A Comparative Study of Triple-Layered Aceclofenac Matrix Tablets Formulated using Xanthan Gum and Guar Gum

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ABSTRACT

The aim of the present study was to develop sustained release, multilayered-matrix tablet of aceclofenac using natural polymers-guar gum (GG) and xanthan gum (XG) as carrier for core matrix and hydroxypropylmethyl cellulose (HPMC K-15M), sodium carboxymethylcellulose (NaCMC) and ethyl cellulose (EC) and polyvinylpyrrolidone (PVP-K30) for preparing bottom and top layers. The formulated tablets were evaluated for uniformity of weight, drug content, friability, hardness, thickness, swelling index and in vitro drug release. The physicochemical properties of tablets were found within the limits. The physicochemical investigation showed that aceclofenac matrix tablet prepared with xanthan gum showed better dissolution profile as compared to that of guar gum. Matrix tablets of xanthan gum with 4% \( W/V \) xanthan gum (MTX1) showed the highest percent drug release (88.98%), while matrix tablets of guar gum with 6% \( W/V \) guar gum (MTG1) showed the highest percent drug release (73.89%) at the end of 8 hours in pH 6.8 phosphate buffer. Among the matrix tablet of xanthan gum MTX4 (with 24% \( W/V \) of xanthan) showed the lowest percent drug release (48.65%) and while among the guar gum tablets MTG4 (with 24% \( W/V \) of guar gum) showed the lowest percent drug release (48.65%) at the end of 8 hours. It was concluded that increasing the concentration of gum from 6% \( W/V \) to 24% \( W/V \) in the formulation decreased the amount of drug release from the tablet. The xanthan gum based matrix tablets of aceclofenac were found to be superior to that of guar gum matrix tablets for potential therapeutic uses.

KEYWORDS: Aceclofenac; matrix tablets; sustained release; xanthan gum; guar gum.

Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is matrix tablet which prolongs and controls the release of drug that is dissolved or dispersed. In other words, matrix is defined as a well composite of one or more drugs with a gelling agent like hydrophilic polymers (Salsa et al., 1997).

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing and spondylitis. Aceclofenac is a newer derivative of diclofenac with low gastrointestinal complications. On long-term administration, aceclofenac shows some adverse side effects most frequently like gastrointestinal (GI) disturbances, peptic ulceration and gastrointestinal bleeding. Moreover, it is poorly water soluble, due to which its dissolution in GI fluid is very low, which in turn adversely affect the bioavailability. The short biological half-life (about 4 hours) and dosing frequency (more than one per day) make aceclofenac an ideal candidate for developing its sustained release products (Gowda et al., 2008; Lichtenberger et al., 1995). To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of aceclofenac is desirable. Matrix tablets composed of drug and polymer as release retarding material offer the most widely investigated approach in designing a sustained release system (Yeole et al., 2006; Verhoeven et al., 2006; Krishnaiah et al., 2002).

Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form. Xanthan gum, a high molecular weight extracellular polysaccharide, is a commercial product obtained by the fermentation of Xanthomonas campesteris (Gram-negative bacterium) (Yeole et al., 2006; Verhoeven et al., 2006).

Guar gum is a polysaccharide derivative glycoside linkage (galactomannan) obtained from the ground endosperm of guar plant (Cyamopsis tetragonolobus). Guar gum has been investigated as a matrix former for controlled release of. It is a nontoxic and nonirritant material. Natural polysaccharides remain undigested in the stomach and the small intestine and are degraded by the vast anaerobic microflora of the colon (Krishnaiah et al., 2002; Varshosaz et al., 2006).

Currently, the NSAIDs tablets available in the market have not yet attained the physiological goal of providing therapeutic effect over an extended period of time without gastric irritation. This approach i.e.
formulation of matrix tablet may minimize the complications associated with NSAIDS, reduce frequent dosing and improve patient compliance (Salsa et al., 1997; Gowda et al., 2008).

The present study aims to develop triple-layer sustained release matrix tablets using hydrophilic natural polymers (xanthan gum and guar gum) for core matrix and HPMC K-15M, NaCMC and Ethyl cellulose (EC) and PVP-K30 for preparing bottom and top layers.

Materials and Methods

Chemicals

Aceclofenac sodium, xanthan gum and guar gum were obtained as gift samples from Intas Pharmaceuticals, Dehradun, Krishna Pharmaceuticals, Baddi (Himanchal Pradesh), Garhwal Traders’, Dehradun respectively. EC, Poly vinyl pyrrolidone K –30, NaCMC, and HPMC were procured from CDH Mumbai. All other chemicals used were of analytical grade.

Preparation of Matrix Tablets

Triple layer matrix tablets were prepared in a three step process as followed.

Preparation of aceclofenac sodium matrix core granules
Core granules were prepared by wet granulation process using gums (xanthan and guar gum) in different ratio with aceclofenac sodium. For formulation lactose (10 mg) was used as diluents, PVP-K-30 (3%) was used as binding agent. Magnesium Stearate (5 mg) was incorporated as lubricant and talc (5 mg) was used to improve flow property.

Preparation of bottom and upper layers granules
The release layer containing HPMC K-15M, NaCMC and Ethyl cellulose (EC) were prepared by wet granulation method. The polymers and 3% PVP-K30 paste were mixed and passed through sieve no. 14 and dried at 50°C for 1 hour. Polymer ethyl cellulose is used due to its compatibility with HPMC K-15M and NaCMC.

Preparation of triple-layered matrix tablet. 50 mg:
150 mg: 50 mg of bottom: core: upper were compressed in single punch machine, respectively. Initially the volume of the die was adjusted equivalent to total weight of three layer matrix tablet. Then pre-weighted amount of granules equivalent to bottom layer were compressed and upper punch is lifted slightly and core material is placed and compressed and finally upper layer granules were compressed.

Evaluation of Aceclofenac Matrix Tablets

Swelling index
Swelling studies were carried out for assessing the extent of swelling for the different formulations. A matrix, upon contact with an aqueous solution, undergoes wetting which starts from the surface followed by the progression into the inner core of matrix through microscopic pores. The nature of the polymer plays an important role in this swelling process of the matrix tablets. The presence of water in the polymer causes a certain amount of stress, resulting in hydration of the polymer, which starts to swell yielding a gelatinous viscous layer. The percent swelling was determined by the following equation.

\[ S\% = \frac{W_s - W_d}{W_d} \times 100 \]

Where, \( W_s \) and \( W_d \) are the dry and swollen weights, at immersion time \( t \) in the test liquid.

Weight variation
Weight variation test was performed for twenty tablets from each batch and average values were calculated and then sum of individual weight was calculated. Then the difference is calculated to determine % variation (Table 2).

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Avg. wt of tablet(mg)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Drug content (%)</th>
<th>Swelling index (%)</th>
<th>Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX-1</td>
<td>250 ± 0.546</td>
<td>0.85±0.015</td>
<td>4.8±0.05</td>
<td>74.5±2.31%</td>
<td>24±10.3</td>
<td>4.9±0.003</td>
</tr>
<tr>
<td>MTX-2</td>
<td>248 ± 0.346</td>
<td>0.78±0.032</td>
<td>5±0.00</td>
<td>89.92±1.62%</td>
<td>30.4±10.1</td>
<td>5.2±0.001</td>
</tr>
<tr>
<td>MTX-3</td>
<td>250 ± 0.982</td>
<td>0.65±0.025</td>
<td>4.9±0.01</td>
<td>69.10±3.52%</td>
<td>34.7±0.009</td>
<td>5.3±0.003</td>
</tr>
<tr>
<td>MTX-4</td>
<td>253 ± 0.0193</td>
<td>0.48±0.012</td>
<td>5.1±0.00</td>
<td>71.78±3.45%</td>
<td>42±0.023</td>
<td>5.1±0.002</td>
</tr>
<tr>
<td>MTG-1</td>
<td>250 ± 1.34</td>
<td>0.66±0.011</td>
<td>5.1±0.021</td>
<td>66.23±2.11%</td>
<td>23±0.061</td>
<td>5.1±0.001</td>
</tr>
<tr>
<td>MTG-2</td>
<td>251 ± 0.438</td>
<td>0.34±0.041</td>
<td>5±0.00</td>
<td>81.96±3.21%</td>
<td>41.8±0.045</td>
<td>5.1±0.005</td>
</tr>
<tr>
<td>MTG-3</td>
<td>249 ± 0.628</td>
<td>0.37±0.038</td>
<td>5.2±0.002</td>
<td>73.39±4.56%</td>
<td>53.8±0.006</td>
<td>4.8±0.002</td>
</tr>
<tr>
<td>MTG-4</td>
<td>249 ± 0.795</td>
<td>0.12±0.032</td>
<td>5.5±0.00</td>
<td>82.26±2.58%</td>
<td>63.9±0.001</td>
<td>5.3±0.001</td>
</tr>
</tbody>
</table>

Where, \( MTX \) = Matrix tablet of xanthium gum
\( MTG \) = Matrix tablet of guar
Percent weight
Variation = (Total weight of twenty tablets) – (sum of individual weight of twenty tablets) / Total weight of twenty tablet × 100

Friability test

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed. The percentage friability was determined using formula:

\[
\text{% Friability} = \frac{W_0 - W_t}{W_0} \times 100
\]

Where \( W_0 \) and \( W_t \) are initial and final weight respectively, before and after hundred revolutions.

Drug content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of aceclofenac was taken in a 100 ml volumetric flask and made up to the volume with pH 6.8 phosphate buffer. The contents were agitated in a magnetic stirrer at 37°C for 24 hours. At the end of 24 hours content were analyzed spectrophotometrically at 274 nm after suitable dilutions (Table 2).

Thickness test

Tablet thickness should be controlled within a ±5% variation of a standard value. Varner calipers was used to determine the thickness of tablet.

Hardness test

The tablets’ hardness was measured by Monsanto hardness tester. For measuring the hardness tablet to be tested was held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet broke and the force required for breaking the tablet was noted.

Disintegration test.

Disintegration time is the time taken by a tablet to break up into smaller particles. The USP disintegration apparatus was used to determine the disintegration time.

| TABLE 1 |
| Composition of matrix tablets using natural matrix forming polymers (xanthan gum and guar gum) and excipients. |

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>MTX1</th>
<th>MTX2</th>
<th>MTX3</th>
<th>MTX4</th>
<th>MTG1</th>
<th>MTG2</th>
<th>MTG3</th>
<th>MTG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Guar gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>06</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>06</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NaCMC</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>EC</td>
<td>24</td>
<td>18</td>
<td>12</td>
<td>06</td>
<td>24</td>
<td>18</td>
<td>12</td>
<td>06</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lactose</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PVP-K30</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Total weight</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>

MTX = matrix tablet of xanthium gum, MTG = matrix tablet of guar gum, NaCMC = sodium carboxy methyl cellulose, HPMC-K15M = hydroxy propyl methyl cellulose-K15M, EC = ethyl cellulose, PVP-K30 = polyvinyl pyrrolidone-K30

Matrix tablet of aceclofenac shows the disintegration time between 2-3 hours (2.58 ± 0.15, n = 2).

In Vitro Drug Release Studies

In vitro dissolution studies prepared tablets were performed in triplicate in a USP XXIII six station dissolution test apparatus (Veego Model No.6 DR, India) at 100 rpm and at 37°C ± 1°C using 900 ml of pH 6.8 phosphate buffer as dissolution medium for 8 h. Aliquots of 5 ml were withdrawn at predetermined time intervals and replaced with an equivalent amount of fresh dissolution media maintained at the same temperature. The samples were filtered, diluted suitably and then analyzed by measuring the absorbance at 274 nm by UV spectrophotometer.

Results and Discussion

A total of eight different formulations of multilayered sustained release matrix tablets of aceclofenac were prepared using four different ratios (1:2:3:4) of two hydrophilic natural polymers (xanthan gum and guar gum). The gums with the drug constituted the core layer of the matrix tablet, while HPMC K-15M, NaCMC, EC and PVP-K30 constituted the bottom and top layers of the triple-layered matrix tablets (Table 1).

The formulated triple-layered matrix tablets showed the compliance with the pharmacopoeial requirement of uniformity of weight. Thickness was uniform in MTX4, MTG2 and MTG3 formulations (5.1 mm) with a slight variation in other formulations. All the tablets confirmed to the requirement of assay, as per I.P. Hardness, percentage friability and thickness was all within acceptable limits (Table 2). The hardness of the tablets was found to be good with less than 1% particle loss in the friability test for all the formulations of the tablets. The variation in weight was within the range of ± 7.5% complying with the pharmacopoeial specifications for tablet below 250 mg. The thickness of formulation was found in the range of 4.8 ± 0.002 mm to 5.3 ± 0.003 mm.
Highest amount of particle loss in the friability test was found in MTX1 and MTG1 formulation (Table 2). Weight variation was almost uniform, though there was slight variation in MTX4 formulation in case of xanthan gum. Drug content uniformity was found to be in the range of 69.10 ± 3.52% to 89.92 ± 1.62%. Highest percent drug content was found with MTX2 (89.92%) and MTG4 (82.26%) in case of xanthan gum and guar gum formulations, respectively.

The swelling index was found to be increased with the time. The weight gain by tablet was increased proportionately with rate of hydration up to 3 hours. Later on, it was found to be decreasing gradually due to the dissolution of outermost gelled layer of tablet into dissolution medium. It was also observed that the swelling index was directly proportional to the gum concentration. Between the two gums (guar gum and xanthan) it was observed that the swelling index of guar gum was more than that of xanthan gum.

The drug release from the tablets was found to be inversely proportional to the gum concentration and swelling index. It was observed that increasing the concentration of gum from 6% W/V to 24% W/V in the formulation decreased the amount of drug released from 88.98 ± 0.73% to 49.61 ± 48% for the tablets prepared with xanthium and from 73.89 ± 0.75% to 48.6 ± 0.48% for the tablets prepared with guar gum at the end of 8 hours. The results of drug release were well supported by some previous studies which also concluded that the amount of drug released was inversely proportional to gum concentration in matrix tablets prepared from xanthan gum (Dhopeshwarkar and Zatzin, 1993; Rasul et al., 2010).

The release of drug from guar gum based matrix tablet was found to be slower as compared to xanthan gum based tablet. The delay in the release of drug from the tablet might be due to formation of a more thick gel layer (as compared to Xanthium gum) around the matrix of guar gum which was also observed during swelling process in the dissolution study. In case of guar gum matrix tablet, hydration of individual guar gum particles results in extensive swelling. And this extensive swelling further adds to sustaining the release by retarding further penetration of the dissolution medium (Krishnaiah et al., 2002; Varshosaz et al., 2006).

Highest % drug release in case of xanthan gum (MTX1) was found to be 88.98% at the end of 8 hours, while in case of guar gum (MTG1) highest % drug release was found to be 73.89% at the end of 8 hours in pH 6.8 phosphate buffer. Lowest % drug release was found to be 49.6% and 48.6% with MTX4 (24% xanthan gum) and MTG4 (24% guar gum), respectively at the end of 8 hours. During dissolution study it was observed that the tablets released the drug from matrix after considerable swelling. The percent drug release from MTX4 and MTG4 formulations was found to be least as compared to MTX1, MTX2, MTX3 and MTG1, MTG2, MTG3 formulations. The order of percent release of drug (at the end of 8 h) was found to be MTX1 > MTX2 > MTG1 > MTG2 > MTX3 > MTG3 > MTX4 > MTG4 (Figure 1 and Figure 2). The better release performance of xanthan gum based matrix tablets are well supported by a comparative study conducted on matrix tablets of metformin prepared by Xanthan and guar gum by Varshosaz et al., 2006.

Highest amount of particle loss in the friability test was in MTX1 and MTG1 formulation in both cases (Table 2). Weight variation was almost uniform, though there was slight variation in MTX4 formulation in case of xanthan gum. Highest percent drug content was found with MTX2 (89.92%) and MTG4 (82.26%) in case of xanthan gum and guar gum formulations, respectively. All the formulations showed a matrix diffusion dependent release and this was confirmed due to linear relationship between the percent drug release and square root of time (Higuchi plots). In Higuchi plot \( r \) values varies from 0.898 to 0.931 in case of tablets prepared by Xanthium gum and 0.926 to 0.956 in tablets prepared by using Guar gum.
The order of release was found to be following first order rate kinetics in all the formulations. The dissolution data of all the formulation were fitted in the first order equation and a linear relationship was obtained with ‘r’ values close to unity (0.944 - 0.990).

Unlike the monolayer matrix tablets, the multilayered matrix systems do not show inherent disadvantages of nonlinearity associated with diffusion controlled matrix devices by providing adequate drug-release rate with time. Some investigators developed multilayer tablets for modulating release of drugs from hydrophilic polymers (Shajahan and Poddar, 2004; Conte and Maggi, 1996; Maggi and Bruni; 2000; Siahi and Jalali, 2005, El-Nabarawi, 2005). In another study, the drug-release rate from multilayered matrix tablets was found to be dependent on the percentage of xanthan gum, pore-forming agent (like pharmatose DCL 11), and surface area of the formulation exposed to the dissolution medium (Gohel and Bariya, 2009).

Conclusion

GI irritation is caused due to rapid dissolution and high concentration of aceclofenac drug, which may be prevented by using aceclofenac in the form of matrix tablet. Aceclofenac drug particles may enter stomach where pH is less than 4 and will empty from stomach along with the liquids into duodenum. However once the drug reaches intestinal fluid where the pH is > 5 it readily dissolves and is absorbed. So it may be concluded that controlled release of drugs from delivery system throughout the GI tract should provide extended therapeutic benefit with minimal GI irritation.

The physiochemical investigation showed that triple-layered aceclofenac matrix tablet prepared with xanthan gum showed better solubility and dissolution profile as compared to that of guar gum. However, the tablets prepared with less concentration of Guar gum were also found suitable.

Thus, it can be concluded that matrix tablet prepared with xanthan gum may be potential use for improving bioavailability and for reducing the GI toxicity of the drug. Matrix tablet may also be developed for other NSAIDS with poor solubility and GI side effect.

References


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