High patient compliance and flexibility in developing dosage forms made the oral drug delivery systems the most convenient mode of drug administration compared to other dosage forms. Of these, matrix systems have gained widespread importance. Matrix drug delivery systems are of two types: diffusion/swellable systems and dissolution systems.

The objective of this study was to investigate the influence of the molecular size of carboxymethylcellulose (cmc) and some hydrophobic polymer additives on the release properties of theophylline from tablet matrices. The cmc matrices were prepared by the conventional wet granulation method. The granules were evaluated for angles of repose, bulk density, compressibility index, and porosity, while the tablets were subjected to hardness, friability and compression tests. All tablet formulations showed acceptable pharmacotechnical properties. Low molecular size cmc (cmc-L) showed the shortest drug release $t_{50\%}$ of 27 min, for medium size cmc (cmc-M) it was 55 min and for high molecular size cmc (cmc-H) 200 min. In general, the results showed that the drug release rate decreases with an increase in the molecular size of cmc. All polymer additives, ethylcellulose, cellulose acetate phthalate and Eudragit L-100 retarded theophylline release from cmc-L and cmc-H, with ethylcellulose having the most pronounced effect on cmc-L. Kinetic studies using Hixson-Crowell and Peppas-Ritger equations showed that different drug release mechanisms were involved in controlling drug dissolution from the tablets. The drug release mechanism was influenced by both the molecular size of cmc and the presence of polymer additives.

**Keywords:** carboxymethylcellulose, hydrophobic polymers, theophylline, sustained-release, release mechanism
In diffusion systems, drug release is mainly governed by the hydration of matrices, followed by diffusion of drug molecules from the hydrated layer to the surrounding bulk solution, and sometimes, partially by erosion/dissolution. Examples include Eudragits and cellulose ethers. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence, achievement of constant drug delivery rate is easier by these systems. Sodium carboxymethylcellulose and natural gums are examples of polymers that are gaining popularity in matrix drug delivery systems.

Cellulose gum (sodium carboxymethylcellulose) is a water-soluble polymer that comes in three molecular sizes: low, medium and high (cmc-L, cmc-M and cmc-H). It has a long history of use as a suspending agent in liquid pharmaceutical preparations. It has also found as tablet binder. Recent work has confirmed the usefulness of cellulose gum in sustained-release applications (1–3).

Drug release from polymer matrices is influenced, among other factors, by the molecular size of the polymer (4). While reports on the effect of the molecular size of hydroxypropyl methylcellulose, gelatin, and sodium alginate on drug release are found in literature, our search reveals that there is currently no such report on cmc. Drug release from hydrophilic polymers may be modified in the presence of additives (5–7). pH sensitive polymers such as cmc (1) could have their release pattern desirably altered in the presence of additives. In this study, we have investigated the effect of molecular size of sodium carboxymethylcellulose (cmc) and some hydrophobic polymers on the sustained release of theophylline from compressed tablets.

EXPERIMENTAL

Theophylline powder (Wako, Japan), sodium carboxymethyl cellulose [Wako] Eudragit L-100 [EUD, methacrylic resin (Rolm Pharma, Germany)], cellulose acetate phthalate (CAP), ethylcellulose (ETC) and Prosolv HD90 [silicified micro crystalline cellulose (Penwest, USA)] were used. All other materials were of analytical or reagent grade.

Preparation of matrix tablets

Theophylline, cmc (cmc-L, cmc-M or cmc-H), ethylcellulose, cellulose acetate phthalate or Eudragit L-100 and Prosolv HD90 were mixed in a blender (BRAUN, Germany). The powder mixture consisting of 33.3% theophylline, 30% cmc, 5% polymer additive (ETC, CAP or EUD) and 31.2% Prosolve HD90 was mixed for 15 min using a tumbler mixer (Karl, Germany) and granulated with water for 5 min using a granulator (Erweka, Germany) fitted with 1.6 mm mesh. Granules were dried at 50 °C for 60 min in a hot air oven (Salvis, UK). The dried granules were re-screened through a 1.7 mm sieve and lubricated with 0.5% talc for 5 min using the tumbler mixer. The final blend was tableted using a single station tablet press (THP Shanghai, Tianxiang, Chentai Pharmaceutical Machinery, China) equipped with 10.5 mm punch and die set. Tablets weighing 300 mg each and containing 100 mg theophylline were compressed at 23.75 kN and a dwell time of 60 s (Table I).
**Micromeritic properties of granules.** – The angle of repose was determined using the method of Martin et al. (8). Bulk, tapped and true density for each powder was determined using standard methods (9). Compressibility of the powder was calculated using Carr’s index (10).

**Tablet thickness and tensile strength.** – Tablet thickness and crushing strength were determined using the apparatus Pharmatest model PTB-311 Germany. Crushing strength was examined by placing a tablet between a stationary and moving spindle force was applied by turning the moving spindle until the tablet cracked diametrically. Tablet tensile strength was calculated according to Fell and Newton (11). Friability of the compacts was evaluated from the mass loss of 10 tablets tumbled for 100 revolutions (25 rpm for 4 minutes) using a friabilator (Erweka).

**Drug release studies**

The in vitro drug release studies were performed using the basket method in an Erweka DT dissolution rate tester (Erweka) at a speed of 100 rpm. A 900-mL volume of SIF (pH 7.5) maintained at 37± 0.5 °C was used as dissolution medium. Aliquots of dissolution medium (3 mL) were withdrawn at 30 min intervals for up to six hours and subsequently at hourly intervals for up to eight hours. The withdrawn amount was replaced with an equal volume of fresh dissolution medium kept at 37 ± 0.5 °C. The withdrawn samples were analyzed for drug content at 292 nm using a Shimadzu UV 160A spec-
trophotometer (Shimadzu, Japan). The data presented are for quadruplicate determinations. For each dissolution profile, the release data was analyzed by fitting in an appropriate release model. The release parameters were computed from the regression line.

**Kinetic studies**

Two equations, Hixson-Crowel (12) and Peppas-Ritger (13), were used for the mathematical modeling of drug release. The Hixson-Crowel cube root kinetic equation describes the relationship between the drug release mechanism and dissolution time:

\[ \frac{w_d}{w_i}^{1/3} = 1 - k_1 t \]

where \( w_d \) is the tablet dry mass at predetermined times after immersion in the dissolution medium, \( w_i \) is initial dry mass of the tablet, \( k_1 \) is the erosion rate constant of the tablet, and \( t \) is the dissolution time. A modified Hixson–Crowel equation (12) that accurately correlates the drug dissolution profile could be used:

\[ [1 - \frac{Q_d}{A}] = 1 - k_2 t \]

where \( Q_d \) is the amount of drug dissolved at time \( t \), \( A \) is the total amount of drug in the matrix, and \( k_2 \) is the apparent rate constant. The Peppas equation describes the influence of polymeric hydration and swelling in drug release rate;

\[ \frac{m_t}{m_w} = k t^n \]

where, \( m_t / m_w \) is the fraction of drug release, \( k \) is the release rate constant, \( n \) is the diffusional release exponent indicative of the drug release mechanism, and \( t \) is the dissolution time. To determine the extent and rate of drug release from the various formulations, the time required for 50% and 70% of the drug to be released (\( t_{50\%} \) and \( t_{70\%} \), respectively) and the dissolution efficiency (DE %) of the formulations were calculated. \( t_{50\%} \) and \( t_{70\%} \) were obtained directly from the dissolution time curves, while dissolution efficiency was calculated from the following equation

\[ \text{DE} (%) = \frac{\text{AUC}_{\text{diss}}[0\rightarrow8h]}{\text{AUC}[1\times8h]} \]

Where DE is dissolution efficiency, \( \text{AUC}_{\text{diss}} \) is the area under the dissolution curve.

**RESULTS AND DISCUSSIONS**

**Micromeritic properties of theophylline granules**

All the granules, irrespective of the cmc molecular size, had potentially good flow, as indicated by the values in Table II. The mixture of cmc and polymer additives result-
ed in increased angles of repose. Reduction in flowability (indicated by the increase in the angle of repose) was higher with the cmc-L than with cmc-M and cmc-H. Interaction between the hydrophilic cmc and hydrophobic polymer additives is mainly due to the binding effect of the soluble portion of cmc in the presence of water (granulating fluid) forming a latex solution, whose characteristics would depend on the nature of the cmc used.

Properties of theophylline tablet

Tablet porosity increased in the presence of additives in all batches (Table III). Ethylcellulose, which is known to undergo plastic deformation during compact formation, a behavior that increases the porosity of the compact, had the greatest effect. Tablet hardness was in the order cmc-H > cmc-L > cmc-M. All hydrophobic polymers reduced the mean hardness of tablets containing cmc irrespective of the molecular size, except ethylcellulose, which increased the mean hardness of cmc-M and cmc-H.

Inclusion of polymer additives in the formulations affected the tensile strength of the compacts, with the nature of the effect dependent on the particular additive and the molecular size of the cmc. The observed effects of ETC and EUD in reducing tensile strength were unexpected since they undergo plastic deformation (15), which should result in enhanced particle cohesion and increased tablet strength. It seems that the overall mechanism of polymer-polymer interaction under pressure is a function of the molecular size of cmc and the nature of the polymer additive.

In vitro release from sustained-release tablets

Effect of molecular size. – Drug release was in the order cmc-L > cmc-M > cmc-H (Fig. 1a). Drug release is mainly dependent upon the rate and extent of water penetration into the tablet matrix and the relative aqueous solubility of both the matrix material and the drug compound(s) embedded in the matrix (14). It is generally accepted that diffusion and release rates decrease with an increase in molecular size (1). The onset of drug release is faster with cmc-L than with cmc-M and cmc-H (Fig. 1a). This observation is similar to that of Braunecker et al. (6).

Effect of polymer additives on theophylline release. – All the polymers used generally decreased the initial drug release from the hydrophilic matrix (Fig. 1b). After 3 hours, however, CAP and EUD I-100 exerted enhancing effects on the drug release. Hydrophilic polymers such as cmc rely on water absorption to produce gel swelling and matrix relaxation, which subsequently facilitate drug dissolution and diffusion from the matrix. The presence of a hydrophobic polymer in the same matrix results in reduced water uptake rate by the matrix, reduced drug dissolution and diffusion, producing a sustained release pattern.

Addition of ETC to cmc-L did not appear to significantly affect the dissolution characteristics of theophylline after 3 hours, probably because of the higher hydration rate and solubility of cmc-L (1).

Only CAP significantly influenced the theophylline release in the presence of cmc-M (Fig. 1c). This is probably due to the higher solubility of CAP under alkaline conditions of SIF, which creates pores in the matrix for drug dissolution and diffusion.
Table II. Some micrometric properties of theophylline granules

<table>
<thead>
<tr>
<th></th>
<th>A₁</th>
<th>A₂</th>
<th>A₃</th>
<th>B₄</th>
<th>B₅</th>
<th>B₆</th>
<th>B₇</th>
<th>B₈</th>
<th>B₉</th>
<th>B₁₀</th>
<th>B₁₁</th>
<th>B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative density</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>2.0 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.6 ± 0.4</td>
<td>2.7 ± 0.2</td>
<td>1.7 ± 0.3</td>
<td>3.6 ± 0.2</td>
<td>3.1 ± 0.2</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td><strong>Tapped density</strong> (g cm&lt;sup&gt;–3&lt;/sup&gt;)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.01</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.5 ± 0.3</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td><strong>Bulk density</strong> (g cm&lt;sup&gt;–3&lt;/sup&gt;)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td><strong>Angle of repose</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.0 ± 0.2</td>
<td>29.0 ± 0.1</td>
<td>28.7 ± 0.0</td>
<td>25.1 ± 0.1</td>
<td>25.0 ± 0.2</td>
<td>23.5 ± 0.1</td>
<td>35.0 ± 0.1</td>
<td>30.0 ± 0.1</td>
<td>29.0 ± 0.3</td>
<td>30.0 ± 0.2</td>
<td>29.5 ± 0.1</td>
<td>30.5 ± 0.1</td>
</tr>
<tr>
<td><strong>Hausner’s ratio</strong></td>
<td>1.1</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Carr’s index (%)</strong></td>
<td>10.0</td>
<td>20.0</td>
<td>13.2</td>
<td>12.7</td>
<td>18.3</td>
<td>19.0</td>
<td>15.6</td>
<td>9.4</td>
<td>11.1</td>
<td>20.0</td>
<td>5.0</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Porosity (%)</strong></td>
<td>57</td>
<td>75</td>
<td>70</td>
<td>76</td>
<td>74</td>
<td>71</td>
<td>86</td>
<td>83</td>
<td>91</td>
<td>88</td>
<td>74</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± SD, n = 3.

Table III. Properties of theophylline tablets

<table>
<thead>
<tr>
<th></th>
<th>A₁</th>
<th>A₂</th>
<th>A₃</th>
<th>B₄</th>
<th>B₅</th>
<th>B₆</th>
<th>B₇</th>
<th>B₈</th>
<th>B₉</th>
<th>B₁₀</th>
<th>B₁₁</th>
<th>B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hardness</strong> (kg) (mean ± SD)</td>
<td>12.6 ± 0.1</td>
<td>12.4 ± 1.5</td>
<td>13.6 ± 0.1</td>
<td>8.7 ± 0.1</td>
<td>11.7 ± 0.1</td>
<td>10.6 ± 0.1</td>
<td>13.8 ± 0.1</td>
<td>13.6 ± 0.0</td>
<td>11.3 ± 0.1</td>
<td>13.8 ± 0.1</td>
<td>13.6 ± 0.1</td>
<td>13.4 ± 0.0</td>
</tr>
<tr>
<td><strong>Friability (%)</strong> (n = 10)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Tensile strength</strong> (MN m&lt;sup&gt;–2&lt;/sup&gt;)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Porosity (%)</strong></td>
<td>4</td>
<td>8</td>
<td>9</td>
<td>50</td>
<td>47</td>
<td>38</td>
<td>63</td>
<td>42</td>
<td>72</td>
<td>68</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>
The polymers exerted no significant influence on theophylline release from cmc-H (Fig. 1d), probably because the higher viscosity of cmc-H overwhelmed the influence of polymer additives. The results indicate that different drug release mechanisms were involved, depending on the molecular size of cmc and the type of the hydrophobic polymer additive present in the formulation. All polymer additives retarded theophylline release from cmc-L and cmc-H, with no significant difference in the extent of retardation as measured by $t_{50}$. Ethylcellulose, however, had the greatest retardation effect in cmc-L (Table IV).

Ethylcellulose, a water-insoluble polymer, when in contact with water, swells and retards drug release. It displays initial surface erosion, which is responsible for the initial fast release. The release rate then decreases because the external layers of the tablet become depleted and water must penetrate the deeper layers of the tablet to reach the undissolved drug (16). This is probably responsible for a more extended $t_{70}$ in tablets containing ETC (Table IV).
Cmc-M containing additives showed enhanced release, as shown by \( t_{50} \) and \( t_{70} \) values (Table IV). Formulations containing CAP, which is soluble in alkaline SIF, had the fastest release profile. The effects seen with these polymeric retardants are imparted through possible interaction between the additives and cmc or the additives actively forming an integral structure within the cmc gel layer (17).

The apparent dissolution rate constants (\( k \)) of various tablet formulations range between 0.130–0.356 h\(^{-1}\) for cmc alone, and 0.119–0.313 h\(^{-1}\) for cmc containing polymer additives (Table V).

Formulations without polymer additives had poor correlation (\( R^2 < 0.9 \)) while there was a significant change in the dissolution rate constants in all formulations with polymer additives. The dissolution rate constant was in the order: cmc-L > cmc-M > cmc-H, suggesting that cmc-L had better water permeability and gel relaxation properties. This is consistent with our earlier observations (3).

In general, tablets made of cmc-M with CAP as polymer additive had the highest rate constant, while cmc-H with ethylcellulose as polymer additive had the lowest rate constant. This indicates that the former had higher water permeability and weaker bonding with alkaline-soluble (CAP) polymers.

In this study, the \( n \) value of various tablet formulations ranged from 0.47–1.17 for cmc without additives and 0.76–1.71 for cmc with additives (Table V). Except for formulations A2, B7 and B9, there was satisfactory curve fitting of the dissolution data. Disso- lution of theophylline from cmc-L appeared to obey a Fickian mechanism, as \( n \) value was less than 0.5 (18). The presence of polymer additives changed this Fickian release from cmc-L to non-Fickian. The super case II release mechanism of cmc-M was also changed to non-Fickian by ETC and CAP. None of the additives had a significant effect on the release kinetics of theophylline from cmc-H.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>( t_{50} ) (min)</th>
<th>( t_{70} ) (min)</th>
<th>DE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>27.9</td>
<td>58.9</td>
<td>87.2</td>
</tr>
<tr>
<td>A2</td>
<td>55.2</td>
<td>76.9</td>
<td>91.9</td>
</tr>
<tr>
<td>A3</td>
<td>201.6</td>
<td>250.6</td>
<td>61.8</td>
</tr>
<tr>
<td>B4</td>
<td>56.7</td>
<td>106.8</td>
<td>83.0</td>
</tr>
<tr>
<td>B5</td>
<td>60.0</td>
<td>94.3</td>
<td>87.3</td>
</tr>
<tr>
<td>B6</td>
<td>60.0</td>
<td>92.1</td>
<td>85.6</td>
</tr>
<tr>
<td>B7</td>
<td>48.9</td>
<td>66.3</td>
<td>89.9</td>
</tr>
<tr>
<td>B8</td>
<td>29.9</td>
<td>40.7</td>
<td>96.7</td>
</tr>
<tr>
<td>B9</td>
<td>53.1</td>
<td>64.2</td>
<td>91.0</td>
</tr>
<tr>
<td>B10</td>
<td>214.6</td>
<td>248.5</td>
<td>59.4</td>
</tr>
<tr>
<td>B11</td>
<td>207.6</td>
<td>240.0</td>
<td>64.4</td>
</tr>
<tr>
<td>B12</td>
<td>222.5</td>
<td>240.0</td>
<td>62.1</td>
</tr>
</tbody>
</table>

DE – dissolution efficiency
Dissolution of theophylline from cmc indicated the involvement of more than one mechanism of anomalous diffusion and matrix relaxation/erosion. The dissolution rate constant decreased as the molecular size increased ($A_1 > A_2 > A_3$). All the formulations containing CAP had higher dissolution rate constants than those containing ETC and EUD, indicating higher water permeability of CAP and weaker bonding with cmc.

**CONCLUSIONS**

This study shows that the molecular size of a matrix-forming polymer such as cmc affects its formulation behavior. The presence of polymeric materials such as ethylcellulose, cellulose acetate phthalate and Eudragit l-100, even at the very low concentration of 5%, modified the initial release performance of cmc and influenced the overall mechanism of release. Careful selection of molecular sizes and adjustments in polymer additives are required during formulations involving polymers of varying molecular sizes. This is the result of a developmental study; therefore, the effect of higher concentrations of the used polymer additives on the different molecular size of cmc will be investigated in order to explore which percentage of polymers can exhibit a desirable release profile.

*Acknowledgements.* – The authors are grateful to Dr. Yakubu Ngwai of the Animal Health Laboratories, University of Ibaraki, Japan, and Dr. Samson Amos of the Department of Neuropathology, University of Virginia, for their assistance. We are also grateful to Abuh Garba, Hadiza Shaibu and Mrs. Stella Bartholomew for their technical and secretarial assistance, respectively.
REFERENCES


U radu je ispitivan učinak molekulske mase karboksimetilceluloze (cmc) i nekih hidrofobnih polimera kao aditiva na profil oslobađanja teofilina iz tabletnih matriksa. Matriksi sa cmc pripremljeni su uobičajenom metodom vlažne granulacije. Granulama je određivana sipkost, gustoća, poroznost i indeks kompresivnosti, dok je tabletama ispitivana tvrdoća, rastrokljivost i kompresibilnost. Sve pripravljene tablete imale su prihvatljiva farmakotehnička svojstva. Najbrže vrijeme oslobađanja $t_{50\%}$ od 27 min postignuto je iz pripravka cmc male molekulske mase (cmc-L), 55 min iz pripravka cmc srednje molekulske mase (cmc-M) 55 min i 200 min iz pripravka cmc velike molekulske mase (cmc-H). Rezultati ukazuju na to da se brzina oslobađanja smanjuje povećanjem molekulske mase cmc. Svi polimerni aditivi, etilceluloza, celuloza acetat ftalat i Eudragit L–100 usporili su oslobađanje teofilina iz pripravaka cmc-L i cmc-H pripravka, a najveći učinak imala je etilceluloza na cmc-L. Kinetičke studije provedene pomoću Hixson-Crowelove i Peppas-Ritgerove jednadžbe ukazuju na to da su u oslobađanju teofilina iz tableta uključeni različiti mehanizmi. Na mehanizam oslobađanja utjecali su i molekulska masa cmc i prisutnost polimernih aditiva.

Ključne riječi: karboksimetilceluloza, hidrofobni polimeri, teofilin, usporeno oslobađanje, mehanizam oslobađanja

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