FORMULATION AND EVALUATION OF CONTROLLED MICROPOROUS OSMOTIC TABLETS OF RIVASTIGMINE HYDROGEN TARTRATE

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ABSRTACT

Extended release formulation of Rivastigmine hydrogen tartrate based on osmotic technology was prepared and evaluated. The tablets were prepared by wet granulation method. Rivastigmine hydrogen tartrate is an ideal candidate for a zero-order drug delivery system because it is freely soluble in water and has short biological half life (6hrs). Sodium chloride and mannitol were used as osmotic agents. Cellulose acetate and polyvinyl pyrrolidone were used as semi permeable membrane and pore forming agent respectively. The effect of different formulation variables, namely, concentration of osmogen in the core tablets and level of pore former in the membrane, were studied. Rivastigmine hydrogen tartrate release from the osmotic tablet was directly proportional to the level of pore former in the membrane. Drug release from the developed formulations was independent of pH and agitation intensity but dependent on osmotic pressure of release media. FTIR results indicated that there was no incompatibility between drug and excipients. The developed formulation could be used for prolong delivery for about 24 hrs of Rivastigmine hydrogen tartrate.

Key words: Rivastigmine hydrogen tartrate, semi permeable membrane, osmogen, level of pore former.

INTRODUCTION

Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems.[1] Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure; there has been increasing interest in the development
of osmotic devices over the past 2 decades. A detailed review of various types of osmotic pumps has been done by Santus and Baker.\(^2\) Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.\(^3\) Controlled porosity osmotic pump (CPOP) system preparation is simple. It is not necessary to consider complicated side drilling and compared to other osmotic pump systems less excipient is required. The coating composition of CPOP includes pore-forming agent, which generates pores in contact with aqueous media.\(^4\)

Alzheimer’s disease (AD) is a progressive illness of the elderly. Patients show increasing declines in cognition, and behavioral symptoms occur in all stages of AD. While all AD patients can present with depression, agitation, and aggressive behaviors, behavioral difficulties are most pronounced in the advanced stages of the disease.\(^5\)-\(^7\) Rivastigmine, inhibiting both acetyl cholinesterase and butyryl cholinesterase, has been widely approved for the symptomatic treatment of AD.\(^8\)

The aim of the study was to formulation and evaluation of microporous osmotic tablets of Rivastigmine hydrogen tartrate which could deliver the drug for about 24hrs.

**MATERIALS AND METHODS**

**Materials:** Rivastigmine hydrogen tartrate was obtained as a gift sample from Sun pharmaceuticals, Mumbai. Sodium chloride and Mannitol were purchased from Finar chemicals limited, Ahmedabad and Nice chemical Pvt.Ltd., Cochin., respectively. Pvp k30, Castor oil and Colloidal silicon dioxide were obtained from Himedia laboratories Pvt.Ltd., Mumbai. PEG -400 and Methanol were procured from Merck specialities private limited, Mumbai. Magnesium stearate,talc, Cellulose acetate, Dichloro methane were purchased from Central Drug house (P) Ltd., Mumbai., Nice chemical Pvt.Ltd., Cochin., Jainpack Pvt.Ltd., Mumbai.,and Finar chemicals limited, Ahmadabad., respectively.

**Formulation development**

Before the preparation of formulation, an FTIR study was conducted to check the compatibility of the drug with excipients. Core tablets of Rivastigmine hydrogen tartrate were prepared by wet granulation method. Rivastigmine hydrogen tartrate was mixed with all the excipients and passed through 30-mesh sieve. The blend was mixed for 10 min and PVP was added. The mixture was granulated with ethanol and the resulting wet mass passed through 18-mesh sieve. The granules were dried at 50 °C (approximately 10 min) to get drying after
which they were passed through 22-mesh sieve. These sized granules were then blended with magnesium stearate, talc, and colloidal silicon dioxide and compressed into tablets having a weight of 360 mg using a multi stroke tablet-punching machine fitted with 9 mm round standard concave punches. Formulae of different core formulations of Rivastigmine hydrogen tartrate are listed in Table 1. The core tablets of Rivastigmine hydrogen tartrate were coated in an automated coating pan. The composition of coating solution used for coating of Rivastigmine hydrogen tartrate tablets is given in Table 2. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of Rivastigmine hydrogen tartrate were placed in the coating pan along with 200 g of filler tablets (tablets made using 7.00 mm round deep concave punches and containing microcrystalline cellulose, starch, dibasic calcium phosphate, magnesium stearate, and colloidal silicon dioxide). Initially, pan was rotated at low speed (2–5 rev./min) and heated air was passed through the tablet bed. Coating process was started once the outlet air temperature reached 28 °C. The revolutions per minute of the pan was kept in the range of 15–20 and coating solution was sprayed at the rate of 5–8 ml/min. Atomization pressure was kept at 1 kg/cm2 and the outlet temperature was maintained above 28 °C by keeping the inlet air temperature in the range of 50–55 °C. Coating was continued until desired weight gain was obtained on the active tablets.\(^9\) Average thickness and average weight gain after coating of semi permeable membrane were found to be 3.47±0.0512 mm and 12.112±0.0224% of core tablet weight, respectively.

**Table 1. Core formulation of Rivastigmine hydrogen tartrate**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>f1</th>
<th>f2</th>
<th>f3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivastigmine Hydrogen Tartrate(mg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sodium chloride (mg)</td>
<td>30</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Mannitol (mg)</td>
<td>287.6</td>
<td>282.6</td>
<td>277.6</td>
</tr>
<tr>
<td>Pvp (mg)</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Magnesium stearate (mg)</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>colloidal silicon dioxide</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Talc (mg)</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Core tablet wt.(mg)</td>
<td>360</td>
<td>360</td>
<td>360</td>
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</table>
Table 2. Formulation of coating solution

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>a</th>
<th>b</th>
<th>c</th>
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</thead>
<tbody>
<tr>
<td>Cellulose acetate(mg)</td>
<td>2.58</td>
<td>3.08</td>
<td>2.22</td>
</tr>
<tr>
<td>PVP(mg)</td>
<td>0.64</td>
<td>-----</td>
<td>1.11</td>
</tr>
<tr>
<td>Castor oil (ml)</td>
<td>0.26</td>
<td>0.31</td>
<td>0.22</td>
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<tr>
<td>PEG-400(ml)</td>
<td>0.52</td>
<td>0.62</td>
<td>0.44</td>
</tr>
<tr>
<td>Methanol(ml)</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>dichloromethane(ml)</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td><strong>Total(ml)</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Dissolution studies

The developed formulations of Rivastigmine hydrogen tartrate were subjected to release studies using USP-I dissolution apparatus at 100 rev./min. Dissolution medium used was phosphate buffer (pH 6.8, 1000 ml) maintained at 37 ± 0.5 °C, which was found to provide sink conditions. The samples were withdrawn (10 ml) at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-mm nylon membrane filters, were analyzed using a validated UV spectroscopic method [9] at 221 nm.

Effect of osmotic agent

Various concentrations of osmotic agents i.e., sodium chloride and mannitol were used in each formulation. Sodium chloride was taken in the concentration of 30mg, 35mg, and 40mg in different formulations. Mannitol was taken in the concentration of 287.6mg, 282.6mg and 277.6mg in various formulations. Sodium chloride and mannitol were used in each formulation. As concentration of sodium chloride increases, the release rate of drug from the osmotic system increases. Effect of osmogen in the formulations was determined by dissolution studies.

Effect of level of pore forming agent

To study the effect of level of pore former (PVP), core formulations of Rivastigmine hydrogen tartrate were coated with coating compositions containing 0, 25 and 50% w/w (of cellulose acetate) level of PVP. Release profile from the formulations of f2a, f2b and f2c were studied. These release profiles of various formulations were conducted in 6.8 pH phosphate buffer in dissolution apparatus. It is clearly evident that the level of PVP had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release.
Various scholars have also got similar results. [10, 11, 12]

**Effect of pH on drug release**

Drug release profiles from the optimized formulations at different pH of buffers were carried out using dissolution test apparatus (USP-I dissolution apparatus). Various media used for the drug release profile study those were 0.1N HCl, 4.4 pH phosphate buffer and 6.8pH phosphate buffer by maintaining 100 rpm at 37 ± 0.5 °C in 6.8 pH phosphate buffer. Drug release profile from optimized formulations conducted to assure the drug release from the dosage form is independent of pH.

**Effect of agitation intensity on drug release**

The optimized formulations of porous osmotic pump tables were tested for the effect of agitation intensity on drug release. The best formulations are undergone dissolution studies by maintaining different rotation speed of 50, 100, 150 rpm and at 37 ± 0.5 °C in 6.8 pH phosphate buffer for 24h using USP dissolution test apparatus (type 1) and compared.

**RESULTS AND DISCUSSION**

**Formulation development**

Dosage form developed was designed as a tablet core and semi permeable coating membrane. Rivastigmine hydrogen tartrate was the drug used in the formulation. Drug has hydrophilic and lipophilic characters. Drug has lower biological half life. The core formulation consists of osmotic agent that is sodium chloride gives osmotic pressure to the dosage form to expel the drug from the formulation. Mannitol was used as diluents and also gives osmotic pressure to the tablets. Magnesium stearate, talc and colloidal silicon dioxide were used as lubricant, glidient and wicking agent. Cellulose acetate used as coating membrane. Polyvinyl pyrrolidone was used as pore forming agent. When formulation contacts with release media forms the pore on the semi permeable membrane. These pores help to imbibe the media in to the tablet and create osmotic pressure. Colloidal silicon dioxide increases the pore size on semi permeable membrane to easy release of the drug from the formulation. Dichloromethane and methanol were used as solvents for coating solution. Castor oil and PEG 400 were used as hydrophobic plasticizer and hydrophilic plasticizer in the formulation, respectively. Plasticizers were used to improve the film forming property of the semi permeable membrane. Following parameters were for the formulations.
FTIR Studies
FTIR was performed for pure drug, blank (only Excipients without drug) and drug with excipients were obtained on FTIR (Perkin Elmer spectrum one, UK) Spectrophotometer. Samples (About 3 mg of sample and 100 mg of potassium bromide) were mixed, compressed into pellets and transmittance was measured from wave number 450 to 4000 cm⁻¹ using FT-IR spectrophotometer (FTIR –T2154, Perkin Elmer, UK). FTIR results are shown in fig 1, fig 2 and fig 3. Results obtained from these studies reveal that there is no incompatibility between drug and excipients.

![Fig 1 FTIR spectra of Drug](image)

![Fig 2 FTIR spectra of NaCl and Mannitol](image)
Content uniformity test

For content uniformity testing, one accurately weighed tablet was added in 100 ml of methanol (n=3). The sample was sonicated for 30 min and filtered through 0.45-mm nylon membrane filter. The filtered solutions, after appropriate dilution with methanol, are analyzed by UV spectroscopy at 221nm. By this test the drug present in the formulation was tested. Obtained results indicate that in all the formulations drug content was uniform and ranged from 91.32% to 98.91%. These results indicate that the drug was uniformly distributed in all formulations and all the formulations are within the specified limits of 85-115%.

In vitro dissolution release studies

Dissolution release studies were conducted for all formulation. The comparison of dissolution profiles are shown in the fig.4. In all formulations, f2a formulation releases the whole drug from the dosage form in 24 hrs to increase the patient compliance. Dissolution profiles of all formulations reveal that f2a formulation was the optimized formulation. All the formulations compared by the pure drug. Other than f2a formulation all formulations released the drug from the formulations before the 24 hrs or after the 24hrs. Pure drug released 100.19±0.12% in 10hrs. 79.08±0.89% of drug from f1a formulation released in 24hrs, 32.43±0.91% of drug from f1b formulation in 24hrs, 87.91±1.23% of active ingredient from dosage form expelled in 24hrs from f1c formulation. Formulation f2a had released 98.84±2.85% drug from dosage form in 24 hrs, 38.89±0.97% of active drug released from f2b formulation in 24hrs, and 95.41±1.94% of active pharmaceutical ingredient from the formulation released in 20hrs from formulation.

Fig 3 FTIR spectra of Drug, NaCl and Mannitol
f2a. 41.26±1.32%, 95.71±1.65% and 100.16±0.99% of drug released from formulations f3a, f3b, and f3c respectively.

Fig 4 Comparison drug release profiles of F1A –F3C formulations and pure form of drug.

Effect of osmotic agent
The release studies of different formulations carried out to assess effect of osmotic agent. It was noted that as the amount of osmotic agent increased, release rate also increased. The formulation f1a showed slower drug release when compared with f2a and f3a formulations. Results are shown in fig 5. Formulation f1a released 79.02±1.3% of drug in 24 hrs, f2a formulation released 98.84±3.15% of drug in 24 hrs and f3a formulation released 95.41±1.32% of drug in 16 hrs.

Fig 5 effect of osmotic agent on drug release

Effect of level of pore forming agent
0, 25 and 50% of pore forming agent used to assess the level of forming of pores by
comparison of drug release profile of various formulations. Fig 6 was concluded that as level of pore forming agent increase, the drug release from the formulation increases. Comparison was done for f2a, f2b and f2b formulations.

![Fig 6](image)

**Fig 6** effect of pore forming agent on drug release

**Effect of pH on drug release**

Optimized formulation was studied for the effect of various media on drug release profile. Results were shown in fig 7 various solutions like 0.1N HCl, 4.4pH phosphate buffer and 6.8pH phosphate buffer were not affected on the drug release profile of the optimized formulations. These results reveal that osmotic tablets are independent of the pH.

![Fig 7](image)

**Fig 7** comparison of drug release in 1.2N HCl, 4.4pH buffer and 6.8 pH buffers

**Effect of agitation intensity on drug release**

Release studies of optimized formulation were carried out at varying rotational speed (50,100 and 150 rev./min).fig 8 concluded that the release rate of optimized formulation doesn’t depend on the pH of the media or independent of the pH of the media.
CONCLUSION
Micro porous osmotic drug delivery system developed and evaluated for various parameters. FTIR results showed that there is no incompatibility between drug and excipients. Effect of pH and effect of agitation intensity on drug release from formulation studied and revealed that there no effect of pH and agitation intensity on drug release. By obtained results the release is proportional to the osmogen concentration and level of pore forming agent.

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REFERENCES


