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Studies on taste masking of levocetrizine di hydrochloride using ion - exchange resins

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ABSTRACT

Levocetrizine Di Hydrochloride is second generation piperazine derivative, a potent H_1 selective anti - histaminic or anti- allergic agent.It has bitter taste. So, the taste has to be masked inorder to reduce its bitterness, to increase its palatability and to improve patient compliance. The purpose of this research work to prepare tasteless complexes of levocetrizine di hydrochloride with Kyron, a cationic ion - exchange resin, to evaluate bitterness and in-vitro drug release from the Drug- Resin complex (DRC). Here, DRC was prepared by Batch method using Kyron T - 104 and Kyron T- 114 and was found that percentage of drug bound to resin was more with Kyron T -114 and selected it for preparing DRC using ratios from 1:1 to 1:3 and it was founded that 1:3 as the optimized one. The optimized complex was characterized by FT- IR Spectroscopy. Finally , in this work, the effect of various parameters like, stirring time,soaking time,temperature, P^H on drug loading efficiency were studied and optimized.The in-vitro drug release studies were also carried out and recorded .Finally ,the bitterness evaluation was performed by involving the volunteers who have rated drug resin complexes as tasteless and agreeable.

Keywords:DRC, Kyron T- 104, Kyron T- 114, Batch method, FT-IR.

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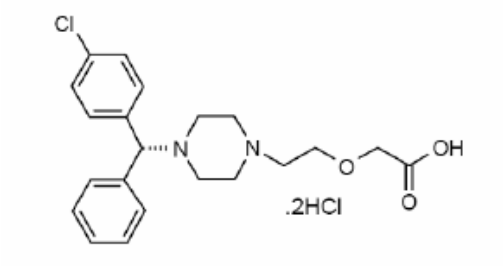
INTRODUCTION

Levo cetrizine Di Hydrochloride [1-5] is chemically designated as 2-[2-[4-[(R)-(4-chloro phenyl)-phenyl-methyl] piperazine-1-yl] ethoxy] acetic acid. Levo cetrizine is the R enantiomer of cetrizine. It is a second generation piperzine derivative, potent H1 selective anti histaminic or anti allergic agent. Levo cetrizine like cetrizine has a potential anti inflammatory effect in the treatment of Allergic Rhinitis with Asthma. It is believed to have a two fold higher affinity to human H1 receptors than cetrizine. But this drug has bitter taste which may lead to patient non compliance. Conventional taste masking techniques such as use of sweetners, aminoacids, flavouring agents are often unsuccessful in masking the taste of highly bitter drugs like levo cetrizine. So ion exchange resins are used in drug formulations to stabilize the sensitive components and for taste masking [2,4]. Ion exchange resins are water insoluble cross linked polymers containing salt forming groups in repeating positions in the polymer chain. In the present work an attempt has been made for taste masking of levocetrizine using ion exchange resins such as kyron T104 and Kyron T114 which are derivatives of cross linked polymer of methacrylic acid [6]. In this work, the effect of various parameters like, stirring time, soaking time, temperature, P^H on drug loading efficiency were studied and optimized. The in-vitro drug release studies and finally bitterness evaluation were also carried out and recorded [9-11].



EXPERIMENTAL

Materials

Levo cetrizine Di Hydrochloride was a gift from CADILA PHARMACEUTICALS LTD (Gujarat, India). The resins Kyron T 104 and Kyron T 114 were gifted from COREL PHARMA-CHEM (Ahmedabad, India).KOH of ultra pure grade was purchased locally.

Methods

Adsorbate preparation

For the preliminary studies, two cation exchange resins were used. Levo cetrizine was mixed separately with both the resins in the drug: resin ratios varying from 1:1 to 1:3.An accurately weighed amount of resin was added to 25 ml of demineralized water and stir continuously for around 10 to 15 min. 2 gms of Levocetrizine Di Hydrochloride is added to the above solution under stirring. The sitting was continued for 5hrs. The mixture was kept a side to allow the particles to settle down and was then filtered and washed with demineralized water to remove the free drug. The amount of free drug in the filtrate was measured spectrophotometrically at 231nm with suitable dilutions. The difference between initial amount of Levo cetrizine and content of collective filtrate give the amount of drug bound to resin. Also the resonates were prepared at various P^H conditions to find the optimum P^H conducive for loading.

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Characterization of Drug: Resin complex by IR spectroscopy

The drug, resin and resinate were subjected to Fourier Transform Infra Red (FTIR) studies to check drug resin interaction using FTIR (Shimadzu 8400 s).

In-vitro release study

Drug release was determined by adding adsorbate equivalent to 50mg of drug to 900ml of dissolution medium using Labindia Disso 2000 an 8 stage dissolution apparatus at a stirring speed of 100rpm.The dissolution medium of varied PH (i.e., 1.2 and 6.8) was used, and samples were withdrawn at suitable time intervals. The filtrates were then assayed by using UV spectroscopy. The data of invitro release study was shown in Table 7.

Taste Evaluation

The healthy human volunteers were used for taste masking and informed consent was obtained from all of them. Bitterness was measured by consensus of a trained taste panel, with 2omg of sample held in the mouth for 5 to 10 seconds. Than spat out; the bitterness level was then recorded. A numerical scale was used with the following values: 0=taste less,1=acceptable bitternes,2=slight bitterness,3=moderately bitterness and 4=strong bitterness. The data is given in Table 8.

RESULTS AND DISCUSSION

Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. It is observed from Table 1 that Kyron T - 114 show maximum adsorption for levo cetrizine which may be attributed to difference of cross linking n exchange capacity and form of resin.the drug loading efficiency was optimized at different drug resin concentrations which showed that 1:3 is the best ratio (Table 2) . While studying the effect of P^H, it is evident from Table 3 that maximum loading occurs at P^H 5.5. While studying the effect of temperature, soaking time, stirring time, it is evident from the Tables 4, 5 and 6 respectively that maximum loading occurs at 40^0c, 90min soaking time and at a stirring time of 5hours. Thus resinate prepared by batch method using Kyron T - 114 in drug:resin ratio of 1:3 at PH 5.5 ,40^0c,90 min soaking time and 5 hours stirring time gave optimum drug loading. Bitterness evaluation results made by the consensus of trained persons were listed in Table 8. It is confirmed that the taste of levo cetrizine was masked by complexing with Kyron T - 114. levo cetrizine release from the DRC was studied in gastric PH of 1.2 ,which showed that the drug release was more than 95% within two hours. The complexation was confirmed by carrying out IR studies which evaluated possible solid-solid interactions between the drug and resin. The IR spectra of complex showed that there was no interaction between drug and resin. Peaks of both drug as well as resin were observed and interpreted.The IR spectra of Drug,Resin and DRC were shown in the Figures 6,7&8 respectively.

Table 1: Selection of Resin

Resin	concentration		Percentage of drug bound to Resin
	Resin	Drug	
Kyron T 104	100	100	49.6
Kyron T 114	100	100	65.7

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Table 2: Effect of Drug : Resin ratio on loading

Resin	Drug :Resin	Percentage of drug bound to Resin
Kyron T 114	1:1	65.7
	1:1.5	73.3
	1:2	78.6
	1:2.5	80.1
	1:3	82.5

Table 3: Effect of Kyron T-114 P^H on Drug loading

Resin	Ratio	PH	Percentage of Drug bound to Resin
Kyron T 114	1:3	2	83.1
		3	85.3
		4	87.6
		4.5	89.2
		5	93.5
		5.5	96.9
		6	94.2
		7.5	93.8
		8	88.3

Table 4: Effect of Temperature on Drug loading

Resin	Ratio	Temperature(^{0}c)	Percentage of Drug bound to Resin
Kyron T 114	1:3	40	97.0
		50	96.2
		60	95.6
		70	95.2
		80	94.7

Table 5: Effect of soaking time of Resin on drug loading

Resin	Ratio	Soaking time(min)	% of drug bound to resin
Kyron T 114	1:3	0	73.1
		10	78.3
		20	82.8
		30	91.3
		60	94.4
		90	98.3

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Table 6: Effect of Stirring time on drug loading

Resin	Ratio	Stirring time(min)	% of drug bound to resin
Kyron T 114	1:3	30	60.4
		60	67.3
		90	72.5
		120	81.2
		150	83.6
		180	88.4
		210	91.8
		240	94.1
		300	97.4

Table 7: Invitro release of Levo Cetrizine from the Drug-Resin complex in 0.1N HCL

Time(min)	% cumulative drug release
5	42.41±1.40
10	44.24±0.32
15	46.64±0.14
30	50.78±0.78
45	54.60±0.50
60	59.24±1.52
75	64.66±1.72
90	84.67±1.57
120	98.12±0.47

Table 8: Bitterness evaluation by Taste panel

	1	2	3	4	5	6
Pure drug	4.0	4.0	4.0	4.0	4.0	4.0
Adsorbate(5sec)	2.0	0.0	0.0	1.0	1.0	0.0
Adsorbate(10sec)	1.0	0.0	1.0	2.0	2.0	0.0

Fig 1: Effect of Kyron T-114 P^H on Drug Loading

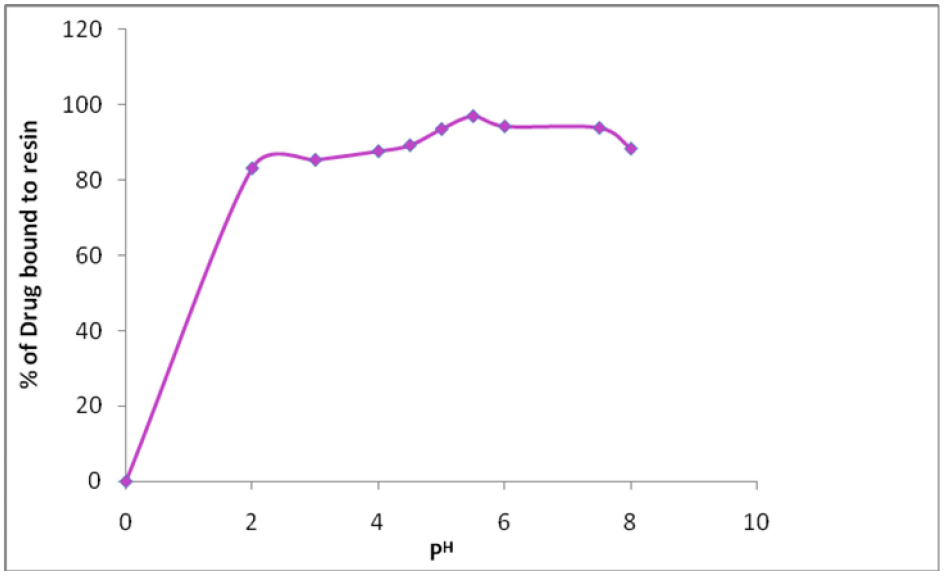

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Fig 2: Effect of Temperature onDrug loading

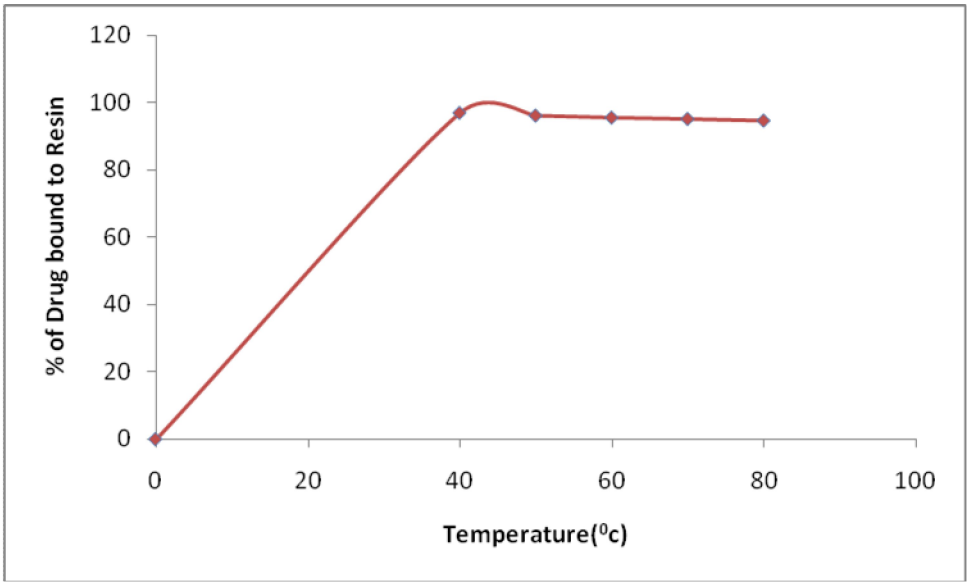

Fig 3: Effect of soaking time of Resin on drug loading

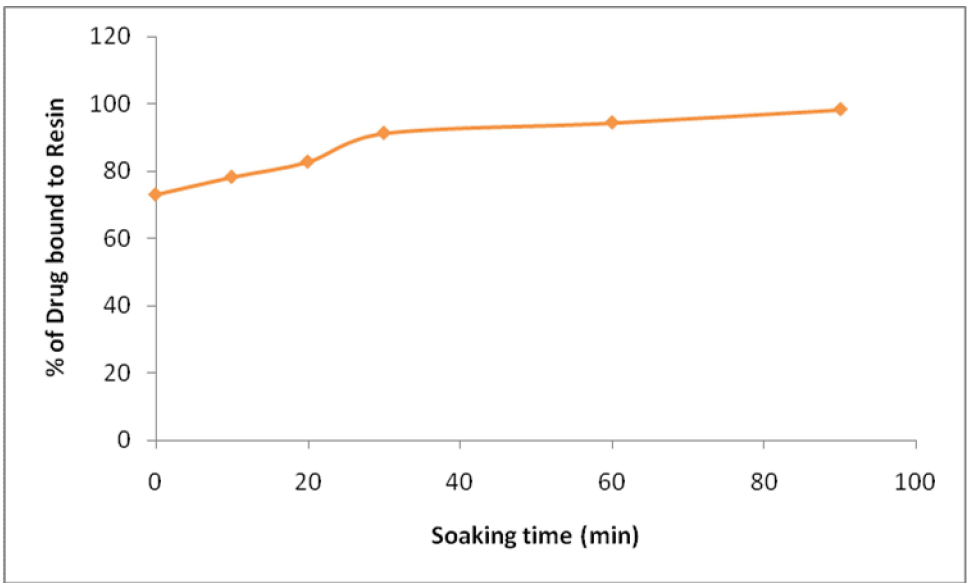

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Fig 4: Effect of Stirring time on drug loading

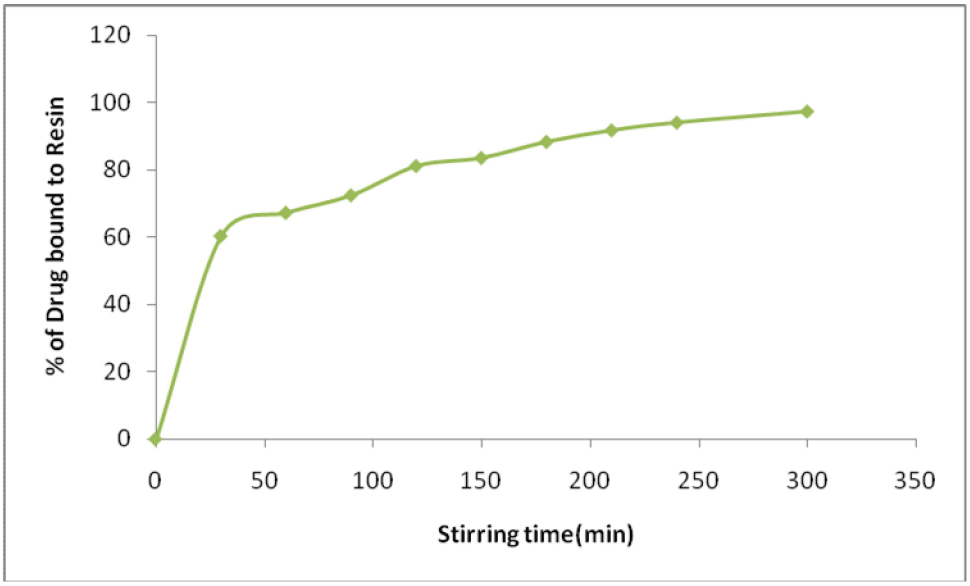

Fig 5: Invitro release of Levo Cetrizine from the Drug-Resin complex
In 0.1N HCL

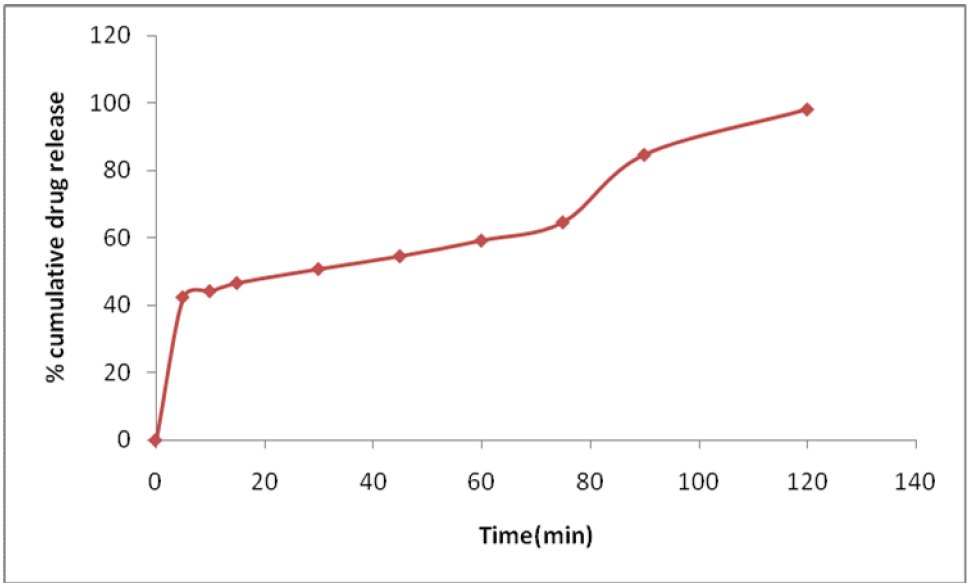

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Fig 6: FT- IR spectra of Drug

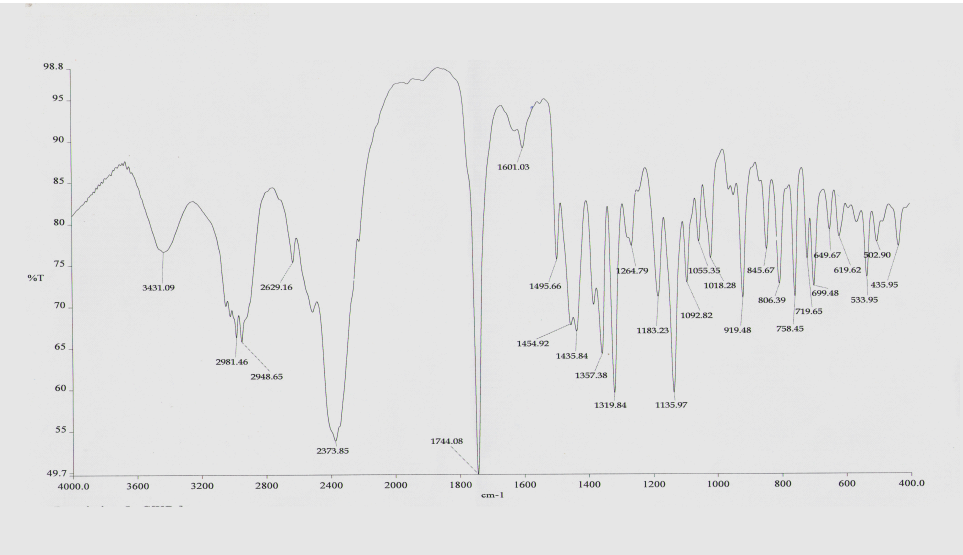

Fig 7: FT-IR spectra of Resin

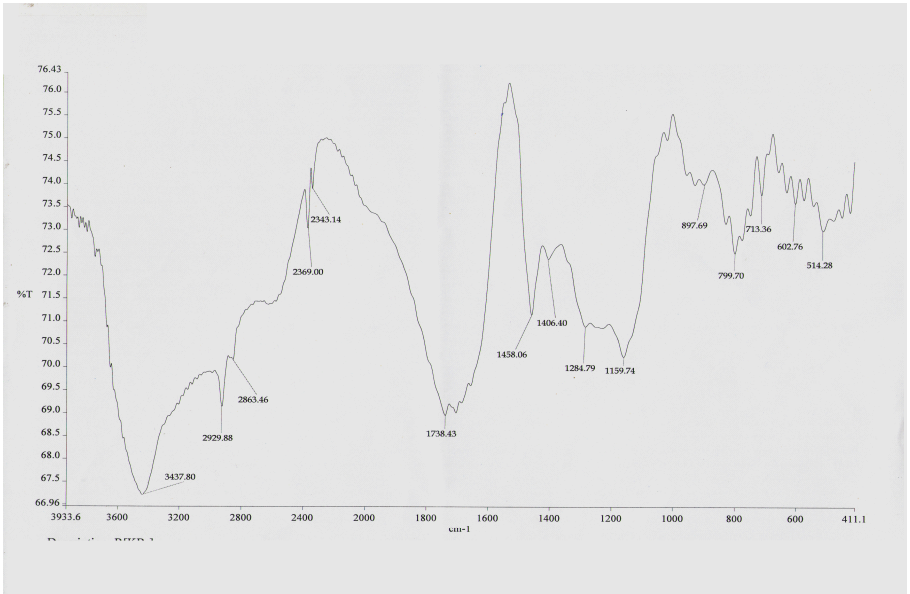

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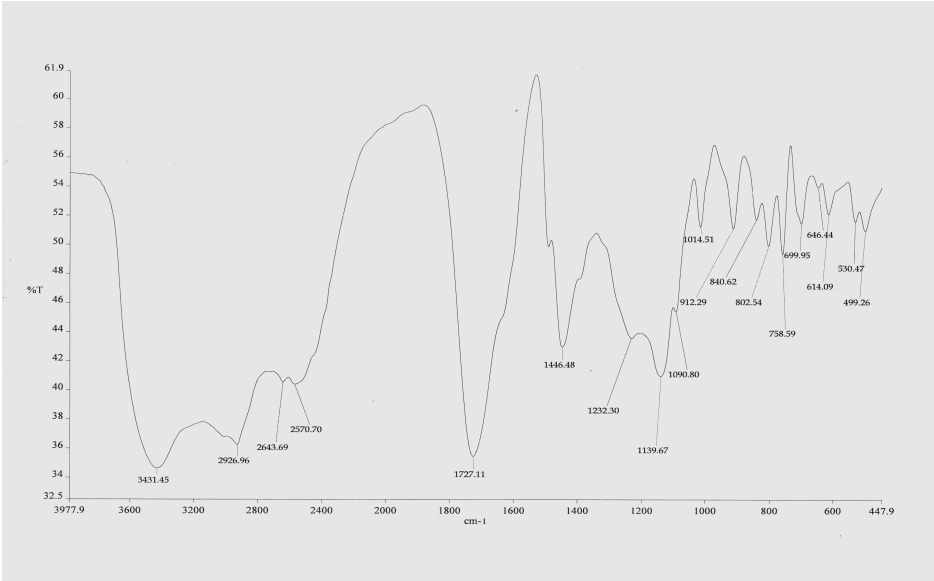
Fig 8: FT-IR spectra of DRC



CONCLUSION

The batch process of complexing levo cetrizine with Kyron T - 114 produced efficient drug loading. The study also suggests that an ion exchange resin system is a useful alternate for masking taste of drugs like levo cetrizine. The results of this study can be extrapolated to other intensely bitter drugs by suitable selection of ion exchange resins.

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