FORMULATION AND EVALUATION OF ONCE DAILY NIAacin EXTENDED RELEASE MATRIX TABLETS

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ABSTRACT

The present study was aimed to develop once daily extended release matrix tablets of Niacin using various polymers like Guar gum, Hydrogenated Castor oil (Cutina HR) individually and combination of both these polymers in different proportions. Guar gum and Hydrogenated Castor oil (Cutina HR) were selected as hydrophilic and hydrophobic matrix former respectively. The formulated tablets were also compared with a marketed product. The results of the dissolution study indicate that formulation N5 showed maximum drug release upto 24 h that is similar to reference product. In case of formulations containing combination of Guar gum and Hydrogenated Castor oil (Cutina HR), the release of the drug was found to be dependent on the relative proportions of hydrophilic and hydrophobic polymers used in the tablet matrix.

Keywords: Niacin, Guar gum, Hydrogenated castor oil (Cutina HR), extended release, matrix tablets.

INTRODUCTION

Niacin (nicotinic acid) is a highly water-soluble vitamin, which has been used as a lipid-lowering agent and is rapidly absorbed from the human GI tract. Delayed and slow-release formulations of nicotinic acid were originally developed to reduce or eliminate unwanted effects such as gastrointestinal disturbances, gastric irritation, and flushing of the skin, it was distinctly shown that slow absorption resulted in hypocholesterolemic effect in a well-controlled clinical trial. Furthermore, it was shown that inhibition of very low density lipoprotein (VLDL) and subsequent reduction in LDL levels in the plasma of patients with a variety of hyperlipoproteinemias were related to prolonged exposure rather than high plasma levels of nicotinic acid. For Niacin, the high load (500 mg) and high water solubility aspects (1.7% at 25_C; pKa = 4.8; MW= 123.11) are challenging in terms of formulation development, especially using simple matrix technology for once-a-day controlled-release delivery. The drug is
freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug.\textsuperscript{[1-2]}

The matrix tablets composed of drug and the release retarding material (polymer), offers the simplest approach in designing an extended-release system.\textsuperscript{[3]} Number of studies shows the use of hydrophilic matrices to formulate the controlled release dosage forms of different drugs.\textsuperscript{[4-8]} Because of their simplicity and cost-effectiveness, hydrophilic gel matrix tablets are widely used for oral controlled release dosage forms. Hydrophilic polymers form a gel like structure around the tablet core which controls the drug release. The use of hydrophilic polymer alone for controlling the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Use of hydrophobic polymers will retard the drug release of such drugs with high water solubility. Thus hydrophobic polymers are suitable, along with a hydrophilic matrix for developing extended-release dosage forms.\textsuperscript{[9]}

Hence, in the present work, an attempt has been made to develop extended-release matrix tablets of niacin using putative hydrophilic matrix materials such as Guar gum, alone and in combination with the Hydrogenated castor oil (Cutina HR) as the hydrophobic polymer, and to study the in vitro release characteristics. The prepared formulations were also compared with a marketed product (MP) (Niaspan) which contained HPMC K15M as the matrix material.\textsuperscript{[10-11]}

MATERIALS AND METHODS:

Niacin USP was a gift sample from Cadila Healthcare Ltd. Guar gum was obtained as gift sample from S.D. Fine Chem. Ltd. Hydrogenated Castor oil was obtained as gift sample from Signet chemicals. Stearic acid and polyvinylpyrrolidone (PVP-K90) were gifted by Mallinckrodt and ISP technologies. Opadry yellow was gifted by Colorcon Asia Pvt. Ltd. All other ingredients used throughout the study were of analytical grade and were used as received.

Preparation of matrix tablets:

Different tablet formulations (Batch size of 100 tablets) were prepared by wet granulation technique i.e. F-I to F-V (Table 1). Accurately weighed quantities of pre-sieved drug, and matrix material (Guar gum and Hydrogenated castor oil) were mixed
uniformly, and wetted with 10% w/v solution of PVP in IPA as granulating fluid, the cohesive mass thus obtained was screened through a sieve No. 18. The granules were air dried at room temperature in an enclosure to protect it from light. The coarse granules so obtained were once again screened using the same sieve. Stearic acid was finally added as anti-frictional agents to the uniformly sized granules and the granules were compressed (17.5 mm diameter, biconvex punches) using a single punch tablet compression machine (Cadmach, Ahmedabad). Each tablet contained 500 mg of niacin and other excipients as listed in Tables 1. Prior to compression, the granules were evaluated for various IPQC tests.

**TABLE 1: COMPOSITION OF EXTENDED RELEASE MATRIX TABLETS OF NIACIN**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>N4</th>
<th>N5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Guar gum</td>
<td>200</td>
<td>-</td>
<td>150</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Hydrogenated castor oil (Cutina HR)</td>
<td>-</td>
<td>200</td>
<td>50</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>PVP K-90</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

**Evaluation of Granules:**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of granules from each formulation, previously lightly shaken to break any agglomerates, 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. After 300 taps, the tapped volume of packing was noted. LBD and TBD were calculated using the formulae; LBD= weight of the powder/volume of the packing, TBD= weight of the powder/tapped volume of the packing.\(^{[12]}\)
The compressibility index of the granules was determined by Carr’s compressibility index \(^{13}\); Carr’s index (%) = \([(TBD-LBD)\times100]/TBD\). The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel, which was maintained at 4 inches from the surface. 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 equation \(^{14}\); \(\tan \theta = \frac{h}{r}\), \(\theta = \tan^{-1}(h/r)\), where \(\theta\) is the angle of repose, \(h\) is height in cm of the powder cone and \(r\) the radius in cm of the powder cone.

Evaluation of matrix tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, diameter, friability and drug content. Tablet hardness was determined for 10 tablets using a Dr. Schleunizer hardness tester (Pharmaton, USA). The weight variation was evaluated on 20 tablets using an electronic balance (Mettler Tolendo PG 403-S, USA), and the test was performed according to the official method \(^{15}\). The thickness and diameter was determined for 10 tablets with the help of a digital Vernier calliper (Mitutoyo, USA). Friability was determined taking 20 tablets in a Roche friabilator (Electrolab, Mumbai) for 4 min at 25 rpm. Drug content of the matrix tablets was determined by weighing and finely grinding 10 tablets of each batch. Aliquot of this powder equivalent to 500 mg of Niacin was accurately weighed, suspended in approximately 100 ml of distilled water and shaken for 15 min. and filtered. The final volume was made by taking 1 ml of above solution and diluted to 100 ml with distilled water. Absorbance of this solution was recorded at 262 nm using UV/Vis spectrophotometer (UV-1700 Shimandzu Co., Japan) against a reagent blank and the content was compared from a calibration curve prepared with standard Niacin in the same medium.

In vitro release rate studies:

The in vitro release rate studies were carried out in USP dissolution test apparatus Type I (Electro lab, Mumbai) in simulated gastric fluid (pH 1.2±0.1) from 0 to 2 h and simulated intestinal fluid (pH 7.2±0.1) from 2 to 24 h. Rotation speed of 50 rpm at temperature of 37±0.5°C and dissolution medium of 900 ml was maintained throughout the experiment. At predetermined time intervals, 10 ml of sample was
withdrawn and replaced with the same volume pre-warmed (37±0.5°C) fresh dissolution medium. The samples withdrawn were filtered through 0.45 μm membrane filters, and drug content in each sample was analyzed after suitable dilution by UV/Vis spectrophotometer at 262 nm. The actual content in samples was read from a calibration curve prepared with standard Niacin. All dissolution studies were carried out in duplicate and repeated at least thrice. The same was carried out on marketed product for comparative evaluation.

RESULTS AND DISCUSSION

Formulation of granules is the key factor in the production of tablet dosage form involving extended release of drug from matrix type particle. Physical parameters such as area, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a complex system. The selection of wet granulation technique for matrix tablet preparation was based on previously reported study which suggested that wet granulation results in harder tablets with lower matrix porosity that give very low release rates when compared to direct compression. In our study 10% PVP in IPA was used as granulating agent. Non-aqueous granulating fluid was used, since it was thought to avoid the use of water and heat during drying of granules.

The granules of different formulations were evaluated for LBD, TBD, compressibility index, angle of repose and moisture content. The LBD and TBD of granules ranged from 0.24±0.07 to 0.36±0.05 g/ml and 0.28±0.03 to 0.39±0.04 g/ml respectively. The compressibility index values ranging from 7.62±2.12 to 14.28±0.78. Generally, compressibility index values up to 15% result in good to excellent flow properties, but readings above 25% indicates poor flow ability. Angle of repose values of all formulations ranged from 24.98±0.15° to 36.67±0.27°. Generally values of angle of repose are rarely less than 20° and values up to 40° indicate reasonable flow properties. All these results indicate that the formulated granules possessed satisfactory flow properties and compressibility. The moisture content of all formulations was found to be satisfactory.

The results of hardness and friability of the prepared matrix tablets ranged from 11.0±0.35 to 13.0±0.21 kg/cm² and 0.27±0.03% to 0.40±0.07%, respectively. The tablet formulations in all the prepared batches contained Niacin ranging from
97.76±1.12% to 103.22±0.74%. As such, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content. The results of thickness of tablets ranged from 6.38 ± 0.07 to 7.85 ± 0.03mm. Thus all formulations showed uniform thickness. Weight variation results of the matrix tablets ranged from 748±1.19 to 753±1.70 mg. The average percentage deviation of all tablet formulations was found to be within the above limit, in compliance with official standards.

Figure 1 shows the invitro drug release of batch N1 and N2 containing guar gum (200mg) and cutina HR (200mg) as a release modifying agents respectively. From the result, it was observed that 62.6% drug was released within 24hrs from the formulation N1 and 100% drug was released within 12hrs from the formulation N2. It indicates that release of drug from N1 is slower and N2 is faster than the reference product.

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. Therefore to control the release of drug further, combination of both polymers were used in the next batches. In formulation N3 and N4, mixture of Guar gum : cutina HR was used in the ratio of 3:1 and 1:3 respectively. Figure 2 shows the comparison of invitro drug release of batch N3 and N4 with reference product.
As the concentration of Guar gum decreases and Cutina HR increases in formulation N3, drug release was increased due to the fast release property of Cutina HR. The combination of both polymers extends the drug release upto 24hr but the drug release was only 82%. So, further change in ratio of polymers has been required to achieve maximum drug release compare to reference product. Thus, in formulation N5 1:1 polymer ratio was taken and invitro drug release has been carried out. The results (Figure 3) indicate the 100% of the drug release within 24 hrs in the dissolution medium.
CONCLUSION

In present study attempt were made to formulate 500mg extended release once daily formulation, which can provide effective drug release for 24 hours. Niacin Extended Release matrix tablets were prepared by wet granulation method. In vitro study showed Batch N5 was well suited to extended release formulation.

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References:


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