Chapter 1
Introduction
Brain tumor is a progressive and degenerative disease leading to increased mortality and morbidity. The expensiveness of the treatment makes it difficult to afford, for the majority of the patients. The problems further add up when chemotherapeutic agents are not able to reach to brain or tumor in sufficient concentration. Temozolomide (TMZ) is the first line alkylating agent used for the treatment of newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma. High dose of temozolomide is required to achieve therapeutic level of drug in brain due to its short half-life. It has been reported that prolonged systemic administration of temozolomide results in side effects such as nausea, vomiting, thrombocytopenia and headache.

Blood-brain barrier (BBB) and brain-tumor barrier (BTB) check the entry of drug to the tumor, resulting in low concentration at the site. To overcome this higher doses are to be administered. This leads to toxicity, high cost burden and other disadvantages. Literature review suggested that colloidal carrier is one of the best approaches to achieve overcome the barrier in brain targeting. Nanosuspension, being simple in its nature and preparation, offers an option to achieve brain concentrations. Further literature search suggested that the preparation of nanosuspension can be improved and expedited using a combination of methods. The combination of available top-down and bottom-up methods can be called second generation techniques or smart technology, resulting in faster production of smaller particles. The modulation of tight junction proteins expressed on the BBB and BTB suggested one more approach. Claudin-5 is a tight junction protein, which predominantly expresses on BBB. The protein can be targeted to modulate BBB and improve the drug delivery through paracellular pathway. Claudin-5 modulation is reported to produce reliable BBB opening for transiently to facilitate the passage of molecules (molecular size less than 800 Da) across the BBB.
Sodium caprate acts as a claudin modulator and increases opening of BBB reversibly that lasts about an hour.

It has been seen that nanosuspensions are effective in brain targeting and claudin-5 is an important constituent of BBB. Extensive literature search has revealed that there are no nanosuspensions of temozolomide prepared by combinative methodology or using claudin modulators reported as of now. The present study was aimed to adopt a simple and affordable approach to increase the drug penetration to glioma. Therefore, we adopted two approaches for the preparation of nanosuspensions using combination technology and nanosuspensions preparation using claudin modulator (sodium caprate in the present study). The prepared nanosuspensions were characterized and optimized for in vitro and in vivo activities. The optimized formulations were evaluated for in vitro permeability and cytotoxicity assays. The optimized nanosuspensions were further evaluated for improved brain permeability, toxicity and therapeutic activities in animals.