Development and In-Vitro Evaluation of Vinpocetine Loaded Bi-Layer Tablet Using Different Polymers

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ARTICLE INFO
Article history:
Received on: 02/11/2012
Revised on: 29/11/2012
Accepted on: 09/12/2012
Available online: 30/12/2012

Key words:
Vinpocetine,
Bi-Layer Tablet,
Sustained Release,
Mean Dissolution Time (MDT), Anomalous / non – Fickian transport, Super case-II.

ABSTRACT
The present study has investigated various ways to formulate a bi-layer tablet dosage form containing an immediate release and a sustained release portion of a neuroprotective compound named vinpocetine. The bi-layer matrix tablet was prepared by simple compresion of the SR granules and IR granules of vinpocetine. The sustained release effect of vinpocetine was achieved with polymers methocel K15M CR, kollidon SR and carbomer 934P. Physical properties of powders, granules and the finished tablets were evaluated. The drug release study of the tablets was studied for 2 hours in 0.1N HCl followed by 8 hours in pH 6.8 phosphate buffer as media using United States Pharmacopoea (USP) XXII paddle type dissolution apparatus. The effect of above mentioned polymers on vinpocetine release profile was investigated. The MDT values of all the formulations were calculated and correlated with the rate retardation capacity of drug release of the polymers used. The release rate of vinpocetine immediate release layer was found to be influenced little by kollidon CL and direct compressible grade lactose. The release rate, extent and mechanisms of sustained release layers were found to be governed by the nature and the extent of the polymer used in the formulation. Kinetic modeling of dissolution profiles revealed that vinpocetine release mechanism ranges from the anomalous / non – fickian transport to super case II transport in the given situations. These studies indicated that the proper balance between a matrix forming agent and a channeling agent can produce a drug dissolution profile similar to a theoretical dissolution profile will overcome the disadvantages of conventional tablets of vinpocetine.

INTRODUCTION
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve the desired drug concentration. That is, the drug-delivery system should deliver drug at a rate dictated by the needs of the body over the period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. Vinpocetine (vinpocetine-ethyl apovincaminate) was synthesized in the late 1960s from the alkaloid vincamine, extracted from the leaf of the lesser periwinkle plant (Vinca minor) (Lorincz et al., 1976). Vinpocetine was made available under the trade name Cavinton in 1978 and has since been used widely in Japan, Hungary, Germany, Poland, and Russia for the treatment of cerebrovascular-related pathologies (Bereczki et al., 1999). Several clinical studies have confirmed the neuroprotective effects of this compound. Vinpocetine, when taken on an empty stomach, has an absorption rate of 6.7 percent (Miskolczi et al., 1990). When taken with food, absorption increases 60-100 percent. Vinpocetine reaches the bloodstream approximately one hour after administration, weather taken with food or on an empty stomach (Lohmann et al., 1992).
The elimination half-life of the oral form is one to two hours and the majority of vinpocetine is eliminated from the body within eight hours. Recent studies, either following i.v. infusion of vinpocetine in patients with cerebrovascular disorders or using positron emission tomography (PET) scans in animals, have shown that vinpocetine crosses the blood-brain barrier and is taken up by cerebral tissue (Polgar et al., 1985 and Gylas et al., 2003). PET studies have also clearly shown in human subjects vinpocetine is preferentially absorbed in the central nervous system at twice the level that would be expected according to total body distribution. PET studies on the uptake and regional distribution of vinpocetine in human subjects. The highest uptake of vinpocetine was seen in the thalamus, putamen, and neocortical regions. All of the above studies used either 10 mg vinpocetine 3 times daily orally or i.v. vinpocetine. Patients with chronic cerebrovascular disorders that were included in the meta-analysis (Nagy et al., 1995) had been on an oral dosage of 10 mg three times daily.

MATERIALS AND METHODS

Vinpocetine was a gift sample from Eskayef Pharmaceutical limited, Bangladesh. Methocel K15M CR was purchased from Coloron Asia Private Ltd., India. Ludipress, kollidon CL and kollidon SR were purchased from BASF, Germany. Magnesium stearate and carbomer 934P were of Cabot Sanmar Limited, India and Libraw Pharma Delhi, India respectively. Lactose was collected from local market of Bangladesh. Trisodium phosphate, hydrochloric acid and sodium lauryl sulphate (powder) were from Merck, Germany. The purified water was collected from research laboratory, Bangladesh.

Preparation of Tablet

Formulations of vinpocetine loaded bi-layer tablet are shown in Table 1.

Preparation of bi-layer tablet (BLT) by direct compression

1. Accurately weighted vinpocetine IR portion (vinpocetine, ludipress and kollidon except magnesium stearate) were taken in a mortar & they were blended well with pestle for about 5 minutes.
2. Then magnesium stearate was mixed with the previous mixture. Particular attention has been given to ensure through mixing & phase homogenization.

3. The appropriate amounts of the mixture were accurately weighted in an electronic balance for the preparation of each layer.
4. Now, this mixture was taken in a Perkin-Elmer hydraulic press equipped with 10 mm diameter flat faced punch and die set (punch & die were previously lubricated with a 1% dispersion of magnesium stearate in ethanol) and using normal hand pressure it was compacted & it was left in this compact state for about 5 minutes.
5. Now, ingredients of vinpocetine SR portion (vinpocetine, Lactose (in Formulations F-S, F-4S and F-6S), kollidon SR/carbomer-934P/methocel K15M CR, mg-stearate and talc) were weighted accurately & taken again in a mortar & mixed properly with pestle.
6. The appropriate amount of mixture was weighted in an electronic balance & again was poured in the die cavity, uniformly distributed by slight shaking, punch was fixed & 4 tons pressure was applied using hydraulic press for about 5 minutes. Earlier it was experimented that if 3 tons, 4 tons pressure were applied, then the two different layers of vinpocetine were separated after ejection. That’s why 5 tons pressure was selected as applied pressure.

Thus, the bi-layer tablets containing immediate release portion & sustained release portion of vinpocetine were prepared.

Measurement of Powder/Granules Characteristics of Vinpocetine Bilayer Tablets

Carr’s Index

Carr (1965) developed a simple test to evaluate flow ability of a powder by comparing the poured (fluff) density & tapped density of a powder & the rate at which it is packed down. A useful empirical guide is given by Carr’s Compressibility Index. Here ‘Compressibility’ is a misnomer since compression is not involved. Density was measured using ‘Pharmatest’ (Germany) densitometer maintaining 1250 tapping frequencies.

\[ CI(\%) = \left( \frac{TD - PD}{TD} \right) \times 100 \]

Where, \( TD = \) Tapped Density, \( PD = \) Poured Density and CI = Carr’s Index.

Hausner Ratio

A similar index has been defined by Hausner (1967) (Hausner, 1967).

\[ \text{Hausner Ratio} = \frac{TD}{PD}, \]

Where, \( TD = \) Tapped Density and \( PD = \) Poured density.

Table 1: Formulations of vinpocetine loaded bi-layer tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Combination</th>
<th>Immediate Release</th>
<th>Sustained Release</th>
<th>Total (Mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vin (Mg)</td>
<td>Ludipress (Mg)</td>
<td>Kollidon CL (Mg)</td>
</tr>
<tr>
<td>F-1</td>
<td>F-1M+F-1S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-2</td>
<td>F-1M+F-2S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-3</td>
<td>F-1M+F-3S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-4</td>
<td>F-1M+F-4S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-5</td>
<td>F-1M+F-5S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-6</td>
<td>F-1M+F-6S</td>
<td>4.5</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>F-7</td>
<td>F-2M+F-1S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>F-8</td>
<td>F-2M+F-2S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>F-9</td>
<td>F-2M+F-3S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>F-10</td>
<td>F-2M+F-4S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>F-11</td>
<td>F-2M+F-5S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>F-12</td>
<td>F-2M+F-6S</td>
<td>4.5</td>
<td>141</td>
<td>0</td>
</tr>
</tbody>
</table>
Angle of repose
A glass funnel (75mm) was secured with its tip at a given height (H) above a graph paper placed on a horizontal surface. Powder or granules (2.5gm) was poured through the funnel until the apex of conical pile touched the tip of the funnel and then the angle of repose (θ) was calculated using the following formula:
\[ \tan \theta = \frac{H}{R} \]
Where R is the radius of conical pile (Gohel et al., 2007)

Measurement of Some Physical Parameters of Vinpocetine Bi-Layer Tablets

Hardness & tensile strength
The ability of a tablet to withstand mechanical handling & transport has been evaluated by various types of tests: abrasion, bending, indentation, hardness, diametral crushing. However the data from these tests seldom can be correlated in a precise manner. Hardness depends on the weight of the material & the space between the upper & lower punches at the moment of compression. If volume of the material or the distance between punches varies, hardness is like inconsistent. Five tablets of each of the formulations were taken and hardness was measured by Hardness tester (Veego, India). The average value was calculated and the testing unit was kg. The most popular estimate of tablet strength has been crushing strength, which is defined as the ‘Compressional force (F) which when applied diametrically to a tablet just to fracture it’. Measurement of tensile strength was conducted in the axial & radial directions with the intact matrix discs. Based on crushing load determined using a hardness tester, tensile strength of Vinpocetine bi-layer tablets in the axial (Kuno et al., 1982) and radial directions were estimated according to the following equations:
\[ T_{axial} = \frac{4F}{(\pi X D^2)} \]
\[ T_{radial} = \frac{2F}{(\pi X DXH)} \]

Thickness Measurement
Six tablets of each of the formulations were taken and thickness was measured by Vernier Caliper. The values were reported in millimeter (mm). Mean was calculated.

Diameter Measurement
Six tablets of each of the formulations were taken and diameter was measured by Vernier Caliper. The values were reported in millimeter (mm). Mean was calculated.

Friability Test
Six tablets of each of the formulations were taken and friability was measured by Friability tester (Pharma Test, Germany). Weights of six tablets were taken. The tablets were introduced into the rotating disk and it was allowed to rotate at 25 rpm for 4 minutes. At the end of the rotation, tablets were collected, dedusted and reweighed. The friability was calculated as the percent of weight loss. Tablet integrity is determined by calculating the percent of friability by using the following formula:
\[ \text{Percent of friability} = \left( \frac{M_1 - M_2}{M_1} \right) \times 100\% \]
Where,
\[ M_1 = \text{Average weight of the tablets before the rotation.} \]
\[ M_2 = \text{Average weight of the tablets after the rotation.} \]

Maximal Water Uptake Capacity
Modified method and apparatus was used for the water uptake study. The apparatus consists of a sample holder and a liquid holding vessel (petri-dish), set on an electronic digital balance. When tablet was placed into perforated sample holder, then fluid was passively withdrawn in to the tablet. The loss of weight from the liquid holder was read from the digital balance. Test was performed in triplicate. All results were reported as mean±SD (Zhao et al., 2005)

Disintegration Time
“Pharma Test” Tablet Disintegration test Unit (BP/USP standard), a product of Germany, was used. To test disintegration time for some formulation and one tablet of each of the batch was introduced into each tube. The assembly was suspended in a beaker containing phosphate buffer of pH 7.4 and observed continuously during operation. The tablets were observed for signs of cracks or disintegration. The disintegration time (minute) taken to disintegrate each tablet was recorded. The tablets passed the test till all the tablets were disintegrated.

In vitro release studies of the Vinpocetine in 6.8 phosphate buffer

Acid stage
The release rate of Vinpocetine from various bi-layer tablets was determined by using Tablet Dissolution Tester (paddle method). The dissolution test was performed using 675 ml 0.1N HCl solution at 37°C± 0.5°C using 50 r.p.m. for first 2 hours. For determining the release rate of Vinpocetine, the 5 mL sample was withdrawn at 20 minutes and 2 Hours time intervals, replacing with 5 mL of the fresh medium to maintain the volume constant. The samples were filtered through a Whatmann filter paper.

Buffer stage
After 2 hours, the acid stage was changed into buffer stage followed by addition of 225 mL 0.2 M trisodium phosphate into 675 mL of 0.1N HCl to raise the pH to 6.8. Now the release rate of Vinpocetine in buffer was measured for next 8 hours, withdrawing 5 mL of sample at 1 hour interval & replacing with 5 mL of the fresh medium to maintain the volume constant. The samples were filtered through a Whatmann filter paper. The wavelength for maximum absorption (λmax) of the solutions was measured at 270 nm for drug Vinpocetine by using a UV Spectrophotometer (Simadzu, Japan). By finding out the λmax by Vinpocetine, percentage of drug release was calculated using an equation obtained from the standard curve. The dissolution study was continued for 2 hour in acid and 8 hours in buffer to get a simulated picture of the drug release in the in-vivo condition and drug dissolved at specified time periods was plotted as percent
release versus time (hours) curve. This drug release profiles were fitted into several mathematical models to get an idea of the release mechanism of Vinpocetin from the bi-layer (IR+SR) tablets.

**Kinetic Modeling of Drug Release**

The dissolution profile of all the batches was fitted to zero order (Mockel et al., 1993), Higuchi (Higuchi, 1963) and Korsmeyer (Korsmeyer et al., 1983) equations to ascertain the kinetic modeling of drug release.

As percent release of Vinpocetin in acid media is very less, kinetic modeling was done considering duration of dissolution in acid media as two hours. The time of two hours in acid media is considered as initial time (two hours) for such kinetic Modeling. So the responses obtained (T25%, T50%, T80% & MDT) show two hours less than the actual value.

After linear transformation of dissolution curves, the results were tested with the following mathematical models:

**Zero order release profile**

The Zero order equation assumes that drug release is constant: \( M = M_o - K_o t \) (I)

In this equation \( M \) is the amount of drug remaining undissolved at time \( t \), \( M_o \) is the amount of drug undissolved at \( t=0 \) and \( K_o \) is the corresponding release rate constant. Zero order plot of drug release is obtained by plotting percent release of drug versus time in hour.

**Higuchi release profile**

A form of the Higuchi Square Root Law is given by equation:

\[ Q = K_{H} \sqrt{t} \] (II)

Where \( Q = 100 - M \) is the amount of drug dissolved at time \( t \) and \( K_{H} \) is the corresponding rate constant. Hence drug release is proportional to the square root of time. Here cumulative percentage of drug release is plotted vs. time. The Higuchi’s model which describes release by Fickian diffusion through a porous matrix (Higuchi, 1963). Two factors, however, diminish the applicability of Higuchi’s equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix (Abdelkader et al., 2007).

**First order release kinetics**

Release behavior generally follows the following first order release equation:

\[ \ln M = \ln M_o - K_1 t \] (III)

Where \( M \) is the amount of drug undissolved at time \( t \), \( M_o \) is the amount of drug undissolved at \( t=0 \) and \( K_1 \) is the corresponding release rate constant.

**Korsmeyer release profile**

The dissolusion data were also fitted according to the well-known exponential Korsmeyer-peppase equation. Release behavior generally follows the following first order release equation:

\[ \frac{M_t}{M_o} = K_{K} t^{n} \] (IV)

Where \( M_t/M_o \) is the fraction of solute release, \( t \) is the release time, \( K_{K} \) is the kinetic constant characteristic of the drug/polymer system and \( n \) is the diffusion exponent or release exponent that characterizes the mechanism of release tracers. Log fraction release as a function of log of time (hour) gives the Korsmeyer release pattern from various formulations of Naproixen tablets. Ritger and Peppas have defined the exponent \( n \) as a function of the aspect ratio for 1- dimensional to 3- dimensional systems (slabs, cylinders, and sphere). The aspect ratio (2a/l) is defined as the ratio of diameter (2a) to thickness (L) (Abdelkader et al., 2007).

**Successive Fractional Dissolution Time**

To characterize the drug release rate in different experimental conditions, \( T_{25\%}, T_{50\%} \) (mean dissolution time) and \( T_{80\%} \) were calculated from dissolution data according to the following equations:

\[ T_{25\%} = (0.25/k)^{1/n} \]
\[ T_{50\%} = (0.5/k)^{1/n} \]
\[ T_{80\%} = (0.8/k)^{1/n} \]

Mean Dissolution Time can also be calculated by the following equation (Mockel and Lippold 1993).

\[ \text{MDT} = (n/n+1). K^{-1/n} \]

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule (Mockel et al., 2008).

**Statistical Analysis**

A one way analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate and comparison of Successive dissolution time (T50%, T80%) of all formulations. A confidence limit of \( P < .05 \) was fixed and the theoretical calculated values of \( F \) (Fcrit and Fcal) were compared for the interpretation of results. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA).

**RESULTS AND DISCUSSION**

**Characterization of powders and granules**

Vinpocetine bi-layer Tablets were prepared with direct compression process. Prior to compression, granules and powders were evaluated for their characteristic parameters. Angle of repose was measured by fixed funnel method. Bulk density and tapped density were determined by cylinder method, and Carr’s Index (CI) and Hausner ratio were calculated (Table 2).
such as hardness, friability as stated earlier. The properties of the diameter punch and die was used to compress Vinpocetine mixture Table 1. Physical properties of Vinpocetine loaded bilayer tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Hardness (Kg)</th>
<th>Tensile Strength</th>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Avg. % Friability</th>
<th>Avg. DT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>10.2</td>
<td>0.283</td>
<td>0.130</td>
<td>9.98</td>
<td>2.3</td>
<td>0.21</td>
</tr>
<tr>
<td>F-2</td>
<td>6.4</td>
<td>0.177</td>
<td>0.081</td>
<td>9.98</td>
<td>2.3</td>
<td>0.19</td>
</tr>
<tr>
<td>F-3</td>
<td>11</td>
<td>0.305</td>
<td>0.140</td>
<td>9.98</td>
<td>2.3</td>
<td>0.19</td>
</tr>
<tr>
<td>F-4</td>
<td>7.4</td>
<td>0.205</td>
<td>0.094</td>
<td>9.98</td>
<td>2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>F-5</td>
<td>7.4</td>
<td>0.205</td>
<td>0.094</td>
<td>9.98</td>
<td>2.3</td>
<td>0.27</td>
</tr>
<tr>
<td>F-6</td>
<td>7.6</td>
<td>0.210</td>
<td>0.097</td>
<td>9.98</td>
<td>2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>F-7</td>
<td>8.4</td>
<td>0.233</td>
<td>0.107</td>
<td>9.98</td>
<td>2.3</td>
<td>0.18</td>
</tr>
<tr>
<td>F-8</td>
<td>8.4</td>
<td>0.233</td>
<td>0.107</td>
<td>9.98</td>
<td>2.3</td>
<td>0.21</td>
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<tr>
<td>F-9</td>
<td>6.8</td>
<td>0.188</td>
<td>0.086</td>
<td>9.98</td>
<td>2.3</td>
<td>0.20</td>
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<tr>
<td>F-10</td>
<td>11</td>
<td>0.305</td>
<td>0.140</td>
<td>9.98</td>
<td>2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>F-11</td>
<td>6.4</td>
<td>0.177</td>
<td>0.107</td>
<td>9.98</td>
<td>2.3</td>
<td>0.19</td>
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<tr>
<td>F-12</td>
<td>8.4</td>
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<td>0.107</td>
<td>9.98</td>
<td>2.3</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Angle of Repose, Compressibility Index and Hausner Ratio of Different Formulations.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Average Angle of Repose (θ) (in Degree)</th>
<th>Density</th>
<th>Compressibility Index (in per cent)</th>
<th>Average Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>24.44</td>
<td>0.573</td>
<td>20.761</td>
<td>2.233</td>
</tr>
<tr>
<td>F-2</td>
<td>22.6</td>
<td>0.576</td>
<td>20.111</td>
<td>2.522</td>
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<tr>
<td>F-3</td>
<td>21.03</td>
<td>0.561</td>
<td>21.866</td>
<td>1.280</td>
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<tr>
<td>F-4</td>
<td>22.88</td>
<td>0.558</td>
<td>23.666</td>
<td>1.310</td>
</tr>
<tr>
<td>F-5</td>
<td>20.4</td>
<td>0.553</td>
<td>24.454</td>
<td>1.324</td>
</tr>
<tr>
<td>F-6</td>
<td>22.68</td>
<td>0.569</td>
<td>23.212</td>
<td>1.302</td>
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<tr>
<td>F-7</td>
<td>22</td>
<td>0.574</td>
<td>20.718</td>
<td>1.261</td>
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<tr>
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<td>23.45</td>
<td>0.572</td>
<td>21.644</td>
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<td>0.558</td>
<td>23.562</td>
<td>1.308</td>
</tr>
<tr>
<td>F-12</td>
<td>23.24</td>
<td>0.542</td>
<td>23.121</td>
<td>1.301</td>
</tr>
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</table>

Table 3: Physical properties of Vinpocetine loaded bilayer tablets.

Table 4: Interpretation of release rate constants and R-squared values for different release kinetics Vinpocetine loaded bi-layer tablets.

Table 5: Data treatment of release profiles of Vinpocetine from Kollidon SR, Carbomer-934P and Methocel K15M CR based bi-layer tablets considering rate constants, R² and n Value.

Table 6: T₂₅₆, T₄₅₆, T₉₅₆ and MDT (Hours) values of F-1S, F-2S, F-3S, F-4S, F-5S and F-6S.

Table 7: Cumulative % Release of all formulations at the end of 10th hr of dissolution.

Characterization of Bi-layer Tablets

“Single punch compression machine” with 10 mm diameter punch and die was used to compress Vinpocetine mixture as stated earlier. The properties of the compressed matrix tablet, such as hardness, friability were determined (Table 3). A slide calipers was used to measure the diameter and thickness of the tablet discs. The average diameter and thickness were found as 9.98 mm and 2.3 mm for all formulations. Hardness of 6 matrix tablets from each formulation was tested using Veego hardness tester. The hardness of tablets was measured in kg. All
formulations were compressed and resulted in tablets in which hardness ranged from 6.4 Kg to 11.00 Kg. Tensile strength in the axial and radial direction was measured from the applied force to fracture the tablet. Friability means the ability to reduce a solid substance into smaller pieces with little effort. The integrity of the tablet formulation was assessed by rotating 10 tablets from each formulation in a tablet friability tester.

Weight of 10 tablets was taken, using tablet friability tester equipped with a specific rotating disk. The tablets were introduced into the rotating disk and it was allowed to rotate at 25 rpm for 4 minutes. At the end of the rotation, tablets were collected and weighed of the tablets were taken.

The average % friability was found less than 0.3%, which was well within the acceptable range of 1% and indicates the tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation until they are consumed. Disintegration time was calculated taking 6 tablets from each formulation. It was found within the range of 10 to 13 minutes. The disintegration time was well within the acceptable range of 15 minutes for uncoated tablets.

**Study of the Maximum Water Uptake**

Higher cumulative percent release is seen in the formulations having higher values of the water uptake except some formulations (Figure 1).

It indicates that generally the water uptaking capacity is directly proportional to the drug releasing capacity of the Formulation (Figure 2).

**Study of the In-Vitro release profile of Vinpocetine from the Sustained Release Layer of the Bi-Layer Tablet**

Zero order (Fig. 3), Higuchi (Fig. 4) and Korsmeyer (Fig. 5) plots of release profile of Vinpocetine from Vinpocetine loaded bi-layer tablets were well demonstrated.

**Fig. 1:** Maximum Water uptake (x-axis indicates the Maximum Water Uptake in percent).

**Fig. 2:** Maximum Water Uptake (in %) Vs Cumulative % Release.

**Fig. 3:** Zero order plot of release profile of Vinpocetine from Vinpocetine loaded bi-layer tablets.

**Fig. 4:** Higuchi plot of release profile of Vinpocetine from Vinpocetine loaded bi-layer tablets.
Data treatment of release profiles of Vinpocetine from Kollidon SR, Carbomer-934P and Methocel K15M CR based bi-layer tablets considering rate constants, $R^2$, $n$ Value (Table 4)

Alderman reported that when the hydrophilic matrix tablet enters an in vitro dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix also begins to swell (polymer relaxation) as soon as hydration with solvent molecules, diffusion of the dissolved drug, and erosion of gelatinous viscous polymer layer into aggregates or granules, and these in turn deaggregate into fine particles that also release their drug content by dissolution.

Data treatment of release profiles of Vinpocetine from Kollidon SR, Carbomer-934P and Methocel K15M CR based bi-layer tablets considering rate constants, $R^2$ and $n$ Value

F-3S, F-4S and F-5S showed time-independent release kinetics with these $n$ values, indicating that the release of the drug was at least partially controlled by viscoelastic relaxation of the matrix during solvent penetration (Table 5). Replacing Kollidon SR and Carbomer 934P with Methocel K15M CR showed a Super case II release mechanism. This phenomenon can generally be attributed to structural changes induced in the polymer by the penetrant. The swelling and hydration property of Carbomer 934P and Methocel K15M CR causes an immediate formation of a surface barrier around the matrix tablet that eliminates the burst release. The high percentage of drug release from this system can be attributed to the erosion of the matrix which takes place after complete hydration of the outer layer.

Data treatment of release profiles of Vinpocetine from Kollidon SR, Carbomer-934P and Methocel K15M CR based bi-layer tablets considering MDT values:

It is shown that the higher the polymer level, the higher the value of MDT (Table 6). These findings were in accordance with those of Reza et al., The MDT values of different formulations manifest affect of various polymers. The F-2S contains least amount of Kollidon SR (nearly half of that of F-1S) & some amount of direct compressible grade Lactose and shows a MDT value of 5.49514 hours, which means drug release rate will be faster from this formulation.

As the concentration of Kollidon SR increases and the concentration of direct compressible grade lactose is made void, the drug release rate becomes slower and MDT value becomes higher. Similarly the amount of Carbomer 934P in the Formulation F-3S is double of that of F-4S; the MDT value of F-3S is 7.5298 Hours whereas the MDT value of F-4S is only 4.670297 Hours. Here the higher value of Carbomer 934P has highly retarded the rate of drug release.

If the MDT values of formulations F-1S, F-2S, F-3S and F-4S are compared the drug release retarding effect of Carbomer 934P is higher than that of the Kollidon SR. In the formulations F-1S and F-3S all the common excipients are in the same amount and the amount of Kollidon and Carbomer 934P are equal in the formulations respectively. The MDT values of F-1S and F-3S are 6.133904 Hours and 7.5298 Hours respectively. It shows that the retarding effect on the rate of drug release of Carbomer 934P is higher than that of Kollidon SR.

In the Formulations F-5S and F-6S, the increase in the amount of Methocel K15M CR has shown the increased retarding effect on the drug release. F-5S having the higher amount of Methocel K15M CR than F-6S has the higher value of MDT.

Study of the effect of polymers on the release kinetics of vinpocetine from the vinpocetine loaded bi-layer tablets.

The percentage of drug release of these formulations at the end of $10^6$ hour of dissolution (Table 7) was used to analyze the effects of Kollidon SR, Carbomer 934P and HPMC K15M CR on the release kinetics of Vinpocetine from the vinpocetine loaded bi-layer tablets.

Effects of Kollidon SR on release kinetics of Vinpocetine from Vinpocetine loaded bi-layer tablets

For these experiment different formulations of Vinpocetine having Kollidon SR polymer in 69 mg, 35 mg, 69 mg and 35 mg (in each tablet of total weight 240 mg) with the formulation codes F-1, F-2, F-7 and F-8 (for bi-layer tablet) respectively were prepared. Their dissolution studies were performed with a rotation of 50 rpm at $37^\circ \pm 0.5^\circ C$ using USP apparatus-II (Paddle method), placed in 625 mL of 0.1N HCl, followed by 900 mL pH 6.8 phosphate buffer media. Four tablets from each formulation are used in each dissolution study and the release pattern of Vinpocetine was monitored up to ten hours. The cumulative percent release of Formulation F-8 at the end of the $10^6$ hour of dissolution is 97.14 %. The F-8 contains only the half of the amount of Kollidon SR present in formulations F-1 and F-7. At the same time it also contains 34 mg of direct compressible grade lactose. The lower amount of Kollidon SR and presence of direct compressible grade lactose in F-8 has accelerated the rate of drug release. Similarly the Formulation F-2 having the same amount of Kollidon SR as that of F-8 has shown the cumulative percent release of 80.35 %. Formulations F-1 and F-7 contain the
same amount of the polymer Kollidon SR and their cumulative percent release at the end of 10th hour is nearly same. The cumulative percent release of formulations F-1 and F-7 are 76.76 % and 74.60 % respectively. The different release rate of Vinpocetine from different polymer based matrix tablets may be also due to the poor solubility of Vinpocetine in water, besides the physico-chemical properties of the polymers used, mentioned above.

Effects of Carbomer 934P on release kinetics of Vinpocetine from Vinpocetine loaded bi-layer tablets

For these experiment different formulations of Vinpocetine having Carbomer 934P polymer in 69 mg, 35 mg, 69 mg and 35 mg (in each tablet of total weight 240 mg) with the formulation codes F-3, F-4, F-9 and F-10 (for bi-layer tablet) respectively were prepared. Their dissolution studies were performed with a rotation of 50 rpm at 37°C ± 0.5°C using USP apparatus-II (Paddle method), placed in 625 mL of 0.1N HCl, followed by 900 mL pH 6.8 phosphate buffer media. Four tablets from each formulation are used in each dissolution study and the release pattern of Vinpocetine was monitored up to ten hours. The cumulative percent release of Formulation F-10 at the end of the 10th hour of dissolution is 98.54 %. The F-10 contains only the half of the amount of Carbomer 934P present in formulations F-3 and F-9. At the same time it also contains 34 mg of direct compressible grade lactose. The lower amount of Carbomer 934P and presence of direct compressible grade lactose in F-10 has accelerated the rate of drug release. Similarly the Formulation F-4 having the same amount of Carbomer 934P as that of F-8 has shown the cumulative percent release of 91.18 %. Formulations F-3 and F-9 at the end of 10th hour has shown the cumulative percent release 71.10 % and 94.20 % respectively. The different release rate of Vinpocetine from different polymer based matrix tablets may be also due to the poor solubility of Vinpocetine in water, besides the physico-chemical properties of the polymers used, mentioned above.

Effects of HPMC K15M CR on release kinetics of Vinpocetine from Vinpocetine loaded bi-layer tablets

For these experiment different formulations of Vinpocetine having Methocel K15M CR polymer in 69 mg, 35 mg, 69 mg and 35 mg (in each tablet of total weight 240 mg) with the formulation codes F-5, F-6, F-11 and F-12 (for bi-layer tablet) respectively were prepared. Their dissolution studies were performed with a rotation of 50 rpm at 37°C ± 0.5°C using USP apparatus-II (Paddle method), placed in 625 mL of 0.1N HCl, followed by 900 mL pH 6.8 phosphate buffer media. Four tablets from each formulation are used in each dissolution study and the release pattern of Vinpocetine was monitored up to ten hours. Formulations F-5 and F-11 contain the same amount of the polymer Methocel K15M CR but the cumulative percent release of F-5 is 83.92 % whereas that of F-11 is 63.44 %. Here the higher cumulative release of F-5 than F-11 is mainly due to the presence of Kollidon Cl. It is present only in F-5 and is absent in F-11. It has accelerated the cumulative percent drug release. In the formulations F-6 and F-12 they have the same amount of the polymer Methocel K15M CR and direct compressible grade Lactose. They also have shown nearly the same cumulative percent drug release and that is 82.20 % and 83.88 % respectively. Here the presence of Kollidon Cl in F-6 has not imparted any note worthy effect on the drug release. The different release rate of Vinpocetine from different polymer based matrix tablets may be also due to the poor solubility of Vinpocetine in water, besides the physico-chemical properties of the polymers used, mentioned above. The HPMC manufacturer (Rosenberg, Germany) recommended 20 to 50% matrix for optimum release.

CONCLUSION

Usually Vinpocetine is required 10 mg three times daily in conventional dosage form. Sometimes the frequency of doses is required to increase considering disease state. Repeated medication via rapid absorption causes non-compliance to patient. Patient non-compliance and nocturnal harassment can be avoided by administering Vinpocetine as a combination of an immediate release layer and a sustained release layer in the form of a bi-layer tablet. Vinpocetine matrices were prepared successfully utilizing different proportion of different excipients. Optimized immediate release layer and sustained release layer of Vinpocetine show satisfactory pre and post compression parameters. Bi-layer tablet of Vinpocetine might be suitable for neuroprotective activities by sequential release of the drug. For once or twice daily immediate release product, formulation changes like changes in the content of polymers or disintegrant produced little change in release pattern among formulations. Release behavior of Vinpocetine was slightly altered due to slight variation in applied pressure used for preparing the tablets. After performing dissolution study, Vinpocetine release profiles were analyzed on the basis of various mathematical models such as zero order kinetic model, Higuchi release pattern and Korsmeyer release pattern. The overall experiment has revealed the effect of polymer on the release kinetics of Vinpocetine from different polymer based matrix tablets. The following features are quite notable from the above study:

1. Maximum formulations displayed highest fitting with Korsmeyer release pattern and in all cases lowest fitting with zero order kinetic model of drug release.
2. Increase of polymer content always displayed a common phenomenon that the drug release rate and extent were decreased in all cases which were indicated by $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and MDT values.
3. With increasing METHOCEL K15M CR content, Korsmeyer or zero order release pattern was followed. With further increase in concentration of polymer zero order release pattern was followed. Again with the increasing content of Kollidon SR and Carbomer 934P, release rate kinetics mainly fitted to either Higuchi or Korsmeyer pattern.
4. The release exponent (n) value for METHOCEL showed that with the increase in polymer content, drug release follows super case-II type of transport and that of Kollidon SR and Carbomer 934P shows that drug release follows non-Fickian or anomalous transport.

5. The low viscosity polymer Kollidon SR offered highest release of drug from matrices followed by METHOCEL K15M CR and Carbomer 934P. This is due to the fact that hydrophilic polymer forms a consistent and homogenous gel-like structure around the tablet matrix and this layer retards the release of drug more efficiently and plastic or hydrophobic polymer by leaching followed by diffusion.

It can be concluded that different METHOCEL and Carbomer grades have the ability to lower the drug release alone to a considerable extent, which may interfere with the therapeutic efficacy of the drug. But proper adjustment of polymer with the drug (as a part of formulation design) will enable a desirable release characteristic of the active ingredient (Vinpocetine). More extensive in vitro-in vivo correlation study on similar formulations deemed necessary to establish a successful formulation from biopharmaceutical viewpoint. Further study would be carried out for finding out the possibilities of formulations containing Vinpocetine having antioxidant, vasodilating and neuroprotective activities.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Mohiuddin Ahmed Bhuiyan, Associate Professor & Head, Department of Pharmacy, The University of Asia Pacific and Mr. Sardar Md. Ashraful Islam, Associate Professor and Program Coordinator (M.S. Pharmaceutical Technology), Department of Pharmacy, The University of Asia Pacific, Dhakoni, Dhaka, Bangladesh for invaluable support, inspiration and encouragement from time to time. The Authors extend their sincere thanks the management of Department of Pharmacy, The University of Asia Pacific, Dhaka, Bangladesh, for providing necessary facilities.

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How to cite this article: