USE OF NATURAL GUMS IN FORMULATION OF CONTROL RELEASED THEOPHYLLINE TABLET

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ABSTRACT

Matrix tablets were prepared using blends of xanthan gum (XG) and Guar gum (GG). Theophylline was used as the model drug. Theophylline controlled release (CR) powder mixtures were prepared and evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausner’s ratio. All the formulation showed good flow properties. The compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and in vitro dissolution studies. All the formulations showed compliance with pharmacopoeial standards. Formulations XG1GG1 and XG2GG1 followed non-fickian transport mechanism via diffusion and erosion while XG3GG1 followed fickian diffusion. The results revealed that increased xanthan gum: guar gum ratio retarded and controlled the release of drug from the matrices. Xanthan gum has a higher retarding ability than guar gum. Among all the formulations XG3GG1 (i.e. polymer ratio 3:1) showed prolong release when compared to other formulations.

Keywords: Guar gum, Xanthan gum, Matrix tablets, Theophylline.

INTRODUCTION

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within therapeutic range over prolonged periods. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. 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 and ease of scale-up and process validation.

Theophylline is a methylxanthine derivative and it is very effective in the chronic treatment of bronchial asthma and bronchospastic reaction. Its therapeutic concentration range is narrow from 10 to 20 g/ml while toxicity usually appears at concentration above 20 g/ml. Since theophylline has a narrow therapeutic index, it can be used as a controlled release product to protect asthma patients from frequent attacks and to prevent toxic side effects.

Developing oral controlled-release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally.

Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Guar gum is a natural nonionic polysaccharide derived from the seeds of Gymnopus tetragonolobus (Family Leguminosae). In pharmaceuticals, Guar gum is used in solid dosage forms as a binder and disintegrant. Xanthan gum is another natural, biosynthetic, edible gum and an extracellular polysaccharide produced by the bacterium Xanthomonas campestris. Xanthan gum consists of glucose, mannose, and glucuronic acid and is used in different foods as thickener and stabilizer.

The objective of this study was to develop matrix controlled-release tablets of theophylline using natural gums (xanthan and guar gum) as suitable hydrophilic matrix systems to deliver the drug continuously with set limits of dissolution profile.

MATERIALS AND METHODS

Theophylline, Guar gum and xanthan gum were all purchased from Sigma Aldrich, USA. Lactose monohydrate and magnesium stearate were procured from BDH, England. All other chemicals used were of analytical grade.

Preparation of controlled release matrix tablets

The polymers (Guar gum, Xanthan gum) were included in the formulation in various combination ratios 1:1 (XG1GG1), 1:3 (XG2GG1) and 3:1 (XG3GG1). The drug was geometrically blended with sufficient quantity of lactose and the various polymers as stated in the formula in Table 1, using pestle and mortar. Mixing was maintained for 10 minutes and the powder mixtures stored in well-closed specimen bottles.

Direct compression method was used. Before each compression, the die (12 mm in diameter) and flat faced punches were lubricated with a 1% w/v dispersion of magnesium stearate in chloroform. Compression was achieved using a single punch tableting machine (THP Shangai, Tianxiang and Chentai Pharmaceutical Machinery Co.Ltd. China) fitted with flat-faced punches and compressed to a target weight of 500 ± 10 mg. Each drug compacts were stored in airtight specimen bottles and allowed to equilibrate 24 hours before further evaluations.

Table 1: Composition of Theophylline CR matrix tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>XG1GG1</th>
<th>XG2GG1</th>
<th>XG3GG1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>XG (mg)</td>
<td>100</td>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>GG (mg)</td>
<td>100</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>Lactose (mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Key: XG = Xanthan gum, GG = Guar gum

Evaluation of powder mixtures

The powder mixtures were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner’s ratio for micromeritic properties.

Evaluation of tablets

The formulated tablets were evaluated for thickness and diameter using a vernier caliper, hardness test using Monsanto hardness tester and friability using Roche friabilator. For weight
variation test\(^{14}\). 20 tablets of each formulation were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation. The results were expressed in table-3. For content uniformity test\(^{15}\), ten tablets were powdered in a mortar. The powder equivalent to 100mg of theophylline was weighed and transferred to 100ml volumetric flask. It was dissolved in pH 7.4. From this appropriate dilution were made and the absorbance was analyzed at 277nm using UV spectrophotometer.

**In-vitro release studies**

Drug release studies were carried out using USP dissolution rate apparatus (Apparatus 1, 100rpm, 37\(^{\circ}\)C) for the first 2h in pH 1.2 simulated gastric fluids (SGF) without enzymes (500ml). Then the dissolution medium was changed to pH 7.4 simulated intestinal fluid (SIF) without enzymes (500ml) and tested for drug release for the remaining 6h. 5ml aliquots of the dissolution medium were withdrawn at hourly intervals up to at least 8h. The withdrawn amount was replaced with an equal volume of fresh dissolution medium kept at 37\(^{\circ}\)C. The withdrawn samples were suitably diluted with pH 7.4 and analyzed at 277nm as blank in a Shimadzu UV Spectrophotometer (Shimadzu, Japan). For each dissolution profile, the release data was analyzed after three repeats.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, the results of invitro release profile were plotted in various kinetic models like zero order, first order, higuchi model and korsmeyer – peppas\(^{18}\).

**Results and Discussion**

The powder mixtures of all the formulations were evaluated for angle of repose, bulk density, tapped density, and compressibility index and hausner ratio. The angle of repose was found to be 33 – 34\(^{\circ}\). It indicates that powder mixtures have a good flow property. The bulk density and tapped density was found to be in the range of 0.395– 0.415 gm/cc and 0.435 - 0.462 gm/cc respectively. The compressibility and hausner ratio was found to be 8.2 to 13.42 and 1.1 to 1.16 indicating good flow character of the powder mixtures (table-2). All the results are within the prescribed limits\(^{14}\).

The hardness of the tablets for all the formulations was in the range of 5-7 kg/cm\(^{2}\). The uniformity weight of 20 tablets of all the formulations was within 5% deviation. The friability of all the formulations was less than 1%. Drug content of all the formulations were found to be in the range of 96 to 99 % (table-3). All the results are within the prescribed limits\(^{14}\).

### Table 2: Evaluation of theophylline controlled release matrix powder mix

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation</th>
<th>XG(_1)G(_1)G</th>
<th>XG(_1)G(_3)G</th>
<th>XG(_3)G(_1)G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose (0)</td>
<td>32 ± 1</td>
<td>34 ± 1</td>
<td>33 ± 2</td>
<td></td>
</tr>
<tr>
<td>Bulk density (gm/cc)</td>
<td>0.65 ± 0.05</td>
<td>0.70 ± 0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapped density (gm/cc)</td>
<td>0.415 ± 0.01</td>
<td>0.395 ± 0.01</td>
<td>0.40 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Compressibility</td>
<td>0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.10 ± 0.04</td>
<td>1.10 ± 0.02</td>
<td>1.16 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>0.05 ± 0.03</td>
<td>0.02 ± 0.02</td>
<td>0.02 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

*All values are expressed as mean ± SD, n=5

The results of the invitro release study for all the formulations are shown in figure-1.

At the end of 8th hours the cumulative percentage drug release for the formulations XG-GG\(_1\), XG-GG\(_3\) and XG-GG\(_1\) were found to be 95, 98 and 60 respectively. Among the three formulations, XG-GG\(_3\) showed prolonged drug release. The controlled drug release may also be due to increased proportion of polymer\(^{19}\).

The release rate kinetic data for all formulations is shown in table-4. When the data were plotted according to zero order, the formulations showed a high linearity with regression co-efficient values (R\(^2\)) between 0.9523 – 0.9942. It showed that the drug release followed zero order\(^{20}\). Diffusion is related to transport of drug from the matrix tablets into the dissolution medium and is concentration dependent. This is explained by Higuchi’s equation. When the data were plotted according to Higuchi’s equations, the regression co-efficient values (R\(^2\)) were between 0.896 – 0.9940.

By using korsmeyer model, the mechanism of drug release was determined. If n < 0.45, it is fickian diffusion and if n = 0.45 - 0.89, it is non-fickian diffusion transport\(^{20}\). The results of all the formulations showed that the n values for XG-GG\(_1\), XG-GG\(_3\) and XG-GG\(_1\) were 0.50, 0.39 and 0.64 respectively. It proved that formulations XG-GG\(_1\) and XG-GG\(_3\) followed non-fickian transport mechanism\(^{20}\) both diffusion and erosion\(^{21}\) while XG-GG\(_1\) followed fickian diffusion.

The results revealed that increased xanthan gum: guar gum ratio retarded and controlled the release of drug from the matrices. Xanthan gum has a higher retarding ability than guar gum.
Table 3: Maximum cumulative release of SAG-formulated Metronidazole tablets

<table>
<thead>
<tr>
<th>Batch</th>
<th>T50 (hrs)</th>
<th>T90 (hrs)</th>
<th>Cmax (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG:GG1</td>
<td>2.5</td>
<td>4.3</td>
<td>95.00</td>
</tr>
<tr>
<td>XG:GG2</td>
<td>1.3</td>
<td>4.0</td>
<td>98.00</td>
</tr>
<tr>
<td>XG:GG3</td>
<td>6.7</td>
<td>-</td>
<td>60.00</td>
</tr>
</tbody>
</table>

Table 4: Kinetics and mechanism of release for formulated theophylline matrix tablets

<table>
<thead>
<tr>
<th>formulation</th>
<th>Zero - order</th>
<th>First - order</th>
<th>Higuchi</th>
<th>Korsmeyer(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG:GG1</td>
<td>0.9866</td>
<td>0.9338</td>
<td>0.994</td>
<td>0.9884 (0.50)</td>
</tr>
<tr>
<td>XG:GG2</td>
<td>0.9942</td>
<td>0.8699</td>
<td>0.988</td>
<td>0.9755 (0.39)</td>
</tr>
<tr>
<td>XG:GG3</td>
<td>0.9523</td>
<td>0.9033</td>
<td>0.896</td>
<td>0.9270 (0.64)</td>
</tr>
</tbody>
</table>

Fig. 1: Release profile of Theophylline tablet batches containing Guar Gum and Xanthan Gum

CONCLUSION

Polymers are frequently used in drug delivery systems. By polymer combinations, formulators may be able to develop sustained release drug dosage forms with better performance than is shown by the individual polymer combinations. Various polymers blends have been studied in order to achieve their desired release kinetics. The presence of more than one polymer may result in spatial configuration, but it is also possible that a polymer additive may become part of a gel network.

Matrix tablets were prepared using blends of Xanthan gum (XG) and Guar gum (GG). Theophylline was used as model drug. The ability of the prepared matrices to control drug release in the gastrointestinal tract (GIT) was evaluated. For this, drug release studies were carried out. The overall rate of release of drug was higher with increased guar gum concentration. These results indicate that Xanthan gum has higher drug retarding ability than Guar gum. Optimum release was observed with formulation XG:GG1.

Results of the present study confirmed that the polymer ratio plays a major role in drug release.

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