TABLE 1
Marketed Preparation of the Intrathecal Drug Delivery System.

S. No.	Marketed Preparation of the Intrathecal Infusion	Drug Content	Application?
1.	Infumorph	Morphine sulfate	Chronic pain treatment
2.	Prialt	Ziconotide	Pain reliever

associated with the conventional delivery. The Section 2 represents the strategies to overcome the barriers associated with ITDT, to ease the delivery and enhance the bioavailability for the actives. The Section 3 signifies the emerging trends in ITDT such as nanoparticulate drug carrier system, hydrogels-mediated drug delivery, microbubble-assisted ultrasound-based drug delivery, intranasal drug delivery, receptor-mediated opening, and carbon-nanotubes. The Section 4 consists of the newer development and the futuristic approach for the researchers in the field of ITDT

2. STRATEGIES FOR INTRATHECAL DRUG DELIVERY

BBB is the main obstacle for the delivery of the drug across the brain. To overcome this barrier, few strategies allow the transfer of the actives through this wall (Fig. 1.) (See Fig. 2.)

2.1. Blood-Brain Barrier Disruption by Ultrasound

BBB is a brain's first-line of defense from harmful substances in the blood stream and composed of endothelial cells which are segmented extremely close to each other forming tight junctions. This tight joint of the tissue acts as main barrier for the penetration of drug and therapeutic effect in case of CNS disorders. The traditional method for drug delivery in the brain was the administration of small molecule drugs, transcranial drug delivery by an invasive catheter. Most small molecule drugs (400–500 Da) are not able to cross the BBB and few neurological conditions such as Parkinsonism and Alzheimer respond to small-molecule drugs [3]. Ultrasounds are mechanical waves with frequency greater than 20 kHz, frequency above the human hearing range. Ultrasound waves cause the disruption of BBB through widening the tight junctions and activating transcellular mechanisms, with little effect on the surrounding parenchyma. Furthermore the opening occurs at acoustic power level orders of magnitude lower than was previous use, making method substantially easier to apply through the intact skull. Ultrasound-induced effects are generated by two major mechanisms: thermal and nonthermal physical and biological effects. Thermal effects of ultrasound include increased blood flow, reduction in muscle spasm, increased ductility of collagen fibers, and a pro-inflammatory response [4]. The nonthermal effects of ultrasound, including cavitation and acoustic microstreaming, affects more in the penetration of actives against the tight conjugate. Recent development in image-guided focused ultrasound clinical system helped ultrasound to the targeted regions in the brain through the intact skull and the animal experiments. The administration of the small- and large-molecule drug to the brain can be delivered using FUS-induced-targeted BBB disruption [5].

2.2. BBB Disruption by Osmotic Mechanism

Osmotic shock is obtained by sudden change in salt concentration leading to disruption of a number of cell types. Sudden osmotic shock to the endothelial cell causes the water withdrawal from the cell. This leads to the shrinkage of the endothelial cell, leading to stretching of the cell. As shown in the Fig. 3, the expansion of cell causes the net flow of water out of the brain cell, leading to the active transportation [6]. In 1972, Rapoport et al. reported CNS tissue staining with Evans blue consequently to intraarterial infusion of hypertonic arabinose. Since dye Evans blue, binds to albumin, is unexpected to permeate through the BBB, this observation suggested a BBB alteration by hypertonic arabinose [7]. Thus the combination of arabinose along with the Evans blue led to the alteration within the cell (hypertonicity). Thus the hypertonicity increases the diffusion of the actives through [8].

2.3. Overcoming Active Efflux at the BBB

Xenobiotics are the foreign materials that are considered to be pharmacologically harmful for regular functioning. Active efflux transporter in BBB acts as a purification system inhibiting the entry of xenobiotic. Drug delivered to the brain acts as a xenobiotic inhibiting its entry into the brain. So, this active efflux plays a major barrier for the ITDT. Structural modification of the drug to reduce the efflux transporter affinity, co-administration of transport inhibitors, and many others are few of the approaches implemented for the delivery of drug across BBB. The CNS protective effect of BBB acts as a barrier for the treatment of brain malignancies or brain metastases, whereas the peripheral diseases are well controlled [9].