ASSESSMENT OF XANTHAN GUM BASED SUSTAINED RELEASE MATRIX TABLETS CONTAINING HIGHLY WATER-SOLUBLE PROPRANOLOL HCL

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Abstract: The present study was carried out to develop oral sustained release tablets of propranolol HCl by different ratios of drug:matrix. Tablets were prepared by direct compression technique using xanthan gum and lactose. All the formulations (tablets) were evaluated for thickness, diameter, hardness, friability, weight variation, content of active ingredient, in vitro dissolution using USP dissolution apparatus-II and swelling index. In case of dissolution, an inverse relationship was noted between amount of xanthan gum and release rate of propranolol HCl and the drug release was gradually enhanced as the amount of the lactose increased. The direct release was observed between swelling index and xanthan gum concentration. Significant difference in different media was observed in release profile, indicating that propranolol HCl has better solubility in HCl buffer pH 1.2. Moreover, dissolution data at differing stirring speeds was also analyzed, indicating that the drug release profile was at 50 rpm comparative to 100 rpm. The kinetic treatment showed the best fitted different mathematical models (zero order, first order, Higuchi’s, Hixson-Crowell and Korsmeyer-Peppas model). Most of the formulations showed linearity in Higuchi’s model. The drug release from these tablets was by Fickian diffusion and anomalous (non-Fickian) mechanisms.

Keywords: Propranolol HCl, matrix tablets, drug release, swelling index and kinetics

Oral route of drug delivery system has been the most expedient due to easy patient adoptability, administration, few sterility constraints and flexibility of its dosage form design. Development of oral controlled release tablets with constant release mechanisms has always been a difficult task for researchers in the field of pharmaceutical technology. Most of these highly water soluble drugs develop rapid and quick release resulting noxious situations for patients and also to manufacturers (1).

Propranolol hydrochloride (PPN) the β-adrenoceptor blocking, anti-anginal, antihypertensive and a secondary amine drug has been selected as a drug candidate for controlled-release dosage forms due to its short half life of 3.9 h to achieve wide therapeutic use. However, many researchers have faced problems in the difficulty to control release due to high aqeous solubility of propranolol hydrochloride (2).

Xanthan gum is a hydrophilic polymer and high molecular weight extracellular hetero-polysaccharide with cellulose like backbone. The primary structure of this naturally occurring polymer consists of 1,4 linked β-D-glucose residues, having a trisaccharide side chain of β-D-mannose-β-D-gluconic acid-α-D-mannose attached to alternate D-glucose units of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain. It has been reported that xanthan gum is a useful candidate for controlled release and provide zero order kinetics. Furthermore, xanthan gum can maintain constant drug plasma levels in vivo (3).

In food, pharmaceutical, cosmetic and technical applications xanthan gum produced by bacteria Xanthomonas campestris is broadly used carbohydrate polymer. In the dilute state it forms viscous solutions, whereas in the dry state it is an amorphous powder (4).

It has been reported that xanthan gum proved a better retarder to drug release than synthetic hydroxypropylmethylcellulose. Xanthan gum and hydroxypropylmethylcellulose were used as hydrophilic matrixing agents for preparing modified release
tablets of diltiazem HCl. In another study, desired release profile by xanthan gum was attained for theophylline delivery and showed capability to drug retard when compared with galactomannan matrices. Zero order release kinetics was observed from xanthan gum (conc. 8%) tablets. Matrix tablets containing metronidazole was reported using xanthan gum and other biopolymers for colon drug delivery (5). Another study revealed that only xanthan gum was found responsible for diffusional controlled release than other polymers (6). It was concluded that by using a suitable blend of hydroxypropylmethylcellulose and xanthan gum desired modified drug release could be achieved (5).

The aim of this paper was to evaluate different formulations of xanthan gum based matrix tablets to provide sustained therapeutic effect of propranolol hydrochloride.

MATERIALS AND METHODS

Propranolol hydrochloride was a gift from GlaxoSmithKline. Xanthan gum was obtained from Hamaz Pharmaceuticals. Lactose and magnesium stearate were obtained from E. Merck. Hydrochloric acid (fuming hydrochloric acid 37% extra pure) was of analytical grade supplied from Scharlau, Spain. Methanol, ethanol, sodium hydrochloride and potassium hydrochloride were of analytical grade obtained from E. Merck.

Preparation of propranolol HCl matrix tablets

Four hundred milligram matrix tablets containing propranolol HCl (dose 80 mg) and other ingredients (Tab. 1) were prepared by direct compression technique. The concentration was kept constant at 20% by weight (80 mg/tablet). The polymeric material was xanthan gum while lactose was as a diluent. Magnesium stearate was integrated as a lubricant. All the ingredients were passed through sieve # 70. To make the powder mixture, the drug, polymer and lactose were mixed with the magnesium stearate of 2% w/w for 5 min.

Tableting

A single punch tableting machine (DP 30 single punch tablet press) was equipped with 11-mm flat-faced punches. The compression force was applied to get a tablet weight of about 400 ± 5 mg. The tablets were compressed in order to obtain 5 to 7 kg hardness. Then, drug blend powder of 400 mg was compressed into a tablet using 11 mm of round, concave punches of single punch machine. The tablets containing xanthan gum and lactose were prepared according to the composition. The composition of drug was kept constant at 20% by weight (80 mg/tablet).

Determination of drug content

Twenty propranolol hydrochloride matrix tablets were finely powdered, accurately weighed (400 mg) and transferred to a 50-mL volumetric flask for drug content testing. Then, the volume was made up with 0.1 M HCl and shaken for 10 min to ensure complete solubility of the drug. The mixture was centrifuged (Centrifuge Machine, Hettich EBA 20, Germany) and 10 mL of the supernatant liquid was diluted 20 times with 0.1 M HCl. After centrifugation, the absorbance was determined spectrophotometrically (UV Vis-2020 spectrophotometer with UV mate) at 290 nm.

Physical evaluation of tablets

Weight variation

The mean and relative standard deviation of the weight were determined based on an official

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Propranolol HCl</th>
<th>Xanthan gum</th>
<th>Lactose</th>
<th>Magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>80</td>
<td>312</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>F2</td>
<td>80</td>
<td>156</td>
<td>156</td>
<td>8</td>
</tr>
<tr>
<td>F3</td>
<td>80</td>
<td>-</td>
<td>312</td>
<td>8</td>
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<td>F4</td>
<td>80</td>
<td>208</td>
<td>104</td>
<td>8</td>
</tr>
<tr>
<td>F5</td>
<td>80</td>
<td>104</td>
<td>208</td>
<td>8</td>
</tr>
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</table>

Total tablet weight 400 mg
method by taking 20 tablets from each formulation and weighed carefully using an electronic balance (Precisa BJ-210, Switzerland).

**Hardness and friability**

The diametrical crushing strength test was performed on 10 tablets from each formulation. Ten tablets were tested using an Erweka (Germany) hardness tester. For each formulation, the friability of 20 tablets was determined using a Pharma test apparatus. Twenty tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation.

\[
\%F = \left( \frac{W_1 - W_2}{W_1} \right) \times 100
\]

**Thickness and diameter**

Thickness and diameter were measured by vernier caliper.

**Swelling behavior of matrix tablets**

The level of swelling was calculated in terms of % weight increase by the tablet. The swelling behavior of formulations F1, F3, F4 and F5 was studied. One matrix tablet of propranolol hydrochloride from each formulation was kept in a Petri dish containing deionized water. At the end of 1 h, the tablet was introvert, soaked with tissue paper and weighed. Then, for every 2 h, weights of the tablet were noted, and the process was continued till the end of 12 h. Percent weight gain by the tablet was calculated by formula; \( S.I. = \left( \frac{M_t - M_0}{M_0} \right) \times 100 \), where, \( S.I. \) = swelling index, \( M_t \) = weight of tablet at time ‘t’ and \( M_0 \) = weight of tablet at time t = 0.

**Solubility determination**

The solubility extent of propranolol hydrochloride at pH 1.2 and in water was measured by adding an excess of drug to the solvents at 37°C. After equilibrium was reached, the drug concentration in the supernatant was determined spectrophotometrically at 290 nm.

**Dissolution tests**

The dissolution behavior of propranolol hydrochloride was recorded continuously using a fully automated dissolution apparatus. The USP dissolution apparatus with rotating paddle assembly (apparatus II) was used (100 rpm, in 900 mL of deionized water and HCl buffer pH 1.2 maintained at 37°C). The mean of three determinations was used to calculate the drug release from the matrix tablets. The samples were withdrawn at predetermined time intervals, filtered, and assayed spectrophotometrically at 290 nm.

**Analytical methods**

Analytical dilutions of pure propranolol HCl were prepared in deionized water. Their absorbances were taken at 290 nm on UV Vis-2020 spectrometer with UV mate and were plotted against their respective concentrations to obtain standard curve. The sample withdrawn each time during dissolution was also calculated at 290 nm in the same way. The amount of propranolol HCl was calculated from standard curve. The percentage of dissolved drug was calculated by using following formula:

\[
\%\text{ dissolved} = \left( \frac{X \text{ mg} \times 900}{\text{Assay amount (mg)}} \right) \times 100
\]

**Data analysis**

To study the release kinetics, data obtained from in vitro drug release studies were measured in various kinetic models Zero-order (\( Q_t = Q_0 + K_0 t \)) first-order (\( \log Q_t = \log Q_0 + Kt / 2.303 \)) Higuchi (\( Q = K H t^{1/2} \)) and Hixson-Crowell (\( Q_0^{1/3} = Q_t^{1/3} = kHt \)) using linear regression analysis (7). It has been reported that the release mechanism deviates from the Fick’s equation, following an anomalous behavior (non-Fickian

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Weight (mg)</th>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Drug content (%)</th>
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<tr>
<td>F1</td>
<td>400 ± 5.25</td>
<td>11.3 ± 0.05</td>
<td>4.7 ± 0.05</td>
<td>0.35</td>
<td>07</td>
<td>100/05</td>
</tr>
<tr>
<td>F2</td>
<td>400 ± 7.66</td>
<td>11.3 ± 0.1</td>
<td>4.6 ± 0.04</td>
<td>0.45</td>
<td>06</td>
<td>98.75</td>
</tr>
<tr>
<td>F3</td>
<td>400 ± 6.46</td>
<td>11.3 ± 0.09</td>
<td>4.3 ± 0.03</td>
<td>1.00</td>
<td>04</td>
<td>102.02</td>
</tr>
<tr>
<td>F4</td>
<td>400 ± 9.22</td>
<td>11.3 ± 0.08</td>
<td>4.2 ± 0.04</td>
<td>0.67</td>
<td>06</td>
<td>99.02</td>
</tr>
<tr>
<td>F5</td>
<td>400 ± 6.32</td>
<td>11.3 ± 0.05</td>
<td>4.5 ± 0.05</td>
<td>0.52</td>
<td>05</td>
<td>99.5</td>
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</table>

Table 2. Results of the physical evaluations of propranolol HCl matrix tablets prepared.
Figure 1. Swelling index behavior of propranolol HCl matrix tablets

Figure 2. Dissolution profile of propranolol HCl in aqueous medium

Figure 3. Dissolution profile of propranolol HCl in HCl buffer pH 1.2
Table 3. Table different release models and dissolution data.

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Korsmeyer-Peppas</th>
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<tr>
<td></td>
<td>r²</td>
<td>K₀ (h⁻¹)</td>
<td>r²</td>
<td>K₁ (h⁻¹)</td>
<td>r²</td>
</tr>
<tr>
<td>Aqueous medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>0.986</td>
<td>3.71913</td>
<td>0.964</td>
<td>0.048851</td>
<td>0.903</td>
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<tr>
<td>HCl buffer pH 1.2</td>
<td>0.966</td>
<td>4.79149</td>
<td>0.995</td>
<td>0.079578</td>
<td>0.998</td>
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<tr>
<td>Aqueous medium</td>
<td>0.989</td>
<td>3.81746</td>
<td>0.937</td>
<td>0.053645</td>
<td>0.981</td>
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<tr>
<td>HCl buffer pH 1.2</td>
<td>0.944</td>
<td>5.87752</td>
<td>0.996</td>
<td>0.129953</td>
<td>0.995</td>
</tr>
<tr>
<td>Aqueous medium</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>HCl buffer pH 1.2</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aqueous medium</td>
<td>0.988</td>
<td>3.41161</td>
<td>0.972</td>
<td>0.046008</td>
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<td>HCl buffer pH 1.2</td>
<td>0.950</td>
<td>4.48432</td>
<td>0.934</td>
<td>0.125083</td>
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<tr>
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<td>5.09762</td>
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<td>0.220706</td>
<td>0.990</td>
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<td>HCl buffer pH 1.2</td>
<td>0.953</td>
<td>6.38260</td>
<td>0.839</td>
<td>0.134369</td>
<td>0.997</td>
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release). So Pappus equation is most useful for these cases. In these cases a more generic equation can be used. Korsmeyer et al. derived a simple, semi-empirical model, relating exponentially the drug release to the elapsed time. Where \( K \) is a constant comprising the structural and geometric characteristics of the tablets; \( Q_t/Q_\infty \) is the fraction of drug released at time \( t \); and \( n \), the release exponent, is a parameter that depends on the release mechanism and is thus used to characterize it.

For characterization of various release mechanisms, Peppas used \( n \) value. This \( n \) value is indicative for fickian diffusion, non-fickian model (anomalous transport), case II transport and super case-II transport in order to characterize different release mechanisms (8).

RESULTS AND DISCUSSION

The use of hydrophilic polymeric matrices can provide a source of acceptable route of retarding the release rate of propranolol HCl (9). Various physical test results for produced tablets are shown in Table 2. The analysis data emphasize the existence of significant difference of drug release by change in concentration of xanthan gum from each formulation. The dissolution of propranolol hydrochloride is the fastest in formulation F5 while the slowest in formulation F1 (Figs. 2, 3). The inverse relationship was noted between amount of xanthan gum in formulations F1, F2, F4 and F5, which resulted in slower rate, and decreased amount of drug release from the tablets. Significant difference in different media was observed in release profile, indicating that propranolol hydrochloride has better solubility in HCl buffer (pH 1.2).

Propranolol hydrochloride revealed a prolonged release time when compared with the other drugs (10). The slow release is because of the formulation of a thick gel structure that delays drug release from matrix tablet, where hydration of individual xanthan gum particles results in extensive swelling. As a result of rheology of hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintain the integrity of the tablet and retarding further penetration of the dissolution medium. The drug release was gradually increased as the concentration of lactose was added into matrix tablets. As lactose is highly water soluble, increased concentration of lactose increased the drug release from the matrix tablet. There was the fast release of drug from the matrix tablet containing only lactose (formulation F3). This result reported that an addition of lactose could enhance the drug release. Sustainable drug release could be achieved as the amount of lactose in matrix tablets was between 25 and 75%.

Propranolol hydrochloride is a weak base and therefore its water solubility is dependent on the pH. More specifically, its solubility is reduced at higher pH values. Propranolol hydrochloride is a weak base and therefore its water solubility is dependent on the pH. More specifically, its solubility is reduced at higher pH values (11). The same results were obtained in our experiments.

Propranolol hydrochloride is a weakly basic drug and its solubility depends on the range of pH of the gastrointestinal tract (10). Solubility of propranolol hydrochloride was found 360 mg/mL in water and 225 mg/mL at pH 1.2. It was noted during experimental study that propranolol hydrochloride provides a release pH dependent solubility from matrix formulations. Release from matrix tablets was higher in HCl buffer pH 1.2 compared with deionized water. Eighty seven and 73% release were observed in deionized water and HCl buffer pH 1.2 after 12 h, respectively.

Swelling index of each formulation was calculated mathematically. Formulation containing higher concentration of xanthan gum showed the highest swelling index. Furthermore, the relationship between swelling index and time was calculated of each formulation (Fig. 1). Each formulation has direct influence on swelling index depending on concentration of xanthan gum. As time increases, weight gain by tablet was increased proportionally with the rate of hydration up to 3 h and the swelling index was increased. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, and as gum concentration increases, swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of xanthan gum.

Dissolution samples were assessed by various kinetics models. Table 3 lists various dissolution parameters computed for all the matrix formulations. To know the mechanism of drug release from the trial formulations, the data were treated according to zero order, first order, Higuchi’s and Korsmeyer and Peppas (12). In zero order, the \( r^2 \) value obtained is in the range of 0.953 to 0.989 and for the first order is in the range of 0.934 to 0.996.
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describing the drug release rate relationship with concentration of drug except formulation F3 with no xanthan gum. In our results, the best linearity was found in Higuchi’s equation plot ($r^2 = 0.998$ in F1 with HCl buffer pH 1.2) indicating the release mechanism governed by diffusion from matrix. This was also reported by Akhtar et al. (13). Data were also assessed with Hixson Crowell cube root law ($r^2 = 0.968$ to 0.996) indicating a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time.

The $n$ values from fitting to Korsmeyer-Peppas equation were in the range of 0.489 to 0.739 except formulation F3. Intermediate values for $n$ reported by Peppas suggest that diffusion and erosion contribute to the overall release mechanism (14). Diffusion is related to transport of drug from matrix tablets which depends on concentration of the polymer (15). However, our results indicated that the drug release from these tablets was by Fickian diffusion and anomalous (non-Fickian) mechanisms. This means that drug diffuses at a comparatively slower rate as the distance for diffusion increases.

CONCLUSION
The use of hydrophilic polymers in oral pharmacotherapy seems promising. Increasing the amount of xanthan gum could control the release of drug from matrix tablets. Increasing the amount of soluble diluent could increase the release rate. Propranolol matrix tablets are influenced by pH because of its pH dependent solubility. By comparison, most dissolution profiles of matrix tablets could provide better fit to Higuchi’s equation than zero and first order kinetics. As sustained release tablets were formulated and analyzed in this study, so in the future prospective, this study may increase compliance, facilitate combination therapy with prolonged-action formulations of other drugs and better maintain therapeutic levels.

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