Preparation of an oral acetaminophen film that is expected to improve medication administration: Effect of polyvinylpyrrolidone on physical properties of the film

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Summary This study investigated the effect of polyvinylpyrrolidone (PVP) on a film containing carboxymethyl cellulose sodium (CMC) as a matrix to improve surface roughness caused by drug recrystallization. Acetaminophen (AA) was used as the model drug. Recrystallization is a problem encountered during the preparation of films that contain high drug doses, making them difficult to take. A film that does not disintegrate for clinical applications requires a smooth surface, moderate strength and elasticity, and a low level of adhesiveness to facilitate taking of the medication. Addition of PVP to the film formulation made the surface significantly smoother, and it was independent of the compounding method. Smooth films were obtained when the CMC concentration was kept constant and the amount of PVP was increased, but it also increased the adhesiveness and strength, and decreased the elasticity of the films. When high polymer concentration was kept constant and the ratio of CMC and PVP was varied, the films with smaller amounts of PVP tended to have a smoother surface and less adhesiveness. However, when the amount of PVP was reduced, the film strength increased and elasticity decreased. The amount of PVP had a negligible effect on drug dissolution behavior, making it useful for preparation of the AA film. However, it is necessary to determine the compounding method and the PVP load considering the adhesiveness, strength, and elasticity of the films.

Keywords: Oral film, acetaminophen, carboxymethyl cellulose sodium, polyvinylpyrrolidone

1. Introduction

Oral preparations are widely used, and are an important type of formulation in pharmacotherapy. Tablets are most commonly used for their convenience, but there can be difficulties for infants and patients who have trouble swallowing. These problems lead to reduced patient compliance followed by reduction in the effectiveness of the drug. Liquids or powders can be used for such patients; however, there may be compliance issues, because these formulations do not have portability and they are also not easy to administer. To improve administration, jelly preparations (1-3), orally disintegrating tablets (4-7), and oral film preparations (8-10) have been developed. Although, almost all films can dissolve in the mouth, the films can only contain a small amount of drug. It makes the films usable for only those drugs that require a clinical dosage of no more than about 25 mg (11). Current drugs are administrated in a range of low to high dosage, such as acetaminophen (AA). In this study, the fundamentals of oral film preparations containing a high dose of AA are discussed. Even if it does not disintegrate, films with moderate strength and elasticity are easier to swallow with water, when they have a smooth surface. Current film preparations often contain hydroxypropyl methylcellulose (HPMC) as a matrix polymer. However we previously suggested that the possibility of using carboxymethyl cellulose sodium (CMC), instead of HPMC, was also evaluated (12). The main problem that
results in rough surfaces is recrystallization of the drug at high doses during film preparation. To overcome this issue, polyvinylpyrrolidone (PVP), which does not crystallize and thereby reduces the effect of crystallization, was used for a solid dispersion (13-15). The effects of PVP addition on crystallization and physical properties of the films were investigated. As an alternative to tablets, the application of this concept for film formulations of other drugs could contribute to improved medication efficacy.

2. Materials and Methods

2.1. Materials

AA and CMC were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as a model drug and as a matrix, respectively. PVP K30 was obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and used as an additive. Glycerin (GL) was obtained from Guaranteed Reagent Nacalai Tesque (Kyoto, Japan) and was used as a plasticizer.

2.2. Film preparation

Films were prepared using the solvent-casting method (Figure 1). AA was dissolved in purified water and mixed with various amounts of CMC and PVP. GL was added at a constant concentration. The mixture was stirred for 24 hours at room temperature using a magnetic stirrer. The resulting dispersed liquid was then dried by casting it on a flat tray at room temperature. The prepared films were cut to a size of 2 cm × 2 cm. Each sheet contained either 50 mg or 100 mg of AA. When the CMC concentration was constant, the amount of PVP was changed, and when concentration of polymer was constant, the mixing ratio of CMC and PVP was changed. The composition of each film is shown in Table 1.

2.3. Film evaluation

2.3.1. Thickness measurement

Film thickness was measured using a micrometer (Mitutoyo Co., Kanagawa, Japan) \((n = 10)\).

2.3.2. AA content measurement

AA content per film sheet was determined using UV spectrophotometry (Shimadzu Co., Kyoto, Japan) at a wavelength of 244 nm \((n = 10)\).

2.3.3. Strength and elasticity measurement

Film strength was measured using a rheometer (Sun Scientific Co. Ltd., Tokyo, Japan). The film was clipped 4 mm from the attachment, pulled down at a speed of 15 mm/min, and stretched until breakage occurred. A stress-displacement curve was obtained using these results. Film strength and extension were calculated from the stress displacement curve using formulae (1) and (2) \((n = 5)\):

\[
\text{Tensile strength (N/mm}^2\) = \frac{\text{Load at failure (N)}}{\text{Strip thickness (mm) × Strip width (mm)}} \tag{1}
\]

\[
\text{Elongation at break (%) =} \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \times 100 \tag{2}
\]

2.3.4. Adhesive study

Film adhesiveness was measured using a rheometer (Sun Scientific Co. Ltd.) as previously described by

\[\text{Table 1. Composition of the film formulations prepared with carboxymethyl cellulose sodium and polyvinylpyrollidone}\]

<table>
<thead>
<tr>
<th>Material</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (mg)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Carboxymethyl cellulose sodium (mg)</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (mg)</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Glycerin (mg)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Total (mg)</td>
<td>120</td>
<td>110</td>
<td>105</td>
<td>170</td>
<td>160</td>
<td>155</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Values indicate the amount per sheet.
2.4. Statistical analysis

The results are presented as the mean ± standard deviation (SD) values. Statistical differences were analyzed using the Tukey-Kramer test for multiple comparisons, and the level of significance was set at $p < 0.05$.

3. Results

3.1. Film characterization

The AA content of prepared films was 90-110%. Thickness of the films containing 50 mg of AA was 0.35-0.47 mm, and the thickness of films containing 100 mg of AA was 0.57-0.67 mm (Tables 2-4).

3.2. Film strength

The CMC concentration was kept constant in the films that contained 50 mg of AA and the amount of PVP was changed as in formulations A, B, and C. The strength of these films was 3.98-7.12 N/mm$^2$. Formulation A, which contained the highest amount of PVP, was the strongest, whereas formulation B was the weakest ($p < 0.05$; Table 2). When the concentration of AA was kept constant and the amounts of CMC and PVP were changed as in formulations G, H, and I, these films had strengths of 0.20-3.13 N/mm$^2$. Formulation I, Tamura et al. (17). The sample film was fixed on a table using double-sided tape and 100 µL of purified water was dropped onto it. Pressure was immediately applied using a circle attachment that had a 10-mm diameter, and the film was pulled down at a speed of 15 mm/min. A stress-displacement curve was obtained using these results. Adhesiveness was calculated based on isolated pressure ($n = 5$).

2.3.5. Surface roughness study

The surface roughness of the films was measured using a compact-sized roughness-measuring instrument, the Surf-test SJ210 (Mitutoyo Co. Ltd.). Six measurements were taken to obtain the arithmetic average surface roughness (Ra) for both sides of the film.

2.3.6. Dissolution study

The basket method, using the JP 16 dissolution apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan), was used for this experiment. The dissolution medium was 900 mL purified water at 37°C, with a stirring rate of 100 rpm. At appropriate time intervals, after the film was put in dissolution medium, samples were withdrawn and replaced with the same volume of purified water. AA concentrations were determined using UV spectrophotometry (Shimadzu Co., Kyoto, Japan) at a wavelength of 244 nm ($n = 3$).

Table 2. Physical characteristics of films containing acetaminophen (50 mg), carboxymethyl cellulose sodium, and polyvinylpyrrolidone

<table>
<thead>
<tr>
<th>Items</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength (N/mm$^2$)</td>
<td>7.12 ± 0.56</td>
<td>3.95 ± 0.67</td>
<td>5.43 ± 0.27</td>
<td>$p &lt; 0.05$: B vs. A and C, C vs. A</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
<td>31.32 ± 2.36</td>
<td>43.62 ± 3.34</td>
<td>42.68 ± 5.18</td>
<td>$p &lt; 0.05$: A vs. B and C</td>
</tr>
<tr>
<td>Adherence (N/mm$^2$)</td>
<td>6.43 ± 0.52</td>
<td>7.27 ± 0.29</td>
<td>3.65 ± 0.23</td>
<td>$p &lt; 0.05$: C vs. A and B</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.45 ± 0.02</td>
<td>0.39 ± 0.01</td>
<td>0.41 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD ($n = 5$).

Table 3. Physical characteristics of films containing acetaminophen (50 mg), carboxymethyl cellulose sodium, and polyvinylpyrrolidone

<table>
<thead>
<tr>
<th>Items</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>Comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength (N/mm$^2$)</td>
<td>3.11 ± 0.42</td>
<td>3.13 ± 0.73</td>
<td>0.20 ± 0.09</td>
<td>$p &lt; 0.05$: I vs. G and H</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
<td>21.7 ± 2.78</td>
<td>29.3 ± 3.86</td>
<td>51.5 ± 6.94</td>
<td>$p &lt; 0.05$: I vs. G and H</td>
</tr>
<tr>
<td>Adherence (N/mm$^2$)</td>
<td>3.62 ± 0.17</td>
<td>2.48 ± 0.23</td>
<td>5.99 ± 0.67</td>
<td>$p &lt; 0.05$: H vs. G and I, G vs. I</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.39 ± 0.05</td>
<td>0.47 ± 0.001</td>
<td>0.35 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD ($n = 5$).

Table 4. Physical characteristics of films containing acetaminophen (100 mg), carboxymethyl cellulose sodium, and polyvinylpyrrolidone

<table>
<thead>
<tr>
<th>Items</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>Comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength (N/mm$^2$)</td>
<td>3.61 ± 0.15</td>
<td>2.91 ± 0.36</td>
<td>0.96 ± 0.08</td>
<td>$p &lt; 0.05$: F vs. A and D, E vs. D</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
<td>33.3 ± 2.99</td>
<td>47.21 ± 4.24</td>
<td>59.1 ± 2.46</td>
<td>$p &lt; 0.05$: F vs. A and D, E vs. D</td>
</tr>
<tr>
<td>Adherence (N/mm$^2$)</td>
<td>5.27 ± 1.09</td>
<td>4.69 ± 0.39</td>
<td>4.48 ± 0.63</td>
<td></td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.67 ± 0.05</td>
<td>0.58 ± 0.05</td>
<td>0.57 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD ($n = 5$).
which included CMC and PVP at a ratio of 1:2, was the weakest ($p < 0.05$; Table 3). When both formulation types were compared, formulations G, H, and I were weaker than formulations A, B, and C.

For films with 100 mg of AA (formulations D, E and F), the strength was 0.96-3.61 N/mm². The strength decreased with decreasing PVP content ($p < 0.05$; Table 4).

### 3.3. Film elasticity

Formulations A, B and C, which included 50 mg of AA, a constant amount of CMC and variable amounts of PVP, had an extension of 31.32-43.62%, which indicated elasticity. Formulation A, which contained the highest amount of PVP, showed the least elasticity (31.32 ± 2.36%, $p < 0.05$; Table 2) whereas formulations B and C showed similar elasticity. Formulations G, H and I, which included 50 mg of AA, variable CMC and PVP mixing ratios, had an extension of 21.7-51.5%. Extension increased with an increase in the PVP mixing ratio. Formulation I, which included CMC and PVP in a ratio of 1:2, had the maximum extension ($p < 0.05$; Table 3). When both formulation types were compared, formulation I had the maximum elasticity among all the film formulations ($p < 0.05$). Formulations D, E and F, which contained 100 mg of AA, had an extension of 33.3-59.1%. Film elasticity increased with a decreasing amount of PVP ($p < 0.05$; Table 4).

### 3.4. Film adhesiveness

CMC concentration in the films that contained 50 mg of AA was kept constant and the amount of PVP was changed as in formulations A, B, and C. These formulations had an adhesiveness of 3.65-7.27 N/mm². Formulation C, which had the lowest amount of PVP, had the lowest adhesiveness (3.65 ± 0.23, $p < 0.05$; Table 2). Formulations A and B also showed similar results. When high polymer concentration was kept constant and the amounts of CMC and PVP were changed (formulations G, H, and I), adhesiveness was 2.48-5.99 N/mm². Formulation H, which included CMC and PVP in a 1:1 ratio, was least adhesive ($p < 0.05$; Table 3). Formulation I, which included CMC and PVP in a 1:2 ratio, had maximum adhesiveness ($p < 0.05$). In films with 100 mg of AA (formulations D, E and F), adhesiveness was 4.48-5.27 N/mm². These films showed almost the same level of adhesiveness regardless of the amount of PVP (Table 4).

### 3.5. Film surface roughness

The upper surface roughness (Ra), which was exposed during film preparation, was compared. The films containing 50 mg of AA had a smooth surface and their Ra was significantly less than the films that did not contain PVP (20.53 vs. 1.86-6.2 µm, $p < 0.001$; Table 5). For PVP films, formulations A and B, which had a constant CMC concentration and a variable amount of PVP, had a similar level of surface roughness. When formulations A, B, and C were compared with each other, formulation C, which had the lowest amount of PVP, showed the highest roughness. Among formulations G, H, and I, which had a constant high polymer concentration and variable amounts of CMC and PVP, formulations G and I showed less roughness, but it was not different from that of formulations A, B, and C. However, surface roughness (Ra) on the lower side of the film, was less in films that had no PVP. Formulations A, B, G and I showed significantly less roughness than the films that did not contain PVP ($p < 0.001$). Similar trends were observed in upper surface roughness in formulations A, B, and C and formulations G, H, and I.

The differences between upper and lower surface roughness were similar. Formulations A, B and G showed less roughness, whereas formulations C, H and I showed comparably higher roughness (Table 5).

For films containing 100 mg of AA, formulation D showed the least upper surface roughness, which increased with a decreasing amount of PVP ($p < 0.05$, D vs. E and F). On the other hand, formulation E

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### Table 5. Surface roughness (Ra) of films containing acetaminophen (50 mg), carboxymethyl cellulose sodium, and polyvinylpyrrolidone

<table>
<thead>
<tr>
<th>Items</th>
<th>no PVP</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>G</th>
<th>H</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top surface</td>
<td>20.53 ± 2.82</td>
<td>1.86 ± 0.19†</td>
<td>1.99 ± 0.32†</td>
<td>6.20 ± 0.75*</td>
<td>2.5 ± 0.70**</td>
<td>4.6 ± 0.42*</td>
<td>3.7 ± 0.40**</td>
</tr>
<tr>
<td>Bottom surface</td>
<td>3.06 ± 0.35</td>
<td>1.02 ± 0.07*</td>
<td>1.33 ± 0.49*</td>
<td>2.61 ± 0.40</td>
<td>1.8 ± 0.69*</td>
<td>3.0 ± 0.33</td>
<td>1.2 ± 0.31*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD ($n = 5$). Top surface: *$p < 0.001$ vs. no PVP; †$p < 0.01$ vs. C, G, H, and I; *$p < 0.01$ vs. H. Bottom surface: *$p < 0.001$ vs. no PVP, C and H.

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### Table 6. Surface roughness (Ra) of films containing acetaminophen (100 mg), carboxymethyl cellulose sodium, and polyvinylpyrrolidone

<table>
<thead>
<tr>
<th>Items</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top surface</td>
<td>2.61 ± 0.31*</td>
<td>4.39 ± 0.77</td>
<td>5.29 ± 0.99</td>
</tr>
<tr>
<td>Bottom surface</td>
<td>1.99 ± 0.25</td>
<td>0.77 ± 0.00p</td>
<td>1.07 ± 0.11*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD ($n = 5$). *$p < 0.05$ vs. E and F; †$p < 0.05$ vs. D and F, *$p < 0.05$ vs. D.
showed the least (lower) surface roughness followed by formulation F and D ($p < 0.05$). Upper and lower surface roughness results were similar for films containing 100 mg of AA and those containing 50 mg of AA. Formulation D showed the smallest difference between upper and lower surface roughness (Table 6).

3.6. Film dissolution behavior

For films that contained 50 mg of AA, such as formulations A, B and C, which had a constant CMC concentration and variable amounts of PVP, there was no difference in the dissolution behavior based on the PVP content. These films showed approximately 100% dissolution at 30 minutes. Formulations G, H and I, which had a constant concentration of high polymer and a variable amount of CMC and PVP, also showed approximately 100% dissolution at 30 minutes. However, there were differences in the initial dissolution behavior when the CMC and PVP mixing ratio was changed. An increase in the PVP mixing ratio resulted in faster dissolution rate. Dissolution at 15 minutes was 59% for formulation G (CMC:PVP, 2:1) and 78% for formulation H (CMC:PVP, 1:1); it was the highest for formulation I (93%), which contained the most PVP (CMC:PVP, 1:2; $p < 0.05$). The dissolution at 15 minutes for all the films that contained 50 mg of AA, when the high polymer concentration was kept constant and the mixing ratio was varied (formulations G, H, and I), the surfaces were smoother than those of formulation C, which contained 5 mg of PVP per sheet as compared to 10, 15, and 20 mg of PVP in formulations G, H, and I, respectively. PVP seemed to have a definite effect on surface smoothness, because these films contained 10-20 mg of PVP per sheet. These results suggest that the problem of drug recrystallization at high drug doses can be prevented by preparing CMC films that use PVP.

In the films that contained 100 mg of AA (formulations D, E, and F), which had a constant CMC concentration and variable PVP levels, dissolution behavior was similar to that of formulations A, B, and C. The dissolution at 30 minutes was 100%, and there were no differences in dissolution behavior in response to changes in the amount of PVP.

4. Discussion

This study investigated films that are easier to swallow, even if it is not a disintegrating film, have a smooth surface and that gel when taken with water. At high AA dose, there is drug recrystallization that results in films with reduced smoothness and a rough surface. In this study, the effect of PVP addition to reduce these problems was investigated.

A mixing method was used for this purpose where CMC was used as a matrix and amount of PVP was varied. The surface roughness of films containing PVP decreased and these films were smoother than the films that did not contain PVP. It has been shown that drug recrystallization is inhibited when a solid dispersion of polymer and PVP are used (18,19), making the surface smoother. This effect was dependent on the amount of PVP used. In both types of films containing either 50 mg or 100 mg of AA, when the CMC concentration was kept constant, surface roughness changed with change in PVP concentration. The film surfaces became smoother as the amount of PVP increased, and the surfaces became rougher as the amount of PVP decreased. For example, in films containing 50 mg of AA, when the high polymer concentration was kept constant and the mixing ratio was varied (formulations G, H, and I), the surfaces were smoother than those of formulation C, which contained 5 mg of PVP per sheet as compared to 10, 15, and 20 mg of PVP in formulations G, H, and I, respectively. PVP seemed to have a definite effect on surface smoothness, because these films contained 10-20 mg of PVP per sheet. These results suggest that the problem of drug recrystallization at high drug doses can be prevented by preparing CMC films that use PVP.

Sufficient strength and elasticity was required for the films prepared in this study (20). Films with 50 mg of AA, a constant amount of CMC, and a large amount of PVP (formulation A) showed higher strength and lesser elasticity than those shown by other films. Films that contained 100 mg of AA and a large amount of PVP showed similar trends: higher strength and lesser elasticity. Strength decreased while elasticity increased with a decreasing amount of PVP. These
results suggested that increasing the amount of PVP increases the film's strength and decreases the film's elasticity when the CMC concentration is kept constant. However, when the polymer concentration was kept constant and the mixing ratio was varied, elasticity increased and strength decreased with an increase in the PVP mixing ratio. Decreasing CMC concentration seems to significantly affect the mechanical properties of films. Thus, adhesiveness of the films was evaluated because it is a major factor for comfort when taking an experimental film formulation. When the CMC concentration was kept constant, formulation C, which included the least amount of PVP (PVP, 5 mg/sheet), had the least adhesiveness. In films with 100 mg of AA, the amount of PVP had little effect on adhesiveness. However, adhesiveness of these films was less than that of films with 50 mg of AA. On the other hand, among films with 50 mg of AA, which had a constant high polymer concentration and a variable CMC and PVP mixing ratio, films composed of a 1:1 mixing ratio showed the least adhesiveness. The adhesiveness of these films increased as the PVP mixing ratio increased. These results suggest that increasing the PVP mixing ratio increased adhesiveness of the films, due to the adhesiveness of PVP. At higher drug content (100 mg of AA), the influence of PVP on mechanical properties of the films may be smaller.

When the polymer concentration was kept constant and the CMC and PVP mixing ratio was varied, AA dissolution from films became faster with increase in the PVP mixing ratio in this condition. All films had 100% dissolution at 30 minutes and the PVP content did not seem to affect the dissolution behavior. In a clinical scene, it seems to be no problem.

These results suggested that films containing PVP have significantly smoother surfaces regardless of the compounding method used. When the CMC concentration was kept constant, an increase in the amount of PVP improved surface smoothness of the films. It increased adhesiveness and strength of the films; however, elasticity was decreased. When the high polymer concentration was kept constant, decreasing PVP mixing ratio improved film surface smoothness, and decreased the adhesiveness. When PVP mixing ratio was decreased, film strength increased and elasticity decreased. However, the amount of PVP did not affect the dissolution behavior of the drug from the films.

Compounding PVP to prepare and formulate AA films is a useful approach. However, it is necessary to consider adhesiveness, strength, and elasticity to determine the best mixing method and mixing loads. AA was selected as a model drug because it is used widely in both children and the elderly, and it requires adjustments in dosage based on body weight and symptoms. Associated with increasing AA dosage are bulky tablet sizes or large amounts of powder, which can cause compliance problems. Films with high concentrations of drug could solve these issues. Application of this concept used in AA film formulation can be applied to prepare films of various other drugs. However, further studies are still required to mask the bitter taste of the drug.

References


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