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Propranolol hydrochloride–anionic polymer binding interaction

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Abstract

Three different anionic polymers namely Eudragit S 100, Eudragit L 100-55 (methacrylic acid copolymers), and sodium carboxymethylcellulose (NaCMC) were used to evaluate the propranolol hydrochloride–anionic polymer interaction. The physical and chemical properties of propranolol hydrochloride and anionic polymer complex were investigated using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The DSC profiles demonstrated that the characteristic peak of propranolol hydrochloride cannot be found in the heating curve of the complexes, indicating that complex is different in physicochemical properties from the physical mixture of drug–polymer. The FTIR spectra also confirmed that there is an interaction between propranolol hydrochloride and methacrylic acid copolymers. The binding of the drug to the polymers was due to the existence of preferential hydrogen bonding between the amino group of the propranolol hydrochloride and the carboxylic functions of the polymers and that pH conditions can influence this binding.

Keywords: Anionic polymer; Methacrylic acid copolymer; Drug–polymer interaction; Complexation

1. Introduction

The formation of complexes due to macromolecular associations in polymer networks has been great interest in the pharmaceutical sciences. Polymer complexes are classified by the nature of the association. The major classes of polymer complexes are stereocomplexes, polyelectrolyte complexes, and intermolecular hydrogen-bonded complexes [1,2].

Polyelectrolyte complexes form readily between polyanions and polycations. These complexes are formed by ionic association of repeating units on the polymer chains. The stability of complexes is dependent on many environmental factors such as nature of solvent, pH, and ionic strength [3,4].

Because of their nature, polyelectrolyte complexes have the ability to function in a wide variety of applications such as taste masking and controlled release systems. Among the method used to formulate oral controlled release products, the system which is based upon ion exchange complexes has shown promise [5–7]. The anionic drug, sodium diclofenac, and the anion exchange resin, cholestyramine (Duolite® ATP-143), were evaluated by Sriwongjanya and Bodmeier [6]. It is observed that the release of drug from the drug–resin complexes or a physical mixture of the drug and resin in water or pH 7.4 buffer was retarded. The method has usually been adopted for basic drugs in the cationic form or acidic drugs in the anionic form, which interact with an anionic/cationic exchange polymers [6,8–10]. A polymeric matrix system for controlled drug release was developed employing the model drugs, salicylic acid and chlorpheniramine maleate, along with two acrylic resin polymers (Eudragits RL and RS) by Jenquin and McGinity [8]. It is reported that the dissolution profiles for salicylic acid and chlorpheniramine maleate were found to directly correlate with the drug–polymer interactions [8].

The electrostatic attraction between the opposite charged ions will be a part/or the main driving force for the initiation of complex formation between the drug and polymer molecules [11]. The interaction between drug and anionic polymer is an equilibrium reaction which, assuming 1:1 complexation, may be presented as Eq. (1) [12]:

$$\text{Polymer} + \text{Drug} \leftrightarrow \text{Complex} \quad (1)$$

An experimentally determined equilibrium binding

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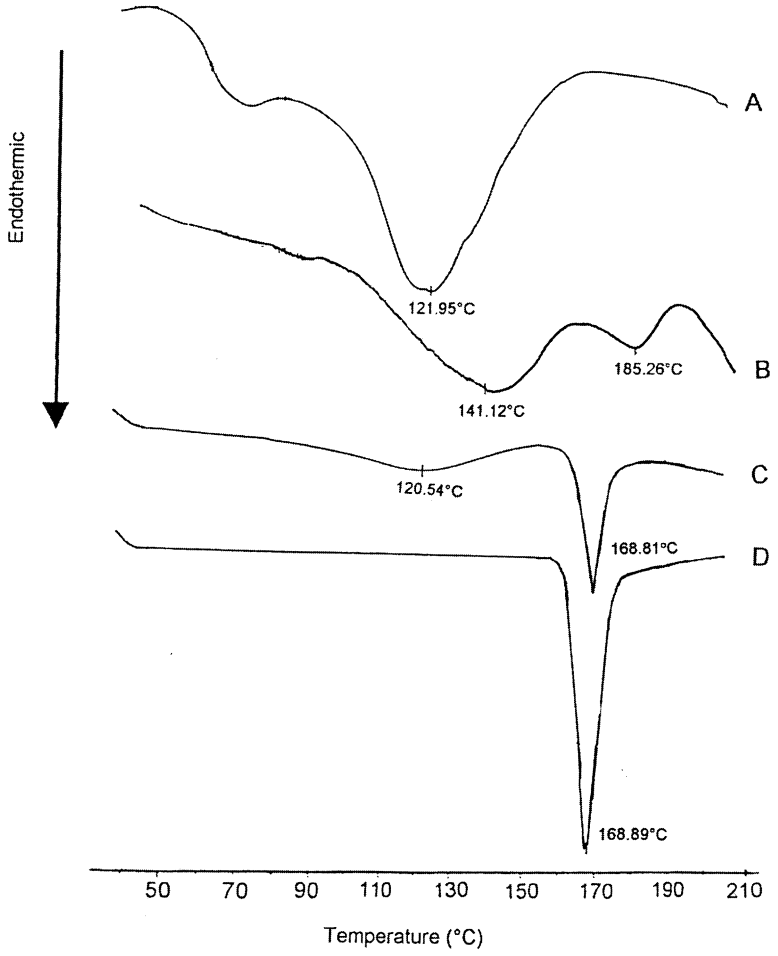

Fig. 1. DSC heating curves of (A) Eudragit S, (B) Eudragit S+propranolol hydrochloride (complex), (C) Eudragit S+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

constant, K_{obs}, is defined as

$$K_{obs} = \frac{\text{Complex}}{\text{Drug} \times \text{Polymer}} \quad (2)$$

In most techniques used to determine binding constants for drugs, the general strategy is to measure some system response (absorbance, mobility, retention time, etc.) to varying polymer concentrations at constant drug concentration. That response may then be related to the relative concentrations of free and bound drug, and subsequently drug–polymer binding constant [13].

Takka et al. [9] used UV spectra method to determine binding constants for propranolol hydrochloride. It is reported that there is a considerable propranolol hydrochloride and anionic polymer interaction depending on the –COOH groups of anionic polymers. Eudragit L 100-55 has the highest binding constant compared to Eudragit S and sodium carboxymethylcellulose (NaCMC).

In the previous study [9], UV–Vis spectra in solution was performed to obtain information on the inclusion mode. In this study, Fourier transform infrared spectroscopic (FTIR) and differential scanning calorimetric (DSC) analyses were used to characterize the complexation of propranolol hydrochloride with the model anionic polymers, Eudragit L 100-55, Eudragit S, and NaCMC, at the solid state.

Both Eudragit L 100-55 and Eudragit S are anionic copolymers based on methacrylic acid and ethyl acrylate, and methacrylic acid and methyl methacrylate, respectively. The ratio of the free carboxyl groups to the ester group is approximately 1:1 in Eudragit L 100-55 and about 1:2 in Eudragit S. Both of them are insoluble acids and pure water, whereas they are soluble in intestinal medium from pH 7 upwards [14]. NaCMC is the sodium salt of a polycarboxymethyl ether of cellulose. The aqueous solubility varies with the degree of substitution (DS) [15].

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: propranolol

hydrochloride (Wyckoff Chemical Company, Inc., MI, USA), methacrylic acid copolymers (Eudragit L100-55, Eudragit S 100; Rohm Pharma, Germany), and NaCMC (Sigma, USA).

2.2. Preparation of propranolol hydrochloride–anionic polymer complex

Propranolol hydrochloride was dissolved in distilled water. The polymers were dissolved in distilled water by adjusting pH to 7.4 by addition of 1.0 M NaOH. The polymer solution was slowly added to the propranolol hydrochloride solution with constant stirring at 37 °C for 2 h. The precipitate formed in the reaction was filtered off and washed with distilled water. The product was dried at 40 °C for 3 days under reduced pressure.

2.3. Differential scanning calorimetry

Thermal analysis was performed on the drug, polymer, drug–polymer physical mixtures, and complex using a Dupont 910S Differential Scanning Calorimeter at a scanning speed of 20 °C/min between 20 and 200 °C.

2.4. FTIR absorption spectroscopy

FTIR analysis was performed on the drug, polymer, drug–polymer physical mixtures, and complex using Vektor 22 Fourier Transform Infrared Spectra according to the KBr pellet method.

3. Results and discussions

3.1. Differential scanning calorimetry

The DSC heating curves for propranolol hydrochloride, anionic polymers, propranolol hydrochloride–anionic polymer complex, and the physical mixture are shown in Figs. 1–3. Propranolol hydrochloride and the polymer were weighed in a 1:1 ratio and then mixed by light trituration in a mortar to prepare the physical mixtures. The DSC scan of propranolol hydrochloride in Figs. 1–3 showed an endothermic peak corresponding to the melting point of the drug at 168.89 °C ($\Delta H =$ 124.9 J/g). The physical mixtures for propranolol hydrochloride–Eudragit S, propranolol hydrochloride–Eudragit L 100-55, and propranolol hydrochloride–NaCMC blends exhibit endothermic peaks corresponding to the initial substances at onset temperatures of 168.81 °C ($\Delta H = 51.54$ J/g), 168.89 °C ($\Delta H = 55.39$ J/g), and 168.36 °C ($\Delta H = 58.92$ J/g), respectively, indicating that the drug is in its crystalline form without undergoing any degradation process. As it is shown in Figs. 1–3, the DSC heating curves of pure Eudragit S, Eudragit L 100-55, and NaCMC exhibited a melting peak at onset temperatures of 121.95 °C ($\Delta H =$ 90.19 J/g), 87.85 °C ($\Delta H = 90.0$ J/g), and 130.93 °C ($\Delta H = 93.10$ J/g), respectively. Furthermore, the drug and anionic polymer complexes exhibited a broad endothermic peak ranging from 60 to 150 °C. Nevertheless, the characteristic peak of propranolol hydrochloride cannot be found in the heating curve of the complexes, indicating that complex is different in physicochemical properties from the physical mixture of drug–polymer. It is thought that molecular state of the drug in the complex was changed from the crystalline to the amorphous state. The amorphous polymers show a typical change in their structures at a temperature known as the glass transition temperature (T_g). It represents a change in the polymer from a brittle state (glass state) to a less brittle one (rubbery state) because of increased segmental mobility [16]. Interactions between the drug and the polymer can influence T_g of the polymer. From DSC heating curves, the T_g values of Eudragit S and Eudragit L 100-55 were found to increase as 20 and 39 °C, respectively, comparing to the complex (Figs. 1 and 2). Similar results were obtained by Halgado et al. [17]. It is reported that the modification in T_g of a polymer is dependent on the interaction degree between this compound and the drug. An increase in the temperature is substantially associated with a strong interaction, which means a fall in the polymer chain mobility.

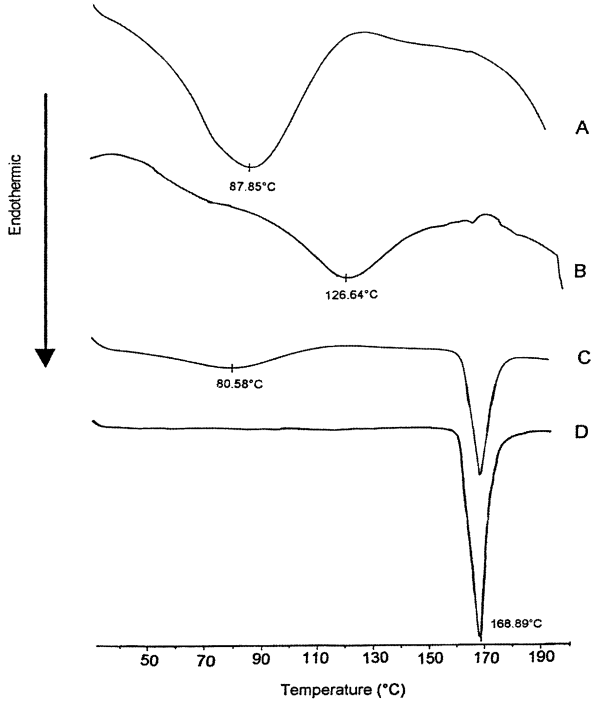

Fig. 2. DSC heating curves of (A) Eudragit L 100-55, (B) Eudragit L 100-55+propranolol hydrochloride (complex), (C) Eudragit L 100-55+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

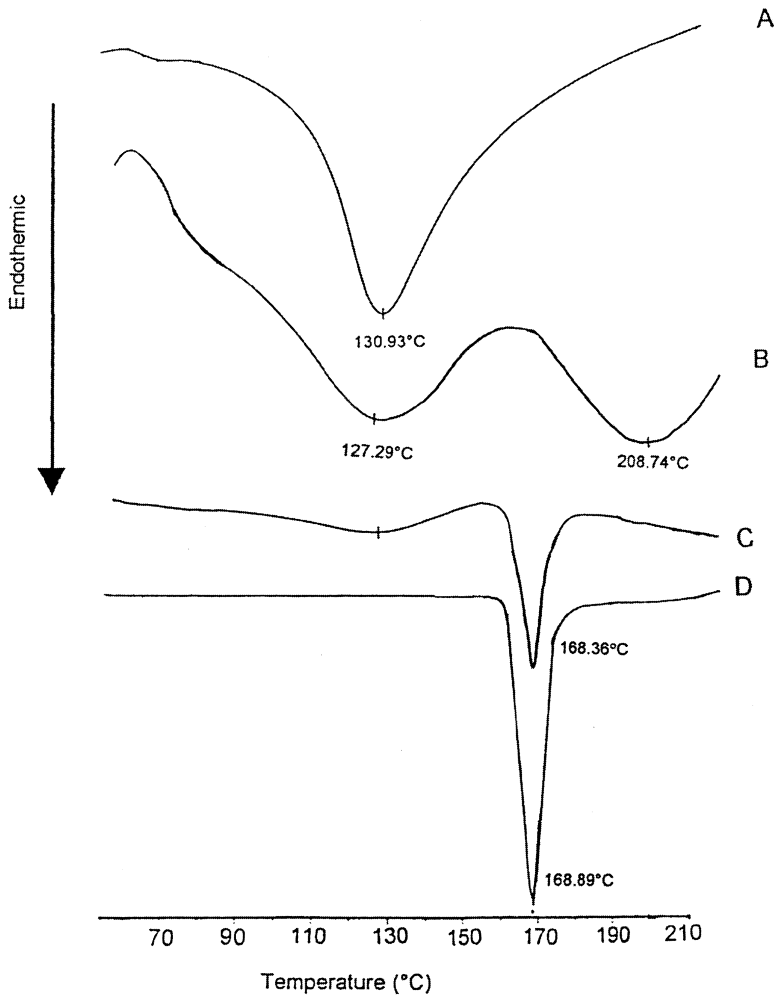

Fig. 3. DSC heating curves of (A) NaCMC, (B) NaCMC+propranolol hydrochloride (complex), (C) NaCMC+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

In contrast, NaCMC complex (Fig. 3) presented a fall in the polymer T_g value (127 °C). Since NaCMC has a large molecular weight and higher COOH bonding groups than drug, the intensity of the cross-linking would be considerably less in the propranolol hydrochloride–NaCMC system. Hence, plasticization due to the disruptive presence of small drug molecules between adjacent polymer segments would be the predominant phenomenon and this results in an increase in its segmental mobility and thus a fall in T_g [18]. These data suggested that the binding between amino group and carboxyl group played an important role in the complexation.

Furthermore, the peaks around 185 and 208 °C in Figs. 1 and 3, respectively, may be the result of a shift of the melting point of propranolol hydrochloride owing to the formation of an ion pair between the amino group of propranolol hydrochloride and the carboxylic acid group of Eudragit S and NaCMC.

3.2. FTIR spectroscopy

FTIR is one technique that has been used to study interactions in drug–polymer blends and it can provide valuable information regarding the interactions of drug–polymer blends at the molecular level [19]. If the drug and polymer interact then the functional groups in the FTIR spectra will show the emergence of additional bands or alterations in wavenumber position or broadening compared to the spectra of the pure drug and polymer [8]. The FTIR spectra in the absorbance mode for the propranolol hydrochloride–anionic polymer blends are shown in Figs. 4–6. Figs. 4 and 5 show the characteristic bands of C=O vibrations of the carboxylic acid groups at 1705 cm^{-1} and of the esterified carboxylic groups at 1735 cm^{-1}. The FTIR spectra of the complex in comparison with the physical mixture are shown in Figs. 4 and 5, which show a new absorption band at 1556 and 1550 cm^{-1} for propranolol hydro-

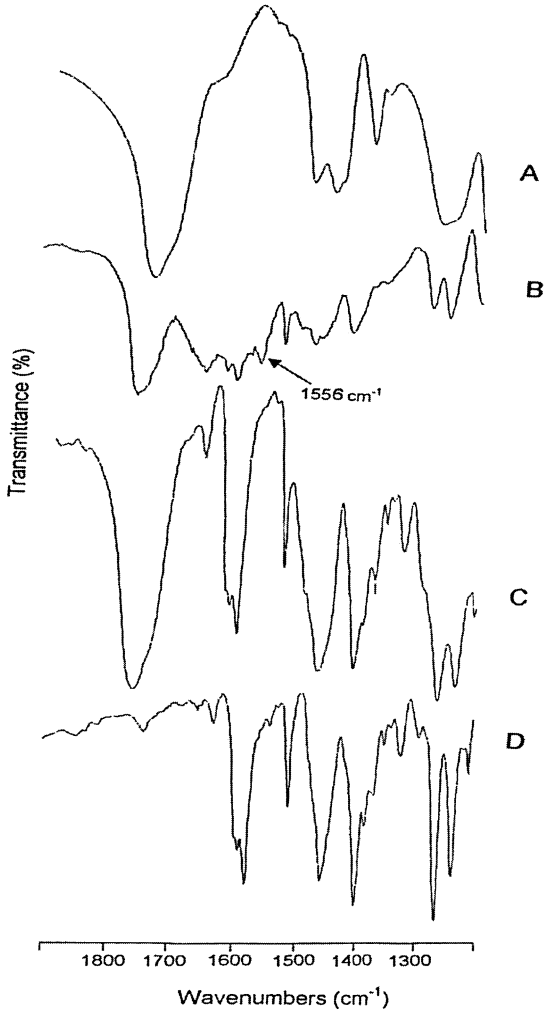

Fig. 4. FTIR spectra of (A) Eudragit S, (B) Eudragit S+propranolol hydrochloride (complex), (C) Eudragit S+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

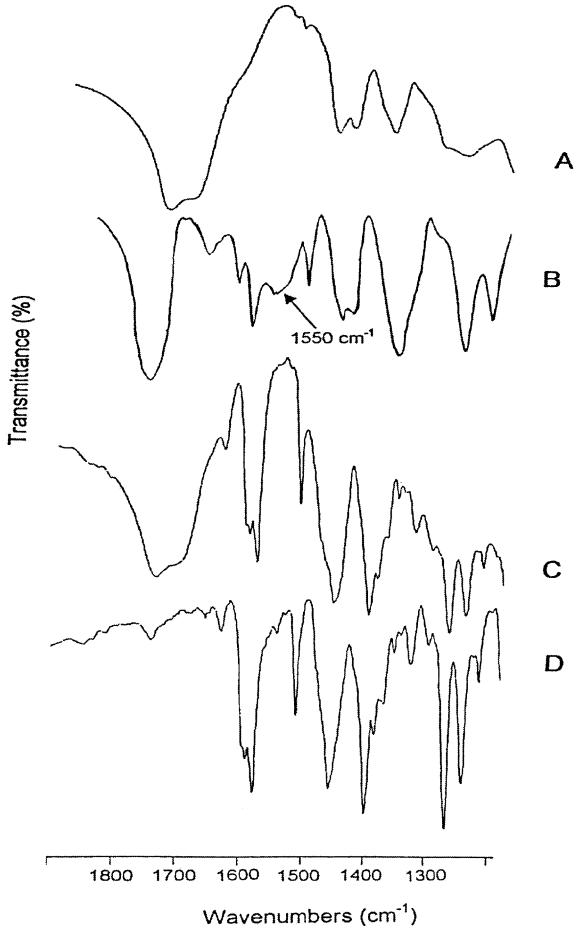

Fig. 5. FTIR spectra of (A) Eudragit L 100-55, (B) Eudragit L 100-55+propranolol hydrochloride (complex), (C) Eudragit L 100-55+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

chloride–Eudragit S and propranolol hydrochloride–Eudragit L 100-55 complexation, respectively. This is considered to be the result of salt formation. The conversion of a carboxylic acid to a salt can be done by the addition of amine group to a solution of the carboxylic acid. When ionization occurs, with formation of the COO^- group, resonance is possible between the two C–O bands. As a consequence, the characteristic carbonyl absorption is replaced by the band in the 1550–1556 cm^{-1} region. This band corresponds to auto-symmetrical vibrations of the COO^- structure and is used as a diagnosis of the COO^- group [20,21]. The results therefore indicate a strong and extensive interaction between methacrylic acid polymers and propranolol hydrochloride by the presence of carboxylic groups in the structure of the latter, enabling the formation of hydrogen bonds with the amine group of the propranolol hydrochloride. However, a new absorption band apparently did not occur in the NaCMC–propranolol hydrochloride complex due to lack of the intensity of the cross-linking hydrogen bond network (Fig. 6). NaCMC has a large molecular weight so that the interaction between propranolol hydrochloride and NaCMC is more complex than methacrylic acid polymers [22]. NaCMC is also a very hygroscopic polymer [15]. The absorption band between 1600 and 1700 cm^{-1} presented in the pure NaCMC, which appeared probably due to the water, was not observed in the physical mixture (Fig. 6).

4. Conclusions

The existence of propranolol hydrochloride–anionic polymer interaction was confirmed with various physicochemical methods. The DSC and FTIR method indicated that the type of anionic polymer affected the complex formation. The ratio of the free carboxyl groups to the ester groups is an important parameter to form the complex formation in methacrylic acid copolymers.

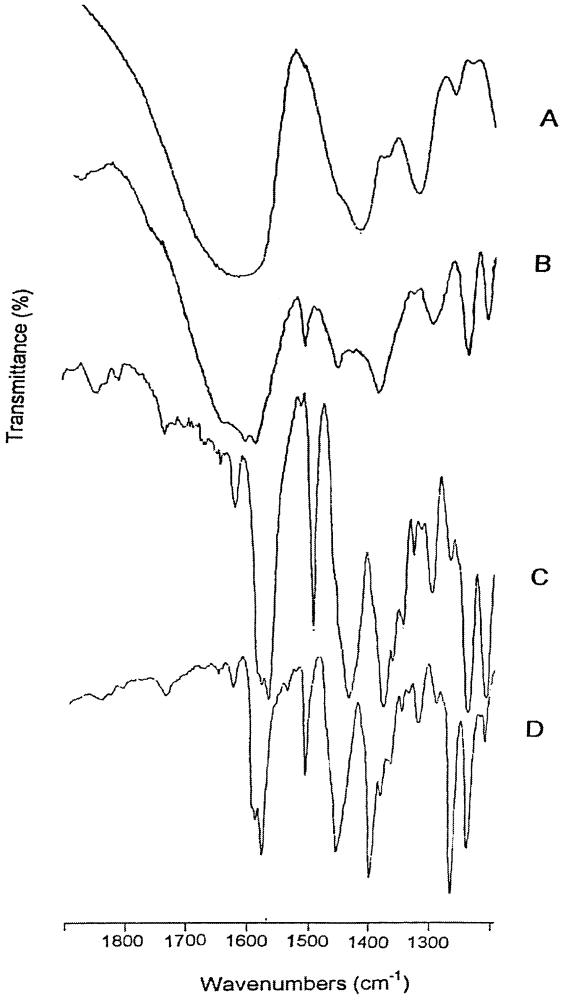

Fig. 6. FTIR spectra of (A) NaCMC, (B) NaCMC+propranolol hydrochloride (complex), (C) NaCMC+propranolol hydrochloride (physical mixture), and (D) propranolol hydrochloride.

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