Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

Recent Advancement in Self Emulsifing Drug Delivery System

Vijay Laxmi Bist[1] and Dr. Abdul Faruk[2]

[1]Research scholar, Department of Pharmaceutical Sciences HNB Garhwal University (A Central University), Chauras Campus, P.O. Kilkileshwar, Via Kritinagar Distt. Tehri Garhwal, Pin-249161, Uttarakhand, INDIA.

[2]Professor & Head of department, Department of Pharmaceutical Sciences HNB Garhwal University (A Central University), Chauras Campus, P.O. Kilkileshwar, Via Kritinagar Distt. Tehri Garhwal, Pin-249161, Uttarakhand, INDIA.

[1]Corresponding Author: vinnybisht12@gmail.com

www.jrasb.com || Vol. 2 No. 2 (2023): April Issue

Received: 30-03-2023	**Revised:** 10-4-2023	**Accepted:** 20-04-2023

ABSTRACT

Every day, researchers make new attempts to identify neurotherapeutics, but few of them make it to clinical trials. The main cause is their low bioavailability, which is connected to low water solubility, low permeability through biological membranes, and the hepatic first-pass metabolism. However, the most significant challenge in administering drugs to the brain is overcoming the blood-brain barrier. In order to get around it, intranasal administration has become more popular, sometimes even more so than oral administration. Because of its structure, the nasal cavity can bypass the blood-brain barrier and transport drugs to the brain directly. Nasal absorption increases the systemic bioavailability of highly processed substances because they bypass the hepatic first-pass metabolism. However, due to their unique physicochemical properties, most neurotherapeutics must be synthesized in lipidic nanosystems as self-emulsifying drug delivery systems (SEDDS). To load large quantities of lipophilic medicines into micro or nanoemulsions, these isotropic mixes of oils, surfactants, and co-surfactants are diluted in water. The goal of SEDDS is to increase the stability of labile pharmaceuticals against enzymatic activity, boost drug penetration through absorptive membranes, and reduce the likelihood of drug precipitation at absorption sites. Therefore, improved brain targeting and bioavailability of medications might be anticipated by combining the benefits of SEDDS with those of the intranasal route for brain delivery. In order to better understand the mechanisms involved in the intranasal administration of pharmaceuticals loaded in SEDDS, this paper provides a comprehensive characterization of SEDDS as a lipidic nanosystem. Finally, the in vivo effects of intranasal or oral delivery of SEDDS, showing their superiority over standard solutions or suspensions, are described.

Keywords- Neurological, Nasal, SEDDS, Blood brain barrier.

I. INTRODUCTION

The incidence of neurological illnesses has been on the rise in recent years. The World Health Organization (WHO) estimates that one billion people worldwide suffer from neurological illnesses in 2021 [1]. Epilepsy affects 50 million individuals worldwide, while cerebrovascular illness affects 62 million, migraines affect 326 million, and Alzheimer's disease and other dementias affect 24 million. Because of this, neurological illnesses are among the leading causes of death and disability [1,2]. In light of this, significant effort is put forth on a daily basis to discover and develop novel and effective neuropharmaceuticals, despite the fact that the vast majority of new entities never make it to clinical trials [3].

Drugs need to avoid being broken down by the body's absorptive membranes, get past the liver's first-pass effect, and then cross the complicated blood-brain barrier (BBB) in order to reach the brain [3,4]. Lipophilic, low-molecular-weight (400 Da), nonionizable at physiological pH, and non-substrates of active efflux transporters are all necessary for molecules to cross absorptive membranes and the BBB [3,5].

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

Because of these factors, between 40 and 70 percent of the newly discovered chemical entities used to treat neurological illnesses are placed in BCS classes II and IV [6,7]. Class II medications are poorly soluble in water but highly permeable at therapeutic levels, while class IV pharmaceuticals are poorly soluble in water and poorly permeable. This can reduce the drug's bioavailability and delay the beginning of its effects [8,9]. It can also reduce the drug's solubility, absorption rate, and extension. Therefore, substantial dosages must be administered to obtain plasmatic therapeutic concentrations, leading to both drug waste and perhaps an increase in side effects and drug-drug or food-drug interactions [10].

To address these issues, new formulations have been created, with lipidic nanosystems receiving increasing attention in recent years. The primary objective of these systems is to maintain the solubility of lipophilic substances in aqueous environments, such as the GIT or nasal mucosa [11]. Lipophilic BCS class II and IV medicines can be easily included into self-emulsifying drug delivery systems (SEDDS) [12,13], a form of lipidic nanosystem. More research into SEDDS technology [14] has been prompted by the commercialization of drugs like SandimmunNeoral®, (cyclosporin A) by Novartis Pharmaceuticals (USA), Norvir® by AbbVie Inc. (North Chicago, IL, USA), and Fortovase® by Roche (Basel, Switzerland). [15,16] In addition to these, there are currently on the market products that are based on liquid SEDDS that are either encapsulated in hard gelatin capsules (Gengraf® (cyclosporine) (AbbVie Inc., North Chicago, IL, USA) or in soft gelatin capsules (Agenerase® (amprenavir) (Glaxo Group, United Kingdom), Depakene® (valproic acid) (AbbVie Inc., North Chicago, [17,18]. It's true that SEDDS might be expanded to include most medications from BCS's classes II and IV. They may be more bioavailable without requiring large dose administration if their aqueous solubility and, subsequently, their absorption are enhanced [19].

Up until now, oral administration of SEDDS has been the primary focus of research [20,21,22]. However, alternative routes of administration can be of great interest for SEDDS, especially if they permit improved brain targeting of CNS-active medicines. In this regard, the investigation of SEDDS and other lipidic nanosystems for the intranasal (IN) delivery of medicines is warranted. The nasal cavity is the only opening in the body that provides direct access to the central nervous system from the outside world. Because medications can be carried partially directly to the brain via this channel, bypassing the BBB [23,24,25], it has become a particularly appealing administration route in the treatment of neurological illnesses. Medications inhaled or sprayed into the nasal cavity can potentially enter the brain via the bloodstream. Because of this, drugs can be absorbed systemically without going through the digestive system or experiencing the "first-pass effect" in the liver [26,27,28,29]. Although highly powerful medications are still needed, the risk of precipitation loading with a SEDDS is decreased due to the nasal cavity's small aqueous volume compared to the GIT. Since the pH range of nasal mucosa is between 5-6.5, [30] IN delivery incorporated into SEDDS can help overcome the problem of medicines becoming unstable in acid settings. Better therapeutic management of patients and increased brain bioavailability could result from combining the advantages of manufacturing neurotherapeutics in SEDDS with the possibilities of the IN route for nose-to-brain transport. Doing so has the potential to prevent a wide range of diseases and therapy-related chronic problems.[31]

In this paper, we present in detail the idea of SEDDS as lipidic nanocarriers, paying special attention to the crucial steps in their evolution. Here, we talk about research that included neurotherapeutic drugs in SEDDS, paying special emphasis to the physicochemical and in vitro evaluation of these substances. We then go on to detail how medications in SEDDS are transported to the brain following intravenous (IN) administration. Finally, we discuss the in vivo parameters obtained following intravenous (IV) or oral administration of neuropharmaceuticals loaded in SEDDS, providing insight into the potential of SEDDS to improve upon the treatment of neurological disorders over more conventional pharmaceutical forms.[32,33]

II. SEDDS DEVELOPMENT FOR DELIVERY OF NEUROTHERAPEUTICS AGENTS TO THE BRAIN

In general, the size of polymeric nanoparticles is between 1 to 999 nm. Poly(D,L-lactic acid) (PLA), poly(-caprolactone) (PCL), poly(lactic-co-glycolic acid) (PLGA), and natural polymers like chitosan and maltodextrins are commonly utilized to create polymeric NPs. Using techniques such as solvent evaporation, nanoprecipitation, super critical fluid technology, and hot or cold homogenization, they are synthesized by the self-assembly of two or more chains of block copolymers of varied hydrophobicity[34,35]. PLGA NPs have been studied extensively as drug delivery systems due to their many benefits, including their ability to easily cross the BBB, their biocompatibility, their stability, their controlled release kinetics, their high drug loading capacity, and their ability to be functionalized with surface ligands for targeted drug delivery [36].[37][38]. In addition, hydrolysis of PLGA NPs yields lactic and glycolic acids, which then enter the Kreb's cycle and are eliminated in the form of carbon dioxide and water [39]. Drug release occurs by breakdown of the bulk matrix; however, the rate of polymer degradation can be affected by various environmental conditions, including pH and the

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

physicochemical features of the NP. As a result, the pattern of release might shift, but usually has two distinct phases [40]. It has been shown that macrophage activation and reactive oxygen species (ROS) production are caused by increases in PLGA NP size and concentration as well as changes in shape, leading to cytotoxicity in vitro. More research on the physiological and toxicological responses to PLGA in vivo is warranted, despite the abundance of evidence suggesting that the material is biocompatible. [41]

2.1 Solid Lipid Nanoparticles

SLNs are 50-1000 nm in size and are colloidal nanocarriers. High pressure homogenization, ultrasonication/high speed homogenization, and solvent emulsification/evaporation procedures can all be used to prepare these solid physiological lipids, which are made up of phospholipids, triglycerides, fatty acids, and steroids [42]. Scalability, repeatability, and the absence of hazardous solvents in production are all advantages of these preparation methods [43]. Homogeneous matrices, drug-enriched cores, and drug-enriched shells are all possible methods of drug incorporation into SLNs. Dependent on lipid content, pH, temperature, and the drug entrapment model, release occurs through particle biodegradation by lipases, erosion, or diffusion [44]. Because of their lengthy shelf life, increased stability, and controlled release of drugs, SLNs are a promising drug carrier [45]. SLNs are biocompatible and readily traverse the BBB [46] since they are made out of biological lipids. These lipids are solid after delivery because their melting point is greater than the internal body temperature [47,48]. Pharmaceutical applications for SLNs include the release of doxorubicin, tamoxifen, docetaxel, and methotrexate for the treatment of cancer; carvedilol for the treatment of high blood pressure; tazarotene for the treatment of skin conditions; chloroquine for the treatment of malaria; and isoniazid and rifampin for the treatment of tuberculosis [49,50,51].

2.2 Surface Charge

Nanoparticle (NP) destiny, biodistribution, and cellular uptake are all affected by their surface charge in biological systems. Positively charged NPs diffuse more slowly in tissues and accumulate less in tumor tissues, while negatively charged NPs do the opposite [52]. Cationic NPs are more readily internalized by cells than neutral or anionic NPs because of their favorable electrostatic interactions with negatively charged cell membranes. Because of this, BBB endothelial cell membranes take in positively charged NPs with greater ease [53]. The quick clearance of cationic NPs from the blood by macrophages is a downside to the ease with which they can be taken up by cells. Furthermore, positively charged NPs are linked to increased liver accumulation, which in turn causes rapid plasma clearance and decreased bioavailability [54]. It has been suggested that positively charged NPs may cause haemolysis and toxicity by reacting with blood components [55]. In addition, cationic NPs have been proven to cause cytotoxicity and disrupt the BBB, although neutral and anionic NPs have not been demonstrated to have these effects [56]. Particle design should give careful consideration to the surface charge of NPs, and the charge should be adjusted as needed. The surface chemistry of PLGA NPs and SLNs can have a favorable or negative effect, depending on the synthesis technique.[57]

2.3 Surface Modification

Biocompatibility, brain targeting, stability, and controlled drug release can all be enhanced by the use of surface-engineered PLGA NPs and SLNs. Chemical grafting or adsorption can be used to coat the surface of PLGA NPs and SLNs with polymers such as poly(ethylene glycol) (PEG), poly(ethylene chloride) (PCL), chitosan, and PEG-based surfactants like polysorbate 80 and poloxamer 188. Reticuloendothelial system (RES) absorption is blocked because these moieties are hydrophilic, which also increases steric hindrance and circulation time [58]. Commonly used to increase circulation time, biocompatibility, and brain uptake, especially in pathological conditions[59],[60],[61], PEGylation of NPs for CNS drug delivery is widely practiced.[62]. As an example, chitosan modification of SLNs protected against particle breakdown at the acidic pH of the stomach after oral delivery [63]. Polymer coatings are not the only way to preserve drugs.

Drug targeting can be enhanced by conjugating proteins, aptamers, peptides, small molecules, and antibodies to the surface of PLGA NPs and SLNs. Drugs with a strong affinity for BBB endothelial cell-expressed receptors and transporters can be directed specifically to the central nervous system. Receptor-mediated transcytosis and carrier-mediated transport processes are aided in the brain's uptake of NPs by ligands like transferrin, lactoferrin, apolipoprotein E, glucose derivatives, and glutathione [64]. The transactivator of transcription is an example of a cell-penetrating peptide (CPP) that can be attached to the surface of NPs via covalent or non-covalent interactions[65]. Increased BBB crossing and cellular absorption of drug-loaded NPs can be achieved through conjugation with CPPs [66]. P-glycoprotein (P-gp) efflux pumps expressed by BBB endothelial cells are linked to multi-drug resistance [67]. CPPs, however, can circumvent these pumps.

Conjugation with mucoadhesive agents enables particles to be inhaled and transported through the nasal passages to the brain. For intranasal drug delivery, chitosan, a bioactive polymer that enhances cell penetration and has mucoadhesive properties, is often included as an excipient (for a recent review of chitosan and its mucoadhesive properties, see Aderibigbe et al. (2019) and Mura et al. (2022) [68][69]). Chitosan can increase cell membrane penetration and residence time by interacting electrostatically with the negatively charged epithelial surfaces of the nasal cavity [70]. This polymer also absorbs water from the mucus lining the

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

nasal canal, making it enlarge when it comes into touch with mucus. As a result, more of the drug is exposed to the membrane before it is able to penetrate into the brain [71]. For this reason, numerous chitosan-based nasal formulations have been proposed as drug delivery systems to the CNS, including chitosan-dopamine and chitosan-tyrosine conjugates for PD [72], chitosan hydrogels for drug delivery in AD [73], chitosan-poloxamer gel for anti-epileptic drug (AED) delivery [74], chitosan nanoemulsions for glioblastoma multiforme (GBM) therapies [75], and chitosan-poloxamer nanoemulsions for the treatment of cerebral ischemia [76].

While NPs can be synthesised from chitosan, it is commonly used as a surface coating to enhance mucoadhesion and particle transport across the nasal mucosa and into the brain.

III. PLGA NPS AND SLNS ARE COMPATIBLE WITH BRAIN CELLS IN VITRO

To confirm the safety of PLGA NPs and SLNs in the brain microenvironment, both particle types have been studied in vitro for compatibility with neurons and other resident brain cells. PLGA NPs did not affect the integrity of human SH-SY5Y neuroblastoma cells, monocytes, and 16 HBE epithelial cells used to model the BBB, rodent PC12 catecholaminergic neurons, brain endothelial cells, primary microglia and primary astrocytes, or murine hippocampal neurons, N2a neuroblastoma cells, and N9 microglia [25][42][43][44][45][46][47][48]. Notably, prolonged PLGA NP exposure did not alter neuronal morphology or affect the viability of primary rat neuronal-glial mixed cultures up to concentrations of 2.5 mg/mL [49]. Remarkably, 20 mg/mL PLGA NPs was not toxic to 16HBE cells [50]. Similarly, the application of SLNs to human hCMEC/D3 cerebral vascular endothelial cells, SH-SY5Y cells, primary rodent astrocytes, and brain endothelial cells or mouse BV-2 microglia, brain endothelial cells, and embryonic fibroblasts did not affect cell viability [13][51][52][53][54][55].

Furthermore, both PLGA and SLN nanosystems have been deemed compatible with various types of stem cell. The growth of mesenchymal stem cells on PLGA-based platforms was unaffected by the presence of polymeric structures [56]. In a study investigating the potential of SLNs to deliver neuronal differentiation factors to induced pluripotent stem cells (iPSCs), SLNs were non-toxic to stem cells [57]. Flow cytometry revealed no difference in the number of live cells when a human iPSC-based BBB model was exposed to 50 and 100 nm PLGA NPs for 20 h [58], highlighting the potential for the safe translation of these nanocarriers to the clinic for drug delivery to the CNS.

3.1 Permeation of In Vitro BBB Models

In vitro models have been established to confirm the ability of PLGA NPs and SLNs to cross the BBB. Cells that make up the BBB can be cultured in a monolayer on transwell devices so that following the application of NPs, the percentage that pass through the cell layer into medium on the basolateral chamber can be quantified (for review of in vitro BBB models, see Williams-Medina et al., 2020 [59]). The modification of PLGA NPs with lactoferrin or anti-transferrin receptor monoclonal antibody increased BBB crossing in vitro [45][60]. Similarly, SLNs effectively crossed cerebral vascular endothelial cells and conjugation with apolipoprotein E or transferrin significantly increased cell uptake [13][51]. In a multicellular BBB model consisting of primary rat brain endothelial cells, astrocytes, and pericytes, SLNs penetrated the barrier and targeting was increased over 3-fold by surface modification with apolipoprotein E [54].

IV. PLGA NP AND SLN DRUG DELIVERY TO IN VITRO CNS DISEASE MODELS

Prior to in vivo evaluation, PLGA NP and SLN drug delivery vehicles have been evaluated in in vitro models of neuroinflammation, neurodegeneration, and brain cancers to assess drug release and drug action.

4.1 Neurodegenerative Disease

In vitro models of neurodegeneration can be achieved by applying disease salient factors to brain-derived cells. Insights into the in vivo efficacy and therapeutic doses of substances released from PLGA NPs and SLNs can be gained through in vitro screening. PLGA-PEG NP delivery of fucoxantin, a marine carotenoid that is reported to have neuroprotective effects, prevented Aβ-induced neurotoxicity, ROS production, and the release of pro-inflammatory cytokines in SH-SY5Y and BV-2 microglia cells [61]. Pre-treatment with resveratrol-loaded PLGA NPs inhibited H_2O_2–induced ROS production and was protective against 1-methyl-4-phenylpyridinium (MPP^+)-induced mitochondrial dysfunction and cytotoxicity in SH-SY5Y cells as an in vitro model of PD [45]. Similarly, the concurrent application of drug-loaded SLNs with 6-hydroxydopamine (6-OHDA)-induction of an SH-SY5Y cell model of PD was cytoprotective [52]. SLNs also successfully delivered anti-inflammatory therapies to lipopolysaccharide (LPS)-stimulated microglial cells, attenuating nitric oxide production, the expression of nitric oxide synthase and cyclooxygenase-2 (COX-2), and the production of pro-inflammatory cytokines [53]. The release of idebenone, an anti-oxidant agent, from SLNs was protective against 2,2′-azobis-(2-amidinopropane)dihydrochloride-induced oxidative stress in primary rat astrocytes, as measured by a reduction in cytotoxicity and the production of ROS [55].

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

4.2 Brain Cancer

Robust in vitro models of brain cancers exist, which involve culturing tumour cells and testing drug efficacy by measuring cell death. PLGA NPs loaded with a derivative of the anti-cancer drug temozolomide were non-toxic to 16HBE cells but reduced the viability of T98G GBM cells to 20% of control [77]. Doxorubicin-entrapped SLNs induced cell death when applied to U87MG GBM cells [62]. Furthermore, PLGA NPs conjugated with an anti-epidermal growth factor receptor (EGFR) monoclonal antibody and loaded with curcumin achieved a reduction in the growth of EGFR-expressing GBM cells at lower concentrations than those required for free curcumin or unmodified curcumin-loaded PLGA NPs to achieve this effect [63]. Lipid-based and polymeric NPs are also being explored for the delivery of chemotherapeutic agents in paediatric cancers (for review see Guido et al., 2022 [78]).

V. INTRANASAL ADMINISTRATION AS AN ALTERNATIVE TO THE ORAL ROUTE IN BRAIN DRUG DELIVERY

The nasal vestibule, respiratory, and olfactory regions make up each half of the nasal cavity, which is divided in half by the nasal septum. The nasal vestibule is a small, hairy area at the nose's entrance that also includes sebaceous glands [79]. It is bordered with squamous epithelium. The nasal cavity is mostly used for breathing. It contains the nasal turbinates and is lined with ciliated pseudostratified columnar epithelium (respiratory epithelium). The nasal turbinates, which are made up of sinusoids and erectile tissue, are vascular structures that serve to humidify and warm incoming air and permit venous congestion. The olfactory area sits atop the nasal cavity, around 7 centimeters from the nostrils. Figure 1 shows that the olfactory epithelium is lined with pseudostratified columnar epithelium and that the olfactory nerve offers direct access to the central nervous system.The nasal vestibule, respiratory, and olfactory regions make up each half of the nasal cavity, which is divided in half by the nasal septum. The nasal vestibule is a small, hairy area at the nose's entrance that also includes sebaceous glands [80]. It is bordered with squamous epithelium. The nasal cavity is mostly used for breathing. It contains the nasal turbinates and is lined with ciliated pseudostratified columnar epithelium (respiratory epithelium). The nasal turbinates, which are made up of sinusoids and erectile tissue, are vascular structures that serve to humidify and warm incoming air and permit venous congestion. The olfactory area sits atop the nasal cavity, around 7 centimeters from the nostrils. Figure 1 shows that the olfactory epithelium is lined with pseudostratified columnar epithelium and that the olfactory nerve offers direct access to the central nervous system.

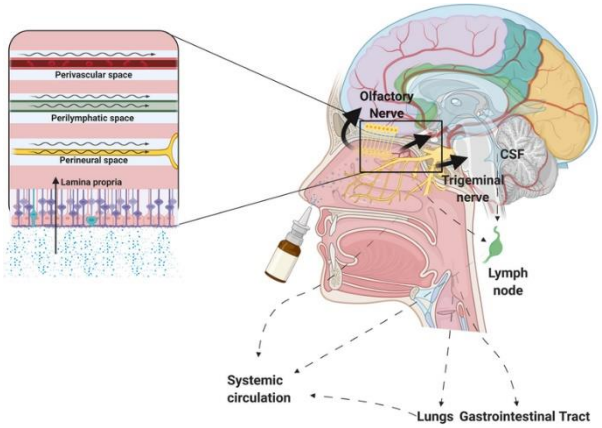

Figure 1: Pathways from the nose to the brain.

The olfactory epithelium in the nasal cavity's upper part is where drugs should be deposited for them to reach their intended target, the brain. The olfactory nerve cells are located in this area, and they have direct access to the brain and CSF without going via the BBB. The continuous lines represent information traveling from the nose to the brain, while the dotted lines represent clearance. The box depicts transport via the perivascular pump, bulk flow, lymphatic drainage, and endoneural transport via the olfactory and trigeminal nerves. It is possible for a little amount of an intranasally delivered medicine to enter the central nervous system via carotid artery branches, however the vascular endothelium's permeability is the key limiting barrier for this route. No considerable systemic absorption occurs via the nasal mucosa.

Pre-clinical research has suggested multiple routes for human nose-to-brain transfer. Due to essential anatomical and physiological distinctions, evidence from animal studies is not easily transferrable to humans. However, clinical investigations have shown that substances can be delivered to the brain via the nasal passages, though the exact paths have yet to be validated.

Airborne particles larger than 12 m are filtered out by the vibrissae, turbulence, and mucosal contact in the nasal vestibule after inhalation [81]. The nasal valve, made up of the turbinates and cartilages of the nose, is the entry point for substances into the respiratory system. Selective autonomic innervation causes congestion and decongestion of the nasal turbinates every 3-7 hours [82]. The nasal valve might temporarily collapse as we age due to increasing tissue elasticity [83]. Airflow is especially sensitive to the nasal valve since it has the smallest cross-sectional area in the nose. The number of chemicals reaching the olfactory system is decreased by this process. However, with the right equipment, up to 45% of a medication can be delivered to the nose [84]. Because of its enormous nasal surface area (about 130 cm2) and extensive vascular supply, the respiratory system may be able to absorb the residual medication [85]. As the maxillary branch of the trigeminal nerve

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

accesses the central nervous system via the pons, it is an important target for CNS drug transport [86.87]. In a recent investigation using rats, researchers were able to confirm that intranasal insulin travels along with the trigeminal nerve's extracellular components to the central nervous system [88]. These results imply that macromolecules delivered intranasally can cross the BBB and reach the central nervous system via the trigeminal nerve [89]. Drugs that are able to bypass the nasal valve reach the olfactory area, the only part of the brain that has direct contact with the environment. It has been hypothesized that drugs delivered through the nose are mostly absorbed by the olfactory epithelium [90]. The human olfactory region has a surface size of 2-10 cm2. The olfactory nerve, on the other hand, may be reachable from a wider area [91]. Drugs undergo intracellular and extracellular transport along the olfactory nerve once they have crossed the olfactory epithelium. Lipophilic medications are transported via paracellular passive diffusion, while hydrophilic drugs are transported via carrier-mediated transport, with a lesser role for endocytosis and axonal transport [92]. Olfactory nerve cells travel through the cribriform plate of the ethmoidal bone to the olfactory bulb in the central nervous system. The amygdala, orbitofrontal cortex, and hippocampus all receive sensory input from the olfactory bulb. Drugs can reach the brain via the olfactory bulb in a few different ways, depending on their properties: axonal transport, passive diffusion, or carrier-mediated transport. Absorption via the paracellular space of the olfactory mucosa, perivascular and perineural transport into the lamina propria, and the Cerebrospinal Fluid (CSF), make up the extracellular route [93]. Different transport processes, including intracellular and extracellular transport, perivascular pumping, and bulk flow, are involved in the drug's journey via the lamina propria through the nerves, arteries, and lymphatics.

Subepithelial layer of loose connective tissue including nerves, blood arteries, and lymphatics (lamina propria) has been shown to transfer chemicals into brain parenchyma [94] by bulk flow and perivascular pumping. In order to propel the contents of the perivascular space forward, the perivascular pump mechanism relies on systolic arterial pressure waves propagating through the vessels [95]. Ethmoidal arteries, which originate in the ophthalmic and internal carotid arteries, provide an abundant blood supply to the nose [8]. Substances can enter the central nervous system via the perivascular areas surrounding these arteries [5,11].Studies comparing intranasal and arterial administration in animals have shown that substances administered in the former route enter the cerebral perivascular spaces within 20 minutes [16], are found in greater concentrations in the dura mater and circle of Willis [17], and are found in greater concentrations in the deep and superficial cervical nodes of rats [95], indicating that they may be transported via lymphatic drainage from the nasal passages and CSF. The maxillary, ophthalmic, and facial arteries, all of which are branches of the carotid artery, are the primary routes through which intranasal medicines reach the central nervous system. The key limiting hurdle for this pathway is the permeability of the vascular endothelium. The nasal cavity is also densely innervated by the body's autonomic nervous system, thus it's not impossible for signals to travel along parasympathetic neurons to the sphenopalatine ganglion. When medications are unable to enter the olfactory system, they are broken down by enzymes and eliminated by the mucosa and cilia. Even if only a little amount of the drug is left, it may be reabsorbed into the systemic circulation through the respiratory mucosa [98,99].

VI. DEVICE FOR NOSE TO BRAIN DELIVERY

Deposition in the nasal epithelium and transport pathways to the CNS can be affected by administration route [100]. The amount of medication deposited on the olfactory epithelium during N-to-B drug transport is crucial to its success. Because of this, a novel nasal drug delivery device is a crucial method for enhancing diagnostic and therapeutic efficacy. Nose droppers, sprays, needleless syringes, breath driven bi-directional nasal devices, pressured meter dosage inhalers, and pressurized olfactory delivery [101] are all examples of nasal delivery devices used in clinical trials. Traditional methods of liquid nasal delivery, such as droppers, spray pumps, and pipettes, are less likely to target the olfactory due to the location of the olfactory epithelium in the upper part of the nose, the restriction of the nasal cavity turbinates, and the effect of changing the head position [102]. Therefore, either mucociliary clearance or systemic absorption occurs [103]. To counteract the drawbacks of the standard nasal delivery systems, scientists have devised devices to administer the medicine in liquid and powder forms. Some of these delivery methods are discussed here, along with study examples that make use of them.

Whether the drug has a local effect, is meant for systemic absorption, N-to-B transport, or a combination of these, Djupesland et al. [104] reviewed the characteristics of nasal delivery devices in general and the aerosol generation to achieve the clinical target of nasal drug delivery to the nose cavity. However, most discussions center on how to maximize dosage deposition in the nasal cavity's upper regions, with the end goal of reaching the brain. Powder formulations are more stable, preservatives may not be necessary, and they frequently adhere to the nasal mucosa before being dissolved and removed [105]. Liquid formulations are the cheapest, most straightforward, and oldest formulations. Catheter-delivered medications are the simplest way to get medication into the nasal cavity, as all you have to do is blow into the other end of the catheter, which is located in the nasal cavity [106].

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

Using an electronic atomizer like the ViaNaseTM, a nasal spray can be directed directly at the respiratory epithelia lining the nasal canal and the olfactory region [107,108]. Humans use ViaNaseTM to administer insulin intranasally [109]. The device comprises of a hermetically sealed nosepiece and a mechanism that generates an active vortex of nebulized particles. The SipNose is a nasal actuator designed to deliver aerosolized microscopic particles to the upper airways, where they will have the least chance of settling [9]. SipNose can be used with a wide range of formulations, including liquids, dry powders, tiny chemicals, big molecules, biologics, and cells [110]. Precision Olfactory Delivery (POD®) by Impel Neuropharma is an aerosol medication delivery system designed to improve N-to-B drug delivery. This gadget employs pressured gas instead of the patient's exhalation force to release the dose [6,9,10]. Manufacturers claim a 50% deposition in the nasal cavity, and it comes with a tank of compressed air or nitrogen, chlorofluorocarbon (CFC), or hydrofluoroalkane (HFA) used as a propellant and air chamber [111].

Powder is preservative-free because, as discussed in the formulation section, it can be given in high doses and the solid condition prevents microbial contamination. Powder particle size, solubility, and flow properties are just a few of the variables that affect how much of the medicine is deposited and absorbed during nasal delivery of a powder formulation [112]. Insufflators, Direct Halers, and Bi-Directional Optinoses are all examples of powder devices [113]. Optinose'sOpt-Powder device is a breath-activated, bi-directional delivery system for delivering liquid or nasal powder formulations directly to the olfactory region of the nasal canal. The closure of the soft palate in this device prevents any powder from entering the lungs [114] and also lessens the amount of powder entering the lower nasal passages [115].

Dry powder inhalers (DPI) are another type of powder delivery device. Common examples of nasal dry inhalers include RhinocortTurbohaler® (Budesonide), Teijin PuvlizerRhinocort® (beclomethasone dipropionate, BDP), RhinicortPuvlizer® (Budesonide), and Erizas® (Dexamethasone Cipecilate) [118]. The Unidose (UDS) Nasal Powder system from Aptar Pharma is a DPI that facilitates the rapid, accurate, and simple administration of a single dose of medication [38]. Bespak's resampled Flit Lizer technology went into their Unidose-DPTM nasal powder sprayer, which features a hermetically sealed container for administering a single dose of medication [119]. Using data from human MRI scans, a nasal cast model was created to test the delivery of an antibody (human IgG) as a dry powder. The deposition pattern of medications within the nose after being given by Unidose-DPTM was determined using Bespak's nasal cast model, a life-size model of the nasal cavity constructed from MRI images. Therefore, the nasal cavity received 95% of the dose; the majority of the dose was deposited in the nasal vestibule and the remaining 30% was deposited deeper in the nasal cavity [18,22]. Vaccines have been administered using SoluVentTM, a powder delivery device created by Beckton Dickinson (BD) [39] that drives the powder to the nasal cavity. The powder is pushed through the nares by an inert gas released by the Naltos device, developed by Alchemy Pharmatech [6].

In humans, adjusting the formulation delivery mechanism, delivery volume, and head position to target specific regions of the nasal cavity results in efficient IN administration to the CNS [8]. A human study using a whole-virus influenza liquid vaccine without adjuvant found that the immune response was enhanced when the vaccine was administered via the breath-powered Bi-DirectionalTMOptiNose device and nasal drops rather than the more conventional nasal spray and oral spray [22]. Dong et al. [40] used a CT-reconstructed nasal model of a healthy 60-year-old adult to test nasal cavity and aerosol delivery system designs. The authors used a computational fluid and particle dynamics approach to draw parallels between the aerosol mask and breath-powered bi-directional systems. Compared to the traditional aerosol mask method, the results demonstrated that the breath-powered medication delivery methodology may provide better olfactory deposition [40]. The Optinose device was also utilized to investigate the dose-response relationship of oxytocin (OT) peptide on social cognition in another investigation. Inhaling into an Optinose device powered by one's breath reduced the amount of OT required for transnasal delivery to the brain. Lower doses were more effective in eliciting a cognitive response [18]; more illustrations of OT administration will be provided below. The aforementioned cases emphasize the need of using an appropriate nasal administration system to ensure the medicine reaches the CNS quickly and effectively.[120]

There have been no human N-to-B trials conducted with any other advanced nasal devices outside the Precision Olfactory Delivery, Optinose, and ViaNase [6]. Research into noninvasive methods of conveying and depositing drugs in the nasal cavity, such as nasal drug delivery systems, has grown in recent years. As a result, various nasal delivery devices have moved forward to the stage of clinical trials. These include powder devices, dry powder inhalers, bidirectional breath-powder delivery devices, meter-dosed spray pumps, nasal sprays, pressurized meter-dosed spray inhalers, nebulizers, atomizers, and pressured olfactory devices. Some nasal drug delivery devices (mainly nasal spray) have already been licensed by the FDA to treat a variety of conditions, including Zomig®, Astelin®, Narcan®, Dymista®, Advancia®, OnzetraTM, and Nasonex®. There have been multiple patent applications for nasal administration systems to transport medications

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

to the brain, as reported by Pandey et al. [119]. In addition, numerous biomedical device manufacturers have secured patents for cutting-edge delivery systems that utilize cutting-edge technology, such as smartphones or a voice command, to initiate the regulated release of the medicine [121].

In 2018, the generic nasal spray and inhalation medicine market was worth $7.8 billion [122]. By the end of 2025, that number is expected to have increased to close to $12 billion. Approved nasal formulations typically take the form of liquid sprays, and their active ingredients can range from small molecules like sumatriptan for migraine treatment to big molecules like vitamin B12 and vasopressin [123]. Nasal medicines for central nervous system problems are typically tiny compounds. However, there are hardly any big molecules approved for use in treating CNS disorders that are administered intranasally. The N-to-B transport of different proteins and peptides, as well as the numerous polymer and lipid-based nanocarrier systems employed for N-to-B delivery of protein and peptides, were all outlined by Agrawal et al. [124]. Non-pressurized dispensers dispense a spray containing a metered dose of the drug, and nasal sprays contain active pharmaceutical ingredients in the form of a solution or suspension with excipients (such as preservatives, buffering agents, viscosity modifiers, emulsifiers) for either systemic or local effects. The spray pump or factory-set tolerances determine the exact dosage. The nasal spray can also be made to dispense the composition in units or up to a certain number of metered sprays [125]. Some features of nasal sprays (e.g., formulation, container closing mechanism, stability, manufacturing, intermediates, and drug product) are distinctive and require special attention throughout development. Dose repeatability is sensitive to the aforementioned factors. Furthermore, the design of the container closure system influences the dosing performance of the drug product, and nasal sprays have unique features such as metering and spray producing (e.g., orifice, nozzle, jet). Energy is required for dispersal of the formulation as a spray by pushing the formulation through the nasal actuator and its orifice.

Nebulizers turn the liquid formulation (solution or suspension) into a fine mist that can be inhaled through the nasal passages by using compressed gases (air, nitrogen, or oxygen) or ultrasonic or mechanical power. Conventional nasal nebulizer devices, as discussed in the nasal device section, deposit the drug in the nasal vestibule and nasal valve regions, where it does not reach the olfactory region [126]. As a result, cutting-edge nebulizer devices have been created for intranasal drug delivery to the olfactory system. The precision olfactory delivery® (POD®) device (Impel Neuropharma, Seattle, WA, USA) and the ViaNaseTM (Kurve Technology, Inc., Lynwood, WA, USA) are two examples of cutting-edge nebulizers.[127]

VII. CONCLUSION

Considering the physicochemical characteristics of neurotherapeutics, SEDDS have been demonstrating a high potential in improving these drugs' bioavailability, comparatively with traditional formulations such as tablets, solutions or suspensions. This is mostly due to the excipients that compose SEDDS, generating nanosized structures after dispersion in the aqueous medium. The large surface area of the formed droplets after aqueous dispersion enhances drug dissolution, permeability, and absorption through biological membranes, leading to higher bioavailability. This not only happens in GIT after oral administration but also if SEDDS are administered through the nasal route. Even though SEDDS have primarily been explored for bioavailability enhancement after oral administration, the application of SEDDS in nose-to-brain delivery is worth being explored more. This is mostly due to all the potential of the IN administration route in delivering drugs directly to the brain, circumventing the BBB. Thus, an even higher brain bioavailability of neurotherapeutics might be expected if these were intranasally administered loaded in SEDDS, compared with the oral route. However, as demonstrated in this review, little research has been developed regarding the field of SEDDS for IN administration. Hence, it is important to identify potential drugs to be loaded in SEDDS at higher concentrations, particularly those that are poorly water-soluble, to then be delivered by the IN route. Nevertheless, there must be an interest in both the scientific community and the pharmaceutical industry in investing in SEDDS for IN administration to make its commercialization possible in the near future.

REFERENCES

[1] Campani, V., Salaroglio, I. C., Nele, V., Kopecka, J., Bernkop-Schnürch, A., Riganti, C., & De Rosa, G. (2022). Targeted self-emulsifying drug delivery systems to restore docetaxel sensitivity in resistant tumors. *Pharmaceutics*, *14*(2), 292.

[2] He-Lin, W. A. N. G., Jin, S. U. N., Chu-Tong, T. I. A. N., & Zhong-Gui, H. E. (2021). Probing the new strategy for the oral formulations of taxanes: changing the method with the situation. *Chinese Journal of Natural Medicines*, *19*(9), 656-665.

[3] Awuchi, C. G., Amagwula, I. O., Priya, P., Kumar, R., Yezdani, U., & Khan, M. G. (2020). Aflatoxins in foods and feeds: A review on health implications, detection, and control. *Bull. Environ. Pharmacol. Life Sci*, *9*, 149-155.

[4] Salawi, A. (2022). Self-emulsifying drug delivery systems: a novel approach to deliver drugs. *Drug Delivery*, *29*(1), 1811-1823.

[5] Nagaraja, S., Basavarajappa, G. M., Karnati, R. K., Bakir, E. M., &Pund, S. (2021). Ion-triggered In Situ gelling nanoemulgel as a platform for nose-to-brain

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

delivery of small lipophilic molecules. *Pharmaceutics*, *13*(8), 1216.

[6] Yadav, A. N., Verma, P., Kumar, R., Kumar, V., & Kumar, K. (2017). Current applications and future prospects of eco-friendly microbes. *EU Voice*, *3*(1), 21-22.

[7] Alkholifi, F. K., Alam, A., Foudah, A. I., &Yusufoglu, H. S. (2023). Phospholipid-Based Topical Nano-Hydrogel of Mangiferin: Enhanced Topical Delivery and Improved Dermatokinetics. *Gels*, *9*(3), 178.

[8] Kumar, R., Saha, P., Lokare, P., Datta, K., Selvakumar, P., & Chourasia, A. (2022). A Systemic Review of Ocimum sanctum (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(2), 221-226.

[9] Halim, A., Jindal, K., &Tarique, M. (2021). Solubility enhancement of poorly soluble drug by self emulsifying drug delivery system: comprehensive review. *World J Pharm Res*, *10*, 840-52.

[10] Umama, Y., Venkatajah, G., Shourabh, R., Kumar, R., Verma, A., Kumar, A., &Gayoor, M. K. (2019). Topic-The scenario of pharmaceuticals and development of microwave as; sisted extraction technique. *World J Pharm Pharm Sci*, *8*(7), 1260-1271.

[11] Maharana, R. L., Swain, S., Mahapatra, S. K., & Jena, B. R. (2023). Quality by design enabled self-nano emulsifying drug delivery systems development for the oral delivery of telmisartan: Improvement of biopharmaceutical performance.

[12] Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., &Saha, P. (2020). Natural BioactivesFor The Potential Management Of Gastric Ulceration. *Turkish Journal of Physiotherapy and Rehabilitation*, *32*(3), 221-226.

[13] Maharana, R. L., Swain, S., Mahapatra, S. K., & Jena, B. R. (2023). Quality by design enabled self-nano emulsifying drug delivery systems development for the oral delivery of telmisartan: Improvement of biopharmaceutical performance.

[14] Kumar, R., &Saha, P. (2022). A review on artificial intelligence and machine learning to improve cancer management and drug discovery. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(3), 149-156.

[15] Keshamma, E., Kumar, A., Jha, R., Amle, V. S., Dudhate, G. S., Patel, D., ... & Kumar, R. (2022). Breast Cancer Treatment Relying on Herbal Bioactive Components. *Journal for Research in Applied Sciences and Biotechnology*, *1*(4), 105-115.

[16] de Carvalho Carneiro, E., de Souza Neto, A. B., Sousa, E. M. L., dos Santos Júnior, J. R., da Silva Pereira, H., Feitoza, Y. P., &Véras, L. M. C. (2023). Desenvolvimento de umaformulaçãosemissólida à base de epiisopiloturina e avaliação da suaestabilidade. *Research, Society and Development*, *12*(3), e20612340551-e20612340551.

[17] Mishra, A., Singh, Y., Singh, R., Kumar, R., Shukla, S., Kumar, R., ... & Pol, S. L. (2022). Ethano-pharmacology activity & Antioxidant activity of Centella asiatica Plant Parts. *NEUROQUANTOLOGY*, *20*(11), 7562-2.

[18] Chen, Y., Zhao, T., Bai, M., Gu, T., Sun, J., He, Z., ... & Luo, C. (2022). Emerging small molecule-engineered hybrid nanomedicines for cancer therapy. *Chemical Engineering Journal*, 135160.

[19] Roshan, K. (2020). Priya damwani, Shivamkumar, Adarsh suman, Suthar Usha. An overview on health benefits and risk factor associated with coffee. *International Journal Research and Analytical Review*, *7*(2), 237-249.

[20] Wang, H., Lu, Q., Miao, Y., Song, J., Zhang, M., Wang, Z., ... & Sun, J. (2022). Boosting SN38-based oral chemotherapy to combine reduction-bioactivated structured lipid-mimetic prodrug with ascorbic acid. *Nano Research*, *15*(10), 9092-9104.

[21] Goswami, N., Sethi, P., Jyoti, A., Nagar, G., Gupta, S. R., Singh, A., & Singh, I. K. (2022). Plant-derived bioactive compounds in Neuroblastoma therapeutics: Current outlook and future perspective. *Chemical Biology Letters*, *9*(4), 400-400.

[22] Keshri, S., Kumar, R., Kumar, D., Singhal, T., Giri, S., Sharma, I., &Vatsha, P. (2022). Insights Of Artificial Intelligence In Brain Disorder With Evidence Of Opportunity And Future Challenges. *Journal of Pharmaceutical Negative Results*, 10853-10867.

[23] Lucas, C. J., Galettis, P., & Schneider, J. (2018). The pharmacokinetics and the pharmacodynamics of cannabinoids. *British journal of clinical pharmacology*, *84*(11), 2477-2482.

[24] Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British journal of pharmacology*, *163*(7), 1344-1364.

[25] Nyarko, R. O., Kumar, R., Sharma, S., & Chourasia, A. (2022). Ayushmann Roy, and PurabiSaha.". *Antibacterial Activity Of Herbal Plant-Tinospora Cordifolia And Catharnthus Roseus*.

[26] Kumar, S., Keshamma, E., Trivedi, U., Janjua, D., Shaw, P., Kumar, R., ... &Saha, P. (2022). A Meta Analysis of Different Herbs (Leaves, Roots, Stems) Used in Treatment of Cancer Cells. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 92-101.

[27] Nyarko, R. O., Awuchi, C. G., Kumar, R., Boateng, E., Kahwa, I., Boateng, P. O., ... &Saha, P. (2022). Evaluation of Cafeteria Diet in Experimental Animal with Plant Extract of Calotropis procera for Obesity Parameter. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 107-113.

[28] Millar, S. A., Stone, N. L., Yates, A. S., & O'Sullivan, S. E. (2018). A systematic review on the pharmacokinetics of cannabidiol in humans. *Frontiers in pharmacology*, *9*, 1365.

[29] Devinsky, O., Patel, A. D., Thiele, E. A., Wong, M. H., Appleton, R., Harden, C. L., ... & GWPCARE1

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

Part A Study Group. (2018). Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology*, *90*(14), e1204-e1211.

[30] Amin, M. R., & Ali, D. W. (2019). Pharmacology of medical cannabis. *Recent advances in cannabinoid physiology and pathology*, 151-165.

[31] Millar, S. A., Maguire, R. F., Yates, A. S., & O'Sullivan, S. E. (2020). Towards better delivery of cannabidiol (CBD). *Pharmaceuticals*, *13*(9), 219.

[32] Blanton, H. L., Barnes, R. C., McHann, M. C., Bilbrey, J. A., Wilkerson, J. L., & Guindon, J. (2021). Sex differences and the endocannabinoid system in pain. *Pharmacology Biochemistry and Behavior*, *202*, 173107.

[33] Iversen, L. L. (2001). *The science of marijuana*. Oxford University Press.

[34] Qian, Y., Gurley, B. J., & Markowitz, J. S. (2019). The potential for pharmacokinetic interactions between cannabis products and conventional medications. *Journal of clinical psychopharmacology*, *39*(5), 462-471.

[35] Birnbaum, A. K., Karanam, A., Marino, S. E., Barkley, C. M., Remmel, R. P., Roslawski, M., ... &Leppik, I. E. (2019). Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy. *Epilepsia*, *60*(8), 1586-1592.

[36] ZAIDI, S., MEHRA, R., & TYAGI, D. S. ROSHAN KUMAR ANUBHAV DUBEY.(2021). Effect of Kalahari Cactus Extract on Appetitte, Body Weight And Lipid Profile In Cafeteria Diet Induced Obesity In Experimental Animal. *Annals of the Romanian Society for Cell Biology*, *25*(6), 13976-13987.

[37] Kumar, R., Keshamma, E., Kumari, B., Kumar, A., Kumar, V., Janjua, D., &Billah, A. M. (2022). Burn Injury Management, Pathophysiology and Its Future Prospectives. *Journal for Research in Applied Sciences and Biotechnology*, *1*(4), 78-89.

[38] Kumar, R., Saha, P., Kahwa, I., Boateng, E. A., Boateng, P. O., & Nyarko, R. O. (2022). Biological Mode of Action of Phospholipase A and the Signalling and Pro and Anti Inflammatory Cytokines: A Review. *Journal of Advances in Medicine and Medical Research*, *34*(9), 1-10.

[39] Singhal, A. K. V., Giri, S., & Kumar, R. (2022). INVESTIGATION OF IN-VITRO ANTI-OXIDANT & ANTI-ULCER ACTIVITY OF ANGIOGENESIS LATIFOLIA ROXB (DHAVA). *NeuroQuantology*, *20*(11), 5680-5686.

[40] Mishra, R. K., Sempionatto, J. R., Li, Z., Brown, C., Galdino, N. M., Shah, R., ... & Wang, J. (2020). Simultaneous detection of salivary Δ9-tetrahydrocannabinol and alcohol using a wearable electrochemical ring sensor. *Talanta*, *211*, 120757.

[41] Hoch, E., Niemann, D., von Keller, R., Schneider, M., Friemel, C. M., Preuss, U. W., ... &Pogarell, O. (2019). How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. *European archives of psychiatry and clinical neuroscience*, *269*, 87-105.

[42] Prajapati, A. K., Sagar, S., & Kumar, R. (2022). Past and Current Prospectives of Herbal Product for Skin Care. *Journal for Research in Applied Sciences and Biotechnology*, *1*(5), 145-160.

[43] Johal, H., Devji, T., Chang, Y., Simone, J., Vannabouathong, C., & Bhandari, M. (2020). Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *13*, 1179544120906461.

[44] Chaudhary, H., Sagar, S., Kumar, R., Bisht, V., &Butola, K. (2022). Herbal Essential Oil use as Ulcer Protective Activity: A Systematic Review. *Journal for Research in Applied Sciences and Biotechnology*, *1*(5), 86-101.

[45] Johal, H., Devji, T., Chang, Y., Simone, J., Vannabouathong, C., & Bhandari, M. (2020). Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *13*, 1179544120906461.

[46] Sultana, A., Singh, M., Kumar, A., Kumar, R., Saha, P., Kumar, R. S., & Kumar, D. (2022). To Identify Drug-Drug Interaction in Cardiac Patients in Tertiary Care Hospitals. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 146-152.

[47] Afzaal, M., Saeed, F., Ateeq, H., Akhtar, M. N., Imran, A., Ahmed, A., ... &Awuchi, C. G. (2022). Probiotics encapsulated gastroprotective cross-linked microgels: Enhanced viability under stressed conditions with dried apple carrier.

[48] Kopustinskiene, D. M., Masteikova, R., Lazauskas, R., &Bernatoniene, J. (2022). Cannabis sativa L. Bioactive compounds and their protective role in oxidative stress and inflammation. *Antioxidants*, *11*(4), 660

[49] Keshri, S., Kumar, R., Kumar, D., Singhal, T., Giri, S., Sharma, I., &Vatsha, P. (2022). Insights Of Artificial Intelligence In Brain Disorder With Evidence Of Opportunity And Future Challenges. *Journal of Pharmaceutical Negative Results*, 10853-10867.

[50] Martin-Santos, R., a Crippa, J., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., ... & K McGuire, P. (2012). Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. *Current pharmaceutical design*, *18*(32), 4966-4979.

[51] Patel, R. K., Gangwar, D., Gupta, H., Sharma, N., & Kumar, R. (2023). Plants Alkaloids Based Compound as Therapeutic Potential for Neurodegenerative. *Journal for Research in Applied Sciences and Biotechnology*, *2*(2), 14-26.

[52] Gaston, T. E., & Friedman, D. (2017). Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy & Behavior*, *70*, 313-318.

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

[53] Awuchi, C. G., Saha, P., Amle, V. S., Nyarko, R. O., Kumar, R., Boateng, E. A., ... &Asum, C. (2023). A Study of Various Medicinal Plants used in Ulcer Treatment: A Review. *Journal for Research in Applied Sciences and Biotechnology*, *2*(1), 234-246.

[54] Bhaskar, A., Bell, A., Boivin, M., Briques, W., Brown, M., Clarke, H., ... & Moulin, D. E. (2021). Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *Journal of cannabis research*, *3*, 1-12.

[55] Kumar, S., Yadav, S. P., Chandra, G., Sahu, D. S., Kumar, R., Maurya, P. S., ... & Ranjan, K. (2019). Effect of dietary supplementation of yeast (Saccharomyces cerevisiae) on performance and hemato-biochemical status of broilers.

[56] Kumar, A., Uniyal, Y., & Kumar, R. (2022). Recent Advancement of Colorectal Cancer and Their Herbal Essential Oil Treatment. *Journal for Research in Applied Sciences and Biotechnology*, *1*(5), 133-144.

[57] Yu, H., Luo, Y., Alkhamis, O., Canoura, J., Yu, B., & Xiao, Y. (2021). Isolation of natural DNA aptamers for challenging small-molecule targets, cannabinoids. *Analytical chemistry*, *93*(6), 3172-3180

[58] Kovalchuk, O., & Kovalchuk, I. (2020). Cannabinoids as anticancer therapeutic agents. *Cell Cycle*, *19*(9), 961-989.

[59] Thompson, R., DeJong, K., & Lo, J. (2019). Marijuana use in pregnancy: a review. *Obstetrical & gynecological survey*, *74*(7), 415.

[60] Kohli, A., & Kumar, R. (2023). Role of Antioxidants of Natural Herbs in Management of Male Infertility. *Journal for Research in Applied Sciences and Biotechnology*, *2*(1), 55-80.

[61] Kumar, S., Yadav, S. P., Chandra, G., Sahu, D. S., Kumar, R., Maurya, P. S., ... & Ranjan, K. (2019). Effect of dietary supplementation of yeast (Saccharomyces cerevisiae) on performance and hemato-biochemical status of broilers.

[62] Popescu, R., Ghica, M. V., Dinu-Pîrvu, C. E., Anuța, V., Lupuliasa, D., & Popa, L. (2020). New opportunity to formulate intranasal vaccines and drug delivery systems based on chitosan. *International Journal of Molecular Sciences*, *21*(14), 5016.

[63] Lin, L., Chi, J., Yan, Y., Luo, R., Feng, X., Zheng, Y., ... & Pan, X. (2021). Membrane-disruptive peptides/peptidomimetics-based therapeutics: Promising systems to combat bacteria and cancer in the drug-resistant era. *Acta Pharmaceutica Sinica B*, *11*(9), 2609-2644.

[64] Othman, S. I., Alturki, A. M., Abu-Taweel, G. M., Altoom, N. G., Allam, A. A., &Abdelmonem, R. (2021). Chitosan for biomedical applications, promising antidiabetic drug delivery system, and new diabetes mellitus treatment based on stem cell. *International Journal of Biological Macromolecules*, *190*, 417-432.

[65] Bashiri, S., Koirala, P., Toth, I., &Skwarczynski, M. (2020). Carbohydrate immune adjuvants in subunit vaccines. *Pharmaceutics*, *12*(10), 965.

[66] Lombardo, R., Musumeci, T., Carbone, C., &Pignatello, R. (2021). Nanotechnologies for intranasal drug delivery: an update of literature. *Pharmaceutical development and technology*, *26*(8), 824-845.

[67] Saha, P. (2020). Evolution of tolbutamide in the treatment of diabetes mellitus. *Diabetes*, *2*(10).

[68] Gupta, V., Haider, S., Verma, M., Singhvi, N., Ponnusamy, K., Malik, M. Z., ... & Lal, R. (2021). Comparative genomics and integrated network approach unveiled undirected phylogeny patterns, co-mutational hot spots, functional cross talk, and regulatory interactions in SARS-CoV-2. *MSystems*, *6*(1), e00030-21.

[69] Gao, X., Liu, N., Wang, Z., Gao, J., Zhang, H., Li, M., ... & Zheng, A. (2021). Development and optimization of chitosan nanoparticle-based intranasal vaccine carrier. *Molecules*, *27*(1), 204.

[70] Subramanian, M., Keshamma, E., Janjua, D., Kumar, D., Kumar, R., Saha, P., ... & Rao, S. (2022). Quality Risk Management Approach for Drug Development and Its Future Prospectives. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 166-177.

[71] Nicolle, L., Journot, C. M., & Gerber-Lemaire, S. (2021). Chitosan functionalization: Covalent and non-covalent interactions and their characterization. *Polymers*, *13*(23), 4118.

[72] Kumar, R., Singh, A., &Painuly, N. (2022). Investigation of in-vitro anti-oxidant & anti-ulcer activity of polyherbal medicinal plants. *Journal of Pharmaceutical Negative Results*, 2077-2088.

[73] Kumar, N., Dubey, A., Mishra, A., & Tiwari, P. (2020). Ethosomes: A Novel Approach in Transdermal Drug Delivery System. *International journal of pharmacy & life sciences*, *11*(5).

[74] Anubhav, S. P. D., Sanjay, K. D., & Roshan, K. (2022). Evaluation of Enzyme Producing K. Pneumoniae and Their Susceptibility to Other Anti-Biotics. *International Journal of Innovative Science and Research Technology*, *7*(5), 351-353

[75] Kumar, R., Saha, P., Keshamma, E., Sachitanadam, P., & Subramanian, M. (2022). Docking studies of some novel Hetrocyclic compound as Acat inhibitors: A meta analysis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 33-41.

[76] Lombardo, R., Musumeci, T., Carbone, C., &Pignatello, R. (2021). Nanotechnologies for intranasal drug delivery: an update of literature. *Pharmaceutical development and technology*, *26*(8), 824-845.

[77] Amle, V. S., Rathod, D. A., Keshamma, E., Kumar, V., Kumar, R., &Saha, P. (2022). Bioactive Herbal Medicine Use for Eye Sight: A Meta Analysis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 42-50

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

[78] Pandey, M., Singh, A., Agnihotri, N., Kumar, R., Saha, P., Pandey, R. P., & Kumar, A. (2022). Clinical Pharmacology & Therapeutic uses of Diuretic Agents: A Review. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 11-20.

[79] Nyarko, R. O., Roopini, R., Raviteja, V., Awuchi, C. G., Kumar, R., Faller, E. M., ... &Saha, P. (2022). Novel Sars-CoV-2 Variants & Therapeutic Effects. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 25-34.

[80] Keshamma, E., Paswan, S. K., Kumar, R., Saha, P., Trivedi, U., Chourasia, A., &Otia, M. (2022). Alkaloid Based Chemical Constituents of Ocimumsantum& Cinchona Bark: A Meta Analysis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 35-42.

[81] Lofts, A., Abu-Hijleh, F., Rigg, N., Mishra, R. K., & Hoare, T. (2022). Using the intranasal route to administer drugs to treat neurological and psychiatric illnesses: Rationale, successes, and future needs. *CNS drugs*, *36*(7), 739-770.

[82] Singh, Y., Paswan, S. K., Kumar, R., Otia, M. K., Acharya, S., Kumar, D., &Keshamma, E. (2022). Plant & Its Derivative Shows Therapeutic Activity on Neuroprotective Effect. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 10-24.

[83] SHAFQAT ZAIDI, R. K., MEHRA, D., SACHIN, T., & ROSHAN, K. A. D. (2021). Effect of Kalahari Cactus Extract on Appetitte, Body Weight And Lipid Profile In Cafeteria Diet Induced Obesity In Experimental Animal. *Annals of the Romanian Society for Cell Biology*, *25*(6), 13976-13987.

[84] Saha, P., Kumar, A., Bhanja, J., Shaik, R., Kawale, A. L., & Kumar, R. (2022). A Review of Immune Blockade Safety and Antitumor Activity of Dostarlimab Therapy in Endometrial Cancer. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(3), 201-209.

[85] Nalimu, F., Oloro, J., Kahwa, I., &Ogwang, P. E. (2021). Review on the phytochemistry and toxicological profiles of Aloe vera and Aloe ferox. *Future Journal of Pharmaceutical Sciences*, *7*, 1-21.

[86] Dumkliang, E., Pamornpathomkul, B., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Yoksan, S., &Opanasopit, P. (2021). Feasibility of chitosan-based nanoparticles approach for intranasal immunisation of live attenuated Japanese encephalitis vaccine. *International Journal of Biological Macromolecules*, *183*, 1096-1105.

[87] Kumar, A. (2019). The Scenario of Pharmaceuticals and Development of Microwave Assisted Extraction Techniques.

[88] Kumar, R., Jain, A., Tripathi, A. K., & Tyagi, S. (2021, January). Covid-19 outbreak: An epidemic analysis using time series prediction model. In *2021 11th international conference on cloud computing, data science & engineering (Confluence)* (pp. 1090-1094). IEEE.

[89] Nyarko, R. O., Boateng, E., Kahwa, I., & Boateng, P. O. (2020). A comparison analysis on remdesivir, favipiravir, hydroxychloroquine, chloroquine and azithromycin in the treatment of corona virus disease 2019 (COVID-19)-A Review. *World J. Pharm. Pharm. Sci*, *9*, 121-133.

[90] Saha, P., Nyarko, R. O., Lokare, P., Kahwa, I., Boateng, P. O., &Asum, C. (2022). Effect of Covid-19 in Management of Lung Cancer Disease: A Review. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 58-64.

[91] Kumar, R., Saha, P., Pathak, P., Mukherjee, R., Kumar, A., & Arya, R. K. (2009). Evolution Of Tolbutamide In The Treatment Of Diabetes Mellitus. *Jour. of Med. P'ceutical& Alli. Sci*, *9*.

[92] Kumar, R., Saha, P., Pathak, P., Mukherjee, R., Kumar, A., & Arya, R. K. (2009). Evolution Of Tolbutamide In The Treatment Of Diabetes Mellitus. *Jour. of Med. P'ceutical& Alli. Sci*, *9*.

[93] Chavda, V. P., Jogi, G., Shah, N., Athalye, M. N., Bamaniya, N., Vora, L. K., & Paiva-Santos, A. C. (2022). Advanced particulate carrier-mediated technologies for nasal drug delivery. *Journal of Drug Delivery Science and Technology*, 103569.

[94] Purabisaha, R. K., Rawat, S. S. N., & Prakash, A. (2021). A Review On Novel Drug Delivery System.

[95] Elamri, A., Zdiri, K., Hamdaoui, M., &Harzallah, O. (2023). Chitosan: A biopolymer for textile processes and products. *Textile Research Journal*, *93*(5-6), 1456-1484.

[96] Nyarko, R. O., Kumar, R., Sharma, S., Chourasia, A., Roy, A., &Saha, P. (2022). Antibacterial Activity of Herbal Plant-Tinospora Cordifolia AndCatharnthus Roseus.

[97] Haddad, H. F., Roe, E. F., & Collier, J. H. (2023). Expanding opportunities to engineer mucosal vaccination with biomaterials. *Biomaterials Science*, *11*(5), 1625-1647.

[98] Nyarko, R. O., Boateng, E., Kahwa, I., Boateng, P. O., &Asare, B. (2020). The impact on public health and economy using lockdown as a tool against COVID-19 pandemic in Africa: a perspective. *J Epidemiol Public Health Rev*, *5*(3).

[99] Taşkonak, B., Aylaz, G., Andac, M., Güven, E., Ozkahraman, B., Perçin, I., &KılıçSüloğlu, A. (2023). Hypericin-Loaded Chitosan Nanoparticles for Enhanced Photodynamic Therapy in A549 Lung Cancer Cells. *BioNanoScience*, 1-13.

[100] Kumar, R., & Dubey, A. (2020). Phytochemical InvestigationAndHeptoprotectiveEvalution Acacia Rubica Extract Isonized And Paracetamol Indused Animal Toxicity. *Turkish Journal of Physiotherapy and Rehabilitation*, *32*(3), 65-69.

[101] Shekari, G., Kalantari, M., &Hashemipour, H. (2022). Synthesis, optimization, characterization, and potential drug release application of nanocomposite hydrogel based on carboxymethyl cellulose-g-itaconic

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023|| PP. 89-101

https://doi.org/10.55544/jrasb.2.2.14

acid/acrylamide. *Journal of Polymer Research*, *29*(7), 292.

[102] Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A Review on Diabetes Mellitus: Type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences*, *9*(10), 838-850.

[103] Jearanaiwitayakul, T., Limthongkul, J., Kaofai, C., Apichirapokey, S., Chawengkirttikul, R., Sapsutthipas, S., ... &Ubol, S. (2022). The STING ligand and delivery system synergistically enhance the immunogenicity of an intranasal spike SARS-CoV-2 vaccine candidate. *Biomedicines*, *10*(5), 1142.

[104] Kumar, R., Saha, P., Sarkar, S., Rawat, N., & Prakash, A. (2021). A Review On Novel Drug Delivery System. *IJRAR-International Journal of Research and Analytical Reviews (IJRAR)*, *8*(1), 183-199.

[105] Saha, P., Kumar, R., Nyarko, R. O., Kahwa, I., & Owusu, P. (2021). Herbal Secondary Metabolite For Gastro-Protective Ulcer Activity With Api Structures.

[106] Sahana, S. (2020). Roshan kumar, Sourav nag, Reshmi paul, Nilayanguha, Indranil Chatterjee. A Review on Alzheimer disease and future prospects. *World Journal of Pharmacy and Pharmaceutical science*, *9*(9), 1276-1285.

[107] MititeluTartau, L., Bogdan, M., Buca, B. R., Pauna, A. M., Tartau, C. G., Dijmarescu, L. A., & Popa, E. G. (2021). Evaluation of Antinociceptive Effects of Chitosan-Coated Liposomes Entrapping the Selective Kappa Opioid Receptor Agonist U50, 488 in Mice. *Medicina*, *57*(2), 138.

[108] Kumar, R., Saha, P., Nyarko, R. O., Kahwn, I., Boateng, E. A., Boateng, P. O., ... & Bertram, A. (2021). Role of Cytokines and Vaccines in Break through COVID 19 Infections. *Journal of Pharmaceutical Research International*, *33*(60B), 2544-2549.

[109] Al-Nemrawi, N. K., Darweesh, R. S., Al-shriem, L. A., Al-Qawasmi, F. S., Emran, S. O., Khafajah, A. S., & Abu-Dalo, M. A. (2022). Polymeric Nanoparticles for Inhaled Vaccines. Polymers 2022, 14, 4450.

[110] Raj, A., Tyagi, S., Kumar, R., Dubey, A., &Hourasia, A. C. (2021). Effect of isoproterenol and thyroxine in herbal drug used as cardiac hypertrophy. *Journal of Cardiovascular Disease Research*, 204-217.

[111] Kumar, R., Sood, U., Gupta, V., Singh, M., Scaria, J., & Lal, R. (2020). Recent advancements in the development of modern probiotics for restoring human gut microbiome dysbiosis. *Indian journal of microbiology*, *60*, 12-25.

[112] Kumar, R., Verma, H., Singhvi, N., Sood, U., Gupta, V., Singh, M., ... & Lal, R. (2020). Comparative genomic analysis of rapidly evolving SARS-CoV-2 reveals mosaic pattern of phylogeographical distribution. *Msystems*, *5*(4), e00505-20.

[113] Daharia, A., Jaiswal, V. K., Royal, K. P., Sharma, H., Joginath, A. K., Kumar, R., &Saha, P. (2022). A Comparative review on ginger and garlic with their pharmacological Action. *Asian Journal of Pharmaceutical Research and Development*, *10*(3), 65-69.

[114] Nyarko, R. O., Prakash, A., Kumar, N., Saha, P., & Kumar, R. (2021). Tuberculosis a globalized disease. *Asian Journal of Pharmaceutical Research and Development*, *9*(1), 198-201.
Sahana, S. (2020). Purabisaha, Roshan kumar, Pradipta das, Indranil Chatterjee, Prasit Roy, Sk Abdur Rahamat. *A Review of the 2019 Corona virus (COVID-19) World Journal of Pharmacy and Pharmaceutical science*, *9*(9), 2367-2381.

[115] Lombardo, R., &Pignatello, R. Nanotechnologies for Intranasal Drug Delivery.

[116] Häfner, S. (2021). Polymeric Promotion. *Microbes and Infection*, 104910-104910.

[117] He, X., Chen, X., Wang, H., Du, G., & Sun, X. (2023). Recent advances in respiratory immunization: A focus on COVID-19 vaccines. *Journal of Controlled Release*, *355*, 655-674.

[118] Gimpl, G.; Fahrenholz, F. The Oxytocin Receptor System: Structure, Function, and Regulation. *Physiol. Rev.* 2001, *81*, 629–683.

[119] Guastella, A.J.; Einfeld, S.L.; Gray, K.M.; Rinehart, N.J.; Tonge, B.J.; Lambert, T.J.; Hickie, I.B. Intranasal Oxytocin Improves Emotion Recognition for Youth with Autism Spectrum Disorders. *Biol. Psychiatry* 2010, *67*, 692–694.

[120] Domes, G.; Lischke, A.; Berger, C.; Grossmann, A.; Hauenstein, K.; Heinrichs, M.; Herpertz, S.C. Effects of Intranasal Oxytocin on Emotional Face Processing in Women. *Psychoneuroendocrinology* 2010, *35*, 83–93.

[121] Leng, G.; Ludwig, M. Intranasal Oxytocin: Myths and Delusions. *Biol. Psychiatry* 2016, *79*, 243–250

[122] MacDonald, E.; Dadds, M.R.; Brennan, J.L.; Williams, K.; Levy, F.; Cauchi, A.J. A Review of Safety, Side-Effects and Subjective Reactions to Intranasal Oxytocin in Human Research. *Psychoneuroendocrinology* 2011, *36*, 1114–1126.

[123] Van Zuiden, M.; Frijling, J.L.; Nawijn, L.; Koch, S.B.; Goslings, J.C.; Luitse, J.S.; Biesheuvel, T.H.; Honig, A.; Veltman, D.J.; Olff, M. Intranasal Oxytocin to Prevent Posttraumatic Stress Disorder Symptoms: A Randomized Controlled Trial in Emergency Department Patients. *Biol. Psychiatry* 2017, *81*, 1030–1040.

[124] Baumgartner, T.; Heinrichs, M.; Vonlanthen, A.; Fischbacher, U.; Fehr, E. Oxytocin Shapes the Neural Circuitry of Trust and Trust Adaptation in Humans. *Neuron* 2008, *58*, 639–650.

[125] Ditzen, B.; Schaer, M.; Gabriel, B.; Bodenmann, G.; Ehlert, U.; Heinrichs, M. Intranasal Oxytocin Increases Positive Communication and Reduces Cortisol Levels During Couple Conflict. *Biol. Psychiatry* 2009, *65*, 728–731.