Chemistry Africa (2022) 5:459–480
https://doi.org/10.1007/s42250-022-00345-0

REVIEW

Comprehensive Review on Applications of Surfactants in Vaccine Formulation, Therapeutic and Cosmetic Pharmacy and Prevention of Pulmonary Failure due to COVID-19

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Received: 19 January 2022 / Accepted: 8 March 2022 / Published online: 21 March 2022

Abstract

Our world is under serious threat of environmental degradation, climate change and in association with this the out breaks of diseases as pandemics. The devastating impact of the very recent COVID-19, The sharp increase in cases of Cancer, Pulmonary failure, Heart health has triggered questions for the sustainable development of pharmaceutical and medical sciences. In the search of inclusive and effective strategies to meet today's demand, improvised methodologies and alternative green chemical, bio-based precursors are being introduced by scientists around the globe. In this extensive review we have presented the potentiality and Realtime applications of both synthetic and bio-based surfactants in bio-medical and pharmaceutical fields. For their excellent unique amphoteric nature and ability to solubilise in both organic and inorganic drugs, surfactants are one of the most potential candidates for bio-medicinal fields such as dermatology, drug delivery, anticancer treatment, surfactant therapy, vaccine formulation, personal hygiene care and many more. The self-assembly property of surfactants is a very powerful function for drug delivery systems that increases the bio-availability of the poorly aqueous soluble pharmaceutical products by influencing their solubility. Over the decades many researchers have reported the antimicrobial, anti-adhesive, antibiofilm, anti-inflammatory, antioxidant activities of surfactants regarding its utility in medicinal purposes. In some reports surfactants are found to have spermicidal and laxative activity too. This comprehensive report is targeted to enlighten the versatile applications of Surfactants in drug delivery, vaccine formulation, Cancer Treatment, Therapeutic and cosmetic Pharmaceutical Sciences and prevention of pulmonary failure due to COVID-19.

Keywords Surfactant · COVID-19 · Pulmonary failure · Vaccine formulation · Drug delivery · Anti-cancer

1 Introduction

The most dangerous global threats against modern science are the fighting against climate change, environmental degradation, ecological downfall and in association with all these the degradation of human health, epidemics and pandemics like most recent COVID-19. Making remedies for the sustainable improvement of both human and environment health are the master tasks for scientists around the globe. In connection to this, environmental scientists are working on invention, discovery and development of sustainable green methodologies to protect environment from further degradation; where as in the field of bio-chemistry and pharmaceutical sciences, the challenge is not limited only in the identification of diseases and formulation of drugs but also characterising the drug's bio-activity, delivery and its potential future effect in human health. Inclusive strategies are thus required that might play pivotal role for the sustainable development of the environment, eradicate externalities, associated climate downfalls to inhibit the outbreak of epidemics and pandemics. A pure, non-contaminated and peaceful environment is the utmost need for good health of every living being on planet earth. In this

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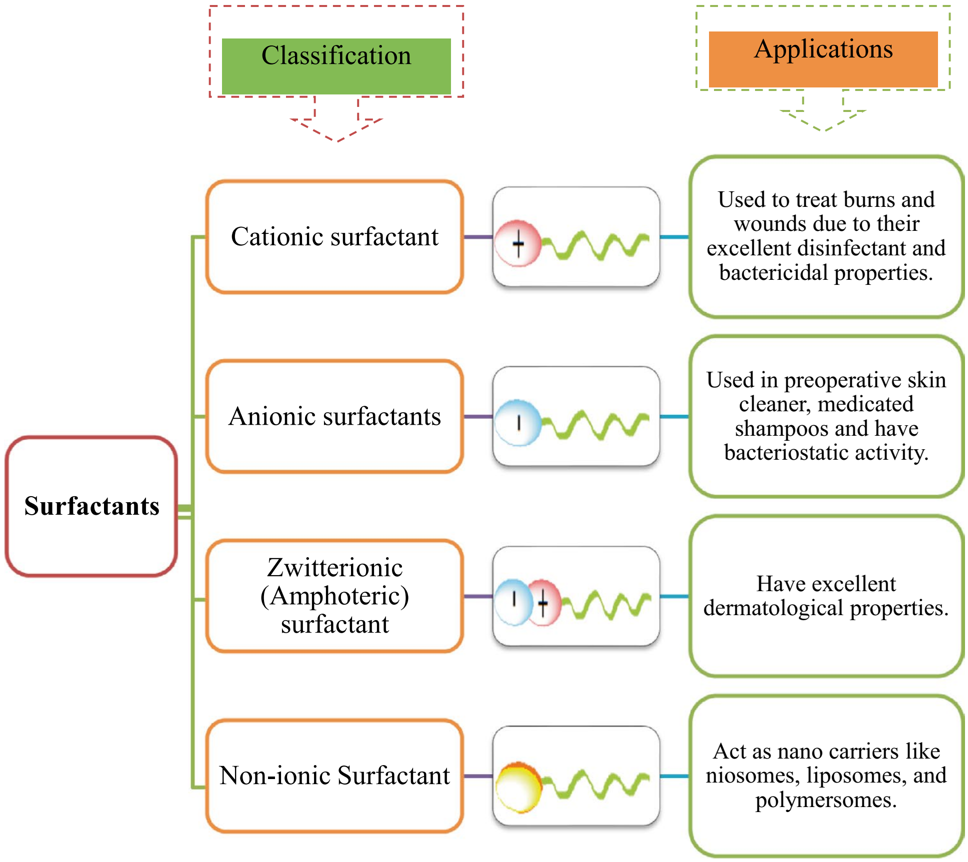


Scheme 1 Different types of Surfactants and their application [1]

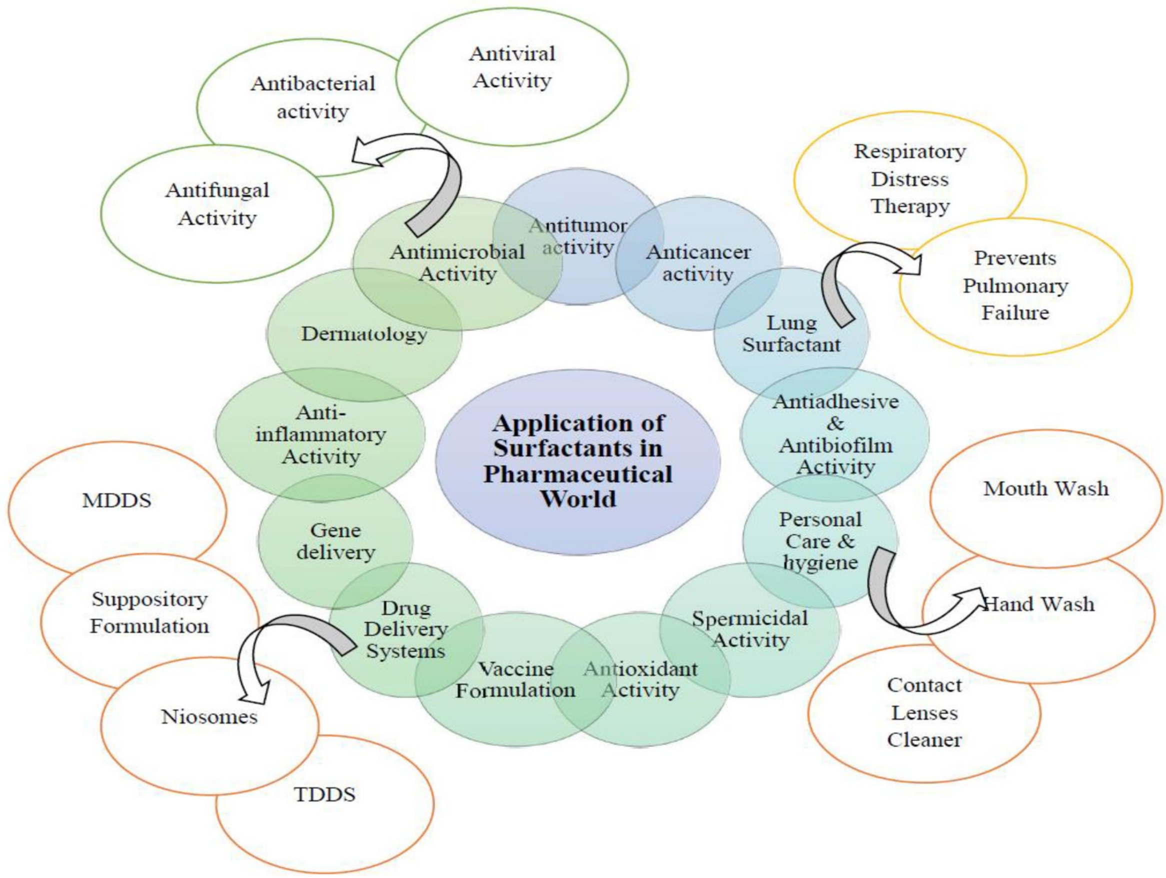
review we are presenting a comprehensive modern-day utilisation of a supreme class of green chemical called 'surfactant' in bio-chemical and medicinal science. Surfactants have all the potentially positive actions towards nature to boost sustainable development of the environment health. We have published articles in this context where the role of surfactants and their bio-congeners the 'bio-surfactants' are elaborately discussed [1–5]. Specifically in this endeavour, we have discussed the role of this super-chemical in drug delivery, vaccine formulation, Cancer Treatment, Therapeutic and cosmetic Pharmaceutical Sciences and prevention of pulmonary failure due to COVID-19.

Surfactants are amphoteric and solubilise both organic and inorganic substances. Surfactants after reaching their CMC (Critical Micellar Concentration) produce micelles/reverse micelles which indeed work as nano-sized supramolecules in solubilisation, emulsification of drugs. This wonderful quality of surfactants is most useful in the bio-medical and bio-chemical fields to improve production, purification and delivery of drugs [7].

In recent years various strategies have been used to tackle this challenge where use of various kinds of surfactants to increase solubility of drug is one of them. Surfactants can act as wetting agent which decreases the surface tension and allows the liquid to spread easily. Apart from that, surfactants can also be used as solubilizers and emulsifiers. Surfactants are organic compounds, derived from petroleum, sugars, natural fats etc., containing hydrophobic tails and hydrophilic heads (amphipathic). Therefore, these two parts of a surfactant molecule shows different affinities towards polar (generally water) and non-polar (generally oil) solvents [8–10].

According to the charge of the head groups, surfactants are classified into four different categories. The cationic, anionic, zwitterionic and neutral surfactants have their specific applications in bio-medicinal and pharmaceutical fields. The Scheme 1 contains a presentation of different types of surfactants and their applications [1].

Excellent unique features and abilities make these surfactants a potential candidate for a wide range of applications in various bio-medicinal fields such as dermatology, drug delivery, anticancer treatment, surfactant therapy, vaccine formulation, personal hygiene care products and many more. They are mainly used as an active component of emulsion and act as stabilizer. The self-assembly property of surfactants is a very powerful function for drug delivery systems [11]. Most of the pharmaceutical products show poor aqueous solubility and, in this regard, surfactants are inevitable to influence the solubility of the products. In medicinal drinks, surfactants are used to



Scheme 2 The vivid application of surfactants in pharma world

solubilize Vitamin E, D, other medicinal materials, and other necessary oil ingredients. Surfactants are useful in ointments formulations as well as in case of creams, lubricants and gels. They are also used to enhance the extent of drug absorption as well as drug penetration. Besides that, surfactants are also used to stabilize semisolid formulations [12]. Over the decades many researchers have reported the antimicrobial, anti-adhesive, antibiofilm, anti-inflammatory, antioxidant activities of surfactants regarding its utility in medicinal purposes. In some reports surfactants are found to have spermicidal and laxative activity too [5, 13].

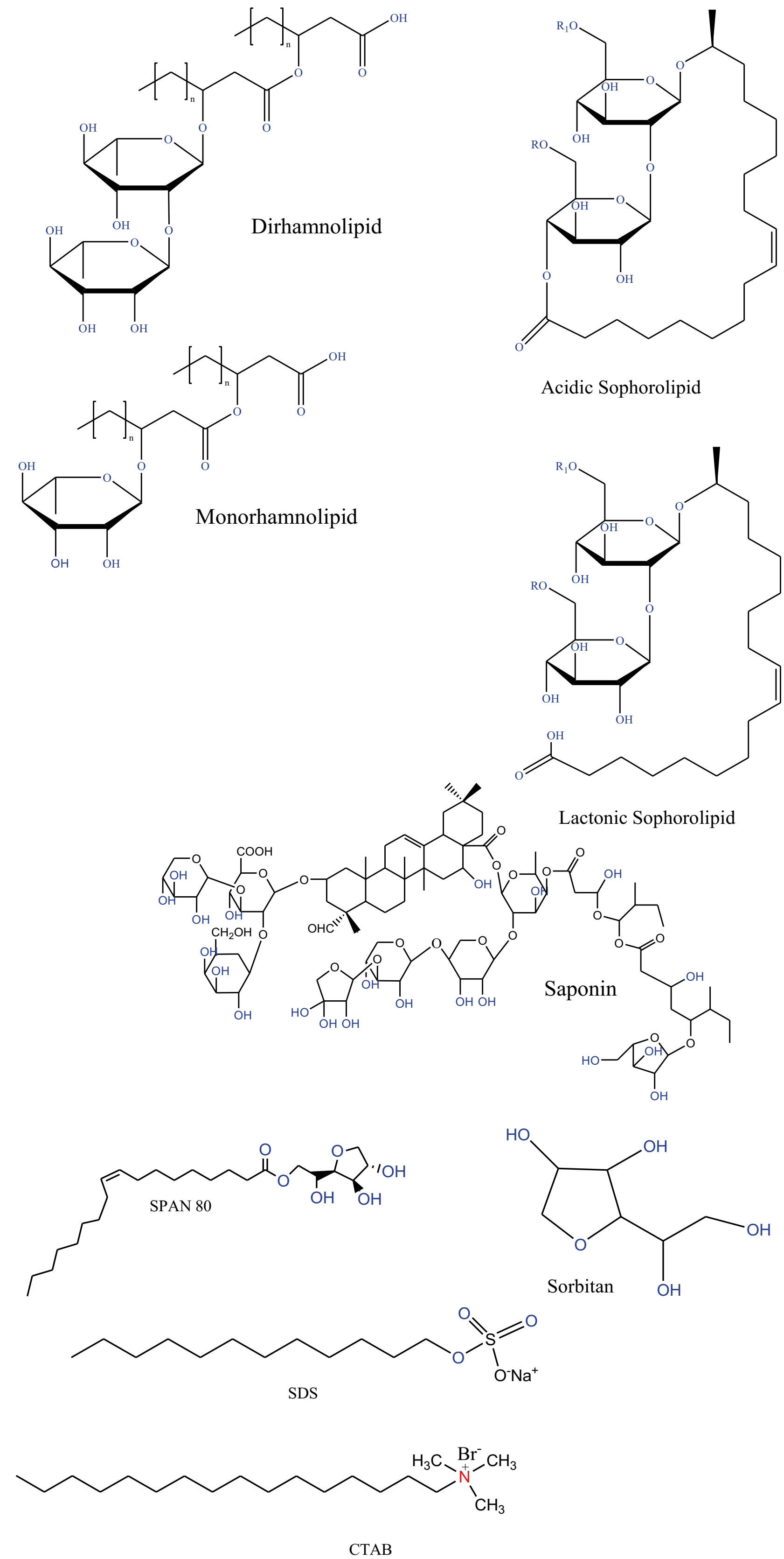
Enormous researches have been reported over versatile applications of surfactants in pharmaceutical world. We will discuss the major applications of surfactants in biomedical field in details in the coming segments. We also have tried to present a future line of the applications of surfactants. The Scheme 2 is a schematic representation of vivid applications of surfactants in bio-medicinal fields we are about to discuss in coming segments [5, 13] (Fig. 1).

2 Effectivity as Lung Surfactant

2.1 Use of Lung Surfactant to Prevent Pulmonary Failure, the Main Reason Behind COVID-19 Mortality

At this day and age, the whole world is suffering due to the pandemic outbreak of COVID-19 across the globe. SARS-CoV-2 is that notorious virus behind the COVID-19 infection, severity and even death and miseries of massive populations. Owing to some special chemical properties, surfactants have tremendous scopes and application in prevention and cure against this global disease, which we are going to learn in this segment. However, prior to that, we first need to know how the SARS-CoV-2infects the internal organs of a human body. ACE2 (angiotensin converting enzyme receptor 2) receptors are one of the important receptors in a human body, it is spread all over the internal organs viz. lungs, gallbladder, kidney, heart etc. SARS-CoV-2enters a human body through openings of nose, mouth and ears, subsequently they easily attack the ACE2 receptors

Fig. 1 General structure of some very useful surfactants extensively used in pharmachemistry



present on the surface of the respiratory tract. The virus then binds with the type II alveolar cell, the defender of alveolus [14–18]. The type II alveolar cell produces the natural pulmonary surfactant [19] (Fig. 2).

The lung-surfactants have important role in the lung's health. A lung surface contains mainly an air liquid interphase. At the time of exhalation, the lung tissue collapse as the surface tension of the liquid (present on the lung surface) is high. The lung surfactant decreases the surface tension and retains the lungs healthy. In a COVID-19 infected body, the SARS-CoV-2 virus destroys the type II alveolar cell which affects the production of pulmonary surfactant which leads to severe respiratory failure, the main reason behind the mortality due to COVID-19 [21]. Now we will focus on how to prevent this severe respiratory failure, we can prevent the SARS-COV-2 virus in two different ways-

(I) *By using recombinant ACE* The addition of recombinant ACE deactivates the SARS-CoV-2 virus by blocking their protein receptors and prohibits them from entering the lung cells [21].

(II) *By using Exogenous Lung surfactant and Surfactant associated protein* Lung surfactants contains Phospolipids and four surfactant proteins (SP) viz, SP-A, SP-B, SP-C and SP-D. Among them SP-A and SP-D are hydrophilic and SP-C and SP-B are lipophilic. The main function of the lung surfactants is basically to reduce the surface tension and to prohibit any tissue damage of the lungs. The SARS-CoV-2 damages the type II alveolar cell and stops the production of pulmonary surfactant [20, 21]. To overcome this exertion, surfactant associated proteins (SFTA) is recently used which shows similar properties like the "classic SP".SFTA 2 shows some properties like SP-A and SP-D and SFTA 3 shows properties amphiphilic nature, which increases the phagocytic activity [20–23].

Another important factor which leads to the pulmonary failure is the cytokine storm. Anti- inflammatory surfactant like anti-TNF, anti-IL6 are used to overcome this difficulty [24].

Recent studies suggested the effectiveness of lung surfactants towards increasing blood oxygen saturation, reducing pulmonary oedema and perfecting the excessive inflammatory reactions observed in the lung autopsies of a COVID-19 victim. It is thus quite evident that surfactant plays a pivotal role to dispose of the pulmonary failure by means of their robust anti-inflammatory and lung protective efficiency. A number of foreign corporations have started trial on different types of synthetic surfactants [20]. Wind-tree therapeutics™ are working on a synthetic lung surfactant called KL4 (https://www.windtreetx.com/) on severely affected COVID-19 pneumonia patients. A German pharma house Lyomark Pharma GmbH is also working on another such synthetic lung surfactants (www.lyomark.com). These lung surfactants are generally obtained from either bovine (bovactant, Alveofact®) or porcine (poractant alfa, Curosurf®) lungs through tissue mincing followed by lipid fraction extraction. Both the surfactants are reasonably

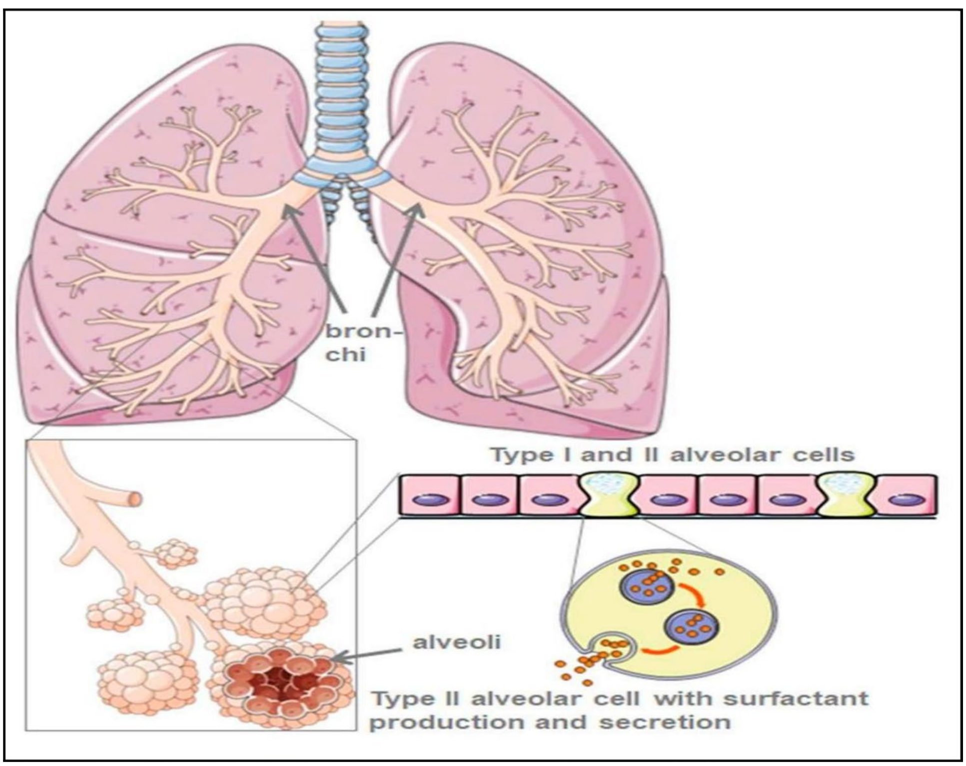


Fig. 2 A schematic presentation showing the lung and alveolar morphology. The type-II alveolar cells produce the lung surfactants. The scheme is reprinted with permission from ref. no. [20] Copyright 2020, Mirastschijski, Dembinski and Maedler

inexpensive, easily available and safer for internal use. These exogenous surfactants cover the outer surface of alveoli and helps to reduce the cytokine production [20, 24]. To prevent tissue damage and lung collapse it helps to restore the pulmonary barrier, not only that these surfactants also improve the breathing process quality and help to recover the patient (Fig. 3).

2.2 Surfactants in the Field of Respiratory Distress Therapy

Another important application of the synthetic lung surfactants is in the replacement therapy for the treatment of respiratory distress in Neonatal. In US about 250,000 babies are born every year with neonatal respiratory distress syndrome (hyaline membrane disease). Approximately 20% of the new-borns are affected with the hyaline membrane disease with a fatality of about 5000 new-borns per year. This respiratory distress among the new-borns occurs due to the substantial deficiency of endogenous lung surfactants which indeed leads to the lungs collapse. The combination of lung surfactant preparations, supplement oxygen along with mechanical ventilation is used to treat this condition. These lung surfactant preparations are known as exogenous surfactant and they are commonly bio-based extracted surfactants [25].

3 Surfactants in Dermatology

3.1 Surfactant as Penetration Enhancer in Transdermal Drug Delivery System (TDDS)

Human skin is basically a barrier between internal organs and the surroundings. It protects our inner organs from the harshness of the outer environment. Along with all these necessities, this barrier property creates complications for the transdermal drug to penetrate inside the skin [26]. To eliminate this difficulty various types of surfactants, generally ionic surfactants are used to increase the permeability of skin, termed as penetration enhancer or the absorption promoters. The Stratum corneum, outermost layer of epidermis, consists of protein and ordered layers of lipids, possess low permeability of skin towards transdermal drug. The polar head groups of ionic surfactants interact with ordered lipid layers of stratum corneum and disrupt the order, and denaturate keratin. Penetration enhancer can also increase skin permeability by leaching out some structural components from Stratum corneum and thus lowering the resistance of consecutive lipid barriers to the diffusion of drugs. In these ways surfactant can act as penetration enhancer [27]. In recent studies it is found that anionic surfactants have higher enhancing ability over cationic or non-ionic surfactants due to their versatility of interactions with both epidermal lipids and keratins [28]. SLS (sodium laurylsulphate) is an Anionic surfactant which is widely used as penetration enhancer [26–28]. There are few specific properties that controls the efficiencies of surfactants as the penetration enhancers [29]-

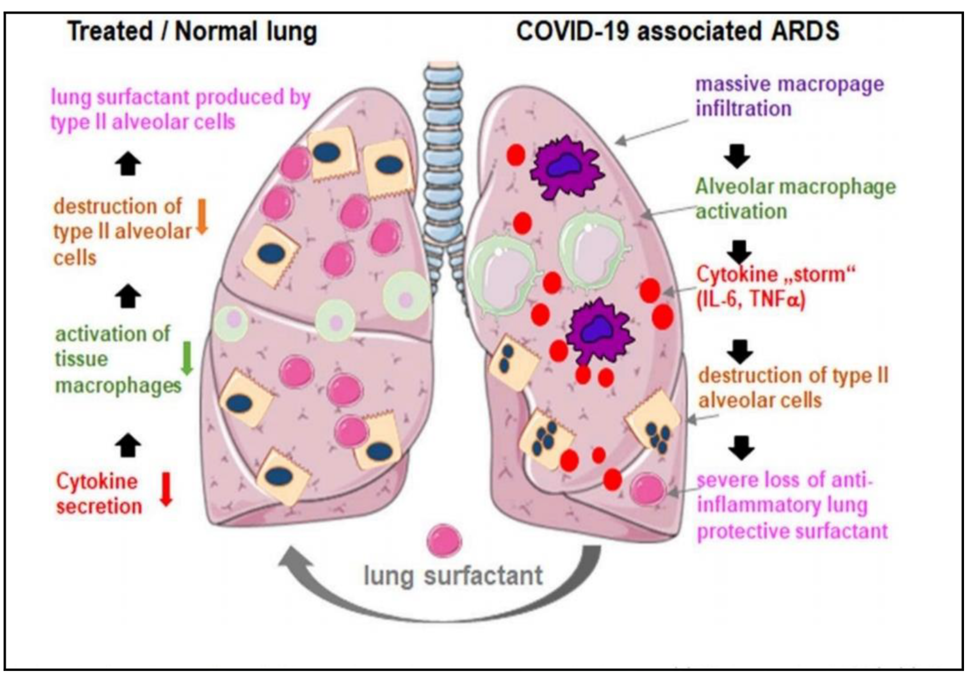


Fig. 3 A hypothetical mechanistic representation of externally applied lung surfactants for pulmonary protection in severe COVID-19 associated ARDS patients.The scheme is reprinted with permission from ref. no. [20]. Copyright 2020, Mirastschijski, Dembinski and Maedler

i) *The CMC of the surfactants* The CMC of a surfactant is a range of concentration of that particular surfactant above which dynamic aggregation of surfactants occur to form different morphological assemblies generally termed as micelles [1]. An apparently concentration dependent biphasic action of surfactants is observed on skin membrane. An increased membrane permeability is observed at lower concentration of the surfactant which gradually decreases with higher concentrations especially above the CMC of the surfactant [30].

ii) *The Chain Length of carbon atoms* Penetration enhancement is greatly affected by the carbon chain in the hydrophobic tail of a surfactant. Usually, it has been observed that surfactant with carbon chain length 10–14 in all types of surfactants is the best suit for the action [31].

iii) *Transdermal gradient* The chief reason for absorption in the skin is the "transdermal gradient" triggered by the variance in water content amongst the dehydrated skin surface (approx 20% water) and the epidermis (close to 100%) [32].

iv) *Hydrophilicity of the head group of the surfactants* For polar molecules surfactants with greater extent in hydrophilicity of the head is more effective than those with lesser hydrophilicity [29, 30].

v) Steric forces: Steric hideous forces are instigated by the absorbed molecules with decreased conformational freedom and changes due to molecule/solvent interactions in the two different surfaces [33] (See Table 1).

Not only the surfactants but there also various other types of chemicals e.g. esters, acids, water, hydrocarbons, amides etc. that are used as enhancer [32] and Azone is very famous among them [34].

3.2 Surfactant as Cerumen Removals

In the external auditory canal, there are sebaceous glands which produce sebum, if the sebum doesn't get cleared, it will combine with internal sweat and form a sticky semi-solid, called cerumen and it holds other foreign bodies like fallen hair dust and shredded epithelial cells, which blocks our ear canal. Excessive amount of cerumen can cause pain, itching and impaired hearing. Previously the combination of hydrogen peroxide and light mineral oil was used to soften the impacted cerumen for its easy removal from ears. Recently synthetic surfactants which have cerumenolytic activity, are used for removing cerumen. Cerumenex drops (tri ethanolamine polypeptide oleate condensate in propylene glycol solution) and Debrox drops (carbamide peroxide

Table 1 List of some surfactant containing drugs which shows excellent application in dermatology and treatment

Permeant	Surfactant	Description	References
Ibuprofen	Tween 80	Higher skin penetration power	[35]
Propranolol, metaproterenol sulfate	Lauric acid	Enhance percutaneous absorption	[36]
Atenolol	Polyoxyethylene-2-oleyl ether	Best enhancer for the transdermal drug delivery of atenolol	[37]
Paclitaxel	Cremophor EL	Enhances the intracellular penetration for liposomal drugs that improves their efficiency against cancer	[38]
Tamoxifen citrate	Cremophore EL, Tween 80	Excellent skin penetration power	[39]
Piroxicam	Tween 80:Span 20	Enhance the penetration power by disturbing stratum corneum layer through different skin models	[40]
Ropinirole	Tween 20	Increases the skin permeation from 20 to 35%	[41]
Hydrocortisone	Span 20: Span 80	Enhance the diffusion through the skin	[42]
Adenosine	medium-chain glycerides, polysorbate 80 and propylene glycol	Enhances the skin penetration power of transdermal drugs	[43]
Acyclovir	Transcutol	Increases the penetration through the skin	[44]
Lidocaine	Cationic surfactants	Enhances the permeation through the excised human skin	[45]
Progesterone	medium-chain mono- and diglycerides	Enhancesthe permeability of membrane by interacting with membrane proteins and lipids. Increases transdermal and topical delivery of PGT	[46]
Chloramphenicol	0.5 and 1% Tween 80	Enhances skin penetration	[47]
Fluoxetine	Labrasol	Increases the permeation significantly	[48]
Fluconazole	Labrasol/EtOH (1:1, w/w) mixture	Possessed highest permeation profile amongst all other formulations	[49]
Hydrocortisone Acetate	2-(2-ethoxy-ethoxy) ethanol (Trans Cutol)	Act as permeation enhancer and solubilizer	[50]

in glycerine) are used as an emulsifier and removing agent of cerumen. When these drops came in contact with cerumen, it produces oxygen and remove the impacted ear wax by disrupting its integrity [51].

4 Surfactants in Advanced Drug Delivery Systems

4.1 Micro Emulsion

Another interesting system is the micro emulsion, here the oil-surfactant -water interface produces different structures to reduce oil–water contact [1, 7, 10]. The basic structures of micro emulsion are micelles (like oil drops in water) and reverse micelles (like water drops in oil).

Micro emulsion also has complex structures like lamellae and spherulite where oil and water construct consecutive layers and surfactant layers usually separates them and forms onion like structure [15] (Fig. 4).

Micro emulsion plays a significant role to develop the drug delivery system (DDS). It increases the oral bioavailability of poor aqueous soluble drugs [1, 12]. Surfactants, lipids and co-surfactants are the major constituents of micro emulsion drug delivery system (MDDS) [52]. There are several ways of drug administration such as oral, topical, nasals, intravenous etc. for MDDS. They are capable of Solubilizing hydrophobic drugs due to their small, size and globular shape [53].

4.2 Niosomes an Extra-Ordinary Versatile Component in Different Fields of Drug Delivery

Niosomes are typically the aggregation of non-ionic surfactants in vesicles shape. These non-ionic surfactant vesicles i.e., Niosomes are extensively used in modern pharmaceutical industry due to their unique ability of encapsulating both hydrophobic and hydrophilic drugs inside bilayer vesicles (uni-lameller and multi-lameller vesicles). Niosomes are much superior over other nano carriers like 'polymersomes' and 'liposomes' because of their excellent in vivo stability and low toxicity. Niosomes are proven as ideal carriers of various types of drugs such as insulin, siRNA, DNA vaccines etc. and for treating deadly diseases like cancer, Alzheimer, diabetes, microbial infections etc. Niosomes shows their versatility also in the routes of drug administration such as transdermal, oral and penetral [52]. Niosomes are also attractive towards researchers of pharma science because of the facts that these nano-carriers are able to prolong the half-life of drugs in serum, avoid uptake by reticulo-endothelial systems (RESs) and reduce non-specific absorption by optimizing its components or building a multifunctional surface and also in the protection of drugs against degradation in storage and in vivo circulations [53]. These non-ionic surfactant vesicles were first.

Non-ionic surfactant vesicles (Niosomes) were initially applied for the more sustainable advancement of cosmetics. Contemporary science has inclusive targeted and focused research on Niosomes as nanocarriers for drug delivery. Doxil® was a kind of liposome first approved by the FDA for clinical trials take the attention of scientists on liposomes. It was found to have excellent bio-compatibility and very less toxicity [54]. Most important fact about the Niosomes is that even in comparison to the liposomes Niosomes are more advantageous with greater stability, low cost, easy to formulate and scaling-up.

It is significant to comprehend the basic structure of Niosomes, to conceptualise the ingredients for Niosomes formation and their application in drug delivery. These non-ionic bilayer vesicles consist with a hydrophobic head opposite to aqueous solution and the hydrophilic heads opposite to the organic solution [55].

These vesicles can be sub divided into unilamellar and bilamellar categories [1, 4, 5]. The multilamellar category of vesicles are concentric circles and are constructed with at least 2 bilayer vesicles embodied in it (Fig. 5).

Three major fields of application of Niosomes in DDS are discussed below.

4.2.1 Niosomes in the Field of Gene Therapy

In modern pharmaceutical science one of the most innovative treatment is 'Gene Therapy' which includes genetic modification by replacing or deactivating defective genes

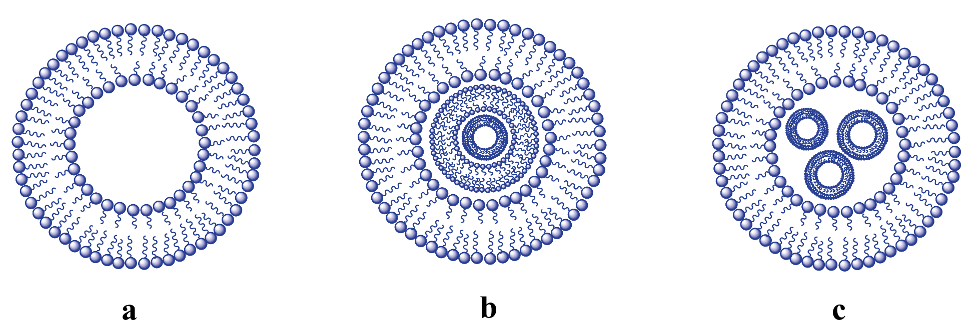


Fig. 4 Schematic representation of non-ionic surfactant vesicles **a** unilamellar vesicle; **b**, **c** multilamellar vesicles

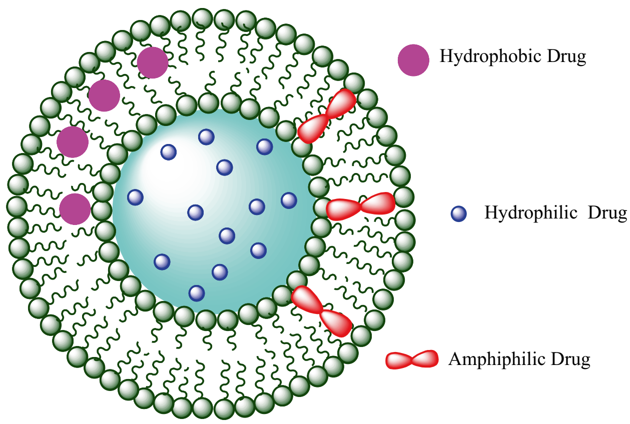


Fig. 5 A pictorial demo of how differently charged drugs interact with surfactant Niosomes

for treatment of various critical diseases. To deliver the gene material, various non-viral gene carriers, generally polymersomes (polymers) and liposomes (lipids) were previously used. But researchers face some difficulties such as, non-specific attachment of gene during in vivo gene therapy and toxicity while using these non-viral gene carriers [56]. But recently, another type of non-viral gene carriers, Niosomes attract researchers due to their excellent physicochemical stability, comparatively smaller size which can easily eliminate the difficulties caused by liposomes and polymersomes. It is proven that niosomes can act as good gene carriers into the targeted cell by protecting DNA from degradation [57]. Niosomes can also act as non-viral vector in DNA vaccine as it provides a simple, highly stable and less expensive solution than that of liposomes and polymersomes [58]. Niosomes play a vital role in the platform of delivering RNAs into human stem cells for promoting cell differential. In this purpose RNAs and niosomes are mixed in a proper ratio to form the complex which act as a specific gene silencer in human mesenchymal stem cells (hMSCs) [59].

4.2.2 Niosomes as Protein and Peptide Drug Carriers

Protein and peptide drugs like insulin, bacitracin is used as a pivotal therapeutic agent for treating various severe diseases e.g. diabetes. But they have some restrictions due to their in-vivo and ex-vivo instability, poor bioavailability and some serious side effects. Niosomes can solve these problems as they can act as a good carrier of various protein and peptide drugs and exhibit excellent ability in the formulation of protein subunit vaccine [60]. For decades researchers are trying to formulate the non-invasive way of insulin administration, but till now they are unable to find that. It was reported that niosomes have the ability to stop the easy degradation by protecting the loaded insulin and they can be delivered via vaginal and parenteral routes [61, 62]. Niosomes are also applied in protein subunit vaccine formulation that plays a pivotal role to eradicate and prevent various diseases. Niosome based vaccine formulations are much more efficient and shows fewer side effects than living organism-based vaccines [63].

Some experimental results are given below which proves that niosomes are promising nano carrier of protein and peptide drugs.

(i) Pardakhty's Experiment [64]

Experiment Preparation of insulin neosomes (containing Birj52,apolyoxyethylene alkyl ether surfactant and Birj 92 or Span 60 and cholesterol) and the study of pharmacokinetic properties in diabetic rats.

Observation The release profile of orally administrated insulin neosome was monitored by measuring the SGF (simulated gastric fluid) and SIF (simulated intestinal fluid).

Result These niosomes are able to protect the loaded insulin, reduce the blood sugar level as expected, bioavailability of Birj 92, Span 60 and Birj 52 are 1.88 ± 0.43, 1.46 ± 0.43 and 1.12 ± 0.57(%) respectively.

(ii) H. Yoshida's Experiment [65]

Experiment Peroral administration of DGAVP (9-desglycinamide 8- arginine vasopressin) loaded in stable niosome, formulated using polyoxyethylenealkylethers. The in-vivo situation was created using intestinal loop model.

Observation The concentration of entrapped DGAVP in the acceptor phase was higher than DGAVP solution and DGAVP + empty niosomes after 120 min.

Result These niosomes can control the release profile of protein and peptide drugs.

(iii) Anil Vangala's Experiment [66]

Experiment Measurement of Zeta-potential and change in vesicle size at two different temperatures of dimethyldioctadecylammonium vesicular adjuvant system where some non-ionic surfactant like 1-monopalmitoyl glycerol (MP), cholesterol (Chol) and trehalose 6,6′–dibehenate (TDB) were added and

Observations At 25 °C the size of MP-Chol-DDA and MP-Chol-DDA-TDB were changes slightly and the adjuvant activity of the formulated vaccine was measured against three subunit antigens in mice.

Result Antibody responses can be induced by both DDA-based and MP-based vesicle formulations.

4.2.3 Niosomes in Chemical Drug Delivery

Niosomes are superior as a nano carrier than liposomes and polymersomes. They possess hydrophobic cavity as well as hydrophilic shell so, they provide us the luxury of delivering two different types of drugs at the same time which helps us to achieve highly efficient therapeutic effect. Niosomes provide us more biocompatibility, biodegradability and low toxicity. They are more efficient than liposomes due to their low cost, good in vivo stability and ease of storage. Niosomes are used as a drug carrier for treating diabetes, cancer, various types of inflammation etc. One of the most significant applications of the niosomes is the improvement of oral bioavailability of some lifesaving medicines like Carvedilol. Carvedilol is widely used for treating coronary artery disease and congestive heart failure, but it possesses some limitations like short half-life after administration and the concentration of it's components significantly decreases before it can reach the systemic circulation (first pass metabolism). These two limitations are most common in orally delivered drugs. Numerous researchers have tried to develop some formulations that can improve the oral bioavailability of carvedilol, and it was found that Niosomes have the capability to stop the easy degradation by protecting the loaded drug and also controls the releasing of the drug components to avoid the first pass metabolism [67]. Carvedilol niosomes, prepared by film hydration method, possesses some excellent properties like very small size (around 167 nm) which made them an efficient carrier of cancer treating chemical drugs (smaller size allows them to penetrate the tumor tissue). They also have the encapsulating rate around 77.7% in different kinds of formulations. Experiment shows that they are stable at $C_{40}S60_{30}T60_{30}$and $C_{50}S60_{25}T60_{25}$ formulation. It is also proven that even after 20 h all the components of the loaded drug reach the systemic circulation without any significant change (almost 100%). The above results justify that niosomes are the pivotal tool to develop the bioavailability of orally delivered drugs [68, 69]. In chitosan/glyceryl monooleate (CH/GMO) and hydrogels niosomes are incorporated as pH sensitive formulation to increase the efficiency of the drug for treating cancer [70]. Here in the Table 2 a list of Niosomes (Used surfactants) and their application in medical field is given below-

4.3 Role of Surfactants for Increasing Dissolution Rate of Hard Gelatine Capsule

In an experiment on the dissolution rate of sparingly soluble benzoic acid in different forms such as loose powder, in size 00 and size 1 capsule. Benzoic acid powder, tightly packed inside the capsule size 1, shows slowest dissolution rate during the experiment. Addition of 0.5% of polyol surfactant into this formulation helps to improve the dissolution rate greatly. Various drugs contain hydrophobic compounds according to their requirement, we can eliminate the deleterious effect of these hydrophobic compounds on drug release by adding 0.1–0.5% surfactant [79].

4.4 Surfactant in Rectal Suppository Formulation

In Recent years, rectal drug delivery is another centre of interest for researchers of medicinal and bio-chemical fields. Riegalman and Crowell have shown that the diffusion rate of

Table 2 list of Niosomes (Used surfactants) and their application in medical field

Surfactant	Loaded drug	Rate of Encapsulation in %	Route of administration	Application	References
Cationic lipid Tween 80 squalene	pCMSEGFP		Ocular	Gene delivery	[57]
Pluronic L64	Doxonrubicin	38.73 ± 1.58	cell level	Anti-caner	[71]
Polyoxyethylene alkyl ethers	Insulin		Oral	Diabetes	[72]
Span 60 Tween 60	Ellagic acid	38.73 ± 1.58	Transdermal	Antioxidant	[73]
Tween61	Tyrosinase Plasmid (pMEL34)	150 µg/16 mg of niosomal compositions	Transdermal (in vitro)	Treatment of vitiligo	[74]
N-Palmitoyl-glucosamine Span 60	Vasoactive Intestinal peptide	24.07 ± 0.83	Intravenous administration	Anti-inflammatory Immunomodulatory neurological Disorders and so on	[75]
Tween 20	Curcumin	74.5 ± 3.2		Anti-inflammatory Anti-cancer Antioxidant	[76]
Polysorbate Cationic lipid	pUNO1-hBMP-7 plasmid			Bone regeneration	[77]
Monopalmitoyl glycerol	H3N2 antigen (Radiolabellin)		Oral Intramuscular	Flu	[78]

drugs to the suppository surface depends on the particle size of the suspended drug and the presence of surfactants. Thus, surfactants are proven for both increasing and decreasing drug absorption rate [80]. Various non-ionic surfactants having similar chemical properties to Polyethylene glycols, such as sorbitan fatty acid ester (Span, Arlacel), polyoxyethylene stearates (Myrj) and polyoxyethylenesorbitan fatty acid eaters (tween) are most commonly used as suppository vehicles [81]. Colonic fluid reduces the surface tension of rectal membrane by washing the mucous. Surfactant containing suppository vehicles facilitates the movement of drugs across rectal membrane barrier by providing additional pore for drug absorption [80]. It has also been reported that various tweens (polyoxyethylenesorbitan fatty acid esters) are designed in such a way that it melts at body temperature and form liquid, which dispersed instantly in body fluids [80].

5 Real time Application of Surfactants in Different Type Cancer Treatment

In this 21st century, cancer is one of the major causes of mortality worldwide. Modern pharmaceutical science has come a long way but till date, researchers are unable to find any proper remedy from this deadly public health issue. Among all types of cancer, breast cancer is the major cause of mortality in women and lung cancer for men [82]. Here in the table below we have presented a list of different types of reported new cases of cancer and death in 2020 (Table 3).

Table 3 % of new cases and % of new death of various types of cancer in 2020. Source: https://doi.org/10.3322/caac.21660

Cancer type	% of new cases	% of new death
Female breast	11.7	6.9
Lung	11.4	18.0
Prostate	7.3	3.8
Nonmelanoma of skin	6.2	0.6
Colon	6.0	5.8
Stomach	5.6	7.7
Liver	4.7	8.3
Rectum	3.8	3.4
Thyroid	3.0	0.4
Bladder	3.0	2.1
Non-hodgkin lymphoma	2.8	2.6
Pancreas	2.6	4.7
Leukemia	2.5	3.1
Kidney	2.2	1.8
Lip and oral cavity	2.0	1.8
Ovary	1.6	2.1
Brain, nervous system	1.6	2.5
Gallbladder	0.6	0.9
Testis	0.4	0.1
Salivary gland	0.3	0.2
Anus	0.3	0.2
Vulva	0.2	0.2
Penis	0.2	0.1
Vagina	0.1	0.1

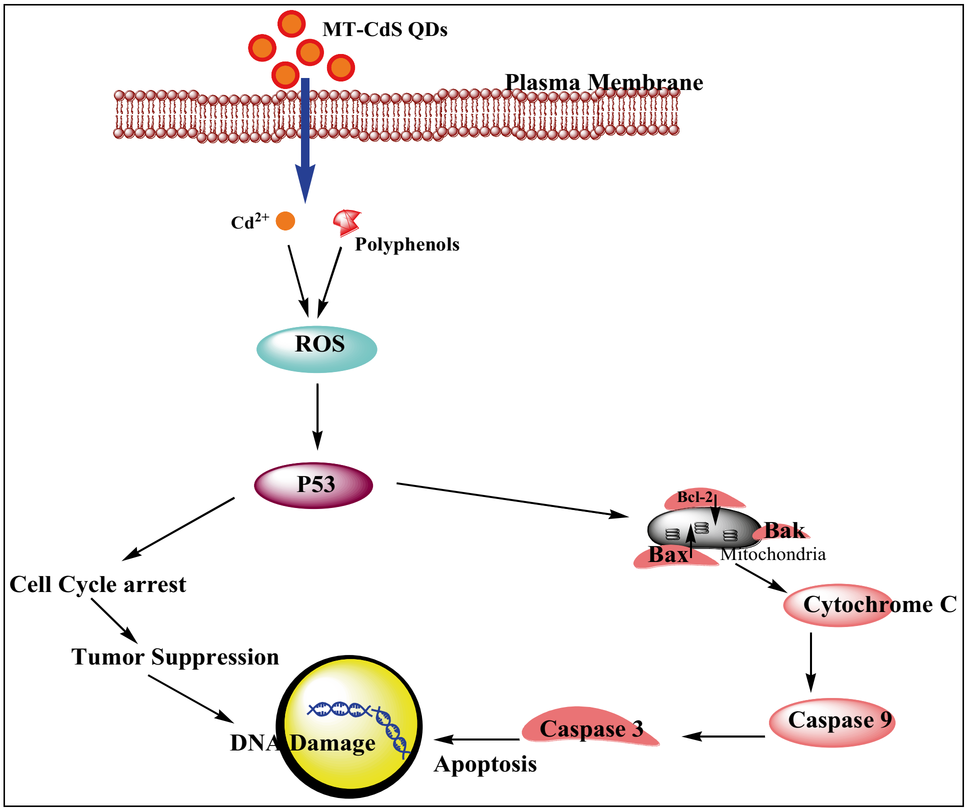
Currently radiotherapy and chemotherapy are applied for treating cancer but the major problem which leads to complications in this treatment is their deleterious side effects on healthy cells [83, 84]. In this situation modern medical science demands discovery of such a drug, which is efficient enough to cure this notorious disease as well as selective towards cancer cells only i.e., less harmful towards healthy cells [85, 86]. In recent time various target-based sophisticated and sustainable treatment strategies have been invented for treating cancers which are selective towards cancers cells only, application of both chemical and bio-based surfactants has made these producers more bio-compatible and inclusive. A brief discussion is presented below-

5.1 Surfactants in the Field of Drug-Resistant Lung Cancer Treatment

Depending on treatment and prognostic purposes lung cancer is classified as SCLC (small cell lung cancer) and NSCLC (non-small cell lung cancer). Best route of drug administration for treating lung cancer is inhalation therapy, a stable formulation containing surfactant, hydrophobic API and co-solvent are frequently used for this purpose. Various surfactant-based drug delivery systems such as nano sized drug carriers, hydrogel, novel powder, microspheres, mixed micellar system etc., are hugely applied in cancer detection, imaging, diagnosis and treatment. The above systems are capable to detect early metastasis, able to overcome various biological barriers and also have the potential to select the targeted cancer cells, which makes them a novel vehicle for treating drug-resistant lung cancer [87].

5.2 Curcumin in Cancer Treatment

Curcumin, a phenolic complex, which has been extracted from *Curcuma longa* plant, exhibit excellent cytotoxic activity towards cancer cells including breast cancer, ovarian cancer, gastrointestinal cancer, hematologic malignancies, neurologic cancer, sarcoma and melanoma. Curcumin exhibit anticancer property towards lung cancer NCL-H460 cell through apoptosis [88].



Scheme 3 Schematic presentation of apoptosis process via intrinsic pathway in breast cancer cells under green synthesised CdS QDs treatment

5.3 Cytotoxic Effects of CdS QDs, Synthesized from Waste and Mature Tea Leaf as Bio-surfactant

In recent years researchers on biomedical ground are trying to synthesis nanoparticle by using green technology. Currently CdS QDs (cadmium sulphide Quantum Dots), synthesized via green route by using waste tea leaves as bio-surfactant, are attracted the researchers due to their wide range of application in biomedical ground and excellent optical properties. MT-CdS QDs (matured and wasted tea leaves derived CdS quantum dots) exhibit excellent cytotoxic properties towards breast cancer cells and their effectiveness is comparable with widely used anticancer drug cisplatin. Waste tea leaves producing bio-surfactant are not only effective in controlling particle size of MT-CdS QDs but also enhance their cytotoxicity (Scheme 3). This QDs are capable to become an promising approach in near future in cancer treatment as they deliver the drugs, selectively towards targeted cancer cells and induced cell death by arresting cell cycle at S, G2/M phase and also destroy the cancer cells by producing ROS(reactive oxygen Species) [89].

5.4 Anticancer Activity of SLP Against Various Types of Cancer

SLP synthesized from *Wickerhamielladomercqiae* exhibit excellent cytotoxicity towards cancerous cell. By inducing apoptosis sophorolipids (SLP) shows their cytotoxic effects towards liver cancer cells of H7402 and human esophageal cancer cells of KYSE 450 and KYSE 109 [90]. Diacetylated lactonic SLP acts as a better inhibitor on esophageal cancer cell lines than monoacetylated lactonic SLP [90]. SLP also shows anticancer activity against pancreatic carcinoma cells by killing them through necrosis mechanism [91].

6 Other Applications of Surfactants in Personal Care, Health and Hygiene

6.1 Surfactants in Sexual Health

Nonoxynol-9 or the N-9 is a surfactant of the nonoxynol family and belongs to the class of non-ionic surfactants. N-9 has established use in cosmetics [92]. Recently it is extensively used in contraceptives due to its spermicidal properties. N-9 attacks the acrosomal membranes of sperm and makes it immobilise. Nonxynol-9 is extensively used in most spermicidal creams, jellies, film, gel foams and suppositories. It is also used as anal and vaginal lubricant with spermicidal activity. Many models of condoms are also lubricated with N-9 [93].

In a study in 2004, Nonxynol-9 was proved to be much effective as vaginal contraceptives with a failure rate of only 10–20% [93].

Almost all commercially available diaphragm jelly, cervical cap and contraceptive sponges contain N-9 as an active ingredient [94].

6.2 Surfactant as Contact Lens Cleansers

Surfactants are also used in contact lens cleaning. Oil, lipids and various inorganic compounds are responsible for the viewing difficulties of contact lens. Surfactants emulsify these oils, lipids and inorganic compounds and help to improve the viewing quality of the contact lens. There are mainly two different mechanisms for cleaning the contact lens: (I) by mechanical cleaning device. (II) by placing few drops of cleansers solution on the lens and rubbing gently with thumb and index finger for 20–30 s. This cleanser contains non-ionic detergent, wetting agents, preservatives (to increase the longevity of cleanser) and buffers (to maintain the neutrality) [80].

6.3 Role of Surfactant in Mouthwashes

Mouthwashes are concentrated aqueous solutions that contain multiple active ingredients and excipients. Mouthwashes are generally used as therapeutic agent and refresher (cosmetic agent). Mouthwashes that are used as therapeutic agents can reduce plaque, stomatitis, gingivitis and dental caries. Surfactants are used in this kind of mouthwashes to remove debris with the help of foaming action. According to the studies by Chokshi et al. [95], non-ionic surfactants are most effective for formulating mouth washes. Surfactants with an HLB vale lesser then 10 are best suit for this purpose. Sorbitontriolate, sorbiton monolaurate, sorbiton monooleate and sorbitonsesqioleate are the most commercially applied surfactants in the production of aerosol dispersions [80]. Mouthwashes can also be used as refresher for reducing bad breath, by using antimicrobial and flavouring agents. Here surfactants are used to solubilise the flavours [81].

7 Biosurfactants, a Blessing in Bio-Medical Field

In modern surfactant science, interest of scientists' centre around a special type of surfactant, derived from microorganisms termed as microbial surfactant. Microbial surfactants have some fundamental characteristics like less pollutant in nature, nature friendly solvent, less toxic, biodegradable and ease of recycling which make them superior over the synthetic surfactants [8]. In contemporary pharmaceutical science, use of microbial surfactant is increasing steadily for betterment of solubility of hydrophobic drugs [1, 9]. Modern Pharmaceutical World demands such Drug Delivery System which is safer and Benign in nature. Lots of researches are performed in this endeavour to accelerate the green revolution in biomedical fields. Non-toxicity and biodegradability are the main features of these natural occurring surfactants.

Microbial biosurfactants possess some excellent properties like antiviral, antibacterial, immunoregulator, skin compatibility, wettability and low toxicity which make them a perfect substitution for the synthetic surfactants and can be used as the main ingredient in the formulation of hand washes [96, 97]. Glycolipids and lipopeptides are the most commonly used microbial surfactants [98–100].

7.1 Antimicrobial Property (Antiviral, Antibacterial, Antifungal)

In recent time, the application of biosurfactant is increasing sharply in biomedical grounds as they exhibit excellent antimicrobial (antivirus, antibacterial, antifungal) activities due to having the ability to influence the permeability of cell membrane. So, as they are very useful in treating various diseases as they can show activity against microbes. In this regard Rhamnolipid and Sophorolipids are potential candidate as they can show antimicrobial property against drug-resistant pathogenic bacteria [101]. Polymyxin A and Polymyxin B derived from *Bacillus polymyxa,*[101]. Surfactin from *Bacillus subtilis* are the mostly know BSs with antimicrobial activity.

Biosurfactants shows inhibitory properties against not only bacteria but also verities of enveloped viruesPumilacidin obtained from *Bacillus pumilus* is prohibitive against herpes simplex virus type 1 hence act as antiviral agent [102]. A mixture of Surfactin and fengycin derived from *Bacillus subtilis* shows inhibitory action against a number of viruses such as Pseudorabies virus, Procine Parvovirus, Newcastle disease virus, Brusal Disease virus [102]. Rhamnolipid obtained from Pseudomonas sp. S17 strain has been found to have antiviral activity against herpessimplex virus [103]. Jin et al. investigated that Rhamnolipid 222B shows anti-viral activity against enveloped viruses namely bovine corona virus and herpes simplex virus type 1 and the obtained results suggests that masks or plastic surface coated with Rhamnolipid 222b are able to reduce the spreading of SARS-CoV2 from one person to another [104].

Upon acetylation of head group, SL become active against HIV and herpes virus and exhibit cytokine -stimulating property [105]. Sophorolipids produced by *C. bombicola* shows virucidal activity against human semen [105]. Lipopeptides produced by various microbes, also shows excellent antifungal and antiviral activity by stimulating our immune system for the production of antibodies [104, 105]. Lipopeptide BS extracted from *Bacillus cereus* strains exhibits significant antiviral, antifungal, antibacterial activity as well as antioxidant potential by DPPH scavenging ability [106].

A mixture of Rhamnolipids have been extracted from *Pseudomonas aeruginosa* have been extracted by Abalos and his co-researchers and among several homologues, seven were found to have excellent antimicrobial activity against majority of the microbes [107].

Biosurfactant derived from Lactobacillus (*Lactobacillus jensenii* P6A and *Lactobacillus gasseri*P65) are found to have antimicrobial ability to prevent gastrointestinal and urogenital infections caused by microbes such as *Escherichia coli* and *Candida albicans*. They also exhibit activity against *Escherichia coli, Staphylococcus saprophyticus, Enterobacter aerogenes* [108]. Some other BSs with antimicrobial property are given in the table below (Table 4):

Table 4 A list of bio-surfactants with anti-inflammatory, anti-fungal and spermicidal properties

Biosurfactant	Microorganism	Function	Target	References
Lipopeptide	*Brevibacilluslaterosporus*	Antimicrobial activity against Gram-positive bacteria	*Staphylococcus aureus, Lactobacillus plantarum, Enterococcus faecalis*	[109]
Lipopeptide	*Bacillus subtilis* SPB1	Antimicrobial activity against bacteria and phytopathogenic fungi		[110]
Lipopeptide	*Bacillus cereus*	Antibacterial and antifungal	*Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Candida albicans,*	[106]
Glycolipid	*Staphylococcus saprophyticus SBPS 15*	Antimicrobial	*Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Vibrio cholera, Klebsiella pneumoniae, Candida albicans*	[111]
Rhamnolipid	*Pseudomonas aeruginosa* SS14	Antifungal	*Trichophyton rubrum*	[112]
Surfactin-Rhamnolipid mixture	*Bacillus amyloliquefacienc-sST34, Pseudomonas aeruginosa* ST5	Antimicrobial activity	*Escherichia coli, Staphylococcus aureus, Candida albicans*	[113]
Fengycin	*Bacillus amyloliquefaciencs-*MEP218	Antimicrobial activity	*Pseudomonas aeruginosa* PA01	[114]
Glycolipopeptide	*Lactobacillus pentosus*	Antimicrobial	*Escherichia coli, Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa, Streptococcus pyogenes, Streptococcus agalactiae*	[115]
Subtilisin	*B.subtilis*	Antimicrobial agent	–	[116]
Aminoacids lipid	*Bacillus sp*	Antimicrobial agent	–	[117]
Cellobiose lipid	*Ustilagomaydis*	Antifungal agent	–	[118]
Peptidelipid	*B.licheniformis*	Antimicrobial agent	–	[119]
Surfactin	*Bacillus subtilis, Staphylococcus aureus*	Anti-inflammatory agent	–	[120]
Mannosylerythritol lipid(MEL)	*Pseudomonas antarctica*	Anti-inflammatory agent	–	[121]
Mannosylerythritol lipid (MEL)	*Kurtzmanomycessp, Pseudozymasiamensis*	Antifungal compound	–	[121]
Sophorolipids	*C. bombicola C. bogoriensis, C. botistae,C.apicola*	Anti-inflammatory Antiviral agent, Spermicidal, neuroprotective agent, immunomodulator	–	[122–124]

7.2 Anti-Inflammatory Action

From various researches it is successfully reported that biosurfactants (BSs), produced by yeast and bacteria, shows excellent anti-inflammatory action [125]. Inflammation occurs due to secretion of arachidonic acid (AA), an inflammatory mediator, and cytosolic phospholipase A2 (cPLA2) regulates the secretion of AA. BSs can be used as potential therapeutic agent for treating inflammatory diseases as BSs are capable to inhibit cPLA2 by interaction with macromolecules and cell membranes [126]. In near future Sophorolipids (SLs), produced from *C. bombicola*, may be a promising therapy for immunomodulation in chronic inflammatory diseases [120] as they lower IgE (immunoglobulin E) level [122, 123] and supress expression of inflammatory cytokine [124]. BS surfactin, originated from various microbes, have extensively used as neuroprotective agent and anti-inflammatory agent as they increase anti-inflammatory effect by reducing pro-inflammatory cytokines [127, 128].

7.3 Biosurfactant Used as Antioxidant

Another interesting application of BSs is to act as antioxidant which is very important and essential for the neutralization and prohibition of free radical and its formation reaction during physiological actions in body. Free radicals are highly reactive in nature and cause oxidative stress resulting in a number of health problems such as arthritis, hypertension, neurological disorder, ischemic diseases and many more [129]. BSs renders antioxidant activity by prohibiting the free radical chain reaction and also the microbial attachment on the surface [130]. Besides of blocking such oxidative chain reaction they also capable of hindering the increment of reactive oxygen and nitrogen species hence can be highly impactful for the therapeutic treatment against cancer, other heart related and neurodegenerative diseases [131]. A number of Lipopeptide BSs have excellent properties such as antimicrobial, antiaging, moisturising as well as free radical inhibiting activities viz. antioxidant activities. Moreover, its potential to heal wound make it suitable ingredient to incorporate safely in the products for dermatological treatment until they would show minimum cytotoxicity against human being [132]. Lipopeptide BSs isolated from *Acinetobactor-junii* and *Bacillus subtilis* SPB1 having high antioxidant ability with wound healing property were reported [132, 133]. Giri et al. reported the antioxidant, antimicrobial as well as antiadhesive properties of BSs obtained from *Bacillus subtilis* VSG4 and *Bacillus licheniformis* VS16 [134]. Another study by Takahashi it was reported that Mannosylerythritol lipids exhibit antioxidant and protective activity towards H_2O_2 induced oxidative stress. [135] Biosurfactants obtained from *Lactobacillus casei* strains confers significant antioxidant potential was reported by Merghini et al. and Mouafo et al. [136, 137].

7.4 In MDDS and Nano Particle Formulation

In recent days MDDS have been formulating to be administered through various paths or routes such as nasal, oral, ocular, intravenous and topical [138].

The challenging task in DDS is to produce, safe, effective, stable and uniform microemulsion system as most of the conventional techniques are highly expensive, frequently results hazardous waste and time consuming [139]. Glycolipids are recently used as bio-emulsifier and stabilizers for the formulation of uniform, non-toxic, stable and biocompatible silver nanoparticle through environmentally acceptable reverse microemulsion technique [138–140]. Several classes of glycolipids such as rhamnolipids, sophorolipids, trehalose lipids etc. have been reported successfully to act as co-surfactant, reverse micelles, shell phase etc. in the field of alcohol free microemulsion and different types of metal-bounded nanoparticle formulation and stabilization [138, 141]. Rhamnolipids are used to synthesize uniform and stable microemulsion formulation with nanoparticles such as Nickel oxide nanoparticles, silver nanoparticles, polymethyl methacrylate nanoparticles (nPMMA) etc. which possess anticancer property, antibiotic activities against gram-positive and negative bacteria and used in biomedical field extensively [137–141].

7.5 Bio-Based Personal Hygiene Products Formulation

In the very present scenario, the whole world is fighting against COVID-19 pandemic. With the course of time the virus is getting more contagious by modifying itself genetically. So, besides vaccination we also have to maintain some restrictions advised by World Health Organization (WHO) [142, 143].

Hand hygiene is the most effective shield to protect ourselves from various microbial infections and so as it helps to prevent COVID-19. Detergents, produced from petrochemicals, are the major component of the soaps, and high concentration of alcohols are used in sanitizers [144]. Soaps kill the microorganisms by disrupting the lipophilic member of cell wall where sanitizers kill them by dissolving their lipid membrane [145]. But both the synthetic detergents and alcohols are not good for our skin health, and frequently washing or cleaning hands by using alcohol-based sanitizers can cause skin dryness and irritation, they are also hazardous to our mother nature [144, 145]. They are generally non-biodegradable and stay in environment for long period of time hampering the ecosystem [145]. Versatile abilities such as antiviral, antibacterial, antifungal, skin biocompatibility, biodegradability, low toxicity moreover detergent properties, wettability make biosurfactants a potential candidate to be used in hand hygiene products [146]. Based on the studies and findings Bakkar and his co-researchers hypothesize that Rhamnolipid biosurfactants can be a considerable alternative of other alcohol and detergent based sanitizers and thus useful for this pandemic situation [147].

7.6 Anticancer and Antitumor Activity of Biosurfactants

During the last few decades, the number of cancer types and its victim is rising continuously over the world. In this regard recent studies have revealed the anticancer and antitumor activity of Biosurfactants having minimum toxic effects. Biosurfactant can inhibit the growth of cancerous cell. Glycolipid BS MEL has been found to influence apoptosis and prohibit growth of mouse melanoma cells. Also, Surfactin is known to induce apoptosis in human breast cancer cells [148]. In another study it has been shown that Surfactin is able to show anti-cancer activities against breast cancer, colon cancer, Ehrlich ascites, leukemia, hapaotma [149]. Another study reveals that Trehalose lipid BS produced from *Nocardia Farcinica* BN26 shows antitumor activity against human cancer cell lines [150]. In a recent study Karapudi and his co-researchers investigated that Glycolipoprotein obtained from *Acinetobacter indicus* M6 exhibits significant antitumor activity against lung cancer cell (A549) [151]. Besides these there are so many established researches on antitumor and anticancer activity of Biosurfactants and researchers are trying to explore more promising strategies to develop better anticancer treatment.

8 Plant Based Surfactant: Saponins and its Potential Application in Pharmaceutical World

Saponins are most widely used plant based biosurfactants which are generally glycosides of high molecular weight. They are obtained as a secondary metabolite from more than 500 plant species. Saponins are secreted from various parts of plants such as bark, stem, seed, fruit, leaf, root etc. [152]. In recent years, interest of the researchers on saponins are increasing sharply as they are natural surfactant and also exhibit excellent characteristics such as foaming properties, flavour enhancer, immune stimulating property, blood cholesterol reducing power, hemolytic action and many other interesting properties [153].

The tree *Quillaja saponaria* has long history of its use in biomedical grounds, Chilean people have used the aqueous bark extract of this tree as natural shampoo as surfactant [154]. Saponins, extracted from the Chilean soap bark tree, *Quillaja Saponaria* have huge application in pharmaceutical, cosmetics, food and photography industry and they are commercially available [153, 154]

Purified Quillaja extract are also used to prepare nucleic acid from WBC (white blood cell) [155]. Saponin DS-1 which is produced from saponin QS-21 are extensively used for increase ocular and nasal delivery of insulin [156]. Saponin DS-1 also enhance the mucosal delivery of antibacterial agent aminoglycosides which are used to treat peritonitis and pneumonia caused by gram-negative bacteria [157]. A mixture of oil rich in omega 3 polyunsaturated fatty acids and purified quillaja extract can act as anti-inflammatory agent [158].

Other types of saponins, such as *saikosaponin*, extracted from root of the plant *Bupleurum marginatum* and *polyphylla saponins* extracted from the tree *Parispolyphylla* have virucidal activity against influenza A virus (H1N1) [159, 160]. Saikosaponin also possess antiviral property at early stages of viral infection against coronavirus H-CoV-22E9 [161].

In India there are almost 22 types of plant species in kumaun region of Uttrakhand which are used as natural surfactant in shampoos and soaps by local people for cleaning and personal hygiene maintenance [162]. So, it may be concluded that natural occurring biosurfactants have potential to substitute alcohol-based sanitizer and synthetic surfactants [163] (Table 5).

9 Saponins in Vaccine Formulation

Quillaja extract containing Quil-A (complex mixture of four saponins) are separated with the help of RP-HPLC [165] and obtained less toxic and most effective saponin QS-21, which is a promising adjuvant for human vaccine formulation [165]. This QS-21 increase both cell -mediated immune responses and antibody and used as an adjuvant in subunit vaccines for treatment of serious diseases like HIV-1, herpes simplex virus, reovirus, plasmodium falciparum malaria, melanoma etc. [152, 166]. Recently Novavax company uses this QS-21 as an adjuvant for COVID -19 Vaccine formulation.

10 Future Prospect and Conclusions

In pharmaceutical world surfactants has enormous applications among which many are implicated commercially. Specifically, in case of personal hygiene care products, surfactants have become inevitable because of its excellent foaming, cleansing, emulsifying, stabilizing, wetting properties. In recent days the covid-19 and its post pandemic phase demand more consciousness about personal health and

Table 5 A list of saponin based surfactants and their uses in medicinal field

Type of Saponin	Extracted From	Applications	References
Quillaja Saponin	*Quillaja saponaria*	Used to prepare nucleic acid from wbc (white blood cell)	[156]
		A mixture of oil rich in omega 3 polyunsaturated fatty acids and purified quillaja extract can act as anti-inflammatory agent	[158]
Saponin DS-1	Saponin QS -21	Enhances ocular and nasal delivery of insulin	[156]
		Enhances the mucosal delivery of antibacterial agent aminoglycosides which are used to treat peritonitis and pneumonia caused by gram-negative bacteria	[157]
Saiko saponin	Root of *Bupleurum Marginatum*	Antiviral Agent	[163]
		Antiviral property at early stages of viral infection against coronavirus H-CoV-22E9	[161]
Polyphylla Saponin	*Parispolyphylla*	Antiviral Agent	[163]
		Have virucidal activity against influenza A virus (H1N1)	[159, 160]
Tribulus saponin	Tribulus terrestris	Immune system booster, antioxidant and anti-inflammatory agent	[164]
Oleanane saponins	Calendula Officinalis	Antispasmodic Agent, Antiseptic Agent, For Treating Various Skin Diseases, Gastric and Menstrual Discomfort	[164]
Steroidal Saponin	Genus Ruscus	For Treatment of Hemorrhoids, Chronic Venous Insufficiency, Orthostatic Hypotension, Varicose Veins Etc	[164]

hygiene which invokes the growing usage of personal care products, detergents, cleaners as well as masks coated with antimicrobial agents to reduce the spread of the virus [104]. So, the rising demand for surfactant-based products and surfactant-based treatments invoke the researchers to explore more effective and innovative applications of surfactant.

But in spite of having its powerful utilities, synthetic surfactants have many adverse effects such as toxicity, non-biodegradability resulting in contamination in ecosystem. For instance, Benzalkonium chloride a cationic surfactant used in various pharmaceutical purposes, has been reported to affect intrinsic neurons in the myenteric plexus of the small intestine [167]. Besides that, Chemical surfactants help the microorganisms to increase their resistance against antibiotics [167].

In this context the use of Biosurfactants is an eco-friendly and more acceptable approach over conventional chemically synthesized surfactants because of its several advantages over chemical or synthetic surfactants, such as lower eco-toxicity, higher chemical stability, higher biodegradability, biocompatibility and most importantly it can be produced from renewable and sustainable feedstock or sources. Moreover, it obeys twelve principles of "green chemistry" and hence entitled as 'green' before its name [1].Therefore, quest for discovering such eco-surfactant to be used in various pharmaceutical applications are also increasing day after day replacing the chemical alternatives.

Acknowledgements The authors acknowledge The University of Burdwan and Government General Degree College, Singur for providing infrastructural facilities.

Author contributions Manuscript was written by BD and BK, they have equal contributions to this project and thus have equal authorships. WB and AB edited the manuscript. MHM and BS have revised the manuscript several times.

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