AN INVESTIGATION ON EFFECT OF VARIOUS HYDROPHILIC POLYMERS ON MATRIX TABLETS OF DESVENLAFAXINE SUCCINATE

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ABSTRACT
The aim of the present research work is to develop sustained release matrix formulations of desvenlafaxine succinate and to investigate the effects of hydrophilic polymers on in vitro drug release. Matrix tablets were prepared by wet granulation method employing different types and levels of polymers viz. sodium alginate, methyl cellulose, hydroxypropyl methylcellululose (HPMC) K15M, HPMC E50LV. The granules were evaluated for angle of repose, density, compressibility index and Hausner’s factor, showed satisfactory results. Compressed tablets were evaluated for thickness, friability, hardness, uniformity of weight, content of active ingredient, swelling and in vitro dissolution studies. FT-IR spectra revealed that there were no interaction between drug and polymers. All the formulation showed compliance with pharmacopoeial standards. It was observed that formulation containing 40% of HPMC K15M exhibited the best release profile and able to sustain the drug release for 9 h. The studies indicated that the drug release can be modulated by varying concentrations of polymers. The formulations were subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. Swelling study suggested that when the matrix tablets come in contact with the dissolution medium, they take up water and swells, forming a gel layer around the matrix. It was also dependent on viscosity of polymers. The release data were fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas, first-order and zero-order to evaluate the release kinetics and mechanism of the drug release found to be diffusion coupled with erosion.

Keywords: Desvenlafaxine succinate, Matrix tablets, Sustained/Controlled release, Hydroxypropyl methylcellululose.

INTRODUCTION
In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. The reduced side effects and lower frequency of administration of extended release (ER) tablets represents increased comfort and improved patient compliance and more reliable intake, which is especially important for patients which are subject to a chronic medication regimen. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, ease of scale-up and process validation. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies. During the past two decades, hydrophilic polymers and especially celluloses have been extremely popular in controlling the release rate of soluble drugs from solid dosage forms. The ease of compression, their ability to accommodate large amounts of drugs and the minimum influence of the processing variables on the release rates are the main reason for their popularity. A new focus has been directed towards investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix excipients to retard drug release. A serotonin-norepinephrine reuptake inhibitor (SNRI), desvenlafaxine succinate (DVS) for the treatment of adult patients with major depressive disorder (MDD). After oral administration, desvenlafaxine reaches $t_{max}$ in 7 to 8 h and is slowly eliminated, with $t_{1/2}$ values of 9 to 15 h. With once-daily dosing, steady-state plasma concentrations are achieved within 4 to 5 days. Therefore development of sustained release dosage form of desvenlafaxine in the form of tablets to be taken once daily is necessary.

Therefore, this work aims at investigating different types and levels of hydrophilic matrixing agents, including methylcellulose (MC), sodium alginate (SA), hydroxypropyl methylcellululose (HPMC) E50LV, HPMC K15M in an attempt to formulate sustained-release matrix tablets containing 50 mg desvenlafaxine succinate and to investigate how polymer characteristics may influence drug release from these systems.

MATERIALS AND METHODS

Materials
Desvenlafaxine succinate was procured from Ami Life Sciences, Baroda. Sodium alginate (viscosity 45 cps), Methylcellulose (350-450 cps), HPMC E50LV were purchased from LobaChemie, Mumbai. HPMC K15M was procured from Yarrow chem. Products, Mumbai. Isopropyl alcohol, lactose, magnesium stearate and talc were obtained from Lobachemie.

Methods
Drug-excipients interaction
This was carried out to find out the compatibility between the drug (DVS) and the polymers such as sodium alginate, methylcellulose, HPMC E50LV, HPMC K15M. 10 mg of
sample and 400 mg of potassium bromide were taken and triturated. A small amount of the triturated sample was taken into a pellet making disc and was compressed using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm\(^{-1}\) to 400 cm\(^{-1}\) in FT-IR spectrophotometer (Alpha, Bruker). Samples were prepared for drug desvenlafaxine and the physical mixtures of drug and polymers. The spectra obtained were compared and interpreted for the functional group peaks.

**Formulation of matrix tablets of desvenlafaxine succinate**

Different matrix tablet formulations as described in Table 1 were prepared by wet granulation technique using various hydrophilic polymers. All the powders were passed through B.S.S. sieve No. 60 and deagglomerated.

**Required quantities of drug, polymer and diluents were mixed thoroughly, and a sufficient volume of granulating agent (isopropyl alcohol and/or water) was added slowly. After enough cohesiveness was obtained, the mass was sieved through B.S.S. 12 No. mesh, dried at 60 °C for 1 h. Once dried, the granules were again sieved through sieve No. 16/44 to obtain almost uniform sized granules. The granules retained on sieve No. 44 were mixed with 15% of fines (granules that passed through sieve No. 44). Talc and magnesium stearate (1% w/w of dried granules) were finally added as glidant and lubricant. The granules were compressed into tablets using hydraulic 10 station rotary tablet press machine (Rimekminipress I, Karnavati, Ahmedabad) equipped with flat faced punches of 8 mm diameter. All the tablets were weighed 200 mg containing 50 mg of DVS.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVS</td>
<td>SA4, SA6, SA8, MC4, MC6, MC8, HLV4, HLV6, HLV8, HK4, HK6, HK8</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>50, 60, 80</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>-</td>
</tr>
<tr>
<td>HPMC E50LV</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>106, 66, 66</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>-</td>
</tr>
<tr>
<td>Water</td>
<td>q.s.</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2, 2, 2</td>
</tr>
<tr>
<td>Talc</td>
<td>2, 2, 2</td>
</tr>
<tr>
<td>Total weight</td>
<td>200, 200, 200</td>
</tr>
</tbody>
</table>

*All quantities are in mg; q.s. indicates quantity sufficient*

**Table 1: Composition of desvenlafaxine succinate matrix tablets**

**Evaluation of granules**

**Angle of Repose**

The angle of repose of granules was determined by the funnel method according to the method reported by Raghuram et al\(^7\). The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation\(^8\).

\[
\tan \theta = \frac{h}{r}
\]

Where 'h' and 'r' are the height and radius of the powder cone respectively.

**Bulk Densities**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by a method reported by Raghuram et al\(^7\). A weighed quantity of granules from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula\(^9\).

\[
\text{LBD} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the packing}}
\]

\[
\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}
\]

**Carr’s Compressibility Index**

Carr’s index is a one-point determination and does not always reflect the ease or speed with which the powder consolidates. The compressibility index of the granules was determined by Carr’s compressibility index\(^10\).

\[
\text{Carr’s index} \% = \left( \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \right) \times 100
\]

**Hausner’s Factor**

Hausner found that the ratio TBD/LBD was related to interparticle friction and as such, could be used to predict powder flow properties\(^11\).

\[
\text{Hausner’s factor (H.F.)} = \frac{\text{TBD}}{\text{LBD}}
\]
Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness screw gauge. Five tablets from each batch were randomly selected, evaluated, and their values were reported in millimeters. The average mean and SD were calculated.

Weight Variation Test

To study weight variation, randomly selected 20 tablets from each formulation were weighed individually using an electronic balance (AR2130, Ohaus Corp.) and the test was performed according to the official method. The percentage deviation from average weight was reported.

Hardness

For each formulation, the hardness of six randomly selected tablets was determined by a Monsanto hardness tester (Campbell electronics). The force of fracture is recorded and values were reported in Kg/cm². The average mean and SD were calculated.

Friability

Six tablets from each formulation were randomly selected, weighed together, and then placed in the friabilator chamber (Campbell electronics). The friabilator was operated for 100 revolutions at 25 rpm. The tablets were then dedusted and re-weighed. The friability was calculated as the percentage weight loss.

% Friability = [(Initial weight-Final weight)/Initial weight] × 100

Drug Content Estimation

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 50 mg drug was extracted with 100 ml of phosphate buffer pH 6.8. The solution was filtered through a filter paper (Whatmann 0.22-μm pore size), properly diluted with phosphate buffer pH 6.8 and then absorbance was measured at 224 nm wavelength using UV spectrophotometer (UV1800, Shimadzu) and the percentage of drug content was calculated.

Swelling Studies

Swelling experiments were conducted on the prepared tablets using USP dissolution apparatus II at rotational speed of 50 rpm at 37°C as per method described by Al-taaniet al. The medium used was 900 ml of phosphate buffer pH 6.8. The tablets were removed using a small basket and swollen weight of each tablet was determined. The percentage of swelling was calculated according to the following formula, where S is the weight of the matrix after swelling and R is the weight of the eroded matrix.

% Swelling = S/R×100

In Vitro Drug Release Studies

In vitro drug release studies were carried out by using USP Dissolution Apparatus II (Paddle type) at 50 rpm. The drug release profile was studied in 900 ml of phosphate buffer pH 6.8 by maintaining at 37 ± 0.5°C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals, filtered, and replaced with another 5 ml of fresh dissolution medium. The amount of drug released was determined by UV spectrophotometer (UV1800, Shimadzu) at 224 nm. The release studies were conducted in triplicate and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results.

Drug Release Kinetics

The kinetics of drug release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction vs. time) to distinct models: zero-order, first-order, and Higuchi. To better characterize the drug release behavior for the polymeric systems studied, namely to understand the corresponding mechanism, the Korsmeyer–Peppas semi-empirical model was applied.

Q/Qt = k·t^n

Where, Qt/Qt is the fraction of drug released at time t; k is a constant comprising the structural and geometric characteristics of the tablet. In addition, for determination of the exponent n, one must use only the initial portion of the curve (Qt/Qt < 0.6). The release exponent n, is a parameter which depends on the release mechanism and is thus used to characterize. For the case of cylindrical tablets, in particular, n = 0.45 corresponds to a Fickian diffusion release (case I diffusional) and non-Fickian (anomalous) release, coupled diffusion and polymer matrix relaxation occurs if 0.45<n<0.89, purely matrix relaxation or erosion-mediated release occurs for n=0.89 (zero order kinetics) and super case II type of release occurs for n>0.89. The release exponent, ‘n’ is the slope of log fraction of drug release vs. log time curve.

Stability studies

The optimized formulation was subjected to stability studies as per ICH guidelines at 40 ± 2°C and 75 ± 5 % RH in a stability chamber (LPC-170G, Labtop Instruments) for a period of six months and at room temperature (25 ± 2°C) in a desiccator. After each month tablet sample was analyzed for physical characteristics and percentage drug content.

RESULTS AND DISCUSSION

The supplied drug passed the various tests of identification and analysis. The pure drug (Desvenlafaxine succinate) and the solid admixture of drug and various polymers used in the preparation of matrix tablet formulations were characterized by FTIR spectroscopy to know the compatibility (Figure 1-S). Granules of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner factor.
The results of angle of repose and compressibility index (%) ranged from (26.98° to 30.81°) and (11.10 to 19.11), respectively in Table 2. The results of loose bulk density and tapped bulk density ranged from (0.321 to 0.490) and (0.397 to 0.583), respectively. The results of angle of repose (<30°) indicate good flow properties of granules. This was further supported by lower compressibility index values. Further, compressibility index values up to 20% result in good to excellent flowability and compressibility. Hausner factor values ranged from 1.124 to 1.236. Hausner showed that granules with low interparticle friction had ratios of approximately 1.2 compared to powders. This indicates good flow properties of the prepared granules as a result of increasing particle size owing to granulation eliminating cohesiveness.

The physical properties of different batches of developed matrix tablets are given in Table 3. The thickness of the prepared tablets was uniform and ranged from 2.434±0.069 mm to 2.878±0.070 mm. Also, it was observed that increasing polymer concentrations resulted in a slight increase in the thickness of the tablet formulations. These results might indicate that the polymers had low binding properties.
Table 3: Evaluation of matrix tablets of desvenlafaxine succinate

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness* (mm)</th>
<th>Hardness** (kg/cm²)</th>
<th>Friability (%)</th>
<th>% Weight Variation*</th>
<th>% Drug Content*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA4</td>
<td>2.528±0.085</td>
<td>5.20±0.15</td>
<td>0.50</td>
<td>1.713±1.11</td>
<td>97.76±0.24</td>
</tr>
<tr>
<td>SA6</td>
<td>2.642±0.063</td>
<td>4.83±0.13</td>
<td>0.57</td>
<td>2.816±1.68</td>
<td>99.88±0.97</td>
</tr>
<tr>
<td>SA8</td>
<td>2.734±0.106</td>
<td>4.73±0.18</td>
<td>0.61</td>
<td>2.421±1.37</td>
<td>96.19±0.33</td>
</tr>
<tr>
<td>MC4</td>
<td>2.482±0.081</td>
<td>5.53±0.13</td>
<td>0.68</td>
<td>2.411±1.48</td>
<td>100.52±0.79</td>
</tr>
<tr>
<td>MC6</td>
<td>2.526±0.060</td>
<td>5.95±0.18</td>
<td>0.64</td>
<td>2.317±1.25</td>
<td>97.89±0.61</td>
</tr>
<tr>
<td>MC8</td>
<td>2.570±0.074</td>
<td>5.88±0.13</td>
<td>0.66</td>
<td>2.271±1.09</td>
<td>96.71±0.24</td>
</tr>
<tr>
<td>HLV4</td>
<td>2.630±0.050</td>
<td>5.23±0.19</td>
<td>0.57</td>
<td>1.998±1.42</td>
<td>98.62±0.54</td>
</tr>
<tr>
<td>HLV6</td>
<td>2.760±0.063</td>
<td>5.21±0.25</td>
<td>0.62</td>
<td>2.487±1.61</td>
<td>97.11±0.67</td>
</tr>
<tr>
<td>HLV8</td>
<td>2.878±0.070</td>
<td>5.58±0.19</td>
<td>0.63</td>
<td>2.278±1.43</td>
<td>99.45±0.35</td>
</tr>
<tr>
<td>HK4</td>
<td>2.434±0.069</td>
<td>6.43±0.21</td>
<td>0.42</td>
<td>2.017±1.35</td>
<td>100.00±0.65</td>
</tr>
<tr>
<td>HK6</td>
<td>2.662±0.078</td>
<td>6.28±0.25</td>
<td>0.44</td>
<td>2.518±1.41</td>
<td>98.93±0.98</td>
</tr>
<tr>
<td>HK8</td>
<td>2.856±0.086</td>
<td>6.15±0.12</td>
<td>0.45</td>
<td>2.495±1.27</td>
<td>99.67±0.54</td>
</tr>
</tbody>
</table>

*All values expressed in mean ± SD, n=5; ** All values expressed in mean ± SD, n=6; ^ All values expressed in mean ± SD, n=20

Table 3: Drug release kinetics of different formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero-order Plots (R²)</th>
<th>First-order Plots (R²)</th>
<th>Higuchi’s Plots (R²)</th>
<th>Korsmeyer-Peppas Plots slope (n)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA8</td>
<td>0.9472</td>
<td>0.8936</td>
<td>0.9963</td>
<td>0.53</td>
<td>0.9752</td>
</tr>
<tr>
<td>MC8</td>
<td>0.9556</td>
<td>0.8981</td>
<td>0.9842</td>
<td>0.45</td>
<td>0.9909</td>
</tr>
<tr>
<td>HLV8</td>
<td>0.9474</td>
<td>0.8673</td>
<td>0.9939</td>
<td>0.46</td>
<td>0.9608</td>
</tr>
<tr>
<td>HK8</td>
<td>0.9593</td>
<td>0.9201</td>
<td>0.9955</td>
<td>0.51</td>
<td>0.9882</td>
</tr>
</tbody>
</table>

The average percentage deviation of 20 tablets of each formulation was less than (±7.5 %), and hence all formulations passed the test for uniformity of weight. Hardness of the tablets fell into the range 4.73 ± 0.18 kg/cm² to 6.43 ± 0.21 kg/cm². The hardness of tablets made of sodium alginate found to be lowest, while of HPMC K15M found to be highest. This may be due to the different binding nature of the polymer. These results were in good agreement with those of thickness and friability. Tablet hardness is not an absolute indicator of strength[11]. Friability of each formulation ranged from 0.42% to 0.68% indicating that the friability is within the prescribed limit of 1% according to European and US pharmacopoeia. It was found that the friability of the prepared tablets increased by increasing the polymer level. Also, MC based tablets showed more friability which may be due to the low binding properties of polymer and these findings are similar with the results of thickness measurements. The values of percentage drug content were found to be uniform and ranged from 96.19 ± 0.33 % to 100.52±0.79%. The percentage swelling of formulation SA8 prepared with sodium alginate at the end of 7 h was found to be 315.20% while of HK8 prepared with HPMC K15M was found to be 391.89% (Figure 6). HPMC based tablets exhibited relatively faster water uptake (swelling) than sodium alginate based tablets. This indicates that the swelling of polymer is dependent on the viscosity of polymer.
The drug was released from the matrix tablets of desvenlafaxine succinate prepared by different formulations showed in Figure 7 and Figure 8. A perusal of Figure 7, the drug release rate from formulations containing 20%, 30% and 40% of sodium alginate released ~80% of the drug over 3, 4.5, 6.5 h respectively. A perusal of Figure 8, drug release from HPMC based matrix tablets showed good release retarding efficiency as ~80% of the drug was released from HLV8 and HK8 over 6 and 7.5 h respectively. The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusional area at lower viscosity as compared with higher viscosity grades of HPMC22. Whereas MC based matrix tablets exhibited significantly lower drug release-retarding efficiency than the other hydrophilic polymers for the same polymer level. This may be attributed to the lower binding property of methylcellulose than the other hydrophilic polymers. Formulations that contained the lower concentration of each polymer, failed to control the release of drug. An increase in the polymer proportion resulted in the increased viscosity of the tablet matrix gel layer as well as the formation of a gel layer with a longer diffusional path. This phenomenon resulted in the decreased effective diffusion of the drug and therefore a reduction in the drug release rate22,23. The above data clearly indicate that the drug release can be effectively controlled by varying the polymer and its ratio. To know the mechanism of drug release from these formulations, the data were treated according to first-order, Higuchi’s and Korsmeyer et al’s equations along with zero order pattern. The regression co-efficients for different prepared formulations obtained for zero-order kinetic were found to be 0.9472 to 0.9593. To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs. square root of time as per Higuchi’s equation were constructed. These plots were found to be linear (R²: 0.9842 to 0.9963) with all the formulations. To confirm the diffusion mechanism, the data were treated according to first-order, Higuchi’s and Korsmeyer et al’s equation. The formulations showed good linearity (R²: 0.9608 to 0.9909) with slope (n) values ranging from 0.45 to 0.53 indicating that the diffusion is the dominant mechanism of drug release with these formulations. The n value, however, appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous (non-fickian) diffusion.

**CONCLUSION**

The matrix tablets were found to be effective in sustaining the drug release up to 9 h prepared with 40%w/w of HPMC K15M and found that concentration of polymer had significant effect on drug release. Drug release was found to be diffusion coupled with erosion with zero order kinetics. Stability studies revealed that there was no significant change in drug content of matrix tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between DVS and other ingredients used. It can be concluded that stable formulation could be developed by incorporating various hydrophilic polymers in a definite proportion. So that the sustained released profile is maintained for an extended period of time.

**REFERENCES**


