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FORMULATION OF PROPRANOLOL HYDROCHLORIDE ORALLY DISINTEGRATING TABLETS BY DIRECT COMPRESSION USING SIMPLEX LATTICE DESIGN

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Abstract: Simple lattice experimental design was used to study the effects of three superdisintegrants; sodium starch glycolate (SG), crospovidone (Polyplasdone® XL, CP) and croscarmellose sodium (Ac-Di-Sol®, CS), on disintegration times of propranolol hydrochloride tablets intended to be prepared as orally disintegrating tablets. The contents of SG, CP and CS were varied according to the simplex lattice design resulting in seven tablet formulations. The PH tablets were prepared by direct compression using microcrystalline (Avicel® PH 102) and spray-dried lactose as diluents. Aspartame, magnesium stearate and talcum were used as sweetening agent, lubricant and glidant, respectively. The prepared tablets were tested for uniformity of weight, hardness, friability, disintegration time and dissolution. The equation representing the tablet disintegration time as function of SG, CP and CS ratios utilized in the tablet formulations was computed. A triangular contour plot of the predicted equation was also drawn. From the predicted equation and the contour plot, an optimum propranolol hydrochloride orally disintegrating tablet formulation yielding the predicted disintegration time of 2.98 seconds was selected. The propranolol hydrochloride orally disintegrating tablet, prepared according to the chosen formulation, provided the observed disintegration time of 3.08 seconds and met the USP drug dissolution requirement.

Keywords: Orally disintegrating tablets, Propranolol hydrochloride, Simplex lattice design.

บทคัดย่อ: ทำการออกแบบการทดลองแบบ simplex lattice เพื่อศึกษาผลของสารช่วยแตกตัวประสิทธิภาพสูงสามชนิด ได้แก่ โซเดียมสตาร์ชไกลโคเลต (SG), ครอสโพวิโดน (Polyplasdone® XL, CP) และครอสคาเมลโลสโซเดียม (Ac-Di-Sol®, CS) ที่มีต่อเวลาในการแตกตัวของยาเม็ดโพรพราโนลอลไฮโดรคลอไรด์ที่ต้องการเตรียมเป็นยาเม็ดชนิดแตกตัวในปาก โดยใช้ปริมาณที่แปรผันของ SG, CP และ CS ที่สอดคล้องกับการออกแบบชนิด simplex lattice เป็นผลให้ได้ตำรับเม็ดรวมเจ็ดตำรับ เตรียมยาเม็ดโพรพราโนลอลไฮโดรคลอไรด์ด้วยวิธีตอกโดยตรงโดยใช้ไมโครคริสตัลลัยเซลลูโลส (Avicel® PH 102) และแลคโตสที่ผ่านการพ่นแห้งเป็นสารเพิ่มปริมาณ ใช้แอสพาเทม แมกนีเซียมสเตอร์เรทและทัลคัมเป็นสารแต่งรสหวาน สารหล่อลื่นและสารช่วยไหลตามลำดับ นำยาเม็ดที่เตรียมได้มาทดสอบหาความสม่ำเสมอของน้ำหนัก ความแข็ง ความกร่อน เวลาในการแตกตัว และการละลายของยาเม็ด คำนวณหาสมการแสดงความสัมพันธ์ระหว่างเวลาในการแตกตัวกับอัตราส่วนของ SG, CP และ CS ที่ใช้ในตำรับยาเม็ดและสร้างแผนภูมิคอนทัวร์ชนิดสามเหลี่ยมของสมการทำนายผลดังกล่าว จากนั้นทำการเตรียมตำรับยาเม็ดโพรพราโนลอลไฮโดรคลอไรด์ที่ให้เวลาในการแตกตัวตามการทำนายจากสมการทำนายผลและแผนภูมิคอนทัวร์เป็น 2.98 วินาที พบว่ายาเม็ดที่ตรียมตามตำรับที่เลือกใช้เวลาในการแตกตัวจริงเท่ากับ 3.08 วินาที และมีการละลายของตัวยาที่สอดคล้องกับข้อกำหนดของ USP

คำสำคัญ ยาเม็ดแตกตัวในปาก โพรพราโนลอลไฮโดรคลอไรด์ การออกแบบการทดลองแบบ simplex lattice

INTRODUCTION

According to the USFDA, the orally disintegrating tablets (ODT) are considered as solid oral preparations that disintegrate rapidly in the oral cavity, with the in-vitro disintegration time of approximately 30 seconds or less, when based on the USP disintegration test method (U.S. Department of Health and Human Services. Food and Drug Administration, 2008). This mode of administration eliminates the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids; thus providing the benefit to pediatric and geriatric patients, to people with conditions related to impaired swallowing and the patients when compliances may be difficult. The technologies that have been employed to prepare ODT include: freeze drying, molding, direct compression, sublimation, spray drying, mass extrusion, cotton-candy process, NanoCrystal® technology and oral films/waters (Hirani, Rathod, Vadalla, 2009). Since direct compression is a commonly method utilized in the tabletting process, therefore the preparation of ODT by direct compression is preferred. This study aimed to formulate a water-soluble drug, propranolol hydrochloride (PH), as orally disintegrating tablets by direct compression using various superdisintegrants. The three superdisintegrants employed in preparing the ODT were sodium starch glycolate (SG), crospovidone (Polyplasdone® XL, CP) and croscarmellose sodium (Ac-Di-Sol®, CS). A statistical experimental design, simplex lattice design, was applied to study the main effects and interactions of these superdisintegrants on tablet disintegration. Scheffe proposed the simplex lattice experimental design to study the effects of the proportions of the mixture components on a mixture property (Scheffe, 1963). For pharmaceutical formulations, the simplex lattice method has been demonstrated as a tool to search for an optimum tablet formulation (Bolton S, 1986).

According to the simplex lattice design of 3 variables, an observed response of the seven designed experimental trials is related to the ratios of the independent variables employed in the tablet formulations by the following equation.

$$Y = B_1(X_1)+B_2(X_2)+B_3(X_3)+B_{12}(X_1)(X_2)+B_{13}(X_1)(X_3)+B_{23}(X_2)(X_3)+B_{123}(X_1)(X_2)(X_3)$$

Whereas

$$(X_1) + (X_2) + (X_3) = 1.0$$

Where X_1, X_2 and X_3 are the ratios of the independent variables utilized in the tablet formulation and Y is the predicted response. In this investigation, the effects of three superdisintegrants: SG, CP and CS, on disintegration time of the PH tablets prepared by direct compression were studied. The predicted disintegration time equation as function of the ratios of the employed three disintegrants was computed by a statistical computer program.

MATERIALS AND METHODS

Propranolol hydrochloride (batch no. 060112) was obtained from Changzhoo Yabang Pharmaceutical Co. Ltd, China. Avicel® PH 102 (lot no. P211828634, FMC BioPolymer, USA), sodium starch glycolate (batch no. ASG/11/241111), crospovidone (Polyplasdone® XL-10EP6, batch no. 20090510, Nanhang Industrial Co. Ltd., China) and croscarmellose sodium (Ac-Di-Sol®, lot no. TN11822911) were supplied by Onimax Co. Ltd, Thailand. Spray dried lactose, magnesium stearate, talcum and aspartame were purchased from Pharmaceutical Science Ltd., Part., Thailand.

Experimental design

Figure 1 represents the simplex lattice design employed to study the effects of 3 independent variables; sodium starch glycolate (SG), crospovidone (CP), and croscarmellose sodium (Ac-Di-Sol®, CS) contents, on a dependent variable, the tablet disintegration time. A

three-variable mix (SG, CP and CS) can be represented by a diagram on a triangular graph as shown in Figure 1. Each vertex represents one of the components at 1.0 or 100%. If any point is plotted within the triangular then the percentages of all the components will always sum to 100. The design contains the three vertices, the midpoints of each face, and the centroid. Seven tablet formulations, each formulation containing different SG:CP:CS ratios (represented by the labeled points in the Figure 1), were established according to the simplex lattice design. The sum of the ratios of the 3 variables utilized in each formulation must be equal to 1.0. The combined content of the three variables (SG, CP and CS) in each formulation was fixed at 8 mg per tablet.

Preparation of propranolol hydrochloride tablets

Seven PH tablet formulations, F1 to F7 (Table 1), according to the simplex lattice experimental design (Figure 1) were prepared by direct compression. Avicel® PH 102 and spray-dried lactose were employed as direct compressible diluents. Aspartame, magnesium stearate and talcum were used as flavoring agent, lubricant and glidant, respectively. The ingredients in the formulations were mixed and compressed into tablets of 9 mm in diameter by a single stroke tabletting machine (Viuhang Engineering, Thailand) with the hardness between 3 to 5 kg. An additional extra formulation (F8) as listed in Table 1 was also prepared.

Construction of predicted response equations

The observed disintegration times of the designed seven PH tablet formulations was related to the SG:CP:CS ratios, utilized in the tablet formulations, by using a multiple linear regression program. The predicted equation of the disintegration time as function of the SG:CP:CS ratios then were derived.

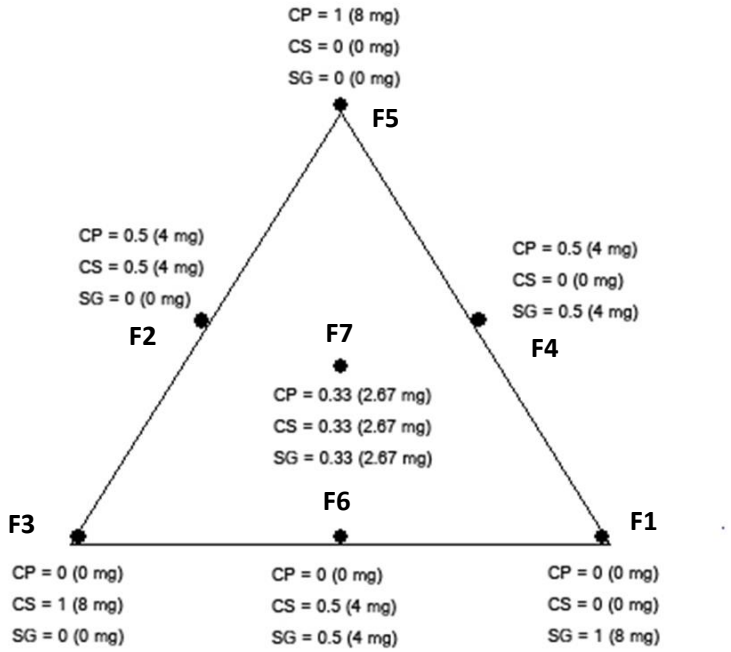

Figure 1. Simplex lattice design of 3 variables; SG, CP and CS ratios. Note: SG+CP+CS = 1.0 (8.0 mg)

Table 1. Formulations of the prepared propranolol hydrochloride tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Propranolol hydrochloride	20	20	20	20	20	20	20	20
Avicel® PH 102	50	50	50	50	50	50	50	50
Sprayed dried lactose	110	110	110	110	110	110	110	110
Sodium starch glycolate	8	0	0	4	0	4	2.67	0
Crospovidone	0	4	0	4	8	0	2.67	4.8
Croscarmellose sodium	0	4	8	0	0	4	2.67	3.2
Magnesium stearate	2	2	2	2	2	2	2	2
Talcum	10	10	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10	10	10

Test for tablet properties

Each tablet formulation was tested for hardness, friability, weight variation, disintegration time. Five tablets from each formulation were tested for tablet hardness (Dr.Schleuniger Co., Type THP-4M hardness tester, Switzerland). Tablet friability of each formulation was tested according to USP 32 and NF 27 (The United States Pharmacopeia, 2009) using a Roche friabilator for 4 minutes at the speed of 25 rpm. Tablet weight variation was tested on 20 tablets using an analytical balance (Sartorius, Model A200S analytical balance, Germany) according to BP 2008 on the test for uniformity of weight (The Department of Health, Great Britain, 2008). Disintegration test was performed on 6 tablets per formulation by USP type disintegrator (K.S.L. Engineering Co., Ltd., Thailand) using distilled water (37 ± 2^{o}C) as medium according to USP 32 and NF 27 (The United States Pharmacopeia, 2009).

Wetting times

The wetting times of the PH tablets yielding satisfied fast disintegration times were studied. (Battu, Repka, Majumdar, Rao, 2007). Five circular tissue papers were placed in a petri dish of 6.5 cm diameter. Six milliliters of distilled water containing a water-soluble dye was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablets and to completely wet then was noted as the wetting time. These measurements were carried out in replicate of five. Wetting time was recorded using a stopwatch.

Dissolution studies

Dissolution studies of the selected PH tablet formulations were also performed according to USP 32 and NF 27 (The United States Pharmacopeia, 2009) using a type I dissolution apparatus (Pharma Test Co., Model TW II, Hamburg, Germany). The basket was adjusted to rotate at 100 rpm. One thousand milliliters of diluted hydrochloric acid (1:1000) was employed as dissolution medium. Six tablets from each formulation were tested for dissolution at 37 ± 0.5^{o}C. Five milliliters of dissolution medium was withdrawn at predetermined time intervals up to 1 hour and assayed for drug content by UV spectrophotometer (Spectronic Instruments, Inc., Spectronic® Genesys™, Rochester, NY, U.S.A) at the wavelength of 289 nm.

RESULTS AND DISCUSSION

Tablet hardness, friability, weight variation and disintegration time of the prepared PH tablets are shown in Table 2. The percentages of tablet friability of the seven tablet formulations varied from 0.18 % to 0.78 %. All the prepared tablet formulations met the requirements on tablet friability (The United States Pharmacopeia, 2009) and uniformity of weight (The Department of Health, Great Britain, 2008). Disintegration times of all formulations were less than 30 seconds (0.5 minute), conforming to the definition of ODT (1).

From tablet disintegration study, the PH tablet consisting of CP alone (F5) provided faster disintegration time (0.04 minute) than those consisting of SG (0.21 minute, F1) or CS (0.33 minute, F3). While the PH tablet containing SG provided faster disintegration time than the PH tablet containing CS. However; when these three disintegrants were used in the PH tablets as combined disintegrants, the disintegration times in the range of 0.05 to 0.39 minutes were obtained. The application of 0.5:0.5 CP: CS (0.07 minute, F2) as combined disintegrants yielded faster disintegration time than that of 0.5:0.5 SG:CP (0.24 minute, F4) or 0.5:0.5 SG:CS (0.39 minute F6). When SG, CP and CS were employed as combined disintegrants in F7, the disintegration time was 0.20 minute.

By using the simplex lattice design in studying the effects of SG, CP and CS on tablet disintegration time of the PH tablets; the equation representing the relationship between disintegration time (DT) and the ratios of SG (X_1), CP (X_2) and CS (X_3) utilized in the tablet formulation was computed using the principles of the mixture experimental design and multiple linear regression.

$$DT = 0.206X_1+0.044X_2+0.329X_3+0.472X_1X_2+0.495X_1X_3-0.450X_2X_3 -1.416X_1X_2X_3$$

and

$$X_1+X_2+X_3 = 1.00$$

Consideration on the predicted DT equation, the several PH tablet formulations that exhibited the satisfied required predicted disintegration times could be identified as shown in Table 3. Therefore, the additional PH tablet formulation (F8) consisting of SG:CP:CS in the ratio of 0:0.6:0.4 (0:4.8:3.2 mg per tablet), which showed the predicted satisfied tablet disintegration time of 0.05 minute in Table 3, was chosen as a validated formulation. The predicted tablet disintegration time, calculated from the predicted equation was 0.050 minute or 2.98 seconds, while the observed tablet disintegration time was found to be 0.051 minute or 3.08 seconds. This result indicates the validity of the predicted disintegration time equation.

Table 2. The SG:CP:CS ratios in the PH tablet formulations predicted to have the required fast disintegration times.

	SG:CP:CS ratio	Hardness (kg)	Friability (%)	Weight Variation (mg)	Wetting time (seconds±S.D.)	Observed Disintegration Time (minute±S.D.)	Predicted Disintegration Time (minute)
F1	1:0:0	3.1± 0.23	0.78	187.04±1.55	-	0.21+0.032	0.201
F2	0:0.5:0.5	4.0±0.05	0.18	188.29±2.55	12.4±0.39	0.07+0.010	0.074
F3	0:0:1	3.9±0.22	0.22	196.76±6.97	-	0.33+0.026	0.328
F4	0.5:0.5:0	3.1±0.08	0.44	190.95±4.47	-	0.24+0.031	0.243
F5	0:1:0	3.6±0.51	0.73	192.07±7.09	15.1±0.35	0.04+0.026	0.044
F6	0.5:0:0.5	3.7±0.47	0.49	188.08±1.99	-	0.39+0.026	0.391
F7	0.33:0.33:0.33	3.6±0.67	0.75	204.95±3.45	-	0.20+0.008	0.198
F8	0:0.6:0.4	3.3± 0.30	0.75	205.39±5.58	19.9±0.54	0.05+0.002	0.050

Table 3. The SG:CP:CS ratios in the PH tablet formulations predicted to have the required fast disintegration times.

SG ratio (mg)	CP ratio (mg)	CS ratio (mg)	Predicted Disintegration time (minute)
0 (0)	0.60 (4.80)	0.40 (3.20)	0.05
0.02 (0.16)	0.92 (7.36)	0.06 (0.48)	0.05
0.03 (0.24)	0.86 (6.88)	0.11 (0.88)	0.05
0.04 (0.32)	0.70 (5.6)	0.26 (2.08)	0.05
0.05 (0.40)	0.70 (5.60)	0.25 (2.00)	0.05
0.05 (0.40)	0.80 (6.40)	0.15 (1.20)	0.05

From the predicted disintegration time equation, the triangular contour plot of disintegration time (Figure 2) as function of the employed ratios of SG, CP and CS was constructed. The presence of the three disintegrants in the PH tablets provided the predicted disintegration times in the wide range as demonstrated in Figure 2. By examining the contour plot, the various ratios of SG:CP:CS resulting in the predicted disintegration times of 0.05 minute or less could be obtained.

The three PH tablets yielding the satisfied fast disintegration times were F2 (0.07 minute), F5 (0.04 minute) and F8 (0.05 minute). Wetting times of F2, F5 and F8 were 12, 15 and 20 seconds (0.20, 0.25 and 0.33 minutes) as listed in Table 2. Therefore, these three formulations provided comparable fast wetting times and similar disintegration times.

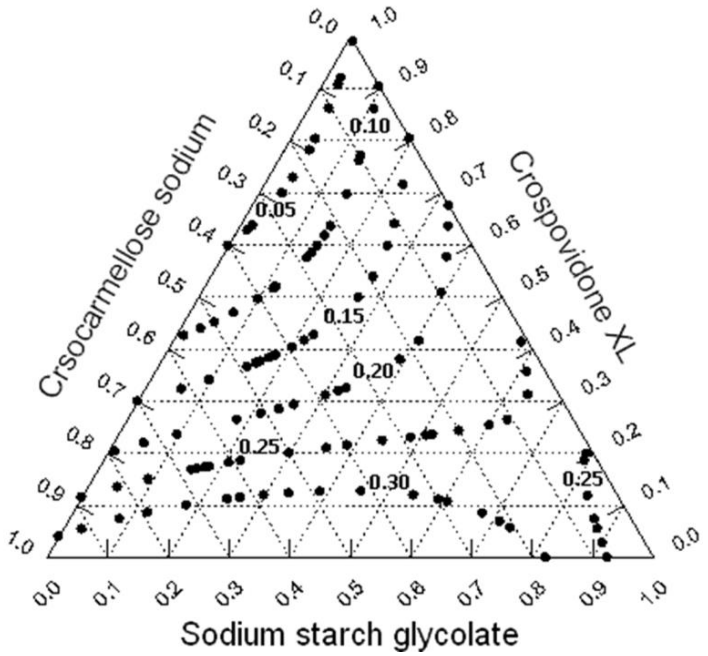

Figure 2. Triangular contour plot of disintegration time (minute) as function of SG, CP

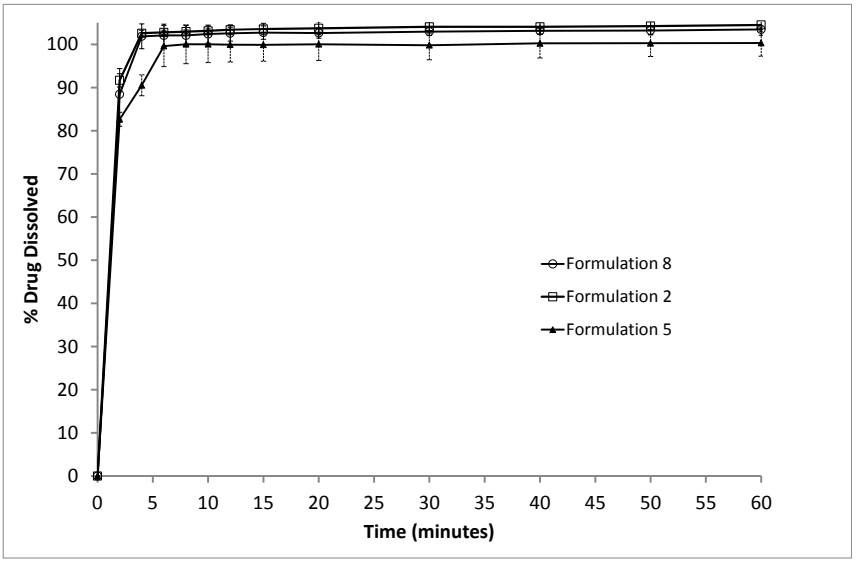

Figure 3. Dissolution profiles of the PH orally disintegrating tablets (F2, F5 and F8).

Dissolution profiles of the three PH tablet formulations having the fastest disintegration times (F2, F5 and F8) are shown in Figure 3. The tolerance of propranolol hydrochloride tablet dissolution states that propranolol hydrochloride is dissolved not less than 75% at the 30th minute time interval (The United States Pharmacopeia, 2009). The percentages of drug release at the 2nd and 4th minute time intervals of F2, F5 and F8 were found to be 91.7%, 82.6%, 88.4% and 102.6%, 90.5%, 101.9%, respectively. At the 6th minute time interval, the three tablet formulations provided the complete tablet dissolution. Therefore, these profiles met the dissolution requirement of the PH tablets (The United States Pharmacopeia, 2009). It appeared that F5 provided slower drug dissolution rate than F2 and F8 even though the disintegration times of the three PH tablet formulations were similar, ranging from 0.04 to 0.07 minutes. F5 consisted of CP while F2 and F8 consisted of CP and CS in the ratios of 0.5:0.5 and 0.6:0.4. Therefore, the usage of the optimum contents of CP and CS as combined disintegrants resulted in faster drug dissolution rates from the PH tablets than that of CP as single disintegrant. Combination of CP and CS disintegration actions might be the reason for the faster drug dissolution rates. Augsburger et al (Botzolakis, Augsburger, 1988) has shown the mechanism of action of disintegrants such as croscarmellose sodium, crospovidone and corn starch by rapid liquid absorption and swelling of disintegrant particles which fills the void spaces and cause the compact to disintegrate rapidly. CP uses a combination of swelling, wicking and deformation mechanism for rapid disintegration of tablets, swells rapidly in water without forming gel but is highly expensive. While CS absorbs water rapidly and swells in water to the extent of 200-300% and is cheaper than CP (Kumar, Nirmala, 2012). With extremely high swelling action of CS, more diffusion pathway was available for the prompted dissolution of the water-soluble drug, PH, during the disintegration process of the tablets containing the combined disintegrants, CP and CS.

Comparing to the usage of CP (F5) as single disintegrant, the application of CP and CS as combined disintegrants, in the optimum ratios (F2 and F8), reduced the production cost while yielded the comparable required fast disintegration of the PH tablets. Faster drug dissolution rates were also observed in the PH orally disintegrating tablets prepared by using the combined disintegrants.

CONCLUSION

The PH orally disintegrating tablets having the required disintegration times of less than 0.5 minutes were successfully prepared by direct compression using various ratios of SG:CP:CS. Simplex lattice design was proven to be useful as a tool to search for optimum ratios of the three superdisintegrants in preparing the PH orally disintegrating tablets. The usage of CP as single disintegrant or CP and CS, in optimum ratios, as combined disintegrants provided the ODT tablets of fastest disintegration times and satisfied rapid drug dissolution.

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