ion-pair species in solution [11]. The passive diffusion of drug, with slight modification in the structure, molecular weight, lipophilicity, polar surface area, and others will help in the penetration of drug across BBB (Figs. 4 and 5).

Polar surface area, charge, and hydrogen bonding: An alternative measure for BBB permeability is the permeability surface area products (PS) which is traditionally expressed as log PS although log P is a reliable indicator of permeability. In case of the liposomes, the change in the surface charge (cationic liposomes) helps in the binding of that nanocarriers toward specific receptor. The polar surface area is the sum of the polar atoms in the molecule. Thus the change in the sum of polar atom leads to surface modification and increases the affinity. Generally, molecules with a large polar surface area remain undiffused through the BBB, with the upper limit estimated between 60 and 90 Å [12].

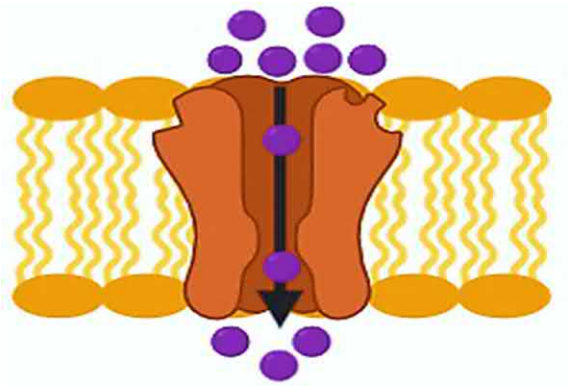

FIG. 4 Passive diffusion of drug through blood-brain barrier (BBB).

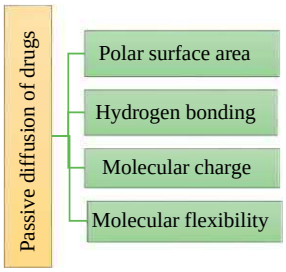

FIG. 5 Parameters for the passive diffusion of the drug across blood-brain barrier (BBB).

3. EMERGING TRENDS IN INTRATHECAL DRUG DELIVERY

3.1. Nanoparticulate Drug Carrier System

Nanocarriers are used in various drug delivery systems such as dendrimes, magnetic nanoparticles (NPs), lipid nanocarriers, and gold particles as shown in Fig. 6.

Dendrimers (DDs) are hyperbranched molecule with nanosized-scale dimensions, composed of three layers of polymers: a central core, branched layer, and terminal functional group. The branched groups are attached to the central core and they usually describe the generation of the DDs. For example, the number of the layers of branched groups is three, it is indicated as a G3 DD and the terminal groups are responsible for the charges created over the surface. The surface groups may have positive, negative, or neutral charges, which act as an important parameter for the penetration across BBB. Poly(amidoamine) (PAMAM) is considered as one of the smallest and precious components for dendrimer synthesis. Because of nanosize and highly compact structure of PAMAM dendrimer, it is considered as ideal form for brain delivery (Table 2). Because of open structure of DDs, small molecules get easily encapsulated and covalently attached to it. DDs are mainly nanosized, and they provide better stability making them ideal for the delivery across BBB [27]. Table 2 indicates the improvement in the bioavailability and stability with the use of DDs as nanocarrier.

Lipid NPs: Lipid-based nanocarriers are composed of physiological lipids, making them well-tolerated, nontoxic, and are degraded to a nontoxic residue. Lipid NPs are divided into two groups: liposomes and other lipid NPs, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Liposomes are bilayer lipid particles mainly composed of phospholipid and cholesterol and size ranging from 100 to 1000 nm. Liposomes are considered as safe and selective therapeutic tool for the delivery of the drug across BBB. The advantages of liposomes for intrathecal drug delivery are as follows: (1) the lipid composition of the liposomes helps in the easy penetration across BBB. (2) Intrathecal delivery of the liposomes allows diffuse distribution. (3) Encapsulation of drug in liposomes changes the pharmacokinetic of the free drug providing control release of the drug. (4) Drug entrapped in the liposomes will avoid the side-effect associated with continuous infusion. The surface-charged liposomes also act as ideal delivery of drugs and genetic material, as they provide facilitate interaction with the cell membrane and improves uptake [28].