Synthesis, Characterization and Comparative Evaluation of Guar Gum Mixed Ester in the Formulation Development of Diclofenac Sodium Enteric Coated Tablet

Makarand V. Puri*, Sagar D. Kore, Ashish Chimbalkar

Siddhant College of Pharmacy, Sudumbre.Pune, Maharashtra. India. 412109

Abstract : Objective: The present research work was aimed to synthesize & compare the release retardant properties of galactomannan esters i.e. guar acetate and guar acetate maleate synthesized from naturally occurring guar gum.

Method : Guar acetate maleate was synthesized from esterified galactomannan i.e. guar acetate. The films of guar acetate & guar acetate maleate were casted by mercury substrate technique. An evaluation of both polymeric films was performed. Diclofenac sodium tablet was formulated with these polymers as release controlling excipient, and dissolution studies were performed to assess the controlled release property of the polymers.

Result : Guar acetate maleate was evaluated for different parameters. The drug polymer compatibility study depicted no interaction between the synthesized polymers & diclofenac sodium. In vitro dissolution profile show the drug release is pH dependent which release drug in basic pH.

Conclusion : The assessment of in vitro dissolution profile shows that drug was released when pH of media was increased to make it alkaline. This property of synthesized polymer can be used to develop an enteric coated tablet.

Keywords : Diclofenac Sodium, Guar gum, esterification, enteric coated tablet.

Introduction

The oral route is one of the most important routes for drug administration. This route is preferably used to administer solid dosage forms of majority of drugs. If the drug is administered orally, the number of doses per day increases in order to maintain the therapeutic drug level in the body. However, doing so may lead to several toxic effects and/ or side effects. Also the biggest problem in such drug delivery systems is low and inconsistent bioavailability, which is due to poor aqueous solubility, slow dissolution rate, low intestinal permeability, and instability in gastrointestinal tract, first-pass metabolism through liver and intestine variable GI transit. Many drugs delivered in the acidic media of stomach cause gastric irritation eventually which may lead to erosion of gastric mucosa & development of ulcer. Similarly fluctuations of drug concentration of some potent drugs may cause under medication or overmedication leading to adverse drug reactions.[1,2] In order to minimize such undesirable effects efforts are placed in a direction to develop novel approach through which plasma drug concentration can be maintained in therapeutic window. One of such attempt is utilization of polymers to coat pharmaceutical solid dosage forms for protective and altering release rate in desired media. They are also used to enhance the chemical and physical stability of the drug, as well as to make it more palatable & acceptable. Most important reason for the application of polymeric coatings is to alter the release characteristics of drugs.[3] Due to such advancements various benefits like desired rate of drug delivery, maintenance of plasma drug level, less amount of active ingredient required, lower cost, less adverse effects and
increased patient compliance.\textsuperscript{[4,5]} But developing such oral controlled release tablet for water soluble drug with a desired release rate has always been a challenge to pharmaceutical scientists. Recent studies suggest that selective delivery of drug to the colon can be achieved using guar gum as a carrier since guar gum protects the drugs from being released in the physiological environment of the stomach and the small intestine.\textsuperscript{[6-8]} Guar gum is a polysaccharide derived from the seeds of \textit{Cyamopsis tetragonolobus}, of the Leguminosae family. It consists of linear chains of (1→4)-\(\beta\)-D-mannopyranosyl carefully units with \(\alpha\)-D-galactopyranosyl units attached by (1→6) linkages. In pharmaceutical formulations, guar gum is used as a binder, disintegrant, suspending agent, thickening agent and stabilizing agent.\textsuperscript{[9]} Natural gums are preferred over comparable synthetic materials due to their non-toxicity, low cost and availability. However, there are certain problems associated with the use of gums like uncontrolled rates of hydration, pH dependent solubility, thickening; drop in viscosity on storage, and the possibility of microbial contamination. To overcome such difficulties natural gums may be chemically modified. Chemical modification of gums will not only minimizes these drawbacks but also enables their use for specific drug delivery purposes.\textsuperscript{[10]}

**Materials and Methods**

### Materials

The gift sample of guar gum was obtained from Premcem Gums Private Limited, Mumbai, India. Diclofenac sodium was received as a gift sample from Emcure Pharmaceuticals, Pune, India. All the other chemicals were of analytical grade.

#### Synthesis of Guar gum mixed ester\textsuperscript{[11]}

Acetylation of guar gum was conducted by slight modification of the procedure described in US patent 2, 523,708. Guar gum [10 parts] was mixed with formic acid [90 parts, 90%]. This mixture was allowed to stand at room temperature 25 °C for 4 h. The mixture was heated to 45 °C for 50 min and then allowed to stand at room temperature overnight for the formation of guar formate. The guar formate was precipitated by gradual addition of acetone with continuous stirring. Then the precipitate was filtered and residue was dried overnight at room temperature. Guar formate [4 parts] was added to an acetylation bath consisting of acetic anhydride [8 parts], maleic anhydride [8 parts], glacial acetic acid [14 parts], \(\alpha\)- phosphoric acid [1 part] and sulphuric acid [1 part]. The resulting mixture was refluxed at 70 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with acetone and filtered. The product guar acetate maleate was precipitated as white fibrous material from water.

#### Characterization of guar gum mixed esters

Characterization of guar acetate and guar acetate maleate has been done using following techniques.

#### Fourier transforms infra-red spectrometry (FT-IR)

FT-IR spectras of guar gum, guar acetate and guar acetate maleate samples 4 mg were obtained by blending them with solid potassium bromide 100 mg for the formation of pellets. These pellets were scanned from 400 to 4000 cm\(^{-1}\) in a Shimadzu FTIR-8400S instrument. IRsolution software was used to analyze the sample.

#### Determination of degree of substitution

Degree of substitution value was determined according to the method of Miladinov and Hanna\textsuperscript{[12]} with some modifications. Powdered esterified guar gum was weighed exactly 0.5 g and placed in a 250 ml conical flask. Distilled water 50 ml was added and adjusted to pH7.0 with 0.002 N hydrochloric acid, after that 25 ml of 0.5 N sodium hydroxide was added and sample was heated on hot plate until a transparent solution was obtained. Excess sodium hydroxide was titrated with hydrochloric acid back to pH 7.0. Triplicate titrations were performed to obtain a mean value.

Degree of substitution was calculated as:
Where, \( N_{\text{NaOH}} \) was normality of sodium hydroxide, \( V_{\text{NaOH}} \) was the volume of sodium hydroxide, \( N_{\text{HCl}} \) was the normality of hydrochloric acid used to back titrate, \( V_{\text{HCl}} \) was volume of hydrochloric acid used to back titrate, and \( W \) was the sample weight.

### Solubility

Solubility of the derivatives in different buffers and organic solvents was gravimetrically determined. Approximately 2g of material with 50 ml of solvent was placed in an airtight screw-capped tube and agitated for 24 h at 25 °C. 2 ml of supernatant liquid was withdrawn in a tared dish. Solvent was evaporated by a mild heat and the tared dish was weighed again. The difference in weight gives the amount of material dissolved in the solvent. Various buffers of pH 1.2, 5.0, 6.8, 7.5 and 10.0, and the organic solvents acetone, isopropyl alcohol, dichloromethane and chloroform were used for this study. The experiment was repeated five times for each solvent/buffer solution. Buffers of different pH were prepared by the method described in Indian Pharmacopoeia.[13]

### Free film preparation and characterization

Free film of guar acetate maleate was prepared by solvent evaporation technique on a mercury substrate. A 30% w/v solution was prepared in acetone and poured in a petry dish containing mercury (area of casting: 20cm²) allowing the solvent to evaporate for 24 h. Film was stored in desiccators at ambient temperature for 24 h before study. Film thickness was measured by a thickness gauge (Oswal Scientific, Ambala, India) and recorded as mean of three determinations. Free film was evaluated for the mechanical properties by a plastic tensile test, performed on Instron Instrument based on ASTM D-412 test. The measurements were made at a gauge length of 50 mm, cross head speed (CHS) of 25 mm/min at 50% RH and 25°C. The tensile strength, percent elongation and modulus of elasticity were computed with at least three repetitions.

### Water vapour transmission rate (WVTR) studies

Film was cut into appropriate dimensions and mounted on a permeation cell containing saturated salt solution (excess salt) of potassium acetate, potassium carbonate, sodium chloride and potassium nitrate to provide relative humidity conditions of 23, 43, 75 and 93%, respectively.[14] The charged cells were weighed and placed in pre-equilibrated desiccators maintained at 0% RH. The cells were reweighed at the end of 24 h. The amount of water transmitted through the film was given by the weight loss of assembled cell. The water vapour transmission rate was computed using Utsumi’s equation taking the film thickness into consideration as shown below.[15]

\[
Q = \frac{WL}{S}
\]

where, \( W \): gram of water transmitted 24 h, \( L \): film thickness (cm), \( S \): surface area (cm²), \( Q \): water vapour transmission (g cm/cm²/24 h).

### Moisture absorption by free films

Film was cut into 25mm × 10mm strips. The strips were transferred to a tarred petry dish and transferred to glass desiccators maintained at controlled relative humidity of 23, 43, 75 and 93%, respectively. The relative humidity in the chamber was controlled by the use of different saturated solutions containing excess solute. The film specimens were accurately weighed placed in relative humidity chambers removed and weighed again at the end of 14 days. Increase or decrease in weight and changes in physical appearance were then observed. Percent moisture absorption was calculated by using the formula:

\[
\% \text{ moisture absorbance} = \frac{a - b}{a} \times 100
\]

Where, \( a \): weight of conditioned film; \( b \): initial weight of film.
Scanning electron microscopy

Surface morphology of films was studied under scanning electron microscope. The dry film sample, spread on a double-sided conducting adhesive tape, pasted on a metallic stud, was coated with platinum in a sputter coating unit for 2 min and observed in a Jeol JXA-840A (London, UK).

Tableting and coating

The core tablets containing 50mg of diclofenac sodium were prepared by wet granulation technique. All the ingredients were previously sifted and weighed. Magnesium stearate 5% w/w was added as a lubricant to the granules and the granules were punched into tablets using 8mm diameter punches on a multi station tableting machine. Compressed tablets were coated by the coating solution containing guar gum mixed esters alone, without any plasticizers prepared in acetone as solvent. The core tablets containing diclofenac sodium were divided into four batches. First two batches (F1 & F2) were coated with the solution of 10% & 15% guar acetate. The other two batches (F3 & F4) were coated with the solution of 10% & 15% guar acetate maleate. The coating process was repeated until the desired level coating weight was achieved.

In vitro dissolution study

In vitro dissolution study of coated tablets was performed was performed by the paddle method according to description in United States Pharmacopoeia XXIII. The dissolution apparatus II (Veego scientific, Mumbai, India) was used at a speed of 50 rpm at 37°C. The test was conducted in 900 ml of simulated gastric fluid for first 2 h followed by 900 ml of simulated intestinal fluid pH 6.8 upto 5 h. Aliquots were withdrawn at predetermined time intervals and the amount of drug released was monitored by measuring the UV absorbance of filtered solution at 285 nm.

Results and Discussion

Synthesis of guar acetate maleate

Various well known standard methods of esterification of carbohydrates were attempted without success. For example, the procedure for esterification using usual esterification bath recommended for the mixed esterification of different gums was tried without success. Likewise pretreatment of the gums with acetic acid and catalyst did not proceed satisfactorily. Thus the usual methods of esterification failed when applied to the galactomannan type of carbohydrate gum. It was discovered that various gum intermediates could be esterified readily by treatment with usual esterifying media. Thus, it was found that the formate esters of gum could be reacted with the usual esterifying media to produce mixed esters of any degree of esterification. In the present study the guar gum mixed esters were synthesized in two step reactions. First step involved the activation of guar gum by treating it with formic acid and formation of guar formate. Second step involved mixed esterification of guar formate using acetic acid, maleic anhydride and a mixture of sulphuric acid and phosphoric acid (1:1) as catalyst to produce guar acetate and guar acetate maleate respectively, as white fibrous matter with slight odor of acetic acid.

The formation of Guar acetate maleate was from guar acetate was confirmed by the FT-IR spectrum Figure No. 1 of the derivative.
Comparison of the FT-IR spectra of native guar gum with esterified gum clearly indicated the introduction of substituent groups [-C=O absorption around 1730–1750 cm\(^{-1}\)]. As the acetylation reaction continued there was an increment in the absorption due to carbon–hydrogen bending (C–H) at 1371 cm\(^{-1}\) in the acetyl group and an enhancement in carbon–oxygen (C–O) stretching at 1230–1240 cm\(^{-1}\) in an -O-(C=O)-CH\(_3\) group compared to those of native guar gum. Absence of peaks in the region 1850–1750 cm\(^{-1}\) indicated that the product is free of unreacted anhydrides and their byproducts (respective acids). Since, three hydroxyl groups are present in each monomeric moiety of guar gum the theoretical maximum for guar acetate is 3.0. The obtained degree of substitution using the equation was 2.9 (theoretical maximum, 3.0). This value proved almost complete acetylation of guar gum. High degree of substitution was essential for controlled release properties of the polymer. Thus FT-IR study confirmed the substitution of acetate function in the synthesized derivative.

**Solubility**

A study of relative solubility was carried out in different solvents and under different pH conditions. Both guar acetate and guar acetate maleate were found to be insoluble in water and soluble in all organic solvents tested as shown in Table no. 1.

**Table No. 1: Relative solubility in different solvents**

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Solubility (g/ml)</th>
<th>Solubility (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guar acetate</td>
<td>Guar acetate maleate</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.0384 + 0.0004</td>
<td>0.0381 + 0.00044</td>
</tr>
<tr>
<td>Acetone</td>
<td>0.0391 ± 0.0002</td>
<td>0.0389 + 0.00071</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>0.0365 ± 0.00025</td>
<td>0.0372 + 0.00070</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.0345 ± 0.00055</td>
<td>0.0334 + 0.00076</td>
</tr>
<tr>
<td>Water</td>
<td>Insoluble</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>

*(mean ± SD, n=3)*
Table No. 2 Solubility in different pH solutions

<table>
<thead>
<tr>
<th>Solvents (pH)</th>
<th>Solubility (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guar acetate</td>
</tr>
<tr>
<td>1.6</td>
<td>5.2x10⁻³</td>
</tr>
<tr>
<td>4.0</td>
<td>11.6x10⁻³</td>
</tr>
<tr>
<td>6.8</td>
<td>28.4x10⁻³</td>
</tr>
<tr>
<td>8.0</td>
<td>36.2x10⁻³</td>
</tr>
</tbody>
</table>

Each value is mean of three determinations.

Acteone being feasible was used as a solvent in the spray coating technique. The solubility increases with increase in the pH of the solution. A low solubility of 0.61± 0.018 g/ml was found at a lower pH of 1.6. This indicates a minimum drug release property in the gastric acid environment. Similarly a higher solubility of 1.12±0.045 g/ml was found in the basic pH of 6.8 this indicates a maximum drug release in the intestine. Hence the coating polymer also protects the upper gastrointestinal tract from the possible irritation due to the drug diclofenac sodium.

Mechanical properties of free films

Results for the mechanical properties of free guar acetate film are shown in Table No.3.

Table No. 3: Mechanical properties of free films

<table>
<thead>
<tr>
<th>Film material</th>
<th>Thickness (mm)</th>
<th>Tensile strength (MPa)</th>
<th>% Elongation</th>
<th>Young’s modulus (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar acetate</td>
<td>0.38 ± 0.03</td>
<td>0.517 ± 0.083</td>
<td>187.11 ± 67.43</td>
<td>53.13 ± 0.971</td>
</tr>
<tr>
<td>Guar acetate maleate</td>
<td>0.33 ± 0.02</td>
<td>0.662 ± 0.062</td>
<td>220.29 ± 93.52</td>
<td>47.07 ± 11.426</td>
</tr>
</tbody>
</table>

*(mean ±SD, n=3)

Tensile strength is the maximum stress applied to a point at which the film breaks. Elongation is defined as a measure of the capacity of the film to deform prior to failure. The guar acetate films showed a good elongation. Young’s modulus is the constant of proportionality of stress to strain and increases with increase in internal stress. No signs of cracking of the free films were observed. This indicates a better film forming property suitable for the coating of tablet formulation with minimum chances of tablet coating defects.

Water vapour transmission rate of free films

As the film thickness is likely to affect the water vapour transmission rate, Utsumi’s equation (Utsumi et al. 1961) has been employed for determination of water vapour transmission rate Table No. 4 taking the film thickness into consideration.

Table No. 4: Water vapour transmission rate of free films guar acetate.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>Film Thickness (cm)</th>
<th>area (cm²)</th>
<th>Q (g/cm²/24 h) at RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar acetate</td>
<td>0.33</td>
<td>7.06</td>
<td>2.54x10⁻³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.64x10⁻³</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td></td>
<td>11.46x10⁻³</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td></td>
<td>28.17x10⁻³</td>
</tr>
<tr>
<td>Guar acetate maleate</td>
<td>0.35</td>
<td>7.06</td>
<td>2.90x10⁻⁵</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td></td>
<td>6.23x10⁻⁵</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td></td>
<td>10.76x10⁻⁵</td>
</tr>
<tr>
<td></td>
<td>93%</td>
<td></td>
<td>27.62x10⁻⁵</td>
</tr>
</tbody>
</table>

*Q: water vapour transmission; RH: relative humidity.

The rate of water vapour transmission was low even at high humidity, viz., $10.43 \times 10^{-5}$ g/cm² at 93% RH, which is indicative of strong moisture protecting ability of the film.
Moisture absorbance

Results of the moisture absorption study by free films conducted at different RH conditions are shown in Table No. 5. Increase in RH increased the moisture absorption. Even at high RH of 75 and 93%, the free films showed nearly 4–5% moisture absorption with slight change in their physical appearance, the films becoming slightly sticky and soft in 14 days. This study indicates a good stability of the coated drug formulation.

Table No. 5: Moisture absorption study of free films

<table>
<thead>
<tr>
<th>Derivative</th>
<th>% moisture absorbed at RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>Guar acetate</td>
<td>0.846±0.038</td>
</tr>
<tr>
<td>Guar acetate maleate</td>
<td>1.036±0.013</td>
</tr>
</tbody>
</table>

*(mean ±SD, n=3)

Scanning Electron Microscopy study

Scanning electron microscopy picture of the free film of the guar acetate maleate have been shown in Figure No. 2. Relatively smooth surface was observed. The film showed many microscopic pores, essential for controlled release, at the magnification of 3000X. The pore diameters were approximately 2-4 μm. Therefore, the scanning electron microscopy study of the film showed the surface morphology and texture suitable for the controlled drug release.

In-vitro Dissolution Studies[17, 18]

Sequential studies in two different media were performed to evaluate the drug release characteristics of formulations by the paddle method. The in-vitro drug release from the four formulations is shown in the graphs of % cumulative drug release vs. time to compare the drug release from tablets coated with varying percentage of different polymers. Comparative graphs of the four formulations (F1 to F4) of the different concentrations of polymers guar acetate & guar acetate maleate have been shown in Figure No. 3. All the formulations showed a controlled drug release pattern up to a time period of 6 h. As revealed by the solubility profile, all the formulation showed a minimum cumulative drug release of less than 10 % in the acidic pH 1.6 for the first 2h. After changing the pH of dissolution medium to 6.8 a gradual rise in the amount of drug release was observed. Also it should be noted that all the formulations of the four guar gum derivatives showed a controlled drug release pattern with a minimum drug release at pH 1.2 & an increasing drug release pattern in the basic pH of 6.8. Nearly all the formulations showed a sigmoid shaped graph of %cumulative drug release Vs time as shown in Figure No.3.
This study reveals that the mixed ester derivative of guar gum showed a good ability to control the drug release from a coated tablet formulation. Of the four formulations, formulation F1, with 10% w/w guar acetate coat buildup, showed a controlled release property with a cumulative % drug release of up to 4 h. Formulation F2 with a 15% w/w guar acetate coat buildup, showed an average release pattern as compared to F1, with a maximum cumulative % drug release of more than 80% at the end of 6 h. On the other hand, formulation F3, with 10% w/w guar acetate maleate coat buildup showed controlled release property with a cumulative % drug release of 60% was witnessed over the period of 3 h & rest amount was released over 6 h. Finally, formulation F4 achieved cumulative % drug release of 82% over 6 h.

Conclusion

The semi-synthetic product guar acetate & guar acetate maleate and were successfully synthesized from natural gum i.e. guar gum. The synthesized derivatives were characterized by FT-IR studies. The present comparative study has examined the film forming and coating property of guar acetate and guar acetate maleate results obtained by relative solubility, mechanical properties, water vapour transmission rate, moisture absorbance and SEM studies indicates good film forming property of both the derivatives. Coating of the tablet formulation with guar acetate and guar acetate maleate polymers resulted in controlling the drug release up to 6 h. Of the two derivatives, guar acetate maleate proved to be a good controlled release tablet coating polymer with a cumulative % drug release of 82% at the end of 6 h. Also it should be noted that all the formulations of the two guar gum derivatives showed a controlled drug release pattern with a minimum drug release at pH 1.2 & an increasing drug release pattern in the basic pH of 6.8. These biomaterials may provide economically viable and potentially biodegradable alternatives to the existing range of materials used in drug delivery systems. The synthesized derivative therefore merits further study in the design of film-coated sustained drug delivery devices.

References:


*****