Formulation and evaluation of osmotic controlled release verapamil tablets

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ABSTRACT

Controlled release tablets of verapamil based on osmotic technology was developed and evaluated. Verapamil half life 2.8–7.4 Hrs, it is short acting drug, developed formulation provide the prolong controlled release formulations. The developed formulation advantage of less steps of manufacturing procedure and no need of laser drilling, verapamil 180 mg core formulation was prepared using with osmogens and coating with different coating materials. The optimize film former (cellulose acetate): mechanical drilling used for pour formation. Effect of different formulation variables namely effect of osmogens. Pour size of membrane are studied. Drug release rate of verapamil directly proportional to pour size in membrane. The optimum drug release at the pour size 800µm for the optimized formulation. All excipients and polymers use in optimized formulation were found to be compatible with the drug, and compatibility study confirmed by FT-IR spectroscopy. Drug release from the optimized formulation independent not depends on concentration. The drug release mechanism follows mixed mechanism combination of diffusion and erosion mechanism. Formulations were stable after one and three months of accelerated stability studies.

Key words: Verapamil, Osmotic controlled release tablets, bioavailability.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration, among all the routes of administration that has been explored for the systemic delivery drug through different pharmaceutical dosage forms. It can be said that at least 90% of all drugs used to produce systemic effect is by oral route. Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc. so overcome this limitation of oral route is replied by parenteral route. This route offers the advantage of reduced dose, targeting of site and avoiding GI stability, hepatic by-pass of drug molecule. In the recent years, pharmaceutical research has led to the development of several novel drug delivery systems. The role of drug development is to take a therapeutically effective molecule with sub-optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits such as Sustained and consistent blood levels within the therapeutic window, Enhanced bioavailability, Reduced inter patient variability, Customized delivery profiles, Decreased dosing frequency, Improved patient compliance, Reduced side effects. The aim of the present study was to design and evaluate controlled release tablets of Verapamil for the treatment of angina, hypertension and prophylaxis based on osmotic technology.

MATERIALS AND METHODS

Verapamil procured from Pangiya pharmacy Hyderabad, Sodium chloride, Potassium chloride, PVP K-30, Micro Crystalline Cellulose were procured from Myl Chem, Mumbai. The tablets were prepared by direct compression method. The core tablets were then coated with cellulose acetate.

RESULTS AND DISCUSSION

Evaluation of coated osmotic tablets: Evaluation of coated formulation using KCl as osmogen. From the different osmogens used, the formulation done using KCl as osmogen has been optimized because of its better yield and coating is done with cellulose acetate.

Effect of KCL as Osmogen: To investigate the effect of orifice size on the release of active material from the tablets, the final coated tablets were drilled tablets to a known orifice of size 400 µm, 800µm, 1200 µm respectively manually with a pre-calibrated micro drill. All the batches of tablets with different orifice sizes were subjected to release studies.

It is observed that in all the formulations that contain KCl as osmogen at an orifice of 400µm, there is no onset of release of drug from tablet up to one hour (lag time) and also a very little amount was released even after 2 hours. This may be due to the insufficient development of enough osmotic pressure inside the core tablet.
It is evident that after coating with semi-permeable membrane of Cellulose acetate, the increase in concentration of osmogen KCl leads to increase in drug release from the tablet due to the osmotic effect. The release of drug from the tablet takes place only after sufficient osmotic pressure builds up in the core. The difference in the osmotic pressure between inside and outside of the tablet causes water penetration into the core, leading to the drug to be solubilised and released from the tablets orifice due to increased hydrostatic pressure. This process continues until the osmogen concentration remains sufficiently in the core to generate osmotic pressure. The imbibition of water will be continued until the osmotic pressure inside and outside environments become equal. This pressure causes the expulsion of drug along with the osmogens from the core to the outside of tablet. As amount of KCl increased in the formulation, there is an enhancement in the release rate of drug from the tablets.

**Effect of orifice Size on Drug Release:** The release profiles from tablets containing different orifice sizes. From the release studies it was clear that at 400µm the delivery rate was low when compared to that of 800µm and 1200µm orifice. There was comparatively rapid release from the orifice size of 1200µm than the 800µm; this may be due to little diffusion from the bigger orifice than small orifice. On the other hand a low release rate was observed for an orifice size of 400µm. In case of smaller orifices the drug release granules may block the orifice, there leading to a low drug release rate. As of large orifice size in 1200 µm, leading to a high drug release rate it is not considered. The controlled zero order drug release profile was observed with 800µm orifice size, thus giving an optimized release rate. The formulation F3 was considered to be best formulation at 800µm orifice size.

**Accelerated stability studies:** Stability studies are defined as the ability of tablet formulation, in specific container to remain within its physical, chemical, therapeutic and toxological specifications. Stability studies performed at stress conditions temperature, moisture, and pressure. Accelerated stability study performed for Osmotic verapamil tablets formulation (F3) at 25±2°C/60±5 RH and 40±2°C/75±5 RH for 1 month and 3 months in stability chamber. After the storage period of 1 month and 3 months and observed for any changes in physical parameters. It was observed that was devoid of any change in colour and appearance of any kind of spots on it. And surface was free from microbial contamination (microbial and fungal growth), and observed for bad odour. No changes in smoothness of tablets are noticed.

### Table 1. Various Formulations of ODDS

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0</td>
<td>45</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mannitol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>Sucrose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45</td>
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<tr>
<td>PVP K-30</td>
<td>20</td>
<td>20</td>
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<td>20</td>
<td>20</td>
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<td>MCC</td>
<td>192</td>
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<td>102</td>
<td>147</td>
<td>102</td>
<td>147</td>
<td>102</td>
<td>147</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
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<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total wt (mg)</strong></td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
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### Table 2. Coating Solution Composition

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Weight</th>
<th>Concentration (%)</th>
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</thead>
<tbody>
<tr>
<td>Cellulose acetate</td>
<td>40gms</td>
<td>4%</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>4 gms</td>
<td>0.4</td>
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<tr>
<td>Acetone</td>
<td>1000ml</td>
<td>Quantity sufficient</td>
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</tbody>
</table>
Figure 1. *In Vitro* Drug Release Of Core Tablet Formulation

Figure 2. Zero Order Plot For Optimized Formulation

Figure 3. First order plot for optimized formulation
CONCLUSION

The following conclusion could be drawn from the research work carried out from the project: FT-IR spectra the interference was verified and found that Verapamil did not interfere with the excipients used in formulation. Osmotic tablets for Verapamil could be successfully prepared with different osmogens in different concentration and could be coated with semipermeable polymer like cellulose acetate and an orifice of known diameter could be drilled on the release for the release of the drug. In vitro release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulation no.-3(1:0.5) containing drug and KCl in the ratio of 1:0.5 has shown 96.9% of drug release in 24 hours and the drug release followed in zero order kinetics. This formulation no.-3(1:0.5) was studied for various effects like influence of orifice size on release. The results have revealed that the release rate was more with an increase in orifice size. The effect of orifice size on cumulative release from Formulation no.-3(1:0.5) formulation was studied with different pore size 0.4 mm, 0.8 mm, 1.2mm. The release rate was low at 0.4mm and high at 1.2mm but desired release rate was obtained with 0.8mm. Formulations of core tablets shown increased drug release rate with an increase in osmogen concentration. Drug release was directly proportional to orifice size. Drug release from the developed formulations follows zero order release kinetics. Drug release from formulation F3 follows Peppas model. Hence verapamil release follows diffusion and erosion rate controlled mechanism. Four other studies go perform the In Vivo studies for these formulation. There is a good scope for the development of elementary osmotic pump system for this drug.

REFERENCES


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