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DEEP EUTECTIC SOLVENTS — A NEW METHOD FOR TRANSDERMAL DRUG DELIVERY

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Abstract. Transdermal drug delivery systems are more advantageous due to non-invasive treatment and pharmacokinetics, which makes / makes this method attractive in pediatric practice. Pharmacokinetic advantages consist of increasing bioavailability due to the absence of the effect of primary passage through the liver and uniform intake of the active substance into the systemic circulation, which is why the concentration curve of the medicinal substance is more uniform. Currently, plasters are used as transdermal delivery systems in the world, but the legal difficulties of commercialization of drugs for obstetric and pediatric audiences limit the possibilities of using transdermal therapeutic systems. In this review, transdermal drug delivery systems based on deep eutectic solvents are discussed. Due to unique properties such as ease of synthesis, low toxicity and cost, high stability and biocompatibility, deep eutectic solvents are attractive delivery systems for active pharmaceutical substances for use in pediatrics.

Key words: deep eutectic solvents; transdermal drug delivery; vaccine; active pharmaceutical substance.

ГЛУБОКИЕ ЭВТЕКТИЧЕСКИЕ РАСТВОРИТЕЛИ — НОВЫЙ СПОСОБ ТРАНСДЕРМАЛЬНОЙ ДОСТАВКИ ЛЕКАРСТВ

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Резюме. Системы трансдермальной доставки лекарственных средств имеют ряд преимуществ благодаря неинвазивному введению и особенностям фармакокинетики, что делает данный способ крайне привлекательным в педиатрической практике. Фармакокинетические преимущества заключаются в повышении биологической доступности из-за отсутствия эффекта первичного прохождения через печень, равномерного поступления действующего вещества в системный кровоток, благодаря чему кривая концентрации лекарственного вещества приобретает более равномерный характер. На данный момент в мире в качестве систем трансдермальной доставки используются пластыри, однако глобальные сложности правоприменительной практики вывода препаратов для акушерской и педиатрической аудитории на рынок лимитируют возможности создания транс-

дермальных терапевтических систем. В данном обзоре рассмотрены системы трансдермальной доставки лекарственных средств на основе глубоких эвтектических растворителей. Благодаря своим уникальным свойствам, таким как простота синтеза, низкая токсичность и стоимость, высокая стабильность и биосовместимость, глубокие эвтектические растворители являются привлекательными системами доставки активных фармацевтических субстанций для применения в педиатрии.

Ключевые слова: глубокие эвтектические растворители; трансдермальная доставка лекарств; вакцина; активная фармацевтическая субстанция.

For a few last decades transdermal drug delivery system (TDDS) has become the third common type of the drug delivery after oral drug introduction and injections. Popularity of transdermal drug delivery systems in the therapy is characterized by convenience of its application and pharmacokinetic peculiarities; taking into account that transdermal introduction is a preferable type of drug introduction for certain groups of patients. This cohort is represented by the patients with chronic pain syndrome when the uniform analgesic introduction maintains analgesic action; with the digestive system disorders, when the absorption of the drug can be disturbed in different parts of the gastro-intestinal tract and with those having difficulties in oral drug delivery, e.g. young children with maxillofacial, neck and mediastinum traumas and with dysphagia of different origins. It should also be noted that oral intake is limited by hydrolytic resistance issue caused by the active substance in acidic environment of the stomach and enzyme activity in the intestines; these substances can be delivered only parenterally.

TRANSDERMAL DRUG DELIVERY SYSEMS FOR ACTIVE PHARMACEUTICAL INGREDIENTS

Effective transdermal drug delivery systems development is relevant for the broad spectrum of active pharmaceutical ingredients. It is known that approximately 40% of available oral medications and 90% of new chemical compounds have low solubility and penetration via the skin which decreases their bioavailability when applied onto the skin [32, 51]. To solve the following issues different methods have been developed which were aimed at physical (dispersion), pharmaceutical and chemical modification of the active pharmaceutical ingredients. Increase of penetration due to chemical methods is achieved by interaction of such substances as water, hydrocarbon (alkanes and ethylenes), alcohol, acids, ether, alkyl esters of amino acids, amides, urea and its derivatives, amines and their bases, sulfoxides, terpens, steroids, dioxanes, pyrrolidone and imidazole derivatives, laurocapram (Azone) [41]. It results in: 1) changes in viscosity of the medication in the stratum corneum due to the lipid alkyl chain modifications; 2) increase of distribution coefficient of the ingredient on the skin; 3) drug reservoir formation on the outer layers of the skin associated with the formation of hydrophilic pores. However, relatively low number of the additional chemical substances (sulfoxide, terpenoid, glycoside, ethanol) are used in commercial drug production which increase transdermal penetration most commonly due to absence of toxicity and characteristic features of active substance interaction and also high cost of clinical trials. Thus, development and research of new biocompatible and biodegradable transdermal drug delivery systems for active medical ingredients in children is a relevant and modern task.

Present day methods of transdermal drug delivery system (TDDS) can be divided into two huge groups: transdermal delivery via active methods (the methods are associated with the drug delivery via ultrasound, current of the certain rate or laser) and transdermal delivery via passive methods (the methods are based on the application of the active pharmaceutical ingredient on different chemical substances or biological objects, which due to their specific functions can penetrate through stratum corneum: natural polymers, vesicles, nanoemulsions).

The active methods are sonophoresis, iontophoresis, electroporation, photomechanical waves, thermal ablation and microneedle drug delivery.

***Sonophoresis*.** A method of sonophoresis is based on low-frequency ultrasound which affects the outer layer of the skin cavitating the connective tissue and inhancing skin permeability. The medication is combined with gel or cream, which conduct ultrasound waves into the skin. Thus, the drug is delivered by the routes permitted by ultrasound with frequency ranging from 20 kHz to 16 MHz. The method allows to increase temperature on a localized part of the skin thus creating heat effect which contributes and enhances permeability of the medical substance [33;38].

The advantages of this method are:

1) Rapid penetration of the medical substance into the affected area and maximum concentration in it;
2) Prolonged effect of the medical substance which is stored in the tissues and released gradually afterwards;

3) Additional destruction of the clots.

The disadvantages may include:

1) More frequent medical procedures that are necessary when compared with the invasive methods;
2) Possible after-effects like tingling, irritation and burning sensations;
3) Inability to use the method when the stratum corneum is damaged.

Iontophoresis. This method is based on the use of the galvanic current of low-frequency, which can affect the outer and medial skin surfaces enhancing release and flow of the ionized active pharmaceutical substances which are characterized by low absorption / permeability. Efficiency of iontophoresis depends on polarity, valence and ability of the medical substance molecule to move (thermodynamic activity), nature of the applied electrical current and compositions of the agent which contains the medical substance [12, 13, 34, 38]. The advantages of the method are:

1) Delivery of polar molecules and high molecular weight compounds;
2) Targeted introduction of the medical substance into the affected area bypassing other organs which reduces allergic reactions and inflammations;
3) By hyperpolirising nerve endings it increases excitability threshold and enhances more analgesic effect.

The disadvantages may include:

1) Risk of burn if the electrodes are applied incorrectly;
2) Difficulty to control stability of the drug agent in the carrier;
3) Difficulty in drug release from the carrier;
4) It is contraindicated to the patients with cardiac pacemakers and metallic implants.

Electroporation. A method is based on application of electric impulses of high current ranging from 5 to 500 V. A short-term exposure of the skin (~ms) results in formation and opening of the minute pores in the stratum corneum. The medical substance is diffused through these pores. The method has confirmed its efficacy in drug delivery both with low-molecular weight such as doxorubicin, mannitol or calcein and high molecular weight anti-angiogenic peptides, oligonucleotides and negatively charged heparin anticoagulant [8, 49].

The advantages of the method are:

1) Muscle stimulating effect which improves tonus and blood circulation, it activates cell metabolism and increases skin rejuvenation;
2) High efficiency in targeted drug introduction.

The disadvantages are, that:

1) it can be used only in small areas;
2) there can be damage of the skin cells due to heating effect;
3) medical substance can be destroyed due to high voltage.

Photomechanical waves generated by the laser expose the skin and extend stratum corneum allowing the medical substances to pass through temporary channels. These waves produce limited ablation due to low radiation dose (nearly 5–7 J/cm^2), with the channel depth of 50–400 μm. For instance, dextran macromolecules with molecular weight of 40 kDa and latex particles with 20 ns can be delivered by photodynamic laser impulse 23 nm [27].

The advantages of the method are:

1) it transports the molecules of the medical substance through plasma membrane *in vitro*, thus preserving cell viability;
2) it does not affect the skin;
3) it is painless procedure.

The disadvantages are absence of clinical trials.

Microneedles. Micron sized needles penetrate the outer layer of the skin that results in drug diffusion through the epidermis or outer dermal layer. As the needles are short and fine the unpleasant pain sensations can be prevented, thus allowing the drug to be delivered directly to the blood capillaries. The microneedles can be: 1) microneedles that create a route allowing the drug to enter the body; 2) microneedles can be coated with the drug; 3) microneedles can be produced by the drugs which are absorbed in the body by “melting”; 4) different patches with microneedles [3, 16, 19, 23].

The advantages are:

1) painless introduction of the active pharmaceutical ingredient;
2) quick recovery of the injected area.

The disadvantages are:

1) only small doses of the substances can be used;
2) the secondary introduction decreases absorption in a certain topical area resulting from microclots and/or change in the blood flow at this site.

Thermal ablation. This method of the pointed distruction of the stratum corneum by local heat exposure delivers the drugs through the microchannels in the skin produced during the procedure. This method is based on exposure to high temperature more than 100 °C, resulting in heating and evaporating of keratonin. Thermal exposure lasts for microseconds and prevents epidermis damage. The defects resulting from the thermal ablation are small enough 50–100 mkm in diameter it allows to prevent painful sensations, bleeding, irritation and infection. The method allows delivering effectively small molecules and high molecular compounds. Thermal ablation can be performed by laser or high radiofrequency methods [3]. Laser thermoablation facilitates the drug delivery for more than 100 times and increases

delivery of both lipophilic and hydrophilic substances including peptides, proteins, vaccines and DNA. The radiofrequent thermal ablation method allows to release and deliver broad spectrum of drugs with hydrophilic origin, including macromolecules [25;37].

The advantages are:

1) the procedure is painless;
2) not expensive and disposable materials are used;
3) quick recovery.

The disadvantages are: the method is not recommended in hemostasis system disorders.

Passive methods are represented by (extracellular) vesicles, nanoparticles and nanoemulsions.

Vesicles are lipid bubbles which are secreted mostly by all the types of the cells. Being the carriers of RNA, membranous and cytoplasmatic proteins, lipids and carbohydrates they perform different functions in the human body, for instance, they take part in intracellular communication. According to their origin the vesicles are divided into ectosomes (originating from the neutrophils/monocytes), vecosomes (associated with the vector of adenovirus) etc. According to the biogenesis mechanism they are divided into exosomes, microvesicles and apoptotic bodies [14]. The size of the vesicles varies, for example the size of the exosomes is between 40–120 nm, microvesicles vary 50–1000 nm [4]. Due to such properties as biocompatibility, low immunogenicity (when obtained from the correct type of the cell) and ability to penetrate the blood-brain barrier (BBB) the vesicles appear to become a prospective mean to deliver different molecules.

The advantages are:

1) Controlled release of the medical substance;
2) Control of the drug absorption due to multileveled structure.

The disadvantages are:

1) Chemical instability;
2) High cost;
3) Restrictions associated with the volume of the drug upload.

Nanoparticles are represented by the nanocarriers with the size of 1–1000 nm. Introduction of the medical substance by means of nanoparticles leads to targeted and controlled release, changes in substance dynamics *in vivo* and increase of duration of the uploaded substance in the body which results in better bioavailability, decrease of toxicity and side effects. Nanoparticles can be polymerized or bound; most commonly biodegradable polymer materials like gelatin and polylactic acid are used [13, 18].

The advantages may be:

1) Targeted drug delivery;
2) Mechanical resistance of the carrier;
3) Different biodegradable materials can be used;
4) Both hydrophilic and hydrophobic substances can be delivered;
5) No immune reaction to the carrier.

The disadvantages are:

1) Difficulty for substance release;
2) Incomplete assessment of toxicity.

Nanoemulsions are represented by mixture with low viscosity, isothropic, thermodynamic and dynamic stability. Mixture is composed of transparent or semitransparent oil globules dispersed in water phase which is stabilized by interphase membrane which is formed due to molecules of the outer active substance. The size of the particles in nanoemulsions varies from 100 to 1000 nm. Due to their small size, significant specific surface area and low surface tension of nanoemulsions determine excellent wettability which allows close contact with the skin. Nanoemulsions demonstrate better properties of transdermal absorption than any of the commonly used local appliances [21, 36].

The advantages are:

1) Thermodynamic stability;
2) High solubility and physical stability.

The disadvantages are: variable kinetics of the processes of distribution and clearance of drug delivery (mechanisms).

DEEP EUTECTIC SOLVENTS

Deep eutectic solvents open promising perspectives of the controlled transdermal drug delivery. It is known that such solvents can penetrate the barrier of the stratum corneum and increase transdermal, intercellular and paracellular transport due to the cell integrity destroy, creation of the diffusion routes and solution of the lipid components of the stratum corneum [44, 47].

Deep eutectic solvents (DESs) were first described by Abbott et al [1]. If DES is composed of components of natural origin it is further described as natural deep eutectic solvent (NADES) [45]. DES/NADES are mixtures of two and more components, namely hydrogen bond acceptors (HBD) and hydrogen bond donors (HBD) which may compose eutectic mixtures characterized by very low melting temperature than in their components.

DESs have several advantages like thermal and chemical stability, fast solubility of the chosen substances, inflammability and low melting temperature. Moreover, DES can be obtained simply and cheaply by combination and heating natural and/or widely used substances. As a result these solutions are cheap, biodegradable with very low or lack of toxicity [52].

DES can be classified into several classes according to the nature of HBA and HBD which was used in their obtaining; thus, the salts of quaternary ammonium and anhydrous metal halides (type 1), the salts of quaternary ammonium and hydrated metal halides (type 2), the salts of quaternary ammonium and neutral organic compounds (type 3), salts of metal chlorides and neutral organic compounds (type 4) and mixtures of nonionic compounds (type 5) [2, 48]. Within these five types of DES the separate components can form binary or ternary eutectic mixtures.

NADES is a DES subgroup, which is composed of natural components like sugar, organic acids, (poly)alcohol, aminoacids, choline chloride and water. NADESs in terms of biological systems may serve as solvents which can be alternative to water and lipids, participate in biosynthesis, storing, transporting of poorly soluble in water biomolecules and conserving organisms at very low temperatures [10]. NADES turn to be highly attractive due to their low volatility; they are biodegradable, stable to the solved substances, resistant to air and simple in synthesis. One of the main advantages of NADES is that their properties can be modeled by changing their components, dissolving with water or synthesizing the targeted mixtures for certain purposes [20].

ChCl (Ch, 2-hydroxyethyl-trimethylammonium, vitamin B_4) is the most investigated and well-known component of DES which is quarternary ammonium salt and alcohol. In eutectic solvent mixtures ChCl acts as acceptor of hydrogen bond with different donors like urea, alcohol, sugar, hydroxyl acids and amino acids [45]. ChCl based DESs are very simple, their synthesis allows to control the characteristic features decreasing or increasing viscosity, pH and polarity; these properties make them attractable for pharmaceutical use, food production and cosmetology [11].

ChCl based DES can be grouped according to hydrogen donor relations: alcohol- and sugar containing, acidic, amidic, aqueous and triple mixtures. Most of such mixtures are liquid at a room temperature and can be used as solvents in various fields.

In alcohol- and sugar containing DES glycol, glycerin and different sugars are commonly used as HBD. These solvents have neutral pH in mixtures; it can be applied in various fields [31].

Acid based DESs are composed of natural carbon acids (lactic, lemon, wine etc.) and amino acids.

The mixture of ChCl and urea is one of the most well-known and investigated among amide DES with a ratio of 1:2 [1]. The synthesis of the triple mixtures by introducing of the third donor of hydrogen relation to DES is also possible. Most commonly water is the third donor. Besides water glycerin, methanol, ethanol, 2-propanal etc. can also be used [42].

DEEP EUTECTIC SOLVENTS AS SYSTEMS OF INSULIN DELIVERY

Insulin is a most common medication in the treatment of diabetes and diabetic complications. Nowadays insulin is introduced subcutaneously, such invasive method is rather painful for the patients; the clinicians and scientists look for non-invasive methods of diabetes therapy. A. Vaidya, S. Mitragorty (2020) used choline and geranic acid based solvents as transdermal system of insulin delivery and controlled release [50]. The medication had a form of viscous gel, which could be introduced perorally, the pharmacological effect of insulin was preserved. It was proved that the local introduction of insulin containing DES (insulin dose 25UN/kg) considerably reduced glucose in blood within 4 hours [24].

The method of nasal introduction of insulin based on DES (deep eutectic solvent was based on choline chloride mixture: malic acid) was studied, the method showed hypoglycemic effect [24]. The trial compared to systems of insulin delivery: on the base of hydrogel and on the base of deep eutectic solvents, it was proved that the system of DES insulin delivery was better than the system of hydrogen based insulin delivery and other traditional insulin solvents. The results show the possibility of deep eutectic solvents application as systems for insulin delivery in diabetes therapy.

Thus, it can be concluded that DES applications to be prospective carriers of insulin in the treatment of endocrine diabetes by means of introducing the mixtures transdermally, through mucous membranes of nasal and oral cavities.

DEEP EUTECTIC SOLVENTS AS SYSTEMS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUG DELIVERY

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed medications to relieve pain syndrome and inflammation. The main effect of these medications is achieved by blocking specific prostaglandin synthesis through inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes. The inhibition of COX-2 plays an important role in the anti-inflammatory mechanism and analgesic effect of the medications, besides these effects it can result in disorders of the cardio-vascular system. The disadvantages of the inhibition of COX-1 are in severe gastrointestinal ulceration and nephrotoxicity. If the side-effect on the gastrointestinal tract can be inhibited by phospholipids or simultaneous intake of stomach protecting medications (like proton pump inhibitors), there is still nothing to prevent heart and kidney side effects [17]. Taking into account that NSAIDs are commonly prescribed medications

the transdermal way of introduction seems to be alternative, effective, safe and psychologically comfortable during the course of treatment.

The trials showed that the drugs traditionally introduced intravenously can penetrate transdermally, too [15]. Thus, many kinds of NSAIDs have become available in various forms like creams, gels, patches and solutions (lotions), which are mainly prescribed to patients with muscular-skeletal pains. However, the production of such NSAIDs systems is complicated due to low water-solubility of the active ingredient, which requires highly concentrated organic solvents, e.g., ethanol.

In order to avoid organic solvents and improve delivery of poor water-soluble molecules deep eutectic solvents were investigated as alternative to pharmaceutical solvents and inhancers of transdermal penetration [6, 39]. It was proved that DES can improve solubility of anti-inflammatory drugs (e.g., ibuprofen, naproxen, ketoprofen [26] and paracetomol [29]), and also increase transdermal penetration of the drugs.

DEEP EUTECTIC SOLVENTS AS SYSTEMS OF ANTINEOPLASTIC (ANTITUMOR) DRUGS

In a case of malignant tumor, driver and "passenger" mutations result in significant alteration of signaling pathways which considerably change metabolism of the tumour cells. The area of tumor formation and character of bloodstream in tumor altered tissue form nucleus, lacking oxygen supply, and conditionally considered as a geometrical center of the neoplasm and/or metastases, where more resistant to nutrient and oxygen deficiency cell clones are selected, thus resulting in local evolution of signaling pathways and tumor cell metabolic reprogramming [30]. Thus metabolic pathways turn to appear most preferable targets in therapy of oncological diseases. For example, it was revealed that limonene induces apoptosis through mitochondrial pathway and affects survival potential / apoptosis of the cells passing through PI3K/Akt signaling pathway in a case of cholorectal cancer [5, 7].

Nowadays a significant number of antitumor drugs are synthesized, they affect different metabolic routes; nonetheless, the issues of selective drug delivery are at the cutting edge of science. There are scientific investigations when deep eutectic solvents were used to treat cancer due to their own antitumor activity or their ability to solve active pharmaceutical substances. It revealed that limonene-based DES (ibuprofen: limonene with a molar ratio of 1:4) can effectively inhibit HT-29 colonic cancer cell proliferation without affecting healthy cell viability [40]. The system could preserve not only the therapeutic effect of limonene and ibuprofen but also increased solubility of the both components reducing limonene side effect concerning healthy cell lines.

Betaine and mandelic acid-based DES was synthesized to deliver antineoplastic drugs perorally (cyclopeptide RA-XII). Solubility and bioavailability of RA-XII by peroral introduction increased 17.5 and 11.6 times respectively [28]. It should be underlined that choline and its metabolite betaine-based DES is of great interest, as these compounds participate in basic physiological processes: sustaining structural stability and membrane elasticity due to phosphatidylcholine formation during the metabolic process, acetylcholine synthesis and participation in homocysteine metabolism [28].

Cytotoxicity of N, N-diethylammonium chloride — based DES and choline chloride-based DES by interaction of these solvents and (HelaS3, AGS, MCF-7 и WRL-68) tumor cell lines were investigated with the help of the methods of molecular dynamics [35, 46]. As a result N,N-diethylammonium chloride-based DES showed higher cytotoxicity than choline chloride-based DES, it indicates that N,N-diethylammonium chloride-based DES is potent as independent anticancer drug.

Interesting results are represented by the research of P. Pradeepkumar et al (2021) [43]. The reserarchers developed serine and lactic acid-based DES, the obtained solvent and biotine were introduced to chitosan a polymer carrier. Then doxorubicin for controlled release was applied. HeLa cell line was the model of anticancer activity and *in vitro* apoptosis investigation.

DEEP EUTECTIC SOLVENTS AS SYSTEMS OF STORING AND VACCINE DELIVERING

The vaccines are usually stored at low temperature (2–8 °C) for stability and safety of vaccine efficiency. The vaccines require certain low temperature and they are at risk of unexpected sudden changes of storage; these factors motivate the researchers to find new systems to sustain increased stability that can prolong vaccine storage, facilitate its storage condition avoiding cooling. Moreover, the vaccination is invasive procedure though nasal introduction has become more popular recently. Both methods have great psychological load to small children. That is why new systems of storing at milder conditions as well as non-invasive drug introduction are urgent and relevant tasks.

The scientific investigation [22] performed DES to store human interferon-α_2 at room temperature, and to stabilize and carry the live attenuated vaccines [53]. The other investigation [9] demonstrated natural deep eutectic system application consisting of trehalose and glycerin to store and deliver the vaccine based on virus-like particles (VLP) and influenza hemagglutinin (HA). DES supported stability and

activity of HA-VLP from 4 to 50 °C (increased stability investigation). Moreover, HA-VLP were stable in the solvent for more than a month in an area with standard room temperature (short-term stability investigation).

These investigations show the prospectives in the field of temperature regimen changing in large protein molecules, vaccines and sera, that will allow cost and storage decrease in the near future.

CONCLUSION

The field of deep eutectic solvents application including pharmaceutical industry has considerably increased for the last decade; it is due to their unique characteristics as low toxicity, thermal and chemical stability, biodegradability and high bioavailability. These solvents can be used for solubility and stability of the systems of transdermal drug delivery and transdermal drug delivery system on their base it seems to be highly important for pediatrics. It should be noted that DES themselves have antibacterial, antifungul and anticancer properties. Due to specific properties of DES "smart" nanovaccines development seems to be attractive. The solvents may include modified nanoparticles to achieve controlled and prolonged transdermal immunization. Unlike the traditional method of invasive drug delivery DES allows to arrange a reservoir of medication in the skin thus prolonging duration of drug activity and showing low toxicity in transdermal immunization, absence of pain syndrome and psychological comfort in pediatric therapy.

Nonetheless, despite all advantages it is difficult to achieve stable and long lasting effect of medication release in most cases of drugs based on deep eutectic solvents; these combinations turn to be the variant for single noninvasive drug delivery. Various investigations to study kinetics of the solved drug release should be carried out to develop transdermal therapeutic systems. Moreover, law enforcement practice of clinical trials with drugs introduced transdermally in the form of gels and based on deep eutectic solvents should also be clarified.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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