Development and Evaluation of Sustained Release Matrix Tablets of Indapamide using Methocel K 15M CR

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INTRODUCTION

Indapamide is a lipid-soluble, thiazide like diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. Indapamide act mainly in the distal tubule to decrease the reabsorption of Na+ apparently by inhibition of a Na+/Cl- cotransporter on the luminal membrane of the distal convoluted tubule. Indapamide is metabolized and excreted by the gastrointestinal tract and the kidneys. It is therefore less likely to accumulate in patients with renal failure and may be useful in their treatment (Harvey et al., 2009). Tablets are defined as ‘solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles (Aulton, 2002). The basic goal of therapy is to achieve steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal (Lachman et al., 1976). The development of sustained release formulation of Indapamide is therefore of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of drug over time. The simplest and least expensive way to control the release of the drug is to disperse it within an inert polymeric matrix and hydrophilic matrices are an interesting option when formulating an oral sustained release (SR) of a drug. The dosage release properties of matrix devices may be dependent upon solubility of the drug in the polymer matrix or, in case of porous matrices, the solubility in the sink solution within the particle’s pore network (Sing, 1968). Hydroxypropylmethylcellulose (HPMC) is dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems (Colombo, 1993). Numerous studied have been reported in literature investigating the HPMC matrices to control the release of a variety of drugs from matrices (Kannan, 2010). The objective of the present study was to develop “once daily” sustained release tablets of Indapamide by direct compression using hydrophilic polymer like Hydroxypropylmethyl cellulose K15M CR.

ABSTRACT

In the present study an attempt has been taken to develop Indapamide sustained release matrix tablet using Methocel K15M CR by direct compression method. Various amount of polymer was used in the five proposed formulations (F-1to F-5) for the study of release rate retardant effect at 26.47%, 29.41%, 32.35%, 35.29% and 38.24% of total weight of tablet matrix respectively. Then the tablets were evaluated in terms of their physical parameters (weight variation, hardness, friability and thickness), drug content and in vitro release studies. All the formulations showed compliance with pharmacopeial standards. The in vitro dissolution study were conducted using USP 30 dissolution apparatus type I (Basket method) in 900 ml phosphate buffer (pH 6.8) at 100 rpm for a total period of 24 hours. The release mechanisms were explored and explained by Zero order, Higuchi, First order and Korsmeyer-Peppas equations. Based on the dissolution data comparison with innovator brand formulation F-3 (32.35% Methocel K15M CR w/w) was found as the best formulation. The drug release profile of this formulation was well controlled and uniform throughout the dissolution studies. The drug release of formulation F-3 followed First Order kinetic model ($r^2 = 0.99$) and the mechanism was found to be non-Fickian/anomalous according to Korsmeyer-Peppas equation.

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MATERIALS AND METHODS

For this present investigation Indapamide was obtained from HANGZHOW FST Pharmaceutical Co. Ltd., China, Methocel K15M CR was procured from Colorcon Asia Pvt Ltd, Aerosil 200 was procured from Evonik Degussa Germany and Magnesium Stearate, was procured from Remo Chemicals Dhaka, Flowlac 100 was procured from MEGGLE Wasserburg Germany, Microcrystalline cellulose PH101, Microcrystalline cellulose PH102 were procured from Local commercial source. All other ingredients used throughout the study were of analytical grade and were used as received. The experiments were carried out in 2012.

Preparation of Indapamide Matrix Tablets

Indapamide tablets were prepared by Direct Compression method according to formula given in the Table. 1. All the ingredients were sieved separately through sieve no. 30 except Aerosil 200 and magnesium stearate which were sieved through #40 and collected. The weighed amount of drug and other ingredients were mixed first. Aerosil 200 and magnesium stearate was finally added and mixed thoroughly. Prior to compression, all prepared granules were evaluated for several tests such as Loose Bulk Density, Tapped Bulk Density, Compressibility Index, Hausner ration and Angle of Repose. The tablets were compressed in Pilot Press Compression Machine (India) using 8 mm standard concave punch.

Table. 1: Composition of different formulations of Indapamide Matrix tablet.

<table>
<thead>
<tr>
<th>Ingredients (mg/Tab.)</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F-1</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.5</td>
</tr>
<tr>
<td>HPMC K15M CR</td>
<td>50.0</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (PH 101)</td>
<td>32.0</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (PH 102)</td>
<td>-</td>
</tr>
<tr>
<td>Flowlac 100 (Spray dried Lactose)</td>
<td>89.0</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1.0</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
</tr>
</tbody>
</table>

Evaluation of Powder Blend

Before final compression of tablets, powdered mixture was subjected to precompression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean ± SD.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of granules lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume observed, the cylinder was allowed to fall under its own height onto hard surface from the height of 2.5 cm at 2 seconds interval. The tapping was continued until no further change in the volume was noted. (LBD) and (TBD) were calculated by using the following formulas (Shah et al., 1997).

\[
\text{LBD} = \frac{\text{Weight of the powder}}{\text{volume of the packing}}
\]

\[
\text{TBD} = \frac{\text{Weight of the powder}}{\text{tapped volume of the packing}}
\]

The compressibility index

The compressibility index of the granules was determined by carr’s compressibility index (Aulton, 2002).

\[
\text{Carr’s index (\%)} = \frac{\left(\text{TBD} - \text{LBD}\right) \times 100}{\text{TBD}}
\]

Hausner’s Ratio

Hausner found that the ratio D/D, related to inter particle friction and as such, could be used to predict powder flow properties.

\[
\text{Hausner’s factor} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}}
\]

Angle of Repose

Static angle of repose of the granules were determined by the funnel method. The accurately weighed granules were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules.

The granules was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Carter, 1986)

\[
\tan \theta = \frac{h}{r}
\]

Where “h” and “r” are the height and radius of the powder cone.

Evaluation of physical properties of matrix tablets:

Weight variation test

To study weight variation, 20 tablets from each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness

For each formulation, the hardness of 6 tablets was determined using the PHARMA TEST Hardness Tester Machine.

Thickness

The thicknesses of the tablets were determined by using a digital slide calipers. Five tablets from each batch were used and average values were calculated.

Friability

Friability of 20 tablets of each proposed formulations were determined using the PHARMA TEST Friability Tester.

Drug Content

The assay of Indapamide matrix tablet was carried out by High Performance Liquid Chromatography (HPLC) method. The drug was extracted in methanol. The solution was filtered through 0.2 µ disc filter. The absorbance was measured at 242 nm after suitable dilution by using a HPLC.
In vitro Release studies

The in vitro dissolution studies were carried out using USP 30 dissolution apparatus type I (Basket method) at 100 rpm in an ERWEKA dissolution tester (Germany). The dissolution was conducted for a total period of 24 hour using 900 ml phosphate buffer (pH 6.8) at 37°C±5°C. Samples were withdrawn from each vessel at 1, 4, 8, 12, 16, 24 hour from starting. The amount of drug present was determined according to USP monograph for Indapamide tablet using HPLC at 242 nm.

Drug Release Kinetics

The in vitro drug release kinetic data were tested with the following mathematical models:

Zero order equation

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

\[ C = K_0 t \]  \hspace{1cm} (1)

Where, \( K_0 \) is the zero order rate constant expressed in unit concentration/time and \( t \) is the time in hour. A graph of concentration \( vs \) time would yield a straight line with a slope equal to \( K_0 \) and intercept the origin of the axes.

First order equation

The release behavior of first order equation expressed as log cumulative percentage of drug remaining \( vs \) time. The equation may be as follows (Wagner, 1969):

\[ \log C = \log C_0 - \frac{kt}{2.303} \]  \hspace{1cm} (2)

Where, \( C \) is the amount of drug undissolved at \( t \) time, the \( C_0 \) is drug concentration at \( t = 0 \), \( k \) corresponding release rate constant.

Higuchi square root law

The Higuchi release model describe as cumulative percentage of drug release \( vs \) square root of time. The equation may be as follows (Higuchi, 1961):

\[ Q = K \sqrt{t} \]  \hspace{1cm} (3)

Where, \( Q \) = the amount of drug dissolved at time \( t \). \( K \) is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer-Peppas equation

The dissolution data can be fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems. The equation may be as follows (Korsmeyer et al., 1983).

\[ \log \left( \frac{M}{M_i} \right) = \log k + n \log t \]  \hspace{1cm} (4)

Where, \( M \) is the amount of drug release at time \( t \); \( M_i \) is the amount of drug release after infinite time; \( k \) is a release rate constant incorporating structural and geometric characteristics of the dosage form; \( n \) is the diffusional exponent indicative of the mechanism of drug release (Korsmeyer et al., 1983).

The log value of percentage drug dissolved is plotted against log time for each formulation according to the equation.

- If \( n = 0.45 \) indicates fickian diffusion
- \( 0.45 < n < 0.89 \) indicates anomalous diffusion or non-fickian diffusion.
- If \( n = 0.89 \) and above indicates case-2 relaxation or super case transport-2.
- Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled rate release.
- Case-2 relaxation or super case transport-2 refers to the erosion of the polymeric chain.

Successive fractional dissolution time

To characterize the drug release rate in different experimental conditions, \( T_{25\%}, T_{50\%}, T_{80\%} \) (mean dissolution time) and \( T_{10\%} \) were calculated from dissolution data according to the following equations:

\[ T_{25\%} = \left( \frac{0.25}{k} \right)^{1/n} \]
\[ T_{50\%} = \left( \frac{0.5}{k} \right)^{1/n} \]
\[ T_{80\%} = \left( \frac{0.8}{k} \right)^{1/n} \]

Mean Dissolution Time can also be calculated by the following equation (Mockel et al., 1993).

\[ \text{MDT} = \frac{n}{n+1} \cdot k^{1/n} \]

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule.

Comparison of Dissolution Data

For assessment of the best formulation difference factor \((f_1)\) and similarity factor \((f_2)\) (Moore et al., 1996) were calculated to compare the dissolution profile with innovator brand. Difference factor \(f_1\) is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor \((f_2)\) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor \(f_1\) and similarity factor \(f_2\).

\[ f_1 = \left( \frac{\sum_{i=1}^{n} (R_i - T_i)^2}{\sum_{i=1}^{n} R_i} \right) \times 100 \]

\[ f_2 = 50 \log \left( 1 + \frac{1}{n \sum_{i=1}^{n} (R_i - T_i)^2} \right)^{-0.5} \times 100 \]

where

- \( n \) is the number of time points
- \( R_i \) is the dissolution value of reference product at time \( t \)
- \( T_i \) is the dissolution value for the test product at time \( t \).
Two dissolution profiles are considered similar and bioequivalent, if \( f_1 \) is between 0 and 15 and \( f_2 \) is between 50 and 100 (FDA, 1997).

Stability Studies

Stability studies were done of one selected batch according to ICH guidelines to assess the drug content and formulation stability (Cartensen, 1995). One selected fabricated tablet batch was strip packaged (Alu-Alu Blister) and kept at at 40 ± 2°C and 75 ± 5% RH. Samples were withdrawn at 30, 60 and 90 days for evaluation of appearance, hardness, drug content and percentage drug release during the stability studies.

RESULTS AND DISCUSSION

Characterization of granules

The granules of different proposed formulations (F-1 to F-5) were evaluated for LBD, TBD, compressibility index and angle of repose (Table 2). The results of LBD and TBD ranged from 0.360±0.02 to 0.530±0.02 g/ml respectively. The bulk densities of granules of the proposed formulation F-1 to F-3 were quite higher than those of other granules. This may be due to the presence of more lactose. The results of compressibility index (%) ranged from 19.689±0.04 to 29.54±0.05. Generally, compressibility index values up to 15% result in excellent flow properties and 18% to 21% results in fair to passable flow properties. So the granules of F-2 and F-3 showed fair flow properties while the flow properties of others were passable to poor. The results of angle of repose ranged from 28.14±0.04 to 32.12±0.05. The results of angle of repose (<30°) indicate good flow properties of granules of F-2 and F-3 which was supported the results found from compressibility index.

Physicochemical evaluation of matrix tablets

The results of physical parameters (weight, hardness, thickness and friability) and drug content of the prepared matrix tablets are shown in Table 3. The thickness of the tablets were found between 3.43±0.06 mm to 3.56±0.02 mm, hardness of the tablets ranged from 6.82±0.40kg/cm2 to 8.13±0.22 kg/cm2 and friability ranged from 0.07% to 0.13%. The weight variations of prepared tablets complied with the pharmacopoeial specifications. The drug content of every formulation was found about to 100% of labeled content. So it can be said that physical properties and drug content of the compressed matrix tablets were satisfactory.

In vitro release study

The release profiles of different formulations (F-1 to F-5) of Indapamide matrix tablets are shown in Fig. 1. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. As per the results of dissolution study formulations F1, F2, F3, F4, F5 showed 91.78%, 87.36%, 83.96%, 56.33% and 52.06% drug release in 24 hours respectively. This showed that the drug release from the tablet was sustained for 24 hr. Drug release decreased with increase of polymer loading as HPMC polymers form viscous gelatinous layer (gel layer) upon exposure to aqueous medium by undergoing rapid hydration and chain relaxation and this gel layer acts as the barrier to release of drug and as a result drug release is prolonged.

Drug release kinetics

The drug release data obtained were extrapolated by Zero order (Figure 1), First order (Figure 2), Higuchi (Figure 3) and Korsmeyer-Peppas equations to know the mechanism of drug release from these formulations. The data from Table. 4 shows that all the formulations were found to follow 1st order and Higuchi release model. F-3 was best fitted in terms of 1st order release kinetics \((r^2=0.990)\) and Higuchi model \((r^2=0.979)\). To confirm the drug release mechanism, the data were fitted into Korsmeyer-Peppas equation. Formulation F-1 to F-5 showed exponent \(n\) values ranging from 0.543 to 0.832, indicating that non-Fickian diffusion or anomalous transport (F-1 to F-5) as if \(n = 0.45\) the release mechanism follows Fickian diffusion and if \(0.45 < n < 0.89\) the release mechanism follows anomalous diffusion or non-Fickian diffusion.
**Fig. 3:** Higuchi release profile of different formulations of Indapamide matrix tablets.

**Successive fractional dissolution time**

Successive fractional dissolution time of five formulations (F-1 to F-5) of Indapamide matrix tablets are shown in Table. 5. MDT, T_{25%} (25% release), T_{50%} (50% release) and T_{80%} (80% release) were changed due to the change of polymers ratio. MDT, T_{25%}, T_{50%} and T_{80%} values were determined to characterize the drug release rate from the matrix tablets and the retaining efficiency of drug of the polymers.

**Comparison of dissolution data**

Difference factor (f1) and similarity factor (f2) of all the formulations (F-1 to F-5) were calculated to compare the dissolution profile with innovator brand which are shown in Table. 6. For formulation F-3 Difference factor was 1.76 and similarity factor was 90.95 which indicates the best compliance with innovator brand which was supported by the comparison of dissolution profile of F-3 and innovator brand (Figure 4).

**Table. 2:** Comparison of bulk density, Compressibility Index, Hausner ratio and Angle of Repose of different formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Loose Bulk Density (LBD)(gm/ml)</th>
<th>Tapped Bulk Density (LBD)(gm/ml)</th>
<th>Carr's Index (%)</th>
<th>Hausner ratio</th>
<th>Angle of Repose (°)</th>
<th>Moist Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>0.512±0.02</td>
<td>0.655±0.06</td>
<td>21.83±0.05</td>
<td>1.279±0.01</td>
<td>28.14±0.04</td>
<td>3.09</td>
</tr>
<tr>
<td>F-2</td>
<td>0.518±0.01</td>
<td>0.645±0.05</td>
<td>19.68±0.04</td>
<td>1.245±0.02</td>
<td>29.14±0.05</td>
<td>3.12</td>
</tr>
<tr>
<td>F-3</td>
<td>0.530±0.02</td>
<td>0.663±0.04</td>
<td>20.06±0.05</td>
<td>1.25±0.01</td>
<td>29.91±0.05</td>
<td>3.42</td>
</tr>
<tr>
<td>F-4</td>
<td>0.358±0.01</td>
<td>0.488±0.03</td>
<td>26.64±0.03</td>
<td>1.363±0.01</td>
<td>31.81±0.03</td>
<td>3.95</td>
</tr>
<tr>
<td>F-5</td>
<td>0.360±0.02</td>
<td>0.511±0.01</td>
<td>29.54±0.05</td>
<td>1.419±0.02</td>
<td>32.12±0.05</td>
<td>3.23</td>
</tr>
</tbody>
</table>

**Table. 3:** Physicochemical properties of Indapamide tablets of different formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Average weight (mg) ± SD (n = 20)</th>
<th>Diameter (mm)</th>
<th>Thickness (mm) ± SD (n = 5)</th>
<th>Hardness (Kp) ± SD (n = 6)</th>
<th>Friability (%) (n = 20)</th>
<th>Drug Content (%) ± SD (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>170.35±0.87</td>
<td>3.52±0.02</td>
<td>7.08±0.44</td>
<td>0.10</td>
<td>100.14±1.17</td>
<td></td>
</tr>
<tr>
<td>F-2</td>
<td>170.3±0.78</td>
<td>3.55±0.04</td>
<td>7.25±0.39</td>
<td>0.12</td>
<td>99.92±1.54</td>
<td></td>
</tr>
<tr>
<td>F-3</td>
<td>169.80±0.78</td>
<td>3.43±0.06</td>
<td>6.82±0.40</td>
<td>0.13</td>
<td>100.0±0.72</td>
<td></td>
</tr>
<tr>
<td>F-4</td>
<td>169.20±0.54</td>
<td>3.46±0.04</td>
<td>8.13±0.22</td>
<td>0.08</td>
<td>99.86±0.97</td>
<td></td>
</tr>
<tr>
<td>F-5</td>
<td>171.14±0.66</td>
<td>3.56±0.02</td>
<td>8.08±0.25</td>
<td>0.07</td>
<td>100.01±1.73</td>
<td></td>
</tr>
</tbody>
</table>

**Table. 4:** Kinetic parameters of Indapamide matrix tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi Model</th>
<th>Korsmeyer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
<td>K₀</td>
<td>r²</td>
<td>Kᵢ</td>
</tr>
<tr>
<td>F-1</td>
<td>0.861</td>
<td>3.857</td>
<td>0.996</td>
<td>-0.044</td>
</tr>
<tr>
<td>F-2</td>
<td>0.918</td>
<td>3.537</td>
<td>0.996</td>
<td>-0.036</td>
</tr>
<tr>
<td>F-3</td>
<td>0.965</td>
<td>3.511</td>
<td>0.990</td>
<td>-0.032</td>
</tr>
<tr>
<td>F-4</td>
<td>0.975</td>
<td>2.317</td>
<td>0.997</td>
<td>-0.014</td>
</tr>
<tr>
<td>F-5</td>
<td>0.982</td>
<td>2.225</td>
<td>0.996</td>
<td>-0.013</td>
</tr>
</tbody>
</table>

**Table. 5:** Successive fractional dissolution time (T25%, T50% and T80%) and MDT (in hours) values of different formulations of Indapamide matrix tablets.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>T_{25%}</th>
<th>T_{50%}</th>
<th>T_{80%}</th>
<th>MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>1.7797</td>
<td>6.379</td>
<td>15.1581</td>
<td>8.0454</td>
</tr>
<tr>
<td>F-2</td>
<td>2.7333</td>
<td>8.5307</td>
<td>18.4569</td>
<td>10.0774</td>
</tr>
<tr>
<td>F-3</td>
<td>4.6904</td>
<td>11.2290</td>
<td>20.2964</td>
<td>11.898</td>
</tr>
<tr>
<td>F-4</td>
<td>7.8512</td>
<td>19.4979</td>
<td>36.1294</td>
<td>20.941</td>
</tr>
<tr>
<td>F-5</td>
<td>9.4600</td>
<td>21.7623</td>
<td>38.2861</td>
<td>22.736</td>
</tr>
</tbody>
</table>
Table 6: Comparison of dissolution data with innovator brand.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>f2</th>
<th>f1</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>38.40</td>
<td>35.98</td>
</tr>
<tr>
<td>F-2</td>
<td>52.68</td>
<td>18.41</td>
</tr>
<tr>
<td>F-3</td>
<td>90.95</td>
<td>1.76</td>
</tr>
<tr>
<td>F-4</td>
<td>37.67</td>
<td>33.22</td>
</tr>
<tr>
<td>F-5</td>
<td>34.29</td>
<td>40.22</td>
</tr>
</tbody>
</table>

CONCLUSION

The results found in dissolution studies of Indapamide tablets prepared by direct compression compared to innovator brand sample shows that there is no significant difference in release properties between the tablets of formulation F-3 and innovator brand.

The formulation with higher percentage of lactose shows slightly better dissolution and other physical characteristics. Therefore in the light of observed data it is suggested that Indapamide should be formulated by direct compression to produce a tablet of better performance at lower cost.

This study reveals that the release of Indapamide critically depends on the rate retarding polymer level in the matrices. Proper adjustment of polymer with drugs enabled a desirable release characteristic of active ingredient which makes it possible to develop a once daily tablet. The optimized formulation F-3 can be used for commercial production of “once daily” sustained release tablets of Indapamide which was found stable over the studies.

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