Formulation and in-vitro evaluation of ketotifen fumarate sustained release matrix tablets using HPMC 4000 cps (methocel K4M CR) and xanthan gum (3:1)

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Abstract
The purpose of this research work was to develop oral sustained release matrix tablets using the combination of HPMC 4000 cps (methocel K4M CR) and xanthan gum (3:1), in order to probe the effect of these polymers on release mechanism from matrix tablets. The matrix tablets of Ketotifen fumarate were prepared by direct compression process using methocel K4M CR and xanthan. The dissolution profiles were carried out by USP apparatus 2 (paddle) at 50 rpm in 500 ml 0.1 N HCl and distilled water. A One way analysis of variance (ANOVA) was used to interpret the result. Statistically significant differences were found among the drug release profile from different matrices. At a higher polymeric content (70% of the total tablet weight), drug release from the combination of methocel K4M CR and xanthan gum (3:1) was slower. On the contrary, at a lower polymeric level (40% of the total tablet weight), the rate of drug release was prominent. The best-fit release kinetics was accomplished with the Higuchi model followed by the zero-order plot, Korsmeyer and Hixson Crowell equations. One formulation showed drug release is more controlled. The data obtained proved that the formulations are useful for a sustained release of ketotifen fumarate. From these formulations corresponded more controlled of the drug release by the higher polymeric level of methocel K4M CR & xanthan and vice versa. The release of the model drug from the higher combination of methocel K4M CR and xanthan gum matrix tablets was prolonged. As a result, an oral release dosage form to evade the frequency of administration of such type of drug.

Keywords: Ketotifen Fumarate, HPMC, Xanthan gum, Matrix tablets, Sustained Release.

Introduction
Oral ketotifen is indicated as an add-on medication in the chronic treatment of mild atopic asthmatic children. Ketotifen is a prophylactic agent to be used on a continuous basis and is not effective in the acute prevention or treatment of acute asthma attacks [1]. Ketotifen fumarate has the properties of the antihistamines in addition to a stabilizing action on mast cells analogous to that of sodium cromoglycate. It is given orally as the fumarate in the prophylactic management of asthma, and also used in the treatment of allergic conditions such as rhinitis and conjunctivitis. Ketotifen fumarate
is taken by mouth in dose equivalent to 1mg of Ketotifen twice a daily with food [2] Relatively selective histamine H1-receptor antagonist and mast-cell stabilizer [3]. Both ketotifen and inhaled budesonide are effective, safe, and well-tolerated in the prevention of asthma exacerbation in children particularly in the country with limited resource [4]. Ketotifen fumarate, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10-H-benzo cycloheptal-,2-b thiophen-10-one fumarate, is used as an antiasthmatic agent [5].

The development of controlled release systems of antiasthmatic antianaphylactic drugs is expected to grow significantly, to avoid acute over dosage. Ketotifen is a perfect candidate for the development of controlled release systems of antiasthmatic antianaphylactic compounds. Its acute toxicity is rather low, since no serious effects have been reported either in children or in adults after the intake of up to 20 mg of ketotifen, which is 10 times the recommended dose and it is well tolerated specially by the children. Ketotifen also induces a moderate to marked symptom improvement in the majority of patients with atopic dermatitis, seasonal or perennial rhinitis, allergic conjunctivitis, chronic or acute urticaria [6-7].

The sorption of water in the both cellulose acetate propionate and cellulose acetate butyrate membranes is quite similar and that the release characteristics of these systems do not follow a zero order profile, indicating that the diffusion mechanism may be Fickian, controlled mainly by the membrane morphology [8].

Hydrophillic polymers are widely used in the formulation of sustained release oral dosage forms. Various natural materials (xanthan, guar gum, and chitosan) have been tried by various researchers. It has been shown that in hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug release rate [9]. Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the Gram-negative bacterium Xanthomonas campestris. Xanthan gum offers potential utility as a drug carrier because of its inertness and biocompatibility.

Xanthan gum not only retards in vitro drug release and provides time independent release kinetics, but also works effectively in vivo and establishes constant drug plasma levels [10]. Dhopeshwarkar and Zatz evaluated xanthan gum as a matrix former for the preparation of sustained-release tablets. It was very effective in prolonging the release of soluble and sparingly soluble drugs [11].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance [12]. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. Hydroxypropyl methylcellulose (HPMC) is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods [13]. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses.

Direct compression was used to compress the tablets, as keeping in mind that HPMC is a hydrophilic polymer that swells to a significant extent upon contact with water. Various studies of drug release mechanism, effect of formulation variables on HPMC matrices are based on direct compression [14,15].

Thus, the purpose of this investigation was to study processing variables at the laboratory and pilot scales that can affect hydration rates of
methocel K4M CR and xanthan gum matrices containing ketotifen fumarate and hence rate of drug release.

Materials and Methods

Materials

Ketotifen fumarate was obtained as gift sample from Beximco Pharmaceuticals Ltd. Dhaka, Bangladesh. HPMC 4000 cps (methocel K4M CR) was a gift sample received from Colorcon Asia Pvt. Limited. Lactose was purchased from Ming Tai Chemical Co. Ltd., (Taiwan). Xanthan gum was procured from Loba chemical, India. Magnesium stearate and Talc were procured from Hanua Chemicals Limited, (Japan).

Preparation of Matrix Tablets

Tablets were prepared by direct compression process. In all cases, the amount of the active ingredient was 2.75 mg and the total weight of the tablet was 150 mg (Table-1).

During granulation process matrix-forming agents, HPMC 4000 cps (methocel K4M CR) & Xanthan gum, magnesium stearate, lactose, talc and the active ingredient were weighed properly. Firstly active ingredient, talc and HPMC 4000 cps (methocel K4M CR) and Xanthan gum (3:1) were mixed for 10 minutes properly. Dried granules were sieved through 20 mesh SS screen to get compressible particle. Lubricants are added during blending part. During blending total mass was taken in a container and blended in a laboratory designed small drum blender machine for about 30 minutes. Particular attention was given to ensure thorough mixing and phase homogenization. The appropriate amount of the mixture were accurately weighed in an electronic balance for the preparation of each tablet and finally compressed using single station compression machine, with a 8.00 mm punch. Before compression, the surfaces of the die and punch were lubricated with purified talc. All the preparations were stored in airtight containers at room temperature for further study.

Physical characterization of matrix tablets

The tablets of the proposed formulations (KF1 to KF4) were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of 10 matrix tablets from each formulation was measured using Hardness tester (Erweka GMBH, 300H model, Germany). Friability of the tablets was determined by testing 10 tablets in a Roche friabilator (Campbell Electronics, Mumbai) for 4 minutes at 25 rpm performed in triplicate. A slide calipers was used to measure the thickness for 5 tablets. Weight variation test was performed by taking 10 tablets using an electric balance (OHAUS LS 200, Switzerland) according to the official method.

Table 1. Formulation of methocel K4M CR and xanthan gum (3:1) based Ketotifen fumarate sustained release matrices.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Ketotifen fumarate (mg/tablet)</th>
<th>Methocel K4M CR</th>
<th>Xanthan Gum (mg/tablet)</th>
<th>Lactose</th>
<th>Mag. stearate</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF1</td>
<td>2.75</td>
<td>45</td>
<td>15</td>
<td>85.25</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>KF2</td>
<td>2.75</td>
<td>56.25</td>
<td>16.75</td>
<td>70.25</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>KF3</td>
<td>2.75</td>
<td>67.5</td>
<td>22.5</td>
<td>55.25</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>KF4</td>
<td>2.75</td>
<td>78.75</td>
<td>26.25</td>
<td>40.75</td>
<td>0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Compression weight of each formulation was 150 mg.
Drug content for Ketotifen fumarate was carried out by measuring the absorbance of the sample at 300 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard Ketotifen fumarate in the same medium by taking 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken, suitably dissolved in distilled water, making dilution and analyzed and carried out in triplicate and mean was taken.

In Vitro Drug Dissolution Studies
Drug release profiles were evaluated in vitro using a dissolution test apparatus (VEEGO VDA 8 DR, Germany). The USP paddle method was selected to perform the dissolution profiles of Ketotifen fumarate. The test for all the formulations was carried out in 500 ml 0.1 N HCl, and distilled, maintained at 37.5 °C (± 0.5°C) at a paddle rotation speed of 50 rpm. Withdrawing 5 ml filtered samples at preselected intervals up to 8 hours monitored progress of the dissolution. The release rates from these polymeric matrices were conducted in a medium of changing pH by starting with a tablet in HCl solution (pH=1.2) for 2 hours. Then, the tablets were immersed into a distilled for next 6 hours. The sample solutions were analyzed for Ketotifen fumarate by UV absorbance at 300 nm using a UV Spectrophotometer (UV-1240 mini, SHIMADZU, Japan). Cumulative percentage of drug release was calculated and the mean of six tablets was used in data analysis.

Release Kinetics
Different kinetic models (zero-order, first-order, Higuchi’s, Korsmeyer’s and Hixson Crowell) were applied to interpret the release profile (the order and mechanism of Ketotifen fumarate release) from matrix system. To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. However, two factors diminish the applicability of Higuchi’s equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems.

\[
\log \left( \frac{M_t}{M_f} \right) = \log k + n \log t \quad \text{……………. (1)}
\]

Where, \( M_t \) is the amount of drug release at time \( t \); \( M_f \) is the amount of drug release after infinite time; \( k \) is a release rate constant incorporating structural and geometric characteristics of the tablet; and \( n \) is the diffusional exponent indicative of the mechanism of drug release. Talukder et al [16] applied this equation to evaluate the drug release mechanism from xanthan gum matrix tablets. To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of \( n = 0.45 \) indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 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 [17].

The Hixson - Crowell cube root equation is:

\[
M_{1/3} = M_{0_{1/3}} - K_c t \quad \text{-------------------- (2)}
\]

Where, \( K_c \) is the cube root dissolution rate constant. Cube roots of percent releases (Cube root of initial drug load minus cube root of % drug remaining) are plotted against time (hour) to demonstrate the Hixson Crowell plot.

Mean dissolution time (MDT) was calculated from dissolution data using the following equation [18].

\[
\text{MDT}= \frac{n}{n+1}.K^{-1/n} \quad \text{……………. (3)}
\]

Statistical Analysis:
A one way analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate and comparison of mean dissolution time (MDT) of all formulations. A confidence limit of $P < .05$ was fixed and the theoretical calculated values of $F$ (Fcrit and Fcal) were compared for the interpretation of results. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA).

**Results**

**Physical Evaluation of Ketotifen fumarate matrix tablets**

The tablets of the proposed formulations (KF1 to KF4) were evaluated for hardness, weight variation, thickness, friability and drug content. The thickness (mean ± SD, n=5) of the tablets were (3.75±0.01, 3.50±0.02, 4.00±0.03, 3.99±0.02 respectively) ranged from 3.5 to 4.00 mm. The hardness (mean ± SD, n=10) and percentage friability ($< 1\%$) of the tablets of all batches (5.50±0.27, 4.70±0.3, 5.50±0.27, 4.90±0.4 respectively) ranged from 4.70 to 5.5 kg/cm² and 0.45% to 0.66 %, respectively. The average percentage weight deviation of 10 tablets of each formula was less than ±5%. Drug content (mean value ± SD within 0.9) among different batches of tablets ranged from 150.50 mg to 151mg.

**Effect of HPMC 4000 cps (methocel K4M CR) and Xanthan gum on release pattern of Ketotifen fumarate**

Matrix tablets of Ketotifen fumarate were formulated using direct compression technique. Different proportion of HPMC 4000 cps (Hydroxypropylmethylcellulose 4000 cps) and xanthan gum (3:1) matrix tablet containing Ketotifen fumarate as active ingredient having methocel K4M CR and xanthan gum polymer (3:1) containing 40%, 50%, 60% and 70% in the matrix tablet with the formulation code KF1, KF2, KF3, KF4 were prepared to evaluate the effect of these polymer. After preparation according to formulation shown in the table 1, their dissolution studies were carried out in basket method at 50 rpm in 500ml distilled water medium at 37 °C (±0.5°C). Six tablets from each formulation were used in dissolution study. The release profile of Ketotifen fumarate was monitored up to 8 hours (Initial 2 hours in simulated gastric fluid (pH 1.2) and next 6 hours in distilled water).

A release profile of Ketotifen fumarate containing having HPMC 4000 cps (methocel K4M CR) and xanthan gum polymer (3:1) polymeric matrix tablets of the formulations was obtained from the graphs (Fig. 1A-1E).
**Fig. 1A**: Zero order plot of release kinetics of Ketotifen fumarate matrix tablets.

**Fig. 1B**: Higuchi plot of release kinetics of Ketotifen fumarate matrix tablets.

**Fig. 1C**: First order plot of release kinetics of Ketotifen fumarate matrix tablets.
**Fig. 1D:** Korsmeyer plot of release kinetics of Ketotifen fumarate matrix tablets.

**Fig. 1E:** Hixson Crowell plot of release kinetics of Ketotifen fumarate matrix tablets.
The total % of Ketotifen fumarate release (mean value ± SD within 0.7, n = 6) from the formulations KF1, KF2, KF3, KF4 was 77.060, 61.910, 51.760, 49.005 respectively. It has been observed that the release rate has been extended with the increase of the amount of polymeric level. The highest percent of drug release within 8 hours is 77.060% obtained from KF1 where methocel K4M CR and xanthan gum polymer (3:1) amount of polymeric level is lower 40%. But in KF4 (methocel K4M CR and xanthan gum) containing amount of polymeric level is higher 70% and the release of drug is 49.005% within 8 hours. The rate of drug release was found to be inversely related to proportion of the polymer present in the matrix structure, i.e. the drug release increased with lower viscosity grade and polymer proportion in the matrix tablet. The release rate was significantly dependent on the proportion of the polymer.

A statistically significant decrease (P <.05, Fcrit (3, 20) = 3.10 and Fcal = 103.29) at the end of first hour, (P <.05, Fcrit (3, 20) = 3.10 and Fcal = 302.09) at the end four hours, (P <.05, Fcrit (3, 20) = 3.10 and Fcal = 8611.97) at the end of eight hours, was observed drug release in the formulation KF1 to KF4, as the polymeric proportion increased from 40% to 70%.

From the table 2, it is mentioned that the proposed formulations KF4 followed Higuchi with regression value 0.91. All formulations followed zero order, first order, Korsmeyer and Hixson Crowell with regression values between 0.96 to 0.98, 0.94 to 0.97, 0.94 to 0.99 and 0.96 to 0.98 respectively.

### Table 2: Release kinetics of formulated Ketotifen fumarate from different proportion of K4M CR and xanthan gum (3:1) based matrices.

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer</th>
<th>Hixson Crowell</th>
</tr>
</thead>
<tbody>
<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>KF1</td>
<td>0.981</td>
<td>9.420</td>
<td>0.939</td>
<td>-0.073</td>
<td>0.905</td>
</tr>
<tr>
<td>KF2</td>
<td>0.982</td>
<td>7.832</td>
<td>0.97</td>
<td>-0.051</td>
<td>0.893</td>
</tr>
<tr>
<td>KF3</td>
<td>0.962</td>
<td>6.928</td>
<td>0.972</td>
<td>-0.042</td>
<td>0.90</td>
</tr>
<tr>
<td>KF4</td>
<td>0.964</td>
<td>6.365</td>
<td>0.967</td>
<td>-0.037</td>
<td>0.888</td>
</tr>
</tbody>
</table>

**Figure 2:** Successive dissolution time of Ketotifen fumarate containing various proportions of methocel K4M CR and xanthan gum (3:1)
\( R^2 \), Correlation coefficients, \( K_0 \), \( K_1 \), \( K_h \), \( K_c \) 
Release rate constant for zero order, first order, Higuchi, and Hixson Crowell release equation, respectively, \( n \), diffusional exponent, indicative of release mechanism in Korsmeyer equation. All formulations followed Supper case II Release

The formulation KF1 showed lowest MDT (mean dissolution time) with \( T_{50\%} \), \( T_{80\%} \) values are 5.30 hr, 5.29 hr, 8.51 respectively of all as it increased the release rate as containing low level of methocel K4M CR and xanthan gum. But, as the polymeric level of methocel K4M CR and xanthan gum is increased in the latter formulations (KF2, KF3 and KF4), MDT values were increased 6.53, 7.06 and 7.82, i.e increase polymer viscosity increase MDT value. Formulation KF1 to KF4, increase polymeric level decrease release rate of the Ketotifen fumarate.

\( T_{25\%} \), \( T_{50\%} \), \( T_{80\%} \) and MDT values of the designed tablets are also shown in figure 2.

Formulation KF4 containing methocel K4M CR and xanthan gum showed highest MDT (7.82 hr) value with \( T_{50\%} \) (7.89 hr), \( T_{80\%} \) (12.35 hr).

The MDT (Mean Dissolution Time) values for the formulations KF1 to KF4 increased significantly \( P < .05 \), \( F_{crit} (3, 20) = 3.10 \) and \( F_{cal} = 768.21 \) as polymeric level was increased from 40% to 70%.

**Discussion**

**Physical Evaluation of Ketotifen fumaratematrix tablets**

The present study was carried out to formulate oral sustained release drug delivery system for Ketotifen fumarate as matrix tablets. The drug content of all formulations was between 100.33% to 100.67 %, indicating the presence of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed acceptable hardness and friability indicating suitable for direct compression method.

**In vitro dissolution study of tablets**

All formulations showed no evidence of initial burst release within the first hour of dissolution test period in pH 1.2 as containing polymeric level from 40% to 70%. However the formulations KF3 and KF4 containing higher polymeric level (60% and 70%) was increased of methocel K4M CR and xanthan gum polymer was observed more controlled within first hour probably to the low solubility of the drug at pH 1.2 and higher proportion of polymer and retained their shape throughout the 8 hours dissolution period.

The release rate decreased significantly and the drug release prolonged as the polymer proportion was increase. Such increase in polymer content results in a decrease in the drug release rate due to a decrease in the total porosity i.e. release is extended to long period. Lactose causes a decreased tortuosity of the path of the drug due to its preferential solubility than methocel K4M CR and xanthan gum, by its swelling effect, additionally weakened the integrity of the matrix [19].

All the formulations, the rate and extent of drug release were decreased with increasing the amount of methocel K4M CR and xanthan gum. This polymer has been well known to retard the drug release by swelling in aqueous media. A polymer’s ability to retard the drug release rate is related to its viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets [20]. The hydration rate of HPMC depends on the nature of the substituents like hydroxypropyl group content. Hence, Methocel K4M CR was used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlled delivery of drug [21].
For the formulation KF3 and KF4 containing highest proportion of polymer and drug release is more controlled both pH 1.2 (less than 10% in first hour) and distilled water (extended more than 8 hours). This may be owing to a more rigid complex formed by presence of higher proportion of methocel K4M CR and xanthan gum which helped in retaining the drug in matrix and did not allow rapid diffusion of drug from the matrix. According to USP specification, for controlled release drug delivery system (Tablet/capsule), at time equal to 0.25D, 20 -50% drug will be dissolved, at time equal to 0.5D, 45-75% dissolved and thereafter at any time up until 1.0D, not less than 75% of drug will be dissolved where D is the labeled usual dosing frequency or interval [22]. With this objective in view, it is observed that only KF3 and KF4 showed drug release according to USP specification.

Kinetic modeling of the drug release
The drug release data obtained were extrapolated by Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations. Equation (1) was used to calculate the n values and to identify the drug release mechanism of drug from the four formulations used in this study.

In this experiment, the in vitro release profiles of drug from all formulations could be best expressed by Zero equation as the plots showed highest linearity (R^2: 0.96 to 0.98). To confirm the release mechanism, the data were fitted into Korsmeyer-Peppas equation. The all formulations showed good linearity (0.94 to 0.99) with slope (n) values ranging from 0.98 to 1.049 indicating that diffusion was the predominant mechanism of drug release from these formulations indicating that the release mechanism was supper case II release (n > 0.89). It can be inferred that the release was dependent on Zero-order release due to the dissolution of polymeric matrix and relaxation of the polymer chain. This finding was also in agreement with results obtained from application of zero-order and Hixson-Crowell equations\textsuperscript{17}. The good correlation coefficients (R^2 values nearly to unity) observed for the kinetic parameters based on the first order model equation were mainly due to the drug release mechanism. First order plot for all formulation showed good linearity. This indicates that the amount of drug released is dependent on the matrix drug load. The release profile of Ketotifen fumarate from all these formulations displayed very fairly good fitting with Hixson-Crowell cube root model of drug release confers that the drug releases by dissolution and with the changes in surface area and diameter of the particles or tablets [23].

MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability and vice-versa. The lowest MDT value (5.3 hrs) was found with formulation KF1 which also showed a low value of T_{50} (5.3 hrs) and a high value of Higuchi release rate (27.58 %/√time). In contrast, all other the formulations containing methocel K4M CR and xanthan gum exhibited a higher value of MDT and a low value of Higuchi release rate than that of batch KF1 indicating the higher drug-retarding ability of these formulations. An inverse relationship was found between proportion of HPMC 4000 cps and xanthan gum in the formulations and the MDT values of the dosage form. The MDT value was found to decrease with HPMC 4000 cps and xanthan gum was increased in the formulations.

Conclusion
From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. According to the release studies, the decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with higher proportion of methocel K4M CR and xanthan gum was shown to be beneficial than lower polymeric level in controlling drug release. The results of release studies indicated the possibility
of achieving a suitable modulation of Ketotifen fumarate release rate by opportunely combination of methocel K4M CR and xanthan gum (3:1) in the matrix tablet.

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