CONTENTS

1.1 DEMENTIA

Memory complaints are common in the geriatric population, and their frequency usually increases with age. Decline of memory function or dementia is usually caused by degeneration in the cerebral cortex, the part of the brain responsible for thoughts, memories, actions and personality. This decline is beyond what might be expected from normal aging. These symptoms eventually impair the ability to carry out everyday activities such as driving, household chores, and even personal care such as bathing, dressing, and feeding. The probability of suffering from dementia increases with age. Dementia mostly occurs in the second half of life, often after the age of 65. The most common symptoms in dementia includes frequent and progressive memory loss, language difficulties, confusion, inability to perform familiar tasks, difficulty with abstract thinking, misplacing belongings, rapid mood swings, behavioral changes an apathy / lack of initiative.

1.2 CAUSES

Dementia can be caused by one or multiple medical problems. It is curable partially or completely when associated with head injury, brain tumors, infections, simple and normal pressure hydrocephalus, hormone disorders, metabolic disorders, hypoxia, nutritional deficiencies, drug abuse or chronic alcoholism. However, it is unfortunate that dementia is often associated with progressive, degenerative and irreversible disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Pick's disease, or Creutzfeldt-Jakob disease etc. Alzheimer's disease is the most common irreversible cause of dementia that accounts for 50% to 70% of all dementia cases whereas, vascular dementia, accounting for about 20% of cases, is the second most common cause of dementia.

1.3 TREATMENT OPTIONS

Treatment of dementia begins with treatment of the underlying disease, where possible. The goal of treatment is to slowdown the progression of dementia-related impairments and to control behavioral symptoms, which may be treated with a combination of psychotherapy, environmental modifications, and medication.

1.3.1 Psychotherapy

Psychotherapy, in particular behavioral approaches, can be used to reduce the frequency or severity of problematic behaviors, such as aggression or socially inappropriate conduct. Identifying what might be triggering a problematic behavior and then devising an intervention that either changes the person's environment or the caregiver's reaction to the behavior can be effective.

1.3.2 Environmental modifications

Environmental modifications can increase safety and comfort while decreasing agitation. Home modifications for safety include removal or lock-up of hazards such as sharp knives, dangerous chemicals, and tools. Child-proof latches may be used to limit access. Bed rails and bathroom safety rails can be important safety measures as well. Another example is

lowering the hot water temperature, which reduces the risk of burning or disabling the stove or using stove childproof knobs may be necessary to prevent cooking accidents.

1.3.3 Medication

Medication can be prescribed to reduce dementia symptoms. There are a number of drugs available today for improving brain function. The more recent anti-dementia agents belong to the so-called acetylcholinesterase inhibitors such as Tacrine, Rivastigmine, Donepezil, Galanthamine, Dihydroergotamine, Piracetam and Noopept etc. Acetylcholine is one of the chemical substances that allow brain cells to communicate with one another, the so-called neurotransmitters. Research suggests that acetylcholine is reduced in the brain of Alzheimer's dementia patients. This kind of drugs prevents acetylcholine to be eliminated too quickly, prolonging its ability to conduct chemical messages between brain cells. It could be shown in clinical trials that, with this kind of drugs, the deterioration of the disease could be delayed by at least 12 months. Apart from preserving and partially improving mental capacities, and coping with daily activities, a delayed onset of behavioral disturbances and a reduction in caring time could also be demonstrated.

Psychotropic drugs can be used as a supportive therapy in the treatment of behavioral problems in dementia. For instance, antipsychotic medications (typically used to treat disorders like schizophrenia) can be effective in reducing delusions and hallucinations. Anti-anxiety medications (typically used to treat anxiety disorders) can also be prescribed to help treating agitation and restlessness. Likewise, antidepressant medication can be prescribed to alleviate depressive symptoms. Treating depression symptoms is important as depression makes it harder for a person with dementia to remember things and enjoy life. It also adds to the difficulty of caring for someone with dementia. Significant improvements can be made by treating depression,

as the patient's mood and their ability to participate in activities may be improved.

A growing number of herbal remedies, vitamins and other dietary supplements such as Fisetin, L-Theanine and Vinpocetine etc. are also promoted as treatments for Alzheimer's dementia and related diseases. They can be appealing to some people as they come from natural ingredients. Although many of these remedies may be valid candidates for treatment, using these drugs as an alternative or in addition to physician-prescribed therapy raise legitimate concerns.

1.4 VINPOCETINE (VPN)

Vinpocetine is a semisynthetic derivative alkaloid of vincamine (a synthetic ethyl ester of apovincamine) [1], an extract from the periwinkle plant. It is reported to have cerebral blood-flow enhancing [2] and neuroprotective effects [3], and is used as a drug for the treatment of cerebrovascular disorders and age-related memory impairment [4]. Vinpocetine is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory. In other words, Vinpocetine may help support brain functions such as concentration and memory by activating cerebral metabolism. Vinpocetine has been identified as a potent anti-inflammatory agent that might have a potential role in the treatment of Parkinson's disease and Alzheimer's disease [5, 6]. The 15-30 mg/day of vinpocetine in three divided dose is generally recommended in treating dementia or cerebrovascular disorders.

1.4.1 Problems associated with VPN oral medication

Although it has been shown to increase the cerebral flow in the ischemic patients with cerebrovascular disease, to increase red cell deformability in stroke patients and to have neuroprotective abilities against brain ischemia [7], the clinical use of its marketed commonly used oral formulations is limited by its poor dissolution profile, and extensive first pass metabolism that results in very low bioavailability (~7%) [8]. This poor oral bioavailability together with the small $t_{1/2}$

(2.54 ± 0.48 hrs) implies the necessity of frequent drug dosing (three times daily), a situation that is inconvenient for patients of dementia and results in poor compliance [9, 10].

1.5 NOOPEPT (NPT)

Noopept or N-phenylacetyl-L-prolylglycine ethyl ester is a synthetic dipeptide molecule derived from the endogenous dipeptide cycloprolylglycine which is a combination of the amino acids glycine and proline in a cyclic configuration [11]. It is commonly prescribed as cognitive enhancer in Russia while readily available and legal in USA. It is well-known for its neuroprotective properties which include an anti-oxidant and anti-inflammatory effect as well as the ability to prevent neurotoxicity caused by excessive calcium and glutamate. It is also found to exert a positive impact on memory formation, consolidation and retrieval [12] and to possess an anxiolytic effect as well as mild psychostimulant-like effects [13]. The mechanism of action is not fully understood but, like the Racetams, Noopept appears to positively modulate acetylcholine neurotransmission. It is observed to increase expression of both neurotropic factors NGF and BDNF in the hippocampus [14]. This may explain why improvements in memory are more apparent following long-term dosage administrations. Noopept is further reported to reduce depression and anxiety in both human and animal studies [12].

1.5.1 Problems associated with NPT oral medication

Preliminary findings based on serum concentrations and excretion kinetics suggested that oral doses of 50 mg/kg are roughly equivalent to injected dosages of 5 mg/kg [15]. This implies that oral bioavailability is only 10% compared to injections.

1.6 TRANSDERMAL ROUTE FOR DRUG DELIVERY

Limitations suffered by oral administration of the Vinpocetine and Noopept necessitate the utilization of some other delivery route for better sustained plasma level of the drug throughout the duration of therapy. In this context, the consideration has been given to non-

invasive, user-friendly transdermal route which is reported to have the potential of avoiding first-pass metabolism, achieving infusion like zero order drug delivery profile, avoiding the trauma associated with parenteral therapy, improving patient compliance by reducing the frequency of administration for short half-life medications [16]. The transdermal route also provides an opportunity to cease absorption in the event of an overdose or other problems.

1.6.1 Overcoming the Stratum corneum barrier

The outermost skin layer, stratum corneum (SC), composed of dead keratinized tissue of about 10–20 μm in thickness [17]. The barrier properties of the SC are now recognized as the major rate-limiting step in the diffusion process of a drug permeating across skin. The structure of the SC, has been related to ''bricks-and-mortar'', where the bricks are the component cells, or corneocytes, and the mortar is the intercellular lipids. The membrane is interrupted only by appendages such as hair follicles and sweat glands. However, it is still considered to be a predominantly dual-compartment system composed of a matrix of corneocytes tightly packed with keratin, surrounded by a complex array of lipids arranged in bilayers. A variety of physical and chemical methods have been explored to breach SC including use of penetration enhancers, lasers, electrical energy, ultrasound, radio frequency, thermal energy and microneedles [16, 18].

1.6.2 Microneedle based skin microporation

Microneedles or other microporation techniques provide a minimally invasive, painless way of creating microchannels in skin which can then allow the transport of drug delivery vehicle across the previously impervious barrier i.e. SC, deeper into the skin and systemic circulation. The structures are small enough that they do not penetrate into the dermis; they do not reach the nerve endings and thereby avoid sensation of pain [19]. The dimensions of the pore created in skin by microneedles are typically around 50-200μm through which even nanosized particulate drug carriers can easily be delivered

transepidermally [19]. These microconduits, in general, designed to deliver hydrophilic molecules but can also be utilized to create a reservoir of lipophilic drugs for infusion like delivery [16].

1.6.3 Dissolving microneedles

A variety of microneedles like metal, silicon, titanium, glass or maltose have been developed [20]. Among them, silicon or metal microneedles suffers the problems of requiring dedicated and costly clean room facilities and chances of accidental needles break off in the skin which may arise complications. In contrast, microneedles made up of hydrophilic biodegradable polymers avoid such drawbacks and can be made by a simple and cheap micromoulding technique, dissolve in the skin to create microchannels [21].

1.6.4 Nanocarriers as drug delivery vehicles

Incorporation of these drugs in to suitable nanocarriers that can easily get deposited and continuously release the drug in the vicinity of papillary area having rich capillary network may ensure better systemic availability of the drugs. To serve the aforementioned purpose, biodegradable nanoparticles and ultradeformable liposomes were selected for present study.

1.6.4.1 Polymeric nanoparticles (PNP)

Nanoparticles have been extensively studied for oral and parenteral administration owing to their sustained drug release. This property of nanoparticles could also be utilized for topical drug administration to support the skin with drug over a prolonged period and to maintain a desired drug concentration in the skin. Many researchers had attempted to use nanoparticles for topical drug delivery, and they found that the drug permeation was enhanced by gradual drug release from the nanoparticles on the skin surface, but did not find the nanoparticle carriers inside the skin [22]. Some other researchers attempted to verify the penetration of nanoparticles across the skin, but found that only few of nanoparticles were able to permeate into the skin passively through the hair follicles while most nanoparticles were

primarily restricted to the uppermost SC layer and unable to penetrate the skin [23]. Here, skin microporation with microneedles could be of great use to assist nanoparticles to overcome the SC barrier and create a mini depot beneath the epidermis for prolonged drug release.

1.6.4.2 Ultradeformable liposomes (UDL)

In contrast to nanoparticles, ultradeformable liposomes have the ability to penetrate the skin intact owing to their vesicle deformability. and act as a drug reservoir to continuously transport drug through the skin [24]. Additionally, solubility of poorly water-soluble drugs can be significantly improved in elastic liposomes than in aqueous solution, which leads to a greater concentration gradient across the skin and subsequently improves permeation [25]. The combination of elastic liposomes and microneedles may provide higher and more stable transdermal delivery rates of drugs without the constraints of traditional diffusion-based transdermal devices, such as molecular size and solubility. Incorporation of these nanocarriers in to hydrogels may also improve the stability and handling of the formulations.

1.6.5 Nanocarriers loaded Microneedle patches

An attempt was also made to incorporate these nanocarriers in dissolving microneedle patch (MNP) to combine skin microporation and drug administration in single step. This may also be beneficial for delivering a constant and calculated fraction of drug each time, providing occlusive condition to prolong the time for which the pore remains opened, better handling and storage of the formulation, providing environmental protection to the ingredients and avoiding any microbial invasion through such pores.

1.7 AIMS OF THE STUDY

The present study is therefore planned to formulate and optimize polymeric nanoparticles as well as ultradeformable liposomes of neuroprotective drugs (Vinpocetine and Noopept), to further incorporate them in to dissolving polymeric microneedles patch and to evaluate their potential for transdermal

application via *ex vivo* and *in vivo* studies with following objectives:

- ✓ Maximizing drugs' permeation
- ✓ Sustaining drug release for prolonged period
- ✓ Improving bioavailability
- ✓ Reducing dose and dosing frequency
- ✓ Patient compliance
- ✓ Effective treatment/management of dementia

1.8 PLAN OF WORK

- Review of related literatures
- Procurement of drugs and excipients
- Authentication of drug samples and drug-excipients compatibility testing
- Development of analytical methods and their validation (UV/HPLC)
- Development & statistical optimization of VPN/NPT loaded UDL
- Development & statistical optimization of VPN/NPT loaded PNP
- Development & statistical optimization of fast dissolving MNP
- Incorporation of VPN/NPT loaded UDL/PNP in fast dissolving MNP
- *In vitro* characterization of developed formulations
- *Ex vivo* permeability and safety evaluations of developed formulations
- Short term stability studies as per ICH guidelines
- *In vivo* pharmacokinetic and pharmacodynamic studies

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