GHATTI GUM BASED MATRIX TABLETS FOR ORAL SUSTAINED DELIVERY OF METOPROLOL SUCCINATE

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ABSTRACT

The present study has been undertaken to develop a sustained-release tablet dosage form for metoprolol succinate drug using naturally occurring ghatti gum as the rate-controlling polymer. The prepared ghatti gum tablets were evaluated for hardness, thickness, friability, weight variation and drug content. The tablets were coated with shellac as an enteric polymer coat and evaluated for tablet properties and enteric coat test. In vitro release studies for the prepared tablets were carried out for 2 hrs in pH 1.2 HCl buffer and 12 hrs in pH 7.2 phosphate buffer. Furthermore, drug interaction in ghatti gum tablet formulation was evaluated by Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). Swelling studies, kinetics of drug release from the matrices and stability of the tablet formulations were also investigated. From the In vitro studies, it was found that the tablets had good mechanical properties and coating with shellac has prevented drug release from stomach. The tablets have retained the drug release till a period of 12 hrs. The data obtained from Peppas model fitting indicated that F5 was optimized formulation. When stability studies were done for three months at 40±2° C and 75±5% RH for optimized formulation, it was found that the tablets showed negligible difference in release mechanism as well as drug content.

Keywords: Ghatti gum, Metoprolol succinate, Matrix tablets, Sustained release.

INTRODUCTION

High patient compliance and flexibility in designing dosage forms have made the oral drug delivery systems to be the most convenient mode of drug administration as compared to other dosage forms 1. To date, oral delivery is still the preferred route of drug administration, especially for chronic therapies where repetitive administration is required. Oral administration assures patients; less pain, higher likelihood of compliance, greater convenience and reduced risk of cross-infection and needle stick injuries 2.3 Thus, formulations of oral drug delivery continue to have more than half of the drug delivery market share 4.

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation, hence frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.

The concept of sustained drug release has emerged from the need for effective management of diseases. Site-specific release systems provide many distinctive advantages over classical methods of drug delivery such as localized delivery of drug to a particular part of the body, reduce need for follow-up care, assurance of treatment continuity in the nocturnal phase and optimised drug absorption 5.6. Sustained drug delivery systems provide an alternative approach to regulate the bioavailability of therapeutic agents. An active therapeutic is embedded into a polymeric network structure in such a way that the drug is released from the material in a predefined manner 7. Depending on the drug delivery formulation and the purpose, the drug release duration may be anywhere for a few hours to a month to several years 5. A variety of synthetic and natural polymers have been studied as drug carriers 8.

Sustained release drug delivery technology offer conspicuous advantages as compared to conventional dosage forms which includes enhanced efficiency, sustained blood levels, reduced toxicity, attenuation of adverse effects, improved patient compliance and convenience 8. To generate controlled release of drug to the gastrointestinal track various mechanisms have been used such as encapsulation dissolution control, matrix dissolution control, reservoir device, osmotically controlled release, pH independent release formulations, time dependent release formulations, ion exchange controlled release and altered density formulations 10. Improved drug release systems can be developed by selecting an appropriate carrier capable of controlling the drug delivery. Suitable matrix systems which swell in water can be developed by compression of a hydrophilic polymer with the drug.

New formulations that make use of different delivery devices from synthetic and natural polymers, which are either hydrophilic or hydrophobic, have been tested for these purposes. The challenge is to design oral drug delivery vehicles, that release drug in sustained form and gets absorbed at an efficient rate in the GI tract in order to be therapeutically effective. Several carbohydrate polymers are able to satisfy these requirements to some extent, and have demonstrated their potential as starting materials for the construction of oral drug delivery vehicles 11.

Success of matrix systems can be linked to carbohydrate polymers as they respond to the presence of water or biological fluids and change their structure to form a gel layer which enables the drug to release slowly from the matrix throughout the gastrointestinal tract (GIT) at the desired rate and time 12. Biodegradable polymers form an excellent platform for sustained drug delivery applications due to their hydrolytic instability, ease of fabrication, non-toxic degradation and matrix permeability 13. Therefore, in contrast to purely diffusion-controlled drug delivery systems, swelling and polymer erosion must also be considered 4.

Carbohydrate and biodegradable polymers have been extensively used to develop the sustained release (SR) formulations to decrease the release rates of drugs having short plasma half-life. Hydrophilic natural carbohydrate polymers, are some of the promising new resourceful carriers for the preparation of oral sustained release (SR) systems 14. A large number of polysaccharides like amylose, guar gum, chitosan, inulin, pectin, cyclodextrins, dextrins, dextrin chondroitin sulphate, and locust bean gum have been investigated for their use in sustained drug delivery systems. Very unique features of these polymers are having optimal proportion of the hydrophobic and hydrophilic parts respectively and the number of free hydroxy groups in the polymeric molecule. One such responsive polymer is ghatti gum.

Gum ghatti is a unique polysaccharide, much accepted for its excellent emulsification property. Recent research explored its complete molecular structure and physico-chemical properties. Pharmaceutically gum ghatti received little attention, and hence a
strong and obvious need exist to make further investigations on ghatti gum to exploit as potential polysaccharide for pharmaceutical/industrial applications 2.

Unlike other water soluble gums, it does not dissolve in water but absorbs it to form a viscous colloidal solution. Powdered gum swells in cold water to an extent that a 3% to 4% sol will produce a gel of uniform smoothness and texture. The backbone is a linear chain of \( \beta \) 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches 13. Due to its non-toxicity behaviour, it can widely be used as a pharmaceutical excipient 14.

Metoprolol (MTL), which is a \( \beta \)-selective adrenergic blocking agent, is prescribed widely in diverse cardiovascular diseases such as hypertension, angina pectoris, arrhythmias and congestive heart failures was selected as model drug 15. Administration of conventional tablets of MTL has exhibited fluctuations in the plasma drug levels finally resulting either in the manifestation of side effects or reduction in drug concentration at the receptor site 16. MTL undergoes extensive first-pass metabolism in the liver, which leads to the low oral bioavailability, which is about 40 - 50% in humans 17, and has a short biological half-life of 4 hrs. In order to avoid these disadvantages, several formulations like tablet, buccal sprays and capsules 18, controlled release dosage forms 19, osmotic pumps 20, 21, pelleted release forms 22 etc., have been developed. The objective of the present study is to develop a sustained-release formulation of metoprolol tablets with ghatti gum and to prove its dissolution behaviour in vitro.

**MATERIALS AND METHODS**

**Materials**

Metoprolol succinate was obtained as gift sample from Dr. Reddy’s laboratories, Hyderabad. Ghatti gum was procured from Girijan Co-operative Society, Govt. of Andhra Pradesh, Hyderabad. Directly compressible lactose (DCL) was obtained as gift sample from Strides Arcolab Ltd, Bangalore, India. All other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

**Collection and purification of ghatti gum**

Initially, the foreign extraneous matter like bark etc., was separated from ghatti gum. Then the gum was powdered by using mortar and pestle and a fine powder of gum was obtained using mixer grinder. The powdered gum was passed through sieve # 80 mesh and used for further studies.

**Preparation of tablets**

Accurately weighed quantities of drug, polymer (ghatti gum) and binder (Poly vinyl pyrrolidone K-30, 4% w/w) were physically mixed with a mortar and pestle. Required quantity of the solvent (ethanol) was added and mixed thoroughly to form a rough mass suitable for preparation of granules. The dough mass was passed through sieve # 22 to form granules which were dried in an oven at 50°C. These granules were mixed with required quantities of diluent (directly compressible lactose) and lubricant (talc, 3% w/w), then compressed to form tablets in a 10 station rotary tablet machine (Rimek, Ahmedabad, India) at 10 rpm and using 9 mm round concave punches at an optimum pressure. Five formulations were prepared by varying the amounts of ghatti gum viz., 30, 40, 50, 60 and 70% w/w of tablet and the formulations were coded as F1, F2, F3, F4 and F5 respectively. The composition of various formulations is given in Table 1.

**Techniques**

The prepared tablets were evaluated for weight variation, friability (Electrolab EF-2 friabilator, Mumbai, India), thickness (Mitotoya screw guage), hardness (Inweka hardness tester IHT 100) and drug content23 using UV-Visible spectrophotometer (Shimadzu, UV-1800).

**Water uptake study**

The water uptake by the formulations can be measured by their ability to absorb water and swell. The water uptake study of the tablet was done by placing the tablet in Electrolab TDL-08L dissolution tester (USP) basket type, 900 ml of distilled water stirred at 100 rpm and at 37 ± 0.5 °C. At regular time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as;

\[ WU(\%) = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100 \]

**Coating of the prepared tablets**

For the purpose of enteric coating, a solution of shellac (10% w/v) in ethanol was used along with glycerol (4% w/w of shellac) as plasticizer. The coating solution was passed through a 0.3 mm sieve prior to coating. The prepared matrix tablets were coated with shellac solution till a weight gain of 2.5% w/w over the tablets. Coating of the tablets was carried out in a conventional coating pan (Ram Scientific Suppliers, Bangalore, India) at an inlet temperature of 55°C, pan rotation speed of 15 rpm, spray pressure of 4 kg/cm² and a spray rate of 1 ml/min. An omega spray gun (Type 79) fitted with a 1 mm atomizing nozzle was used to spray the solution. The coated tablets were evaluated for enteric coat test, hardness and drug content.

**Enteric coat test**

The enteric coat test for the tablets was done by placing the tablets in Electrolab TDL-08L dissolution tester (USP) basket type, 900 ml of pH 1.2 HCl buffer solution at 100 rpm for 2 hrs. At regular intervals, sample was withdrawn and analyzed by UV-Visible spectrophotometer for presence of drug.

**Content uniformity**

Twenty tablets of metoprolol succinate were weighed and powdered. Crushed powder of tablets equivalent to 0.15 g was weighed and dissolved in pH 6.8 phosphate buffer solution. The solution was filtered, diluted and drug content was analyzed spectrophotometrically at about 222 nm.

**In vitro drug release study**

To understand the release kinetics of tablets, release studies were carried out using USP XXII dissolution apparatus, basket type at 100 rpm and at 37 ± 0.5°C. The release studies were carried out for the shellac coated tablets in triplicates in simulated gastric condition (pH 1.2 HCl buffer) initially for 2 h and at later for 12 h in simulated intestinal condition (pH 7.2 phosphate buffer). A 10 ml aliquot of the dissolution solution was withdrawn at regular intervals of time and analyzed for drug content using a UV-visible spectrophotometer at \( \lambda_{max} \) of 222 nm. A 10 ml of the same solution was replaced back to the dissolution vessel so as to maintain the sink conditions.

**Mechanism of drug release**

The different mathematical models may be applied for describing the kinetics of the drug release process from tablets; the most suitable model is selected based upon the experimental results. The kinetics of metoprolol succinate release from tablet formulations were determined from best fit plots of release data of Korsmeyer-Peppas 25. The Korsmeyer-Peppas equation is as follows;

\[ M_t / M_\infty = A \cdot (kt)^n \]

Where, \( M_t / M_\infty \) is the fractional amount of the drug released and \( t \) is the time in hrs. In this study, the release constant, k and constant, A
was calculated from the slopes and intercepts of the plots of \( \ln \left( \frac{1-M_t}{M_\infty} \right) \) versus time \( t \) respectively. Where, \( M_t \) is the amount of drug release at time \( t \); \( M_\infty \) is the amount of drug release after infinite time; \( k \) is a release rate constant incorporating structural and geometric characteristics of the tablet; and \( A \) is the diffusional exponent indicative of the mechanism of drug release. To find out the release exponent, the log value of percentage drug dissolved was plotted against log time for each batch according to the above equation.

Value \( A \) equivalent to 0.5 indicates Fickian (case I) release; greater than 0.5 but less than 1 for non-Fickian (anomalous) release and \( A \) is greater than 1 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.

### Fourier transform infrared spectroscopy

FTIR spectra of the pure metoprolol succinate and the optimized formulation were recorded using a Fourier transform infrared spectrophotometer (FTIR, 8400 Shimadzu, Japan). Samples were prepared using KBr pellets and scanned from 4000 to 400 cm\(^{-1}\).

### Stability studies

Stability studies of the optimized formulation of metoprolol succinate tablets was carried out in order to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40\(^\circ\) C/75\% RH for 3 months (Thermolab, Mumbai, India). Formulation was analyzed every 15 days for its hardness and % drug content.

### RESULTS AND DISCUSSION

The prepared tablets were having an average diameter of 9 mm. Percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) limits. From Table 2 it is clear that, as the amount of ghatti gum polymer concentration in the tablet increased, the hardness of the core tablets increased. Formulation containing 70% w/w of ghatti gum showed maximum hardness among the various ratios selected (30, 40, 50, 60 and 70% w/w). The measured percentage of drug content in these formulations lies in the range 97.4 - 102.3 %.

### Table 2: Physico-chemical data for the ghatti gum/metoprolol succinate tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Avg. weight (mg)</th>
<th>% weight variation*</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm(^2))</th>
<th>Friability (%)</th>
<th>% Drug content*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>302.4</td>
<td>-1.9 to +2.2</td>
<td>5.0±0.11</td>
<td>5.4±0.48</td>
<td>0.82±0.61</td>
<td>98.1±0.53</td>
</tr>
<tr>
<td>F2</td>
<td>301.5</td>
<td>-2.5 to +3.6</td>
<td>5.0±0.12</td>
<td>5.9±0.38</td>
<td>0.86±0.82</td>
<td>97.4±0.36</td>
</tr>
<tr>
<td>F3</td>
<td>299.8</td>
<td>-3.3 to +2.4</td>
<td>5.0±0.12</td>
<td>6.2±0.72</td>
<td>0.72±0.41</td>
<td>100.1±0.37</td>
</tr>
<tr>
<td>F4</td>
<td>300.7</td>
<td>-2.6 to +3.8</td>
<td>4.97±0.13</td>
<td>6.6±0.83</td>
<td>0.72±0.37</td>
<td>101.2±0.31</td>
</tr>
<tr>
<td>F5</td>
<td>300.6</td>
<td>-3.8 to +2.2</td>
<td>5.01±0.12</td>
<td>6.9±0.69</td>
<td>0.41±0.39</td>
<td>102.3±0.44</td>
</tr>
</tbody>
</table>

*Average of 3 determinations

The swelling behaviour of the ghatti gum matrix tablet was determined at different time intervals. The equilibrium swelling was achieved by the end of 8 hr, hence percentage swelling of water was determined at the end of 8 hr for all the formulations. Figure 1 shows swelling behavior of the prepared ghatti gum tablets at 0 hr to 8 hr. It was observed that all the tablet formulations showed better radial and axial swelling, but maximum swelling was seen in F5 formulation, and the least percentage of swelling was found in F1, as shown in Figure 1.
Water uptake values increased from 200 to 490 % (F1 to F5) with increase in concentration of hydrophilic ghatti gum in the formulation. The water uptake behaviour increases steeply with increase in ghatti gum concentration from 30 to 50% and further a gradual increase in water uptake behaviour was noticed for formulations F4 and F5. As described by Seimann and Peppas diffusion of drug significantly depends on the water content of the tablet [25]. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving rise to high swelling of the system. Consequently, faster and higher swelling of the tablet led to increase in dimensions of the tablet, leading to increasing the diffusion pathways and thus increasing the drug release. So the drug release was found to be initially high and then gradually decreased, this was true in formulations F4 and F5.

The tablets coated with enteric polymer, shellac were subjected to enteric coat test for a period of 2 hr. Coat test results showed that there were no signs of cracking, peeling or disintegration in 1.2 pH HCl buffer. There was no absorbance seen at 222 nm, when the sample was scanned in UV-Visible spectrophotometer, indicating that drug has not leached from the shellac-coated tablets.

In vitro drug release studies were carried out in phosphate buffer (pH 7.2) and it was observed that the formulations containing 30 and 40% w/w of ghatti gum matrix did not show sustained release whereas, the formulation containing 60% of ghatti gum showed sustained drug release from the coated tablets over a period of time. Formulations containing 30% and 40% w/w of polymer, released almost entire drug within 8 and 10 hrs of dissolution respectively. Formulation containing 30% w/w showed almost 60% of the drug release within 4 hr whereas, the formulation containing 70% w/w showed 25 % of the drug release for the same duration. On the other hand, tablets containing 60% and 70% w/w of ghatti gum exhibited only about 81.89 and 73.87% of drug release at the end of 10 hr of dissolution respectively. Hence, the order of drug delivery from the coated tablets with reference to polymer concentration is: 30 > 40 > 50 > 60 > 70 % (Figure 2).

![Graph showing in vitro drug release data for the prepared ghatti gum formulations](image1.png)

The data obtained from in vitro drug release studies was fit into Peppas model. From the plots of log M_t/M_∞ versus t, the parameters such as release constant (k), and the regression coefficient (R^2) were calculated and are given in Table 3.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Slope (m)</th>
<th>Intercept (A)</th>
<th>Regression coefficient (R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-0.0008</td>
<td>1.1101</td>
<td>0.99177</td>
</tr>
<tr>
<td>F2</td>
<td>-0.0007</td>
<td>1.1109</td>
<td>0.99655</td>
</tr>
<tr>
<td>F3</td>
<td>-0.0006</td>
<td>1.0687</td>
<td>0.99762</td>
</tr>
<tr>
<td>F4</td>
<td>-0.0006</td>
<td>1.4836</td>
<td>0.99716</td>
</tr>
<tr>
<td>F5</td>
<td>-0.0004</td>
<td>1.4874</td>
<td>0.99904</td>
</tr>
</tbody>
</table>

For all the ghatti gum matrix tablets, the values of 'A' were found to be more than 1. The result clearly indicated that the release of drug from the polymer matrix formulations was found to be super case-II transport, i.e., drug release by more than one mechanism. Super case II transport generally refers to erosion of polymeric chain and anomalous transport. Based on the 'A' values obtained, the formulation F5 was concluded as optimized formulation for 12 hr study period.

The characteristic IR absorption peaks of metoprolol succinate at 3600-2300 (NH_2, -OH, aliphatic and aromatic CH), 1580 (carboxylic acid salt), 1515 (aromatic ring), 1250 & 1015 (aromatic ether), 1180 (isopropyl group), 1100 (aliphatic ether, secondary alcohol) and 820 cm^-1 (1,4 disubstituted benzene) were obtained. The FTIR spectra of the pure drug as well as coated formulation indicated that no chemical interaction occurred between the metoprolol succinate and the polymers used. But, a slight shift in absorption peaks position was noticed. This result revealed that physical interaction occurred between drug and the polymer.
Stability studies of the drug formulations were performed to ascertain whether the drug undergoes any degradation during its shelf life. In the present study, the optimized formulation F5 was selected for stability studies. The obtained results of the stability studies are given in Table 4. From the stability study data, it was concluded that the drug was stable in the optimized formulation for the study period.

Table 4: Stability studies data for the optimized formulation (F5)

<table>
<thead>
<tr>
<th>Sampling Interval (days)</th>
<th>Hardness * (kg/cm²)</th>
<th>Drug content* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.5 ± 0.45</td>
<td>100.2 ± 0.47</td>
</tr>
<tr>
<td>15</td>
<td>6.6 ± 0.47</td>
<td>101.4 ± 0.65</td>
</tr>
<tr>
<td>30</td>
<td>6.6 ± 0.53</td>
<td>100.5 ± 0.76</td>
</tr>
<tr>
<td>45</td>
<td>6.5 ± 0.87</td>
<td>102.3 ± 0.18</td>
</tr>
<tr>
<td>60</td>
<td>6.5 ± 0.76</td>
<td>98.9 ± 0.54</td>
</tr>
<tr>
<td>75</td>
<td>6.6 ± 0.54</td>
<td>99.4 ± 0.42</td>
</tr>
<tr>
<td>90</td>
<td>6.6 ± 0.21</td>
<td>100.2 ± 0.24</td>
</tr>
</tbody>
</table>

*Average of 3 determinations

DSC thermograms of pure drug and the optimized formulation are presented in Figures 4 (a) and 4 (b) respectively. In optimized formulation, a broad peak was noticed in the temperature range 55 - 125°C which is due to the presence of water and a small peak above 140°C was noticed, which may be due to other additives present in the tablet. An endothermic peak corresponding to the melting point of pure drug was prominent. There was no significant shift in the peak temperature which clearly suggests that the drug was present in an unchanged form.
CONCLUSION

From the above said studies, it clearly indicates that ghatti gum could be useful as matrix system for sustained drug delivery and various polymers/ingredients/additives could be used to modulate the drug release from the matrix tablet. The 12 hr drug release study indicated that the ghatti gum formulation was ideal for sustained release. Enteric coating and the rate of swelling favored sustained release of the drug from the formulation. Peppas model fitting data indicated that F5 was the optimized formulation and the in vitro data obtained showed that the drug release from the optimized formulation was sustained till 12 hrs. The final product is expected to have the advantage of being natural, biodegradable and pH dependant. Hence, it can be concluded that sustained release drug formulation can be designed using ghatti gum, a naturally available, environmental friendly, non-toxic and biodegradable gum as carrier.

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