The dementia associated with Alzheimer’s disease (AD) is the most common cause of progressive mental deterioration in people of advanced age. There is a growing realization that the care of older people with disabilities makes enormous demands on their careers. Terms like Dementia and Alzheimer’s disease are now better understood. However, this was not the case when the Alzheimer’s and Related Disorders Society of India (ARDSI) initiated awareness program in 1992. Dementia remains a largely hidden problem in India, especially in those parts of India where poverty and illiteracy levels are high. (Shaji et al, 2010)

The global age standardized death rate for AD and other dementias is 6.7 per 100,000 for males and 7.7 per 100,000 for females. For India and the WHO South East Asia sub region, the dementia mortality rate is 13.5 per 100,000 males and 11.1 per 100,000 females (Mathers and Leonardi, 2000). Compared to other chronic medical conditions (heart diseases, cancer and stroke), AD is the fourth leading cause of death in the Asia Pacific region. A 15 year community-based follow-up study in the United States of 1670 adults aged over 65 years reported a 40% mortality risk for AD and predicted AD as being a leading cause of death and shortened survival time of older people (Ganguli et al, 2011). A systematic review reported a direct relationship between the levels of cognitive impairment and increasing risk of mortality showed a two-fold mortality risk for severe cognitive impairment (Dewey and Saz, 2001).

Most of the evidence on these associations between dementia and mortality are from studies undertaken in developed countries. However, studies from developing countries have also found increased mortality risk for older people with dementia (PWD).
A study from Chennai, investigated predictors of mortality among older people living in the community (Jotheeswaran et al., 2010). After adjusting for age and gender, the risk for mortality was 2.3 times more for older people who received a diagnosis of dementia at the baseline survey and that risk was linearly correlated to the severity of cognitive impairment.

The effect of living for one year with disability depends upon the disability weight attached to the health condition concerned. In the consultation for the Global Burden of Disease report, disability from dementia was accorded a higher disability weight (0.67) than that for almost any other condition, with the exception of severe developmental disorders.

1.1 Current Estimation and Future Projection

The future projections are estimated on the assumption that prevalence of dementia is stable over time, which may not be true. If the incidence of dementia or with increasing life expectancy the number of older people increases, the prevalence of dementia will increase. In India the number of people with AD and other dementias is increasing every year because of the steady growth in the older population and stable increment in life expectancy. Thus, an estimated twofold increase by 2030 and threefold by 2050 can be expected. By the year 2025 UK is projected to have 1 million people with dementia (Dementia UK Report, 2007). According to current estimates; India has more than 3 million People with Dementia and is expected to overtake USA in number of PwD by 2015.
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Figure 1.1: Estimated number of PwD (People with dementia) >60 years in India, UK and USA (Shaji et al, 2010)

Figure 1.2: Projected changes between 2006 and 2026 in number of people living with dementia by State (Shaji et al, 2010)
1.2 Treatment of Alzheimer’s disease

Many drugs have come in the recent past for the Alzheimer’s disease, but few drugs were discontinued due to severe adverse event reports. There are five prescription drugs approved by the USFDA (Alzheimer’s Association). The four are cholinesterase inhibitors viz, Razadyne® (galantamine), Exelon® (rivastigmine), Aricept® (donepezil), and (tacrine) out of which one drug tarcine (Cognex®) is discontinued from use in 2013, because of continuing concerns over safety and availability of other acetylcholinesterase inhibitors. The other FDA approved NMDA receptor blocker for Alzheimer’s disease is Namenda® (memantine). In-spite of the availability of several Anti-Alzheimer’s drugs, limitations associated with these drugs are also very high, in particular when administered through oral route. These limitations are mainly due to factors such as high adverse events, multiple dosing frequencies due to shorter half life of drug and eventually poor patient compliance. The adverse events are primarily due to rapid increase in plasma concentration within shorter time. (Mona Mehta et al, 2012)

One way to circumvent the problems of the currently available drugs is to improve their pharmacokinetic properties by novel formulation strategies. The details of the drugs widely used in treatment of Alzheimer’s disease and the adverse events associated with them are summarized in Table 1.1 (Alzheimer's Association, 2012a and Bethune, 2010)
Table 1.1: Drugs used in treatment of Alzheimer’s disease and their adverse effects (Alzheimer’s Association, 2012a and Bethune, 2010)

<table>
<thead>
<tr>
<th>Generic Name and Brand Name</th>
<th>Innovator Company</th>
<th>Indication</th>
<th>Manufacturer’s dosage forms</th>
<th>Common Side effects</th>
</tr>
</thead>
</table>
| Donepezil (Aricept®)        | Pfizer Inc        | Mild to severe Alzheimer’s disease (AD) | • 5 mg, 10 mg and 23 mg tablets (IR)  
   • 5 mg and 10 mg orally disintegrating tablets (ODT). | Nausea, vomiting, diarrhea |
| Galantamine (Razadyne®)     | Janssen Pharmaceuticals | Mild to Moderate Alzheimer’s disease (AD) | • 4 mg, 8 mg and 12 mg tablets (IR)  
   • 4mg/mL oral solution  
   • 8 mg, 16 mg and 24 mg capsules (ER) | Nausea, vomiting, diarrhea, weight loss, loss of appetite |
| Rivastigmine (Exelon®)      | Novartis Pharmaceuticals Corporation | Mild to moderate AD  
   Also used to treat dementia from Parkinson’s Disease | • 1.5mg, 3mg, 4.5mg and 6mg Capsules (IR)  
   • 2mg/mL oral solution  
   • 4.6mg/hr and 9.4mg/hr transdermal dosage form (TDDS) | Nausea, vomiting, diarrhea, weight loss, loss of appetite, muscle weakness |
| Tacrine (Cognex®)           | Parke - Davis Pharmaceuticals | Mild to Moderate Alzheimer’s disease (AD) | • 10mg, 20mg, 30mg and 40mg Capsules (IR)  
   • (Discontinued due to safety reasons) | Diarrhea, nausea, vomiting, abdominal discomfort, dizziness, headache and liver toxicity |
| Memantine (Namenda®)        | Forest Laboratories, Inc. | Moderate to severe Alzheimer’s disease (AD) | 5mg and 10 mg tablets (IR)  
   2mg/mL oral solution  
   7 mg, 14 mg and 21 mg and 28mg (ER) | Dizziness, headache, constipation, confusion |
1.3 Oral Controlled release drug delivery systems:

For many years, oral route has been the most acceptable route of drug administration. This is due to many advantages such as convenience of administration, non-invasive nature, patient’s acceptance, ability to accommodate numerous drugs and cost effective manufacturing process.

The immediate release dosage forms have some limitations such as: (Brahmankar and Jaiswal, 1995)

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery systems that could modify the use of medication and provide the best therapeutic benefits. (Chein, 1992) The figure 1.3 shows the plasma concentration profile of an immediate release and a controlled release formulation.
Gastrointestinal (GI) absorption of drugs delivered through oral route is affected by properties of the drug molecule such as solubility, ionization constant (pKa), partition coefficient, particle size / surface area, polymorphism and solution state stability under physiological pH, enzymatic stability; physiological factors such as pH of gastrointestinal fluids, enzymes, membrane structures, transport mechanism (passive diffusion, active transport, pinocytosis and facilitated diffusion), efflux mechanism, presence or absence of food and transit time in different regions of the GIT. Formulation related factors such as type, size and physical behavior of the dosage form, disintegration time, drug release / dissolution, nature of excipients; patient related factors such as disease state, time of administration and posture etc. Different technologies and strategies have been developed to achieve desired in vivo performance of drugs that widely vary in their physico-chemical and pharmacokinetic properties.
The oral controlled release dosage forms have been developed as an extension to the product life cycle and to minimize the limitations associated with immediate oral release dosage forms. Many approved commercially controlled release dosage forms are available in the market.

Rivastigmine tartrate (RT) is a carbamate derivative that reversibly inhibits the metabolism of acetylcholinesterase (AChE). The drug is available in various dosage forms such as immediate release capsules, oral solutions and transdermal patches (as rivastigmine). Each dosage form have limitations due to high solubility of the drug, short elimination half-life GI adverse reactions such as nausea, vomiting, diarrhea, anorexia, dehydration due to prolonged vomiting or diarrhea, poor patient compliance due to multiple dosing and monitoring/attention required by caregivers. The transdermal dosage forms have limitation such as skin reactions, patch being detached before its usual replacement time and poor patient compliance. The GI side effects of rivastigmine lead to large fluctuations in plasma level with a rapid rise in plasma level ($C_{\text{max}}$) followed by rapid fall in plasma level ($C_{\text{min}}$) with a high fluctuation index ($\text{FI}_{\text{IR}}$). The adverse events can be reduced by reducing $C_{\text{max}}$, increasing the time to reach the maximum plasma concentration ($t_{\text{max}}$) and thereby reducing the fluctuation index. Thus there is a need for an oral CR dosage form which overcomes the above limitations.

The most distinct advantage with controlled release drug delivery systems (CRDDS) is that they can be formulated in the form of simplest and most commonly used dosage form, i.e. tablet using approved excipients. This further leads to the easy, cost effective and efficient scale-up to commercial scale. While methods employed in the manufacture of microsphere (multiparticulate), osmotic drug delivery and polymer coating based CR formulations suffer significant shortfalls and limitations (e.g., the
multistep process, use of organic solvents which must be removed from the final formulation, requirement for high shear conditions, and a lengthy processing time period) that potentially hinder commercial success. The preparation of CR tablets is well established at the commercial level due to the use of technology similar to that used to manufacture IR tablets.

In the present study, attempt has been made to prepare once a day controlled release (CR) tablet formulations of Rivastigmine tartrate with reduced frequency of administration, reduced adverse effects thereby improving patient compliance.