matrix (ECM) allows them easy encapsulation of the hydrophilic drugs and excellent bioavailability. Due to their high tuneable mechanical property (0.5 kPa to 5 MPa) hydrogels are used as excellent carrier for proteins and enzymes to avoid their degradation. Highly matrix structure of hydrogel allows control and sustained release for both drug and nucleotide-based drugs such as plasmid DNA [35] (Table 3). In case of the spinal damages, nanosized and microsized particles injected for the control release of the actives. Unlike hydrogel, many of the nanoparticles are unable to fill the helix-loop-helix transcription. The ideal system for the spinal injuries should provide local and sustained release, be biodegradable, be single doe administration and noninflammatory in the CNS. Due to in situ gelation, hydrogels can be exactly injected to fill up the spinal damages by exact geometrical reshaping to avoid more surgeries. As shown in the Fig. 8, in situ hydrogel are thermolabile, that is, change in the temperature leads to gelation leading to control release of the drug. Thus hydrogels are promising carriers for controlled drug release, single dose administration and biocompatibility for clinical application [39].

3.3. Microbubble-Assisted Ultrasound-Based Drug Delivery

Microbubbles (MBs) is a noninvasive method used for the increasing the permeability through BBB. MBs are used in the analysis and medical treatment of diseases, due to its tunable and transient effect on vasculature. Because of their high compressibility and tendency to cavitate, microbubbles can transform the kinetic energy from the traveling acoustic wave to the local microenvironment. This acoustic wave helps in the penetration across the BBB creating a gas bubble. While cavitating, microbubble increases the fluid streaming within the diameter's range away their surface. By the period, the fluid stream reach the surface of the tissue, this creates the bubble. The bubble helps in the penetration of the actives through the cell, and thus increasing the bioavailability of the drug. As the main component of ultrasound contrast agent, MBs with diameter less than 10 μm can pass through pulmonary circulation and enhance the contrast of ultrasound imaging in diagnosis [40].

MBs therapy used along with IV method helps in widening the interendothelial clefts and tight-junctions of the BBB. This method is also known as sonoporation. The method relies on the mechanical action of the gas MBs in ultrasonic pressure waves. The MBs are about 1–10 μm in diameter containing a lipid or protein shell loaded with heavy gasses, which can be excreted by exhalation and make MBs more stable. In MBs, molecules are attached to the layer of the BBB and through the caustic wave's drug penetrate to the stem cell and also viral vectors [41].

TABLE 3
Hydrogel-Mediated Intrathecal Drug Delivery System.

S. No.	Formulation	Material and Methods	Observations	References?
1.	Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury	Sodium hyaluronate, methylcellulose, poly(lactic glycolic acid), poly(vinyl alcohol). Water-oil-water double emulsion method	Composite hydrogel was well tolerated in intrathecal space of spinal cord injured rats and no significant effect on locomotor function up to 28 days	[36]
2.	Click cross-linked injectable hyaluronic acid hydrogel is safe and biocompatible in the intrathecal space for ultimate use in regenerative strategies of the injured spinal cord	Furan-modified hyaluronic acid, 2-(*N*-Morpholino)-ethanesulfonic acid, 4-(4, 6-dimethoxy-1, 3, 5-triazin-2-yl)-4-methylmorpholiniumchloride Water/oil/water (W/O/W) double emulsion procedure	Encapsulation efficiency of hyaluronic acid hydrogel was found to be 47.2% and a loading of 34.6 ng BDNF/mg nanoparticles was obtained. Delayed release upto 76 ± 9% was obtained	[37]
3.	Hydrogel-assisted antisense LNA gapmer delivery for in situ gene silencing in spinal cord injury	2′ *O*-methyl RNA-DNA AON gapmer, acetonitrile, *bis*-diphenylacetyl disulfide, ammonium hydroxide	75% downregulation was obtained within 5 days after hydrogel-assisted antisense LNA gapmer injection	[38]