are just a few examples.

**1. Synthetic Blood**

**Fig 1: Synthetic blood**




The cellular and non-cellular components of human blood are separated. White blood cells, red blood cells, and platelets are located in the cellular portion, while plasma is found in the non-cellular portion. It is a specific sort of connective tissue. It serves a variety of functions in our bodies. Plasma is an extracellular substance made up of water, ions, and other proteins that helps blood clot when combined with platelets. Serum, on the other hand, is a liquid that does not include any clotting agents. Plasma proteins react with oxygen and harden to stop additional bleeding. The immune system is controlled by the WBC.

Artificial blood closely resembles the blood present in the human body. The artificial blood offers the advantages of not requiring compatibility testing, being free of blood-borne pathogens, having a long shelf life, and not requiring refrigeration[2]. Surfactant, inorganic salt, thickening agent, buffering agent, and distilled water make up synthetic blood[3].

Our body's RBCs transport oxygen and carbon dioxide. The RBC in our blood contributes to the red colour of our blood. One billion red blood cells can be found in just two droplets of blood. These cells are in charge of transporting oxygen and carbon dioxide around the body. As a result, a person can only use blood that is compatible with his blood type. Synthetic blood products are now only intended to replace serum's function [4].

**Characteristics for ideal artificial blood**

First, it must be both safe and compatible with the human body. This indicates that when artificial blood is utilized, differing blood types should not matter. It also implies that artificial blood can be processed to eliminate all disease-causing factors like viruses and bacteria.

Second, it must be capable of transporting oxygen throughout the body and releasing it when and where it is required.

Third, requirement is that it be shelf stable. Artificial blood, unlike donated blood, can be preserved for up to a year. While, real blood can only be preserved only for one month.

Fourth, ideal for research and experimental work which replace the real blood. Such as the plasma property can be studies with this synthetically prepared blood.

It must be free of infections and poisons that might cause the human body's immune system to react.

The artificial blood substitutes devoted to oxygen-carrying substitutes were explored by Phioppe Schneider (1992). Artificial blood substitutes have primarily used synthetic colloids, gelatins, dextrans, and hydroxyl ethyl starches[5].

Iran's Moradi et al. (2016) investigated artificial blood substitutes as a means of ushering in a new era in transfusion. Their primary focus was on red blood cell substitutes and an evaluation of blood's oxygen-carrying capacity[6]. Kim et al. (2007) investigated the use of Poly (lactic-co-glycolic acid)(PLGA) tubes as a framework for artificial blood arteries using hybridization of smooth muscle cells and endothelial cells from canine bone marrow. These vasculature had good mechanical strength and acceptable endothelial and smooth muscle cell hybridization activity[7].

Gupta (2017), Bio-inspired Nano-medicine techniques for artificial blood synthesis were investigated. synthetic and semi- synthetic RBC substitutes for facilitating oxygen transmission, WBC substitutes, and platelet substitutes with the use of nanotechnology branch materials engineering methodologies This review study outlines a variety of methods for creating synthetic blood cells [8]. Un et al. (2019) Turkey investigated the artificial realization of natural hemoglobin molecule functions and motions in erythrocytes. Recombinant hemoglobin can be synthesized in yeast, according to studies[9].

Haldar et al. (2019), Lucknow, India, investigated artificial blood for transfusion sciences, designing blood for the transport and distribution of oxygen in the body to replace allogenic human blood transfusion[2]. Rengasamy et al. (2020), Pittsburgh, investigated the resistance of N95 filtering face piece respirators and surgical N95 respirators to synthetic blood penetration that have been approved by the National Institute for Occupational Safety and Health. N95 masks were tested at speeds of 450 and 635 cm/sec using the ASTM F1862 technique, and the results were compared against third-party lab data. Blood permeation through multiple layers of mask filters was studied. There were no test failures at any velocity, according to the results[10].

Benefits of the artificial blood in as compared to real blood in following ways[11]

A. Price: When compared to genuine blood, the price is inexpensive.

B. Availability: the item is readily available.

C. Compatibility: extremely compatible with a wide range of tests and research.

D. Shelf life: Does not require refrigeration and has a long shelf life.

E. Disease Transmission: Because it is made in a laboratory, there is little chance of disease transmission.

F. Immunological effects: There are no known immunological effects.

## II. Artificial saliva

Human saliva is a mixture of fluids generated by the parotid, submaxillary, and sublingual glands, each of which has been found to differ in content and volume[12].

Natural saliva is an important physiological liquid that is necessary for the maintenance of good oral health and the overall health of the human body. It is the site of digestion from where digestion starts and thus contributes to the supply of nutrients and health maintaining substances that the body requires. It is impossible to make a synthetic saliva formula that is exactly the same as genuine saliva[13]. Artificial saliva is employed as a wetting agent in mouth drying and for enamel development research in the construction of artificial teeth.

The following features of artificial saliva are very comparable to those of real human saliva.

1. Mineral content; in general, all products contains phosphate and calcium ions.
2. Viscosity, when compared to real human saliva, CMC (carboxymethylcellulose), mucin, and glycerin are commonly used to make saliva viscous.
3. To simulate actual saliva, the preservatives propyl paraben and methyl are utilised as preservatives
4. Mint, sorbitol, and xylito are commonly used to increase palatability.[14]

Levine et al. (1993), Development of artificial saliva for the xerostomia condition and defining the structure function relationship of salivary molecules dysfunction, oral diseases[15]. Polonczk et al. (2000) Cracow, Poland, study reviewed the use of artificial saliva for models in stomatological and bio-availability studies of biological active molecules in biological research. Research have shown that the biological active substances is not the same as in their quantity released in digestive system and basic assumption in preparing an artificial saliva is its similarity to real saliva in context of their physical characteristics and chemical structure[13].

The study by Gal et al. (2001) looked at 60 artificial salivas to see what role substances met in proposed formulae played. The buffer effect was studied, as well as the role of calcium ions, carbon dioxide gas, hydrogenocarbonates, and thiocyanates. Some in vitro behavioral experiments of dental biomaterials were examined using the SAGF medium as a reference. They were able to specify the role of fluoride ions emitted from glass ionomer cements and examine the behavior of dental amalgams thanks to this SAGE medium[12]. Amal et al. (2015) East Jawa, Indonesia, synthetic saliva was designed to mimic real saliva both chemically and physically. Studies produce the saliva substitutes that can serve as mouth and throat lubricants. Formula they selected was the most suitable due to their viscosity and pH properties which closely similar real saliva and mucin based saliva substitutes[14].

The investigations of Poland's Lysik et al. (2019) looked into the crucial aspects of manufacturing artificial saliva. The major goal was to investigate saliva's rheological and lubricating properties, as well as the antibacterial properties of commercially manufactured salivae. They investigated the development of salivary substitutes, notably in terms of antibacterial qualities, using nanotechnology [16].

Wang et al. (2011) conducted research in Hamburg on the effect of artificial saliva on the apatite structure of damaged enamel in human teeth. Scanning electron microscopy, total reflectance infrared spectroscopy, and electron probe microanalysis were used to investigate citric acid-induced alterations in the structure of enamel preserved in artificial saliva. The administration of artificial saliva for several hours leads to a partial recovery of the local structure of eroded enamel apatite, according to the findings[17].

## III. Synthetic urine

Synthetic urine is a solution of water and organic and inorganic components. It is a human pee-like substance that has the appearance, smell, and consistency of real human urine. It's made to contain realistic levels of urea, uric acid, sulphates, chlorides, phosphates, and creatinine, as well as to match the pH level of genuine urine. In terms of its contents, urine is a very rich body fluid. In the last three decades, over 2900 metabolites have been identified in urine[18]. Urine components have the potential to serve as key biomarkers and diagnostic tools for a variety of disorders.

The exact composition of urine is both costly and difficult to determine, as it varies by gender, race, food ingested, medicine taken, and activity, as well as changing throughout the day in the same individual to meet the needs of regular biological functions. Another issue is the collection and storage of data, which has been highlighted in numerous studies. The presence of communicable disease agents in urine specimens is also a risk factor that should be considered by a researcher. Because of these drawbacks, artificial urine (AU) is becoming more popular for research reasons because it is both feasible and quick to obtain. To develop comparative-controlled studies, the formulation can be simply changed. AU specimens have been investigated in a variety of studies.

Brooks et al, (1996), UK, The goal of the research was to create artificial urine medium (AUM) that was similar to those observed in human urine. The recovery of a large variety of urease favourable and unfavourable urine pathogens was made possible by AUM consolidated with agar. The results demonstrated that AUM may be used as a substitute for normal urine in a variety of tests. [19].The efficiency of magnesium ions and alloys as a class of antibacterial and biodegradable material in ureteral applications was investigated by Lock et al. (2013) of California. Over the course of a three-day incubation period in an artificial urine (AU) solution, magnesium alloys lowered E. Coli viability and colony forming units[20].

Arndt et al. (2018), In this work, researchers looked at the lengthy cytotoxicity using PLGA-b-mPEG (PLGA-PEG) polymer carriers & artificial urine (AU) against human UROtsa cells. Beneficial urothelial UROtsa cultured in RPMI 1640 medium comprising foetal bovine serum or treated with a variety of AU concentrations for 24 hours and 7 days. Cell viability was determined using the XTT technique and live/dead staining. For the first time, the impact of AU on regular cytotoxicity assays associated to biomaterials with urinary-tract applications has been discovered [21].

According to, Sarigul et al. (2019), Artificial urine was designed to replicate the urine of healthy people. Three procedures are also compared to 28 healthy people's samples. ATR-FTIR spectroscopy (attenuated total reflection-Fourier transform infrared spectroscopy) was used by the researchers. When the multi-purpose artificial urine (MP-AU) protocol was compared to the other two protocols, it came out on top. Finally, infrared spectra of nine compounds were supplied, allowing absorption bands to be assigned to specific compounds[18].

Sueksakit et al. (2021), Bangkok, explored the optimization of a synthetic urine formula for in vitro cellular studies vs genuine urine. To do so, numerous artificial urine formulae that closely resemble genuine urine have been devised. The effects of adding 0-10 percent foetal bovine serum (FBS) to the well-known AU-Siriraj regimen on MDCK renal tubular cells were investigated. When compared to total culture medium, both native urine and AU- Siriraj without/with FBS reduced the time of deformation. According to the findings, 2.5 percent FBS in AU-Siriraj can delay deformation and improve polarisation of renal tubular cells[22].

Liang et al. (2020) investigated the respiratory chain with P.aeruginosa cells grown in Luria Broth (LB) as well as modified artificial urine media. (mAUM). In both LB and mAUM, the proton-pumping NQR complex was found to be the primary NADH dehydrogenase. This study depicts that pathogen's aerobic respiratory chain in great detail, as well as the key roles of NQR with terminal oxidases in urine [23].

## IV. Artificial Tear

Artificial tears are eye drops that are used to lubricate dry eyes and keep the outer surface of your eyes wet. Age, some drugs, a medical issue, ocular problems, or environmental factors such as smoky or windy surroundings can all cause dry eyes, and these eye drops can assist. There is no particular brand that works best for all types of dry eyes. Some artificial tears accelerate eye healing while others try to prevent tear evaporation in addition to moisturising your eyes. Artificial tears with thickening agents retain the solution on your eyes' surface for longer.

Artificial tears are divided into two categories

1. Eye drops with preservatives: This type can be found in multi-dose bottles that comprise chemicals (preservatives) that inhibit bacteria from reproducing after the bottle is opened. Whether you have mild to severe dry eyes, the preservative may damage them.
2. Chemical (Preservative) free eye drops: When you use artificial tears and over four times another day or have mild to severe dry eyes, you should consider using preservative-free eye drops; this kind has fewer chemicals and is recommended. Preservative-free eye drops in single-dose vials are available[24].

Lubricating eye drops work by adding some of the same components to your tears. As a result, your tear film can better protect the surface of your eyes[25].

Bohnert et al. looked into the protein adsorption of artificial tear solutions onto contact lens materials (1988). FTIR spectroscopy was used to evaluate protein adsorption. Protein absorption through contact lens materials depends greatly just on polymer makeup, according to the research. [26]. Bernal et al. (1993) looked into the composition of artificial tears and the regeneration of injured corneal epithelium or severe dry eye syndromes[27]. In 1990, Alan Tomlinson explored the role of preservatives of artificial tear solution upon that film's lipid layer. To study the effects, the retinal evaporation rate was measured using a customized servomed evaporimeter. As per the findings, the amounts of chlorbutanol or benzalkonium chloride had no effect just on tear film lipid layer's stability. [28].

Berdy et al. (1992) investigated artificial tear preparations that were free of preservatives. Scanning electron microscopy was utilised to examine the corneal epithelium of rabbit eyes after they were given two preservative-free artificial tears-1 (Hypotears) and tear-2 ocular lubricants (Refresh). The preservation-free artificial tear solutions-1 and -2 were found to be free of the harmful effects associated with preserved solutions[29]. Margarita Calonge investigated the use of artificial tears to treat dry eyes in 2001. Punctal occlusion is the most common treatment, which prevents natural or artificial tears from emptying. They can be used to replace as well as retain tears not obviously healing the condition. Because it is believed to stop the viscous circle of irritation with cell destruction just on ocular surface with lacrimal glands, cyclosporin A has been examined inside the treatment of severe eye[30].

Pucker et al. (2016) investigated the efficacy toxicity of more than artificial tear treatments in the symptoms of dry eye condition, as well as formulations of over-the-counter artificial tears. According to the findings, and under artificial tears may help improve dry eye problems and are typically safe, although there are certain risks. [31]. Tong et al., 2017, examined artificial tear formulations for dry eye patients and identified the numerous over-the-counter treatments as well as their drawbacks[32].

## V. Conclusion

In this paper, we give an overview of the artificial biological fluids that are currently accessible as well as recent findings. We have discussed artificial saliva, synthetic blood, urine, and tears, as well as contemporary research on these artificial biological fluids. It is critical for researchers to grasp the differences between different artificial biological fluids, since this will aid in the preparation of artificial biological fluid reference standards and any drug testing study. They can be employed in a variety of fields, including medicine, pharmacy, and metrology, and additional research will help to further the creation of artificial biological fluids.

## References:


[1] C. Lote and C. Lote, *Principles of renal physiology*. 1994.

[2] R. Haldar, D. Gupta, S. Chitranshi, M. K. Singh, and S. Sachan, “Artificial Blood: A Futuristic Dimension of Modern Day Transfusion Sciences,” *Cardiovasc. Hematol. Agents Med. Chem.*, vol. 17, no. 1, pp. 11–16, Jun. 2019, doi: 10.2174/1871525717666190617120045.

[3] “ISO - ISO 16603:2004 - Clothing for protection against contact with blood and body fluids — Determination of the resistance of protective clothing materials to penetration by blood and body fluids — Test method using synthetic blood.” https://www.iso.org/standard/32247.html (accessed Feb. 15, 2022).

[4] L. de F.-M. (Buenos Aires) and undefined 1998, “SYNTHETIC BLOOD SUBSTITUTES Vasoactive properties of synthetic blood substitutes,” *medicinabuenosaires.com*, Accessed: Jan. 27, 2022. [Online]. Available: http://www.medicinabuenosaires.com/demo/revistas/vol58-98/4/syntheticblood.htm.

[5] P. Schneider, “Artificial blood substitutes,” *Transfus. Sci.*, vol. 13, no. 3, pp. 357–370, 1992, doi: 10.1016/0955-3886(92)90148-A.

[6] S. Moradi, … A. J.-N.-… I. B., and undefined 2016, “Artificial blood substitutes: first steps on the long route to clinical utility,” *journals.sagepub.com*, vol. 9, pp. 33–41, Oct. 2016, doi: 10.4137/CMBd.s38461.

[7] M. J. Kim, J. H. Kim, G. Yi, S. H. Lim, Y. S. Hong, and D. J. Chung, “In vitro and in vivo application of PLGA nanofiber for artificial blood vessel,” *Macromol. Res.*, vol. 16, no. 4, pp. 345–352, 2008, doi: 10.1007/BF03218527.

[8] A. Sen Gupta, “Bio-inspired nanomedicine strategies for artificial blood components,” *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology*, vol. 9, no. 6, Nov. 2017, doi: 10.1002/wnan.1464.

[9] K. Kobayashi, “Artificial blood,” *Nippon Geka Gakkai zasshi*, vol. 106, no. 1, pp. 31–37, 2005, doi: 10.5606/dsufnjt.2019.005.

[10] S. Rengasamy, D. Sbarra, and J. N. Ba, “Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ’ s public news and information ,” no. January, 2020.

[11] B. TSCHIRREN, “Artificial blood substitutes.,” *Schweiz. Med. Wochenschr.*, vol. 93, pp. 596–601, 1963.

[12] J. Y. Gal, Y. Fovet, and M. Adib-Yadzi, “About a synthetic saliva for in vitro studies,” *Talanta*, vol. 53, no. 6, pp. 1103–1115, 2001, doi: 10.1016/S0039-9140(00)00618-4.

[13] J. Pytko-Polonczyk, … A. J.-J. P., and undefined 2017, “Artificial saliva and its use in biological experiments,” *jpp.krakow.pl*, 2000, Accessed: Jan. 27, 2022. [Online]. Available: http://jpp.krakow.pl/journal/archive/12_17/pdf/807_12_17_article.pdf.

[14] A. Sri, S. Amal, S. Hussain, and M. Amin Jalaluddin, “Preparation of Artificial Saliva Formulation,” *Proceeding - ICB Pharma II* , no. April, p. 7, 2015.

[15] M. J. Levine, “Development of artificial salivas,” *Crit. Rev. Oral Biol. Med.*, vol. 4, no. 3–4, pp. 279–286, 1993, doi: 10.1177/10454411930040030401.

[16] D. Łysik, K. Niemirowicz-Laskowska, R. Bucki, G. Tokajuk, and J. Mystkowska, “Artificial saliva: Challenges and future perspectives for the treatment of xerostomia,” *Int. J. Mol. Sci.*, vol. 20, no. 13, 2019, doi: 10.3390/ijms20133199.

[17] X. Wang, B. Mihailova, A. Klocke, S. Heidrich, and U. Bismayer, “Effect of Artificial Saliva on the Apatite Structure of Eroded Enamel,” *Int. J. Spectrosc.*, vol. 2011, pp. 1–9, 2011, doi: 10.1155/2011/236496.

[18] N. Sarigul, F. Korkmaz, and İ. Kurultak, "A New Artificial Urine Protocol to Better Imitate Human Urine," *Sci. Rep.*, vol. 9, no. 1, Dec. 2019, doi: 10.1038/s41598-019-56693-4.

[19] T. Brooks and C. W. Keevil, "A simple artificial urine for the growth of urinary pathogens," *Lett. Appl. Microbiol.*, vol. 24, no. 3, pp. 203–206, Mar. 1997, doi: 10.1046/J.1472-765X.1997.00378.X.

[20] J. Y. Lock *et al.*, "Degradation and antibacterial properties of magnesium alloys in artificial urine for potential resorbable ureteral stent applications," *J. Biomed. Mater. Res. - Part A*, vol. 102, no. 3, pp. 781–792, Mar. 2014, doi: 10.1002/JBM.A.34741.

[21] P. Arndt, N. D. Leistner, S. Neuss, D. Kaltbeitzel, G. A. Brook, and J. Grosse, "Artificial urine and FBS supplemented media in cytocompatibility assays for PLGA-PEG-based intravesical devices using the urothelium cell line UROtsa," *J. Biomed. Mater. Res. - Part B Appl. Biomater.*, vol. 106, no. 6, pp. 2140–2147, Aug. 2018, doi: 10.1002/jbm.b.34021.

[22] K. Sueksakit and V. Thongboonkerd, "Optimization of artificial urine formula for in vitro cellular study compared with native urine," *Int. J. Med. Sci.*, vol. 18, no. 14, pp. 3271–3279, 2021, doi: 10.7150/IJMS.61720.

[23] P. Liang *et al.*, "The aerobic respiratory chain of Pseudomonas aeruginosa cultured in artificial urine media: Role of NQR and terminal oxidases," *PLoS One*, vol. 15, no. 4, Apr. 2020, doi: 10.1371/journal.pone.0231965.

[24] "Artificial tears: How to select eyedrops for dry eyes - Mayo Clinic." https://www.mayoclinic.org/diseases-conditions/dry-eyes/expert-answers/artificial-tears/faq-20058422 (accessed Feb. 14, 2022).

[25] "Lubricating Eye Drops for Dry Eyes - American Academy of Ophthalmology." https://www.aao.org/eye-health/treatments/lubricating-eye-drops (accessed Feb. 14, 2022).

[26] J. Bohnert, T. Horbett, … B. R.-… ophthalmology & visual, and undefined 1988, "Adsorption of proteins from artificial tear solutions to contact lens materials.," *researchgate.net*, Accessed: Feb. 13, 2022. [Online]. Available: https://www.researchgate.net/profile/Thomas-Horbett/publication/19813408_Adsorption_of_proteins_from_artificial_tear_solution_to_contact_lens_materials/links/00b495217729c4fa50000000/Adsorption-of-proteins-from-artificial-tear-solution-to-contact-lens-mat.

[27] D. L. Bernal and J. L. Ubels, "Artificial tear composition and promotion of recovery of the damaged corneal epithelium," *Cornea*, vol. 12, no. 2. pp. 115–120, 1993, doi: 10.1097/00003226-199303000-00004.

[28] A. Tomlinson and G. R. Trees, "Effect of preservatives in artificial tear solutions on tear film evaporation," *Ophthalmic Physiol. Opt.*, vol. 11, no. 1, pp. 48–52, 1991, doi: 10.1111/j.1475-1313.1991.tb00194.x.

[29] G. J. Berdy, M. B. Abelson, L. M. Smith, and M. A. George, "Preservative-Free Artificial Tear Preparations: Assessment of Corneal Epithelial Toxic Effects," *Arch. Ophthalmol.*, vol. 110, no. 4, pp. 528–532, 1992, doi: 10.1001/archopht.1992.01080160106043.

[30] M. Calonge, "The Treatment of Dry Eye Tear Substitution : Artificial Tear," *Surv. Ophthalmol.*, vol. 45, no. MARCH, 2001.

[31] A. Pucker, M. Marrone, and J. J. Nichols, "Over the counter (OTC) artificial tear drops for dry eye syndrome," *Cochrane Database Syst. Rev.*, no. 2, 2012, doi: 10.1002/14651858.cd009729.

[32] L. Tong, A. Petznick, S. Lee, J. T.- Cornea, and undefined 2012, "Choice of artificial tear formulation for patients with dry eye: where do we start?," *journals.lww.com*, Accessed: Feb. 13, 2022. [Online]. Available: https://journals.lww.com/corneajrnl/Fulltext/2012/11001/Choice_of_Artificial_Tear_Formulation_for_Patients.6.aspx.