Preparation and in vitro-in vivo evaluation of acyclovir floating tablets

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Abstract

In the current study, floating dosage form containing acyclovir was developed to increase its oral bioavailability. Effervescent floating tablets containing 200 mg acyclovir were prepared by direct compression method with three different rate controlling polymers including Hydroxypropyl methylcellulose K4M, Carbapol 934, and Polyvinylpyrrolidone. Optimized formulation showed good floating properties and in vitro drug release characteristics with mean dissolution time and dissolution efficacy of about 4.76 h and 54.33%, respectively. X-ray radiography exhibited that the tablet would reside in the stomach for about 5 ± 0.7 h. After oral administration of floating tablet containing 200 mg acyclovir, the $C_{\text{max}}$, $T_{\text{max}}$, and $AUC_{0-\infty}$ of optimized gastroretentive formulation were found to be 551 ± 141 ng/mL, 2.75 ± 0.25 h and 3761 ± 909.6 ng/mL/h, respectively.

Keywords: Acyclovir; Floating tablet; HPLC; X-ray radiography

INTRODUCTION

Gastroretentive systems are able to increase residence time of dosage forms in the stomach thereby increase the bioavailability of drugs with narrow absorption window, drugs with less water solubility in alkaline pH of small intestine or drugs with poor stability in the intestinal or colonic environment (1,2). These include polymeric bioadhesive systems, expandable systems, high density systems, floating drug delivery systems (FDDS), super porous hydrogels, and magnetic systems (3,4).

They are more suitable for drugs that are well absorbed in the duodenum and upper jejunum segment or those that are locally active in the stomach (3,4). FDDS are divided into two categories: (a) non-effervescent systems, and (b) effervescent systems. Non-effervescent systems are prepared with the help of gel forming hydrocolloid polymers which swell in contact with gastric fluid and achieve a bulk density less than water. The formed buoyance systems are able to sustained release of drug through gelatinous mass. Effervescent systems use swellable polymers in combination with effervescent components generating carbon dioxide upon contact with gastric fluids (3).

Acyclovir is a synthetic purine nucleoside analogue mainly used for the treatment of viral infections such as herpes simplex virus (types 1 and 2) and varicella-zoster virus (herpes zoster and chickenpox). The oral bioavailability of acyclovir has been reported to be about 15-30%.

The half-life of acyclovir is 1.30 - 2.30 h. The drug is well absorbed in the duodenum after oral administration (5). Preparation of a floating dosage form containing acyclovir may increase oral bioavailability of the drug through the increase of gastric residence time of drug allowing acyclovir to reach the site of absorption in a controlled way (6).

Until now different FDDS of acyclovir have been developed and characterized in vitro.
In the study conducted by Kharia, et al (7), effervescent FDDS of acyclovir was developed by wet granulation method using psyllium husk and hydroxypropyl methylcellulose (HPMC) K4M as the matrix forming polymers and sodium bicarbonate as a gas generating agent in order to deliver the drug at a controlled rate to its absorption site to enhance oral bioavailability. It was found that all formulations floated on dissolution medium for more than 24 h. In another study by Tavakoli, et al (6), floating tablets containing 20-30% HPMC K4M, 30% Na CMC (and/or 20% polyvinylpyrrolidone (PVP) or 20% Na alginate) and 12-15% gas generating agent exhibited satisfactory floating and drug release properties in vitro. In the present study, effervescent floating matrix tablets of acyclovir were prepared by direct compression method using three hydrophilic swellable polymers including HPMC K4M, Carbopol 934p and PVP. The effect of different combination of polymers on floating behavior and in vitro drug release were studied. Then, the optimized formulation was selected for further investigation in healthy human volunteers for determination of gastric residence time and the systemic availability of the drug.

MATERIALS AND METHODS

Materials

Acyclovir (Farabi Pharmaceutical Co., Iran, as a gift), metronidazole (Amin Pharmaceutical Co., Iran), Carbopol 934p (Colorcon, England), HPMC K4M, PVP, magnesium stearate, sodium bicarbonate, citric acid, methanol (HPLC grade), acetonitrile, isopropyl alcohol, dichloromethane, KH2PO4, triethylamine, and orthophosphoric acid (from Merck, Germany). All other chemicals and excipients were analytical grade.

Preparation of floating formulations

Floating tablets containing acyclovir were prepared by direct compression method. In order to prepare tablets, all the ingredients (Table 1) were weighed accurately and screened through sieve #18. Powders were mixed for 10 min using a cubic blender, magnesium stearate was then added as lubricant and mixing continued for another 2 min.

Then the mixed powders were compressed by using oval shape single punch tablet compression machine (GMBH-KS Kilian, Germany). The tablet punching machine was fitted with 14 mm punch with 60 N in hardness. Formulation compositions are listed in Table 1.

Evaluation of blends before compression

Carr's index

Carr’s index was determined using following formula:

\[ \text{Carr's Index} (\%) = \frac{Tapped \ density - Bulk \ density}{Tapped \ density} \times 100 \]  

where, bulk density and tapped density were determined by cylinder method (8).

Angle of repose (\( \theta \))

Angle of repose was determined by funnel method using following formula (9):

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

where, \( \theta \) is angle of repose, \( h \) is the height of the heap, and \( r \) is radius of the heap.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Acyclovir (mg)</th>
<th>HPMC K4M (mg)</th>
<th>Cp934 (mg)</th>
<th>PVP (mg)</th>
<th>NaHCO3 (mg)</th>
<th>Citric acid (mg)</th>
<th>FLT (min)</th>
<th>TFT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H250G50</td>
<td>200</td>
<td>250</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>25</td>
<td>4.8 ± 0.26</td>
<td>23.7 ± 3.05</td>
</tr>
<tr>
<td>H175C75G50</td>
<td>200</td>
<td>175</td>
<td>75</td>
<td>-</td>
<td>25</td>
<td>25</td>
<td>0.8 ± 0.20</td>
<td>7.7 ± 1.53</td>
</tr>
<tr>
<td>H75C175G50</td>
<td>200</td>
<td>75</td>
<td>175</td>
<td>-</td>
<td>25</td>
<td>25</td>
<td>0.6 ± 0.10</td>
<td>20.3 ± 0.47</td>
</tr>
<tr>
<td>C250G50</td>
<td>200</td>
<td>-</td>
<td>250</td>
<td>-</td>
<td>25</td>
<td>25</td>
<td>17.1 ± 2.25</td>
<td>22.5 ± 2.25</td>
</tr>
<tr>
<td>H175P75G50</td>
<td>200</td>
<td>175</td>
<td>-</td>
<td>75</td>
<td>25</td>
<td>25</td>
<td>1.8 ± 0.31</td>
<td>16.8 ± 1.76</td>
</tr>
<tr>
<td>H125P100G75</td>
<td>200</td>
<td>125</td>
<td>-</td>
<td>100</td>
<td>37.5</td>
<td>37.5</td>
<td>0.3 ± 0.08</td>
<td>14.4 ± 0.80</td>
</tr>
<tr>
<td>H125P100G50</td>
<td>200</td>
<td>125</td>
<td>-</td>
<td>100</td>
<td>25</td>
<td>25</td>
<td>0.4 ± 0.12</td>
<td>14.8 ± 1.47</td>
</tr>
</tbody>
</table>

H and HPMC (Hydroxypropyl methylcellulose), C and Cp934 (Carbopol 934p), P and PVP (Polyvinylpyrrolidone), G (gas forming agent), FLT (floating lag time), and TFT (total floating time).
**Evaluation of floating tablets**

**Physical properties of floating tablets**

Tablet hardness, weight variations, friability, and content uniformity of floating tablets were determined by procedure stated in the USP 35 (10).

**Floating lag time and total floating time**

Floating lag time (FLT) and total floating time (TFT) of floating tablets were measured visually in dissolution apparatus type II containing 100 mL 0.1 N HCl with a paddle rotated at 50 rpm (pH 1.2) at 37 ± 0.5 °C (11).

**Swelling index**

The prepared tablets were placed in a glass containing 200 mL of 0.1 N HCl at 37 ± 0.5°C. The percentage of swelling at different time interval was calculated by the following equation (12).

\[
SI(\%) = \frac{W_t - W_o}{W_o} \times 100
\]  

(3)

Where, SI is swelling index, W_t is weight of tablet at time t, W_o is weight of the dry tablet before placing in the glass.

**In vitro drug release**

**In vitro** release study was carried out using USP dissolution apparatus type II containing 900 mL of HCl 0.1 N (pH 1.2) at 37 ± 0.5 °C. At predetermined time intervals, an appropriate amount of medium was removed and replaced with equal volume of medium. Then samples were analyzed spectrophotometrically at 258 nm (13). Mean dissolution time (MDT) and dissolution efficacy until 12 h (DE_{12h}) were calculated by following equations:

\[
MDT = \frac{\int_0^t (M_\infty - M_t) dt}{M_\infty}
\]  

(4)

where, M_t is amount of the drug dissolved at time t and M_\infty is the amount of drug dissolved at infinite time (14).

\[
DE_{12h}(%) = \frac{\int_0^{12h} y dt}{y_{100}} \times 100
\]  

(5)

where, y is the percent of drug released as a function of time, t is the total time of drug release and y_{100} is 100% of drug release (15).

**Kinetic analysis of dissolution data**

To elucidate the drug release kinetics, the *in vitro* release data of different formulations were fitted to various kinetic models including zero order (Q_t = Q_0 + K_0t), First order (ln (Q_t/Q_0) = ln Q_0 + K_1t), Higuchi (Q_t = K_H t^{0.5}), Hixson-Crowell cube root law (W_o^{1/3} - W_t^{1/3} = K_C t) and Korsmeyer Peppas model (M_t / M_\infty = K t^n).

In these model equations, Q_t is the amount of drug released at time t, Q_0 is initial amount of drug in the pharmaceutical dosage form, t is the release time, M_t / M_\infty is the fraction of drug released at time t, n is the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form, K_0 and K_1 is rate constant, K_H is Higuchi dissolution constant, K_C is Hixson-Crowell dissolution constant, and K is constant incorporating the surface-volume relation. Based on the highest r^2 value, the best-fitted model was selected. n is the diffusion coefficient indicating the mechanism of drug release. For cylindrical shape tablets, n ≤ 0.45 corresponds to Fickian diffusion mechanism, 0.45 < n < 0.89 is related to non-Fickian release, n = 0.89 for Case II release, and n > 0.89 indicates super case II release mechanism (16).

**In vivo radiographic studies**

X-ray stomach radiography was used to determine the gastric residence time of the tablets. The optimized floating tablet formulation (H125P100G75) was used for this purpose. The tablet should be opaque for X-ray detection, therefore 20 mg of the drug was replaced with barium sulfate (all other ingredients were kept constant). The amount of barium sulfate in tablet should be sufficient to provide visibility by X-ray and at the same time preserve floating ability. For *in vivo* evaluation of gastric residence time, three healthy volunteers swallowed the tablet with a glass of water. The radiographic image of the tablet was recorded at intervals of 0.5, 1, 3, and 5 h post ingestion of the tablets.

**In vivo bioavailability studies**

In this study, six healthy adult male volunteers aged between 22 and 24 years weighing 65 to 85 kg were recruited. Each subject signed an informed written consent after explaining the nature and purpose of the study. Before experiment, the health of each subject was evaluated based on laboratory tests.
including hematology, blood biochemistry and urine analyses. No medications were used at least 2 weeks before the study. Thirty minutes after serving a standard breakfast, volunteers received a single oral dose of 200 mg acyclovir floating tablet (optimized formulation) with 200 mL of water and blood sampling was taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after drug administration. Then blood samples were centrifuged and plasma was separated and frozen until analysis (17).

**HPLC determination of acyclovir**

The concentration of acyclovir in plasma was determined by the HPLC method developed in our laboratory. The method was validated for linearity, accuracy, and precision. The HPLC system consisted of a Younglin SP930D HPLC pump, UV/730D absorbance detector, Chromatopac integrator and a Rheodyne injector was employed to carry out the acyclovir assay. A C18 µ-Bondapack HPLC column (250 × 3.9 mm, Waters, Ireland) was used for the separation of analytes.

The mobile phase was mixture of potassium dihydrogen phosphate (0.02 M) / acetonitrile (97:3, v/v) with final pH of 2.5 ± 0.1. The aqueous phase was eluted at a flow rate of 1.6 mL/min and eluent was monitored at 258 nm. On the day of analysis, 50 µL of metronidazole (as internal standard) and 100 µL of phosphate buffer (0.05 M) were added to 1 mL of plasma and then mixed for 30 s. To extract drug and internal standard from plasma, 6 mL of the mixture of isopropyl alcohol:dichloromethane (60:40) was added and vortexed for another 3 min. Afterward, the mixture was centrifuged at 3000 rpm for 15 min. Then organic phase was isolated from plasma residuals and transferred to clean test tubes and dried under the nitrogen gas. Finally dried residue was reconstituted in 100 µL mobile phase, vortexed for 30 s and centrifuged at 5000 rpm. 50 µL volume of the final clear solution was then injected in to the HPLC system.

**RESULT**

**Physical characteristics of the powders**

Carr’s index and angle of repose ranged 13.9 - 17.1 and 24.6 - 30.5, respectively which revealed good flow properties for the powder.

**Physical characteristics of the tablets**

The floating tablets of acyclovir showed the uniform content (± 3.4% variations) and appropriate friability (0.42 - 0.76%). The weight variation for all seven formulations was in its acceptable limits. The hardness was captured at 60.5 - 69.8 N

**In vitro buoyancy studies**

FLT and TFT were between 0.3 - 17.1 min and 7.7 - 23.7 h, respectively (Table 1). With increase in gas forming agents, FLT significantly decreased. PVP incorporation in dosage forms decreased FLT significantly. In the optimized formulation (H125P100G75), the FLT was about 18 s and remained buoyant for 14.4 h.

**Swelling index**

Incorporation of Carbopol 934p in dosage form increased swelling of the tablet ($P < 0.05$). Swelling index decreased with increasing the concentration of PVP ($P < 0.05$). The increased amount of gas forming agent in the formulation had no effect on the swelling index ($P > 0.05$).

**In vitro drug release**

The drug release profiles of acyclovir from formulations containing different amount of excipient are shown in Fig. 1. As shown in Fig. 1, tablets containing HPMC K4M/PVP exhibited earlier release. By increasing the amount of Carbopol 934p, drug release rate decreased (Fig. 1, Table 2). As concentration of PVP increased, the drug release rate was increased (Fig. 1). Direct relationship was observed between the investigated concentration of the gas forming agent and the drug release rate. Formulation H125P100G75 containing the highest concentration of gas-forming agents showed the highest drug release rates.

**Drug release kinetics**

Based on highest correlation coefficient, all formulations were best fitted with zero order and Hixon-Crowell equations (Table 2). Optimized formulation (H125P100G75) fits better to Hixon-Crowell equation ($r^2 = 0.994$). Calculated release exponent in all formulations
were between $0.45 < n < 0.89$ indicating that both diffusion and polymer relaxation affected drug release. Release parameters and exponents of all formulations are shown in Table 2. The effect of polymers on drug release profiles are qualified by MDT and $\text{DE}_{12h}(\%)$. For adopted formulation $\text{H125P100G75}$, the MDT and $\text{DE}_{12h}$ were calculated to be 4.76 h and 54.33%, respectively. The reverse order exists between release rate and MDT. MDT value was the highest (8.23 h) for $\text{C250G50}$ formulation and lowest (4.76 h) for $\text{H125P100G75}$. $\text{DE}\%$ changes directly with dissolution rate, and $\text{H125P100G75}$ showed the highest $\text{DE}\%$ (Table 2).

**Fig. 1.** The effect of different amounts of excipients on drug release properties.

**Fig. 2.** X-ray photographs of the BaSO4-loaded floating tablets in the stomach at (a) 0.5h, (b) 1h, (c) 3h, and (d) 5h.

**Table 2.** Drug release kinetics of acyclovir from floating formulations.

<table>
<thead>
<tr>
<th>Formulations code</th>
<th>Kinetic models ($r^2$)</th>
<th>Peppas parameters</th>
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<tr>
<td></td>
<td>Zero order</td>
<td>First order</td>
</tr>
<tr>
<td>H250G50</td>
<td>0.988</td>
<td>0.979</td>
</tr>
<tr>
<td>H175C75G50</td>
<td>0.987</td>
<td>0.977</td>
</tr>
<tr>
<td>H75C175G50</td>
<td>0.988</td>
<td>0.983</td>
</tr>
<tr>
<td>C250G50</td>
<td>0.985</td>
<td>0.99</td>
</tr>
<tr>
<td>H175P75G50</td>
<td>0.977</td>
<td>0.983</td>
</tr>
<tr>
<td>H125P100G75</td>
<td>0.97</td>
<td>0.985</td>
</tr>
<tr>
<td>H125P100G50</td>
<td>0.984</td>
<td>0.985</td>
</tr>
</tbody>
</table>

(MDT) mean dissolution time, ($\text{DE}_{12h}$) dissolution efficacy at 12 h, (n) diffusion coefficient.
Floating tablets behavior in stomach

The FLT and hardness of BaSO₄-containing tablet (Ba-H125P100G75) were 23 ± 5 s and 69 ± 3.6 N respectively. Fig. 2 showed X-ray images of BaSO₄-loaded floating tablets in the stomach. The residence time of adopted formulation H125P100G75 in stomach was 5 ± 0.7 h.

HPLC assay of acyclovir and pharmacokinetic parameters

The chromatograms of blank human plasma and blank human plasma spiked with internal standard and lowest standard concentration (100 ng/mL) or highest standard concentration (1500 ng/mL) and human plasma 4 h after oral ingestion of acyclovir-loaded tablet are shown in Fig. 3. The method was well set, accurate and applicable as already reported by Emami, et al (17). Calibration curves were constructed by plotting peak area ratio of acyclovir to the internal standard versus acyclovir concentrations.

The standard curves were linear over the concentration ranges of 100 - 1500 ng/mL with a regression coefficient of 0.991. Inter-day and intra-day precision and accuracy of the assay meet the standard limits (Table 3). This method was used to determine acyclovir concentrations in plasma following single oral administration of acyclovir floating tablet 200 mg in 6 healthy volunteers. The mean plasma concentration-time profile is illustrated in Fig. 4.

Cmax and T_max of optimized gastroretentive formulation (H125P100G75) were found to be 551 ± 141 ng/mL and 2.75 ± 0.25 h, respectively. The AUC₀-₁₂ and AUC₀-∞ for optimized formulation were about 3003.1 ± 674 and 3761 ± 909.6 ng/mL/h, respectively.

Fig. 3. Chromatograms of (A) blank plasma, (B) plasma spiked with internal standard, (C) plasma spiked with internal standard and 100 ng/mL of acyclovir, (D) plasma spiked with internal standard and 1500 ng/mL of acyclovir, and (F) human plasma 4 h after oral administration acyclovir loaded tablet.
**Fig. 4.** Concentration-time curve of acyclovir after single oral dose of floating tablet containing 200 mg of acyclovir.

**Table 3.** Inter- and intra-day variations of acyclovir determination by HPLC.

<table>
<thead>
<tr>
<th>C (ng/mL)</th>
<th>Inter-day variability</th>
<th>Intra-day variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (ng/mL)</td>
<td>SD</td>
</tr>
<tr>
<td>100</td>
<td>112.6</td>
<td>18.7</td>
</tr>
<tr>
<td>200</td>
<td>203.6</td>
<td>18.6</td>
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<tr>
<td>500</td>
<td>504.4</td>
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<tr>
<td>1000</td>
<td>966.0</td>
<td>92.1</td>
</tr>
<tr>
<td>1500</td>
<td>1530</td>
<td>23.0</td>
</tr>
</tbody>
</table>

(C) Concentration, (SD) Standard deviation, (CV%) percent of coefficient of variation.

**DISCUSSION**

The aim of this study was to develop an optimized dosage form of acyclovir to obtain predictable sustained release floating tablets in 12 h. Hydrophilic polymers including HPMC K4M and Carbopol 934p, which played an important role in floating tablet, were used to form floating tablet matrix. They hydrated in contact with gastric fluids and form low gravity matrix, with buoyant properties while active pharmaceutical ingredients were incorporated inside the matrix to create controlled release kinetics (18).

Carbon dioxide was generated upon contact of floating tablets with acidic contents of stomach. The generated gas was trapped inside the hydrophilic matrix making tablets buoyant. Increasing gas forming agents decreased FLT by decreasing tablet density rapidly below 1 due to an increase in carbon dioxide liberating in the matrix (19). The increase in amount of gas-forming agents also led to an increase in the rate of pore formation in dosage form causing an increment in drug release rate from the formulation. Similar result was obtained by Sermkaew, et al. (20) who studied floating tablets of tetrahydrocurcumin.

HPMC K4M was the most important ingredient to adjust the release profile of acyclovir and buoyancy properties. This importance comes from the ability of the polymer for producing rapidly viscose gelatin layer, pH-independent hydration, and high capacity for loading of therapeutic agents (21,22). By increasing amount of HPMC K4M, TFT increased. This finding could be attributed to increased gel strength of matrices that prevents escape of entrapped generated gas from matrices, leading to decreased density (23). Incorporation of PVP in floating tablet containing HPMC K4M led to the increase release rate. In a parallel line, finding of Rahman, et al. (24) showed the addition of PVP into floating tablet containing HPMCK-15M increased the release rate of captopril.
This was due to hydrophilic nature of PVP-K30 allowing easy penetration of the medium into the matrix and a more rapid release of captopril. In contrast, formulations containing HPMC K4M and Carbopol 934p exhibited a more controlled release profile because Carbopol 934p remains unionized in the acidic dissolution medium. Thus the particles of Carbopol 934p acting as a physical barrier to control drug release (24). This finding was also in agreement with previous result reported by Rahman, et al (24). Swelling index depends on polymer type and percentage which used in the formulation. It was observed enhancing concentration of Carbopol 934p increased the swelling index of floating tablets. This indicates that Carbopol 934p retained more water compared to other polymers. This was in accordance with study of Siddam, et al. who showed the increase in concentration of Carbopol 934p result in an increase of swelling index (25).

H125P100G75 was the optimized formulation with the Hixson-Crowell release kinetics and non-Fickian diffusion. X-ray images taken after ingestion of optimized floating tablets containing BaSO4 showed that the gastroretentive tablet could be retained in the upper part of GI tract for 5 h. This observation confirms the buoyancy of the tablets in GI tract. In previous pharmacokinetic study conducted by Jankowskiet, et al (26), it was indicated that pharmacokinetics of acyclovir was linear over the dosing range of 200-400 mg. The AUC0–∞, Cmax, and Tmax reported by Emami, et al (17) after oral administration of 400 mg acyclovir (Acyclostad®) were 6972 ± 1727 ng/mL/h, 1167 ± 300 ng/ml, 1.94 ± 0.59 h, respectively. In the present study, the AUC0–∞, Cmax, and Tmax after oral administration of floating tablet containing 200 mg acyclovir were found to be 3761 ± 909.6 ng/mL/h, 551 ± 141 ng/mL, and 2.75 ± 0.25 h, respectively. Although the Cmax values for the floating tablet and reference formulation (Acyclostad®) seems to be similar at equal doses, the Tmax of the floating tablets was remarkably delayed compared to that of the reference tablet. These findings could be due to sustained absorption, or the prolonged gastric residence time (28).

**CONCLUSION**

Promising sustained-release floating tablets of acyclovir with gastroretentive ability were successfully formulated by effervescent technique using direct compression. Tablets containing 350 mg HPMC K4M, 50 mg PVP, 37.5 mg NaHCO3, and 37.5 mg citric acid showed desirable in vitro kinetic properties. The optimized formulation released the drug in a controlled fashion and demonstrated a short buoyancy lag time, with total floating time of at least 14 h. The gastroretentive formulation developed in this study based on HPMC K4M and PVP polymers has a good potential for delivery of acyclovir in a sustained manner in management of viral infections.

**ACKNOWLEDGEMENTS**

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