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Redesigning valproic acid therapy in pregnancy: intranasal liposomes for targeted maternal treatment

Bruna Corradetti, *[a,b] Luigi C. Zangari,[c] Francesco Mainardi, [c] Tamara Pezzotta, [c] Richard H. Finnell[a,d] and Francesca Taraballi[e,f]

Valproic acid (VPA) is a potent antiseizure medication and mood stabilizer, yet its teratogenicity severely limits safe use during pregnancy. Despite guidelines advising against VPA use in women of reproductive age, it remains indispensable for certain drug-resistant epilepsies, highlighting the urgent need for safer and more targeted delivery strategies. Intranasal (IN) administration *via* nanocarriers represents a promising approach to enhance brain uptake while minimizing systemic exposure and placental transfer. In this review, we evaluate the scientific rationale and translational potential of IN nanoformulations of VPA specifically designed for use during pregnancy. We discuss strategies to engineer nanocarriers that achieve effective maternal brain delivery while reducing fetal risk, and we analyze preclinical data on biodistribution, placental passage, and therapeutic efficacy. Importantly, we highlight how gestational changes in maternal physiology and placental architecture can inform the rational design of pregnancy-adapted nanocarriers. By integrating insights from nanotechnology, pharmacology, and maternal-fetal medicine, this review outlines a paradigm shift from drug avoidance to precision delivery that maximizes reproductive safety. This strategy not only addresses the unmet need for safer VPA use in pregnancy, but also establishes a versatile framework for broader applications of nanomedicine in neurological and systemic disorders in women of childbearing age.

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1. Introduction

Valproic acid (VPA) is a cornerstone in the management of epilepsy, particularly for patients with genetic generalized epilepsy (GGE) and juvenile myoclonic epilepsy (JME), where few alternative antiseizure medications (ASMs) match its efficacy.[1] However, its use during pregnancy is associated with a markedly increased risk of congenital malformations, including a tenfold higher incidence of neural tube defects, as well as a range of neurodevelopmental disorders.[2,3] These risks have prompted stringent regulatory recommendations to avoid VPA use in women of childbearing potential and to encourage the adoption of alternative therapies whenever possible.[4] Nonetheless, in certain patients, switching to alternative ASMs fails to achieve adequate seizure control, making VPA an essential option despite its well-established teratogenic risk. This clinical dilemma highlights the urgent need for innovative strategies that preserve the therapeutic benefits of VPA while minimizing systemic and fetal exposure.

In this review, we examine advanced strategies to enhance the targeted brain delivery of VPA while minimizing systemic exposure and placental transfer. Emphasis is placed on the importance of tailoring nanoparticle (NP) design to the physiological and pharmacokinetic changes that characterize pregnancy. We focus on intranasal (IN) nanoformulated VPA because this route offers a dual advantage: maintaining seizure control in patients for whom VPA is indispensable while reducing fetal exposure. Special focus is given to nanocarrier features that support efficient IN brain delivery and restrict placental passage. Finally, we review current nanocarrier platforms used for IN administration and evaluate physicochemical parameters associated with transplacental transport or exclusion, providing guidance for the development of safer VPA formulations during pregnancy.

[a]*Center for Precision Environmental Health, Baylor College of Medicine, Houston, Texas, USA. E-mail: bruna.corradetti@bcm.edu*
[b]*Department of Medicine, Section Hematology/Oncology Baylor College of Medicine, Houston, Texas, USA*
[c]*Department of Pharmacy and Biotechnology (FaBIT), University of Bologna, Bologna, Italy*
[d]*Departments of Molecular and Human Genetics, Molecular and Cellular Biology, and Medicine, Baylor College of Medicine, Houston, Texas, USA*
[e]*Center for Musculoskeletal Regeneration, Houston Methodist Academic Institute, Houston, Texas, USA*
[f]*Orthopedics and Sports Medicine, Houston Methodist Academic Institute, Houston, Texas, USA*

2. Valproic acid: metabolism, teratogenicity, and emerging nanomedicine strategies

VPA is a broad-spectrum ASM with proven efficacy in the treatment of various epilepsy syndromes, including generalized and focal seizures.[5,6] Its clinical utility also extends to bipolar disorder and migraine prophylaxis.[7,8] However, therapeutic use of VPA is complicated by its narrow therapeutic index and significant risks of systemic toxicity, hepatotoxicity, and teratogenicity.[9] These adverse effects are closely linked to the metabolic fate of VPA, which involves complex biotransformation pathways producing both pharmacologically active and toxic metabolites. Understanding these metabolic pathways is therefore critical to developing safer therapeutic strategies, particularly for vulnerable populations such as pregnant women, where fetal safety is paramount.

2.1 Metabolic complexity and teratogenic risk of VPA

VPA is almost entirely metabolized in the liver, with only minimal amounts of the unmetabolized drug excreted renally. Its metabolism involves multiple enzymatic pathways, including oxidation, glucuronidation, β-oxidation, and conjugation with carnitine or glycine.[10,11] This metabolic complexity yields a spectrum of pharmacologically active and toxic metabolites, linking systemic exposure to hepatotoxicity, neurotoxicity and teratogenic risk.[12–18] Among these, cytochrome P450 (CYP)-dependent metabolites such as 2-propyl-4-pentenoic acid (4-ene-VPA) and 2-propyl-2-pentenoic acid (2-ene-VPA) have been most strongly associated with hepatotoxic and neurotoxic effects.[12,19–21] The 4-ene-VPA metabolite is highly teratogenic, while the 2-ene-VPA metabolite is much less so.[22,23] While glucuronidation *via* UGT enzymes produces valproate glucuronide, the major excretory product.[10,12,21]

VPA-associated teratogenicity has been linked to metabolite-driven disruption of embryonic gene regulation and cellular homeostasis, affecting pathways involved in neuroepithelial integrity and neurulation.[12,24–26] Toxic metabolites contribute to teratogenicity through the downregulation of genes, including *IGF2R, RGS4, COL6A3, EDNRB*, and *KLF6*. Genetic and environmental modifiers of VPA sensitivity converge on these same metabolic pathways, as demonstrated by strain-dependent metabolomic alterations correlating with susceptibility to VPA-induced neural tube defects in murine models.[27,28] In parallel, *in vitro* neurulation models have shown that both genetic variants and VPA exposure impair neuroepithelial junctional organization, providing mechanistic insight into how systemic metabolic perturbations translate into failed neural tube closure.[24]

Given these risks, the WHO recommends avoiding VPA therapy in women of childbearing potential, emphasizing effective contraception and switching to alternative ASMs when pregnancy is planned.[4] Nonetheless, VPA remains the most effective treatment for specific epilepsy syndromes, including primary generalized tonic-clonic seizures (PGTCS), GGE, and JME.[1,9] Clinical data illustrate the difficulty of discontinuing VPA: while substantial proportion of women of reproductive age can withdraw from treatment, seizure relapse rates remain high, particularly in patients with GGE.[29,30] These findings highlight a persistent clinical dilemma in which seizure control must be balanced against fetal safety.

Collectively, these data indicate that VPA-associated teratogenicity is primarily driven by systemic maternal exposure and efficient placental transfer of the parent compound and its metabolites. Strategies capable of preserving central nervous system efficacy while reducing maternal plasma concentrations therefore represent a rational approach to mitigating fetal risk, particularly during pregnancy when physiological adaptations further complicate systemic PK.

2.2 The transformative potential of nanoformulated VPA

Given the central role of VPA metabolism in driving systemic toxicity and teratogenicity, strategies capable of modulating biodistribution and limiting off-target exposure are urgently needed. Nanoformulated delivery systems offer a means to decouple central nervous system (CNS) efficacy from systemic exposure, thereby potentially reducing hepatic metabolism and the formation of toxic metabolites while preserving antiseizure activity. This approach is particularly relevant in pregnancy, where fetal risk is tightly linked to maternal plasma exposure. Several VPA-containing nanoformulations have been reported, employing both lipid-based and polymeric carriers (Table 1). Among these, IN formulations are of particular interest because they enable direct nose-to-brain transport and achieve high CNS exposure with reduced systemic distribution.

Nanostructured lipid carriers (NLCs) represent another lipid-based strategy. Eskandari *et al.* (2011) and Correia *et al.* (2024) reported VPA-loaded NLCs. Eskandari *et al.* (2011) reported the first IN VPA formulation using nanostructured lipid carriers (NLC), demonstrating in a male rat Maximum Electroshock Seizure model comparable efficacy to intraperitoneal administration of free VPA, while achieving a >20-fold higher brain-to-plasma concentration ratio at a 37-fold lower dose (4 mg kg^{-1}).[32] These findings highlight the ability of IN nanoformulations to markedly enhance CNS targeting while minimizing systemic exposure. More recently, Correia *et al.* (2024) optimized VPA-loaded NLCs for IN delivery using a design-of-experiments approach, although *in vivo* validation was not performed.[38]

IN liposomal delivery of VPA has also been explored. Yuwanda *et al.* (2022) evaluated IN-administered VPA-loaded liposomes in male Wistar rats and reported a two-fold increase in plasma concentration compared with free VPA, confirming enhanced bioavailability and CNS delivery.[31] While systemic levels were not eliminated, the disproportionate increase in brain exposure relative to plasma supports partial pharmacokinetics (PK) uncoupling between CNS efficacy and systemic distribution.

Although fetal exposure was not directly assessed in these studies, the consistently elevated brain-to-plasma ratios achieved *via* IN delivery strongly suggests a reduction in sys-

Table 1 Summary of VPA nanoformulations reported in the literature. When multiple formulations were described in the same reference, only the formulation identified by the original authors as the most promising is included. Physical characterization data, as well as *in vitro*, *ex vivo*, and *in vivo* testing, are reported where available. The analyzed formulation is indicated in brackets [formulation tested]. PDI: polydispersity index; EE, encapsulation efficiency, ZP: zeta potential; DL: drug loading; DR: drug release

Type of formulation	Components	Formulation	Physical characterization	*in vitro*/*ex vivo* testing	*in vivo* testing (animal model/ outcome)
Intranasal administration					
Liposomes[31]	Phosphatidylcholine, cholesterol	[Lipo-VPA-4]	**Size:** 92.01 ± 1.87 nm	Permeation on sheep nasal mucosa; plasma and brain tissue HPLC analysis	Male Wistar rats
		Thin-film hydration	**PDI:** 0.21 ± 0.01	**Outcome:** four-fold increase in penetration compared to control	**Outcome:** increased C_{max} and AUC in plasma and brain tissue with respect to free VPA
			ZP: −43.47 ± 2.59 mV **EE:** 85.5 ± 1.07%		
NLCs[32]	Cetyl palmitate, lecithin, octyldodecanol, poloxamer 188	Emulsion-solvent diffusion, evaporation, ultrasonication	**Size:** 154 ± 16 nm	Plasma and brain tissue GC analysis	Male Wistar rats MES model
			PDI: 0.2 ± 0.1	**Outcome:** brain/plasma concentration ratio 20 times higher compared with VPA IP	**Outcome:** IN NLC (4 mg kg^{-1}) achieves the same protection as free VPA IP (150 mg kg^{-1}) with a 37-times lower dose
			ZP: −10 ± 0.5 mV **DL:** 47 ± 0.8% **DR:** 75 ± 1.9% over 21 days		
Intraperitoneal administration					
VANE[33]	Lecithin, safflower seed oil, medium chain triglyceride, alpha-tocopherol, Tween-80	[F3] ultrasonication	**Size:** 142.4 ± 2.45 nm	BBB permeation model (hCMEC/ D3 and CC-2565) and cytotoxicity	Sprague–Dawley rats
		Homogenization	**PDI:** 0.089 ± 0.015	**Outcome:** higher viability with F3, same permeation compared to free VPA	**Outcome:** higher plasma and brain concentration, half-life and decreased clearance with respect to free VPA
			Drug concentration: 158.26 ± 3.48 μg mL^{-1} **EE:** 99.29 ± 4.57%		
PLGA-NPs[34]	Poly-lactic glycolic-acid, Tween 80, span 20	Double emulsion-solvent evaporation	**Size:** 220 ± 78 nm	Plasma level, biochemical evaluation of brain samples	PTZ-induced male Wistar rats
			ZP: −32.9 mV	**Outcome:** reached therapeutic levels	**Outcome:** protection against seizures at 6h
			DL: 13.96% **EE:** 30%		
Amphiphilic block polymer NPs[35]	Methoxy-ended-poly(ethylene glycol)-*b*-poly(vinyl valproate block copolymer)	[PEG-*b*-PV(VPA)]	**Size:** 38nm	Spleen weight, hematological parameters, and liver function were evaluated by ALT and AST	PTZ-induced mice
		dissolution in *N*,*N*-dimethylformamide and dialysis	**PDI:** 0.1	**Outcome:** no toxicity compared to free VPA administration	**Outcome:** seizure protection even with weekly administration
Intravenous administration					
NBCA- NPs[36]	Butylcyanoacrylate, Tween 85, Tween 80 dextran 70 000	Polymerization in acidic medium	N/A	Brain and plasma level GC analysis	NMRI mice **Outcome:** comparable levels compared to free VPA, slower metabolism and lower metabolites concentrations

Table 1 *(Contd.)*

Type of formulation	Components	Formulation	Physical characterization	*in vitro*/*ex vivo* testing	*in vivo* testing (animal model/ outcome)
Other studies					
Cationic nanoemulsion gel[37]	Emulsion: Safflower seed oil, Tween 80, + lecithin (1 : 1), Phosphatidylglycerol, stearylamine Gel : Carbopol 934, triethanolamine	[CVE6]	**Size:** 113 nm	Drug release with dialysis machine	N/A
		Nanoemulsion *via* slow and spontaneous titration.	**PDI:** 0.26	**Outcome:** complete release at pH 6.8, drug deposition in goat nasal mucosa, 60–70% DD at 6 h	
		[CVE6 gel 0.35% w/w VPA] Gel obtained by mixing carbopol gel and lyophilized formulation	**ZP:** + 34.7 mV **Size:** 129 nm **ZP:** + 21.9 mV **Viscosity:** 1837 cP		
NLCs[38]	Compritol® ATO 888, Miglyol® 812, Gelucire® 59/14, Tween®80, cetrimide	Emulsion and ultrasonication	**Size:** 76.1 ± 2.8**pH:** 6.8 nm **PDI:** 0.190 ± 0.027 **ZP:** 28.1 ± 2.0 mV **EE:** 85.4 ± 0.8%	Biocompatibility study on SH-SY5Y, RPMI 2650, HepG2 cells; Mucin binding efficiency test **Outcome:** <75 μg mL^{-1} is deemed safe; estimated mucin binding efficiency: 58.66 ± 2.26%	N/A

temic (and by extension fetal) exposure compared with oral or IV administration. This inference is supported by the broader principle that placental transfer is driven primarily by free drug concentrations in maternal plasma, which are expected to be lower following IN administration than after systemic dosing.[39] Other nanoformulation strategies have been developed using systemic routes of administration. Lipid-based nanoemulsions reported by Tan *et al.* (2017) and Hussain *et al.* (2023) employed safflower seed oil, lecitin, and Tween80 to enhance BBB penetration.[33,37] Polymeric nanocarriers, including PLGA-based NPs and covalent VPA conjugates, have likewise demonstrated improved seizure control and, in some cases, reduced levels of toxic metabolites following IP or IV administration.[34–36] While these approaches improve therapeutic indices, their reliance on systemic delivery limits their capacity to restrict maternal-fetal transfer during pregnancy.

Together, these findings support the potential of IN nanoformulations to achieve effective CNS delivery of VPA while reducing systemic exposure, providing a mechanistic rationale for fetal sparing delivery strategies in the context of pregnancy. These considerations motivate deeper examination of the mechanistic basis of IN drug transport and the pregnancy-specific physiological factors that influence PK and maternal-fetal transfer.

3. Targeting the brain *via* the nasal route: mechanistic insights and liposome-enhanced drug delivery

Building on the metabolic and systemic determinants of fetal risk discussed in Section 2, this section examines the IN route as a strategy for CNS drug delivery that may alter maternal systemic exposure and, by extension, placental drug transfer. Unlike oral or IV administration, where CNS efficacy is achieved through sustained maternal plasma concentrations, IN delivery enables partial direct transport to the brain with important implications for systemic exposure, maternal PK, and fetal risk.

3.1 IN delivery as a non-invasive route for CNS targeting and systemic exposure modulation

The IN route, first described over a century ago, offers a non-invasive and promising strategy for delivering CNS-directed therapeutics by bypassing the BBB.[40] Conventional oral or parenteral drug delivery relies on systemic circulation to reach the CNS but is constrained by hepatic first-pass metabolism, enzymatic degradation, systemic clearance, and physiological barriers such as the intestinal epithelium and the BBB,[41,42] which excludes the majority of small molecules.[43] Alternative approaches, including intrathecal administration or intracerebral infusion, can bypass the BBB but are invasive, unsuitable for chronic use, and associated with procedural risks.[44] IN delivery provides direct access to the brain through two principal neural pathways: the olfactory and trigeminal nerves[41] (Fig. 1). The olfactory nerve (cranial nerve I) enables transport

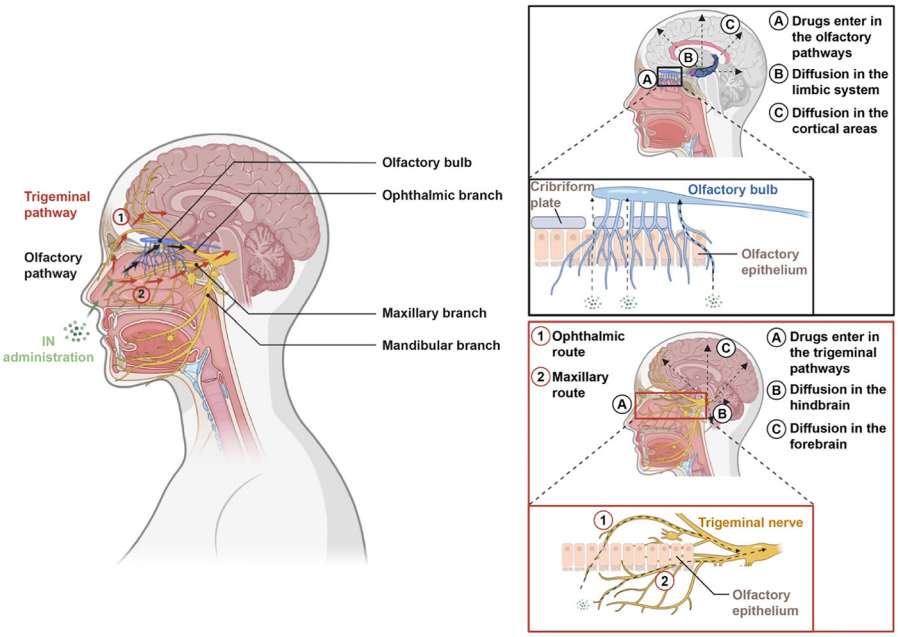

Fig. 1 Schematic representation of the nose-to-brain delivery route. Left panel: following intranasal administration of biomolecules (green), drugs can reach the brain either *via* the olfactory pathway (black) or through the ophthalmic (1) and maxillary (2) branches of the trigeminal nerve (red). Right panel: The two pathways are shown separately. The upper diagram illustrates the olfactory pathway, with absorption at the olfactory bulb (A), followed by diffusion into the limbic system (B) and cortical areas (C). The lower diagram depicts the trigeminal pathway, including the ophthalmic branch (1) and maxillary branch (2). After absorption (A), drugs travel along the trigeminal branches and subsequently diffuse into the hindbrain (B) and forebrain (C).

via axonal pathways and perineuronal channels,[45,46] while the trigeminal nerve (cranial nerve V) facilitates drug delivery to the hindbrain and forebrain through intracellular and extracellular mechanisms such as bulk flow and perivascular diffusion.[47–50] Because these pathways allow CNS exposure without requiring high or sustained maternal systemic plasma concentrations, IN delivery can reduce peripheral exposure and off-target effects while improving central bioavailability, making it particularly attractive for CNS indications requiring rapid onset and dose sparing.

Several IN formulations have already reached clinical use, including Spravato® (esketamine, Johnson & Johnson) for depression,[41] NAYZILAM® (midazolam) and VALTOCO® (diazepam) for acute seizures,[40] and Zavegepant, the first GCRP receptor antagonist nasal spray approved by the FDA for migraine.[51,52] Additional candidates under clinical investigation include IN ketamine for major depressive disorder (Seelos Therapeutics, NCT04669665) and IN insulin combined with empagliflozin for early Alzheimer's disease patients (Wake Forest University, NCT05081219). Notably, while these agents demonstrate the feasibility of IN delivery for CNS disorders, systematic evaluations of maternal systemic and fetal exposure remain extremely limited.

3.2. Determinants of nose-to-brain transport and systemic spillover

Despite its advantages, IN delivery does not completely eliminate systemic absorption. The fraction of drug reaching the brain *versus* entering the systemic circulation is governed by both patient-dependent and drug-dependent factors. Patient-dependent variables include mucin secretion, mucociliary clearance, enzymatic degradation, P-glycoprotein (P-gp) efflux activity, and vascular absorption, all of which reduce the fraction of drug reaching the brain.[41,53] Mucin, which constitutes ~2.5–3% of the nasal mucosa,[54] acts as a physical barrier,[55,56] particularly impeding hydrophobic or charged hydrophilic molecules.[46,57] Mucociliary clearance further limits residence time and absorption,[41,58] with clearance occurring more rapidly in the respiratory epithelium than in the olfactory region.[46,59]

Enzymatic degradation in the nasal cavity can function as a pseudo-first-pass effect,[41,60] while P-gp, highly expressed in the olfactory epithelium, actively effluxes drugs and contributes to variability in absorption and systemic distribution.[41,61,62] Drug-dependent factors, including molecular weight, lipophilicity, solubility, pH, viscosity, and osmolality,[41,46] further shape the balance between CNS uptake and systemic spillover.[41,46] From a maternal-fetal pharmacology perspective, these parameters are critical, as placental transfer is driven primarily by free drug concentrations in maternal plasma. Consequently, IN formulations that maximize nose-to-brain transport while limiting vascular absorption are expected to yield lower maternal plasma C_{max} and area under the curve (AUC) compared with oral or IV administration, thus reducing fetal exposure.

3.3 Liposomes as modulators of brain targeting and maternal plasma exposure

A promising strategy to enhance nose-to-brain transport is the use of nanoformulated drugs, which can improve permeability, extend residence time, and increase brain concentrations.[41,63] Among these, liposomes have emerged as versatile nanocarriers due to their biocompatibility, structural adaptability, and ability to encapsulate both hydrophilic and lipophilic drugs.[64] Structurally, liposomes consist of one or more phospholipid bilayers surrounding an aqueous core and are commonly classified as unilamellar vesicles (single bilayer), multilamellar vesicles (multiple concentric bilayers), or multivesicular vesicles (non-concentric aqueous compartments).[65,66]

Liposomes offer several advantages, including protection of labile drugs, controlled or targeted release, and reduced systemic toxicity.[64,67] Their clinical utility, however, can be constrained by limited loading capacity, physicochemical instability leading to leakage or degradation, and rapid clearance by the mononuclear phagocyte system (MPS), primarily *via* the liver and spleen.[68] Early approaches to improve systemic stability focused on optimizing lipid composition, including cholesterol content, to increase membrane rigidity.[69] A transformative step was polyethylene glycol (PEG) functionalization (PEGylation), which generates a hydrophilic, neutrally charged steric barrier that reduces opsonization and MPS uptake and can prolong circulation time.[70–73] While systemic half-life is not the primary goal for IN formulations, these surface modifications remain relevant because they influence mucus interactions, epithelial transport, and downstream biodistribution after any systemic absorption.

The functional performance of liposomes depends on key physicochemical parameters. Particle size, typically ranging from 50 nm to several micrometers, influences biodistribution, and cellular uptake and can be modulated by lipid composition (*e.g.*, cholesterol-to-phospholipid ratio).[74,75] A polydispersity index (PDI) ≤ 0.3 is generally used as an indicator of formulation uniformity and stability,[76] while zeta potential (ZP) values above ±30 mV can enhance colloidal stability by reducing aggregation.[74] Encapsulation efficiency (EE) reflects the fraction of drug successfully incorporated, with hydrophobic molecules partitioning into the lipid bilayer and hydrophilic compounds localizing within the aqueous core.[77] Collectively, these parameters can be tuned to favor nose-to-brain transport while minimizing systemic spillover, an especially relevant consideration in pregnancy, where fetal exposure is strongly influenced by maternal plasma concentrations.

In the context of IN delivery, liposomes have shown considerable promise. Preclinical studies in male rats demonstrated that liposome-encapsulated drugs (*e.g.*, DSPC : CHOL : PEG, 1 : 2 : 0.5 mol/mol/mol; and EPC : DSPE-PEG2000 : CHOL, 20 : 1 : 5 mol/mol/mol) achieved significantly higher brain exposure than free drug delivered intranasally or orally.[78,79] In addition, Yuwanda *et al.* reported that phosphatidylcholine-rich liposomes (~92 nm) enhanced VPA brain bioavailability following IN administration.[31] Importantly, while systemic levels were not eliminated, disproportionate increases in brain exposure relative to plasma support partial PK uncoupling between CNS and efficacy and systemic distribution, consistent with the goal of reducing maternal plasma exposure while maintaining CNS delivery.

Surface charge and PEGylation also critically shape regional brain distribution and mucus interactions. Kurano *et al.* evaluated liposomes with different surface charges across multiple brain regions (including olfactory bulb, forebrain, hindbrain, bulbospinal tract, and trigeminal nerve) and found that neutral PEGylated liposomes (DSPE-PEG2000-coated) enabled broader distribution, whereas positively charged liposomes tended to accumulate in the olfactory bulb *via* electrostatic interactions with mucin.[80] PEGylation may further facilitate parenchymal penetration. Narayan *et al.* reported that PEGylated liposomes (LP-16, SPC : CHOL : MPEG-DSPE, 8 : 1 : 0.20) achieved higher brain AUC compared to IV administration or non-PEGylated liposomes.[81] Moreover, PEGylation of larger NP (200–500 nm) markedly improved mucus penetration, countering earlier assumptions that PEG necessarily increases mucoadhesion. Low molecular weight PEG chains (~2 kDa) improved particle mobility by reducing hydrophobic interactions and hydrogen bonding, yielding diffusion rates up to 100–1000 times higher.[82,83] Interestingly, 200 nm polystyrene-PEG (PS-PEG) NP diffused more efficiently than 100 nm particles, likely due to greater PEG surface coverage.[84] Collectively, these formulation-dependent parameters can be leveraged to favor nose-to-brain transport while further limiting systemic spill-over, thereby indirectly reducing the potential for transplacental diffusion.

From a translational perspective, liposomes are supported by a strong clinical precedent, with more than 20 lipid-based formulations approved by the FDA or EMA across multiple indications.[85] While current delivery routes include parenteral, intrathecal, epidural, and inhalation, the IN pathway remains comparatively underexplored yet highly promising for CNS-targeting. Notably, although pregnancy-specific pharmacokinetic data for nano-enabled nose-to-brain delivery remain extremely limited, a recent preclinical study showed that this approach improved seizure control and prevented congenital malformations in pregnant epileptic rats compared with systemic administration, providing initial functional support for its relevance during pregnancy.[86] Accordingly, conclusions regarding maternal-fetal exposure following IN liposomal delivery must currently rely on mechanistic principles and preclinical brain-to-plasma exposure data, motivating the pregnancy-specific discussion of placental remodeling and the limited functional and clinical observations presented below. Table 2 summarizes key studies focused on liposome-based IN delivery.

4. Physiological changes in pregnancy: structural remodeling, implications for maternal-fetal transfer, and drug pharmacokinetics

To understand how IN drug delivery may reduce fetal exposure compared to oral or IV administration, it is essential to con-

sider two interacting processes: (i) gestation-dependent placental barrier remodeling and (ii) pregnancy-induced alterations in systemic PK that govern maternal-fetal drug transfer. In the context of CNS-targeted therapies, these processes determine how route of administration influences maternal plasma exposure, placental transfer, and ultimately fetal drug burden. Pregnancy triggers a cascade of anatomical and physiological adaptations that evolve across gestation and affect therapeutic performance, particularly for drugs with narrow therapeutic indices such as VPA. In this section, we examine placental barrier remodeling and systemic pharmacokinetics, with specific emphasis on how these factors differentially impact systemic (oral/IV) *versus* IN delivery strategies.

4.1 Placental permeability across gestation

The human placenta is a transient, multifunctional organ that develops early in gestation to mediate the bidirectional exchange of gases, nutrients, metabolic waste, hormones, and immune factors between maternal and fetal circulations. Beyond its endocrine functions, it acts as a dynamic barrier regulating fetal exposure to exogenous compounds, including therapeutics. Maternal-fetal transfer occurs *via* passive (transcellular or paracellular) diffusion, facilitated diffusion, active transport by membrane-bound transporters, and endocytosis or transcytosis.[87] Structurally, the human hemochorial placenta consists of chorionic villi lined by a continuous syncytiotrophoblast (STB) layer bathed in maternal blood. Beneath the STB lie cytotrophoblasts and fetal capillary endothelial cells. In early gestation, the trophoblast barrier is multilayered and reinforced by tight junctions (TJs), including proteins such as occludin and ZO-1, that confer high paracellular resistance.[88,89] As gestation progresses, the placenta undergoes extensive morphological remodeling: the STB thins into a monolayer, fetal capillaries approach the villous surface, and TJ localization shifts primarily to the fetal endothelium (Fig. 2).

Despite this anatomical thinning, passive diffusion remains restricted. Perfusion studies show that mid-sized molecules (40–70 kDa), such as horseradish peroxidase and dextrans, can cross the term placenta, likely *via* structural discontinuities in the STB, providing syncytial breaks and fibrin deposits.[87,90] Recent imaging studies using three-dimensional electron microscopy have identified millions of trans-syncytial nanopores (TSNs) spanning the STB, providing a size-selective pathway for solute passage.[91] Importantly, these placental transfer mechanisms are primarily engaged by drugs present in the maternal systemic circulation; delivery strategies that limit maternal plasma exposure, such as IN administration, are therefore expected to reduce interaction with placental transport pathways. Animal studies further illustrate the dynamic nature of placental permeability. In rats, paracellular pore diameters are wider at mid-gestation and narrows near term, indicating a gestation-dependent modulation of barrier properties.[88,91]

Collectively, these findings highlight that fetal drug exposure is closely tied to maternal plasma concentrations and placental engagement, reinforcing the importance of delivery strategies that minimize systemic exposure when fetal sparing is desired.

4.2 Pharmacokinetics alterations during pregnancy and implications for VPA exposure

Understanding placental remodeling is essential for the rational design of therapeutics aimed at modulating maternal-fetal transfer. However, successful implementation also requires consideration of broader PK changes during pregnancy, which significantly affect drug absorption, distribution, metabolism, and excretion. Pregnancy induces profound physiological adaptations that reshape the PK and pharmacodynamics (PD), altering drug efficacy and fetal exposure.

One of the most pronounced changes is plasma volume expansion, which increases progressively across gestation, resulting in hemodilution and reduced total plasma drug concentrations.[92] Concurrently, serum albumin levels decline,[93] reducing protein-binding of highly bound drugs, such as VPA. Hepatic metabolism is also altered, with upregulation of uridine glucuronyl transferases (UGTs), the primary enzymes mediating VPA clearance, thereby accelerating elimination.[94,95] Clinical data indicate that while total VPA plasma concentrations decline during pregnancy, free VPA levels remain relatively stable or may even increase near term due to reduced protein binding.[96–99] As a result, free VPA concentrations are considered a more reliable indicator of fetal exposure than total levels, although they are infrequently monitored in clinical practice.[100,101]

VPA also displays substantial inter-individual variability in plasma concentrations, with variability more pronounced at lower doses.[100,102,103] Importantly, higher cord blood VPA concentrations have been inversely associated with neonatal birth length, independent of maternal dose,[104,105] highlighting the clinical relevance of maternal PK variability for fetal outcomes. These findings emphasize the need for individualized therapeutic drug monitoring during pregnancy.

Crucially, the impact of these physiological changes differs depending on the route of administration. In the context of oral or IV delivery, pregnancy-associated alternations in plasma volume, protein binding, hepatic metabolism, and placental permeability directly influence maternal systemic exposure and fetal drug transfer. By contrast, IN delivery is expected to partially decouple CNS exposure from systemic PK by enabling direct nose-to-brain transport. As a result, maternal plasma concentrations, and consequently, placental transfer, may be substantially lower following IN administration compared with oral or IV routes, even when therapeutically relevant CNS concentrations are maintained.

Despite these insights, almost nothing is known about the PK of IN-administered drugs during pregnancy, and no systematic studies have evaluated trimester-specific effects on absorption, distribution, or metabolism. The most widely used IN therapies in pregnancy are corticosteroids, whose safety evaluations have focused on congenital malformations rather than PK, with no increased risk compared to non-exposed

Table 2 Summary of liposomal characteristics influencing brain bioavailability. Reported outcomes include transport, overall bioavailability, and regional brain distribution, comparing conventional, PEGylated, and charged liposomes with free drug or alternative administration routes. PDI: polydispersity index; EE, encapsulation efficiency; ZP: zeta potential

Encapsulated Drug	Liposome composition	Physical Characterization	Testing approach	Administration route	Outcome
Donepezil[78]	DSPC : CHE : PEG **Ratio:**1 : 2 : 0.5	**Size:** 102 ± 3.3 nm **PDI:** 0.28 ± 0.03 **ZP:** 28.31 ± 0.85 mV **EE:** 84.91% ± 3.31%	Wistar rats	IN	↑ Brain bioavailability compared with the free drug
H102 peptide[79]	EPC, DSPE-PEG_{2000} **Ratio:** 20 : 1 : 5	**Size:** 12.2 ± 6.4 nm **PDI:** 0.185 ± 0.012 **ZP:** −2.96 ± 0.38 mV **EE:** 71.35 ± 0.87%	Male Sprague-Dawley rats	IN	↑ Cerebral absorption, particularly in the hippocampus, *vs.* nasal solution
VPA[31]	[Lipo-VPA-4 (F4)] DRUG : CHOL : PC **Ratio:** 1 : 10 : 75	**Size:** 92.01 ± 1.87 nm **PDI:** 0.21 ± 0.01 **ZP:** −43.47 ± 2.59 mV **EE:** 85.50% ± 1.07%	Sheep nasal mucosa (*ex vivo*); Wistar rats	IN	↑ BBB penetration and brain levels *vs.* free drug (*in vivo*); ↑ Penetration (*ex vivo*) ↑ Phosphatidylcholine → ↓ particle size
N/A[80]	*Positively charged* DOTAP : DOPC : CHOL : DSPE-PEG_{2000} **Ratio:** 2 : 1 : 2 : 0.5	*Positively charged* **Size:** 80.1 ± 0.4 nm **PDI:** 0.234 ± 0.009 **ZP:** + 28.8 ± 0.50 mV	Rat brain tissue slices, human brain cortex (*ex vivo*)	IN	*Neutral PEGylated* ↑ AUC in the forebrain, hindbrain, spinal cord, and trigeminal nerve *vs.* PEGylated positive and negative liposomes ↑ AUC *vs.* to non-PEGylated neutral liposomes in all tissues examined ↓ AUC in plasma compared to other formulations
	Neutral liposome (PEGylated) DOPC : CHOL : DSPE-PEG_{2000} **Ratio:** 3 : 2 : 0.5	*Neutral liposome (PEGylated)* **Size:** 89.7 ± 2.3 nm **PDI:** 0.256 ± 0.004	Male mice (of the Deutschland, Denken, and Yoken (ddY) strains)		*PEGylated and charged* *+Charge* ↑ AUC in the olfactory bulb compared to other liposomes. *− Charge* ↑ AUC compared to positive liposomes in the trigeminal nerve and a slight ↑ in plasma
	Neutral (non-PEGylated) DOPC : CHOL : DSPE-PEG_{2000} **Ratio:** 3 : 2 : 0	**ZP:** −18.8 ± 0.38 mV *Neutral (non-PEGylated)* **Size:** 84.0 ± 0.9 nm **PDI:** 0.222 ± 0.028 **ZP:** −7.8 ± 0.17 mV			
	Negative liposome DOPC : DOPS : CHOL : DSPE-PEG_{2000} **Ratio:**1 : 2 : 2 : 0.5	*Negative liposome* **Size:** 86.4 ± 1.1 nm **PDI:** 0.260 ± 0.010 **ZP:** −39.3 ± 1.14 mV			
Risperidone[81]	[LP-16] SPC : CHOL : MPEG-DSPE **Ratio:** 8 : 1 : 0.20	**Size:** 98.51 ± 6.82 nm **ZP:** -28.60 ± 3.62 mV **EE:** 58.86% ± 1.38%	Wistar Albino rats	IN *vs.* IV	*Liposomal formulations* ↑ Brain exposure ↓ Plasma levels *vs.* IV drug *PEGylated LP-16* ↑ Risperidone absorption *vs.* conventional liposomes

pregnancies.[106] Limited data from IN-administered fentanyl during labor suggests lower maternal plasma concentrations compared with non-pregnant adults, with detectable but reduced fetal exposure.[99,107] These observations support the premise that IN delivery may confer PK advantages during pregnancy, but dedicated studies are urgently needed to define gestation-specific effects and optimize dosing strategies for fetal-sparing CNS therapies.

Altogether, these adaptations complicate prediction of maternal and fetal drug exposure, particularly for drugs with narrow therapeutic indices such as VPA or those delivered *via* alternative routes like IN administration. Dedicated studies are urgently needed to define gestation-specific effects on the PK of IN therapeutics, to enable optimized dosing that ensures maternal efficacy while safeguarding fetal development.

5. Nanocarriers for drug delivery during pregnancy

Building on the placental physiology and pregnancy-specific PK considerations outlined in Section 4, this section focuses on systemically administered nanocarriers, primarily liposomes, that have been empirically evaluated in pregnancy models. The aim is to identify formulation features associated with restricted placental and fetal exposure once a nanocarrier is present in maternal circulation, and to define the limitations of systemic nanomedicine when fetal protection is the primary therapeutic objective. IN delivery strategies, which rely on distinct transport mechanisms and bypass systemic circulation, are discussed separately in Section 3.

To evaluate which liposomal parameters restrict or permit placental transfer following systemic administration, we reviewed selected lipid-based nanoformulations tested in pregnancy models. Although several liposomal systems have been reported, many lack critical physiochemical or biological characterization (*e.g.*, ZP, EE, or release profiles), limiting meaningful comparison. Therefore, only formulations with sufficient detail were included. Two reports describing placental or fetal localization were excluded due to inadequate validation or unclear biological significance. The intent of this analysis is not to provide an exhaustive catalog, but to highlight formulation trends and persistent knowledge gaps.

The formulations summarized in Table 3 were evaluated in pregnant mice, most commonly at gestational day 16. Across these studies, none of the listed nanoformulations crossed the placental barrier or localized within the fetus, despite differences in lipid composition or sterol content. Reported formulations generally shared a narrow physicochemical range, with particle sizes between 68 and 102 nm, high EE (≥90%), and near-neutral surface charge. While these characteristics are associated with limited fetal localization in the reported models, the absence of direct comparative studies constrains broader interpretation. Notably, variations in sterol type or abundance within formulations did not alter the lack of transplacental passage observed under these conditions.[108] A small number of systemically administered liposomal formulations have been engineered to preferentially localize to the placenta following intravenous delivery in pregnancy models. While informative, these placenta-targeting approaches fall outside the primary scope of this review, which focuses on strategies, particularly IN delivery, that minimize systemic exposure and avoid direct placental engagement.[109] In a complementary approach, liposomal encapsulation has been used to prevent fetal exposure to drugs known to be harmful during pregnancy. Refuerzo *et al.* demonstrated that indomethacin encap-

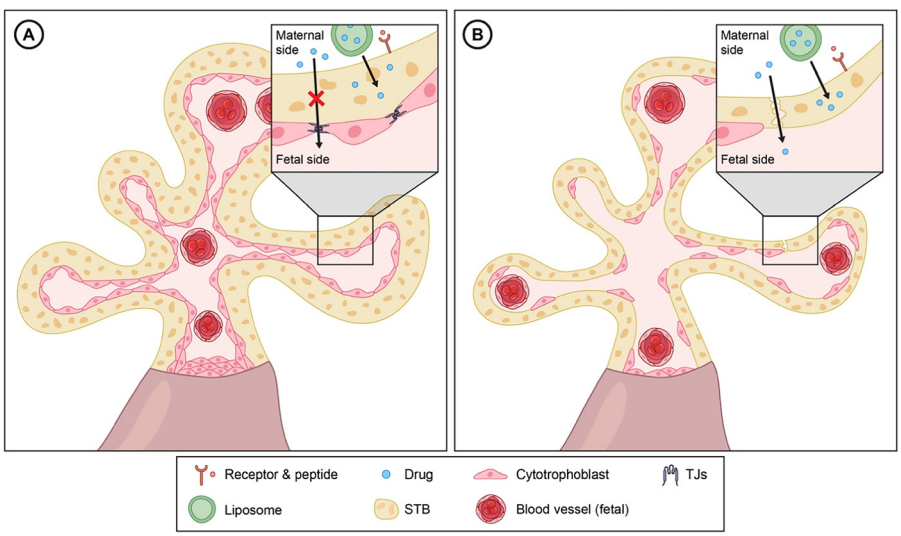

Fig. 2 Comparison of placental villi at early (A) and late (B) stages of pregnancy. From early to late gestation, the syncytiotrophoblast (STB) and cytotrophoblast layers progressively thin, fetal capillaries migrate toward the villous periphery, and STB/cytotrophoblast permeability increase due to remodeling of tight junctions (TJs), enabling diffusion of small solutes. Placental localization of liposomes functionalized with peptide ligands is also shown.

sulated in liposomes and administered intravenously to pregnant mice on gestational day 18 remained restricted to the maternal compartment without detectable fetal transfer.[110] Such strategies are particularly relevant when treatment discontinuation is neither feasible nor safe, as in the case of valproic acid, where withdrawal during pregnancy is generally discouraged despite teratogenic risk.[66] Importantly, systemically administered nanocarriers do not eliminate maternal plasma exposure, even when fetal accumulation is prevented. Following intravenous delivery, nanoparticles remain subject to maternal circulation, hepatic uptake, and interaction with the placental barrier. As a result, placental exposure may still occur, particularly for drugs with narrow therapeutic indices. This limitation distinguishes systemic nanocarrier approaches from IN delivery, which offers a mechanistically distinct strategy by enabling direct nose-to-brain transport with reduced reliance on sustained maternal plasma concentrations. For this reason, IN liposomal delivery represents a complementary approach when minimizing fetal exposure is a primary therapeutic goal.

Notably, until recently, no IN administered nanoformulations had been evaluated in pregnancy models. A newly published study has now examined IN delivery of a teratogenic dose (1250 mg kg^{-1} day^{-1}) of niosome-formulated pregabalin in epileptic PTZ-treated pregnant rats, comparing this approach with oral pregabalin and standard diazepam administration. IN nano-delivery resulted in enhanced antiepileptic efficacy and, importantly, prevented congenital malformations relative to systemic treatment modalities.[86] However, this study did not directly assess maternal plasma concentrations, placental transfer, or fetal drug levels. Accordingly, while these findings provide the first functional evidence supporting the potential of IN nanotherapeutic delivery during pregnancy, all formulations summarized in Table 3 remain grounded in systemic pharmacokinetic paradigms. The lack of quantitative maternal-fetal exposure data following IN administration remains a key limitation and motivates future pregnancy-specific pharmacokinetic studies. Given the structural and functional similarities between niosomes and liposomes,[114] these observations nevertheless provide indirect support for the translational relevance of IN liposomal platforms in pregnancy.

6. Conclusions and future directions

The widespread use of ASMs among women of reproductive age continues to raise critical concerns regarding fetal safety. VPA remains indispensable for specific refractory epilepsy syndromes, yet its clinical utility is constrained by well-established teratogenic risks that are closely linked to systemic maternal exposure and placental transfer. Pregnancy-associated physiological changes further complicate PK, highlighting the need for delivery strategies that preserve maternal efficacy while limiting fetal exposure. In this context, IN liposomal delivery offers a compelling alternative to systemic or oral administration. By enabling direct brain targeting while reducing dependence on sustained maternal plasma concentrations, IN delivery is expected, based on established PK principles, to lower maternal C_{max} and systemic AUC. Given that the fetal exposure is primarily driven by free drug levels in maternal plasma, this shift in exposure profile provides a mechanistic rationale for reduced placental transfer, even in the absence of direct fetal PK measurements. From a translational perspective, liposomes represent a mature and scalable drug-delivery platform. Established manufacturing strategies, including ethanol or solvent injection, high-pressure homogenization, extrusion-based size control, and continuous-flow or microfluidic mixing, are already implemented at clinical and commercial scale under GMP conditions for approved liposomal formulations.[115–118] These paradigms support the feasibility of scaling IN liposomal systems for clinical translation.

Importantly, the relevance of safer VPA delivery strategies extends well beyond epilepsy. VPA is widely prescribed for additional neurological and psychiatric indications, including bipolar disorder, migraine prophylaxis, and mood stabilization, substantially expanding potential exposure across the general population, including women who may become pregnant unintentionally. This broader clinical use further heightens the public health imperative for delivery approaches that decouple central nervous system efficacy from systemic and fetal exposure. More broadly, IN liposomal delivery may provide a generalizable framework for maternal-restricted CNS targeting, with potential applicability to other ASM and neuropsychiatric therapies used during pregnancy. By shifting maternal-fetal care from risk avoidance toward precision-guided delivery, such strategies may ultimately reduce fetal exposure while ensuring access to effective, evidence-based neurological treatment. Versatile platform with far-reaching implications. From a public health perspective, reducing fetal exposure through precision delivery has the potential to lower the incidence of congenital malformations, decrease long-term healthcare costs, and support regulatory pathways for the safer use of essential but teratogenic medications. More broadly, this approach reflects a shift in maternal-fetal therapeutics towards precision-guided delivery strategies that preserve maternal efficacy while minimizing fetal risks.

Author contributions

B. C. conceived the review, led the manuscript preparation, and wrote the main text. L. C. Z., F. M., and T. P. contributed equally to the literature review, manuscript drafting, and the preparation of tables and figures, each providing deep input throughout the process. R. H. F. contributed to the discussion. F. T. contributed equally with B. C. in conceptual guidance and manuscript development. All authors reviewed and approved the final version of the manuscript.

Table 3 Summary of lipid-based nanoformulations evaluated for transplacental passage in pregnancy models following systemic administration. Reported parameters include particle size, encapsulation efficiency, surface charge, and composition. None of the listed nanoformulations crossed the placental barrier or were reported to localize in the fetus. All formulations were administered IV in pregnant mice at gestational day 16

Ionizable lipid	Phospholipid	Sterol	Lipid-PEG	Molar ratio	Size (nm)	Zeta potential (mV)	Encapsulation Efficiency (%)	PDI	Encapsulated molecule
C12-494 [111]	DOPE	Cholesterol	C14-PEG2K	35 : 16 : 46.5 : 2.5	101.6 ± 0.3	−7.0 ± 2.1	95.9 ± 0.6	0.19 ± 0.02	Indomethacin
C12-494 [111]	DOPE	Campesterol	C14-PEG2K	35 : 16 : 46.5 : 2.5	91.7 ± 0.4	−8.4 ± 1.9	94.6 ± 0.2	0.24 ± 0.02	Indomethacin
C12-494 [111]	DOPE	β-Sitosterol	C14-PEG2K	35 : 16 : 46.5 : 2.5	93.0 ± 0.6	−7.6 ± 0.7	94.2 ± 0.6	0.18 ± 0.02	Indomethacin
C12-494 [111]	DOPE	Stigmastanol	C14-PEG2K	35 : 16 : 46.5 : 2.5	92.1 ± 0.8	−7.4 ± 1.8	94.7 ± 0.1	0.13 ± 0.02	Indomethacin
C12-494 [111]	DOPE	Cholesterol	C14-PEG2K	35 : 16 : 31.5 : 2.5	68.1 ± 1.3	N/A	90.0 ± 3.5	0.13 ± 0.02	Indomethacin
C12-494 [111]	DOPE	Cholesterol	C14-PEG2K	35 : 16 : 61.5 : 2.5	77.0 ± 0.3	N/A	90.0 ± 1.5	0.14 ± 0.02	Indomethacin
C12-494 [112]	DOPE	Cholesterol	C14-PEG2K	35 : 16 : 46.5 : 2.5	72.9 ± 3.4	4.07 ± 0.95	94.9 ± 0.3	0.36 ± 0.01	mCherry mRNA
C12-200 [113]	DOPE	Cholesterol	C14-PEG2K	35 : 16 : 46.5 : 2.5	~80	—	—	—	Luciferase mRNA

Conflicts of interest

The authors declare no conflict of interest.

Abbreviations

ASM	Antiseizure medication
BBB	Blood-brain barrier
CNS	Central nervous system
GGE	Genetic generalized epilepsy
HDAC	Histone deacetylase
IN	Intranasal
IV	Intravenous
IP	Intraperitoneal
JME	Juvenile myoclonic epilepsy
MES	Maximum electroshock seizure
NLC	Nanostructured lipid carrier
NP	Nanoparticle
PD	Pharmacodynamics
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PGTCS	Primary generalized tonic-clonic seizures
PK	Pharmacokinetics
STB	Syncytiotrophoblast
TDM	Therapeutic drug monitoring
MPS	Mononuclear phagocyte system
TJ	Tight junction
TSN	trans-Syncytial nanopores
VPA	Valproic acid
VANE	VPA nanoemulsion
PDI	Polydispersity index
MPEG-DSPE	Methoxy polyethylene glycol-distearoyl phosphatidylethanolamine

Data availability

Data sharing is not applicable to this article as no new data were generated or analyzed. The data supporting the findings of this review are available within the article and cited in the references.

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