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Measurement of the swelling force in ionic polymeric networks: II. Swelling force and disintegration of controlled release dosage formulations using pH-sensitive components

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Abstract

The swelling behavior of disintegrating agents produced from microparticles of crosslinked, hydrophilic polymers was investigated as a function of time by using a swelling force measurement apparatus. The swelling force produced due to swelling of poly(acrylic acid-co-2-hydroxyethyl methacrylate) and poly(acrylic acid) was measured in various buffered solutions as a function of time and the swelling ratio of the continuously swelling polymer. The results were related to the swelling mechanism of disintegration.

Keywords: Swelling; Swelling force; Poly(acrylic acid); Poly(2-hydroxyethyl methacrylate); Disintegration

1. Introduction

Our goal in this work was to evaluate pH-sensitive polymers as potential disintegrating agents for controlled release dosage forms. The role of disintegrating agents is to promote the break-up of dosage forms. Disintegration is created by either swelling in the presence of water, or by capillary action which disrupts interparticulate bonds. Typical disintegrating agents include microcrystalline cellulose, sodium starch glycolate, crosslinked poly(*N*-vinyl pyrrolidone) (PVP), poly(vinyl alcohol), and poly(methacrylic acid). Important properties which affect the disintegrating efficiency are water uptake, particle swelling and particle dimensions (Caramella et al., 1984).

The disintegrating force has been analyzed by Peppas and Colombo (1989) as the result of two coupled mechanisms: a diffusion-controlled process caused by the swelling of polymer particles

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and an interfacially controlled process that causes the break-up of bound particles from the pharmaceutical formulation. Researchers in the same group investigated the disintegrating force developed due to the absorption of water into the tablet. Catellani et al. (1989) studied the disintegration force of Emcompress® tablets which contained 6 wt% maize starch, and 1 wt% magnesium stearate as binding and lubricating agents, respectively. An instrument to measure the disintegration force as a function of water uptake was developed and tested for various formulations (Catellani et al., 1989; Khare et al., 1992).

Marshall et al. (1991) investigated the stability of various disintegrating agents (including alginic acid, sodium starch glycolate and crosslinked PVP) at elevated temperatures and humidity. This study revealed that these particular disintegrants were stable at both elevated temperature and humidity for at least 1 year. The disintegration force was found to be a linear function of water content, a functional behavior somewhat simpler than our studies have shown. The most important finding was that these three disintegrants provided a broad range of initial water absorption required to produce a significant force. Sodium starch glycolate was found to require the least amount of water to initiate the disintegration procedure for fast release.

Peppas and Colombo (1989) proposed a model to describe the disintegration force developed during water penetration into the porous tablets.

$$F = C_d q^{1/2} + C_c q \quad (1)$$

Here, F is the disintegrating force, q denotes the water absorbed (g water/g dry polymer), and C_d and C_c are the diffusive and convective constants, respectively. The diffusive characteristic of the disintegration process is represented by the first term in Eq. 1, which describes the diffusion controlled transport of particle layers caused by particle swelling. The second term represents the convective contribution, which describes the detachment of particles from each other and from the central tablet core. The diffusive and convective constants, C_d and C_c, were used to compare the significance of each process in the development of the disintegration process.

2. Experimental

2.1. Preparation of polymers

Poly(acrylic acid-co-2-hydroxy ethyl methacrylate) (P(AA-co-HEMA)) copolymers were prepared as described before (Am Ende et al., 1995). Briefly, acrylic acid (AA, Aldrich Chemical Co., Milwaukee, WI) was vacuum distilled while 2-hydroxyethyl methacrylate (HEMA, Aldrich Chemical Co., Milwaukee, WI) was passed through a Dehibit-100 column to eliminate the inhibitor. The two monomers were mixed at different molar ratios and ethylene glycol dimethacrylate (EGDMA, Aldrich Chemical Co., Milwaukee, WI) was added at 0.001–0.02 mol% as a crosslinking agent. The initiator was azobisisobutyronitrile at 0.1 wt%. The mixture was diluted with deionized water or ethanol at a 50:50 volume ratio. The reaction occurred at 50°C for 1 h, 60°C for 2 h and 70°C for 24 h in polypropylene vials. The copolymer produced was in the form of a non-equilibrated gel swollen in water or ethanol. It was cut into thin disks and dried at 25°C for 5 days. These disks were then ground in particles and used to prepare compressed disks.

Poly(acrylic acid) (PAA) homopolymers were also prepared by solution polymerization. Aqueous solutions of acrylic acid monomer (35 wt% AA) were neutralized up to 40 or 60% using an 0.2 M NaOH solution. Crosslinking was achieved using trimethylolpropane triacrylate (TMPTA, Sigma Chemical Co., Inc., St. Louis, MO) at nominal crosslinking ratios of 0.001, 0.005, and 0.01 mol TMPTA/mol AA. A redox initiator system of sodium metabisulfite (Fisher Scientific, Inc., Fair Lawn, NJ) and ammonium persulfate (Polysciences, Inc., Warrington, PA) was added to the reaction mixture in the amount of 0.6 wt% monomer. Polymerization occurred at 37°C for 24 h in polypropylene vials. The resulting polymer was then cut and ground into particles.

2.2. Preparation of polymer disks

The tablets composed of 300 mg of polymer powder were prepared in a Carver Laboratory Press using a die diameter of 11 mm, and oper-

ated under 12 atm pressure for 2 min. No excipients were incorporated to ensure that the swelling force measurements evaluated only the polymer.

The true density of the polymer powders was measured using a multivolume pycnometer (model 1305, Micrometrics, Norcross, GA), courtesy of Chiesi Farmaceutica (Parma, Italy). The tablet porosity was determined from the true density, weight and tablet dimensions. The water content of the polymer powders at equilibrium was determined by the weight loss on drying. The experimental setup involved placing the powder in a glass vial that was inserted into a drying apparatus which was equilibrated under vacuum (4 mmHg) with anhydrous phosphorus pentoxide.

2.3. Measurement of swelling / disintegration force

A disintegrating force-water uptake apparatus was used for these studies (Khare et al., 1992), where a balance was used to measure the dynamic weight of water contained in the covered Petri dish. The polymer tablets were placed between two sintered glass disks and positioned into a steel cage. An extensiometric load cell was located directly above the cage, and was used to measure the force exerted by the polymer when it was placed in contact with the buffered solution in the Petri dish.

3. Results and discussion

The experiments conducted in this investigation to characterize the copolymer included determining the water content, density, porosity, and particle size distribution. The mechanical characterization involved monitoring the water absorption and disintegration force developed.

The polymer samples were dried to equilibrium to evaluate the water content, which ranged from 10 to 15 wt% depending on crosslinking content and percentage of AA in the copolymer (see Table 1). A multivolume pycnometer was utilized to evaluate the true density of the polymers, which varied from 1.3 to 1.9 g/ml depending on the crosslinking and solvent used for the polymerization reaction. The porosity of the polymers was determined as a ratio of the void to the original volume and the results are presented in Table 1.

The copolymers used in this investigation were prepared with varying ratios of AA to HEMA in the polymerization reaction ranging from 30 to 40 and 50 mol% AA with crosslinking ratios of 0.001 and 0.004 mol EGDMA/mol monomer. These copolymers were also polymerized in two different solvents, water (samples denoted by W) and ethanol (samples denoted by E), and the physical properties of the ensuing polymers are listed in Table 1.

Table 1
Physical properties of P(AA-co-HEMA) with varying amounts of crosslinking agent and AA

AA:HEMA ratio in feed[a]	P(AA-co-HEMA) copolymer properties			
	Crosslinking ratio (mol EGDMA/mol monomer)	Water content (g water/g polymer)	Density (g/ml)	Porosity (%)
30:70E	0.001	15.0	1.47	24.6
40:60E	0.001	11.8	1.29	–
50:50E	0.001	13.6	1.47	18.5
30:70E	0.004	12.3	1.44	22.5
40:60E	0.004	10.8	1.36	17.5
50:50E	0.004	9.2	1.46	–
30:70W	0.001	10.6	1.46	–
40:60W	0.004	11.7	1.88	45.2
50:50W	0.001	13.6	1.90	58.3

[a]E, prepared in ethanol; W, prepared in water.

The polymer density was found to be approximately the same for all samples polymerized in ethanol. The polymer density was greater for those polymerized in water. This behavior was attributed to the polar solvent forming linear oligomers which allowed closer packing, whereas the nonpolar solvent favored dimer alignment during polymerization which produced a more random configuration that decreased the observed density. These results are consistent with the polymerization of AA in polar and nonpolar solvents which was investigated by Chapiro and Dulieu (1977).

The porosity in the tablets increased with HEMA content for polymers prepared in ethanol, especially due to the longer side chain of the HEMA monomer. For the cases in which water was the solvent used during polymerization, the porosity was 3-times as great as for those polymerized in ethanol.

The water absorption was monitored as a function of time, as shown in Fig. 1 for P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 solution. An obvious advantage of this apparatus was that the swelling system was not disrupted for measurements of the sample weight, since the data were automatically acquired.

The effect of variables such as temperature, crosslinking ratio, water content at equilibrium, particle size, hydrophilicity, and solvent used during polymerization on the disintegration force was investigated. The force developed during the beginning of the swelling process was a linear function of time for P(AA-co-HEMA) containing 50 mol% of AA and HEMA, and 0.001 mol EGDMA/mol monomer in pH 5 solution (Fig. 2). A lag time was observed prior to the constant development of the disintegration force, consistent with the previous studies mentioned. This behavior suggested the disintegration process was caused by capillary effects rather than swelling at this point.

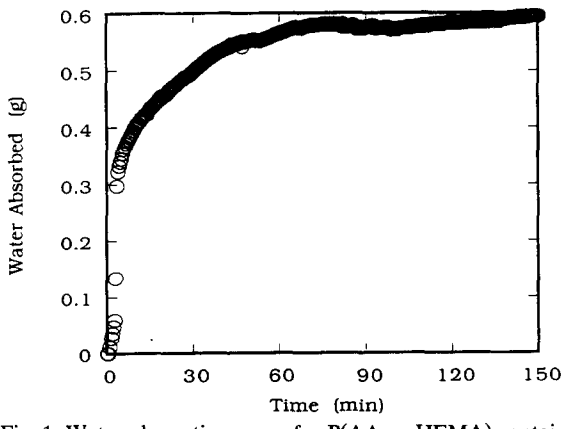

Fig. 1. Water absorption curve for P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 solution.

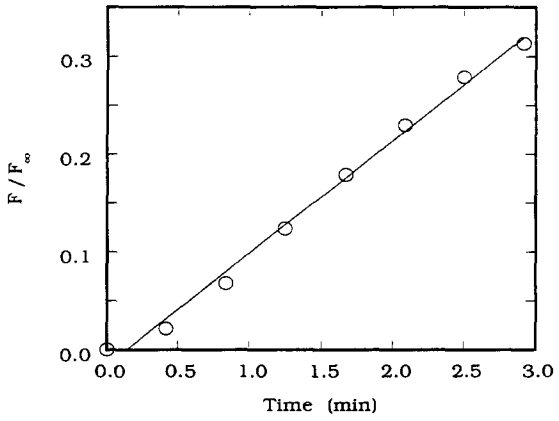

Fig. 2. Disintegration force developed for P(AA-co-HEMA) containing 50 mol% of AA and HEMA, and 0.001 mol EGDMA/mol monomer in pH 5 solution..

The effect of temperature on the disintegration force is shown in Fig. 3 for P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 solution. An increase of 6°C in the experimentation temperature produced an increase in the equilibrium force, F_∞, from 5.3 to 14.6 N. Extrapolating this behavior to a temperature of 37°C, the equilibrium force developed was determined to be approx. 40 N, consistent with the currently used disintegrating agents that produce 20–50 N of force.

Fig. 4 depicts the effect of polymer crosslinking ratio on the disintegrating force developed by P(AA-co-HEMA) samples containing 30 mol% AA and 70 mol% HEMA immersed in pH 5 solution. It was observed that the samples crosslinked with 0.001 mol EGDMA/mol

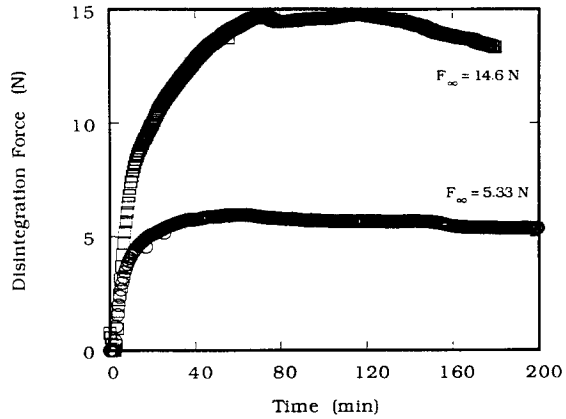

Fig. 3. Disintegration force developed for P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 as a function of temperature: $T = 19°C$ (○); $T = 25°C$ (□).

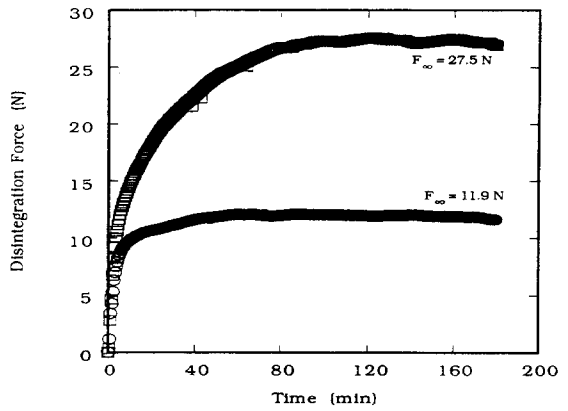

Fig. 5. Effect of water content in the polymer at equilibrium for P(AA-co-HEMA) containing 50 mol% AA and 50 mol% HEMA with 0.001 mol EGDMA/mol monomer: dried powder (○); 13.6% water (□).

monomer exhibited a more gradual approach to equilibrium. This was caused by the higher modulus for the higher crosslinked polymer, which responded in an elastic manner to the induced stress caused by swelling of the tablet. It should be noted that the equilibrium disintegration force was the same regardless of crosslinking levels, at 17.5 and 17.7 N for crosslinking of 0.001–0.004 mol EGDMA/mol monomer.

The effect of water content in the polymer powder at equilibrium was investigated for P(AA-co-HEMA) containing 50 mol% AA and 50 mol% HEMA with 0.001 mol EGDMA/mol monomer (Fig. 5). For tablets prepared by compressing initially dry polymer powder, the maximum disintegration force exerted was 11.9 N. It was also noted that the compression of dry powder into tablets was a difficult procedure. On the other hand, the tablets prepared from powder initially containing 13.6 wt% water attained an equilibrium disintegration force of 27.5 N. From this study, it was concluded that water aided in the particle binding necessary to maintain the tablet form, and allowed a much greater force to be developed due to absorption of water.

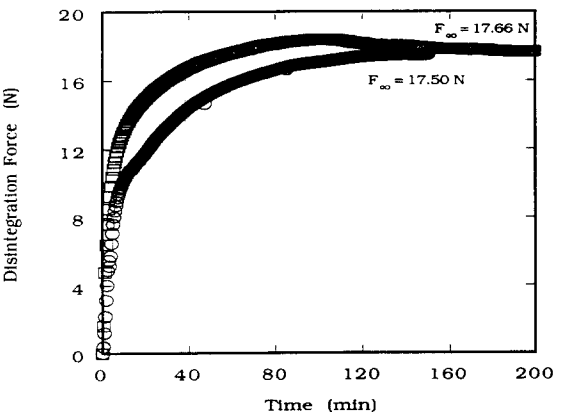

Fig. 4. Disintegration force developed for P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA in pH 5 solution as a function of crosslinking ratio: $X = 0.001$ (○); $X = 0.004$ (□).

The polymer particle size was found to affect the disintegration force, as shown in Fig. 6 for P(AA-co-HEMA) containing 50 mol% AA and 50 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 solution. The tablets compressed from particles with an average diameter of 2.6 μm were found to have a larger surface area to volume ratio, which subsequently provided additional area for water absorption to occur that induced a faster swelling and disintegrating process compared to particles with diameter of 17.4 μm.

The hydrophilicity of the copolymers was controlled by the amount of AA added during polymerization, since AA is the most hydrophilic component. Fig. 7 shows the effect of hydrophilicity on the disintegration force developed for

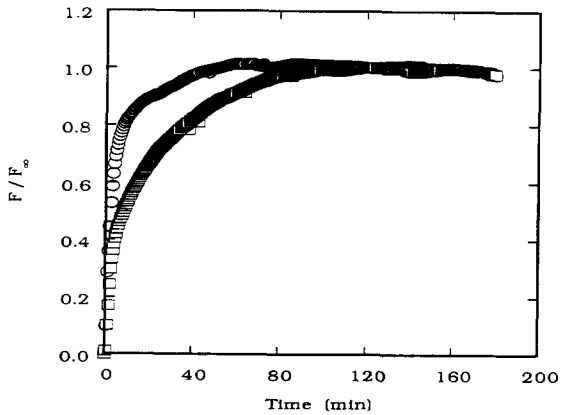

Fig. 6. Disintegration force developed for P(AA-co-HEMA) containing 50 mol% AA and 50 mol% HEMA with 0.001 mol EGDMA/mol monomer in pH 5 as a function of particle size: $d = 2.6$ μm (○); $d = 17.4$ μm (□).

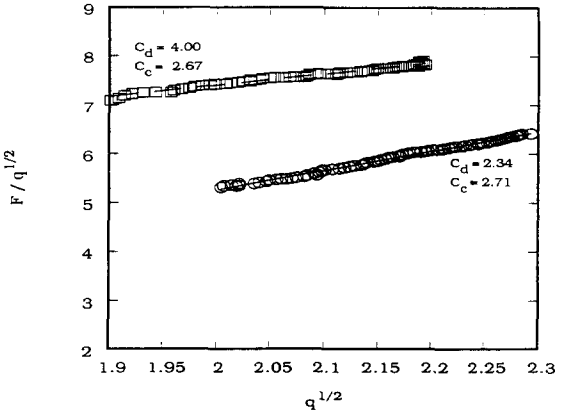

Fig. 8. Analysis of disintegration force developed in P(AA-co-HEMA) containing 30 mol% AA and 70 mol% HEMA as a function of crosslinking ratio: $X = 0.001$ (○); $X = 0.004$ (□); using Eq. 1 and the theory of Peppas and Colombo (1989).

copolymer samples crosslinked with 0.001 mol EGMDA/mol monomer immersed in a pH 5 solution. For the copolymer containing 30 mol% AA, the equilibrium disintegration force attained was 17.5 N, whereas the copolymer containing 50 mol% AA exerted an 11.9 N force. It should be noted that these copolymers contained approximately the same amount of water prior to compaction of the powder. The higher concentration of ionizable AA in the copolymer contributed to an increase in the rate of water absorption.

The results of this research were evaluated according to the model of Eq. 1 proposed by Peppas and Colombo (1989) as shown in Fig. 8. For the copolymer tablets prepared from powder that was crosslinked with 0.001 mol EGDMA/mol monomer, the relative contribution (as noted by comparison of C_d and C_c) of diffusion to convection processes was determined to be approximately the same. The diffusive contribution to the disintegrating force ($C_d = 4.00$) was more significant for the higher crosslinked copolymer, since the increased crosslinks provided more restrictions to expansion of the polymer network.

Further analysis of the swelling behavior was done by using pure, crosslinked poly(acrylic acid)

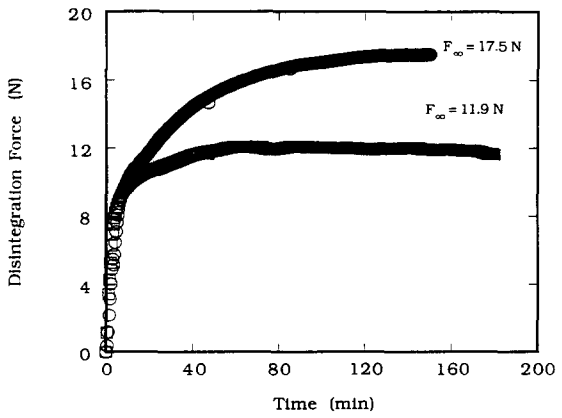

Fig. 7. Effect of hydrophilicity on the disintegration force developed for copolymers containing 0.001 mol EGMDA/mol monomer in pH 5 solution: 30:70E (○); 50:50E (□).

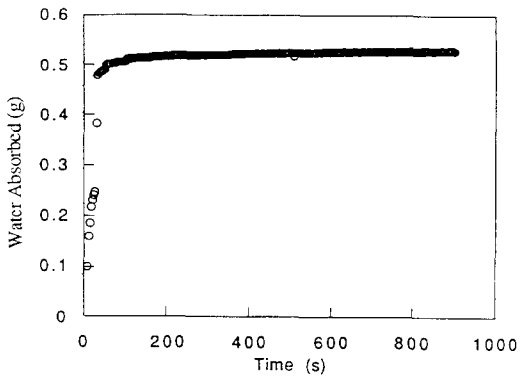

Fig. 9. Water absorption curve for 60% neutralized PAA containing 0.001 mol TMPTA/mol AA.

Table 2
Swelling force analysis of poly(acrylic acid) disks using Eq. 1

Crosslinking ratio (X) (mol/mol)	Equilibrium weight swelling ratio (q) (g/g)	Maximum swelling force (F_m) (N)	C_d	C_c
0.001	0.35	11.7	−2.93	42.15
0.005	0.26	7.0	−3.70	33.51
0.010	0.13	7.0	−11.67	76.36

polymers which were prepared in the form of compressed tablets. Fig. 9 and 10 show the water absorbed and disintegration force as a function of time for tablets prepared with PAA crosslinked at $X = 0.001$ mol TMPTA/mol AA. Table 2 shows the swelling behavior of such systems. In general, increased crosslinking lead to an decrease in the amount of water absorbed by the sample. Analysis of these results using Eq. 1 led to an evaluation of the diffusional and convectional contributions to the swelling force, C_d and C_c, respectively. In general, the diffusional contribution decreased with increasing crosslinking ratio, indicating that relaxations are important in densely crosslinked systems.

These studies are extremely important in further understanding the process of disintegration, as they were conducted with well controlled polymer structures of progressively increasing crosslinking ratio, and pH-sensitive (hydrophilic) component (AA) content.

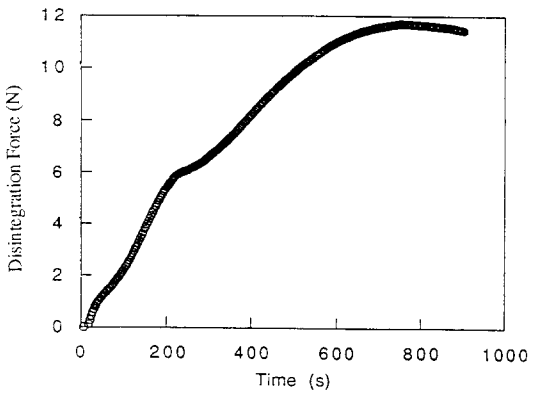

Fig. 10. Disintegration force developed for 60% neutralized PAA containing 0.001 mol TMPTA/mol AA.

4. Conclusions

The results of this investigation indicated the significance of the polymer physical properties in the development of the disintegration force. The water content aided in particle binding. The powder density was affected by the solvent used during polymerization, and the porosity of the tablets was a function of the crosslinking ratio and the solvent of polymerization.

Another important result of this investigation was that the desired disintegration behavior was achieved by altering the polymerization conditions and physical properties. In particular, the disintegration force profile could be modified by changing the crosslinking ratio, hydrophilicity, particle size, or solvent used during polymerization. It was concluded that P(AA-co-HEMA) provided a disintegration force in the same range of 20–50 N as currently used disintegrating agents which indicated that the force developed was adequate in promoting tablet break-up.

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