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Development and Evaluation of a Nose to Brain Drug Loaded Microemulsion

Ram Kale[1], Pranjali Thakare[2], Sudhanshu Sakharkar[3], Ajinkya Lodhe[4], Kunal Davhale[5], Avinash Solanki[6]

Dr.*Vedprakash Patil Pharmacy College ,Chha.Sambhaji ,Nagar* [1]
Laxmi Narayan College of Pharmacy ,Bhopal [2]
Gawande college of Pharmacy Sakherkherda ,Chikhli [3]
Gawande college of Pharmacy Sakherkherda ,Chikhli [4]
Gawande college of Pharmacy Sakherkherda ,Chikhli [5]
Gawande college of Pharmacy Sakherkherda ,Chikhli[6]

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ABSTRACT
The delivery of drugs from the nose to the brain has recently garnered significant interest as an alternative to other modes of administration, particularly the widely used oral route. The nasal cavity possesses unique anatomical characteristics that enable the direct delivery of drugs to the central nervous system when administered intranasally. This approach offers a crucial advantage in circumventing the blood-brain barrier that surrounds the brain, thereby preventing the entry of external substances into the central nervous system. Additionally, the targeted delivery to the brain could potentially minimize the peripheral side effects of pharmacotherapy. The main obstacles associated with nose-to-brain drug delivery primarily stem from the limited capacity of the nasal cavity and inadequate absorption of drugs from the nasal mucosa. However, these challenges can be mitigated by employing a well-designed drug carrier. Microemulsions, as prospective drug delivery systems, exhibit favorable solubilizing properties and the ability to enhance drug permeation through biological membranes. The objective of this review is to provide a comprehensive overview of the current state of research focused on microemulsion-based systems for nose-to-brain drug delivery, with particular emphasis on the extensively investigated neurological and psychiatric conditions, such as neurodegenerative diseases, epilepsy, and schizophrenia.

Keyword : Microemulsions, nose , neurodegenerative diseases, epilepsy, delivery

I. INTRODUCTION

The successful treatment of various neurological and psychiatric disorders relies heavily on the efficient delivery of active pharmaceutical ingredients (APIs) to the brain. When using conventional formulations administered orally or through injection, the drug must traverse multiple biological barriers in order to reach the brain circulation. The primary obstacle that significantly hampers the effectiveness of this treatment is the blood-brain barrier (BBB), an exceptional structure that safeguards the brain. the blood-brain barrier (BBB) serves as a protective shield against potentially harmful external elements, such as chemicals and microbes [1]. Unlike other similar cells in the body, the BBB is comprised of specialized endothelial cells that are densely packed. The key characteristic that determines its functionality is the presence of tight junctions between adjacent cells, which reside in the paracellular space. These tight junctions consist of specific transmembrane proteins, including claudin, occludin, and junction adhesion molecules [2], and play a vital role in regulating the permeability of the BBB to hydrophilic molecules like drugs. In addition to this physical barrier, the BBB is supported by an enzymatic barrier, low pinocytic activity, and various drug efflux mechanisms, such as P-glycoprotein and other multidrug resistance proteins. These mechanisms are responsible for eliminating exogenous substances from the circulation within the brain [1,3]. Pardridge [4] suggests that overcoming this barrier is a challenging task, as it is a common occurrence for more than 98% of small molecule drugs to be unable to cross it. This is true even for drugs with low molecular weight (not exceeding 400 Da) and high lipophilicity, which are typically considered favorable for permeation [5]. Due to its near impermeability to macromolecular compounds [6], the BBB is widely regarded as the most

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formidable biological membrane when it comes to drug delivery [3]. The main factors that influence BBB permeability are summarized below. Figure 1.

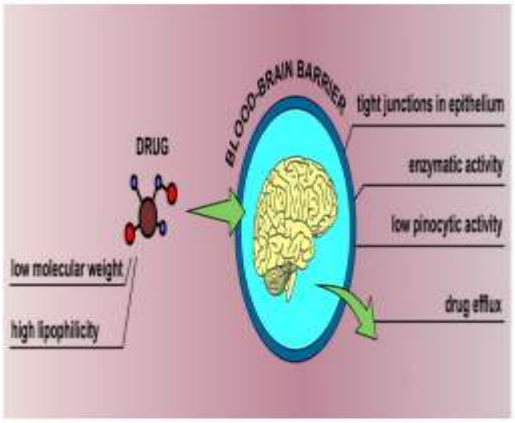

Figure 1
Basic factors affecting the permeability of the blood–brain barrier.

In the past, various invasive and semi-invasive methods have been suggested to effectively deliver the active ingredients to the brain [7]. The invasive techniques encompassed direct intracerebral therapies [8], which involved injecting or infusing a concentrated dose into the parenchymal region of the brain [9]. Another approach entailed using intracerebral implants that release the drug gradually by employing a biodegradable polymer containing the medication. An example of such a manufactured implant is Gliadel™ (Eisai Inc.), which is a polymer wafer with carmustine embedded in the cavity left after the surgical extraction of malignant glioma from the brain [10]. Additionally, drugs can also be administered directly into the cerebrospinal fluid in the subarachnoid space surrounding the brain and in the central canal of the spinal cord. This method is referred to as intrathecal drug administration. All of the aforementioned techniques possess varying degrees of invasiveness, which may lead to complications during and after the operation, such as hemorrhages, catheter dysfunction or misplacement, or catheter-related infections [11,12,13].

Less invasive techniques utilized to overcome the problems related to low BBB permeability include its disruption by approaches like application of hyperosmotic agents [14] or ultrasounds [15]. In all methods involving temporary BBB disruption, the importance of reversibility and duration of tight junctions opening must be emphasized in order to maintain both therapeutic efficacy and safety, especially when considering repeating the procedure. It is noteworthy that increasing permeability of BBB to drugs also exposes the brain to potentially harmful exogenous agents [16].

Numerous studies have been conducted to address the challenges associated with delivering drugs effectively to the brain and mitigate potential side effects of direct methods. The development of innovative, secure, and non-intrusive techniques has been the primary aim of these studies. Chemical modification of drugs to enhance their permeability across the blood-brain barrier (BBB) is the most commonly employed approach. To achieve this, the active ingredient can be chemically bonded to a transport vector, creating what is known as a "Trojan" method. carrier systems have been developed to facilitate the transport of drugs to brain tissue, overcoming the challenges posed by the blood-brain barrier (BBB). Brain-selective vectors such as insulin, transferrin, and low-density lipoproteins have been found to effectively penetrate the barrier through receptor-mediated transport. Peptide-based active ingredients can be converted into their cationic form, allowing them to interact with negatively charged structural elements of the BBB. Another strategy involves the use of inactive prodrugs, which exhibit enhanced ability to cross the tight junctions in the epithelium and are then transformed into active ingredients at the target site. Additionally, drugs intended for brain tissue can be encapsulated in various carrier systems, including cyclodextrins, liposomes, and nanoparticulate systems, to enhance their BBB-crossing ability.

In recent years, nasal cavity administration has emerged as a non-invasive method for drug delivery to the central nervous system. This route offers advantages such as ease of application and rapid absorption of active ingredients from the nasal mucosa, allowing for direct transport to the brain without undergoing hepatic first-pass metabolism, thus maintaining efficacy. Notably, this route bypasses the BBB, making the molecular mass of the drug less crucial for absorption. Studies have shown successful delivery of both small and large molecules through this method. However, there are certain drawbacks associated with nasal cavity administration, including drug degradation in the nasal mucosa, limited capacity of the nasal cavity, and high clearance. To address these limitations, various carriers such as mucoadhesive formulations, polymeric and lipid nanoparticles, micelles, nanostructured lipid carriers,

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nanoemulsions, and microemulsions are employed to enhance the effectiveness of nose-to-brain drug delivery.

In this review, our focus was directed towards microemulsions, which are classified as one of the most extensively studied classes of nanodispersions. The initial description of microemulsions can be traced back to the 1940s [43], and since then they have been subjected to a plethora of scientific investigations, particularly in the context of developing novel carriers for drug delivery [44,45,46,47]. Over the course of several decades, it has been established that microemulsions possess significant potential in enhancing the bioavailability of active pharmaceutical ingredients, especially those with poor water solubility [47,48,49,50,51]. The objective of this study was to provide a comprehensive summary of the existing literature pertaining to microemulsions and the use of microemulsion-based media as vehicles in nose-to-brain drug delivery. Moreover, we aimed to highlight the potential utility of these systems in brain-targeting therapeutic approaches, elucidating both their advantages and disadvantages. It is worth noting that nose-to-brain drug delivery has emerged as one of the most extensively explored therapeutic approaches, wherein the appropriate selection of the carrier plays a crucial role in determining treatment efficacy. Microemulsions can be regarded as promising vehicles for delivering various therapeutic agents through this route; however, it is important to acknowledge that they are not without limitations, as indicated by the research findings presented in this review.

II. MICROEMULSION

2.1.Definition.

Microemulsions were initially described by Hoar and Schulman [43] through an experiment involving the titration of coarse emulsions with a co-surfactant. This led to the observation of turbid emulsions spontaneously transforming into transparent, isotropic liquids, which were later identified as microemulsions. As per the widely accepted definition formulated by Danielsson and Lindman [52], a microemulsion is a thermodynamically stable and optically isotropic liquid system consisting of water, oil, and an amphiphile, typically enhanced by a co-surfactant. This definition allows for a clear distinction between microemulsions and other colloidal systems such as micellar solutions that contain only polar or non-polar phases, coarse emulsions, and thermodynamically unstable nanoemulsions or anisotropic liquid crystals. It is evident that the qualitative composition of a microemulsion shares similarities with the components required to form a coarse emulsion. However, the key differentiating factor lies in the transparency exhibited by microemulsions. It is important to highlight that the diameter of the dispersed phase particles in microemulsions is typically... he size of the dispersed phase particles in the system is such that it does not go beyond 100 nm, a value significantly smaller than the wavelength of visible light [53,54]. Consequently, the light that traverses the system does not engage in any interaction with these particles and is not subjected to diffraction

The term 'microemulsion' can be misleading as it suggests that the particle sizes are in the micrometer range. However, microemulsions are actually nanodispersions. Despite this, they share many similarities with nanoemulsions, although they are fundamentally different systems from a thermodynamic perspective. Both types of dispersions consist of polar and non-polar phases that are stabilized by one or more surfactants. Furthermore, nanoemulsions are often perceived as transparent or translucent liquids due to the presence of small droplets in the dispersed phase. However, it is important to note that nanoemulsions are only kinetically stable, meaning they exist in a metastable state and can potentially undergo destabilization over time. Nevertheless, the presence of physical factors such as steric and electrostatic repulsion, Brownian motion, and others, prolongs the destabilization time by preventing droplet coalescence. On the other hand, microemulsions are thermodynamically stable, meaning they have achieved a state of minimum free energy and do not have a tendency to transform into separate phases. It is worth mentioning that nanoemulsions are also considered as promising drug delivery systems, particularly for nose-to-brain drug transport, and have been the subject of numerous studies. For a more comprehensive review of the current research on the application of these systems in nose-to-brain drug delivery, refer to other comprehensive reviews.

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Microemulsions consist of polar and non-polar phases which are stabilized by an amphiphilic agent that reduces the interfacial tension between these two components, as previously mentioned. It should be noted that the interfacial tension in microemulsions is exceptionally low. In order to achieve values that approach zero, an additional agent that enhances the surfactant effects is often required. In this context, co-surfactants, which are low molecular weight compounds with a strong affinity for both phases, are commonly employed. Short-chain alcohols like ethanol, isopropanol, and propylene glycol are frequently used in pharmaceutical formulations [58,59,60].

Classification of Microemulsions

Depending on the quantitative composition of the system, three different microemulsion types can be formed:

- Water-in-oil (W/O) with water as the dispersed phase and oil as the continuous one,
- Oil-in-water (O/W) with oil as the dispersed phase and water as the continuous one,
- Bicontinuous with water and oil forming interpenetrating three-dimensional domains without the possibility to discern internal and external phases.

It is important to note that the presence of bicontinuous systems is exclusively typical for microemulsions, whereas both W/O (water-in-oil) and O/W (oil-in-water) systems can also be observed in other types of dispersions, such as coarse emulsions and nanoemulsions. This distinctive system typically forms when there are equal amounts of polar and non-polar phases, while W/O and O/W systems are observed when higher quantities of oil and water are utilized, respectively [63]. It is worth mentioning that transformations between O/W and bicontinuous systems, as well as W/O and bicontinuous systems, can be observed when there is an increase in the content of water or oil. Similar transformations can also be achieved through changes in temperature and are extensively described as percolation transitions..

Winsor [64] proposed an alternative classification for microemulsions. According to this classification, there are four types of microemulsions. Winsor I and II represent O/W and W/O microemulsions, respectively. As mentioned earlier, these microemulsions consist of one phase dispersed in the form of droplets within another phase. In pseudoternary phase diagrams commonly used to depict phase equilibria in microemulsions, Winsor I and II remain in equilibrium with the water and oil phases, respectively. On the other hand, Winsor III is a bicontinuous microemulsion that coexists with both the oil and water phases. Lastly, Winsor IV is a single phase microemulsion region that occurs when the surfactant content increases, and it does not coexist with any other phase.

Formation Process and Microemulsion Stability

Microemulsion possesses a notable characteristic in its spontaneous formation process, which sets it apart from nanoemulsions that are typically prepared using ultrasound or high-shear homogenization [61]. This unique phenomenon can be attributed to the thermodynamic properties of the system. The alteration in free energy linked to the formation of microemulsion can be elucidated by the Gibbs–Helmholtz equation (Equation (1)),

$$\Delta G_{form} = \Delta A \gamma_{o/w} - T\Delta S_{conf} \quad (1)$$

The change in free energy during the formation process, ΔG_{form}, is influenced by various factors such as the change in interfacial area between polar and non-polar phases, ΔA, the interfacial tension, $\gamma_{o/w}$, temperature, T, and the configurational entropy change, ΔS_{conf} [62]. In order for a spontaneous process to occur, ΔG_{form} must have negative values. As previously mentioned, the interfacial tension is close to zero, resulting in a very low value for $\Delta A\gamma_{o/w}$, despite the significant increase in interfacial area due to the formation of numerous small droplets. Considering that droplet formation also leads to an increase in entropy, it becomes evident that $T\Delta S_{conf} > \Delta A\gamma_{o/w}$. Consequently, ΔG_{form} is negative in the case of microemulsions. It is worth noting that an extremely low interfacial tension plays a crucial role in this process.

The necessity of a co-surfactant in most systems is elucidated, highlighting its crucial role in the technological process and production costs. This attribute holds immense significance as it eliminates the need for specialized equipment that consumes substantial energy, owing to the spontaneous formation it facilitates..

- **Nose to Brain Mechanism of Deliverry:**

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The nasal cavity is divided into two areas for drug delivery: the respiratory area and the olfactory area. The olfactory area is located high up in the nares, while the respiratory area is closer to the nostrils. Extensive research has been conducted

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to investigate the feasibility of using olfactory neurons as a direct route for drug transport to the cerebrospinal fluid (CSF) and brain. We now understand that drugs can enter the brain from the nasal cavity through two different pathways. One pathway is through the systemic circulation, where some of the drug is absorbed into the rich vasculature of the respiratory epithelium and then crosses the blood-brain barrier (BBB) to reach the brain. The other pathway is through the olfactory pathway, where the drug is directly delivered to brain tissue, bypassing the BBB. The drug can cross the olfactory epithelial cells by moving slowly through the tight interstitial space between cells or by being transported across the cell membrane through endocytosis or vesicle carriers and neurons. There are three likely mechanisms for the direct nose-to-brain drug delivery, including at least one intracellular transport-mediated route and two extracellular transport-mediated routes. The exact mechanism by which compounds transfer from the nasal mucosa to the brain is not fully understood, but it is known that absorption occurs at the olfactory and respiratory epithelia. The transfer of compounds through the olfactory area of the nares to the olfactory bulb can occur either transcellularly through sustentacular cells or through exposed olfactory sensory neurons. The intracellular transport-based route is relatively slow, taking hours for intranasally administered substances to reach the olfactory bulb. The olfactory neurons in the olfactory epithelium can uptake molecules through processes such as endocytosis. The olfactory bulb can be reached through axonal transport, which allows for the rapid entrance of drugs into the brain shortly after intranasal administration. There are two potential extracellular transport-based routes that could facilitate this process. In the first route, substances administered intranasally can cross the gaps between olfactory neurons in the olfactory epithelium and then be transported into the olfactory bulb. The second route involves substances being transported along the trigeminal nerve, bypassing the blood-brain barrier. Once they reach the olfactory bulb or trigeminal region, these substances can diffuse into other areas of the brain. It is worth noting that intranasally administered drugs can also partially enter the central nervous system through systemic blood circulation from the nose. One significant advantage of the nose-to-brain route is the potential to reduce plasma exposure, as has been demonstrated.

Clinical Use of Nose-to-Brain Delivery:

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