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Review Article

Novel Drug Delivery for efficient therapy

Encapsulated Cell Delivery of Neurotrophic Factors in the Treatment of Alzheimer's and Parkinson's Disease

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Abstract: Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are the most common in older people. Current treatment includes oral medications which is not sufficient and cannot target the brain directly due to limitation like susceptibility to metabolism leading to poor bioavailability and difficulty in crossing Blood Brain Barrier. Hence treating these diseases with Neurotrophic Factors can provide better protection against neuronal degeneration. Neurotrophic factors playsa major role in survival and protection of neurons. Parkinson's disease and Alzheimer's disease show changes in regulation of particular Neurotrophic Factors. Appropriate and targeted delivery of these factors directed to various portions of the brain is a major challenge due to the tendency of depletion of majority of drug in metabolism as well as inability of drug to penetrate blood brain barrier. Cell encapsulation mechanism can remove these barriers to a greater extent. Cell encapsulation technology represents an alternative, non-viral approach for the delivery of biologically active compounds to required site of action. This strategy involves the immobilization of genetically engineered producer cells within semi permeable membrane. These genetically engineered cells secrets a protein with certain therapeutic potential. The cells are encapsulated in an immune-isolating material that makes them suitable for transplantation. Various Neurotrophic factors have been evaluated in animal models for their effect on neurodegenerative disease. Cell encapsulation is able to provide targeted and continuous delivery of therapeutic molecules that can be distributed in various region of the brain. This review will summarise the various neurotrophic factors, their functions and their use in the treatment of Parkinson's and Alzheimer's disease via cell encapsulating approach.

Keywords: Alzheimer's disease, Parkinson's disease, Neurotrophic Factors, Cell encapsulation technology

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1. INTRODUCTION

Neurodegenerative diseases are the conditions in which degeneration of neurons occur. Neurons are building blocks of the brain and spinal cord. Progressive loss of neurons and nerve cells gives rise to symptoms of neurological disorders. It can occur at any age range but most widely seen in old age people. Neurodegenerative diseases present greater risk to human health [1]. Alzheimer's disease and Parkinson's disease are the most common among than other neurodegenerative diseases like, Amyotrophic lateral sclerosis and Huntington's disease. Alzheimer's disease is characterised by memory loss, language impairment and reduced mental function while in Parkinson's disease loss of motor function, difficulty in movement and tremors are observed [2]. The pathophysiology of Alzheimer's disease shows presence of Amyloid Beta (Aβ) plaques and neurofibrillary tangles extracellular in the brain [3]. Amyloid beta is an abnormal byproduct of the amyloid precursor protein. These plaques and tangles lead to induction of immune response which results in cell death and neuronal degeneration [4]. Parkinson's disease characterised by degeneration or loss of dopaminergic neurons in midbrain leads to tremors and muscle stiffness [5]. These diseases involve degeneration of neurons in the brain which may often lead to death if left untreated. Current medication for Parkinson's disease contains a precursor of dopamine, L-DOPA. It is taken orally because direct or systemic infusion of L-DOPA leads to chronic side effects [6]. Cholinesterase inhibitors like Rivastigmine, Galantamine, Tacrine and Donepezil are available for oral administration for Alzheimer's disease [1]. These orally ingested drugs are unable to target directly to the brain because of the presence of a blood brain barrier which prevents the entry of molecules into the central nervous system [7]. Also, many of drug candidates are poorly soluble in aqueous solutions [1]. These medications and therapies do not prevent further neurodegeneration, as it only focuses on symptomatic relief [8]. So, targeting these therapeutic drugs directly to the brain for accurate treatment is the big challenge. Neurotrophic Factors show great potential in the treatment of brain disease as they protect nerve cells from death and protect them from degeneration, thus showing a way to overcome limitations of currently available treatment[6]. Neurotrophic Factors are the endogenous proteins involved in the neuronal differentiation, survival and functional recovery of neurons [10]. It was demonstrated the beneficial effects of various neurotrophic factors in the treatment of Alzheimer's and Parkinson's disease. Nerve Growth Factor has shown a therapeutic effect against Alzheimer's disease. Studies on rodents and non-human primate models of Alzheimer's disease have shown that Nerve Growth Factor prevents degeneration of cholinergic neurons[3]. Parkinson's disease pathology has been linked to Glial cell Derived Neurotrophic Factor deficiency. Therefore, the delivery of Glial cell Derived Neurotrophic Factor to brain via intrathecal and intracerebral injection has shown potential in reducing symptoms in animal models of Parkinson's disease. These Neurotrophic Factors requires targeted delivery in the brain to exert their effect [6]. Systemic delivery of Neurotrophic Factors may lead to severe side effects. Earlier, various approaches for delivering Neurotrophic Factors have been used like direct brain infusion, gene therapy, cell based therapy and biomaterial based therapy, but none of these came out as an appropriate method for delivering Neurotrophic factors. Encapsulated cell technology serves to be a better option since it overcomes majority of the limitations of other mentioned approaches (Table 1) [11].

Table 1: Limitations of various approaches for delivering neurotrophic factors [11]

Name	Method	Disadvantages
Direct brain infusion	A catheter is used for delivery of molecules and pump is attached for controlling time and rate of the infusion	-poor protein stability -leakage from pump can occur -inadequate distribution of the molecules from point source
Gene therapy	Injection of Viral vector is used for producing Neurotrophic factors, by local neurons	-expression of gene and the treatment cannot be stopped once the vector is injected -safety related problems might be arised
Cell based therapy	Injection of genetically engineered cells to produce factors	-cells cannot be retrieved -cell rejection from patient's body can occur -cell migration is not controlled
Biomaterial based drug delivery	Molecules are integrated in implantable biomaterials which helps in promoting regeneration.	-not suitable for chronic CNS diseases -can not provide long term delivery -not clinically viable

1.1. NEUROTROPHIC FACTORS

Neurotrophic factors play a major role in prevention of neural degeneration in central and peripheral nervous system. When new neurons are in developing stage, they act as a survival factor and control neuronal differentiation[12,13]. Due to their prominent role in the survival and maturation of cholinergic and dopaminergic neurons, trophic factors come out as a possible treatment approach for the Alzheimer's and Parkinson's disease [12]. Delivering neurotrophic factors as a therapeutic molecule is challenging because of their limited diffusion in the brain due to blood brain barrier, poor bioavailability and short *in vivo* half life[13].

1.2. Family of Neurotrophic Factors

Neurotrophic factors family comprises of Neurotrophins which includes Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF), Glial cell Derived Neurotrophic Factors (GDNF) family of ligands, Ciliary Neurotrophic Factor (CNTF) [14](Table 2)[12,21].

1.3. Neurotrophins (NTs)

Brain Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) are combinedly known as Neurotrophins (NTs). Other Neurotrophins are Neurotrophin 3 and Neurotrophin 4 [15]. Nerve Growth Factor was identified as the first member of the Neurotrophins and exhibits protective effect on developing neurons [17]. Nerve Growth Factor was found to be effective in targeting Basal Forebrain Cholinergic Neurons which releases cholinergic neurons. Cholinergic neurons are directly involved in memory enhancement and learning activity. Thus NGF can be used as a the treatment approach for Alzheimer's disease [18]. BDNF regulates neuronal outgrowth, cell survival and plasticity. BDNF have neuroprotective action against various substances as well as injury. Reduced level of BDNF leads to inhibition of dopamine synthesis and movement disorders. Also, it can cause memory related problems in individuals[19] .

1.4. GDNF (Glial cell Derived Factor) Family

It is a potent neurotrophic factor which has a predominant effect on prevention of the midbrain dopaminergic effect. Neurturin (NRTN), Artemen (ARTN), Persephin (PSPN) are other members of this family [12]. Glial cells secrete agents that have the effect of neuronal protection and also stimulate the natural neural repair [19]. It has a strong affinity towards dopaminergic neurons, which leads to building them as a potential candidate for the treatment of Parkinson's disease [20].

1.5. CNTF (Ciliary Neurotrophic Factor) Family

This family is known as Neurokine or Neuropoietic cytokines family[21]. It prevents degeneration of motor neurons, dopaminergic neurons and parasympathetic neurons. Another trophic factor of this family includes Cardiotrophin (CT), Neuropoietin (NPN), Oncostatin M (OSM), Leukemia Inhibitory Factor (LIF), Interleukin (IL)-6,11,27 and Cardiotrophin like cytokines (CLC) [12].

Table 2: Neurotrophic Factor Classification and their role in nervous system [12,21]

Name of family	Neurotrophic factors	Role in nervous system
Neurotrophins	Nerve Growth Factor (NGF)	-First identified member of family -necessary for protection and survival of peripheral nervous system -Synthesized in hippocampus and transported to basal cholinergic neurons -involved in cognition and attention process
	Brain Derived Neurotrophic Factor(BDNF)	-established as main central neurotrophic factor -mediates hippocampal activity in adulthood -plays role in learning activities
Glial cell derived factors family of ligand(GFLs)	Glial Cell Derived Neurotrophic Factor(GDNF)	-essential role in survival of dopaminergic neurons in substantia nigra - supports outgrowth of mesencephalic neurons and their survival
Neurokine or neuropoietic cytokine family	Ciliary Neurotrophic Factor(CNTF)	-involved in survival and protection of motor, dopaminergic and parasympathetic neurons

Cerebral Dopamine Neurotrophic Factor (CDNF) and Mesencephalic Astrocyte derived Neurotrophic Factors(MANF) are structurally different from the traditional neurotrophic factors [21]. They show preventive action on midbrain neurons in many neuronal diseases. However, further study is needed for therapeutic application due to various safety aspects[22].

1.6. Delivery of Neurotrophic Factors

Delivering Neurotrophic Factors as therapeutic molecules is challenging owing to their limited diffusion in the brain due to the presence of blood brain barrier and other pharmacodynamic issues. The adequate efficiency of Neurotrophic Factors in the treatment can be seen only when they are distributed as closely as possible to their relevant target, since that enhances the chances of better bioavailability. However, many of the localized drug delivery systems to the brain when utilized to deliver GDNF, NGF, BDNF in the treatment of Alzheimer's and Parkinson's disease, does not show significant improvement in trials owing to various limitations of individual drug delivery systems. Cell encapsulation technology is one of the unexplored technologies that has all prerequisite conditions that can offer better targeted drug delivery systems by overcoming majority of the challenges faced by previous systems. This methodology can be seen as reliable and promising one in delivering various Neurotrophic Factors to the targeted region.

1.7. CELL ENCAPSULATION TECHNOLOGY

Cell encapsulation is the technology in which physically isolated cells from an external environment are immobilized within a semi permeable membrane (figure 1)[6].

The Semi permeable membrane allows the entry of nutrients, gases and therapeutic molecules, but restricts the entry of host cells. This membrane defends the cells from outer stress and the host's immune system [24].

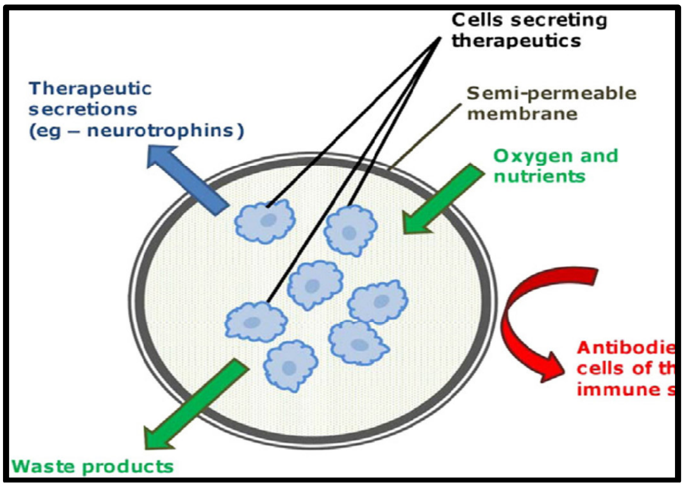

Figure 1[6]: Basic representation of encapsulated cells immobilized in semi permeable membrane[6]

The membrane defends the cells from outer stress and the host's immune system [24]. Alginate is the most preferable polymer used as a semi permeable membrane due to its exceptional biocompatibility and Biodegradability[25]. Immobilized genetically engineered cells or therapeutically active cells impart a greater advantage than encapsulated proteins or peptides [25]. Major advantage is that immunosuppressive agents are not required and cells from multiple sources can be used for encapsulation [26]. In 1934, Vincenzo Bisceglie reported encapsulation of tumor cells in polymer, later in 1964 Thomas Chang described " artificial cell " using semipermeable microcapsules. In 1980, the concept of encapsulated pancreatic islet cells for diabetes was proposed by Sun and Lim and the first clinical trial was carried out. Encapsulation technology provides an improved platform for delivering various proteins such as Neurotrophins which shows severe side effects when incorporated systematically. This technology has shown to be effective in the treatment of various neurodegenerative diseases like Alzheimer's and Parkinson's diseases [12] because it allows diffusion of therapeutic molecules directly into brain parenchyma [27] and can survive for a longer period of time. In mid 1990, the first clinical trial was performed for encapsulation therapy in amyotrophic lateral sclerosis[6]. Encapsulation of genetically modified cells to secrete neurotrophic factors such as NGF, GDNF, BDNF proved to be efficient in the treatment of Parkinson's and Alzheimer's disease [8,28]. Encapsulation of cells can be achieved by two ways, either by micro-platform based method or macro-platform based method[24,29]. Microcapsules are spherical shaped clusters and surrounded by membranes. These microcapsules are fragile and cannot be removed once implanted [30]. Microcapsules are thin, tubular shaped hollow cylinders surrounded by polymeric membranes. This device is more durable and can be easily removed when necessary. These are made with tether and other devices which helps in easy removal of device [7]. Both the methods have been explored for neuronal disorders, but for the most part preclinical and clinical work is focused on the microcapsules [8,11].Various types of cells can be encapsulated in order to secrete growth factors. Immortalised or dividing cells, such as PC12 are able to produce dopamine naturally and hence can be utilised in Parkinson's disease [11]. Xenogeneic Baby Hamster Kidney(BHK) cells can also be used to secrete neurotrophic factors. But they show poor viability [13]. Genetically engineered human cell line, such as ARPE-19 (Human Retinal Pigment Epithelial cell) and fibroblasts can deliver Nerve Growth Factor in Alzheimer's disease [11].

1.8. NEUROTROPHIC FACTORS IN THE TREATMENT OF ALZHEIMER'S DISEASE (AD) VIA CELL ENCAPSULATION

Basal forebrain cholinergic neuron degeneration occurs in Alzheimer's disease and changes in some Neurotrophic Factors such as NGF (Nerve Growth Factor) and BDNF (Brain Derived Neurotrophic Factor) are seen. Cholinergic basal forebrain neurons respond strongly to NGF, but weakly to BDNF[39]. NGF plays a major role in the protection and survival of cholinergic neurons in basal forebrain [12]. Decreased levels of NGF have been seen in AD patients. Cell contraction of cholinergic neurons takes place in the absence of NGF [31]. These effects can be reversed by the delivery of growth factors directly to the brain. Systemic delivery of trophic factors are not possible due to their inability to cross the blood brain barrier [9,18]. Targeted and safe delivery of NGF with cell encapsulation can overcome these problems. NGF is the most widely investigated Neurotrophin in experimental models of AD. Vascular endothelial growth factor (VEGF) and Ciliary Neurotrophic Factor (CNTF) have also been studied to have a role in neuroprotection when delivered using encapsulation technology [34,35].

1.9. Encapsulated cell delivery of NGF

The pilot studies were carried out using an Encapsulated cell bio delivery to produce NGF. The implant called NsG0202 (Figure 2)[23] comprises a hollow cylindrical fibre in which cell lines are loaded and framed by semi permeable polymer matrix [23]. Human retinal pigment epithelial cells, ARPE-19 cell lines were used to secrete nerve growth factor. From this cell line, maximum NGF producing clone NGC0295 were isolated for better improvement [11]. These cells were encapsulated within the hollow fibre comprising of Polyethersulfone. The cell lines were protected by a semi permeable membrane polyvinyl alcohol foam matrix which prevents cells from immune rejection [23]. This NsG0202 device was implanted into the basal forebrain of the AD patient. The first clinical trial was carried out on six patients, after one year implants were removed surgically from all patients. The implants were found to be undamaged without any degeneration. Clinical Evaluations were performed on patients, and none of those patients showed any serious side effects. Thus, this first generation NsG0202 device emerged as safe for human brain implantation with long term delivery of NGF[8,11,23]

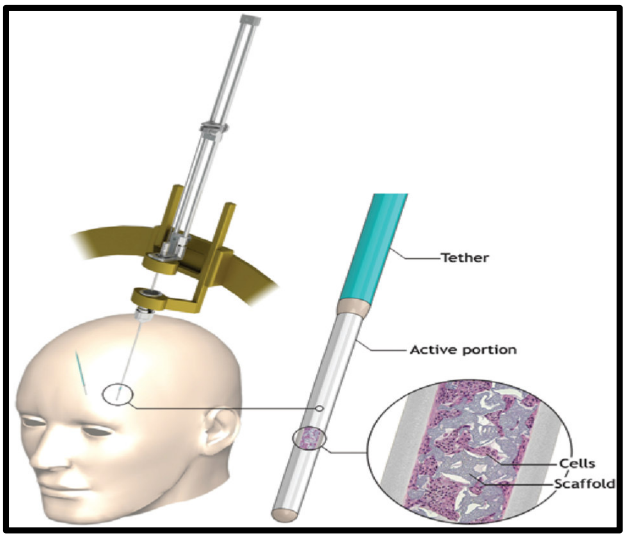

Figure 2[23]: Schematic representation of NsG0202 device (centre) with implantation process (left). Cut-out view (right) of active part shows immobilized cells in matrix [23.23]

After successful implantation of NsG02O2 , the second generation of this device NsG0202.1 was created with some modification in cell lines and a polymer matrix to secrete a potential amount of NGF[36]. New cell line NGC0211 were generated from ARPE-19 Human retinal pigment epithelial, with Sleeping Beauty(SB) transposon expression system[37]. This system makes use of SB transposase that mediates genomic integration of multiple copies of transgene inserted between two transposon terminal inverted repeat. These NGC0211 shows ten times higher NGF expression than clone NGC0295 [37]. Polyester terephthalate(PET) yarn matrix was used as an inner membrane instead of poly vinyl alcohol(PVA) in the second generation of device NcG0202 (Figure 3)[37].

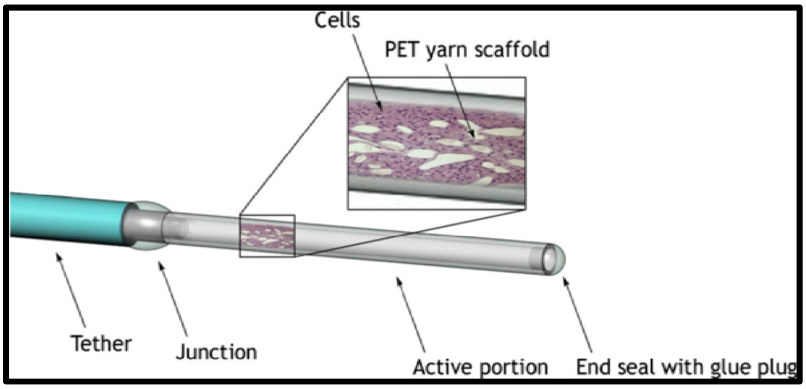

Fig 3[37]: Second Generation Device[37]

This membrane provides protection against cell rejection and provides better cell adherence. Preclinical studies were performed on animal models for checking the safety and toxicity [37]. This device was then implanted into the basal forebrain of four AD patients with the surgical procedure. After six months the implant was successfully removed without any adherence. Patients developed no side effects other than mild headache and fatigue. No focal neurological signs were observed. The Implant was found to be well tolerated and showed greater cell survival than the first generation after explanation. After the treatment, Cerebro-spinal fluid analysis of patients showed increased cholinergic markers and improved cognition [36]. The major advantage of the device is that, the treatment can be stopped at any time by removing the implant[37].However, there could be some challenges involving cell survival and NGF release. There could be some factors like amyloid beta peptides that might affect cells and release of NGF from the cells[8,38] . These devices (Table 3) [11,23,37] are in clinical trials sponsored by NsGene[23] and results are awaited for its market availability.

Table 3: First and second generation NcG0202 devices [11,23,37]		
Parameter	**First generation device NcG0202**	**Second generation device NcG0202.1**
Cell line used	Human Retinal Pigment Epithelial cell (ARPE 19)	ARPE 19 with sleeping Beauty (SB) transposon expression system
Clone used	NGC0295	NGC0211
Semi permeable membrane	Poly Vinyl Alcohol (PVA) foam matrix	Polyester Terephthalate (PET) yarn matrix
Hollow fibre material	Poly ether sulfone	Poly ether sulfone
No of patients involved in clinical study	Six	Four

1.10. Encapsulated cell delivery of Vascular Endothelial Growth Factor(VEGF)

In Alzheimer's, beta amyloid peptides are formed across the blood brain barrier. Due to deposition of amyloid beta peptide, endothelial wall of the brain often degenerates. VEGF has effects on survival and proliferation of endothelial cells and also have regulatory effects on brain angiogenesis and brain integrity. Hence, VEGF could be a novel approach to treat Alzheimer's disease[34].Genetically engineered Baby Hamster Kidney (BHK) cell fibroblast to produce VEGF were encapsulated in alginate microcapsules. These microcapsules were implanted into the cerebral cortex of transgenic mouse[34]. After three months, whole Immunocytochemistry was done on sacrificed animals. Results suggest that VEGF microcapsules improves behavioural impairment and reduces beta amyloid (Aβ) load in a mouse brain. VEGF microcapsules can increase neuronal and endothelial cell culture [34]. On the basis of these outcomes, it can be said that encapsulated VEGF might emerge as novel treatment approach for Alzheimer's disease.

1.11. Encapsulated cell delivery of Ciliary Neurotrophic Factor (CNTF)

Ciliary neurotrophic factor as members of cytokines regulate properties of cells in mature and developing nervous systems[12]. Due to its role in the protection of neurodegeneration it might be effective in AD pathology[35]. The treatment with encapsulated cell releasing CNTF shows significant improvement in cognitive function in mouse model[6]. And it has been demonstrated that CNTF protects neurons from degeneration caused by amyloid beta (Aβ) oligomer[6].Alginate microcapsules were used to encapsulate C2C12 myoblast cells which were genetically engineered to produce CNTF. Microcapsules implanted Intracerebroventricularly into amyloid beta injected two mice models. The results showed that encapsulated CNTF protects the amyloid beta oligomer induced neuronal degeneration and protects neurons from amyloid beta toxicity, however, it has not been evaluated in clinical trials in perspective of Alzheimer pathology[35].

1.12. NEUROTROPHIC FACTORS IN THE TREATMENT OF PARKINSON'S DISEASE (PD) VIA CELL ENCAPSULATION

Parkinson's disease is characterised by degeneration of dopaminergic neurons in substantianigra. Dopaminergic neurons are protected by Glial cell Derived Neurotrophic Factor (GDNF) and to a smaller extent by Brain Derived Neurotrophic Factor (BDNF). Decreased level of BDNF in the brain leads to movement disorders. GDNF has a prominent role in the protection and survival of dopaminergic neurons in the brain [39]. GDNF has found to be most specific among all other neurotrophic factors [39]. This effect of GDNF has been tested in various animal models using cell encapsulation technology. The results were demonstrated that GDNF is able to protect dopaminergic neurons from degeneration in PD animal models[39]. Many studies have been conducted on animal models by using different cell lines to secrete GDNF.

1.13. Encapsulation of PC12 cells

Experimental studies using chromaffin or PC12 cells, which are a pheochromocytoma cell line that naturally releases dopamine has been carried out on rat models. These cells were encapsulated in alginate microcapsules and implanted into rat striatum[6]. The results showed increased efficiency of systemically administered L-dopa. But it was observed for short time durations in the perspective of PD pathology. Hence, further development is needed[6,7].

1.14. Encapsulation of BHK cell

Baby Hamster Kidney cells (BHK) were transfected to secrete human GDNF. These cells were encapsulated and implanted into rat striatum. 6-hydroxydopamine (OHDA) was administered into the rat brain before implantation[7,40]. 6-hydroxydopamine is the neurotoxic drug which is used to induce neurodegeneration in Parkinson model[26]. After six months implants were removed successfully without any damage and cells were also found viable[40]. Studies show that long term secretion of GDNF from cells were able to protect neurons from degeneration animal models of Parkinson disease[40]. However, these xenogeneic cells have shown some issues related to regulatory aspects. To pass these hurdles, recent human cell lines have been used and have shown better survival in encapsulation environment[13].

1.15. Encapsulation of cells from Human cell line

Allogeneic cell lines, such as Human Retinal Pigment Epithelial (ARPE-19) cell and immortalised fibroblasts have the capacity for unlimited clone expansion in vitro and can survive in encapsulated condition. GDNF secreting clones can be generated from this cell line[13]. Encapsulated ARPE-19[41] and fibroblast [11,20]to secrete GDNF have shown neuroprotective effects on dopaminergic neurons in rodent models. Encapsulated GDNF secreting fibroblasts in hollow fibre, when implanted into striatum of 6-hydroxydopamine lesioned rat models demonstrated behavioural improvement up to 6 months [20].Further studies involve encapsulation of ARPE-19 cells. These studies were carried out on rat models and for evaluation of clinical sized device minipig models were used. Both the animals were treated with 6-hydroxydopamine before the implantation. Encapsulated microcapsules were implanted into rat striatum and putamen of the minipig. Results showed increased amount of GDNF in the targeted striatum and improved neuronal protection. Long term effects were demonstrated over six months in rat[41].Animal models of rats, monkeys and minipigs show the potential effect of encapsulated cells secreting GDNF in the protection of dopaminergic neurons. However, dozens of implanted microcapsules will be needed for the human brain and efficacy in the human brain needs to be tested [6]. This treatment approach could be useful in PD patients requiring long term effects of trophic factors[13]. Number of Neurotrophic Factors have been tested for their effect on Alzheimer's and Parkinson's disease using different cell lines via cell encapsulating approach. However, additional development will be needed for clinical trials (Table 4) [6,23,26,34,35]

TABLE 4: Summary of various neurotrophic factors that have been tested via cell encapsulating approach [6,23,26,34,35]

Disease	Neurotrophic Factor	Cell line	Experimental Model	Outcome
Alzheimer's disease	Nerve Growth Factor (NGF) **NsG0202 device**	Human retinal pigment epithelial (ARPE 19)	Human	In clinical trials
	Vascular Endothelial Growth Factor (VEGF)	Baby Hamster Kidney (BHK) cells	Transgenic mouse	Needs to be tested on humans
	Ciliary Neurotrophic Factor (CNTF)	C2C12 myoblast cells	Mice	Not evaluated in clinical trials
Parkinson's disease	Glial cell Derived Neurotrophic Factor (GDNF)	PC12 cells	Rat	Action observed for short time duration
		Baby hamster kidney (BHK) cells	Rat	Not evaluated in clinical trials
		Human retinal pigment epithelial (ARPE 19)	Rats and mini pigs	Needs to be tested on humans
		Fibroblasts	Rat	Needs to be tested on humans

2. CONCLUSION

From the studies on animal models, it is confirmed that encapsulated delivery of Neurotrophic Factors could be possible alternative treatment in neurological disorders. Encapsulation technology can also be used in various CNS disorders other than Alzheimer and Parkinson. Since all Neurotrophic Factors have different roles in protecting neurons, particular neurotrophic factors can be utilized as an entity to treat different neurological disorders as per their requirement. GDNF has prominent effect on dopaminergic neurons. Similarly NGF protects cholinergic neurons. Safety and tolerability was demonstrated for encapsulated cell delivery of NGF via device NsG0202 for Alzheimer's disease and currently being tested in clinical trials for its clinical use. The positive outcomes of studies support further development of encapsulated cell delivery of other Neurotrophic Factors such as GDNF and BDNF for Parkinson's disease and other neurodegenerative diseases. There are certain aspects that are required to be kept in mind while developing an encapsulation device with respect to the neurological disorder. Selection of accurate cell lines to produce various Neurotrophic Factors is one of the important factors. Another factor of importance is that selected cells should have good viability and must be able to survive in encapsulated condition. Hence, selecting and producing new cell lines to produce neurotrophic factors and selection of polymer in encapsulation device will be the great area of research in designing a encapsulating device for more predictable and targeted delivery to the brain. Various aspects of encapsulated devices for neurological disorders that are been discussed throughout the article throws light on the possibility of this new technology and neurotrophic factors becoming a novel approach for the treatment of neurological disorders.

3. AUTHORS CONTRIBUTION STATEMENT

Miss Riya Mistry conceptualized and gathered the data with regard to this work. Dr.Mashru and Apeksha Kadam analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors contributed to the final manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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