FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF GABAPENTIN

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ABSTRACT

Oral administration is one of the most convenient forms for the intake of drug due to ease of administration, painless, versality and paramount patient compliance. The demand of fast disintegrating tablets has been growing, during the last decades especially for geriatric and pediatric patients due to dysphasia. So the new drug delivery known as orally disintegrating tablets came to existence. An attempt has been made to prepare fast dissolving tablets of Gabapentin using super disintegrants like croscarmellose sodium, crospovidone, PVP K-30. All the formulations were evaluated for post-compression parameters like hardness, friability, drug content uniformity, dissolution test and disintegration test. The $\lambda_{\text{max}}$ of gabapentin was scanned for 0.1N HCL buffer. The maximum absorbance 221 nm was done. Finally F3 formulation is best formulation based on drug release characteristics

KEYWORDS: Gabapentin, crospovidone, croscarmellose sodium, PVP K-30, Mannitol.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within
the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system.\cite{1}

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance.\cite{1}

**Mechanism of sublingual administration**\cite{2}

The absorption potential of the buccal mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis); the ionisation (pH); and the molecular weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lower (more acidic) and decrease with a lowering of pH (more alkaline).

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weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lower (more acidic) and decrease with a lowering of pH (more alkaline). The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The buccal mucosa are similar to the sublingual mucosal tissue. The sublingual mucosal tissue is similar to that of buccal mucosa. The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth.\(^2\)

**Advantages**
- Rapid onset of action is achieved as compared to the oral route.
- Liver is bypassed and also drug is protected from metabolism due to digestive enzymes of the middle gastro intestinal tract.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.\(^3\)

**Disadvantages**
- Sublingual medication cannot be used when a patient is uncooperative.
- This site is not well suited to sustained-delivery systems.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the vessels.
- This site is not well suited to sustained-delivery systems.

**MATERIALS AND METHODS**

**Materials**
Gabapentin was obtained from creative labs, Mumbai. Cros povidine was obtained from Accord labs, Cros carmellose sodium was obtained from Accord labs, PVP K30 was obtained from Accord labs, Micro crystalline cellulose was obtained from Accord labs, Mannitol was obtained from Accord labs, Aerosil was obtained from Accord labs, Magnesium stearate was obtained from Accord labs, Secunderabad.

**Method**
Mouth dissolving Gabapentin tablets were prepared by using different super disintegrants like Cros Povidine, Croscarmellose sodium, PVP K-30 with the help of Direct compression method. Binder like Micro crystalline cellulose, sweetner like mannitol, lubricant like Magnesium stearate were used for preparation of tablets. The composition of all six
formulations was made by using super disintegrants like cros povidine, croscarmellose sodium, PVP K30. Aerosil is used for easy flow of particles and piperment oil is used as flavor. All the ingredients were uniformly blended and passed through sieve # 44 to get fine particles. The resultant mixture was compressed into tablets by using single punch rotary tablet compression machine. All the formulation F1-F6 containing 500 mg of drug were prepared and punched.

**Pre-formulation Evaluation**

Fourier transform infrared spectroscopy (FT-IR) study was conducted using shimadzu-8400S to identify purity of the drug and test the compatibility of drug with excipients.

**Pre-compression Evaluation**

The flow properties for Bulk density, Tapped density, Hausner’s ratio, % compressibility, Carr’s index, Angle of repose were evaluated.

**Evaluation of Gabapentin sublingual tablets**

Tablets were tested for physical appearance, thickness using vernier calipers, weight variation using Digital weighing balance, Hardness tester, Friabilator, Drug content uniformity, invitro disintegration and dissolution were studied.

**Weight variation**

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. The results were tabulated.

**Hardness**

The hardness of the tablets was determined by a Pfizer hardness tester. A tablet hardness of about 3-4 kg is considered adequate for mechanical stability. Determinations were made in triplicate. [4]

**Friability**

The tablets were tested for friability testing using a Roche Friabilator. For this test, six tablets were weighed and subjected to a combined effect of abrasion and shock in the plastic chamber of the Friabilator revolving at 25 r.p.m. for 4 min and the tablets were then dusted and re-weighed.
Content uniformity test
Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of drug was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at its maximum wavelength after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determination.\[^{[5]}\]

_In vitro_ dispersion time
Tablet was added to 10 ml of buffer solution at 37 ± 0.5°C. Time required for complete dispersion of a tablet was measured. The results were tabulated.

Dissolution study
_In vitro_ dissolution of sublingual tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5°C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbances at its maximum wavelength. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of drug released was calculated and plotted against time.\[^{[6]}\]

Wetting time
The tablet was placed at the center of two layers of absorbent paper fitted into a petridish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.\[^{[7]}\]
RESULTS AND DISCUSSIONS

FTIR ANALYSIS

Figure 1: Gabapentin pure drug

Figure 2: Gabapentin drug and Cros Povidine
Table 1: Formulation Table of Sublingual Tablets of Gabapentin (F1-F6)

<table>
<thead>
<tr>
<th>Formulation/Ingredients</th>
<th>F1 (mg)</th>
<th>F2 (mg)</th>
<th>F3 (mg)</th>
<th>F4 (mg)</th>
<th>F5 (mg)</th>
<th>F6 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cros povidine</td>
<td>4</td>
<td>5</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cros carmellose sodium</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>PVP K30</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>250</td>
<td>248</td>
<td>246</td>
<td>250</td>
<td>248</td>
<td>246</td>
</tr>
<tr>
<td>Mannitol</td>
<td>230</td>
<td>230</td>
<td>230</td>
<td>230</td>
<td>230</td>
<td>230</td>
</tr>
</tbody>
</table>
**Aerosil** 0.6 0.6 0.6 0.6 0.6 0.6
Magneismum stearate 1 1 1 1 1 1
Piperment oil q.s q.s q.s q.s q.s q.s

Pre evaluation parameters

Table 2: pre-evaluation parameters.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk Density gm/cc</th>
<th>Tapped Density gm/cc</th>
<th>Hausner's Ratio</th>
<th>% Compressibility (%)</th>
<th>Angle of Repose (Degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.264±0.01</td>
<td>0.335±0.03</td>
<td>1.268±0.5</td>
<td>21.19±0.5</td>
<td>29.55±0.5</td>
</tr>
<tr>
<td>F2</td>
<td>0.312±0.03</td>
<td>0.413±0.04</td>
<td>1.223±0.3</td>
<td>20.02±0.4</td>
<td>29.54±0.5</td>
</tr>
<tr>
<td>F3</td>
<td>0.320±0.12</td>
<td>0.332±0.05</td>
<td>1.201±0.2</td>
<td>19.04±0.3</td>
<td>30.19±0.5</td>
</tr>
<tr>
<td>F4</td>
<td>0.430±0.44</td>
<td>0.412±0.03</td>
<td>1.141±0.1</td>
<td>20.04±0.4</td>
<td>31.08±0.5</td>
</tr>
<tr>
<td>F5</td>
<td>0.332±0.22</td>
<td>0.430±0.05</td>
<td>1.321±0.6</td>
<td>21.11±0.5</td>
<td>29.31±0.5</td>
</tr>
<tr>
<td>F6</td>
<td>0.274±0.05</td>
<td>0.441±0.02</td>
<td>1.321±0.6</td>
<td>18.05±0.2</td>
<td>28.33±0.5</td>
</tr>
</tbody>
</table>

Post- evaluation parameters

Table 3: post evaluation parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Average weight (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability(%)</th>
<th>Content Uniformity(%)</th>
<th>Disintegration time (sec)</th>
<th>Wetting time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>500±2.33</td>
<td>7.66±2.51</td>
<td>1</td>
<td>0.495±0.021</td>
<td>98.3</td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td>F2</td>
<td>500±2.33</td>
<td>8.66±2.08</td>
<td>1</td>
<td>0.505±0.007</td>
<td>100.01</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>F3</td>
<td>501±2.35</td>
<td>10.66±2.08</td>
<td>1</td>
<td>0.495±0.007</td>
<td>98.5</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>F4</td>
<td>498±2.23</td>
<td>16.33±4.61</td>
<td>1</td>
<td>0.525±0.007</td>
<td>100.02</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>F5</td>
<td>492±2.10</td>
<td>14.66±3.13</td>
<td>1</td>
<td>0.542±0.014</td>
<td>98.6</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>F6</td>
<td>501±2.33</td>
<td>16.33±4.61</td>
<td>1</td>
<td>0.525±0.007</td>
<td>100.01</td>
<td>4</td>
<td>25</td>
</tr>
</tbody>
</table>

**FIGURE 5: Comparision of wetting time**
Dissolution profile

Table 4: Dissolution profile

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>56.42</td>
<td>66.34</td>
<td>73.43</td>
<td>46.32</td>
<td>53.43</td>
<td>62.53</td>
</tr>
<tr>
<td>10</td>
<td>63.57</td>
<td>71.90</td>
<td>88.45</td>
<td>56.95</td>
<td>62.89</td>
<td>71.82</td>
</tr>
<tr>
<td>15</td>
<td>75.24</td>
<td>92.56</td>
<td>99.01</td>
<td>64.37</td>
<td>75.21</td>
<td>85.90</td>
</tr>
<tr>
<td>30</td>
<td>91.06</td>
<td>100.0</td>
<td>100.02</td>
<td>76.56</td>
<td>87.12</td>
<td>92.31</td>
</tr>
</tbody>
</table>

DISCUSSION

In the present study, an attempt has been made to formulate and evaluate sublingual tablets of gabapentine by direct compression technique. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose and for post compression parameters such as hardness, weight variation, drug content uniformity, wetting-time, water absorption ratio disintegration time and invitro dissolution studies.

Pre-compression parameters of blends

The bulk density of pre-compression blends was found to be in the range of 0.264 to 0.430 g/cc, tapped density in the range of 0.332 to 0.441 gm/cc, the Carr’s index values were in the range of 18.05% to 21.19%, Hausner’s ratio in the range of 1.141 to 1.321% and angle of repose between 28.33% to 31.08%. All the values were found to be within the prescribed limits according to the I.P, thus ensuring good flow properties to the formulation blends.

Post compression parameters

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 7.66 to 16.33 kg/cm². The friability and thickness values were found to be in the range of 0.495 to 0.542% and 0.98 to 1.10% respectively, which was found to be according to the I.P limits and thus ensuring good mechanical strength to all the formulations.

Uniformity of weight

All the prepared mouth dissolving tablets of gabapentin were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits.
Uniformity of drug content
The values indicate uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 98.3 to 100.02%.

Disintegration time, wetting time and water absorption ratio
Among the tablets prepared, F3 formulation was found to be promising and has shown an average disintegration time of 0.4 sec, wetting time of 30 sec which was found to be within the IP limits.

In vitro dissolution study
In vitro dissolution studies were performed in 0.1N HCl buffer maintained at a temperature of 37±0.5°C at an RPM of 100 in a USP II apparatus. The absorbance’s were noted at 221 nm. The dissolution results showed a gradient increase with the increase in the concentration of the superdisintegrants. Among all the formulations, F3 was found to show best results with 100.02% release within 30 mins.

CONCLUSION
The concept of formulating Sublingual tablets containing gabapentin offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability.

Many patients find it difficult to swallow tablets and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Sublingual tablets formulation. In the present work, Sublingual tablets of gabapentin were designed with a view to enhance patient compliance. Different batches of formulations were prepared using such as superdisintegrants namely, crospovidone, crosscarmellose sodium were used. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, in vitro dispersion time.

Among the promising formulations, the formulation F3 emerged as the overall best formulation based on drug release characteristics, which showed 100.02% release of drug in 30 min when compared other super disintegrants. The main evaluation for a Sublingual tablet
is the invitro dispersion time or disintegration time which was found to be the least (4 sec) for F3- formulation when compared to all the other formulations. IR-spectroscopic studies indicated that there are no drug-excipient interactions.

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REFERENCES