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DESIGN AND *IN-VITRO* CHARACTERIZATION OF CHLORDIAZEPOXIDE EFFERVESCENT FLOATING TABLETS

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ABSTRACT: Chlordiazepoxide is a sedative and hypnotic medication which is used to treat anxiety, insomnia, and withdrawal symptoms from alcohol and/or drug abuse. Chlordiazepoxide has a medium to the long half-life, but its metabolite is pharmacologically active and has a very long half-life. In the present work, an attempt has been made to develop effervescent floating tablets of Chlordiazepoxide. Methocel K4M, Methocel K15M & Xanthan gum were employed as polymers. All the formulations were prepared by direct compression method using 6mm flat punches. The blend of all the formulations showed a better angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The prepared tablets exhibited excellent hardness, friability, drug content, buoyancy lag time, duration of buoyancy, swelling index. Among all the formulations, the F7 formulation floated for more than 12 h, showed short buoyancy lag time of 96±0.92 seconds, high swelling indices of 2.4±0.12 %, and showed maximum cumulative percent drug release of 98.21±0.24 % in 12 h. Consequently, formulation F7, made using xanthan gum in 10mg/unit tablet weight concentration, was considered as an optimized formulation. The mechanism of drug release was found to be following zero-order release kinetics and non-Fickian diffusion.

INTRODUCTION: Chlordiazepoxide, a benzo-diazepine derivative, is mainly employed to treat anxiety and acute alcohol withdrawal symptoms and fear before surgery [1]. Floating drug delivery systems offer gastric retentive behavior, improved drug absorption, increased gastric residence time and make the formulation spend more time at its absorption site, controlled delivery of drugs, delivered drugs for local action, and minimized mucosal irritation due to the drugs, and site-specific delivery [2].

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Chlordiazepoxide is a benzodiazepine BCS class II drug that binds to the GABA receptor and aggravates the inhibitory neuronal activity of GABA receptor [3]. Oral Chlordiazepoxide is rapidly and completely absorbed; peak plasma concentrations appear 30 min after dosing. Chlordiazepoxide is mostly absorbed from the upper gastrointestinal tract and stomach [4].

Multiple-dose treatment leads to the accumulation of parent drugs and active metabolites, which precedes extreme sedation, respiratory depression, and muscle fatigue. Chlordiazepoxide conventional dosage form has more dosing frequency, which causes plasma peak fluctuation. Therefore, Chlordiazepoxide given through the gastro retentive system in a controlled release manner reduces the accumulation of drug and side effects by maintaining plasma blood level and also

increases patient compliance [5]. The floating drug delivery system remains in the stomach for several hours, bypassing the gastric transit. These dosage forms can float in the stomach [6], drug releases, and gets absorbed in a controlled manner for prolonged periods of time [7]. Different types and concentrations of the swellable polymer were used that can swell and control the drug release rate [8]. Hence FDDS improves their bioavailability, therapeutic efficiency [9] and proffers possible reduction of the dose [10] and many pharmacokinetic advantages like maintenance of therapeutic levels, reduction of dose size and improvement of the drug's solubility that is less soluble in high pH environment [11].

MATERIALS AND METHODS: Chlordiazepoxide was kindly supplied as a gift sample from Hetero Drugs Pvt. Ltd, Hyderabad, India. Methocel K15M and Magnesium stearate were supplied by SD fine Chemicals, Mumbai, India. Methocel K4M, Xanthan gum, Citric acid, Sodium bicarbonate, microcrystalline cellulose, and Talc were supplied by Merck Specialties Pvt Ltd, Mumbai, India. Analytical grade chemicals and distilled water were used throughout the experimental studies.

Formulation of Floating Effervescent Tablets of Chlordiazepoxide: In the present work, preliminary studies were done using sodium bicarbonate as a gas releasing agent. Various formulations of floating effervescent tablets were prepared using the direct compression method. The excipients used were Methocel K4M, Methocel K15M, Xanthan gum (swelling and rate-controlling polymers), Citric acid (acidifying agent), Sodium bicarbonate (gas-forming agent), microcrystalline cellulose (diluent), Magnesium stearate and Talc (lubricant) in various ratios. Accurate amounts of Chlordiazepoxide and all excipients were weighed and passed through sieve number #60. Barring magnesium stearate and talc, all other ingredients were added into the glass mortar in ascending order, mixed uniformly and homogeneously.

Finally, magnesium stearate and talc were added for lubrication and triturated for 2 to 3 min. The final blend was passed through sieve number #40. The blended materials were compressed by using 12 station rotary tablet compression machines with 6mm flat punches [12].

Precompression Parameters: Before compression, the formulation blend was evaluated for angle of repose, bulk, and tapped density. The angle of repose studies ascertained the flow properties of the powder blend. Compressibility index and Hausner's ratio were calculated from bulk and tapped density [13].

Post Compression Parameters: The prepared tablets were evaluated for weight variation, hardness, friability, drug content and buoyancy lag time, duration of buoyancy, swelling index, and *in-vitro* dissolution release studies [14].

Weight Variation test: Twenty tablets were taken randomly from each batch, and the weight was determined individually. After calculating the average weights, individual weights were compared to the average. Not more than two of the individual weights should deviate from the average weight by more than the percentage, and none should deviate by more than twice the percentage. The mean and deviation were determined (not more than ±10%). The percentage variation was calculated using the following formula [15].

Percentage weight variation = (Average weight – Initial weight / Average weight) × 100

Hardness: The crushing strength of the tablet was determined by applying the force that is required for breaking the tablet into two halves using a Monsanto hardness tester. Six tablets from each batch were randomly picked and analyzed for hardness. Average, mean, and standard deviation were calculated [16].

Tablet Friability: The mechanical strength of tablets was determined using Roche's fabricator. Pre-weighed ten tablets were subjected to the combined effect of attrition and shock by placing them in the chamber and then revolved for 4 minutes at 25rpm. The tablets were removed from the chamber, dedusted, and re-weighed, and the percentage of friability was calculated [17].

Tablet Thickness: Ten tablets were randomly selected, and the thickness was determined using a Vernier caliper (For-bro Engineers, Mumbai, India) [18].

Determination of Drug Content: Ten tablets were randomly selected, weighed individually, and

crushed. The powder equivalent to themes of one tablet weight of Chlordiazepoxide was transferred to a 100ml flask containing 50ml water and was shaken properly to ensure complete solubility of the drug. Volume was made up to 100ml with water. Suitable dilutions were made from this solution, and the absorbance was measured at 240nm using a UV visible spectrophotometer [19]. (Lab India, Mumbai, India)

***In-vitro* Buoyancy Studies:** The *in-vitro* buoyancy was ascertained by the floating lag time and total floating time. The floating lag time (FLT) is determined by taking three tablets randomly and placing them in a beaker containing 200 mL of 0.1 N HCl with a temperature maintained at 37±0.5 ºC using a water bath.

The time required for the tablet to rise from the bottom of the beaker to the surface and float was determined. The total floating duration that is, the time during which the tablet remains buoyant was recorded to be the Floating Lag Time (FLT) [20,] and the duration of time in which the tablet constantly floated is called Total floating time [21].

Swelling Indices: The swelling behavior of the tablets was determined in triplicate; tablets were weighed individually (W_1g) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, placed in a water bath at 37 ºC ± 0.5 ºC. At fixed time intervals, the tablets were removed, and the excess surface liquid was carefully removed using tissue paper. The swollen tablets were then re-weighed (W_2g). The percentage swelling Index (SI) was calculated using the formula [22, 23].

$$\text{Percentage swelling Index (SI \%)} = (W_2\text{-}W_1) / (W_1) \times 100$$

***In-vitro* Dissolution Studies:** The *in-vitro* dissolution study was performed using USP dissolution apparatus type II (paddle) at a rotational speed of 100 rpm. Exactly 900 mL of 0.1 N HCl was used as the dissolution medium, and the temperature was maintained at 37±0.5 °C. 10 ml of sample solution was withdrawn from the baskets at fixed intervals up to24 h and at each interval; the same volume was replaced with 0.1N HCl as dissolution medium. The samples were filtered through Whatman filter paper, diluted to a suitable concentration with the same dissolution medium, and the absorbance of these solutions was measured at 240 nm using a UV visible spectrophotometer [24]. The best formulation was selected based on the release of the drug at different time points for all formulations. Dissolution release data was tabulated and shown graphically as Cumulative % drug released versus time and release kinetics was applied.

Stability Studies: Optimized formulation F7 was subjected to accelerated stability studies by retaining the tablets in a stability chamber (Thermo lab, USA) kept at 40 ±2 °C and 75% ±5% RH for 3 months as per ICH guidelines. Tablets were investigated for hardness, friability, floating lag time, total floating time, swelling index, and drug content every month for 3 months.

RESULTS AND DISCUSSION: In this present study, Chlordiazepoxide effervescent floating tablets were developed to treat anxiety, acute alcohol withdrawal symptoms, and fear before surgery. Compared with oral multiple-dose therapy, these floating gastro retentive tablets can release the drug in a controllable manner that reduces drug accumulation and side effects and aims at better plasma concentration and patient compliance.

Total nine chlordiazepoxide effervescent floating tablet formulations were prepared using various concentrations of release retarding gel-forming polymers like methocel K4M, methocel K15M and xanthan gum a gas-forming agent such as sodium bicarbonate, and an acidifying agent such as citric acid. Preliminary studies were done using sodium bicarbonate as an effervescent gas generating agent. It helped the formulation to float. Various concentrations of sodium bicarbonate were employed during preliminary studies. Based on floating lag time and floating duration, the concentration of sodium bicarbonate was finalized and preceded for further formulations.

MCCpH102 was used to impart better flow, improved compaction of powder material. Swelling of the tablet when in contact with gastric fluid led to enhanced water uptake and improved floating abilities due to the presence of MCCpH102. All nine powder formulations were compressed by direct compression method using talc and magnesium stearate as lubricants. Formulae were shown in **Table 1.**

TABLE 1: FORMULATION TABLE OF CHLORDIAZEPOXIDE FLOATING TABLETS

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlordiazepoxide	10	10	10	10	10	10	10	10	10
Methocel K4M	10	20	30	-	-	-	-	-	-
Methocel K15M	-	-	-	10	20	30	-	-	-
Xanthan gum	-	-	-	-	-	-	10	20	30
Sodium bicarbonate	5	5	5	5	5	5	5	5	5
Citric acid	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC pH 102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight (mg)	100	100	100	100	100	100	100	100	100

Pre-compressional Parameters: All nine (F1 to F9) powder formulations were evaluated for pre-compressional parameters. The angle of repose was found to be in the range of 29.1±0.07 ^{0}C to 30.0±0.12 ^{0}C, compressibility index (%) and Hausner's ratio was found to be in the range of 10.46±0.95 to 14.87±0.32 and 1.12±0.21 to 1.18±0.33, respectively. Hence all powder formulations possessed good flow and compressibility characteristics, as shown in **Table 2.**

TABLE 2: PRECOMPRESSION PARAMETERS OF THE POWDER BLEND

Formulation Code	The angle of repose (0)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	29.8±0.14	0.22±0.45	0.26±0.29	14.87±0.32	1.18±0.33
F2	29.5±0.16	0.30±0.56	0.34±0.19	11.64±0.15	1.13±0.18
F3	29.3±0.11	0.22±0.32	0.25±0.31	12.01±0.42	1.14±0.54
F4	29.1±0.17	0.26±0.47	0.29±0.73	10.46±0.95	1.12±0.21
F5	29.5±0.13	0.26±0.12	0.30±0.23	13.48±0.51	1.15±0.95
F6	29.4±0.14	0.25±0.91	0.29±0.12	13.64±0.65	1.16±0.21
F7	29.2±0.11	0.30±0.22	0.34±0.11	11.64±0.75	1.13±0.64
F8	30.0±0.12	0.25±0.31	0.28±0.53	10.58±0.51	1.13±0.23
F9	29.1±0.07	0.25±0.13	0.28±0.42	10.87±0.18	1.12±0.52

(F1 to F9) (n=3, mean ± sd).

Post Compression Parameters: All nine chlordiazepoxide effervescent tablet formulations were off-white, smooth-surfaced, and oval. The results of post-compression parameters were presented in **Table 3.** The thickness of all the formulations was almost uniform. The weight variation of each formulation was calculated and found to be in the range of 98±0.22 to 109±0.32mg showing uniformity in weight. All the tablets hence follow uniformity in weight as per pharmacopeial limits of ±10%. The hardness of all the tablets ranged from3.3±0.37 to3.6±0.68Kg/cm^2, showing sufficient mechanical strength and hardness. The percentage friability of all tablet formulations ranges from 0.51±0.15 to 0.59±0.55. The values below 1% show that tablets are having sufficient resistance to mechanical shock and abrasion. Drug content uniformity for all the formulations was found to be between 97.21±0.13 to 99.58±0.78%.

TABLE 3: POST COMPRESSION EVALUATION PARAMETERS

Formulation code	Weight variation(mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content
F1	109±0.32	3.5±0.31	0.59±0.41	98.09±0.53
F2	108±0.53	3.6±0.68	0.55±0.17	99.38±0.81
F3	103±0.91	3.4±0.81	0.57±0.15	98.17±0.34
F4	104±0.64	3.3±0.37	0.58±0.21	99.08±0.53
F5	106±0.23	3.5±0.53	0.59±0.55	98.06±0.46
F6	102±0.57	3.6±0.38	0.52±0.21	97.21±0.13
F7	98±0.22	3.5±0.51	0.53±0.52	99.58±0.78
F8	99±0.16	3.5±0.32	0.50±0.94	98.29±0.31
F9	100±0.31	3.6±0.57	0.51±0.15	97.80±0.56

***In-vitro* Buoyancy Studies:** *In-vitro* buoyancy studies were performed to evaluate the duration of buoyancy and buoyancy lag time in the presence of various rate-controlling polymers. The duration of buoyancy varied from 9±0.77 h to >12±0.52 h, and buoyancy lag time varied from 96±0.92 to 104±0.46 sec for all formulations. F7 formulation exhibited a short buoyancy lag time of 96±0.92 sec as well as a high swelling index of 2.4±0.12. Xanthan gum is a natural, sustainable polymer having zero-order drug release. When this natural xanthan gum is present along with citric acid, upon influx into the stomach, carbon dioxide is released, causing the formulation to float in the stomach, thereby improving the bioavailability of the drug with substantial benefits, reducing the drug wastage. *In-vitro* buoyancy study data is represented in **Fig. 1** and **Table 4.**

FIG. 1: PHOTOGRAPH TAKEN DURING *IN-VITRO* BUOYANCY STUDY OF F7 FORMULATION IN 200 ML 0.1N HCL AFTER 12 H

TABLE 4: *IN-VITRO* BUOYANCY STUDIES AND SWELLING INDEX OF CHLORDIAZEPOXIDE EFFERVES-CENT FLOATING TABLETS

Formulation code	Buoyancy lag time (sec)	Duration of buoyancy (h)	Swelling index (%)
F1	99±0.64	9±0.16	2.1±0.53
F2	100±0.48	>12±0.02	2.03±0.68
F3	101±0.53	10±0.35	1.9±0.19
F4	100±0.79	>12±0.37	1.8±0.45
F5	98±0.21	>12±0.19	1.7±0.28
F6	104±0.46	12±0.43	1.68±0.74
F7	96±0.92	>12±0.52	2.4±0.12
F8	97±0.43	9±0.77	2.1±0.56
F9	102±0.57	12±0.52	2.2±0.19

(N=3, Mean ± Sd).

Swelling Indices: The hydration ability of the formulation may have a significant result on tablet buoyancy and release kinetics. The swelling behavior of a tablet depends on the swell-able polymers present in the formula. The formulations F1, F2, and F3 have 10mg, 20mg, and 30mg of Methocel k4M. An increase in the concentration of methocel k4M showed an increase in the viscosity of the gel layer and an increase in the time for water to reach the inner core of the tablet. F1 to F3 formulations showed swelling indices of 2.1±0.53, 2.03±0.68, and 1.9±0.19, respectively. Formulations F4, F5, and F6 formulations showed swelling indices of 1.8±0.45, 1.7±0.28, and 1.68±0.74, respectively.

Formulations F7, F8, and F9 showed swelling indices of 2.4±0.12, 2.1±0.56, and 2.2±0.19, respectively. The formulation F7 showed the highest swelling index (2.4±0.12) among all nine formulations and contained 10mg of xanthan gum per tablet as shown in **Table 4.**

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies of all the floating effervescent tablet formulations of Chlordiazepoxide were carried out in 0.1NHCl for up to 12 h. At different time intervals, cumulative percent drug released was calculated. The *in-vitro* drug release data of all formulations from F1 to F9 was tabulated in **Table 5**. The percent cumulative drug release verse time in hours was plotted and was shown in **Fig. 2.**

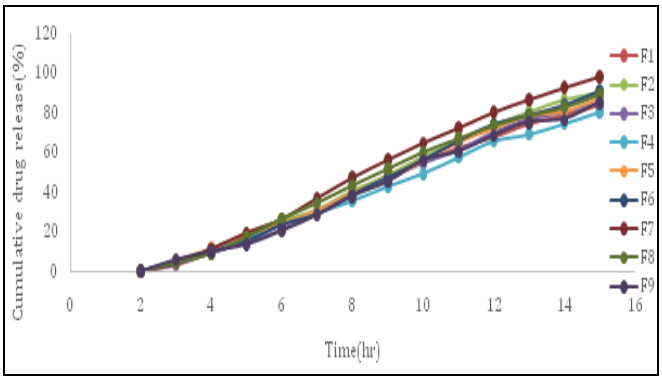

FIG. 2: *IN-VITRO* DRUG RELEASE OF FORMULATIONS F1 TO F9

TABLE 5: CUMULATIVE PERCENT DRUG RELEASE OF FORMULATIONS F1 TO F9 (N=3, MEAN ± SD)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	3.12±0.92	4.22±0.31	3.56±0.91	5.22±0.19	5.24±0.53	4.08±0.54	4.23±0.28	4.32±0.42	5.86±0.41
1	9.52±0.53	10.17±0.32	9.13±0.43	10.45±0.15	11.52±0.47	9.56±0.31	11.31±0.14	9.05±0.37	10.21±0.23
2	15.87±0.42	18.95±0.42	14.84±0.34	16.87±0.37	18.42±0.52	15.24±0.32	19.42±0.93	17.32±0.43	13.55±0.53
3	23.85±0.46	25.38±0.71	21.07±0.18	23.61±0.46	24.09±0.63	23.62±0.45	26.34±0.18	26.47±0.37	20.53±0.48
4	30.45±0.89	31.09±0.78	30.42±0.23	29.42±0.29	30.47±0.82	29.07±0.13	36.93±0.42	34.51±0.65	28.41±0.41
5	38.13±0.31	40.56±0.43	39.57±0.14	35.57±0.43	39.53±0.48	38.86±0.71	47.22±0.63	43.42±0.35	37.93±0.46
6	48.42±0.52	48.31±0.64	47.12±0.83	42.84±0.56	46.32±0.33	47.54±0.96	56.23±0.65	51.73±0.82	45.22±0.51
7	55.06±0.38	57.76±0.54	54.87±0.17	49.43±0.38	55.67±0.57	56.32±0.42	64.74±0.44	60.14±0.28	55.92±0.43
8	62.14±0.74	65.43±0.23	61.46±0.45	57.52±0.56	65.09±0.84	66.21±0.74	72.23±0.61	66.95±0.45	60.43±0.56
9	67.45±0.31	73.67±0.18	70.45±0.37	65.74±0.32	72.08±0.53	74.53±0.35	80.21±0.52	73.52±0.75	68.52±0.36
10	74.21±0.71	80.32±0.91	77.21±0.38	69.15±0.56	78.56±0.42	79.22±0.27	86.63±0.46	78.63±0.92	75.32±0.33
11	78.42±0.53	86.54±0.56	80.43±0.31	74.53±0.28	80.54±0.15	84.21±0.48	92.62±0.82	82.64±0.51	76.78±0.47
12	83.67±0.81	90.06±0.16	85.12±0.24	80.51±0.46	87.43±0.53	91.45±0.45	98.21±0.24	89.31±0.46	85.32±0.24

Formulations F1, F2 and F3 has Methocel K4M at 10mg,20mg and 30mg concentrations while, formulations F4, F5 and F6 contained Methocel K15M in 10mg, 20mg and 30mg concentrations and formulations F7, F8 and F9 were prepared using xanthan gum in10mg, 20mg and 30mgconcentrations, respectively. Among all formulations, F7 showed the maximum percentage of drug release (98.21±0.24 %) within 12 hours. Hence F7 formulation containing xanthan gum in 10mgwas considered to be optimized.

Application of Release Rate Kinetics to Dissolution Data: From the *in-vitro* dissolution studies, the optimized formulation F7 was furthermore tested for the mechanism of drug release kinetics. The data were fitted into Zero order, First order, Higuchi and Korsmeyer-Peppasmathematical models to study the drug release mechanism. The drug release mechanism was inferred to be zero-order and non-Fickian diffusion in the sense that drug release was independent of the concentration of drug, and the mechanism of drug release could be both by swelling (diffusion) and erosion.

TABLE 6: MATHEMATICAL KINETIC MODEL APPLIED TO IN VITRO RELEASE DATA OF F7

Formulation code	Zero-order r2	First-order r2	Higuchi kinetics r2	Korsmeyer-Peppas	
				N	R2
F7	0.998	0.978	0.925	0.6736	0.992

Evaluation of Stability Studies: The effect of storage of optimized formulation F7 at 40 ±2 °C and 75% ±5% RH for 3 months was not detrimental. Drug content did not vary much, staying in the range of 99.08-99.58 % over 3 months. Hardness, friability, and swelling index stayed close to initial values. Tablets stayed afloat for more than 12 h throughout the testing period.

TABLE 7: STABILITY STUDIES OF OPTIMISED FORMULATION F7 (N=6, MEAN±SD)

Dayof testing	Hardness (Kg/cm^2)	Friability (%)	Buoyancy lag time (sec)	Duration of buoyancy (hr)	Swelling index (%)	Drug content (%)
Day 1	3.5±0.51	0.53±0.52	96±0.92	>12±0.52	2.4±0.12	99.58±0.78
Day 30	3.5±0.43	0.53±0.5	95±0.32	>12±0.45	2.3±0.1	99.43±0.17
Day 60	3.52±0.45	0.54±0. 05	95±0.29	>12±0.32	2.4±0.09	99.08±0.23
Day 90	3.52 ±0.5	0.54±0.08	96±0.28	>12±0.23	2.3±0.11	99.08±0.24

CONCLUSION: In the present study, effervescent floating tablets of Chlordiazepoxide were prepared using the direct compression technique. The rate-controlling polymers used were Methocel K4M, Methocel K15M, and Xanthan gum. Citric acid was used as acidifying agent, sodium bicarbonate as a gas-forming agent, and microcrystalline cellulose as the diluent in this research work. Out of nine prepared formulations, the F7 formulation containing xanthan gum in the concentration of 10 mg showed acceptable results concerning buoyancy lag time, duration of buoyancy, swelling index, adhesion retention period, sustained drug release rates, and maximum percent drug release (98.21%). The best fit model with the highest R2 coefficients from the release mechanism was shown by both the Zero-order and Korsmeyer-Peppas models.The optimized F7 formulation showed zero-order independent of release of dissolved substances andnon-Fickian diffusion, which implies Chlordia-

zepoxide diffuses and erodes to release into the medium. Optimized formulation F7 was subjected to accelerated stability studies as per ICH guidelines. The F7 formulation showed better physical stability, buoyancy lag time, and buoyancy duration even when stored at 40° C ± 75% RH for 3 months.

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